COMPREHENSIVE ORGANIC SYNTHESIS

Selectivity, Strategy & Efficiency in Modern Organic Chemistry

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Preface

The emergence of organic chemistry as a scientific discipline heralded a new era in human development. Applications of organic chemistry contributed significantly to satisfying the basic needs for food, clothing and shelter. While expanding our ability to cope with our basic needs remained an important goal, we could, for the first time, worry about the quality of life. Indeed, there appears to be an excellent correlation between investment in research and applications of organic chemistry and the standard of living. Such advances arise from the creation of compounds and materials. Continuation of these contributions requires a vigorous effort in research and development, for which information such as that provided by the *Comprehensive* series of Pergamon Press is a valuable resource.

Since the publication in 1979 of *Comprehensive Organic Chemistry*, it has become an important first source of information. However, considering the pace of advancements and the ever-shrinking timeframe in which initial discoveries are rapidly assimilated into the basic fabric of the science, it is clear that a new treatment is needed. It was tempting simply to update a series that had been so successful. However, this new series took a totally different approach. In deciding to embark upon *Comprehensive Organic Synthesis*, the Editors and Publisher recognized that synthesis stands at the heart of organic chemistry.

The construction of molecules and molecular systems transcends many fields of science. Needs in electronics, agriculture, medicine and textiles, to name but a few, provide a powerful driving force for more effective ways to make known materials and for routes to new materials. Physical and theoretical studies, extrapolations from current knowledge, and serendipity all help to identify the direction in which research should be moving. All of these forces help the synthetic chemist in translating vague notions to specific structures, in executing complex multistep sequences, and in seeking new knowledge to develop new reactions and reagents. The increasing degree of sophistication of the types of problems that need to be addressed require increasingly complex molecular architecture to target better the function of the resulting substances. The ability to make such substances available depends upon the sharpening of our sculptors' tools: the reactions and reagents of synthesis.

The Volume Editors have spent great time and effort in considering the format of the work. The intention is to focus on transformations in the way that synthetic chemists think about their problems. In terms of organic molecules, the work divides into the formation of carbon–carbon bonds, the introduction of heteroatoms, and heteroatom interconversions. Thus, Volumes 1–5 focus mainly on carbon–carbon bond formation, but also include many aspects of the introduction of heteroatoms. Volumes 6–8 focus on interconversion of heteroatoms, but also deal with exchange of carbon–carbon bonds for carbon–heteroatom bonds.

The Editors recognize that the assignment of subjects to any particular volume may be arbitrary in part. For example, reactions of enolates can be considered to be additions to C—C π-bonds. However, the vastness of the field leads it to be subdivided into components based upon the nature of the bond-forming process. Some subjects will undoubtedly appear in more than one place.

In attacking a synthetic target, the critical question about the suitability of any method involves selectivity: chemo-, regio-, diastereo- and enantio-selectivity. Both from an educational point-of-view for the reader who wants to learn about a new field, and an experimental viewpoint for the practitioner who seeks a reference source for practical information, an organization of the chapters along the theme of selectivity becomes most informative.

The Editors believe this organization will help emphasize the common threads that underlie many seemingly disparate areas of organic chemistry. The relationships among various transformations becomes clearer and the applicability of transformations across a large number of compound classes becomes apparent. Thus, it is intended that an integration of many specialized areas such as terpenoid, heterocyclic, carbohydrate, nucleic acid chemistry, *etc.* within the more general transformation class will provide an impetus to the consideration of methods to solve problems outside the traditional ones for any specialist.

In general, presentation of topics concentrates on work of the last decade. Reference to earlier work, as necessary and relevant, is made by citing key reviews. All topics in organic synthesis cannot be treated with equal depth within the constraints of any single series. Decisions as to which aspects of a topic require greater depth are guided by the topics covered in other recent *Comprehensive* series. This new treatise focuses on being comprehensive in the context of synthetically useful concepts.

The Editors and Publisher believe that *Comprehensive Organic Synthesis* will serve all those who must face the problem of preparing organic compounds. We intend it to be an essential reference work for the experienced practitioner who seeks information to solve a particular problem. At the same time, we must also serve the chemist whose major interest lies outside organic synthesis and therefore is only an occasional practitioner. In addition, the series has an educational role. We hope to instruct experienced investigators who want to learn the essential facts and concepts of an area new to them. We also hope to teach the novice student by providing an authoritative account of an area and by conveying the excitement of the field.

The need for this series was evident from the enthusiastic response from the scientific community in the most meaningful way — their willingness to devote their time to the task. I am deeply indebted to an exceptional board of editors, beginning with my deputy editor-in-chief Ian Fleming, and extending to the entire board — Clayton H. Heathcock, Ryoji Noyori, Steven V. Ley, Leo A. Paquette, Gerald Pattenden, Martin F. Semmelhack, Stuart L. Schreiber and Ekkehard Winterfeldt.

The substance of the work was created by over 250 authors from 15 countries, illustrating the truly international nature of the effort. I thank each and every one for the magnificent effort put forth. Finally, such a work is impossible without a publisher. The continuing commitment of Pergamon Press to serve the scientific community by providing this *Comprehensive* series is commendable. Specific credit goes to Colin Drayton for the critical role he played in allowing us to realize this work and also to Helen McPherson for guiding it through the publishing maze.

A work of this kind, which obviously summarizes accomplishments, may engender in some the feeling that there is little more to achieve. Quite the opposite is the case. In looking back and seeing how far we have come, it becomes only more obvious how very much more we have yet to achieve. The vastness of the problems and opportunities ensures that research in organic synthesis will be vibrant for a very long time to come.

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Abbreviations

The following abbreviations have been used where relevant. All other abbreviations have been defined the first time they occur in a chapter.

Techniques

CD	circular dichroism
CIDNP	chemically induced dynamic nuclear polarization
CNDO	complete neglect of differential overlap
CT	charge transfer
GLC	gas–liquid chromatography
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
ICR	ion cyclotron resonance
INDO	incomplete neglect of differential overlap
IR	infrared
LCAO	linear combination of atomic orbitals
LUMO	lowest unoccupied molecular orbital
MS	mass spectrometry
NMR	nuclear magnetic resonance
ORD	optical rotatory dispersion
PE	photoelectron
SCF	self-consistent field
TLC	thin layer chromatography
UV	ultraviolet

***Reagents, solvents,* etc.**

Ac	acetyl
acac	acetylacetonate
AIBN	2,2′-azobisisobutyronitrile
Ar	aryl
ATP	adenosine triphosphate
9-BBN	9-borabicyclo[3.3.1]nonyl
9-BBN-H	9-borabicyclo[3.3.1]nonane
BHT	2,6-di-*t*-butyl-4-methylphenol (butylated hydroxytoluene)
bipy	2,2′-bipyridyl
Bn	benzyl
t-BOC	*t*-butoxycarbonyl
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
BSTFA	*N*,*O*-bis(trimethylsilyl)trifluoroacetamide
BTAF	benzyltrimethylammonium fluoride
Bz	benzoyl
CAN	ceric ammonium nitrate
COD	1,5-cyclooctadiene
COT	cyclooctatetraene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
CSA	camphorsulfonic acid
CSI	chlorosulfonyl isocyanate
DABCO	1,4-diazabicyclo[2.2.2]octane
DBA	dibenzylideneacetone
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAC	diethylaluminum chloride
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate (+ or –)
DHP	dihydropyran
DIBAL-H	diisobutylaluminum hydride
diglyme	diethylene glycol dimethyl ether
dimsyl Na	sodium methylsulfinylmethide
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPT	diisopropyl tartrate (+ or –)
DMA	dimethylacetamide
DMAC	dimethylaluminum chloride
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMI	*N,N'*-dimethylimidazolone
DMSO	dimethyl sulfoxide
DMTSF	dimethyl(methylthio)sulfonium fluoroborate
DPPB	1,4-bis(diphenylphosphino)butane
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1'-bis(diphenylphosphino)ferrocene
DPPP	1,3-bis(diphenylphosphino)propane
E^+	electrophile
EADC	ethylaluminum dichloride
EDG	electron-donating group
EDTA	ethylenediaminetetraacetic acid
EEDQ	*N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
EWG	electron-withdrawing group
HMPA	hexamethylphosphoric triamide
HOBT	hydroxybenzotriazole
$IpcBH_2$	isopinocampheylborane
Ipc_2BH	diisopinocampheylborane
KAPA	potassium 3-aminopropylamide
K-selectride	potassium tri-*s*-butylborohydride
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LICA	lithium isopropylcyclohexylamide
LITMP	lithium tetramethylpiperidide
L-selectride	lithium tri-*s*-butylborohydride
LTA	lead tetraacetate
MCPBA	*m*-chloroperbenzoic acid
MEM	methoxyethoxymethyl
MEM-Cl	β-methoxyethoxymethyl chloride
MMA	methyl methacrylate
MMC	methylmagnesium carbonate
MOM	methoxymethyl
Ms	methanesulfonyl
MSA	methanesulfonic acid
MsCl	methanesulfonyl chloride
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide

NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidone
Nu^-	nucleophile
PPA	polyphosphoric acid
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
phen	1,10-phenanthroline
Phth	phthaloyl
PPE	polyphosphate ester
PPTS	pyridinium *p*-toluenesulfonate
Red-Al	sodium bis(methoxyethoxy)aluminum dihydride
SEM	β-trimethylsilylethoxymethyl
Sia_2BH	disiamylborane
TAS	tris(diethylamino)sulfonium
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
TBDMS-Cl	*t*-butyldimethylsilyl chloride
TBHP	*t*-butyl hydroperoxide
TCE	2,2,2-trichloroethanol
TCNE	tetracyanoethylene
TES	triethylsilyl
Tf	triflyl (trifluoromethanesulfonyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPBS-Cl	2,4,6-triisopropylbenzenesulfonyl chloride
TIPS-Cl	1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane
TMEDA	tetramethylethylenediamine [1,2-bis(dimethylamino)ethane]
TMS	trimethylsilyl
TMS-Cl	trimethylsilyl chloride
TMS-CN	trimethylsilyl cyanide
Tol	tolyl
TosMIC	tosylmethyl isocyanide
TPP	*meso*-tetraphenylporphyrin
Tr	trityl (triphenylmethyl)
Ts	tosyl (*p*-toluenesulfonyl)
TTFA	thallium trifluoroacetate
TTN	thallium(III) nitrate

1.1

Synthesis of Alcohols and Ethers

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1.1.1 INTRODUCTION

Alcohols can be obtained from many other classes of compounds such as alkyl halides, amines, alkenes, epoxides and carbonyl compounds. The addition of nucleophiles to carbonyl compounds is a versatile and convenient method for the the preparation of alcohols. Regioselective oxirane ring opening of epoxides by nucleophiles is another important route for the synthesis of alcohols. However, stereospecific oxirane ring formation is prerequisite to the use of epoxides in organic synthesis. The chemistry of epoxides has been extensively studied in this decade and the development of the diastereoselective oxidations of alkenic alcohols makes epoxy alcohols with definite configurations readily available. Recently developed asymmetric epoxidation of prochiral allylic alcohols allows the enantioselective synthesis of 2,3-epoxy alcohols.

For reason of space, emphasis will be placed on the reaction of functionalized epoxides with carbon nucleophiles. However, isomerization of epoxides and intramolecular oxirane ring opening leading to cyclic compounds could not be included. In order to avoid overlap with other articles in this series, reductive cleavage of epoxides is not discussed. Some 1,2-rearrangement reactions leading to alcohols are described because the reactions are apparently useful for the preparation of alcohols with high stereoselectivity. Substitution at the carbon atom adjacent to oxygen, which is an important method for the conversion of ethers, could not be considered. The conventional but still important classes of displacement reactions such as those involving alkyl halides or amines are discussed briefly. Readers are referred to excellent reviews and monographs.[1-3]

1.1.2 PREPARATION OF ALCOHOLS

1.1.2.1 Substitution of Alkyl Halides

Although the hydrolysis of alkyl halides to alcohols has been extensively investigated,[1] an alternative two-step sequence involving substitution with carboxylate ion is more practical for the preparation of alcohols.[4] Activation of the carboxylate anion prepared by the reaction of the acid with a base can be achieved:[5] (i) by use of a polar aprotic solvent; and (ii) by use of aprotic apolar solvents under phase transfer catalysis, polymer conditions, or with crown ethers.

The second-order alkylation rates of carboxylate salts are influenced by the nature of the cation, solvent and the alkyl halides. In general, carboxylate anions with soft (large) counterions are more reactive than those with hard counterions because of higher charge separation in the former.[6] Thus, the anticipated order of increasing reactivity $Li^+(1) < Na^+(1.1) < K^+(1.5) < Cs^+(2)$ was observed in the reaction of 2-methyl-2-propylpentanoate with 1-iodopentane at 60 °C in HMPA–EtOH (1:1 v/v).[6]

Rapid and nearly complete alkylation of carboxylate salts with reactive organic halides has been demonstrated in nonpolar and polar solvents. With less reactive alkyl halides, the use of dipolar aprotic solvents for alkylation has been marginally successful.[6] The rate of alkylation of potassium 2-methyl-2-propylpentanoate with 1-chlorohexane in four dipolar aprotic solvents at 60 °C decreased in the order HMPA > *N*-methylpyrrolidone > DMSO > DMF.[6]

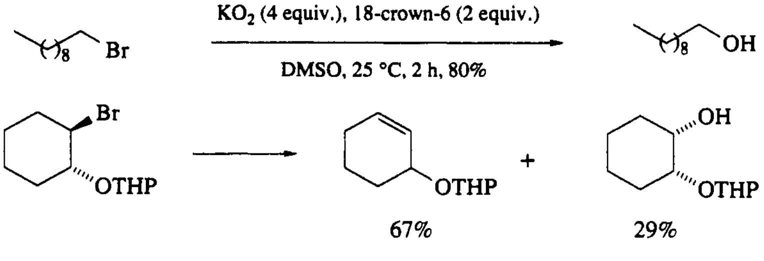
The order of reactivity of the halogen in simple alkyl halides in S_N2 reactions is I > Br > Cl. The relative rates of the alkylation of potassium 2-methyl-2-propylpentanoate with 1-iodopentane, 1-bromopentane and 1-chlorohexane in HMPA at 60 °C are reported to be 587, 35 and 1.[6]

Elucidation of rates with variation in cation, solvent and halide ion indicates that the combination of alkyl iodides and cesium salts in HMPA offers the optimum alkylation conditions for preparative use.[6] The reactions of cesium carboxylates with alkyl halides and sulfonates will be discussed in Section 1.1.2.5 in connection with inversion processes.

One of the crucial side reactions in the displacement reactions of alkyl halides is elimination, which can generally be neglected in the reaction of primary alkyl halides. On the other hand, a considerable amount of alkene invariably forms in the reaction of secondary alkyl halides. This undesirable side reaction can be minimized by the use of cesium carboxylates.[7]

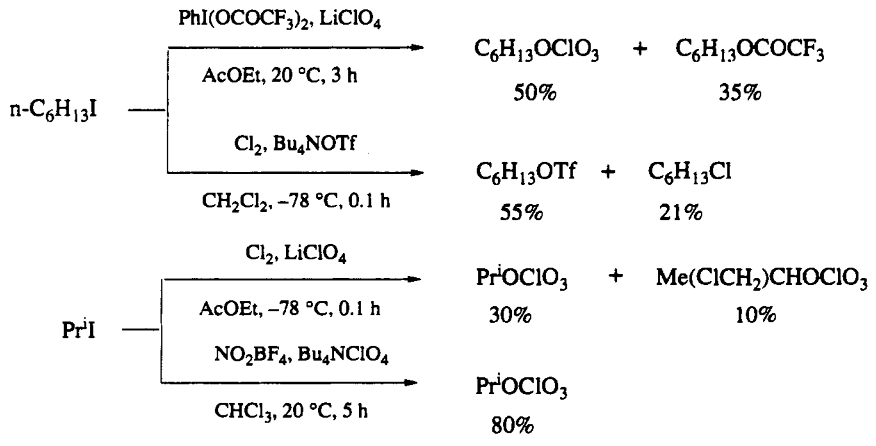
The reaction of potassium carboxylates with alkyl halides without the use of a solvent in the presence of catalytic amounts of a tetraalkylammonium salt proceeds smoothly to give the corresponding esters in good to excellent yields, except for cyclohexyl bromide where elimination mainly takes place.[5] Alkylation of *o*- and *p*-hydroxybenzoic acid selectively takes place at the CO_2K group.[5a]

A more direct procedure for the displacement step is the use of a very powerful nucleophilic superoxide radical ion where an alkyl halide or sulfonate is directly converted into the corresponding alcohol (Scheme 1).[8] Elimination is an important side reaction in certain cases.[8a]



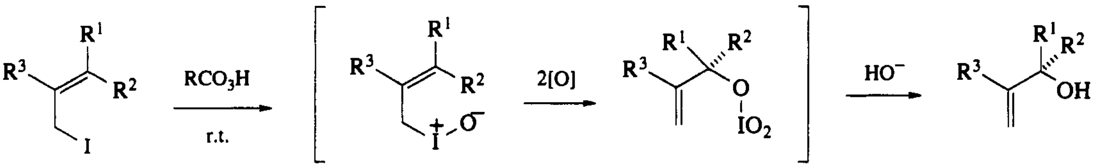
Scheme 1

On treatment with suitable oxidizing agents, alkyl iodides are transformed into products of either elimination or nucleophilic substitution, depending on the initial structure and the reaction conditions.[9] Effective oxidants include Cl_2, Br_2, HNO_3, N_2O_5, $AcONO_2$, $NOBF_4$, NO_2BF_4, $K_2Cr_2O_7$, $KMnO_4$, Cl_2O_7, $ClOClO_3$, Cl_2O, $(FSO_2O)_2$, $I(CO_2CF_3)_3$, $PhI(CO_2CF_3)_2$ and MCPBA (Scheme 2). The intermediacy of hypervalent organoiodides has been proposed; groups containing hypervalent iodine are good leaving groups. For example, otherwise unreactive 1-iodonorbornane can be converted into the corresponding bromide.[9]



Scheme 2

Allylic iodides with excess amounts of peroxy acids in a two-phase system in the presence of an inorganic base give the corresponding rearranged allylic alcohols in good yields (Scheme 3).[10] It has been demonstrated that the reaction proceeds under milder conditions than the Mislow–Evans reaction.[10]



Scheme 3

Bis(tributyltin) oxide acts as a mild and neutral oxygen transfer agent in converting primary alkyl iodides and bromides into alcohols in the presence of silver salts in DMF (Scheme 4).[11]

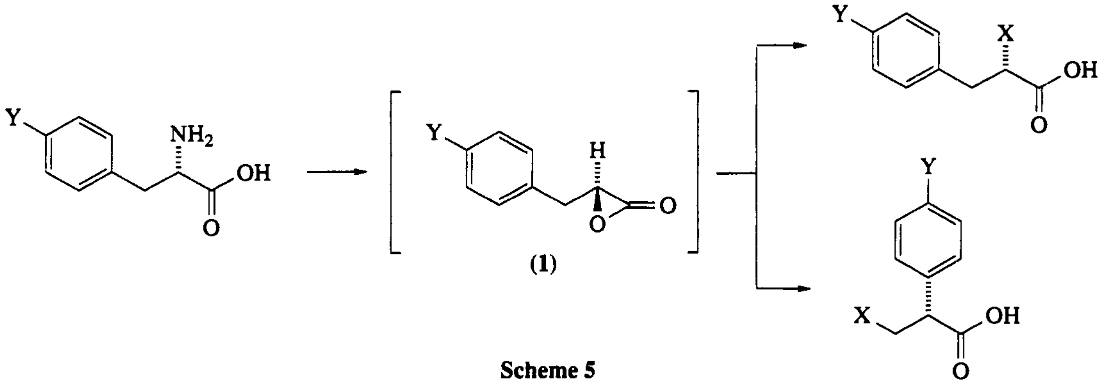
$$\mathrm{RX} + (\mathrm{Bu_3Sn})_2\mathrm{O} \xrightarrow[\text{DMF}]{\text{AgOTf or AgNO}_3} \mathrm{ROSnBu_3} \xrightarrow[(\mathrm{H_2O})]{\text{work-up}} \mathrm{ROH}$$

Scheme 4

1.1.2.2 Deamination of Amines *via* Diazonium Salts

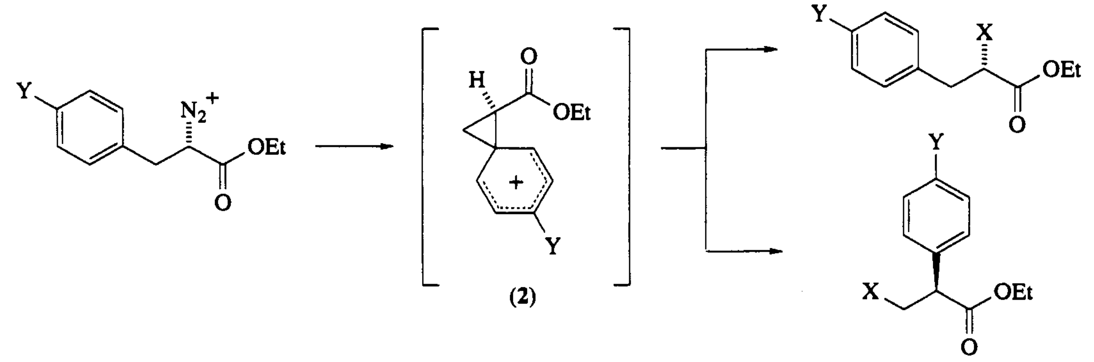
Treatment of a primary aliphatic amine with nitrous acid or its equivalent produces a diazonium ion which results in the formation of a variety of products through solvent displacement, elimination and solvolysis with 1,2-shift and concurrent elimination of nitrogen.[12] The stereochemistry of the deamination–substitution reaction of various secondary amines was investigated as early as 1950, when an S_N1-type displacement was suggested.[13] Thus, the process can hardly be utilized for the preparation of alcohols except in cases where additional factors controlling the reaction course exist. Deamination–substitution of α-amino acids can be utilized for the preparation of chiral alcohols.

The reaction of optically active α-amino acids with nitrous acid or nitrosyl chloride gives α-hydroxy or α-halo acids with retention of configuration due to the neighboring carboxylate participation.[14–17] Examination of the reaction of phenylalanine and its *para*-substituted derivatives revealed that the product distribution and outcome of the stereochemistry depend on both the solvent used and the substituent on the aromatic ring. The results may be rationalized by assuming the intermediacy of an unstable lactone (**1**). When a solvent of high nucleophilicity is used, it attacks the α-carbon of (**1**) from the backside of the oxygen to give the corresponding substituted product with net retention of configuration. When the reaction is carried out in a solvent of low nucleophilicity, the aryl group migration takes place prior to intermolecular displacement to afford the migration product (Scheme 5).[18]



Scheme 5

Contrary to the case of free α-amino acids, deamination–substitution of esters of α-amino acids generally proceeds with racemization with excess inversion about the α-carbon atom.[13,18] However, reaction of the ethyl ester of phenylalanine and its derivatives with sodium nitrite in trifluoroacetic acid affords substitution products with retention of configuration and migration products with inversion of configuration. This result may be explained by assuming initial formation of the phenonium intermediate (**2**; Scheme 6).[18]



Scheme 6

1.1.2.3 Oxirane Ring Opening by Carbon Nucleophiles

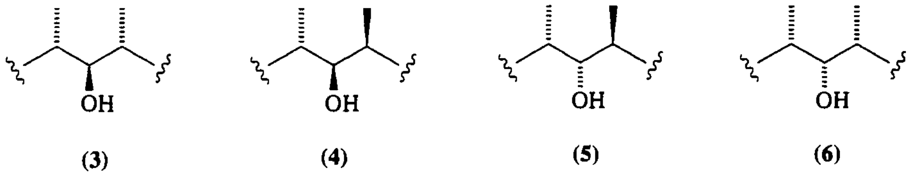
1.1.2.3.1 Reaction of epoxides with organometallic reagents

The reaction of epoxides with carbon nucleophiles generates new carbon–carbon σ-bonds, and this reaction can be utilized as a versatile procedure for the preparation of a variety of alcohols, provided that the ring opening takes place in a regioselective manner. This section deals with the reactions of organometallic reagents with 2,3-epoxy alcohols and conjugated epoxides, *i.e.* where the oxirane ring is directly bonded to a π-electron system. The behavior of conjugated epoxides toward nucleophiles can be rationalized in terms of the principle of 'hard and soft acids and bases (HSAB)'.[19]

The reactions of epoxides with organometallic reagents are sometimes curtailed owing to competing reactions arising from the Lewis acidity or basicity of the organometallics used.[20] The hardness of the organometallic reagent (RLi > RMgX > RCu or R_2CuLi) is directly related to the metal atom.[21] Of carbon nucleophiles, organocuprates are the reagents of choice, while Grignard reagents sometimes result in concomitant formation of side products arising from the substitution by halide ion.[19a,20] Higher order mixed organocuprates of the general formula $R_2Cu(CN)Li_2$ are superior to R_2CuLi.[22] The cyanocopper reagents are considered to be softer than the cuprate and simple copper reagents.[19c] The reactions using organoaluminum reagents are interesting alternatives to those using organocopper reagents where complementary regioselectivity is generally observed.[23] It is noteworthy that the addition of $BF_3 \cdot Et_2O$ causes enhancement of reactivity.[23e]

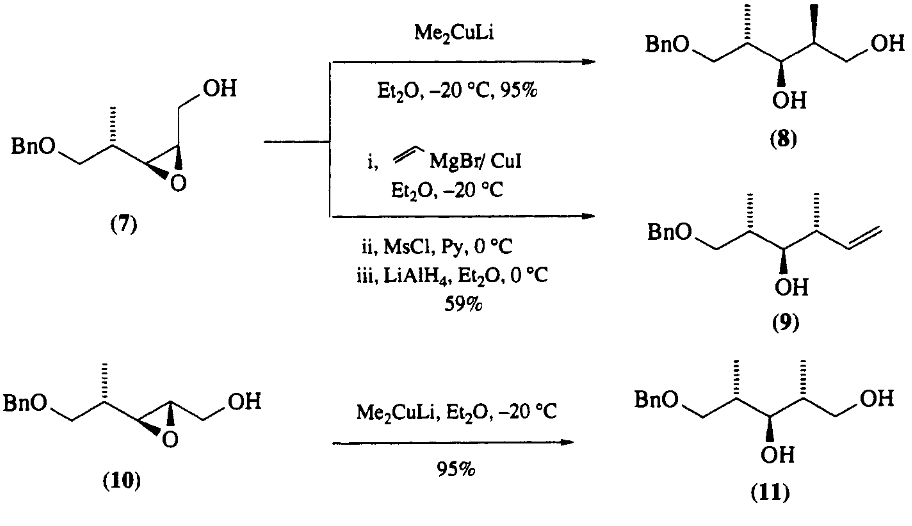
1.1.2.3.2 2,3-Epoxy alcohols

The partial structural unit with definite configuration at three consecutive chiral centers, (**3**), (**4**), (**5**) or (**6**), is often found in natural products (Scheme 7).



Scheme 7

Kishi and coworkers have studied the ring opening of 2,3-epoxy alcohols having different stereochemistry.[24] (*Z*)-Epoxy alcohol (**7**) reacted with Me_2CuLi to give exclusively (**8**). Alternatively, the reaction of (**7**) with vinylcuprate followed by deoxygenation afforded (**9**). The reaction of (**10**) with Me_2CuLi gave (**11**; Scheme 8).[24]



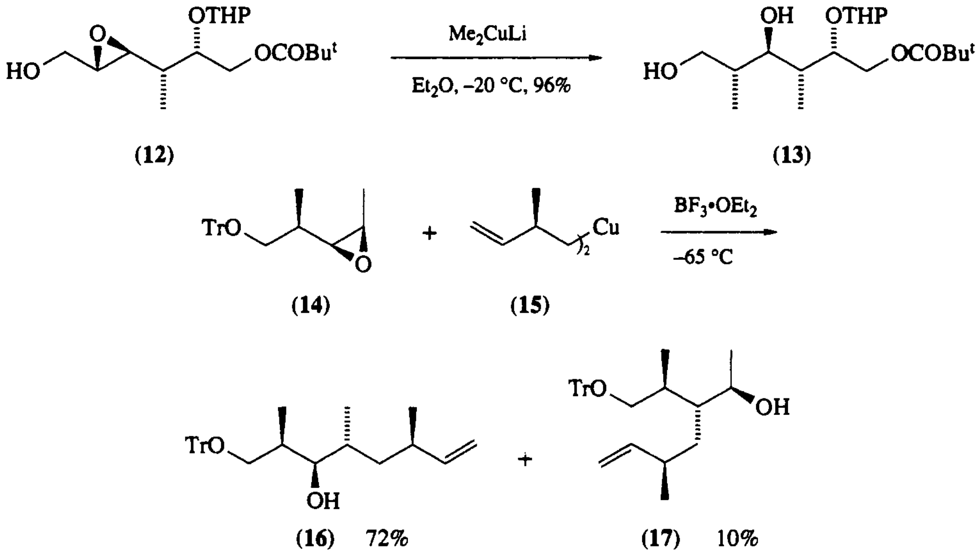
Scheme 8

The reaction of (**12**) with Me_2CuLi also takes place at C-2 to give (**13**) without contamination of the regioisomeric 1,2-diol.[25] In the reaction of tritylated 3,4-epoxy alcohol (**14**; Scheme 9) with homoallylcuprate (**15**), addition of $BF_3 \cdot Et_2O$ was required for the initiation of the reaction producing (**16**) along with a small amount of (**17**).[26]

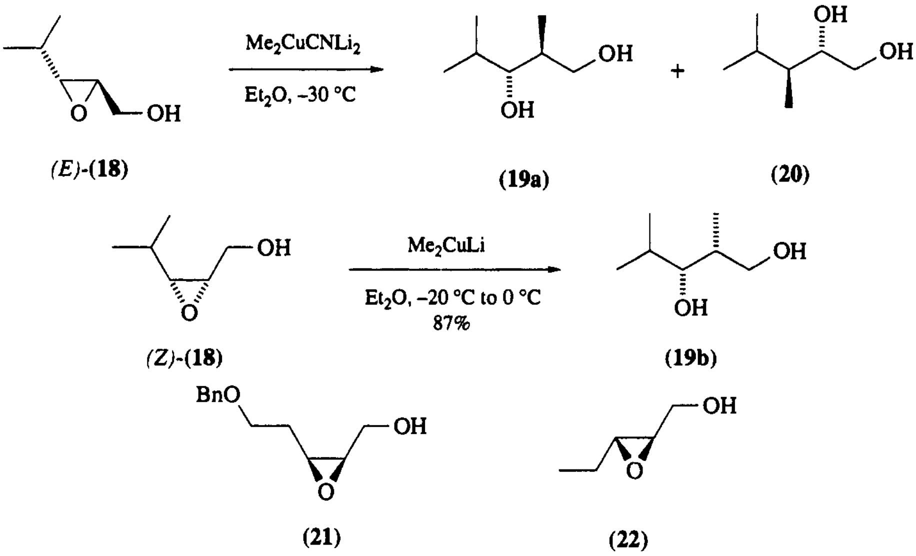
The reaction of (*E*)-(**18**) with $Me_2CuCNLi_2$ shows a moderate level of regioselectivity, giving a 6:1 ratio of 1,3-diol (**19a**) and regioisomeric 1,2-diol (**20**).[27a] The corresponding (*Z*)-epoxide (*Z*)-(**18**) reacts with Me_2CuLi to give the 1,3-diol (**19b**) as the sole product.[27b] The reaction of the less-hindered epoxide (**21**) or (**22**) with Me_2CuLi does not show any regioselectivity, affording a mixture of isomeric diols in a ratio of 1:1 (Scheme 10).[24a,27c] These results suggest that the regiochemical preference observed in the reactions of epoxy alcohols appears to be steric in origin.[27d]

On the other hand, the reaction of (**23a**) with Me_2CuLi yields a 55:45 mixture of 1,2- and 1,3-diols. The reaction of the TBDMS derivative (**23b**) with Me_2CuLi under identical conditions results in the formation of (**24**) with about 20:1 regioselectivity. In this case, the regioselectivity observed has been attributed to complexation of the nucleophile with the substrate.[28]

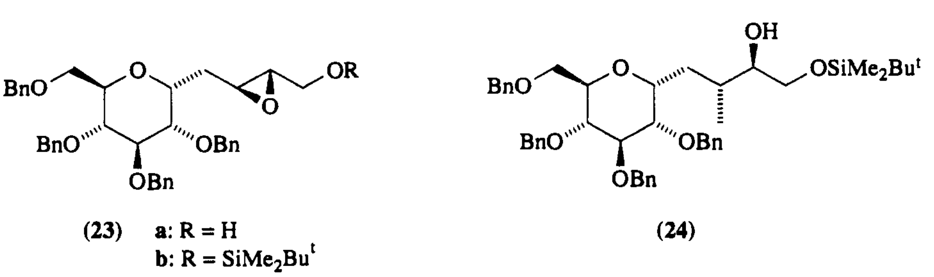
C-3 selectivity has been attained by the use of 2,3-epoxy alcohols having a bulky protective group. Thus, (**25**) reacts with alkenylmagnesium bromide (**26**) in the presence of a catalytic amount of CuI to



Scheme 9

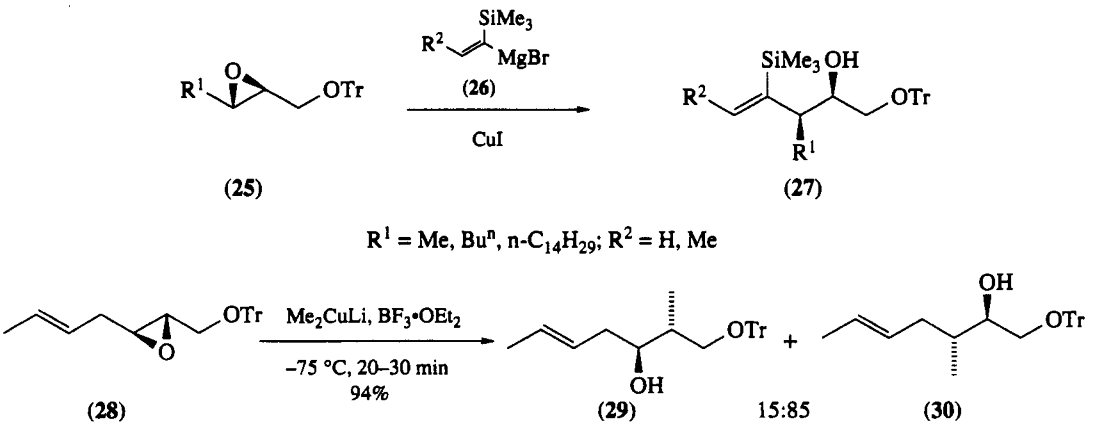


Scheme 10



Scheme 11

give (**27**) as the sole product.[29a] Contrary to the case of (**25**), the reaction of (**28**) with a variety of organocuprates gives (**29**) and (**30**) in ratios ranging from 1:1 to 1.5:1, favoring the 1,3-diol derivative (**29**). However, when the reaction was carried out with 2 equiv. each of Me$_2$CuLi and BF$_3$·Et$_2$O, (**29**) and (**30**) were formed in a ratio of 15:85 (Scheme 12).[29b]



(25) (27)

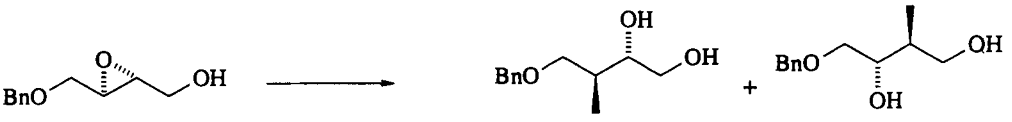
$R^1 = Me, Bu^n, n\text{-}C_{14}H_{29}$; $R^2 = H, Me$

(28) (29) (30)

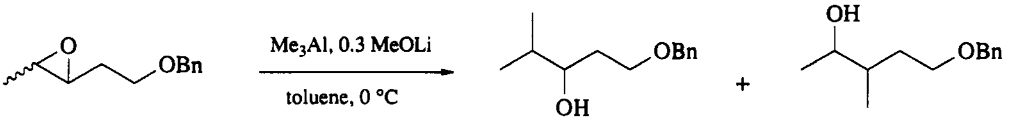
Scheme 12

C-3 attack predominantly takes place in the reaction of 2,3-epoxy alcohols with organoaluminum compounds such as Me_3Al, $PhC\equiv CAlEt_2$, $Me_3SiC\equiv CAlEt_2$, $Bu^i{}_2AlH$ and $Bu^i{}_3Al$.[30] The yield and stereochemical outcome depend on the substrates and organoaluminum reagents used.[30c]

The following examples illustrate the complementary regioselectivities exhibited in the reactions using Me_2CuLi and Me_3Al (Scheme 13).[30a,30b] One problem which remains to be solved, however, is the proclivity of alkylaluminum reagents such as Et_3Al to serve as hydride donors.[30a]



Conditions	*Ratio*
Me_2CuLi, Et_2O, −20 °C	1:6
Me_3Al, CH_2Cl_2, 0–23 °C	5:1

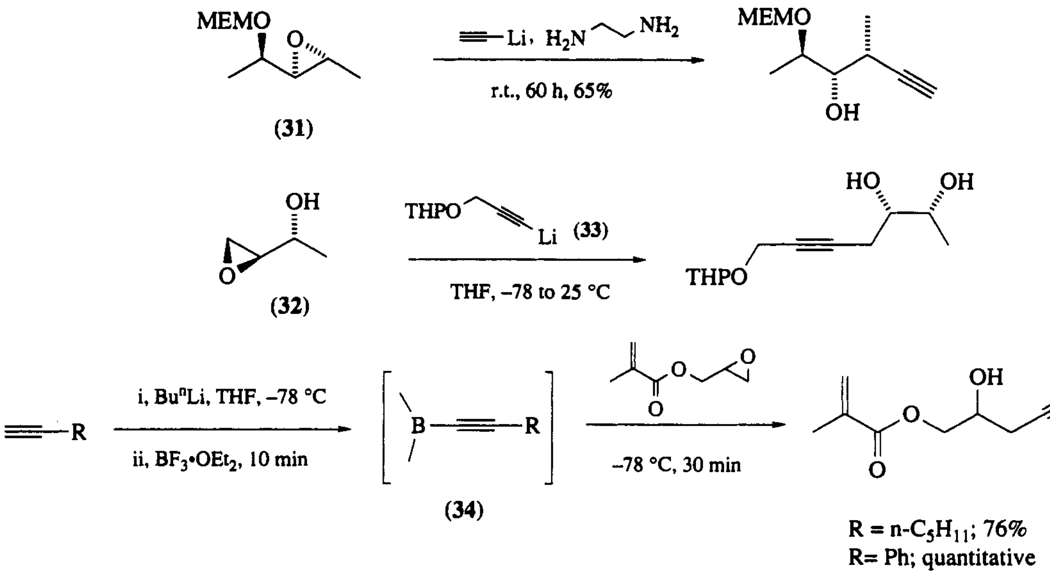


Reagents	*Yield (%)*	*Ratio*
(*Z*)-epoxide	87	95:5
(*E*)-epoxide	85	99:1

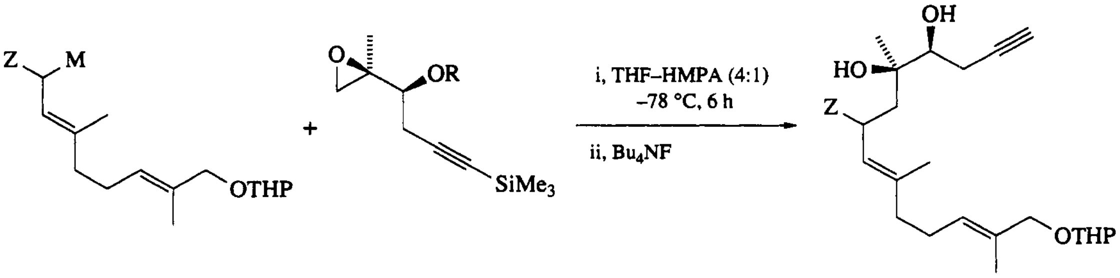
Scheme 13

Epoxide (**31**) reacts with 2 equiv. of lithium acetylide–ethylenediamine complex at the C-3 position.[31] Terminal epoxide (**32**) reacts smoothly with the lithium alkynide (**33**) to give a 1,2-diol in good yield.[32] Alkynylboranes (**34**) have been demonstrated to be useful for alkynylation of epoxides (Scheme 14).[33]

The reactions of 2,3-epoxy alcohols with organometallic reagents are influenced by various factors which include not only the solvent and the structure of the reactants but also the gegen cation of the oxyanion of the epoxy alcohol. Sulfone-stabilized allyllithium (**35b**) reacts sluggishly with lithium alkoxide (**36a**) in THF–HMPA to give the coupled product (**37a**) in 9% yield with 90% recovery of (**35a**). Under identical conditions, however, the magnesium epoxide (**36b**) gave (**37a**) in 70% yield as an 8:1 mixture of diastereomers. In contrast, (**36a**) reacts negligibly with (**35b**) in THF. Furthermore, the TMS ether (**36c**) and the ethoxyethyl (EE) ether (**36d**) give no coupling product at all with (**35b**). Although the thiophenyl-stabilized allyllithium (**35c**) is more reactive than (**35b**), the corresponding coupling product (**37b**) is obtained as a 1:1 mixture of diastereomers (Scheme 15).[34]



Scheme 14



(35) a: Z = SO_2Ph; M = H
b: Z = SO_2Ph; M = Li
c: Z = SPh; M = Li

(36) a: R = Li
b: R = MgBr
c: R = $SiMe_3$
d: R = CH(Me)OEt

(37) a: Z = SO_2Ph
b: Z = SPh

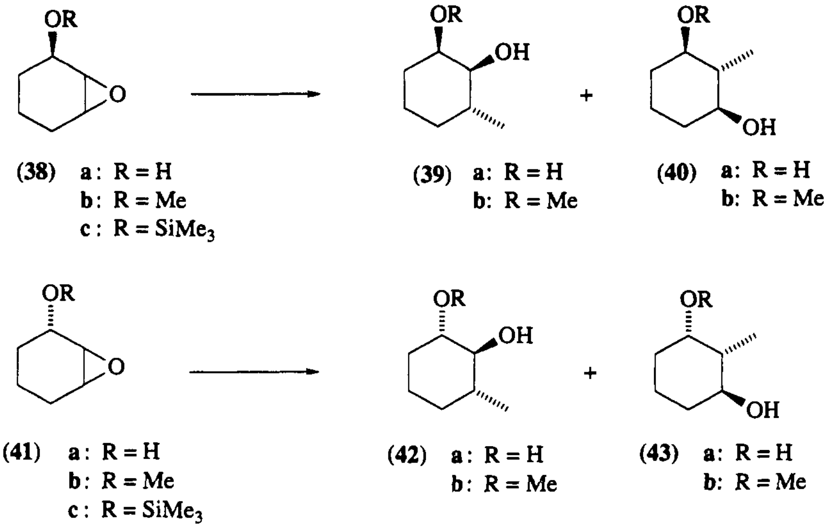
Scheme 15

The reaction of (*Z*)-3-hydroxycyclohexene oxide (**38a**) with Me_2CuLi gave 1,2-diol (**39a**) in preference to 1,3-diol (**40a**), while the (*E*)-isomer (**41a**) showed the reversed regioselectivity. The corresponding methyl ethers (**38b**) and (**41b**) showed even lower regioselectivity than the unprotected substrates.[35a] These results suggest that the regioselectivity is controlled by various factors, including conformational effects.

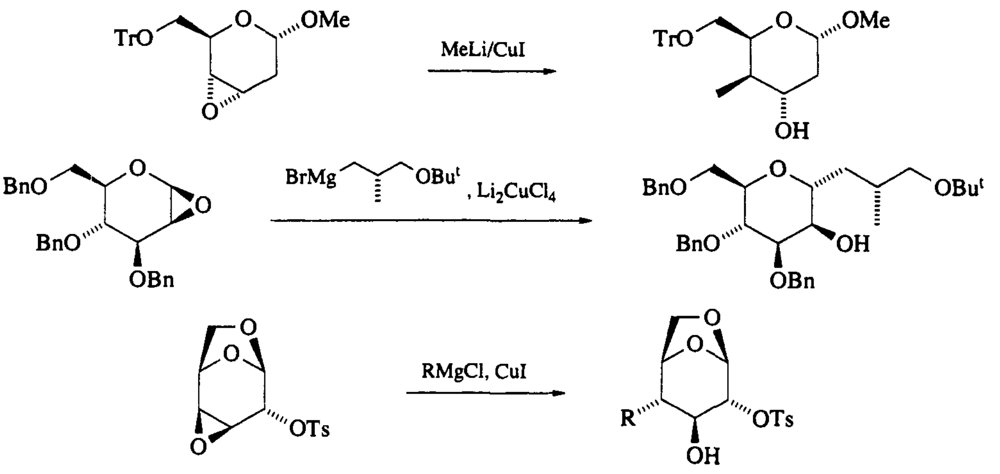
Danishefsky and coworkers have studied the ring opening reactions of a series of (*Z*)- and (*E*)-epoxides, (**38a**), (**38c**), (**41a**) and (**41c**), with $^-CH_2CO_2^-$ and with $Et_2AlC{\equiv}COEt$ and have demonstrated that the reaction course in the alane opening depends largely on the stereochemical relationship between the oxy function and the epoxide, and only to an insignificant extent on whether the oxygen is initially in the form of a hydroxy group or a trimethylsilyl ether. On the other hand, in the dianion case, the nature of the oxygen, rather than its stereochemical relationship with the epoxide, is decisive for the regioselectivity of the ring opening.[35b]

Regioselectivity is markedly enhanced in conformationally more biased systems such as carbohydrates and fused bicyclic compounds. Some examples are shown in Scheme 17.[36–38]

In view of the large number of naturally occurring polyols having definite configuration, a variety of methodologies to construct such systems by utilizing the reactivity of epoxides have been reported.[39]



Scheme 16



Scheme 17

1.1.2.3.3 Vinyl epoxides

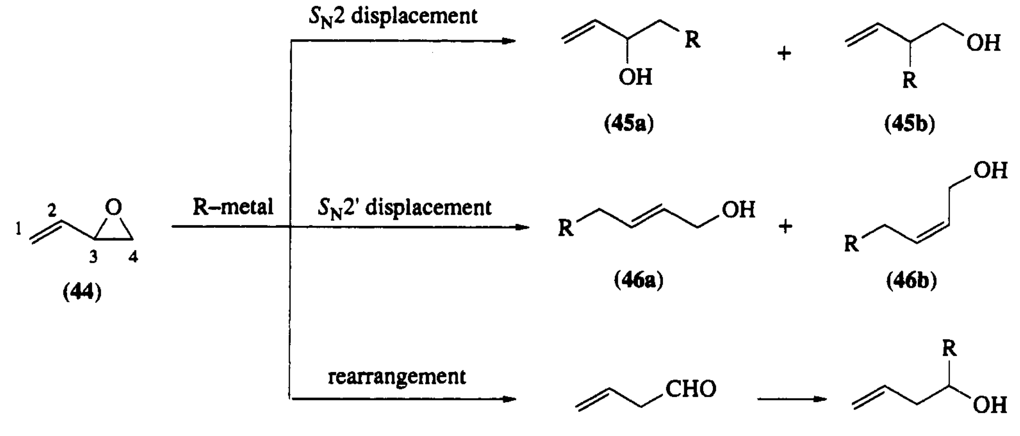
The reaction of 3,4-epoxy-1-butene (**44**) with Grignard reagents affords a mixture of products resulting from direct attack on the oxirane ring (S_N2) and on the double bond (S_N2'). The product distribution depends on the nature of the Grignard reagents. Alkyllithiums are favored for the direct attack on the oxirane carbon (C-3 attack), while lithium dialkylcuprates give the S_N2' displacement products (C-1 attack) with high regioselectivity (Scheme 18, Table 1).[20b,22,40]

The regioselectivity of the reaction of organo-yttrium and -lanthanoid reagents with (**44**) is complementary (C-3 attack) to that obtained with organocuprates (Table 1).[40b]

In contrast to the reactions of acyclic substrates, 3,4-epoxycyclohexene (**48**) reacts with Me_2CuLi to give both S_N2 and S_N2' displacement products (**49**) and (**50**).[41] By the use of MeCuCNLi, however, (**48**) gives (**49**) in 95% yield (100% *trans*).[42a] The resulting product of general formula (**51**) can be converted into an epoxy enol ether (**52**) which again undergoes anti-S_N2' reaction with MeCuCNLi to produce (**53**) in essentially quantitative yield (Scheme 19).[42b,43]

The reaction has been extended to 1,4-chirality transfer. For instance, epoxide (**54**) reacts with lithium isohexylcyanocuprate to afford isomerically pure (**55**; Scheme 20).[42c] This strategy has been applied to the total synthesis of prostaglandins.[42d]

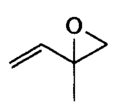
In general, S_N2' displacement on cyclic vinyl epoxides by organocopper reagents has been found to proceed with inversion (*anti* pathway). However, acyclic vinyl epoxides can react *via* either *s-cis* or

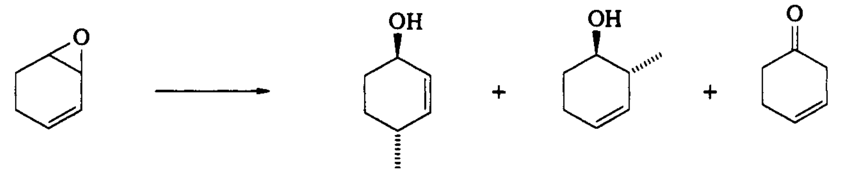


Scheme 18

Table 1 Reaction of (**44**) with Organometallics (Scheme 18)

R–metal	*Yield (%)*	*Product distribution*					*Ref.*
		(45a)	*(45b)*	*(46)*	*(46a:46b)*	*(47)*	
MeMgBr		1	36	44	(3.1:1)	19	20b
Me_2Mg		1	81	16	(4.7:1)	2	20b
MeLi		17	63	20	(1.1:1)		20b
Me_2CuLi			6	94	(3.8:1)		20b
$Ph_2CuCNLi_2$	96			100	(4:1)[a]		22
Me_3Al	54	<1	85	13	(6:1)		40b
MeLi/Sm[N(TMS)$_2$]$_3$	85	2	95	<2	(1:1)		40b
MeLi/Y[N(TMS)$_2$]$_3$	80	<1	96	<3	(1:1)		40b

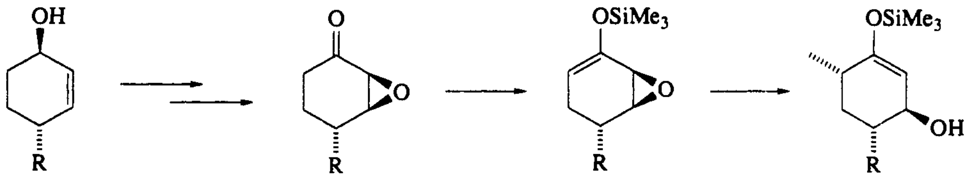
[a]  was used.



(**48**) (**49**) (**50**)

Me_2CuLi 42% 35% 23%

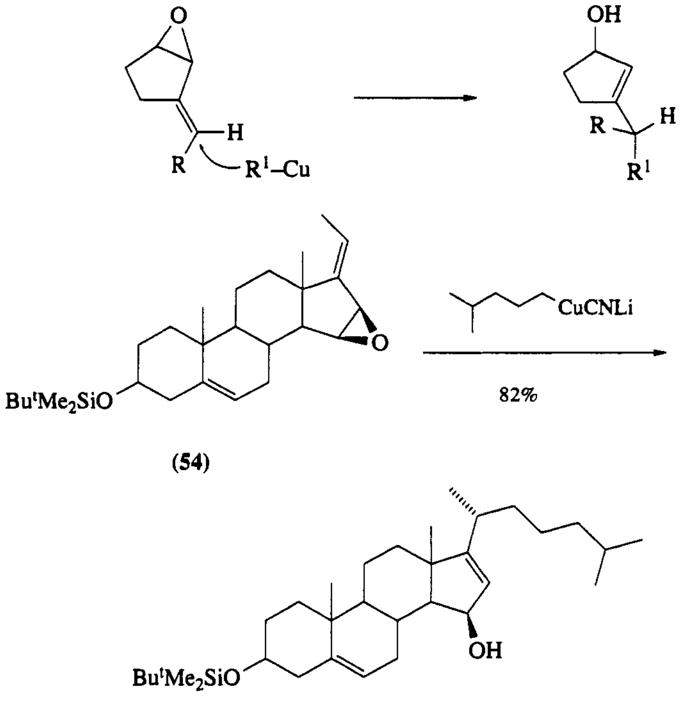
MeCuCNLi 95%



(**51**) (**52**) (**53**)

Scheme 19

s-trans conformers and thus yield mixtures of (*E*)- and (*Z*)-products of S_N2' reaction.[44] Marshall and coworkers have studied the reactions of (*E*)- and (*Z*)-vinyl epoxides, (*E*)-(**56**) and (*Z*)-(**56**), with methylcuprates where not only S_N2' displacement products (*E*)-(**57**) and (*Z*)-(**57**) but also S_N2 displacement



(54)

(55)

Scheme 20

products (*E*)-(**58**) and (*Z*)-(**58**) are formed, and diene (**59**) as well (Scheme 21, Table 2).[44] The more-substituted systems, (*E*)- and (*Z*)-(**60**), and (*E*)- and (*Z*)-(**61**), yield only S_N2' displacement products. In all the cases examined (Me_2CuLi, THF/Et_2O 4:1, 0 °C and MeCuCNLi, Et_2O, 0 °C), *anti* attack is more favorable than *syn* attack.[44]

On treatment with a palladium(0) catalyst, vinyl epoxides undergo facile unimolecular rearrangement to give dienols or enones depending on the substitution pattern of the substrate.[45] In the presence of an active methylene compound in the reaction system, however, a single alkylation product is formed.[46] Cyclic and acyclic vinyl epoxides participate equally well. The reaction proceeds with clean alkylation from the same face as the oxygen of the epoxide, and proceeds with allyl inversion (Scheme 22).[46]

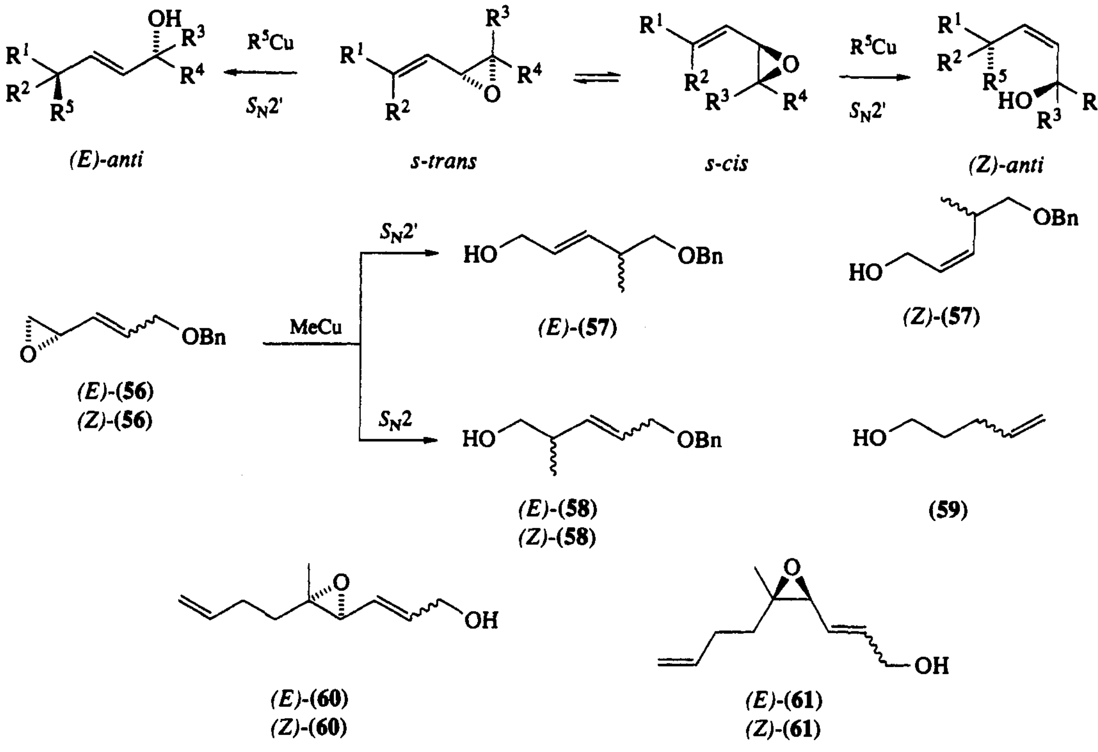
1.1.2.3.4 2,3-Epoxy acids

The reactions of organometallics with 3-substituted glycidic esters proceed through C-2 or C-3 attack depending on the nature of the reagent. With organocuprates, preferential C-2 attack generally takes place.[47] Thus, the ring opening reactions of methyl 2,3-epoxycarboxylates (**62a**) to (**62d**) with organocuprates proceed with perfect regio- and stereo-control to give the corresponding 3-hydroxycarboxylates (**63**) in around 60% isolated yields with >99% inversion at C-2.[48] However, 2,3-epoxy esters having α-branched substituents at the C-3 position (**62e**, **62f**) are inert and are recovered unchanged (Scheme 23).[48]

On the other hand, terminal epoxy esters react with cuprates R_2CuM (M = Li, Mg) at the C-3 position to afford exclusively 2-hydroxy esters (Scheme 23).[47a]

C-3 attack on nonterminal 2,3-epoxy esters takes place when organoaluminum reagents are used instead of cuprates (Scheme 24).[49]

The reactions of (*E*)-2,3-epoxy acids (*E*)-(**64**) with organocopper reagents afford the products of attack at C-2 (**65**) in preference to those at C-3 (**66**), while (*Z*)-isomer (*Z*)-(**64**) undergoes C-3 attack to give (**68**) as the main products (Scheme 25).[50]

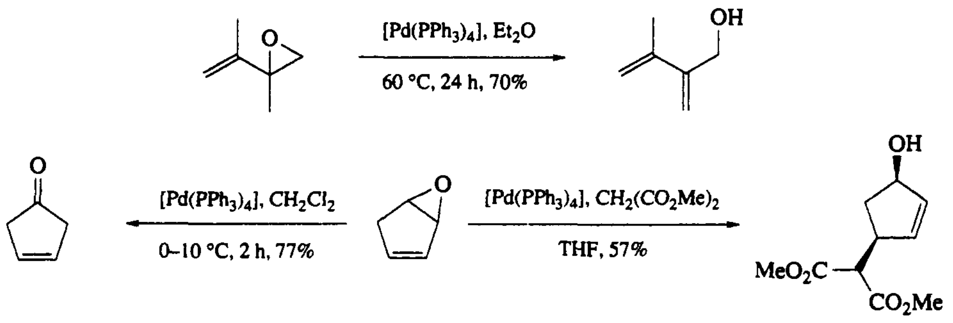


Scheme 21

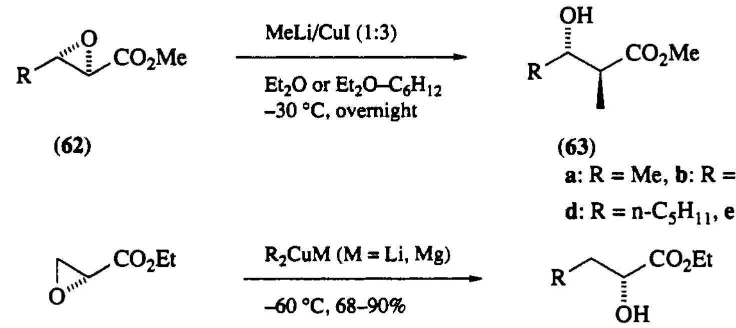
Table 2 Cuprate Addition to (*E*)-(**56**) and (*Z*)-(**56**) (Scheme 21)[44]

Substrate	*Method*[a]	*Yield* (%)	S_N2' *(E)-(57)*	*(Z)-(57)*	S_N2 *(E)-(58)*	*(Z)-(58)*	*(59)*	S_N2'/S_N2
(*E*)-(**56**)	A	87	69.5	7.3	11.8	0	11.4	5.6
(*Z*)-(**56**)	A	83	81.0	0	2.9	6.1	10.0	9.0
(*E*)-(**56**)	B	76	28.2	60.6	12.2	0	0	7.9
(*Z*)-(**56**)	B	78	82.2	0	0	11.8	6.0	7.0

[a] A: MeCuCNLi, Et_2O, 0 °C. B: MeLi, CuI, $BF_3 \cdot Et_2O$, THF/Et_2O (5:1), −78 to 25 °C.



Scheme 22

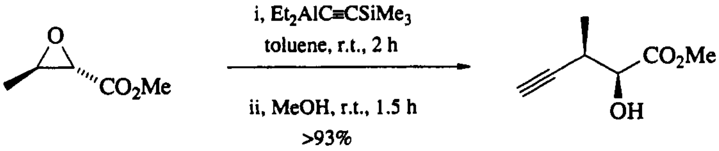


(62) **(63)**

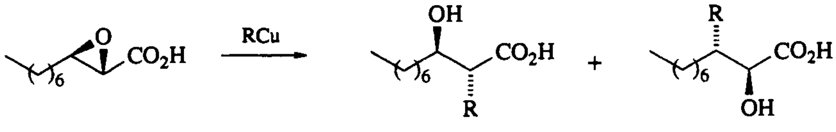
a: $R = Me$, **b**: $R = Et$, **c**: $R = Pr^n$,
d: $R = n\text{-}C_5H_{11}$, **e**: $R = Pr^i$, **f**: $R = Bu^t$

$R = Bu^n$, $Me_2C{=}CH–$, $Me_2C{=}CHCH_2–$, *etc.*

Scheme 23

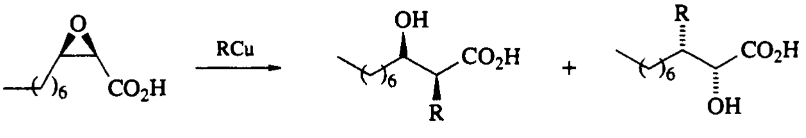


Scheme 24



(E)-**(64)** **(65)** **(66)**

Reagent	*Yield (%)*	*Ratio (65):(66)*
Me_2CuLi	91	8:1
$Bu^n{}_2CuLi$	93	12:1
$Bu^n{}_2CuCNLi_2$	87	8:1
$Ph_2CuCNLi_2$	81	6:1



(Z)-**(64)** **(67)** **(68)**

Reagent	*Yield (%)*	*Ratio (67):(68)*
Me_2CuLi	84	1:17
$Bu^n{}_2CuLi$	88	1:11
$Bu^n{}_2CuCNLi_2$	89	1:16
$Ph_2CuCNLi_2$	82	1:7

Scheme 25

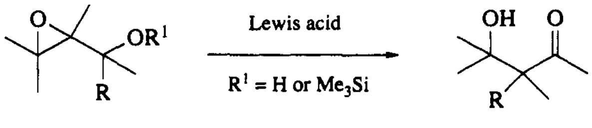
1.1.2.4 Rearrangement Reactions Leading to Alcohols

1.1.2.4.1 Sigmatropic rearrangement

[2,3] Sigmatropic rearrangements such as the Wittig rearrangement and the rearrangements of sulfoxides and selenoxides are considered as intramolecular S_N2' reactions producing unsaturated alcohols and have long received widespread interest because of their synthetic importance. The reactions involving 1,2-shift can, in a sense, also be considered as intramolecular displacements and generally take place with high stereospecificity with respect to the migrating group and the migration terminus. This section briefly deals with some 1,2-rearrangement processes which can be utilized in the preparation of chiral alcohols. Since [2,3] sigmatropic rearrangements and organoboron chemistry have been surveyed in excellent review articles and monographs,[51] these subjects are not covered in this section.

1.1.2.4.2 Epoxy silyl ether rearrangement

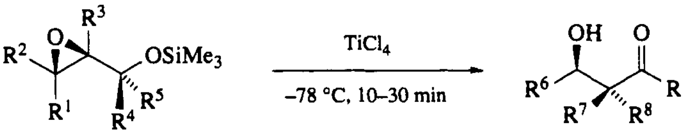
The Lewis acid mediated rearrangement of epoxy silyl ether (**69**) affords the corresponding β-hydroxycarbonyl compound (**70**; Scheme 26).[52]



(69) **(70)**

Scheme 26

In the reaction of α,α,β-trialkyl derivative (**71a**), facile migration of the alkyl group is observed, whereas the aryl group migrates preferentially from the alkyl aryl derivative (**71b**; Scheme 27, Table 3).[52]



(71a)–(71g) **(72)–(77)**

Scheme 27

In the case of β-monosubstituted derivatives (**71c**) to (**71g**), only aryl and alkenyl groups participate in the selective 1,2-rearrangement, reflecting the low migratory aptitude of the alkyl group. The rearrangement is highly stereoselective with respect to the geometry of the epoxide moiety but not to the configuration of the alkoxy α-carbon. Thus, both *erythro–trans* isomer (**71c**) and *threo–trans* isomer (**71d**) give the same *threo*-aldol (**74**) as the sole isolable product, while *threo–cis* isomer (**71e**) exclusively gives *erythro*-aldol (**75**). Epoxides (**71f**) and (**71g**) give (**76**) and (**77**), respectively.[52] These results can be interpreted as the rigorous *anti* migration of the phenyl and alkenyl groups with complete retention of the alkene geometry.[52,53]

Concerning Lewis acids, a catalytic amount of Me_3SiI or Me_3SiOTf, as well as a stoichiometric amount of $TiClO_4$ or $BF_3{\cdot}Et_2O$, is effective. The favorable choice of Lewis acids with respect to the substitution pattern of the substrates has been reported.[54] This methodology has been successfully utilized in the total synthesis of natural products which include avenaciolide and mycinolide IV.[54,55]

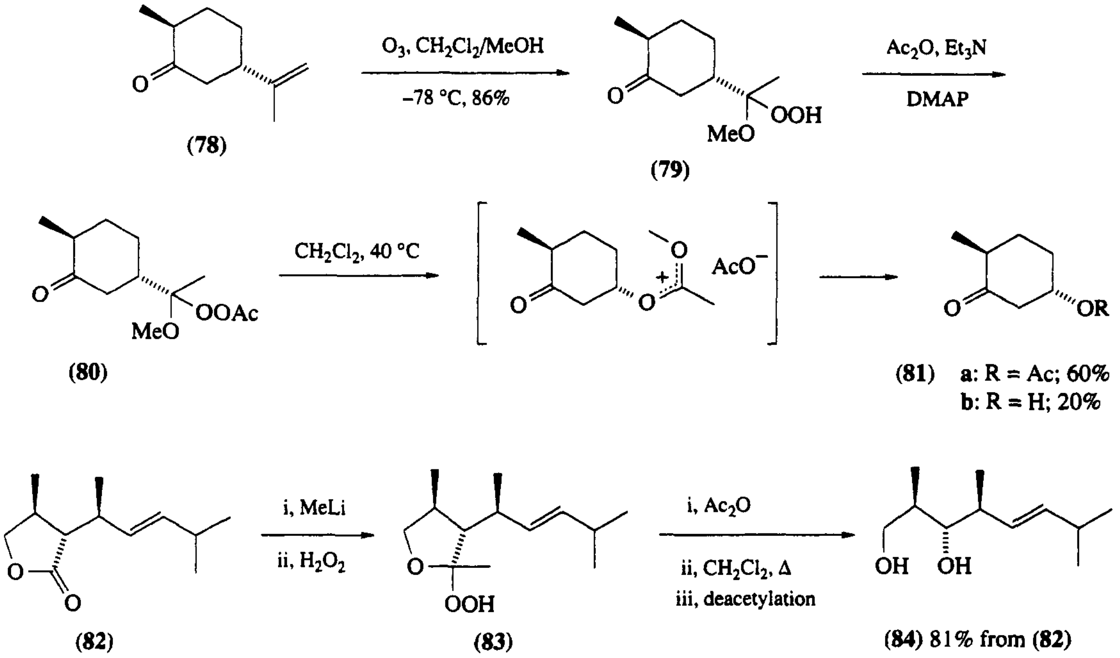
1.1.2.4.3 Criegee rearrangement

The acylations of α-alkoxy hydroperoxides such as (**79**) furnish peroxy esters that are related to the intermediate produced in the Baeyer–Villiger reaction.[56–58] The peroxy ester undergoes the Criegee rearrangement to a dioxonium ion which in turn is converted into an ester. Thus, ozonolysis of (+)-(*E*)-dihydrocarvone (**78**) affords a 1:1 mixture of diastereomers (**79**). Acetylation and rearrangement

Table 3 Rearrangement of (71) (Scheme 27)[52]

	Substrate					Product	Product				
(71)	R^1	R^2	R^3	R^4	R^5	*number*	R^6	R^7	R^8	R^9	*Yield (%)*
a	H	H	Me	Me	Me	(72)	H	Me	Me	Me	48
b	H	H	Me	Ph	Me	(73)	H	Me	Ph	Me	75
c	H	Me	H	Ph	Me	(74)	Me	H	Ph	Me	95
d	H	Me	H	Me	Ph	(74)					79
e	Me	H	H	Me	Ph	(75)	Me	Ph	H	Me	81
f	H	Pr	H	CH_2CH_2Ph, $CH_2{=}CTMS$		(76)	Pr	H	$CH_2{=}CTMS$	CH_2CH_2Ph	98
g	Pr	H	H	CH_2CH_2Ph, $CH_2{=}CTMS$		(77)	Pr	$CH_2{=}CTMS$	H	CH_2CH_2Ph	75

provides (**81a**) and (**81b**) in 60% and 20% yields, respectively, after aqueous work-up.[56] The intermediate peroxy acetate (**80**) can be isolated (84% yield) and purified (Scheme 28).[56] Similarly, lactone (**82**) is successfully converted into (**84**), which is differentially functionalized at the termini of the growing chain, *i.e.* primary hydroxy group and double bond.[58]



Scheme 28

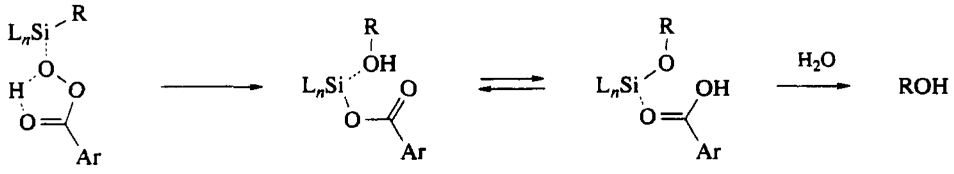
1.1.2.4.4 Oxidative cleavage of silicon–carbon bonds leading to alcohols

Certain functionalized silyl groups bonded to sp^3- or sp^2-carbon atoms (**85**) are readily converted into hydroxy groups on treatment with peroxy acids or H_2O_2 (Scheme 29).[59–61]

$$\underset{(\mathbf{85})}{R_nSiF_{4-n}} \quad + \quad \text{MCPBA} \longrightarrow n\text{ROH}$$

Scheme 29

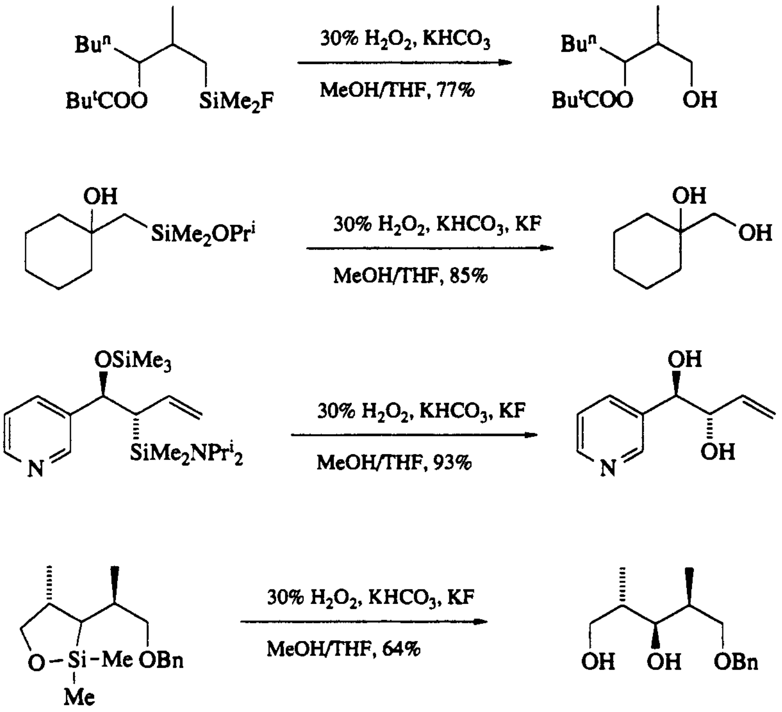
The oxidative cleavage reactions are considered to proceed through the intramolecular migration of the organic group to the oxygen in extracoordinate silicon intermediates (Scheme 30).[59] Typical oxidation conditions and silyl groups amenable to conversion to OH groups are summarized in the literature.[59]



L = F, R, and/or donor solvent

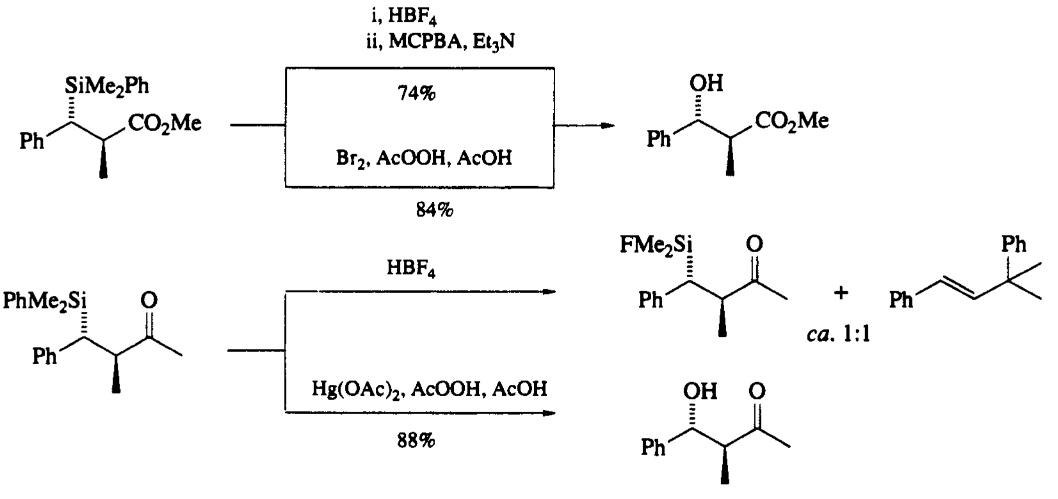
Scheme 30

The rearrangement regularly takes place with retention of configuration at the carbon atom to which the silyl group is attached, and it is compatible with ketone and ester groups. In the case of β-hydroxysilanes, no Peterson-type elimination occurs. Some representative reactions are shown in Scheme 31.



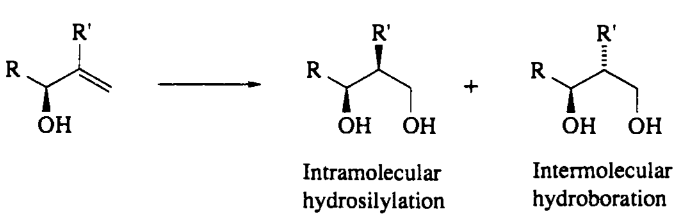
Scheme 31

When organosilicon compounds of general formula $PhMe_2Si—R$, $(CH_2{=}CHCH_2)Me_2Si—R$ and $(RMe_2Si)_2O$ are used, the Ph—Si, CH_2—Si or SiO—Si bond must first be cleaved by fluoride ion to give fluorosilanes which subsequently react with peroxy acids or H_2O_2. Recently, the use of Br_2–AcOOH or $Hg(OAc)_2$–AcOOH systems has been reported to be effective for the conversion of $PhMe_2Si—R$ into the corresponding alcohols, allowing the two-step sequence to be carried out in one operation (Scheme 32).[62a] The $PhMe_2Si$ group has recently been demonstrated to be superior to the $(Pr^iO)Me_2Si$ group in carbohydrate chemistry.[62b]



Scheme 32

A one-pot synthesis of anti-Markovnikoff alcohols from terminal alkenes has been achieved by hydrosilylation (catalyst: H_2PtCl_4, $[RhCl(PPh_3)_3]$) with alkoxysilanes and subsequent oxidation.[59,63] Although hydrosilylation of internal alkenes is difficult, intramolecular hydrosilylation of allylic and homoallylic alcohols proceeds smoothly with high regio- and stereo-selectivities.[63] In view of the high regioselectivity and the wide range of functional group compatibility, the present method may be a useful alternative to the hydroboration–oxidation process. It is noteworthy that the 1,3-diols formed by intramolecular hydrosilylation–oxidation of allylic and homoallylic alcohols have structures which are complementary to those obtained by the intermolecular hydroboration–oxidation reaction (Scheme 33).[59a,63a] Approaches to construct 1,3-diol skeletons have been demonstrated.[59,63]



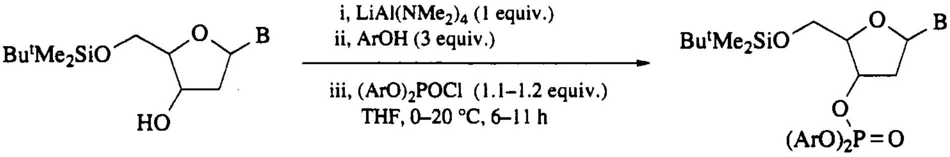
Scheme 33

1.1.2.5 Inversion of Alcohols

1.1.2.5.1 Activation of hydroxy groups

Alcohols are available in a variety of cyclic and acyclic forms, and, as such, have been utilized as versatile starting materials for the construction of carbon compounds including natural products with many centers of chirality. In order to functionalize and manipulate the hydroxy group in alcohols by a displacement process, activation of the hydroxy group is an important step which involves: (i) activation of the O—H bond to enhance the nucleophilicity of the oxygen; or (ii) activation of the R—O bond to convert the alcohol into a reactive alkylating reagent.

Conversion of alcohols into metal alkoxides is a common procedure for the enhancement of nucleophilicity in which the nature of the metal cation affects strongly the reactivity of the alkoxide.[64] Noyori and coworkers have demonstrated that metals having greater affinity to oxygen than to nitrogen allow selective activation of the hydroxy group of NH_2-unblocked nucleosides.[65] Thus, lithium alkoxytriaryloxyaluminates $LiAl(OAr)_3$—OR (R = nucleoside residues) react with diaryl phosphorochloridates to give the corresponding nucleotides in 69–88% yields with little (<1%) or no formation of *N*-phosphorylated products (Scheme 34).



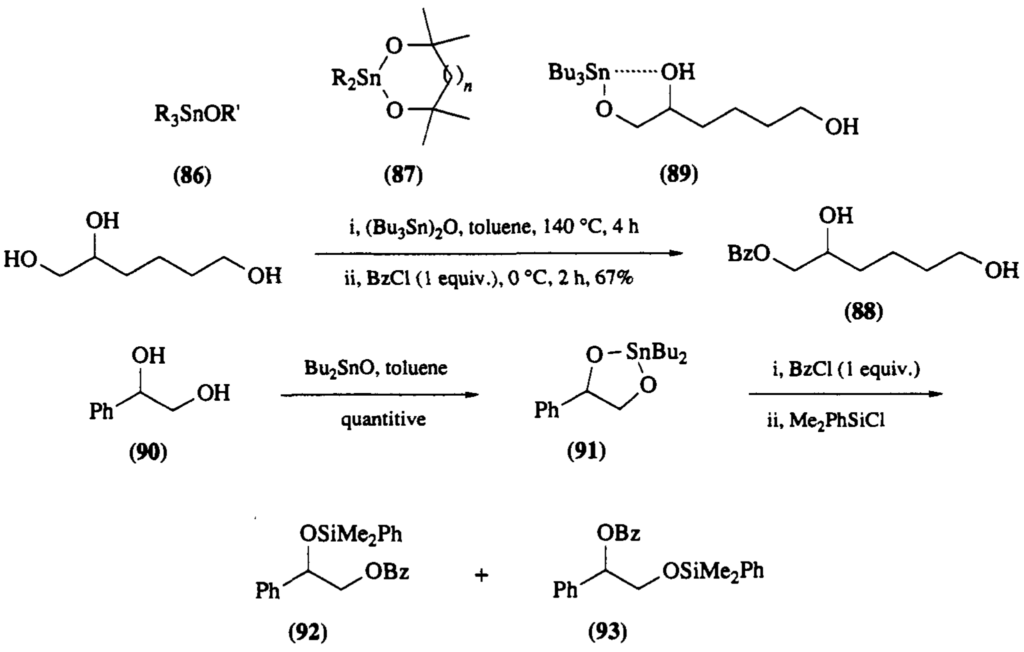
Scheme 34

Trialkyltin alkoxides (**86**) and dialkylstannylene[5] (**87**) have recently attracted attention because a tin atom attached to an oxygen atom enhances the nucleophilicity of the latter without increasing its basicity.[64] The synthetic applications of tin alkoxides manifest most remarkably in the case of polyols. For example, 1,2,6-hexanetriol was first stannylated with 1 equiv. of $(Bu_3Sn)_2O$, followed by treatment with benzoyl chloride giving (**88**) in 67% yield. Intermediacy of the tributyltin ether (**89**) was proposed for the regioselective benzoylation (Scheme 35).[66a]

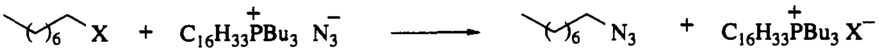
Benzoylation of 1,2-diol (**90**) by the conventional method (BzCl, Py) and subsequent silylation affords primary ester (**92**) in preference to the secondary ester (**93**) in a ratio of 96:4 (81% yield). A dramatic reversal of chemoselectivity is observed when (**90**) is first converted into dioxastannolane (**91**) followed by treatment with benzoyl chloride and work-up, giving (**92**) and (**93**) in a ratio of 5:95 (Scheme 36).[66b]

Another type of activation of the hydroxy group of alcohols involves the introduction of functional groups in order to facilitate the carbon–oxygen bond cleavage in the subsequent nucleophilic displacement reactions, *i.e.* conversion of an alcohol into a reactive alkylating reagent.

Sulfonation of alcohols is a most common approach to this end. The reactivity of sulfonates is strongly influenced by the solvent used. The kinetic study of the nucleophilic substitution of a series of *n*-octyl derivatives $C_8H_{17}X$ (X = Cl, Br, I, OTs and OMs) with N_3^- in different solvents (MeOH, DMSO, PhCl and cyclohexane) reveals the following nucleofugacity scales: OTs > I > OMs ≥ Br >> in MeOH; I > Br



Scheme 35

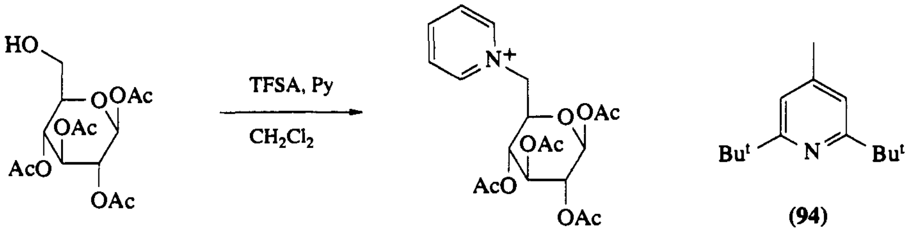


X = TsO, MsO, I, Br, Cl

Scheme 36

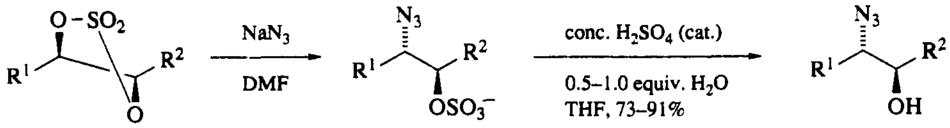
> OTs > OMs > Cl in DMSO; I > OTs ~Br > OMs >> Cl in PhCl; and OTs > OMs > I > Br > Cl in cyclohexane (Scheme 36).[67]

Triflates are more reactive than mesylates and tosylates.[68] Triflates are generally prepared by the reaction of alcohols with triflic anhydride in the presence of pyridine at low temperature. In the case where concomitant pyridinium salt formation lowers the yield of the desired triflate, more-hindered bases such as (**94**) have been used (Scheme 37).[69]



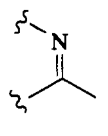
Scheme 37

Nucleophilic openings of cyclic sulfonates which are less hindered, or activated by an adjacent carbonyl group, occur at room temperature in usually less than 30 min. In these reactions, DMF is the solvent of choice. Selective hydrolytic removal of the sulfate group can be achieved under controlled conditions (Scheme 38).[70]

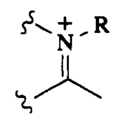


Scheme 38

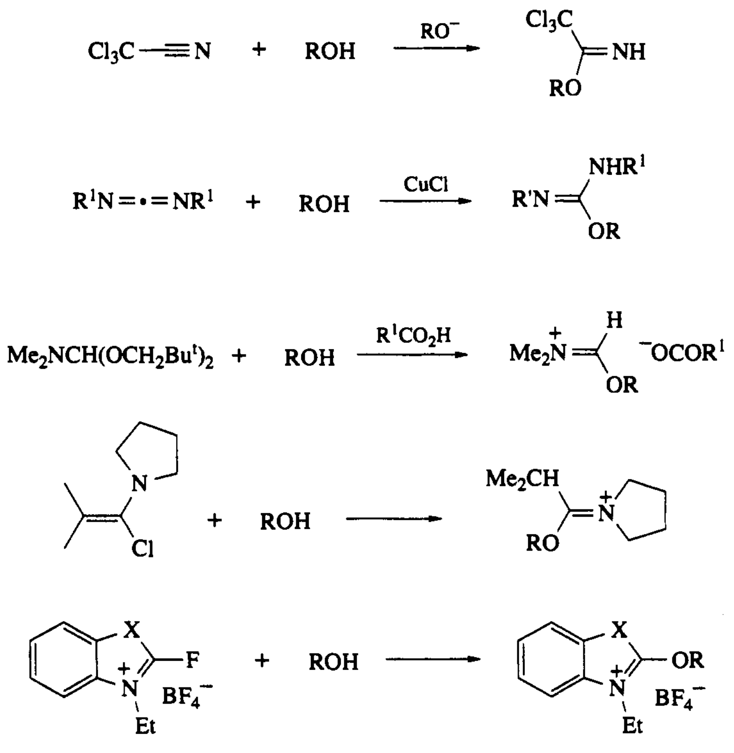
Introduction of partial structure (**95**) or (**96**) into the hydroxy group of an alcohol is also effective for activating the carbon–oxygen bond. Typical reactive imino and imidium ethers are shown in Scheme 39.[71-75]



(95)



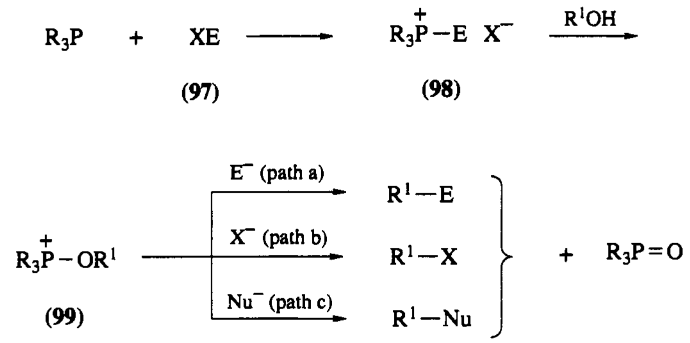
(96)



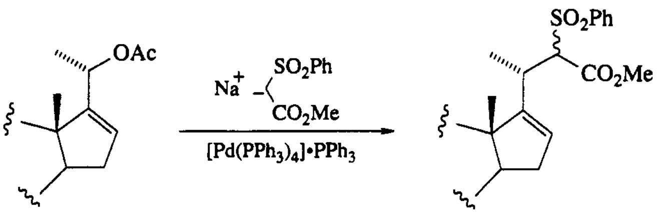
Scheme 39

Alkoxyphosphonium salts (**99**), formed by the reaction of trivalent phosphorus compounds with oxidizing electrophiles (**97**) in the presence of alcohols, have been recognized as versatile and reactive alkylating reagents. Although the mechanism has not yet been fully elucidated, the reaction might involve initial formation of (**98**). Compound (**98**) in turn reacts with an alcohol to give (**99**) which can undergo nucleophilic substitution either with its own counteranion (path a or b) or with other nucleophiles present in the reaction system (path c in Scheme 40). Thus, in order to facilitate the alkylation of external nucleophiles (path c), the choice of (**97**) is crucial for the success of the conversion. The reaction generally proceeds under mild conditions and possesses some valuable features such as regioselectivity; no allylic rearrangement; and inversion of configuration at the secondary carbinol centers. Comprehensive review articles on this process have been published.[76]

π-Allylpalladium complexes formed by the reaction of allyl acetates with palladium(0) compounds react with nucleophiles yielding the allylic alkylation products. In this catalytic process, the allylic position of the allyl alcohols is activated by acetylation.[77] The displacement reactions of sulfonates or alkoxyphosphonium salts generally take place with inversion of configuration. In contrast, the palladium-assisted alkylation proceeds with net retention of configuration (Scheme 41).[77]



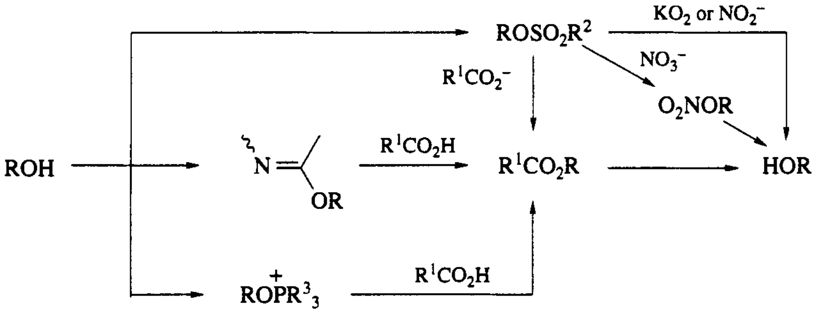
Scheme 40



Scheme 41

1.1.2.5.2 Inversion of alcohols

Although many useful methods to produce chiral alcohols have recently been developed, there is still need of a convenient procedure to invert the configurations of secondary carbinol centers. In principle, the inversion of configuration could be accomplished by initial activation of the R—OH bond of an alcohol and subsequent *S*N2 displacement using oxyanions. The reaction sequences that can be used in the inversion of configuration are summarized in Scheme 42.

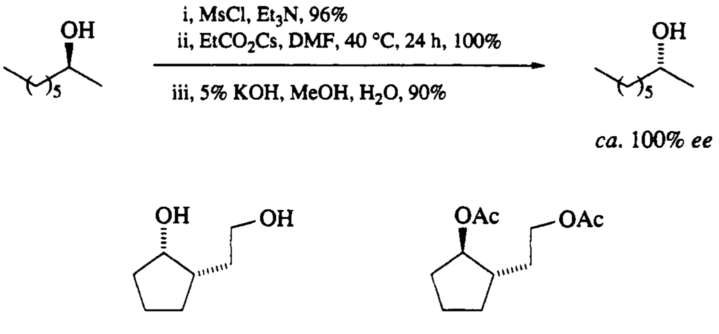


Scheme 42

The reactions of alkyl sulfonates with sodium, potassium or tetraalkylammonium carboxylates generally proceed with inversion of configuration. In the case of *s*-alkyl sulfonates, however, a varied amount of elimination products is invariably formed.[78] Of all metal carboxylates, cesium salts (Scheme 43) have proved vastly superior with respect to reactivity and the suppression of undesirable side reactions.[79]

The addition of 18-crown-6 to the reaction system is effective for suppression of the elimination reaction. Thus, the mesylate of (**100**; Scheme 43) reacts with AcOCs in the presence of 18-crown-6 (0.5 equiv.) in benzene (reflux, 1 h) to afford the inverted acetate (**101**) in 70% yield along with a small amount of elimination product (<5%). Without the crown ether, the elimination product is predominantly formed.[79e]

Nitrate ion can be another effective nucleophile for inversion. It has been demonstrated that, due to the low basicity of the nucleophile, the competing elimination reaction is almost completely suppressed and the resulting nitro esters can be readily converted into alcohols by reductive processes.[80] One serious



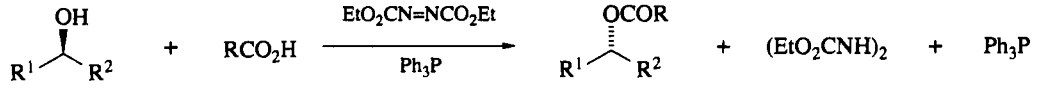
(100) **(101)**

Scheme 43

drawback of the procedure is that racemization takes place to some extent under the reaction conditions. However, the racemization can be circumvented by the use of more efficient leaving groups such as the pyridylsulfonyloxy group.[80]

The reactions of alkyl sulfonates with superoxide ion and with nitrite ion directly afford the corresponding inverted alcohols.[8,81] Although displacement by superoxide ion has been successfully utilized in prostaglandin chemistry, elimination again takes place to some extent, depending on the structures of the substrates. In the reaction with nitrite ion, ketone and nitroalkane are also formed. The inversion of cyclopentanol derivatives *via* tosylates has been studied by the use of various methods involving displacement by benzoate, nitrite ion and superoxide ion as well as the diethyl azodicarboxylate (DEAD)–Ph_3P procedure, where varied amounts of elimination products are invariably formed.[81a]

Imino ethers and 2-alkoxybenzthiazolium salts prepared from chiral alcohols react with carboxylic acids to give the esters of the corresponding inverted alcohols (Scheme 39).[71c,72d,73,75a] The reaction of a chiral alcohol with a carboxylic acid, DEAD and Ph_3P affords the ester of the inverted alcohol (Scheme 44).[82] Diisopropyl or dimethyl azodicarboxylate can be used instead of DEAD. Little difference between these reagents has been reported.[83]



Scheme 44

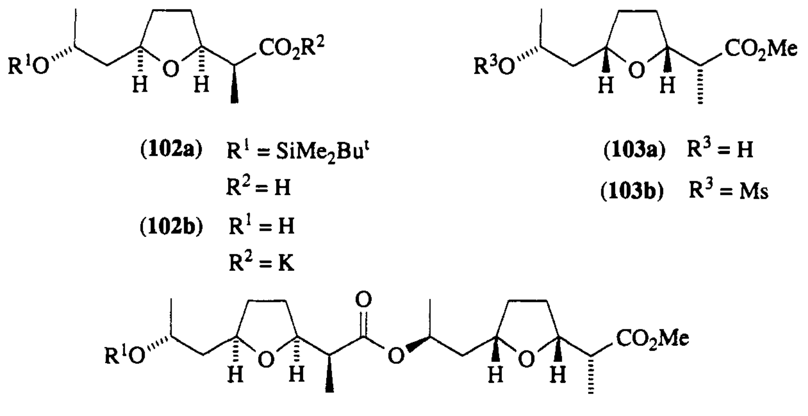
Although the DEAD–Ph_3P procedure has been utilized in the inversion of a variety of alcohols, sterically crowded hydroxy groups do not enter into the reaction. In such cases, the sulfonate route can be used. For example, the coupling of free acid (**102a**) with alcohol (**103a**) by the use of DEAD and Ph_3P affords the desired inverted ester (**104a**) in <30% yield, while mesylate (**103b**) reacts with potassium carboxylate (**102b**) (DMF, 75 °C, 18 h) to give (**104b**) in 86% yield (Scheme 45).[84]

The reagent formed by combining Ph_3P with benzoyl peroxide (BPO) reacts with alcohols to give benzoates in moderate to good yields. The reaction proceeds with essentially complete inversion of the configuration at the secondary carbinol stereocenters. It is noteworthy that 1,2-diols are benzoylated at the secondary hydroxy group in preference to the primary one (Scheme 46).[85] The product ratio is practically the same as that obtained by the DEAD–Ph_3P procedure.[86] Therefore, as far as benzoylation is concerned, the BPO–Ph_3P procedure seems attractive because the removal of hydrazine dicarboxylate from the desired product is sometimes troublesome in the DEAD–Ph_3P procedure.

1.1.3 PREPARATION OF ETHERS

1.1.3.1 Cyclic and Acyclic Ethers

Acyclic and cyclic ethers are synthesized by the reaction of activated alcohols with alkoxide or aryl oxide anions. Alkyl halides and epoxides can also be utilized as versatile electrophiles for the preparation

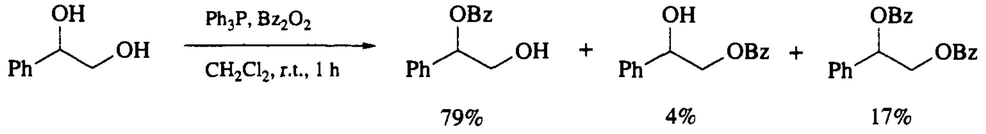


(102a) $R^1 = SiMe_2Bu^t$
$R^2 = H$
(102b) $R^1 = H$
$R^2 = K$

(103a) $R^3 = H$
(103b) $R^3 = Ms$

(104a) $R^1 = SiMe_2Bu^t$
(104b) $R^2 = H$

Scheme 45



Scheme 46

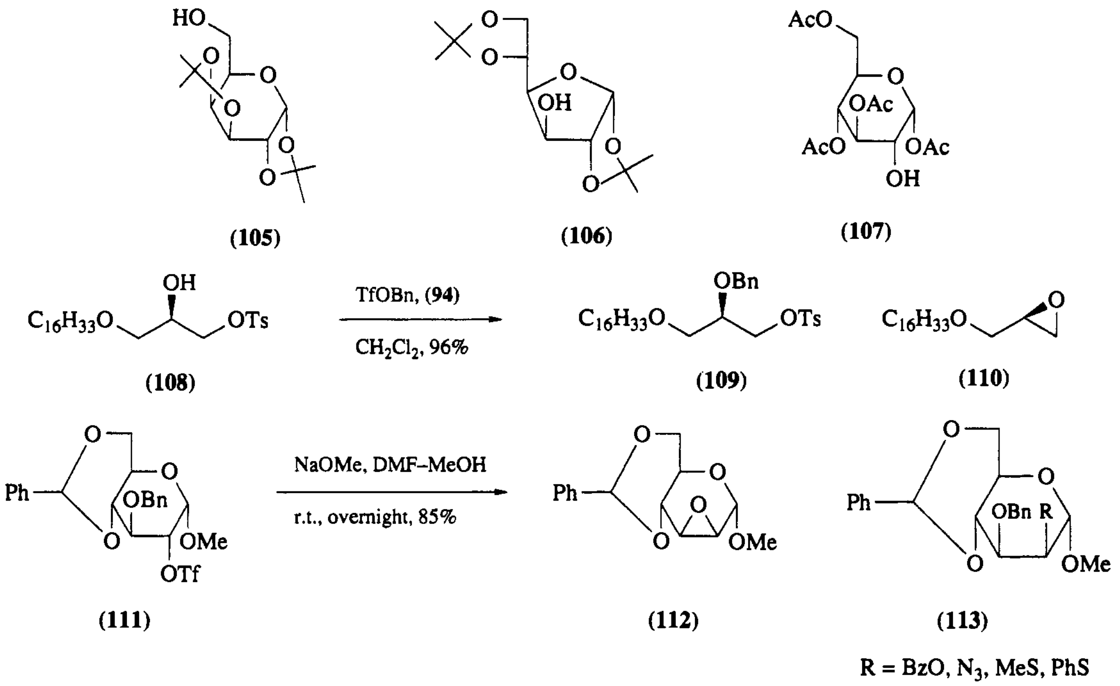
of ethers. Since comprehensive reviews of the preparation of ethers have been published,[2,87] only a limited number of examples will be described in this section.

Of the activated alcohols described in Section 1.1.2.5.1, alkyl sulfonates are convenient alkylating reagents because they can be readily prepared and handled. The correct choice of sulfate–alcoholate combination is often crucial for successful ether synthesis. Thus, for the preparation of cholesteryl ethers from the tosyl derivative of cholesterol and alkoxides, the reaction must be carried out at 110 °C for 2.5 h in a sealed tube. Alternatively, the sodium salt of cholesterol can be reacted with an alkyl mesylate at 80 °C for 1 h in DMF to give the corresponding ether in 62–68% yield.[88]

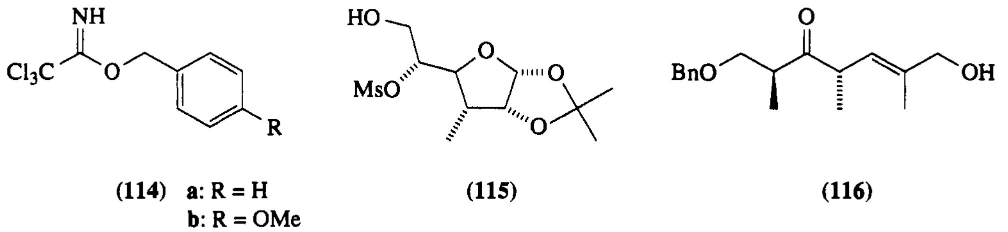
Benzyl, 4-methoxybenzyl and triarylmethyl groups are used in the protection of the hydroxy groups. Compared to typical benzylation conditions (BnBr, NaH in DMF), benzylation by triflate proceeds under milder conditions without affecting alkali labile groups. Treatment of carbohydrates (**105**), (**106**) and (**107**) with benzyl triflate, generated from benzyl alcohol and triflic anhydride in 2,6-di-*t*-butylpyridine at –70 °C, gives the corresponding benzylated derivatives in 93%, 89% and 60% yields, respectively. Similarly, the methyl ethers are prepared using methyl triflate, but the reaction requires heat and longer reaction time.[69a,89] Benzylation of (**108**) is successfully carried out with preformed benzyl triflate to afford (**109**) in 96% yield without epoxide formation. By the reaction with K_2CO_3, (**108**) gives epoxide (**110**).[90] Triflate (**111**) reacts with various nucleophiles (BzO^-, N_3^-, RS^-) to give the corresponding mannopyranosides (**113**) in 82–89% yields. On the other hand, the reaction of (**111**) with NaOMe exclusively gives anhydromannopyranoside (**112**; Scheme 47).[91]

Benzyl trichloroacetimidate (**114a**) reacts with alcohols in the presence of TFA to afford benzyl ethers.[92] 4-Methoxybenzyl trichloroacetimidate (**114b**), which is much more reactive than (**114a**) and very sensitive to strong acids, reacts smoothly with various kinds of alcohol to give the corresponding methoxybenzyl ether. The catalyst used is CSA (10 mol%), PPTS (10 mol%), $TrClO_4$ (3 mol%) or TFA (0.3 mol%). Under these conditions, alcohols having either acid or base labile groups, such as (**115**) and (**116**), are successfully protected (Scheme 48).[93]

Selective protection of the primary hydroxy group in polyols by the trityl group can generally be accomplished by the reaction with trityl chloride in pyridine. The use of DMAP (0.04 equiv.) and Et_3N (1.5 equiv.) facilitates the reaction.[94] Selective phenylation of one hydroxy group of diols can be carried out by the reaction with triphenylbismuth diacetate. While regioselectivity for primary–secondary vicinal diols is poor, only secondary alcoholic functions are converted to the phenyl ether in secondary–tertiary vicinal diols. Although phenylation of glycols occurs smoothly, monohydroxy alcohols are left essentially intact.[95]



Scheme 47

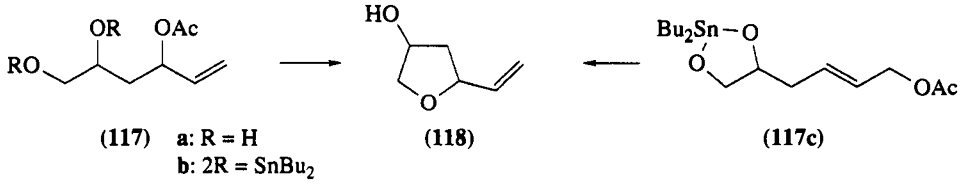


Scheme 48

In view of the fact that many complex dihydro- and tetrahydro-furans possess valued biological properties, a variety of procedures for the construction of such systems has been reported.[2f] The reactivity pattern of the cyclic ether formation with respect to ring size has been briefly discussed.[3i,96]

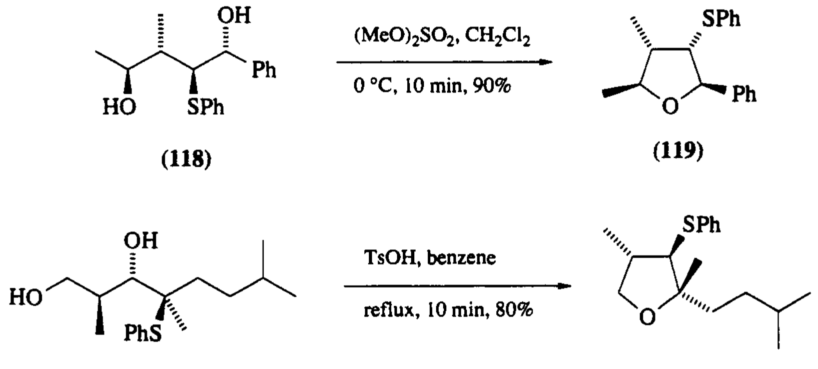
Of the alkylation systems described in Section 1.1.2.5.1, the DEAD–Ph$_3$P procedure cannot be used in the preparation of acyclic dialkyl ethers, but alkyl aryl ethers and cyclic ethers have been synthesized. The Ph$_3$P–CCl$_4$ system is also effective for the cyclodehydration of 1,4- and 1,2-diols to tetrahydrofurans and epoxides, respectively.[97]

In the presence of a palladium(0) catalyst, allyl acetates having hydroxy functions afford cyclic ethers. Thus, exposure of (**117a**)–(**117c**), 1:1 diastereomeric mixtures, to [(DBA)$_3$Pd$_2$]/CHCl$_3$–Ph$_3$P at room temperature gives rise to the same cyclic ether (**118**) in 92–96% yields as a 9:1 isomeric mixture. No cyclization products derived from the secondary alcohol serving as the nucleophile are detected (Scheme 49). By this procedure, five- to seven-membered cyclic ethers have been prepared.[98]



Scheme 49

The acid-catalyzed cyclodehydration of (±)- and meso-2,5-hexanediol has been shown to proceed with inversion of configuration in most cases, affording *cis*- and *trans*-2,5-dimethyltetrahydrofuran, respectively. However, various extents of racemization are observed in the actions of certain Lewis acids and H_2SO_4.[99] The stereospecific cyclization of diols to tetrahydrofurans occurs if phenylthio participation is involved. The reactions of 2-phenylthio-1,4-diols such as (**118**) with dimethyl sulfate afford (**119**) with net retention of configuration, whereas acid-catalyzed cyclizations of 4-phenylthio-1,3-diols such as (**120**) take place with PhS migration and hence inversion at both the migration origin and terminus (Scheme 50).[100]



(**118**) (**119**)

(**120**) (**121**)

Scheme 50

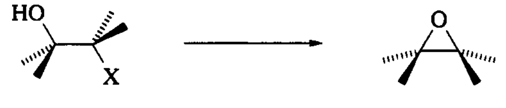
A transition metal catalyzed synthesis of ethers by carbene insertion into the O—H bond has been reported. Not only saturated but also unsaturated alcohols can be utilized in this catalytic process.[101]

Intermolecular and intramolecular oxirane ring opening reactions by alkoxides and phenoxides also provide efficient and stereospecific preparations of acyclic and cyclic ethers. The procedures have been surveyed in detail.[3]

1.1.3.2 Epoxides

Perhaps the most widely used procedure for epoxide synthesis is peroxide or peroxy acid oxidation of alkenes, which is discussed in Volume 7, Chapters 3.1 and 3.2.

Another important method involves intramolecular S_N2 displacement of an alcohol with an appropriate leaving group in the β-position (**122**; Scheme 51). In this approach, the preparation of β-functionalized alcohols having definite configuration at both the α- and β-carbon atoms is prerequisite. The most promising strategy to achieve the correct construction and configuration of the intermediates is the transformation of natural products by stereochemically unambiguous processes. For details on this approach, the reader is referred to an excellent review.[102]



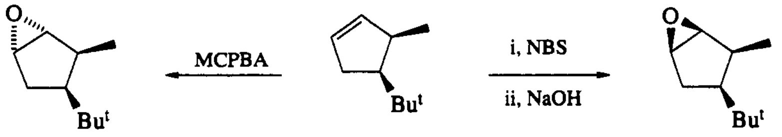
(**122**)

X = halogen, RSO_3, $R_2\overset{+}{S}$, $R_3\overset{+}{P}O$, *etc.*

Scheme 51

Stereoselective preparation of precursors to epoxides can also be achieved by the aid of the structure of the substrates, especially in the cyclic systems. Scheme 52 illustrates the stereochemical outcome of epoxide formation *via* the bromohydrin route and the peroxy acid oxidation procedure.[103]

Intramolecular participation of an appropriately placed nucleophile promises to be a useful strategy for the stereocontrolled synthesis of acyclic systems. Thus, halocyclization of unsaturated carboxylic acids, alcohols and functionalized alcohols (**123**) can be effected by a variety of electrophilic halogenating



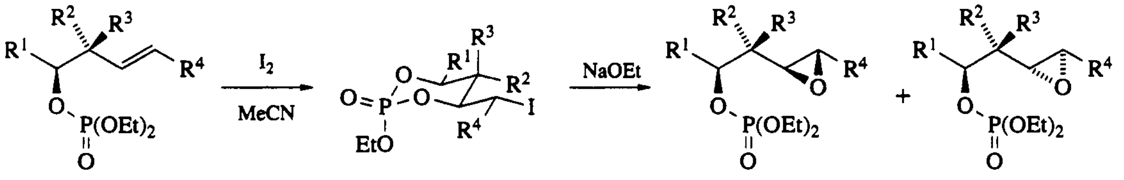
Scheme 52

agents affording stereochemically biased halomethyl heterocycles. Lactones, cyclic carbonates and cyclic phosphates thus formed are in turn converted into epoxides *via* halohydrins (Scheme 53).[104]

(123) $Z = CO_2R, OC(O)OR, OP(O)(OR)_2$, *etc.*

Scheme 53

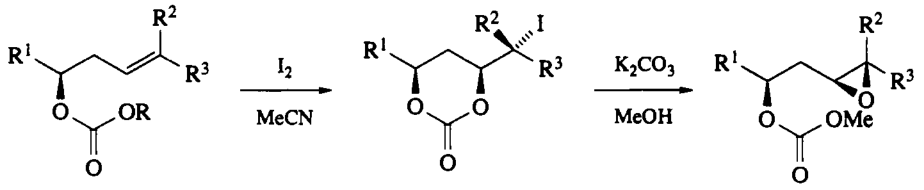
Treatment of homoallylic phosphates with I_2 results in the formation of thermodynamically more stable cyclic phosphates which are converted into *erythro*-epoxides with high stereoselectivity (Scheme 54).[105] The procedure (phosphate extension) allows otherwise difficult stereoselective conversion of homoallylic alcohols into 3,4-epoxy alcohols.



80–98 : 20–2

Scheme 54

Iodolactonization and iodocarbonylation can also be utilized for the stereoselective epoxidation of alkenic esters and alcohols (Scheme 55).[106,107]

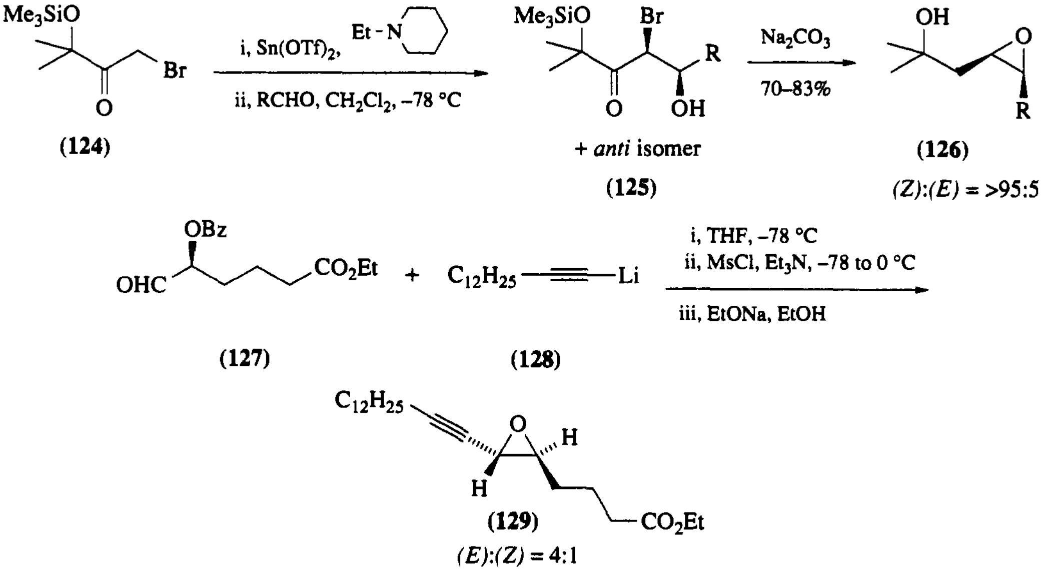


major isomer

Scheme 55

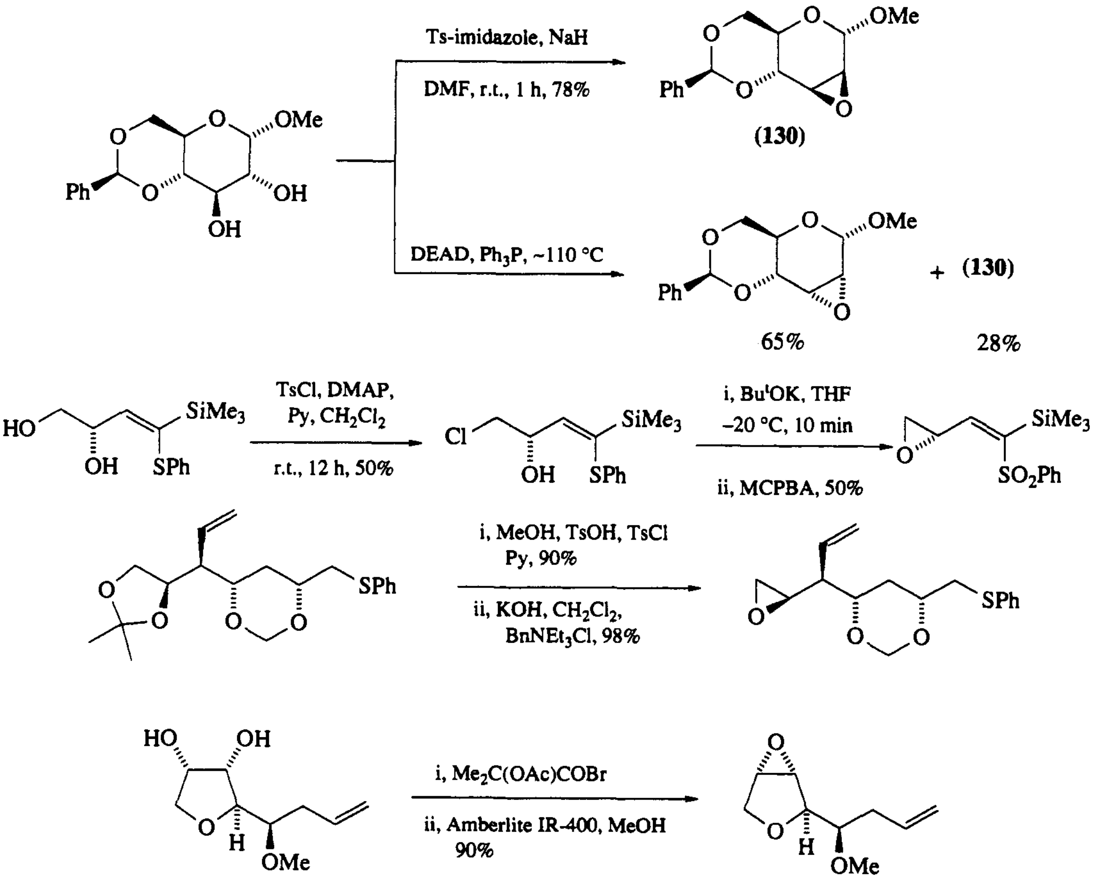
Tin(II) triflate mediated cross aldol reactions between α-bromo ketone (**124**; Scheme 56) and aldehydes afford *syn*-α-bromo-β-hydroxy ketones (**125**) with high stereoselectivity. The resulting halohydrins are converted to the corresponding (*Z*)-2,3-epoxy ketones (**126**).[108] Chiral aldehyde (**127**) reacts with lithium alkynide (**128**) followed by mesylation and base treatment to give chirally pure (*E*)-epoxide (**129**). The initially formed alkoxide anion should be trapped *in situ* by mesylation, otherwise partial racemization takes place owing to benzoate scrambling (Scheme 56).[109]

Epoxides can also be prepared from a variety of β-functionalized alcohols such as β-hydroxy sulfoxides,[110] β-hydroxysulfonium salts,[111] β-hydroxy selenides[112] and vicinal diols. In the use of unsymmetri-

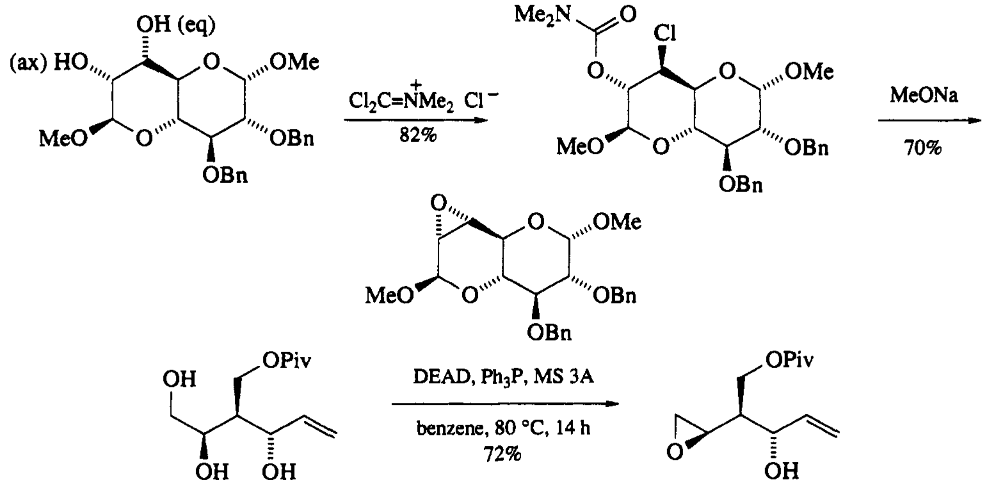


Scheme 56

cal vicinal diols, regioselective activation of one hydroxy group of the two is prerequisite.[87] Scheme 57 illustrates some examples of the preparation of epoxides from vicinal diols.[113-119]



Scheme 57



Scheme 57 *(continued)*

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1.2
Synthesis of Glycosides

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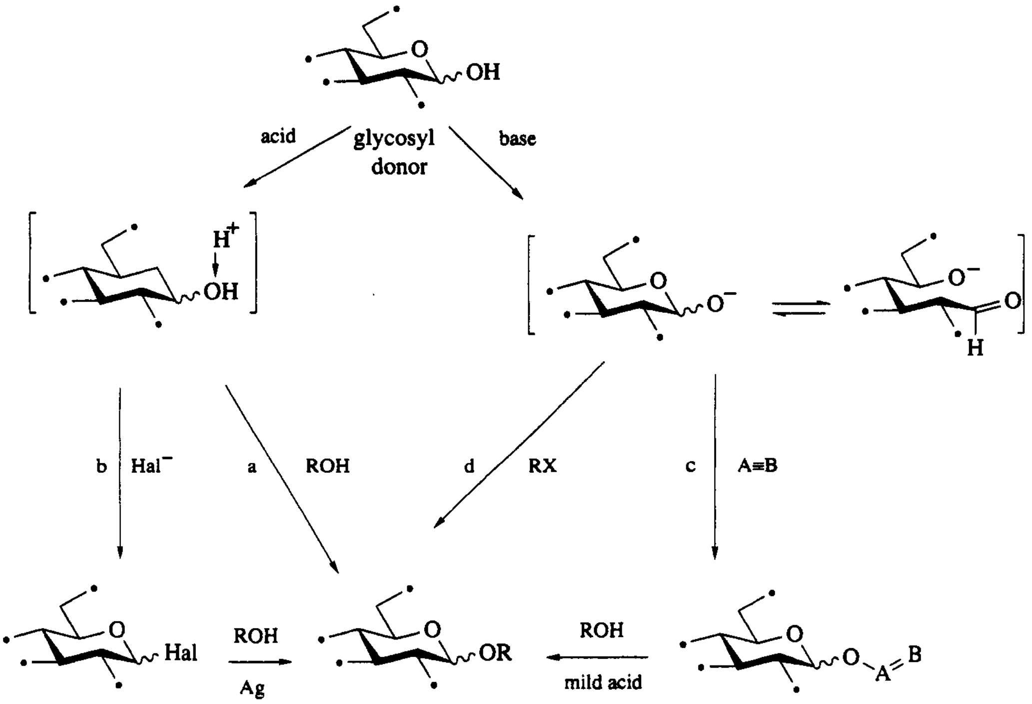
1.2.1 INTRODUCTION

Glycoside synthesis is a very common reaction in nature, providing a great variety of compounds, for instance oligosaccharides as such, or glycoconjugates with lipids (glycolipids), proteins (glycoproteins) and many other naturally occurring substances. However, the important biological implications of the attachment of sugar moieties to an aglycon are only now becoming more and more obvious, creating a growing interest in this field. For instance, the presence of complex carbohydrate structures as integral constituents of membranes and cell walls has led to manifold activities in recent research.[1–7] An especially important role amongst these glycoconjugates seems to be played by the glycosphingolipids,[1–3] the glycophospholipids[1] and the glycoproteins.[1–6] Their manifold functions are based on a great structural diversity of the oligosaccharide portion, which is inherent to the variability in glycoside bond formation.[1,4] This point was recently impressively illustrated,[1] rendering oligosaccharides ideal as carriers of biological information and specificity.

This knowledge is based on an enormous extension and improvement of the methodologies for structure determination[8] and for chemical synthesis,[1,2,5,6,9–12] as will be outlined below. The synthesis of glycosides, oligosaccharides and glycoconjugates is characterized by a much larger number of possibilities for coupling than that of other biopolymers, such as peptides or proteins and ribo- or deoxyribo-nucleotides.[1] In contrast to peptides and nucleotides, in which the informational content is determined solely by the number and sequence of different monomer units, the informational content of oligosaccharides is fixed additionally by the site of coupling, the configuration of the glycosidic linkage (α or β) and the occurrence of branching. Thus, oligomers made up of carbohydrates can carry considerably more information per atomic unit than proteins and nucleotides.[1]

The structural variety complicates the synthesis of glycosides and even more so of complex oligosaccharide structures. It has only recently been possible to develop methods for the synthesis of complex oligosaccharides and glycoconjugates. The results obtained in glycoside and saccharide synthesis will be summarized as outlined in Scheme 1 (paths A–D). (a) The Fischer–Helferich method, describing the direct acid-catalyzed acetalization procedures, where direct substitution of the anomeric hydroxy group takes place. (b) The Koenigs–Knorr method and its variants. In the classical Koenigs–Knorr method, and the subsequently developed efficient variants, the generation of glycosyl donor properties is achieved through exchange of the anomeric hydroxy group for a halide leaving group (halide = bromide, chloride and recently fluoride, with some special properties) and reaction of the glycosyl halides in the presence of heavy metal salts. This general principle also includes the use of thioglycosides and 1,2-epoxides as glycosyl donors. (c) The trichloroacetimidate method and other anomeric oxygen activations. The direct base-catalyzed activation of the anomeric oxygen with trichloroacetonitrile (and related compounds; see Section 1.2.4.2) yields *O*-glycosyltrichloroacetimidates, which exert very high glycosyl donor properties under mild acid catalysis. Related approaches *via* sulfonate, phosphate, acetate and orthoester formation respectively are included. (d) The anomeric *O*-alkylation method. The direct anomeric *O*-alkylation of pyranoses and furanoses is a completely different substitution process, requiring 1 equiv. of base for the removal of the anomeric hydroxy group proton.



(a) Fischer–Helferich (acid activation); (b) Koenigs–Knorr (Br, Cl, (I) activation, F activation and RS activation); (c) trichloroacetimidate ($OC(NH)CCl_3$ activation and OAc, OSO_2R, OPO_3R_2 activation); (d) anomeric *O*-alkylation (base activation)

Scheme 1 Synthesis of glycosides and saccharides

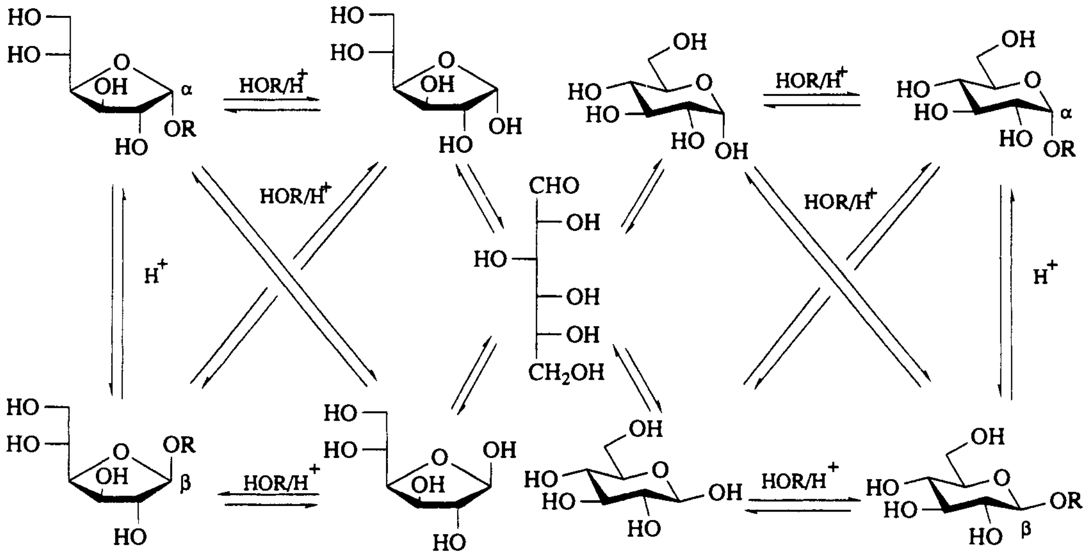
Other methods have gained practically no importance. Special problems in the application of methods (a)–(d) to 2-deoxyglycoside synthesis will be reported in Section 1.2.7.

1.2.2 THE FISCHER–HELFERICH METHOD

In a glycoside synthesis, a polyfunctional sugar component must be linked to an acceptor (which is another sugar component in saccharide synthesis). Regioselectivity is generally achieved when the glycosylating component (*i.e.* the glycosyl donor) possesses selectively protected hydroxy groups and an activating group at the anomeric C-atom, and when the component with the acceptor group (*i.e.* the glycosyl acceptor, for instance O-, N-, S- or C-nucleophiles) possesses protective groups at all other acceptor functions (Scheme 1). Thus, complicated protection strategies (Volume 6, Chapter 3.1) and suitable procedures for activation at the anomeric C-atom are required. In addition, the coupling step must occur diastereoselectively with respect to formation of an α- or β-linkage.

In the classical Fischer–Helferich method *O*-glycosides are obtained from hemiacetals and alcohols in an acid-catalyzed reaction as a variant of the common acetal formation (Scheme 1).[9] This reaction is reversible; it is therefore not applicable to the synthesis of compounds with more than one glycoside bond (*i.e.* to the synthesis of oligosaccharides and glycoconjugates) because other glycosidic bonds will be affected. In addition, the diastereocontrol at the anomeric position is based on thermodynamic energy differences between the corresponding α- and β-anomers. The axial position for the anomeric OR group is disfavored by steric arguments (unfavorable 1,3-diaxial interactions) and favored by the anomeric effect (favorable stereoelectronic interactions between the ring oxygen and the anomeric carbon–oxygen bond).[13] These two opposing effects often have similar magnitudes, therefore usually an anomeric mixture of products is obtained, or, due to a slight preponderance of the anomeric effect, more of the α-anomer is formed.

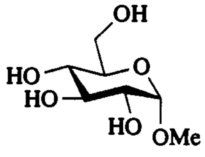
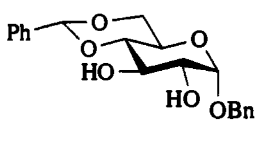
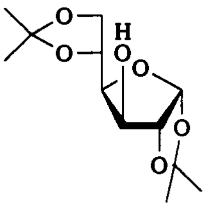
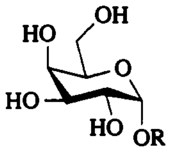
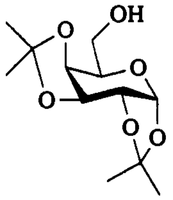
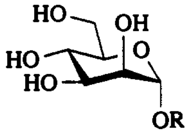
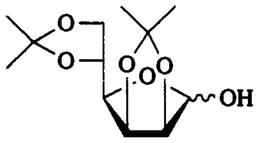
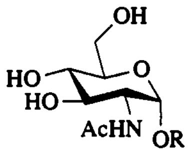
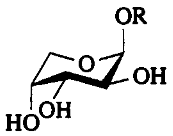
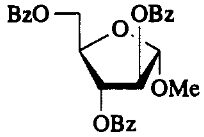
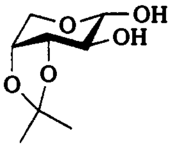
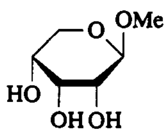
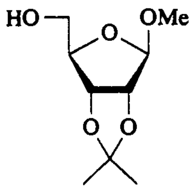
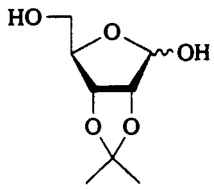
The merits of the Fischer–Helferich method today are mainly in its use for the synthesis of simple glycosides required as starting materials in oligosaccharide synthesis and as chiral synthons.[14] The strategy for sugar protection usually starts with the formation of a methyl, benzyl or allyl glycoside directly from the unprotected sugar, followed by selective introduction of additional protective groups (benzylidene, isopropylidene, benzyl, silylacetyl, benzoyl, *etc.*). Due to ring–chain tautomerism (Scheme 2), with excess alcohol and acid as catalyst, α- and β-furanosides and α- and β-pyranosides can be obtained, leaving three hydroxy groups unprotected in the case of pentoses and four in the case of hexoses. The result is dependent on the individual sugar and the reaction conditions. Due to the ring strain, other glycoside ring sizes are not commonly found and furthermore the open chain *O*,*O*-acetal is not formed *via* this route. Furanose formation is usually faster than pyranose formation, a phenomenon also typical for other saturated ring closure reactions.[15] However, the occurrence of several acid-catalyzed equilibration reactions (as indicated in Scheme 2) with different kinetics makes product control difficult. Therefore the



Scheme 2

search for procedures resulting in the convenient isolation of one product has gained tremendous importance. Some typical examples are given in Table 1.[16–31]

Table 1 Acid-catalyzed Formation of 1-*O*-Protected Sugars Commonly Used in Sugar Transformations[a]

Starting material		*1-O-Protected sugars*	
Glc	 (ref. 16)	 (ref. 17)	
Gal	 R = Me (ref. 19) R = Allyl (ref. 20)	 (ref. 21)	
Man	 R = Me (ref. 22) R = Bn (ref. 23)	 (ref. 18)	
GlcNAc		R = Allyl (ref. 20) R = Bn (ref. 24)	
Ara	 R = Me (ref. 25) R = Bn (ref. 26)	 (ref. 27)	 (ref. 28)
Rib	 (ref. 29)	 (ref. 30)	 (ref. 31)

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[a] References for the syntheses are given in brackets.

The combination of this simple acid-catalyzed glycoside synthesis with additional acetal formations in the presence of a ketone (mainly acetone and cyclohexanone) furthers the versatility of this method. Thus, from *O*-unprotected hexoses and pentoses respectively, in convenient acid-catalyzed procedures compounds with only one or two *O*-unprotected hydroxy groups are directly accessible, providing convenient functional group control in subsequent reactions (Table 1; in some cases even the sugar aldehyde group is left unprotected). Most of these compounds are now commercially available. They are extensively used as starting materials in research laboratories and even in technical processes. For instance, diacetone sorbose (obtained from acetone and L-sorbose under acidic conditions) is an intermediate in the commercial vitamin C synthesis[32] and D-arabinose derivatives could become starting materials for a short (+)-biotin synthesis.[33,34]

However, another application of the Fischer–Helferich method clearly exhibits its limitations. Long chain alkyl glycosides have gained interest as nonionic surfactants.[35] Their technical synthesis is based on acid catalysis of the reaction between glucose and alcohol. Due to the inherent solubility problems, typical drawbacks of the Fischer–Helferich method are encountered: the technical product consists of a mixture of different anomers and, due to the fact that excess alcohol cannot be used for solubilization of the reaction mixture, reaction of glucose with itself is also found.

Due to the drawbacks of the Fischer–Helferich method it was early recognized that other approaches to glycoside and saccharide synthesis had to be introduced.

1.2.3 THE KOENIGS–KNORR METHOD AND ITS VARIANTS: ACTIVATION THROUGH ANOMERIC OXYGEN EXCHANGE REACTIONS

1.2.3.1 General Aspects of Glycoside Bond Formation

A versatile and generally applicable method for a diastereocontrolled glycoside and saccharide synthesis seems to necessitate a two-step procedure with the following requirements.[1]

The first step, activation of the anomeric center generating the glycosyl donor, requires: (i) convenient formation of a sterically uniform glycosyl donor; (ii) adoption, according to choice, of either α- or β-configuration; and (iii) thermal stability of the glycosyl donor at least to room temperature; eventually chromatographic purification should be possible.

The second step, the glycosyl transfer to the acceptor providing the glycoside, the oligosaccharide or the glycoconjugate, requires: (i) catalysis of the glycosyl transfer by simple means; (ii) irreversibility of the reaction; (iii) that the configuration of other glycosidic bonds is not affected in the process; (iv) high chemical yield; and (v) high α- or β-selectivity *via* diastereocontrolled inversion or retention of configuration at the anomeric center (usually attained in a kinetically controlled reaction).

1.2.3.2 The Koenigs–Knorr Method: Bromide and Chloride as Leaving Groups

In the classical Koenigs–Knorr method, dating from 1901,[36] and the subsequently developed efficient variants, the activation step is achieved through the formation of glycosyl halides (halogen = bromine and chlorine) and their reaction in the second step, the glycosyl transfer step, in the presence of heavy metal salts (preferentially silver and mercury salts). This method has been critically reviewed,[1,5] giving the following general picture.

1.2.3.2.1 Glycosyl halide formation

The exchange of the anomeric hydroxy group for bromine or chlorine, carried out with typical halogenating agents (and all other hydroxy groups *O*-protected), leads mainly to the product with the halogen atom in an axial position. Because the subsequent discussion is mainly restricted to the important sugars D-glycopyranose (Glc), 2-acetamino-2-deoxy-D-glucopyranose (GlcNAc), D-galactopyranose (Gal), 2-acetamino-2-deoxy-D-galactopyranose (GalNAc) and D-mannopyranose (Man), which prefer the $^{1}C_{4}$ conformation, axial orientation at the anomeric position corresponds with the α-anomer and equatorial orientation with the β-anomer, respectively.

1.2.3.2.2 Glycosyl halide stability and reactivity

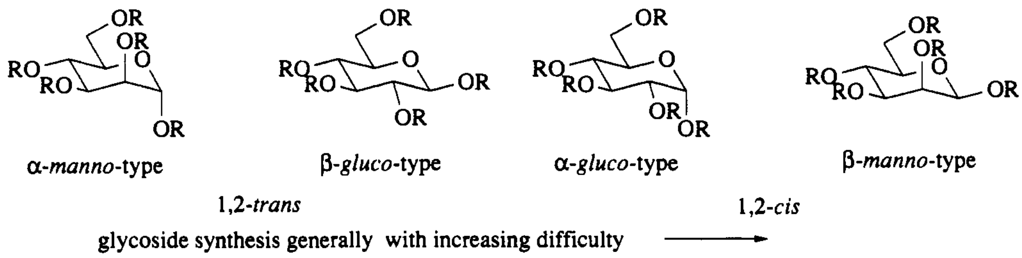
The stability and reactivity of the glycosyl halides is greatly dependent on the halogen, the sugar and the protective groups. The thermal stability increases from bromide to chloride and by substituting electron-donating protective groups for electron-withdrawing protective groups. Dramatic changes in stability are observed; thus the well-known acetobromoglucose (2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide) can be readily prepared and stored at 0 °C, whereas the frequently used 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide is thermally unstable as low as –78 °C (glycosyl iodides are usually too unstable). Therefore, many glycosyl halides are prepared *in situ* and used without further purification, thus necessitating the use of compounds which are frequently sterically nonhomogeneous and sometimes even impure. In addition, the glycosyl halides are highly sensitive to hydrolysis.

The reactivity of the glycosyl halides increases in reverse order compared with stability; protective groups at different positions exert 'remote electronic effects'. The influence of these groups does not depend only on the distance to the anomeric carbon atom;[37] thus electron-withdrawing *O*-protective groups at C-4 lower the C-1 reactivity quite strongly due to through-bond interactions.

1.2.3.2.3 α/β-Selectivity in glycoside synthesis

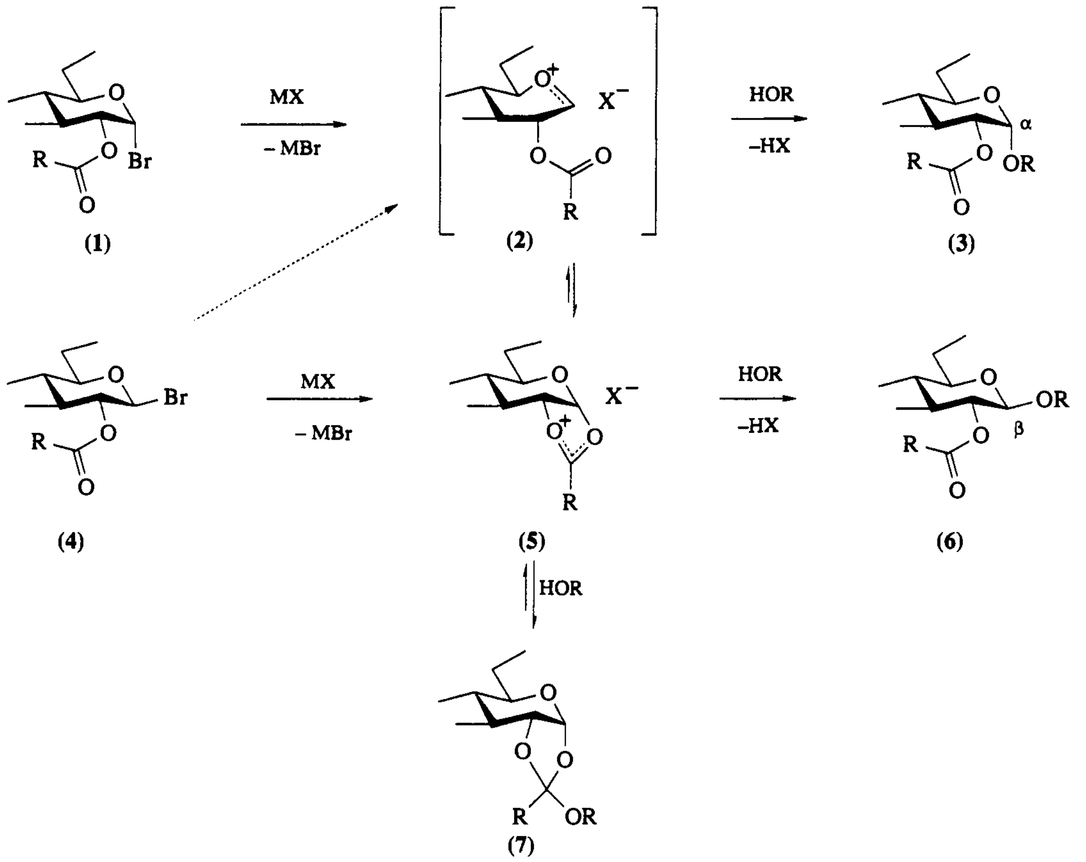
A stereocontrolled nucleophilic substitution of the glycosyl halogen by an S_N2 mechanism would provide the β-glycosides from the generally readily available α-glycosyl halides. Thus the only existing problem would be the generation of the thermodynamically less stable β-halogenoses. However, the situation is much more complicated, because most glycosyl acceptors are not reactive enough for a simple base-catalyzed nucleophilic substitution at the anomeric center. Therefore, the reactivity of the glycosyl halide itself has to be adjusted to the special synthetic problem by varying the halide and the protective group pattern, and, above all, by selecting a proper halophilic 'catalyst' (required in equimolar amounts) as a coactivator. In addition, appropriate solvents and temperatures have to be chosen in relation to the glycosyl acceptor reactivity (which can also be varied by varying the protective group pattern). The fact that glycosyl halides will eventually exhibit the features of α-halogen ethers implies that at least the reactive representatives will favor S_N1-type mechanisms which are not stereoelectronically controlled. Therefore all the other factors mentioned above will play important roles in diastereoselection.

Due to the general structure of hexoses (and pentoses) and due to the importance of the hydroxy group next to the anomeric position, four different structural situations are generally differentiated (Scheme 3). The ease of formation of these different anomeric linkages is mainly dependent on the strength of the anomeric effect, which is comparatively stronger in the α-*manno*-type than in the α-*gluco*- (and the α-*galacto*-) type sugars, and possible neighboring group participation of protective groups at the functional group at C-2. Thus the readily available α-glucosyl halide (**1**; Scheme 4), presumably *via* a tight (or a solvent-separated) ion pair (**2**), or the β-glucosyl halide (**4**), collapses to a dioxolanium intermediate (**5**), which is attacked by the glycosyl acceptor almost exclusively from the β-face, cleanly providing β-glucopyranosides (**6**). In the reaction course conformational changes to half-chair forms are required for oxygen lone pair orbital overlap with the C-1 carbonium ion. Due to the intramolecularity of formation of (**5**), bimolecular attack at (**2**) from the α-face, providing α-glucopyranosides (**3**), can be obtained only with difficulty, usually necessitating thermodynamic control. Obviously orthoester (**7**) formation is a competing side reaction, which can be reversed by acid treatment. Therefore orthoesters (**7**) can also be successfully applied to β-glucopyranoside (**6**) synthesis (see Section 1.2.4.1)



Typical examples – *gluco*-type: D-Glc, D-GlcNAc, D-GlcA, MurAc, D-Gal, D-GalNAc, L-Fuc;
manno-type: D-Man, L-Rha

Scheme 3



Scheme 4

These considerations explain the experimentally found ease of formation of α-*manno*-type structures (Scheme 3) because they are favored by the anomeric effect and by neighboring group participation (Scheme 3). β-*Gluco*-type structures are also readily accessible when neighboring group participation is applicable. However, the formation of α-*gluco*-type structures depends strongly on thermodynamic control (or S_N2-type reactions) without recurrence to neighboring group participation. Obviously, the formation of β-*manno*-type structures is supported neither by the thermodynamic anomeric effect nor by neighboring group participation. It is strictly dependent on an S_N2-type reaction starting from the readily accessible α-*mannosyl*-type halides. Therefore this structural type is most difficult to prepare.

1.2.3.2.4 Other variables in glycoside bond formation

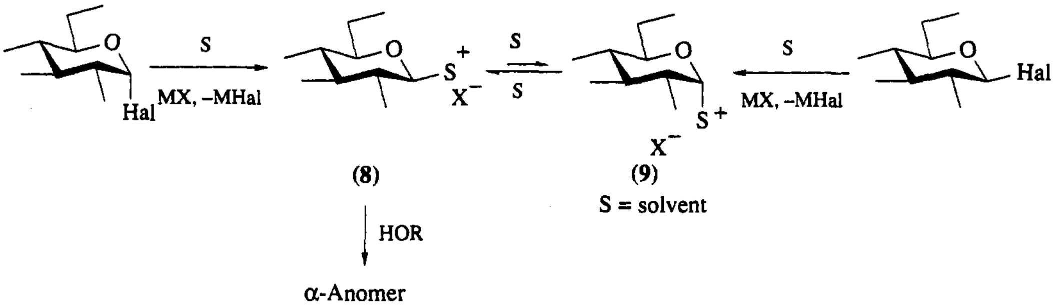
The above conclusions concerning the stability and reactivity of glycosyl halides and their diastereocontrol in substitution reactions with glycosyl acceptors have to be complemented by the other variables in glycoside bond formation.

(i) The catalyst

As catalysts (or coactivators, required in at least equivalent amounts), various silver or mercury salts are applied. Mercury-containing components, especially $Hg(CN)_2$ in nitromethane as solvent or cosolvent, were introduced by Helferich and coworkers,[38] and are therefore often referred to as 'Helferich conditions'. Important aspects are differences in reactivity and the generation of equivalent amounts of acid and/or water in the course of glycoside bond formation. For the most common catalysts the following order of reactivity has been generally confirmed: $AgOTf/Ag_2CO_3$ > $AgClO_4/Ag_2CO_3$ > $Hg(CN)_2/HgBr_2$ > $Hg(CN)_2$.[5] The formation of acid can be circumvented by the addition of Ag_2CO_3 in combination with catalytic amounts of AgOTf or $AgClO_4$ and the use of a base, for instance collidine. Water is commonly removed with Drierite or molecular sieves (3Å and 4Å).

(ii) The solvent

Solvents which are poor donors are commonly used in glycoside synthesis, for instance dichloromethane, cyclohexane or petroleum ether. These solvents favor S_N2-type reactions. Solvents which are better donors, for instance ethers (diethyl ether, THF, *etc.*), acetonitrile, pyridine, nitromethane *etc.*, each result in a typical change in the reaction course due to their different participation in the stabilization of the reaction intermediates. With ethers, acetonitrile and pyridine participation leads to onium-type intermediates (Scheme 5; **8** and **9**), which eventually provide, *via* fast equilibration, mainly the β-anomer (**8**), due to their higher thermodynamic stability, based on the 'inverse anomeric effect'.[13,39] Thus α-product formation is often favored in these solvents (see Section 1.2.3.2.5). Solvents with even higher dielectric constants commonly result in lower diastereocontrol in glycoside synthesis.



Scheme 5

Recently, *in situ* generation of onium-type intermediates from pentenyl glycosides was suggested by Fraser-Reid and coworkers[40] for glycoside synthesis. Thus far the α,β-selectivities in this process have mainly been found to be low.

(iii) The temperature

Due to the low thermal stability of many glycosyl halides reaction temperatures above room temperature are usually not applied. The general tendency to favor the stereoelectronically controlled S_N2-type reaction is reason to use reaction temperatures as low as possible. However, solubility and reactivity are commonly the decisive factors for reaction temperature selection.

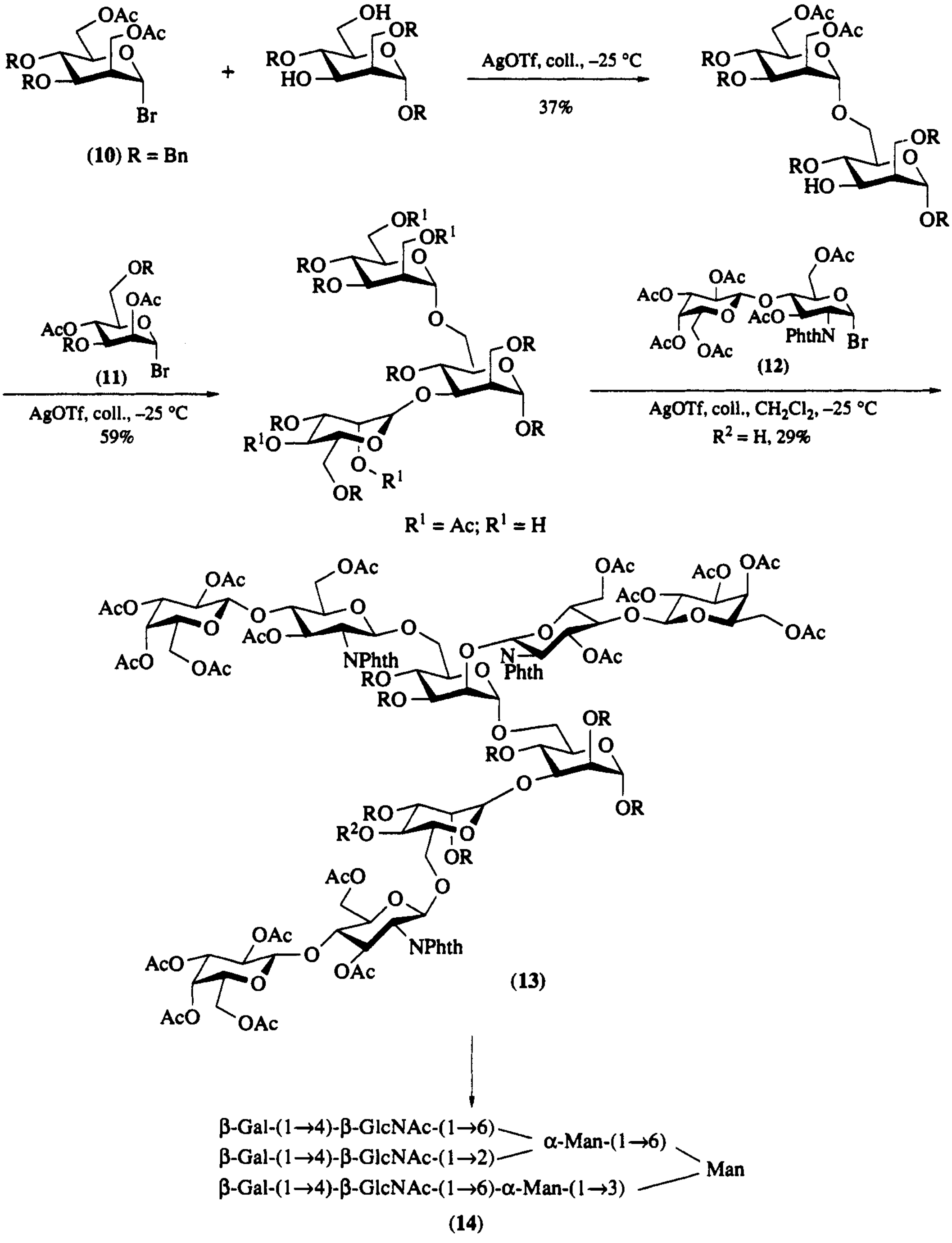
(iv) The acceptor

The acceptor reactivity exhibits big differences, which are due to steric, stereoelectronic (*e.g.* anomeric configuration) and inductive (*e.g.* electronic character of protective groups effects), with the steric effect usually predominating. When all groups are equatorial (for instance *gluco*-type in $^{1}C_4$-conformation) the following reactivity order is observed: 6-OH > 3-OH > 2-OH > 4-OH.[5] Axial hydroxy groups are usually less reactive than equatorial hydroxy groups (3-OH *versus* 4-OH in galactopyranose). These observations were successfully applied in regioselective saccharide syntheses with partially *O*-protected glycosyl acceptors (see Section 1.2.3.2.5).

1.2.3.2.5 Examples

Prominent oligosaccharide structures found in glycoconjugates include blood group antigenic determinants, the carbohydrate–peptide connections of *O*- and *N*-glycoproteins, the carbohydrate–ceramide connections of glucosphingolipids, fundamental structures of *O*- and *N*-glycoproteins and of glycosphingolipids, and oligosaccharide units of lipopolysaccharides;[1–7] these have attracted the interest of synthetic chemists. The versatility of the Koenigs–Knorr method has been demonstrated in this area in the last 20 years.[5]

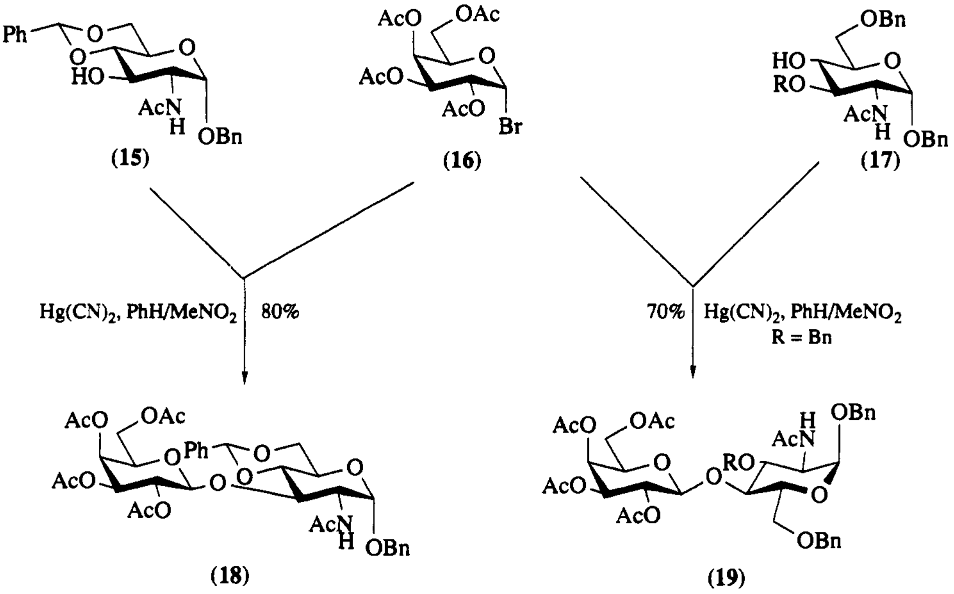
The ease of α-*manno*-type connection starting from 2-*O*-acetyl-α-mannopyranosyl bromides (**10**) and (**11**) is exhibited in the synthesis of fragments (**14**) of the *N*-glycosidically linked carbohydrate portion (**13**) in glycoproteins (Scheme 6).[41] However, other important aspects of efficient oligosaccharide syntheses are also exhibited in this example: these are partial *O*-protection for starting material synthesis with the help of regioselective stannylation and subsequent benzylation, regioselective mannosylation and block synthesis for the attachment of the lactosaminyl residue. The required lactosaminyl donor (**12**) is obtained from lactal *via* azidonitration by the cerium ammonium nitrate route introduced by Lemieux and coworkers.[42]



Scheme 6

The α-Rhamnopyranosyl connection often met in repeating units of lipopolysaccharides is obtained by analogous procedures.[5,43]

β-Glucopyranosyl and β-D-galactopyranosyl connection (β-*gluco*-type) can be readily attained if the reactivity of 2-*O*-acyl-protected donors is sufficient for the acceptor reactivity. Scheme 7[44] demonstrates this difference clearly. The galactosyl donor (**16**) reacts with the acceptor (**15**) cleanly to give the β-disaccharide (**18**). However, under the same conditions compound (**17**) with R = acetyl gives practically no product, and compound (**17**) with R = benzyl is still much less reactive than compound (**15**), although the corresponding β-disaccharide (**19**) is obtained in good yield after longer reaction time.

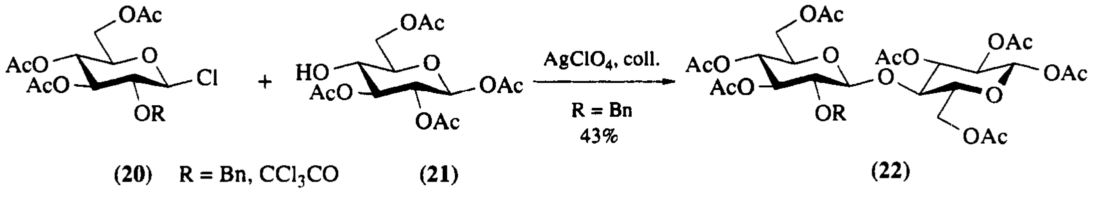


Scheme 7

Neighboring group participation for β-glucosamine and β-galactosamine connection is best achieved with the 2-deoxy-2-phthalimido group. Because of the excellent leaving group properties of the generated oxazolinium intermediate, high yields and high β-selectivities are usually observed (Scheme 6).[41] The required removal of the phthalimido group (with hydrazine) for the subsequent *N*-acetylation (to provide the acetamino compounds found in natural products) has already inspired work using the 2-acetamino group as a neighboring group in β-selective glycoside syntheses. However, due to the presence of an NH group, stable oxazolines are obtained from the corresponding glycosyl halides. Under strong acidic catalysis (attack of the acid at the oxazoline nitrogen) these intermediates exert glycosyl donor properties with reactive acceptors possessing the required acid stability.[5]

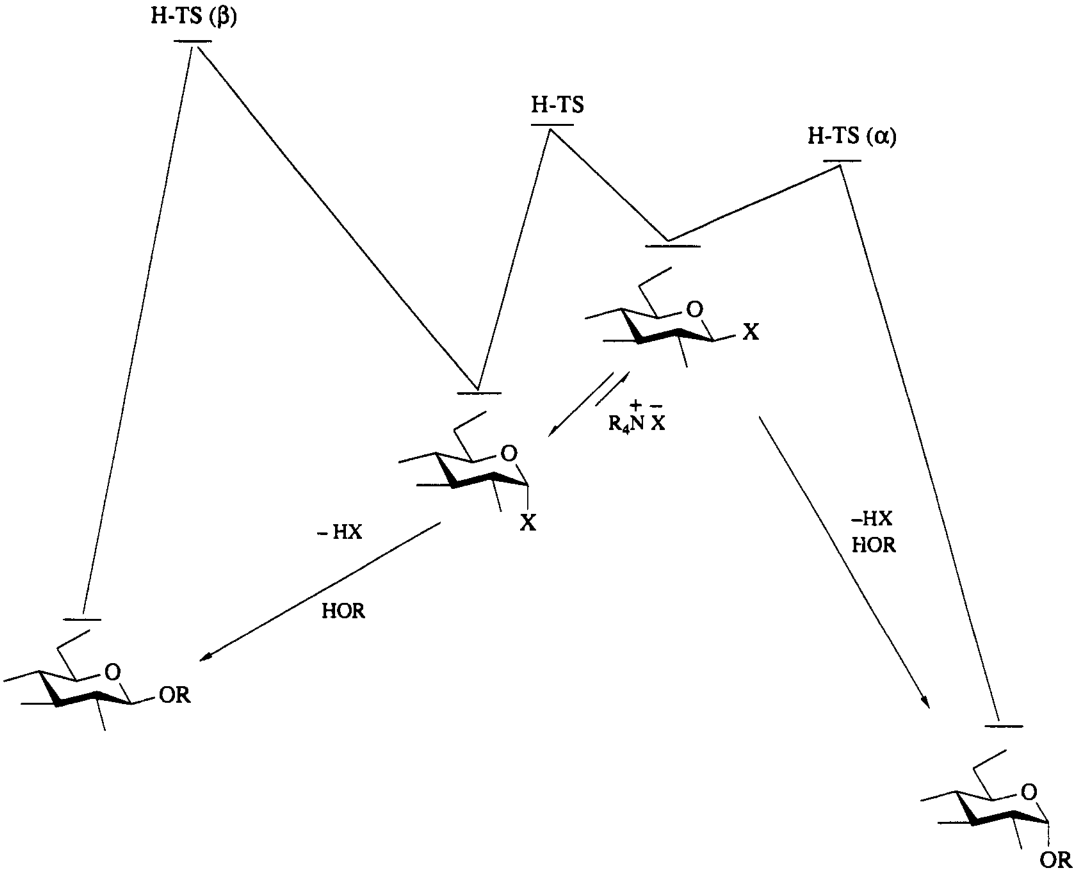
The investigation of 2-azido-2-deoxy sugars in glycoside synthesis has demonstrated that this group is largely a nonparticipating group. It was therefore mainly applied to corresponding α-*gluco*-type syntheses.[5]

The frequent occurrence of the α-D-galactopyranosyl, 2-acetamino-2-deoxy-α-D-galactopyranosyl, α-L-fucopyranosyl and α-D-glycopyranosyl connections in glycosides and saccharides has intensified the search for appropriate variations of the Koenigs–Knorr method. Obviously, nonparticipating groups (*e.g.* 2-*O*-benzyl, 2-azido-2-deoxy, *etc.*) and β-glycosyl halides were best applied to promote an S_N2-type reaction. The viability of this approach is demonstrated in Scheme 8,[45] where, with the help of electron-withdrawing *O*-protection in the donor (**20**) and the acceptor (**21**), the cellobiose derivative (**22**) is obtained. The decreased reactivity had to be overcome by the use of strong silver catalysts.



Scheme 8

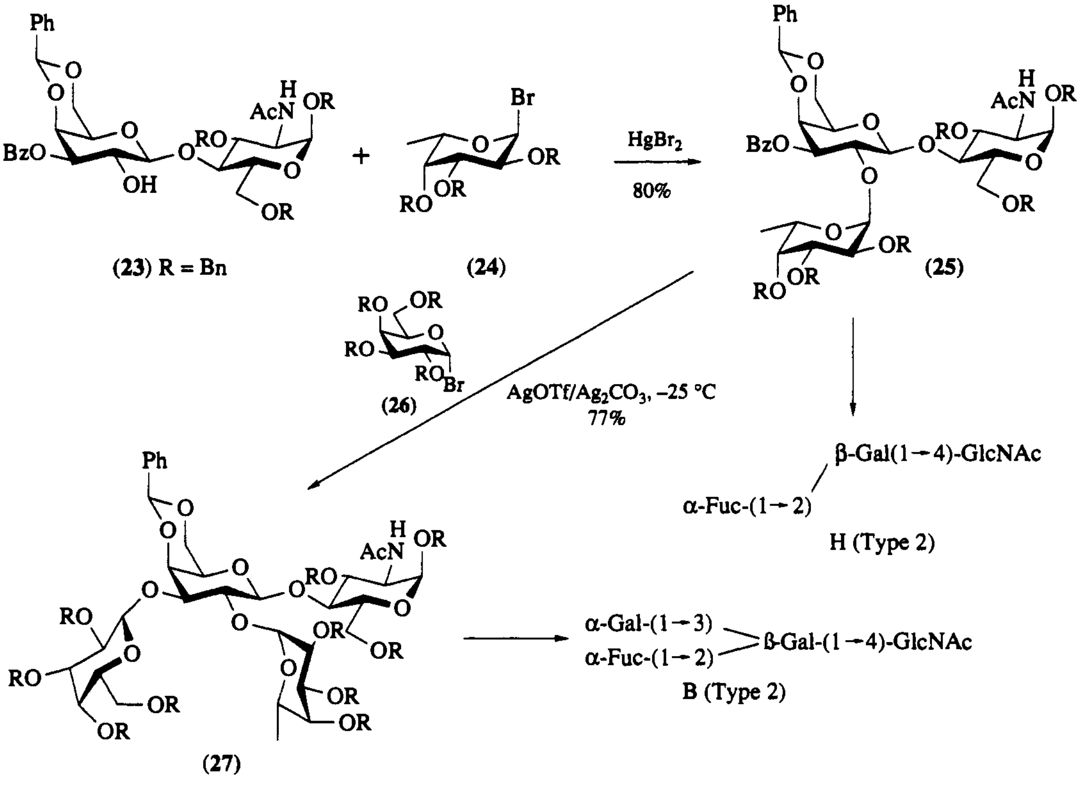
All this points to finding a means for the generation of the less stable β-glycosyl halides. This problem was solved by Lemieux and coworkers[46] with the help of the '*in situ* anomerization' of α-halogenoses with halide ions. Thus the β-halogenoses which are obtained are higher in ground state energy and more reactive towards glycosyl acceptors than α-halogenoses, preferentially affording, *via* an S_N2-type reaction, the α-glycosides. This is qualitatively demonstrated in Scheme 9. For the transition state geometries, half-chair-like geometries are suggested. Lemieux and coworkers[47] applied tetraalkylammonium halides for catalysis of this reaction, which turned out to be efficient only for reactive glycosyl donors. Later it was found by Paulsen and coworkers[48] that other soluble catalysts ($Hg(CN)_2$, $HgBr_2$, $AgClO_4$, AgOTf) are more efficient, providing α-glycosides using less reactive glycosyl donors under mild conditions. For instance, the important A, B and H blood group antigenic determinants were obtained with the help of this method (Scheme 10).[49,50] The synthesis of the H and B (type 2) determinants is exhibited starting from the lactosamine acceptor (**23**), which is first connected with the fucosyl donor (**24**), providing trisaccharide (**25**), and then with the galactosyl donor (**26**) to yield the tetrasaccharide (**27**). Subsequent deprotection of saccharides (**25**) and (**27**) provided the desired blood group determinants. In this α-glycosylation procedure, intermediates with the counterions of the catalysts or complexes with the complete catalyst are presumably generated[5] which correspond to β-halogenoses in their reaction behavior. This relates this process to the influence of participating solvents, which exert a similar effect. This could be successfully demonstrated in α-D-glucopyranuronic acid synthesis (Scheme 11).[51] Acetonitrile proved to be particularly suitable; with the glycosyl donor (**28**) excellent yields of α-glycosides (**29**) were obtained with various acceptors. Nitrilium–nitrile association, as shown in structures (**30**), presumably hinders attack by the acceptor at the nitrilium carbon.



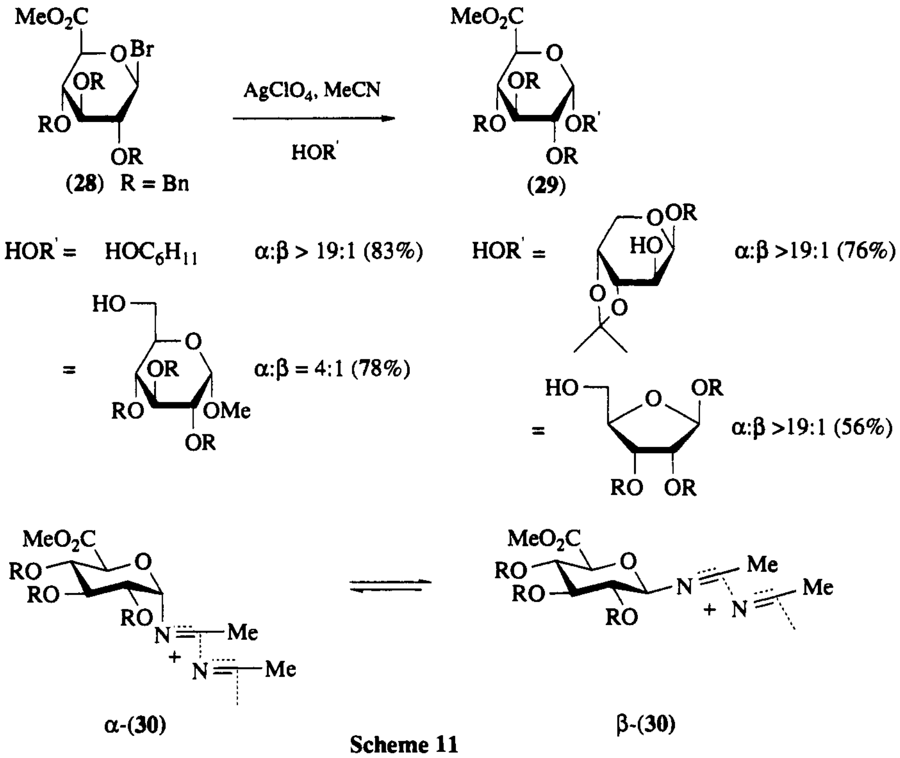
H-TS = half-chair transition state

Scheme 9 *In situ* anomerization procedure

β-*Manno*-type connection became important because this glycoside bond was found in the branching position of *N*-glycoproteins. Previous investigations with α-mannosyl bromide and reactive acceptors in the presence of insoluble silver oxide[52] inspired Paulsen and coworkers[53] to develop an insoluble heterogeneous silver silicate catalyst system, which proved to be very successful in β-mannopyranoside formation. Later silver zeolite was introduced by Garegg and coworkers[54] for the same purpose. A key synthesis was the β-mannopyranosyl connection to the 4-O of *N*-acetylglycosamine found in *N*-glycoproteins. An example of these investigations is exhibited in Scheme 12.[55] The mannosyl donor (**31**), with a nonparticipating 2-O protective group, reacts in good β-selectivity with the 1,6-anhydro-2-azidoglu-



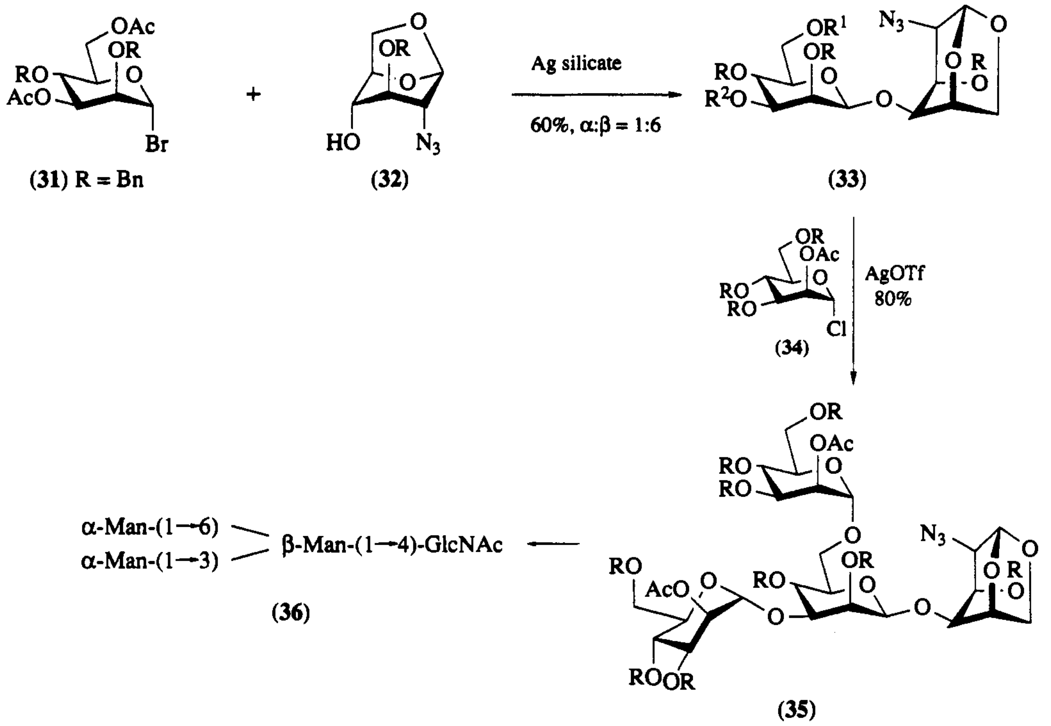
Scheme 10



Scheme 11

cose acceptor (**32**), which is more reactive than a corresponding $^1C_4$-conformer, to give the desired disaccharide (**33**). Subsequent α-selective dimannosylation with (**34**), which has a participating group in the

2-*O*-position, provides the branched tetrasaccharide (**35**) in high yield. Further processing furnishes the unprotected tetrasaccharide (**36**).



Scheme 12

β-Rhamnopyranoside structures, found in repeating units of the lipopolysaccharides of bacteria, have been also obtained with the help of these procedures.

1.2.3.2.6 Summary

In conclusion, the results with the Koenigs–Knorr method can be summarized as follows.

Firstly, the reactivity of the glycosyl donor can be varied over wide ranges by the choice of the halogen, the protecting group pattern, the catalyst, the solvent and the temperature. In this way the glycosyl donor reactivity can be adjusted to the glycosyl acceptor reactivity (which can also be varied).

Secondly, diastereoselectivity in the glycoside formation is attained by: (i) participation of neighboring groups for β-glycosides of glucose, glucosamine, galactose and galactosamine and for α-glycosides of mannose, fucose and rhamnose; (ii) *in situ* anomerization of the α-glycosyl halide to the more reactive β-glycosyl halide, which reacts preferentially to give the more stable α-glycosides of glucose, glucosamine, galactose and galactosamine (*i.e.* exploitation of the thermodynamic anomeric effect); and (iii) heterogeneous catalysis, which gives good results in the difficult formation of the β-mannose and β-rhamnose linkage.

The application of these observations has also led to many excellent results in *N*-glycoside synthesis. (The discussion of the special aspects of *N*- and *C*-glycoside synthesis is beyond the scope of this chapter.) However, severe, partly inherent disadvantages of the Koenigs–Knorr method could not be overcome. These include the low thermal stability and the sensitivity to hydrolysis of many glycosyl halides, and the use of at least equimolar amounts of heavy metal salts as 'catalysts', which are partly toxic or even explosive, to mention only a few aspects. This had led to an increased search for improved methods applicable also to large scale preparations.

1.2.3.3 Fluoride as Leaving Group

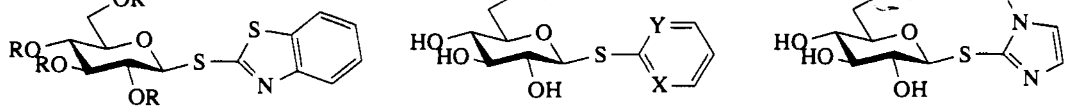
For the generation of glycosyl donor properties, other anomeric oxygen exchange reactions have been investigated. Closely related to the Koenigs–Knorr method, where bromide and chloride are the leaving groups, fluorine has been introduced as a leaving group by Micheel and coworkers (Scheme 1)[56] and has recently been investigated for glycoside synthesis.[1,5,6,12] The higher thermal stability and the higher stability towards many reagents is due to the higher strength of the carbon–fluorine bond as compared to the other carbon–halogen bonds. This enabled even base-catalyzed modifications of unprotected hydroxy groups in the presence of an anomeric fluorine atom.[57] For instance, successful *O*-benzylation of *O*-unprotected α-D-glucopyranosyl fluoride was recently described, exhibiting possible advantages in terms of the strategy of glycoconjugate synthesis.[57] However, the higher strength of the carbon–fluorine bond may concomitantly lower the glycosyl donor properties of glycosyl fluorides. Therefore, specifically fluorophilic promoters were searched for. The $SnCl_2/AgClO_4$ system was introduced by Mukaiyama and coworkers[58] and applied by several groups[59] to glycoside syntheses, resulting in good yields and reasonable α-selectivity with nonparticipating 2-*O*-protective groups. In addition, several methods for the synthesis of glycosyl fluorides were recently reported.[59,60]

Because of the complexity of the $SnCl_2/AgClO_4$ catalyst system several other fluorophilic Lewis acids were investigated as catalysts in this reaction, for instance SiF_4,[61] SnF_4,[62] TiF_4,[62] $BF_3 \cdot OEt_2$[63] and TMSOTf.[61] Thus with relatively reactive acceptors good glycoside yields were usually obtained; however, good diastereoselectivities were generally only observed for reactions with 2-*O*-participating groups. In cases with nonparticipating groups, the α:β ratio of the products depends on the solvent used rather than on the stereochemistry of the glycosyl fluoride, disproving a direct S_N2 reaction course as expected due to the special character of the carbon–fluorine bond. Even a retentive glycoside formation mechanism has been discussed for the TiF_4 catalyst.[62,64]

Relatively few applications of glycosyl fluorides in complex oligosaccharide syntheses have been reported thus far.[65] Therefore a general statement of the importance of glycosyl fluorides as glycosyl donors is not possible. Up to now the value of glycosyl fluorides seems to be limited. Glycosyl fluorides have also proved useful in the synthesis of *C*-glycosides.[63a,66]

1.2.3.4 Sulfur as Leaving Group

Recently thioglycosides, where the anomeric oxygen is replaced by an alkyl- or aryl-thio group, have attracted considerable attention as glycosyl donors (Scheme 1).[67] As with the glycosyl fluorides, thioglycosides offer efficient temporary protection of the anomeric center, and, in addition, several sulfur-specific activation reactions for generating glycosyl donor properties exist. Particularly obvious is the selective activation of thioglycosides by thiophilic metal salts. These include mercury(II) salts ($HgSO_4$,[68] $HgCl_2$,[69] PhHgOTf,[70] $Hg(OBz)_2$,[71] $Hg(NO_3)_2$[72]), copper(II) triflate[73] and lead(II) perchlorate.[74,75] However, besides the disadvantageous use of heavy metal salts, the activation itself was too weak to be of general applicability to glycoconjugate synthesis. The problem was partly circumvented by using heterocyclic thioglycosides.[75,76] For instance, Mukaiyama and coworkers[73] used benzothiazolyl thioglucoside (**37**; Scheme 13) in the presence of $Cu(OTf)_2$ as catalyst. Hanessian and coworkers[72] studied the reaction of the *O*-unprotected glucosyl thio heterocycles (**38**) and (**39**) with reactive glycosyl acceptors, employing $Hg(NO_3)_2$ as the catalyst and acetonitrile as the solvent. They obtained *O*-glycosides and the disaccharide Glc(1 → 6)Gal in good yields, but with only modest α/β selectivities. Comparative studies on the effect of proton activation with phenyl thioglucoside (**38**; X = Y = CH) and pyridyl thioglucoside (**38**; X = N, Y = CH), demonstrated the dramatic effect of the heteroatom (termed 'remote activation') as a basic anchor for the proton, resulting in a better leaving group due to the electron-withdrawing character. Not surprisingly, this kind of approach to glycoside synthesis has been successfully applied to the more reactive 2-deoxyglycosyl donors (see Section 1.2.7), for instance in the synthesis of erythromycin,[74] avermectin[75] and digitoxin.[69]



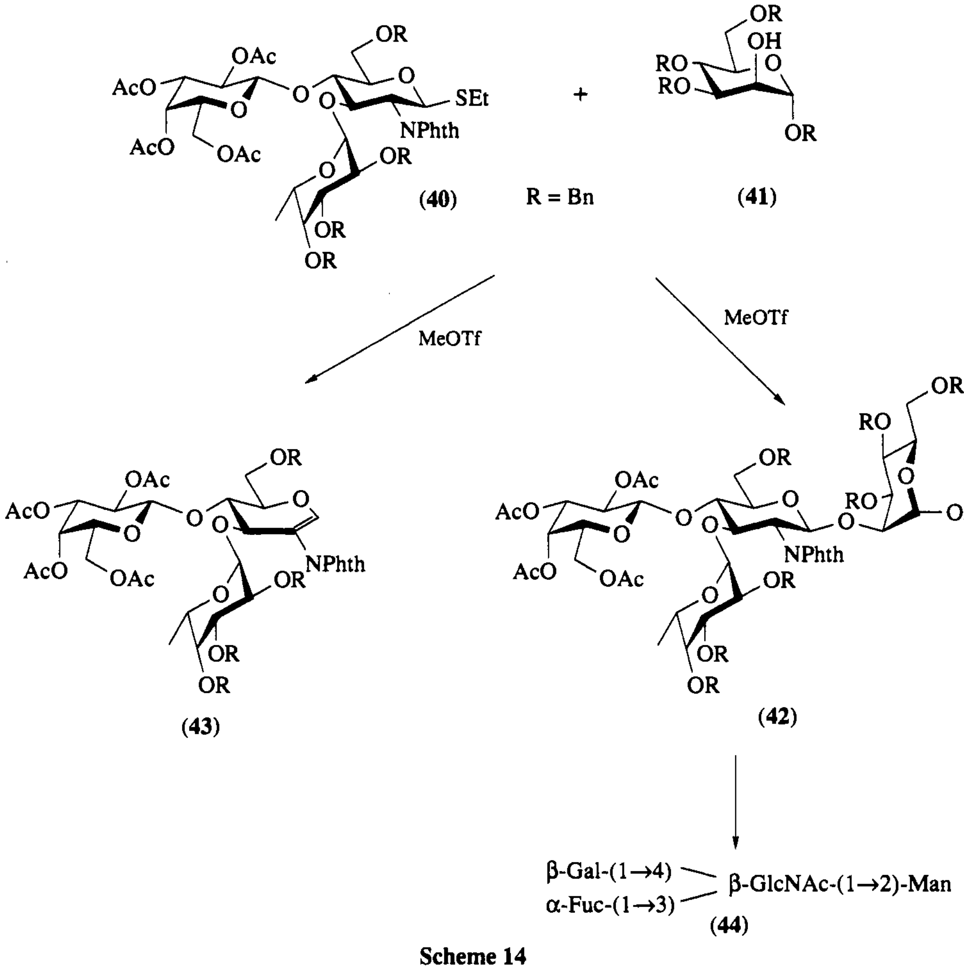
(**37**) R = Bn (**38**) (**39**)

X = N, Y = CH; X = Y = N; X = Y = CH

Scheme 13

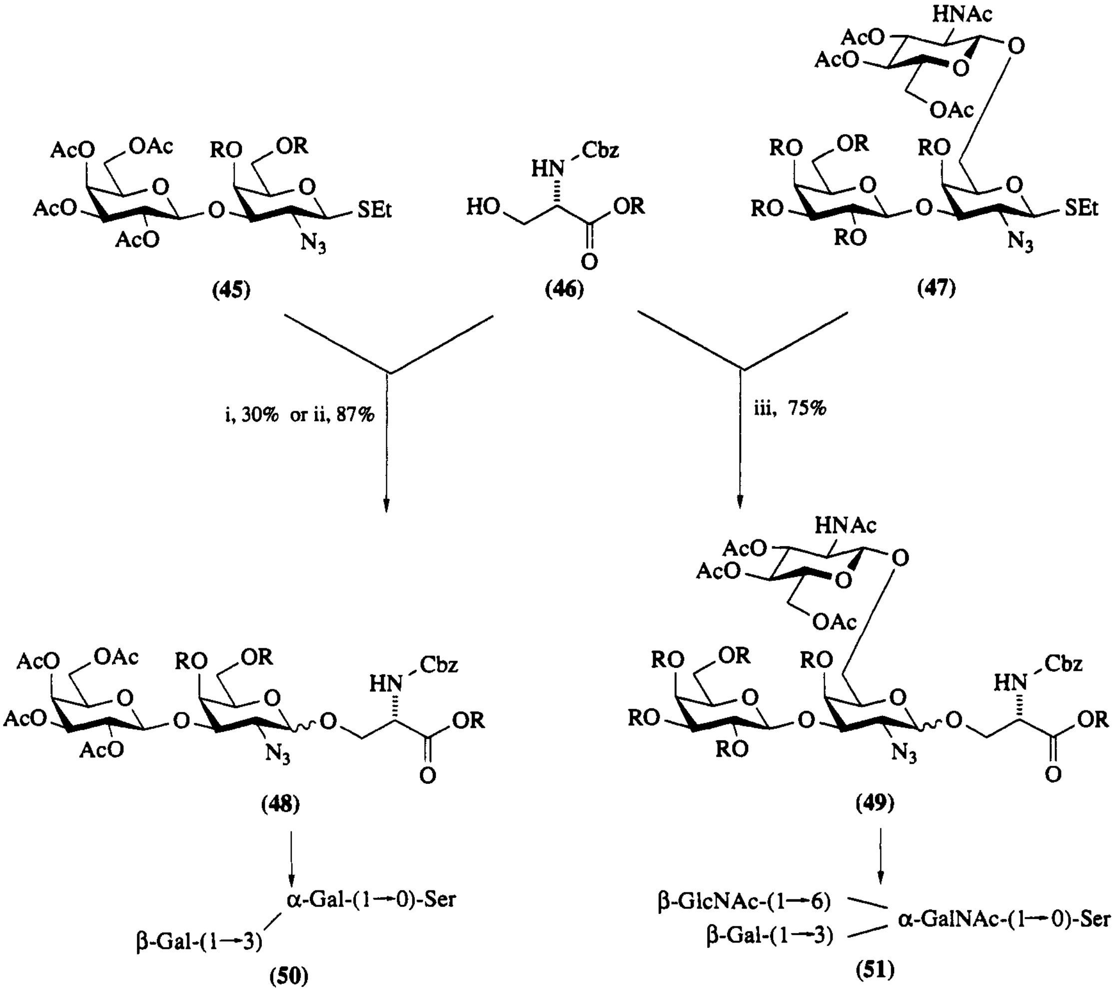
Besides metal salts (and protons), bromonium and chloronium ions are also highly thiophilic. Recent work has demonstrated that, in a two-step process, thioglycosides can first be transformed with bromine and chlorine into the corresponding glycosyl halides (providing the thermodynamically more stable α-halides), thus subsequently enabling the application of the Koenigs–Knorr method.[67,77] If the counterion of the halonium is a poor nucleophile (for instance in *N*-bromosuccinimide), then direct reaction with alcohols as competing *O*-nucleophiles should be preferred. This has been confirmed[72] and, starting from phenyl thioglycosides, a wide scope for this reaction observed;[76] however, low α,β-selectivities were frequently obtained.

Sulfonium, ammonium and phosphonium groups are suitable as leaving groups for nucleophilic displacement reactions at the anomeric center. Schuerch and coworkers[78] have studied these groups and found the following order of reactivity: sulfonium > ammonium > phosphonium compounds, putting the interest mainly on thioglycosides. Thus Lönn reported good glycosidation results for sulfonium leaving groups obtained from alkylthioglycosides and methyl triflate.[79,80] One example is exhibited in Scheme 14.[79] Starting from thioglycoside (**40**) and the mannose acceptor (**41**), owing to phthalimido group control the β-connected tetrasaccharide (**42**) was obtained in good yield. The corresponding unprotected compound (**44**) has been found as a constituent of glycoproteins in the urine of patients suffering from fucosidosis.[80] 1,2-Elimination in this glycosidation procedure, previously reported by Kronzer and Schuerch,[78] was also observed as a competing reaction leading to the glycal derivative (**43**). The low α/β-selectivity observed for nonparticipating 2-*O*-protective groups, the health hazard of methyl triflate and the formation of methylation products in other side reactions are additional disadvantages of this methodology.[79] However, dimethyl(methylthio)sulfonium triflate (DMTST), recently introduced by Fügedi and Garegg,[81] is highly thiophilic and gives rise to faster glycosylations than does methyl triflate. Glycosyl donors with neighboring group partication during reaction generate 1,2-*trans*-linked glycosides (α-*manno*-type, β-*gluco*-type) in excellent yields and virtually complete stereospecificity. However, with nonparticipating groups the α/β-selectivity is usually low.[79] Recent application for generating the α-



Scheme 14

gluco-type linkage found in *O*-glycoproteins of the mucin-type core structures (**50** and **51**; Scheme 15) met with limited success.[82] The donor properties of compounds (**45**) and (**47**) towards serine derivative (**46**) were low with methyl triflate but excellent with DMTST, giving the saccharides (**48**) and (**49**). Good α-selectivity was only obtained for (**45**).



i, MeOTf, 8 d (α:β ≈ 4:1); ii, DMTST, 12 h (α:β ≈ 5:1); iii, DMTST, 1 h (α:β ≈ 1:2)

Scheme 15

Due to the interest in thioglycosides, the methods of their synthesis from glycosyl halides with thiolates or by *S*-alkylation of 1-thioaldoses[83] have been complemented by new methods.[76,84]

Glycosyl disulfides, sulfonic acids and sulfones have not exhibited interesting glycosyl donor properties.[85]

1.2.3.5 Anhydro Sugars as Glycosyl Donors

1,2-Anhydro sugars promise good glycosyl donor properties due to the ring strain in the alkoxy epoxide moiety. Brigl's anhydride was thus used for the synthesis of disaccharides,[86] iridoid glycosides[87] and aryl glycosides;[88] however, only modest results were obtained. Obviously, as stated earlier,[1] the possibilities of this reaction are not exhausted. Therefore renewed interest in this reaction seems promising.[89]

Other 1,*x*-anhydro sugars ($x > 2$), possessing lower ring strain, exhibit lower reactivity.[1]

1.2.4 THE TRICHLOROACETIMIDATE METHOD AND OTHER ANOMERIC OXYGEN ACTIVATION METHODS FOR GLYCOSIDE SYNTHESIS

1.2.4.1 Introduction and Earlier Examples of Oxygen Activation

The requirements for glycoside synthesis introduced in Section 1.2.3.1 are obviously not met by any of the methods described. However, it seems that the general strategy for glycoside synthesis is reasonable, namely: (i) that the first step should involve a sterically uniform activation of the anomeric center with formation of a stable glycosyl donor having either an α- or β-structure; and (ii) that the second step should involve a catalyzed, sterically uniform, irreversible glycosyl transfer to the acceptor, proceeding with either retention or inversion at the anomeric center in high chemical yield and without affecting other bonds.

Apart from the direct acid activation (Scheme 1, path a) or acid-supported anomeric oxygen exchange for a leaving group (Scheme 1, path b), base-catalyzed transformation of the anomeric oxygen into a good leaving group (Scheme 1, path c) should be possible. Therefore, it is not surprising that 1-*O*-toluenesulfonylation has been known for a long time.[90] However, these compounds were prepared by reaction of the corresponding α-glycosyl halides with silver toluenesulfonate, providing predominantly α-toluenesulfonates; their use in glycoside synthesis could not gain any general importance even though several variations were investigated; for instance, introduction of electron-withdrawing *O*-protection to increase the S_N2 character of glycoside synthesis[1] or the use of a better leaving group.[1] The amounts of reagent and the difficult stereocontrol of both intermediate and product prevented a broader application of glycosyl sulfonates. Apparently the route *via* glycosyl halides and their activation with silver triflate[91] (see Section 1.2.3.2), demonstrating the close relation of these methods, is considerably more efficient.

Glycosyl transfer in nature takes place *via* glycosyl pyrophosphate or phosphate derivatives of nucleosides.[92] Surprisingly, only a few nonenzymic investigations with glycosyl phosphates have appeared.[93] The imitation of specific enzymatic processes in the laboratory requires an arsenal of enzymes which is not as yet available. However, interesting investigations with glycosyl transferases and also with glycosyl hydrolases have been reported.[94]

Studies on 1-*O*-activation with the Mitsunobu reagent have not attained general importance.[1]

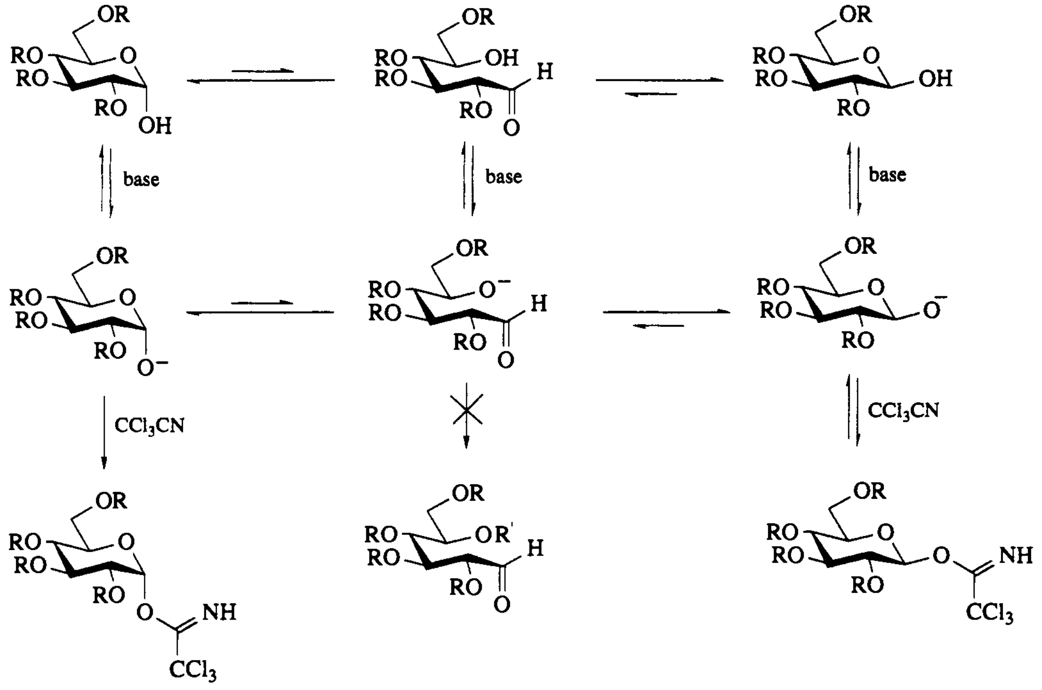
Activation of the anomeric oxygen by 1-*O*-acylation results in relatively low glycosyl donor properties. Therefore, either high temperatures in glycoside synthesis (carbonate activation[95]) or strong acidic catalysts are required. The acid lability of the sugar can be lowered by *O*- and *N*-acetylation, *O*-benzoylation and *N*-phthalimidoylation respectively, providing neighboring group active protective groups. This approach ultimately leads to the conditions of the Fischer–Helferich method (Scheme 1), which does not require a 1-*O*-activated intermediate but builds up the glycosyl donor potential solely by the action of strong acids. Thus the conversion of 1-*O*-acylated sugars into simple *O*-glycosides was successfully performed with the help of Lewis acids, for instance $ZnCl_2$, $SnCl_4$, $FeCl_3$, $BF_3{\cdot}OEt_2$ and Ph_3CClO_4.[1] In recent years the use of trimethylsilyl triflate as catalyst has afforded good results for *O*-[5,96] and *N*-glycoside[97] synthesis. The simplicity of the procedure offers valuable additions to glycoside and saccharide synthesis.

1-*O*-Silylation, for instance, providing 1-*O*-trimethylsilyl glycosides from 1-*O*-unprotected sugars in an anomerically pure form, has been shown by Tietze and coworkers to be useful in phenyl glycoside and 1,1′-diacetal (see Section 1.2.5) synthesis with *O*-silylated acceptors[98] and trimethylsilyl triflate as catalyst. The diastereoselectivity was dependent on *O*-protection.

The synthesis of orthoesters from 2-*O*-acylglycosyl halides and their mercury salt catalyzed rearrangement to glycosides and saccharides have been known for a long time.[5,9] The alkylating character, known for orthoesters especially under acidic conditions, generates the glycosyl donor properties. Thus, carboxylic acids furnish 1-*O*-acyl compounds.[99] The development of the orthoester method by Kochetkov and coworkers[100] has exhibited one major disadvantage, the formation of 2-*O*-unsubstituted sugars by a competing acid attack at the 2-*O*-atom. This side reaction could be overcome by formation of the acyloxonium intermediate and trapping it with cyanide or with an alkylthio group. Then *O*-trityl sugars as acceptors and trityl perchlorate or trityl tetrafluoroborate as coactivator result in good yields of 1,2-*trans*-linked disaccharides of glucose, galactose, mannose and rhamnose.[100]

1.2.4.2 The Trichloroacetimidate Method:[1,2] Derivation of New Principles for Glycoside Synthesis; Trichloroacetimidate Formation

The anomeric oxygen activations described above could not fulfill the requirements put forward. Either they failed to provide both activated intermediates or both anomeric glycosides were not obtained. Obviously, for a stereocontrolled activation of the anomeric oxygen, the anomerisation of the 1-OH, or the 1-O⁻, group in the presence of base has to be taken into account (Scheme 16). Thus, in a reversible activation process and with the help of kinetic and thermodynamic reaction control both activated anomers should eventually be obtainable.



Scheme 16

These considerations suggested that pyranoses and furanoses should undergo base-catalyzed addition directly and in a stereocontrolled manner to suitable triple bond systems A≡B (or compounds containing cumulative double bond systems A=B=C, Scheme 1, path c). Only instability of aldehydic intermediates in basic media and insufficient or undifferentiated reactivities of the α- and β-alkoxides seemed to lower the expectations for a stereocontrolled anomeric *O*-activation.

The formation of stable *O*-activated intermediates can be promoted by independent catalysis of the activation and glycosylation steps. Thus, after basic activation and trapping of the *O*-activated intermediates (first step), mild acid treatment, leading to irreversible acetal formation (second step), remains as the simplest form of catalysis for the glycosylation. The stable intermediates thus obtained in the first step should, by appropriate choice of the centers A and B (or A, B and C), have good glycosyl donor properties in the presence of acid. The water liberated in the glycoside formation is transferred, in two separate steps, to the activating agent A≡B (or A=B=C), thus providing the driving force for the reaction. This concept should fulfill the requirements given above for a good glycoside or saccharide synthesis, as demonstrated by the trichloroacetimidate method.

Electron deficient nitriles such as trichloroacetonitrile (A≡B; A = N, B = CCl_3) are known to undergo direct and reversible base-catalyzed addition of alcohols to give *O*-alkyl trichloroacetimidates.[1] This imidate synthesis has the advantage that the free imidates can be isolated as stable adducts, which are less sensitive to hydrolysis than their salts.

A detailed study of trichloroacetonitrile addition to 2,3,4,6-tetra-*O*-benzyl-D-glucose showed[1,101] that from the 1-oxide the β-trichloroacetimidate is formed preferentially or even exclusively in a very rapid and reversible addition reaction (Scheme 16). However, this product anomerizes in a slow, base-catalyzed reaction (*via* retroreaction, 1-oxide anomerization and renewed addition) practically completely to the α-trichloroacetimidate, with the electron-withdrawing 1-substituent in an axial position as favored by the thermodynamically efficient anomeric effect.[101,102] Thus with different bases, for instance K_2CO_3 and

NaH, both anomers can be isolated in pure form and high yield *via* kinetic and thermodynamic reaction control. Both anomers are thermally stable and can be stored easily.

The higher nucleophilicity of the β-oxide can be attributed to a steric effect in combination with a kinetically effective stereoelectronic effect, resulting from repulsions of lone electron pairs or from dipole effects (Scheme 17).[101,102] This effect should be more pronounced in β-pyranosyl oxides than in β-pyranosides due to differences in oxygen lone pair orbitals. In addition, this kinetic anomeric effect should be particularly efficient in the β-mannopyranosyl oxide where the thermodynamic anomeric effect, favoring the α-anomer, is also stronger. This is confirmed in anomeric *O*-alkylation (see Section 1.2.5).

(a) Dipole–dipole interaction

(b) Lone-pair–orbital interaction

Scheme 17 Enhanced nucleophilicity of β-oxides (kinetic anomeric effect)

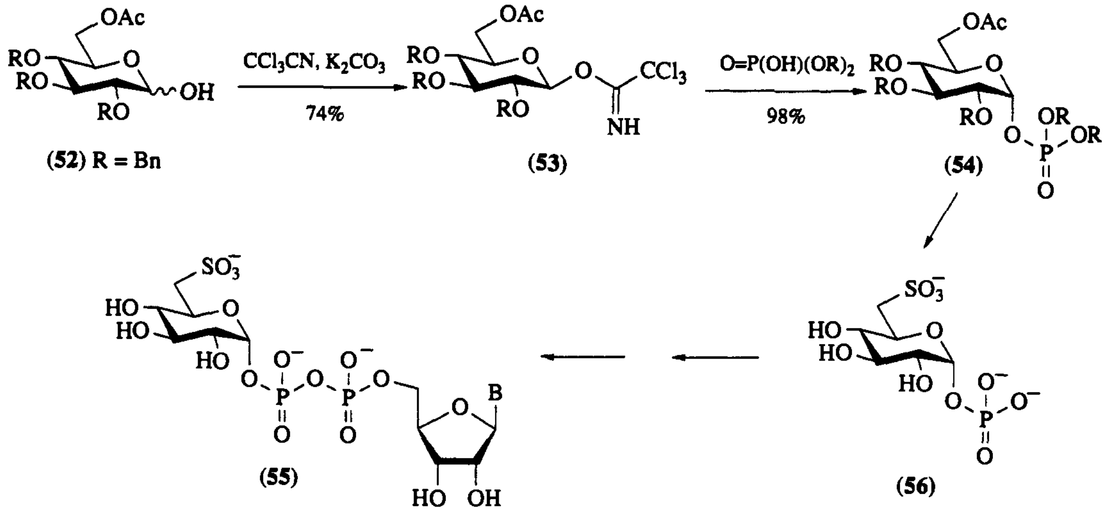
The stereoselective anomeric *O*-activation of carbohydrates and their derivatives through the formation of *O*-glycosyl trichloroacetimidates is applicable to all important *O*-protected hexopyranoses (Glc, Gal, Man, Fuc, Rha, GlcN, GalN), hexofuranoses, pentopyranoses and pentofuranoses, as well as to glucuronic acid, galacturonic acid and muramic acid, commonly providing stable compounds in a stereocontrolled manner. Thus the requirement for the first step, generation of an appropriate glycosyl donor, is fulfilled.

1.2.4.3 The Trichloroacetimidate Method: Application to Glycoside and Saccharide Synthesis

Ultimately, the significance of the *O*-glycosyl trichloroacetimidates is derived solely from their glycosylation potential under acidic catalysis. This potential has indeed been confirmed in various laboratories.[1,10–12,82,103–110]

The direct glycosylation of Brønsted acids is a particularly advantageous property of these new glycosyl donors.[1] Carboxylic acids usually react with inversion of configuration at the anomeric center to give *O*-acyl compounds without addition of any catalyst. The uncatalyzed glycosyl transfer from *O*-glycosyl trichloroacetimidates to phosphoric acid mono- and di-esters opens a simple route to glycosyl phosphates and glycophospholipids,[111] which are of interest as intermediates in biological glycosyl transfer and as constituents of cell membranes. Thus, from trichloroacetimidate (**53**; Scheme 18) the glycosyl phosphate (**54**) was obtained[112] and transformed *via* (**56**) into (**55**), which is an important intermediate in plant sulfolipid formation.[113] The anomeric configuration of the phosphate products obtained is determined by the acidity of the phosphoric acids applied; weak acids provide the inversion products, stronger acids lead directly to the thermodynamically more stable anomer. Phosphonates and phosphinates can be obtained similarly.[114]

Alcohol components for reaction as glycosyl acceptors generally require the presence of an acidic catalyst.[1] Boron trifluoride etherate at –40 °C to room temperature in dichloromethane or dichloromethane/hexane as solvents has proved to be very suitable with regard to yield and diastereoselectivity. This is exemplified by many successful applications of this method, until now mainly to hexopyranoside synthesis.[1,2] With neighboring group participation of 2-*O*- or 2-*N*-protective groups the 1,2-*trans*-products were obtained; with the nonparticipating 2-*O*-benzyl protective group or with the 2-azido-2-deoxy group inversion of configuration at the anomeric center was found to be preferred. For 1,2-*cis*-products (α-hexopyranosides of Glc, Gal, GlcN, GalN, Man, Rha, Fuc) good results were obtained *via* inversion of

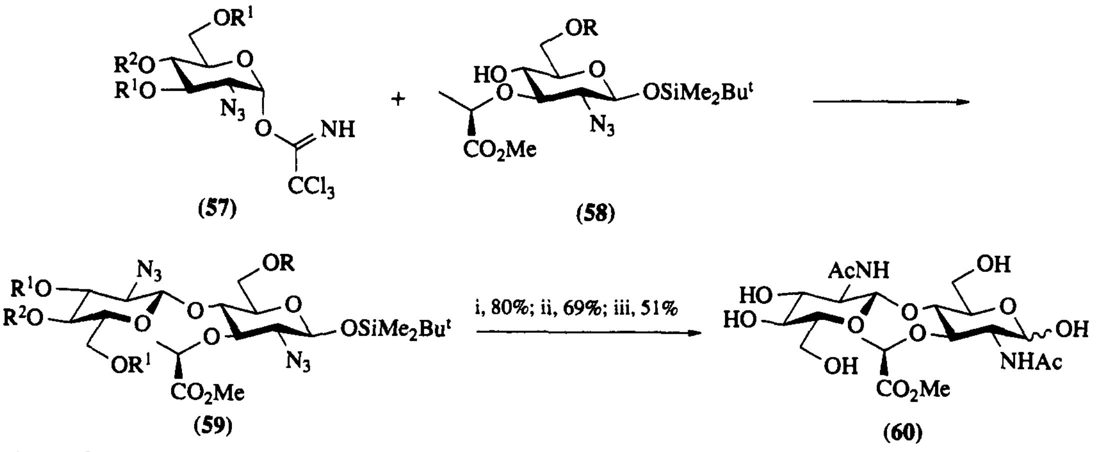


Scheme 18

configuration at the anomeric center or performing the reaction with diethyl ether as the solvent and trimethylsilyl triflate as the catalyst.[115]

Because of the great importance of glycoconjugates as cell wall constituents of bacteria and as cell membrane constituents of all vertebrates (essentially glycosphingolipids and glycoproteins), a few applications to their syntheses will be discussed.

Amongst cell wall constituents of bacteria the cell wall peptidoglycan (called murein) has become increasingly important.[116] This peptidoglycan chain has a β(1 → 4)-linked glycan chain consisting of alternating *N*-acetylglucosamine and *N*-acylmuramic acid units (Scheme 19), which are cross-linked by a peptide chain (*e.g.* by L-Ala-D-iso-Glu-*meso*-DAP-D-Ala and Gly). The resulting peptidoglycan network and fragments of it exhibit pronounced immunostimulatory and antitumor properties. Therefore, the



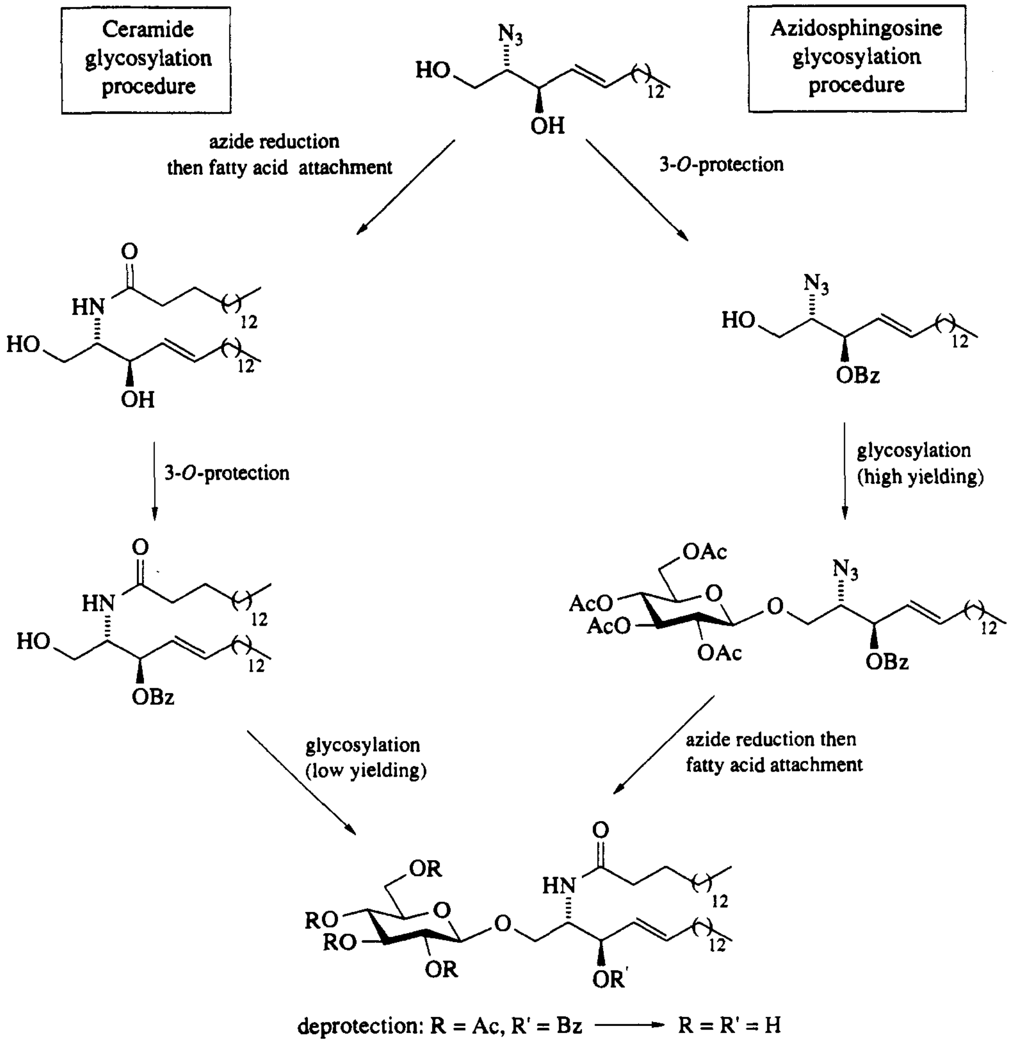
R^1	R^2	R	Catalyst	β (%)	α (%)
Bn	Bn	$SiMe_2Bu^t$	$BF_3{\bullet}OEt_2$	low	low
Bn	Bn	$SiMe_2Bu^t$	Me_3SiOTf	39(57)	23(33)
Bn	Bn	Bz	Me_3SiOTf	8	16
Bn	Bn	Bn	$BF_3{\bullet}OEt_2$	76	–
Bn	Allyl	Bn	$BF_3{\bullet}OEt_2$	86	–

i, TBAF, Ac_2O, THF; ii, $NiCl_2$, $B(OH)_3$, $NaBH_4$, Ac_2O; iii, NaOMe, MeOH then Pd/C, MeOH, dioxane

Scheme 19

synthesis of partial structures is of interest. For the synthesis of the GlcNAc β(1 → 4) MurNAc disaccharide (Scheme 19),[117] based on the trichloroacetimidate method, the donor (**57**) and the acceptor (**58**) were treated with an acidic catalyst. However, as indicated in the table in Scheme 19, the result was very much dependent on the 6-*O*-protection of the acceptor (**58**). Bulky groups, *e.g.* *t*-butyldimethylsilyl (TBDMS), or electron-withdrawing groups, *e.g.* benzoyl (Bz), did not improve the known low reactivity of the 4-OH group in glucosamine and derivatives. However, when a benzyl (Bn) group was introduced for 6-*O*-protection, the trichloroacetimidate method afforded in excellent yields and complete β-selectivity the desired disaccharides (**59**). Application of standard deprotection procedures resulted in the GlcNAc β(1 → 4) MurNAc disaccharide (**60**), which had already been synthesized *via* the Koenigs–Knorr procedure.[118]

The glycosphingolipids, being membrane constituents, possess a lipophilic ceramide (*N*-acylated sphingosine) moiety, which is part of the outer plasma membrane bilayer. The hydrophilic oligosaccharide moiety is therefore located on the outer membrane surface (see Section 1.2.1). After several investigations it became obvious that the best method for the glycosylation of these compounds proved to be the trichloroacetimidate method, which afforded better yields in glycosphingolipid syntheses than syntheses applying the Koenigs–Knorr method and variations of it.[119] This ceramide glycosylation procedure (Scheme 20) was recently also successfully applied by Ogawa and coworkers, for instance, to the synthesis of the G$_{M3}$ ganglioside and other tumor-associated antigens.[108] However, the yields are still not satisfactory, even though an improvement could be obtained by a sugar 2-*O*-pivaloyl group.[120] Therefore, based on a new sphingosine synthesis,[121] a versatile azidosphingosine glycosylation method was introduced by us[2,122] which was high yielding even in a recently performed *lactoneo*tetraosyl ceramide



Scheme 20 Glycosphingolipid synthesis

synthesis.[123] This is also exhibited in the synthesis of cerebrosides (**64**) and (**65**) from *Tetragonia tetragonoides* possessing antiulcerogenic activity (Scheme 21).[124] The glucosylation with the *O*-acetylated trichloroacetimidate (**61**) to yield the intermediates (**62**) and (**63**) was β-specific.

1.2.4.4 The Trichloroacetimidate Method: Conclusions

The requirements for new glycosylation methods, outlined at the beginning, are practically completely fulfilled by the trichloroacetimidate method. This is indicated by the many examples and can be summarized as follows.

Features of the activation of the anomeric center are: (i) convenient base-catalyzed trichloroacetimidate formation; (ii) controlled access to α- or β-compounds by choice of the base; and (iii) thermal stability of α- and β-trichloroacetimidates up to room temperature (if required, silica gel chromatography can be performed).

Features of the glycosyl transfer are: (i) catalysis by acids (mainly Lewis acids) under very mild conditions; (ii) irreversible reaction; (iii) that other glycosidic bonds are not affected; (iv) usually high chemical yield (reactivity corresponds to the halogenose/silver triflate system); and (v) that stereocontrol of glycoside bond formation is mainly good to excellent: (a) participating protective groups give 1,2-*trans*-glycopyranosides, yielding β-glycosides of Glc, GlcN, Gal, GalN, Mur, Xyl, 2-deoxy-Glc and α-glycosides of Man, Rha; and (b) with nonparticipating protective groups, $BF_3{\cdot}OEt_2$ as catalyst favors inversion of anomer configuration, yielding β-glycosides of Glc, GlcN, Gal, GalN, Xyl, Mur and GlcA, while TMSOTF as catalyst favors the thermodynamically more stable anomer, yielding α-glycosides of Glc, GlcN, Gal, GalN, Man, Fuc and Mur.

Besides the oxygen nucleophiles discussed here, nitrogen,[125] carbon,[126] halogen,[1,2] sulfur[127] and phosphorus nucleophiles[128] have also been used successfully as glycosyl acceptors for this reaction, illustrating in terms of stability, reactivity and general applicability the outstanding glycosyl donor properties of *O*-glycosyl trichloroacetimidates, which resemble in various aspects the natural nucleoside diphosphate sugar derivatives. Thus, the base-catalyzed *O*-glycosyl trichloroacetimidate formation has become a very competitive alternative to glycosyl halide and glycosyl sulfide formation.

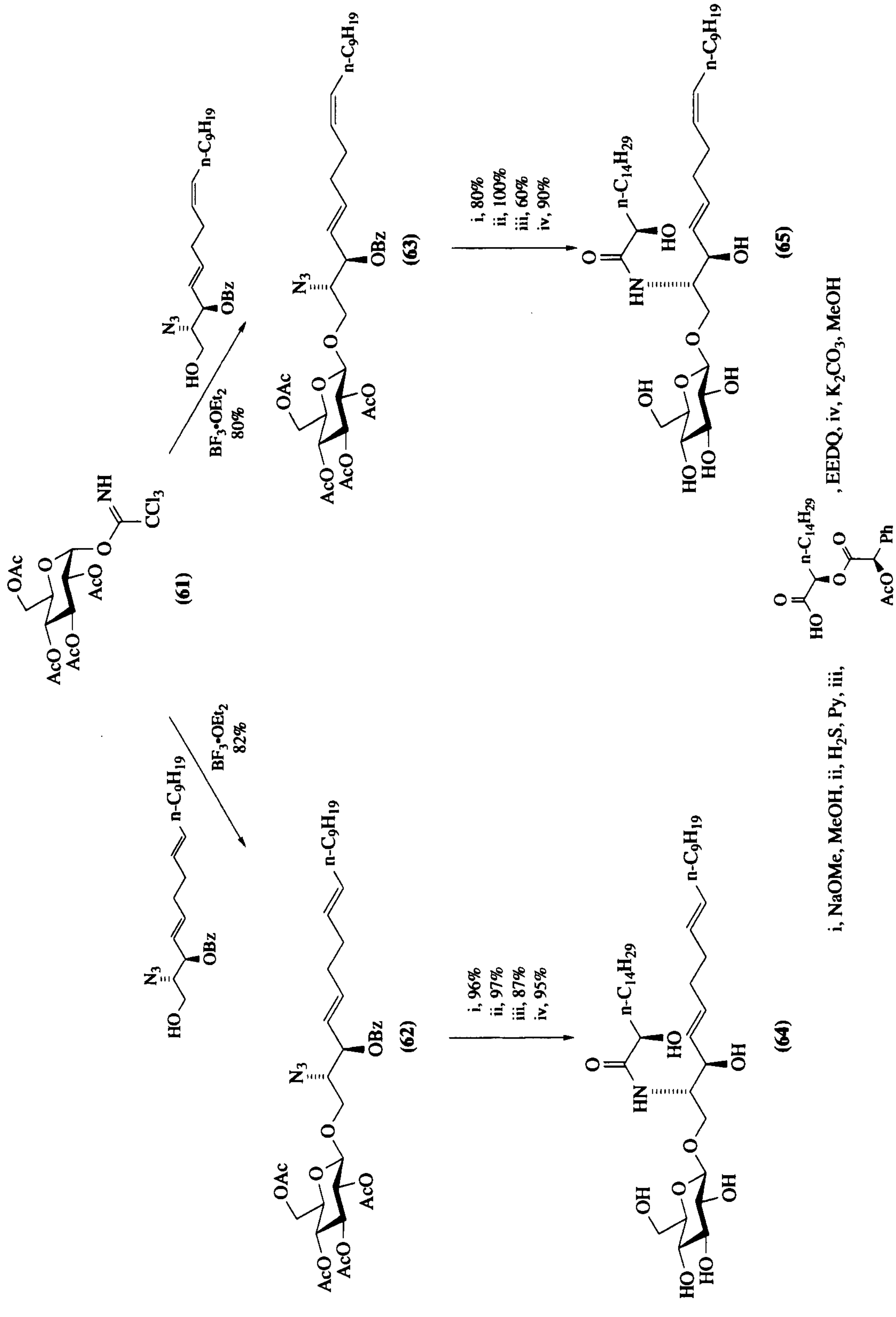
1.2.4.5 Related Methods

The β-glycosyl imidates prepared by Sinay and coworkers[129] from α-glycosyl halides and *N*-substituted amides (particularly *N*-methylacetamide) using 3 equiv. of silver oxide have proven to be relatively unreactive in acid-catalyzed glycosidations.[5] The reactions proceed with inversion of configuration to form α-glycosidic linkages.[130] Neighboring group active protecting groups such as 2-*O*-acetyl lead to orthoester formation and not directly to the glycoside or saccharide.[130] The laborious synthesis of these imidates and their comparatively low reactivity have led to only a few special applications.[1,5]

Reactions with the Vilsmeier–Haack reagent,[1] with 2-fluoro-1-methylpyridinium tosylate[131] and with 2-chloro-3,5-dinitropyridine[131] for anomeric *O*-activation were investigated. The last reagent provided a glycosyl transfer method which is most closely related to the trichloroacetimidate method. However, routes for the specific preparation of the corresponding intermediates with the β-configuration have not been developed, and hydroxy groups that are difficult to glycosidate have not been studied to date. The isourea group, generated by carbodiimide reactions,[132] requires drastic conditions for reactions with glycosyl acceptors, limiting their usefulness.

1.2.5 THE ANOMERIC *O*-ALKYLATION METHOD[1,2]

The direct anomeric *O*-alkylation of furanoses and pyranoses with simple alkylating agents, for instance excess methyl iodide and dimethyl sulfate, has long been known.[1] Depending on the reaction conditions, either α- or β-glycosides are formed. A case of trehalose formation can be interpreted similarly.[1] Surprisingly, no studies to use this simple method in more complex glycoside and saccharide syntheses have been reported previously. At first direct anomeric *O*-alkylation (Scheme 1, path d) seemed very unlikely to fulfill all the requirements for a glycoside and saccharide synthesis. When all the remaining hydroxy groups are blocked by protecting groups, the ring–chain tautomerism between the two anomeric forms and the open-chain form (Scheme 17) already give three possible sites for attack of the alkylating agent. Thus the yield, the regioselectivity and the stereoselectivity of the direct anomeric *O*-alkylation



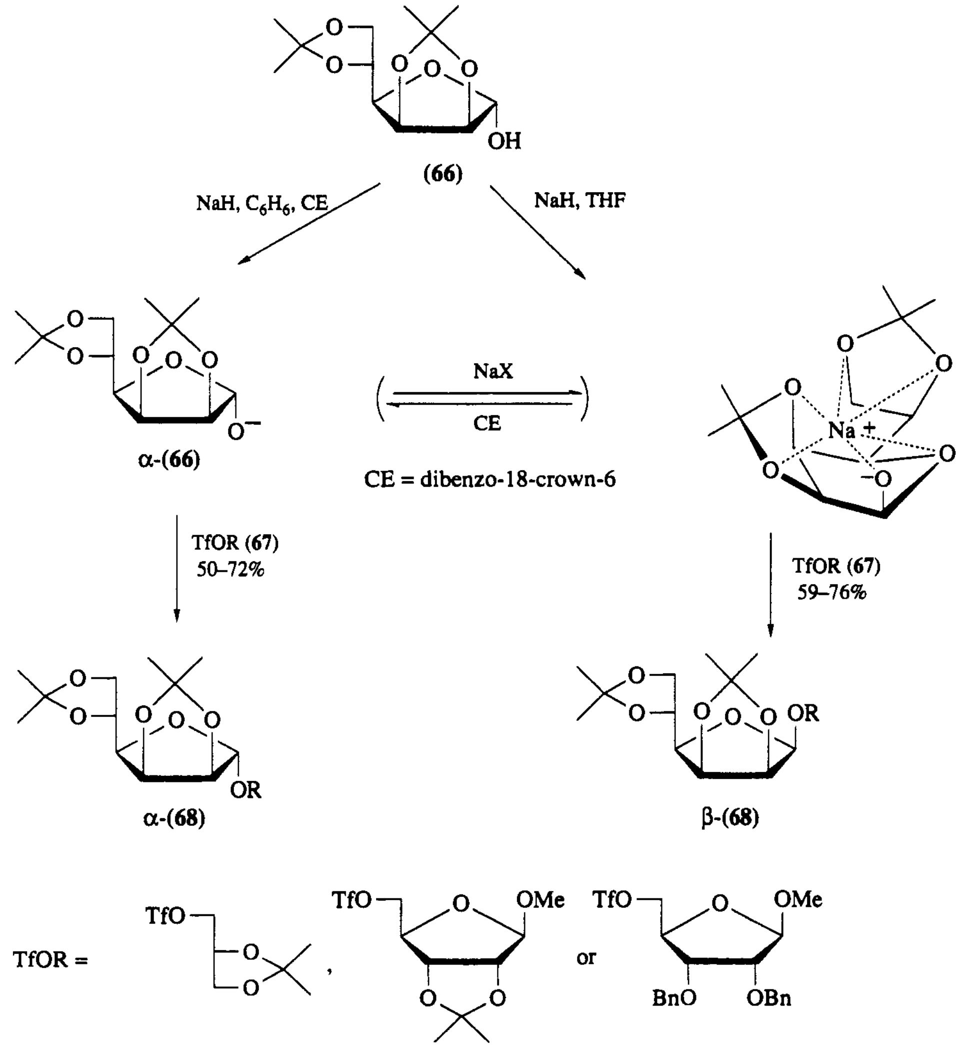
i, NaOMe, MeOH, ii, H_2S, Py, iii, , EEDQ, iv, K_2CO_3, MeOH

Scheme 21

are governed by at least the following factors: (i) the stability of the deprotonated species; (ii) the ring–chain tautomeric equilibrium and its dynamics; and (iii) the relative reactivities of the three *O*-deprotonated species. Due to the irreversibility of the *O*-alkylation reaction, a kinetically regio- and stereo-controlled reaction course is required for selective product formation.

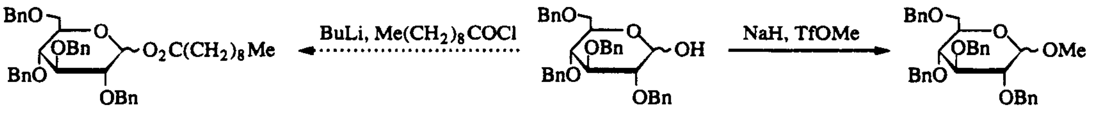
The first experiments with iodides revealed that better alkylating agents are required. Excellent reactivity was found for triflates providing, for instance with 2,3-*O*-isopropylidene-D-ribose and derivatives, depending on the reaction conditions, very high yields of α- and β-disaccharides respectively.[133]

Even partial *O*-protection was compatible with this reaction. The stereocontrol was effected by intramolecular metal–ion complexation. This could be substantiated by investigations on D-mannofuranose (**66**; Scheme 22).[134] Structure β-(**66**) shows that the β-oxide has practically ideal crown ether geometry, which probably stabilizes the β-configuration in less solvating media but decreases the reactivity.[134] Good β-selectivity with especially reactive electrophiles is thus to be expected under kinetic control. Accordingly, with the triflates (**67**) the β-D-mannofuranosides β-(**68**) were obtained almost exclusively. Furthermore, the expected influence of the reactivity of the electrophile on the anomeric ratio could be confirmed. If the intramolecular complexation is responsible for the high β-selectivity, more strongly solvating conditions should promote the α-selectivity. This was confirmed by the addition of an equimolar amount of crown ether. The alkylating agents then gave exclusively the corresponding α-D-mannofuranosides α-(**68**). Added sodium iodide had a competitive effect. Thus, for the furanoses studied, the stereocontrol results primarily from steric and chelate effects.



Scheme 22

2,3,4,6-Tetra-*O*-benzylglucose (Scheme 16) exists at room temperature in benzene or THF in an α:β anomeric ratio of ≈4:1.[135,136] This ratio is presumably not much changed on 1-*O*-deprotonation. However, when the acylation of the 1-*O*-lithiated species with decanoyl chloride is studied as a function of solvent and temperature, other relations are obtained (Figure 1).[135,138] Higher temperatures, especially in benzene, favor the β-product. Essentially the same result is obtained with the sodium salt and methyl triflate as alkylating agent.[138] The rate of α/β-anomerization and, due to the kinetic anomeric effect, the increased nucleophilicity of the β-oxide are responsible for this result. The addition of crown ether had no significant influence. Therefore, intramolecular complexation probably does not play a major role.[138]



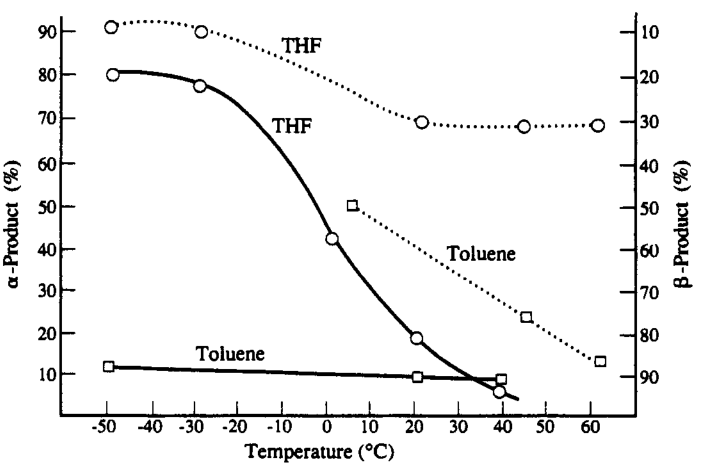
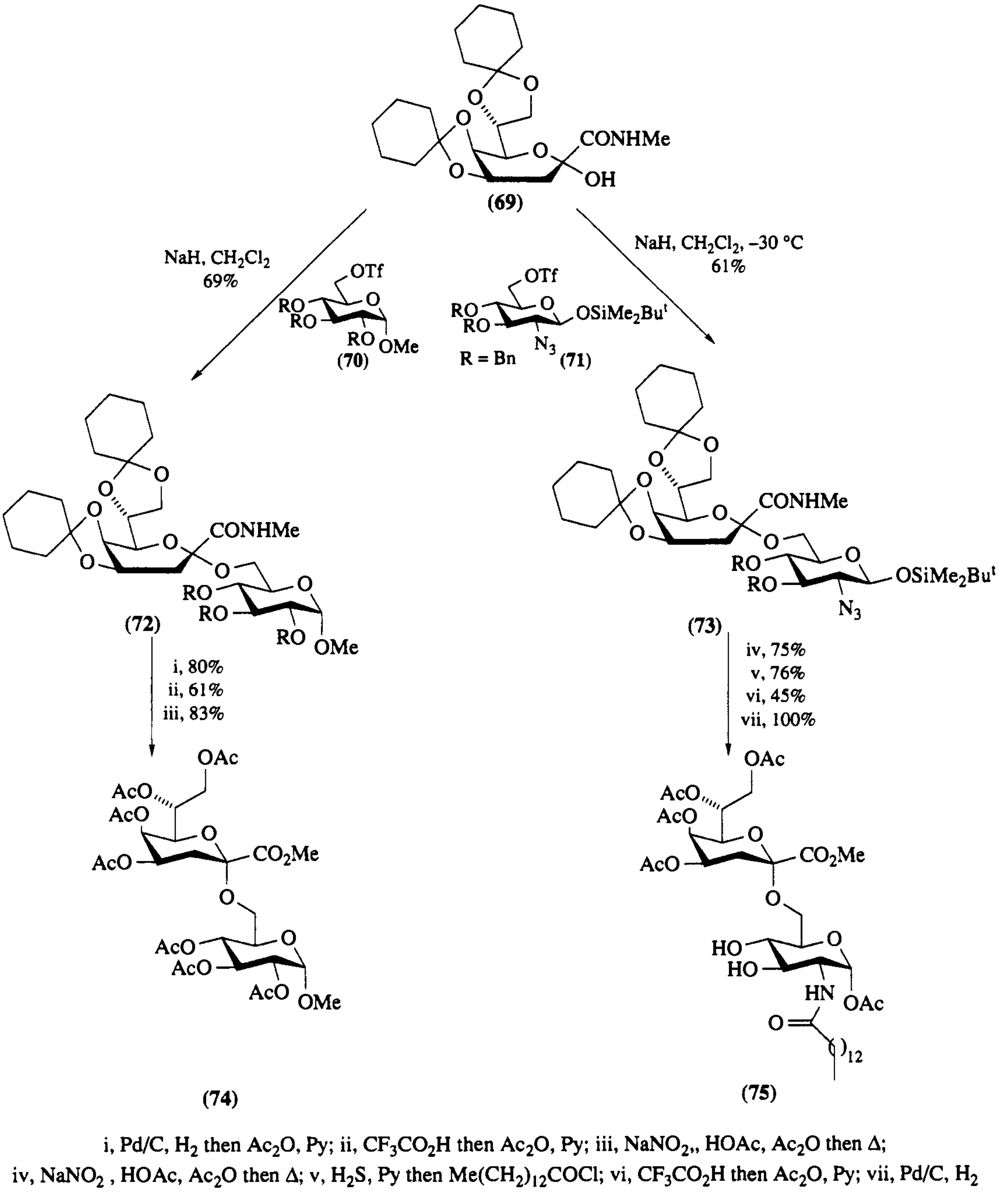


Figure 1 Reaction of 2,3,4,6-tetra-*O*-benzyl-D-glucose in the presence of base with *n*-decanoyl chloride[135] (·········) and with methyl triflate[138] (———) as a function of temperature and solvent

Thus, for instance, 2,3,4,6-tetra-*O*-benzyl-D-glucose, 6-*O*-unprotected 2,3,4-tri-*O*-benzyl-D-glucose and 2,3,4-tri-*O*-benzyl-D-galactose, 2,3,4,6-tetra-*O*-benzyl-D-mannose and 2,3,4-tri-*O*-benzyl-D-xylose were selectively transformed into the corresponding β-D-pyranosides, providing the corresponding glycosides and disaccharides in high yields. With bulky groups in the 6-*O*-position even α-selectivity could be reached in some cases.[1,2,133,134,137–139] Thus, the direct anomeric *O*-alkylation of sugars by primary triflates has become one of the most simple methods for stereocontrolled glycoside and saccharide synthesis. 1,1′-Diacetal formation has also been suggested to follow this reaction course.[1] However, further experiments are required to extend this method to high yield reactions with secondary triflates.[1]

The hydrophilic part of lipopolysaccharides consists of a complex oligosaccharide which is linked *via* KDO (3-deoxy-D-manno-2-octulosonate; α(2 → 6′)-connection) to a β(1 → 6)-linked glucosamine disaccharide.[7] The application of the Koenigs–Knorr method to generate this type of α-glycoside bond with KDO-halogenoses as donors has mainly led to unsatisfactory results due to hydrogen halide elimination and β-glycoside formation.[140] (Similar problems are encountered with neuraminic acid.) Better results were recently reported for fluoride as the leaving group.[141]

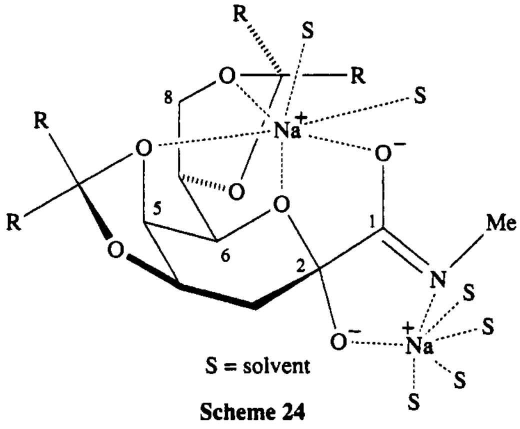
Base-catalyzed anomeric *O*-activation of KDO seemed to cause serious problems due to ring–chain tautomerism and due to the presence of the additional carboxylate group. However, for the application of the anomeric *O*-alkylation procedure solutions to these problems could be found.[142] The 4,5:7,8-di-*O*-cyclohexylidene derivative (**69**; Scheme 23) prefers the boat conformation providing, with the carboxamide group and the oxygens of C-5 and C-8, a tetradentate chelate ligand for the complexation of metal ions (Scheme 24). This complexation, generating dianionic species, offers high nucleophilic reactivity and α-diastereoselectivity, providing, with the 6-*O*-triflate of glucose (**70**) and glucosamine derivative (**71**), the desired α(1 → 6)-connected disaccharides (**72**) and (**73**) in good yield; they were transformed into compounds (**74**) and (**75**), respectively.



i, Pd/C, H_2 then Ac_2O, Py; ii, CF_3CO_2H then Ac_2O, Py; iii, $NaNO_2$,, HOAc, Ac_2O then Δ;
iv, $NaNO_2$, HOAc, Ac_2O then Δ; v, H_2S, Py then $Me(CH_2)_{12}COCl$; vi, CF_3CO_2H then Ac_2O, Py; vii, Pd/C, H_2

Scheme 23

In conclusion, the direct anomeric *O*-alkylation is an especially simple procedure for glycoside and saccharide synthesis, giving generally high yields and excellent diastereoselectivities, depending on intramolecular complexation, rate of anomerization and varying nucleophilicities of the α- and β-anomeric oxides. The limitation to primary alkylating agents will hopefully be overcome by different reaction conditions.



S = solvent

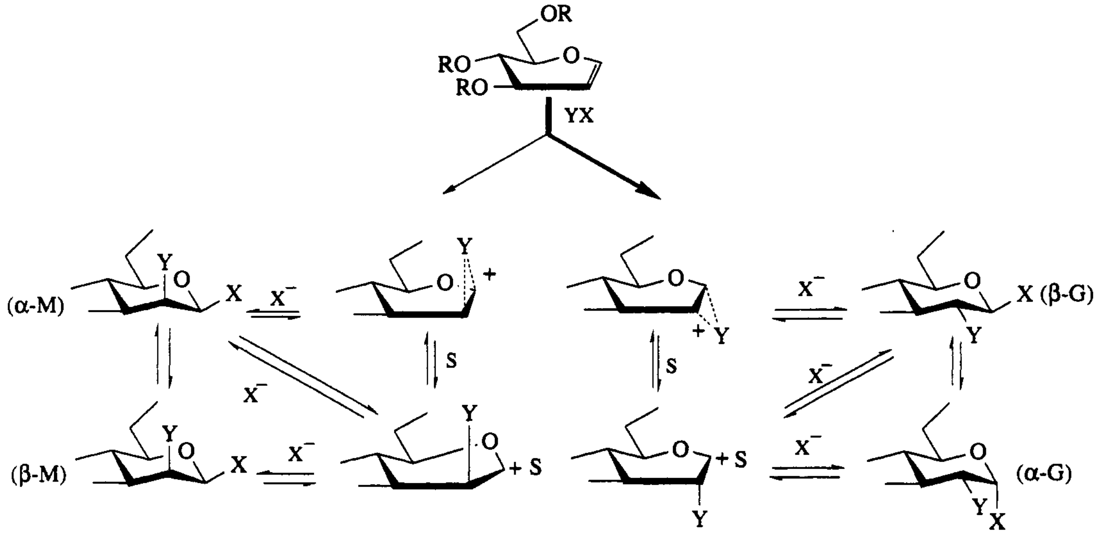
Scheme 24

1.2.6 SPECIAL METHODS

For acetal formation, besides the methods discussed thus far, further possibilities exist. For instance, oxidation/reduction methods could be envisaged. Thus, as described,[143] the acceptor can be oxidized to the acid. Anomeric *O*-acylation is a convenient process (see Section 1.2.4), requiring in the final step reduction of the acyloxy group to the alkoxy group, which could be performed in simple cases with borane. Similarly the donor could be oxidized to the lactone stage (and derivatives) and then acceptor addition and reduction would lead to the desired product. However, the efficiency of such methods has to be evaluated on the basis of the existing methodology.

1.2.7 GLYCOSIDES AND SACCHARIDES OF 2-DEOXY SUGARS

With 2-deoxy sugars, which lack an electron-withdrawing 2-substituent and also lack neighboring group participation, generally low stability of the glycosyl halides and low α/β-selectivity in glycoside and saccharide synthesis has been encountered. With modifications these statements are also true for KDO and neuraminic acid, which possess an electron-withdrawing caboxylate group at the anomeric position. (A detailed discussion of these two sugars met in glycoconjugates is beyond the scope of this chapter; for anomeric *O*-alkylation of KDO see Section 1.2.5.) Therefore a temporarily anchimerically assisting group was required in the 2-position, which is most readily introduced starting from glycals. This is demonstrated in Scheme 25 for a D-glucal derivative. Y^+X^- addition can take place from the



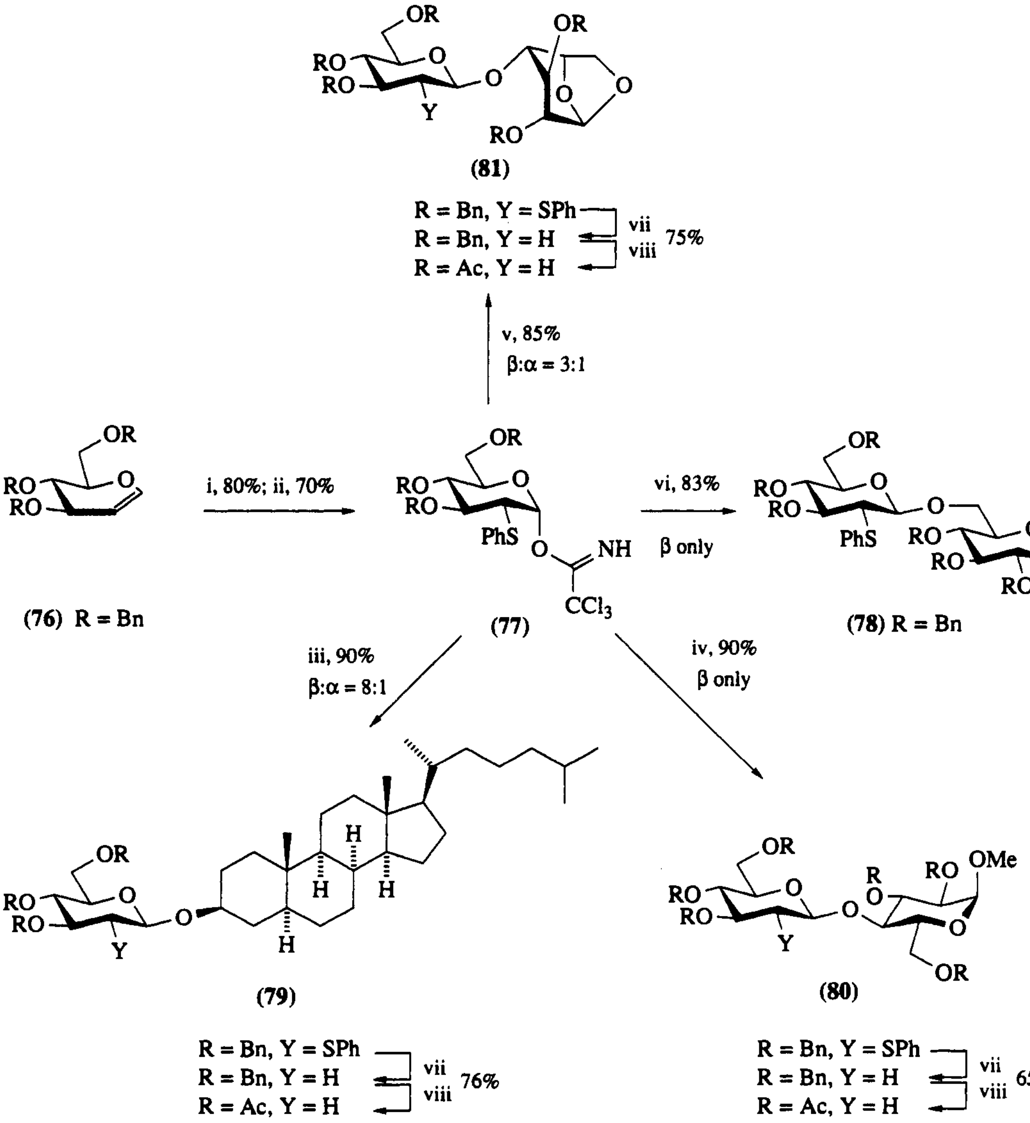
Y = anchimerically assisting, removable group; X = leaving group or HOR' (acceptor); S = solvent

Scheme 25

β-site (Y^+) giving α,β-D-*manno* (M) configuration or from the α-site (Y^+) giving α,β-D-*gluco* (G) configuration. Neighboring group participation of the 2-substituent, Y, favors α-glycoside formation from the *manno* isomers and β-glycoside formation from the *gluco* isomers.

Several YX additions have been investigated. Reaction with iodine, silver salts and base in the presence of the glycosyl acceptor gave mainly the α-isomer.[144] The same result was obtained for *N*-bromosuccinimide,[145] *N*-iodosuccinimide (NIS)[146] and phenylselenyl chloride[147] in acetonitrile in the presence of the glycosyl acceptor. From these methods the NIS method, introduced by Thiem and coworkers,[146] has gained relatively wide use. Phenylsulfenate ester addition[148] gave varying *manno*:*gluco* addition ratios, resulting, after removal of the temporary phenylthio group, in α:β glycoside ratios from 1:1 to 1:4.

The recent addition of benzenesulfenyl chloride[149] to 3,4,6-tri-*O*-benzyl-D-glucal (**76**) resulted in practically complete *gluco* formation, providing easy access to the corresponding α-trichloroacetimidate (**77**; Scheme 26),[149] which turned out to be an exceptionally reactive glycosyl donor, even though the com-



i, PhSCl, THF then Na_2CO_3, H_2O/THF, Δ, 2 h; ii, CCl_3CN, NaH; iii, HOR', $BF_3{\bullet}OEt_2$, r.t.; iv, HOR', $BF_3{\bullet}OEt_2$, 0 °C; v, HOR', $BF_3{\bullet}OEt_2$, –95 °C; vi, HOR', $BF_3{\bullet}OEt_2$, –40 °C; vii, Raney Ni, THF; viii, Pd/C, H_2, EtOAc then Py, Ac_2O

Scheme 26

pound is relatively stable. With various glycosyl acceptors the desired 2-deoxy-β-D-glucopyranosides (**78**–**81**) were obtained in high yields and with good β-selectivities at temperatures as low as –95 °C. Previous methods for 2-deoxy-β-glucopyranoside synthesis required the independent generation of 2-bromo-2-deoxy- or 2-deoxy-2-phenylthioglucopyranosyl halides.[150]

ACKNOWLEDGEMENT

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1.3

Synthesis of Amines and Ammonium Salts

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1.3.1 INTRODUCTION

This chapter covers only the reactions of nitrogen nucleophiles with substrates having appropriate leaving groups and with epoxides and aziridines.[1] The reactions of electrophiles with the anion on the carbon atom adjacent to the nitrogen atom, have recently attracted attention in connection with asymmetric synthesis of chiral amines.[2a–2c] To keep this chapter to a reasonable length, however, this subject is not described. For the same reason, rearrangement reactions leading to amines and their derivatives are not included.[2d,2e]

1.3.2 ALKYLATION OF AMINES AND AMINE SYNTHONS

1.3.2.1 Alkylation of Amines by Alkyl Halides

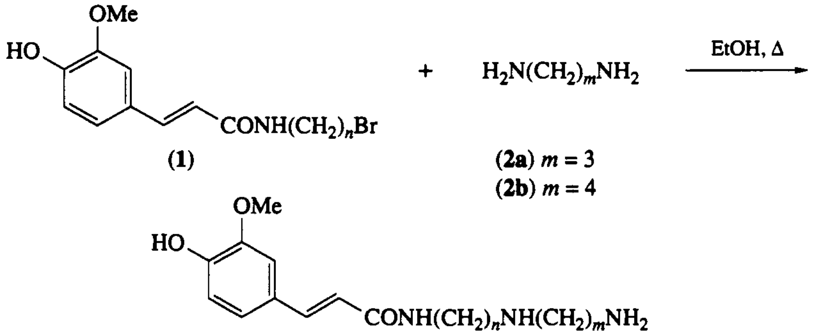
Alkylation of ammonia and another amine is, in principle, the most straightforward route to an amine. It is well known, however, that the value of this method in the laboratory is sometimes limited because of concomitant polyalkylation (Scheme 1).

For this reason, primary amines are generally prepared *via* azides or by the Gabriel synthesis and related procedures which will be described in Section 1.3.2.3. For the preparation of secondary amines, a

$$NH_3 + RX \longrightarrow RNH_2 + R_2NH + R_3N + R_4N^+X^-$$

Scheme 1

suitable excess of the amine component is generally used. Thus, the reaction of bromide (**1**) with an excess of 1,3- or 1,4-diamines (**2a**) and (**2b**) afforded the expected polyamine (**3a**) and (**3b**) (Scheme 2).[3]



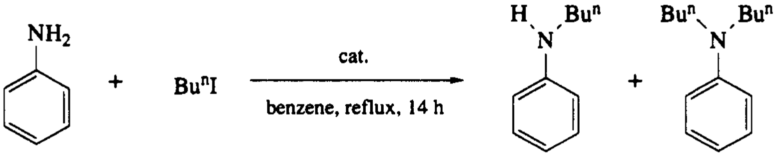
(**1**)

(**2a**) $m = 3$
(**2b**) $m = 4$

(**3a**) $n = 4$, $m = 3$; 68%
(**3b**) $n = 3$, $m = 4$; 49%

Scheme 2

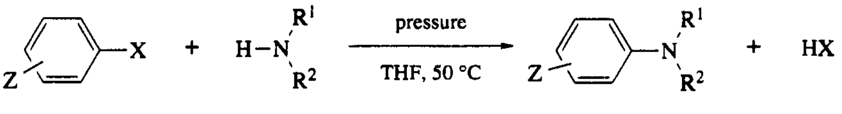
Onaka and coworkers have reported highly selective *N*-monoalkylation of aniline and its derivatives over alkali cation exchanged X- and Y-type zeolites. The intrinsic pore structures of X and Y zeolites are assumed to be responsible for the high selectivity. Linde 3A zeolites cannot promote the alkylation of aniline because of their smaller pore structure (Scheme 3).[4a] Aniline derivatives having strong electron-withdrawing substituents, such as *p*-nitroaniline, which is otherwise hardly alkylated even in the presence of KOH, can be successfully alkylated in benzene.[4b,4c] Celite coated with KF is also effective for the alkylation of amines.[5,6]



cat.,		
KX	(64%)	74:1
KY	(67%)	97:1
NaY	(58%)	120:1
3A	(0.8%)	–

Scheme 3

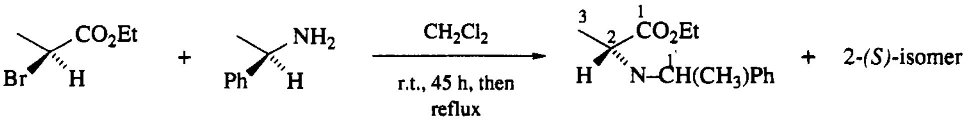
The use of phase-transfer catalysts in the presence of inorganic bases accelerates the alkylation of aromatic amines.[7] High pressure conditions have been used in the arylation of amines. Thus, no reaction took place between *p*-nitrochlorobenzene and acyclic aliphatic amines, such as Bu^nNH_2, Bu^iNH_2, Bu^sNH_2, Bu^tNH_2 and Bu_2NH at 80 °C under 1 atm, while the corresponding secondary and tertiary aromatic amines were obtained under high pressures of 6–12 kbar (1 kbar = 10^5 kPa) in THF at 50 °C for 20 h (Scheme 4). Cyclic amines (morpholine, piperidine and pyrrolidine) showed extremely high reactivity to give the corresponding *N*-*p*-nitrophenyl derivatives in quantitative yields under 6.0 kbar.[8]



X = Cl, Br, I; Z = *p*-NO_2, *o*-NO_2, *m*-NO_2, *p*-CN, *p*-Ac

Scheme 4

The amination of the α-carbon atom of carboxylic acid derivatives has been extensively studied by Effenberger and coworkers.[9] Ethyl (*S*)-α-bromopropionate reacted with (*R*)-1-phenylethylamine to give (2*R*,1′*R*)- and (2*S*,1′*R*)-*N*-(1′-phenylethyl)alanine ethyl ester, *e.g.* (2*R*,1′*R*)-(**4**) and (2*S*,1′*R*)-(**4**). Prolonged reaction time afforded the products in higher yields with decreasing stereospecificity (Scheme 5).

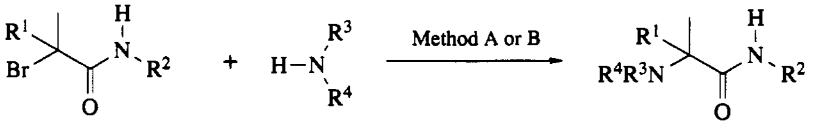


(2*R*,1′*R*)-(**4**) (2*S*,1′*R*)-(**4**)

Reflux (h) (*Yield*, %)	*(2R,1′R)-(4):(2S,1′R)-(4)*
48 (35)	9:1
117 (60)	7:1
248 (80)	5:1

Scheme 5

α-Bromocarboxamide (**5a**) reacted with amines in the presence of NaH (method A) or phase-transfer catalysts (method B) to give α-aminocarboxamides (**6**). Sterically hindered amines, such as *t*-butylamine or diethylamine, can be successfully introduced. Nonionizable amide (**5b**) afforded only the corresponding acrylamide. In view of these results, zwitterions (**7a**) have been assumed as intermediates rather than aziridinones (**7b**; Scheme 6).[10]

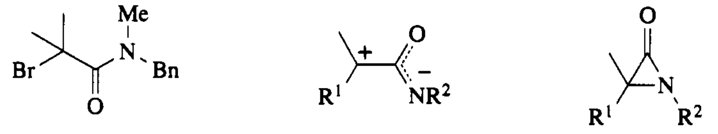


(**5a**) (**6**)

R^1 = Me, Et; R^2 = Bu^t, Bn, Ph

Method A: NaH, THF, 75 min, 66–88%

Method B: NaOH aq. (50%), CH_2Cl_2, Bu$^n_4$NBr, 4–10 h, 68–80%



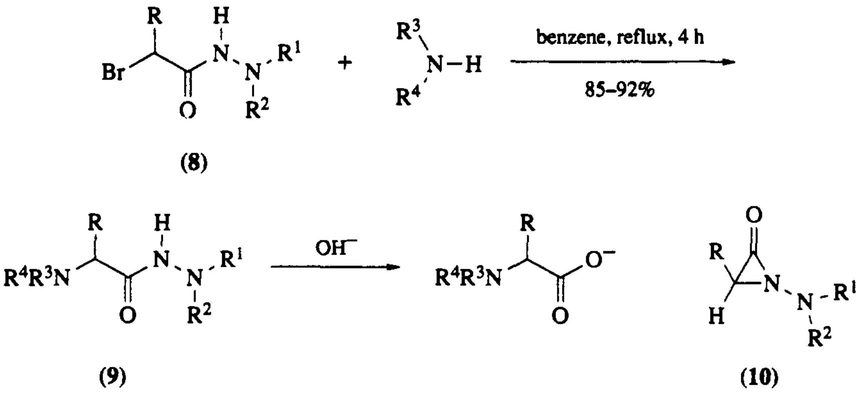
(**5b**) (**7a**) (**7b**)

Scheme 6

α-Bromocarboxyhydrazides (**8**) reacted with amines to give the corresponding α-aminocarboxyhydrazides (**9**), which were converted into free acids by alkaline hydrolysis (Scheme 7). Intermediacy of aziridinone (**10**) has been assumed.[11]

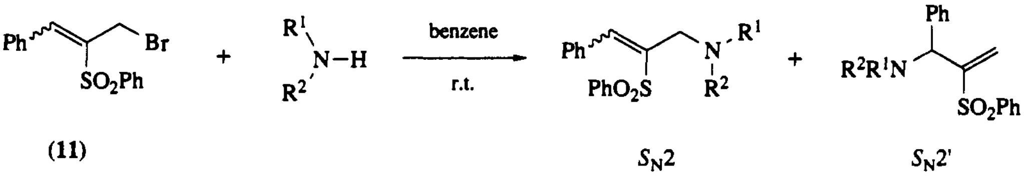
Various methods for the synthesis of allylamines have been reported.[12–15] Reaction of allylic bromide (**11**) with amines gave S_N2 and S_N2' substitution products in the ratio S_N2:S_N2' ranging from *ca.* 1:20 for the reaction with piperidine to 9:1 for the reaction with diisopropylamine (Scheme 8).[12] The product distribution changes with a slight change in the electron-withdrawing capacity of the arenesulfonyl group, as well as the structure of the amines.

Functionalized β-amino-α,β-unsaturated lactones,[13a] esters[13b] and nitriles[13b] can be prepared by nucleophilic vinylic substitution of halogen atoms by amines on the corresponding β-halo-α,β-unsaturated compounds (**12**), (**13**) and (**15**) (Scheme 9). 3-Bromo-2-butenoates (*E*)-(**13**) and (*Z*)-(**13**) reacted with secondary amines to give (*E*)-β-aminopropenoates (*E*)-(**14**) regardless of the initial stereochemistry, while the reaction with primary amines yielded a mixture of (*E*)- and (*Z*)-(**14**), when R^1 = H, with the latter predominant. In contrast, the substitution of (*E*)- and (*Z*)-nitriles, (*E*)-(**15**) and (*Z*)-(**15**), with second-



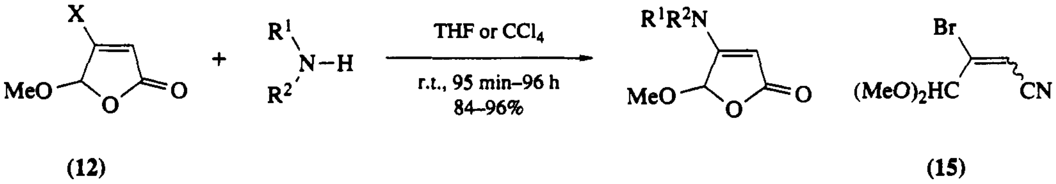
R = 4-MeC_6H_4, 4-ClC_6H_4, 3,4-$Cl_2C_6H_3$, Et; R^2 = CO_2Me, COMe, COPh;
R^3R^4NH = Et_2NH, $PhNH_2$, $BnNH_2$, Bu^tNH_2

Scheme 7

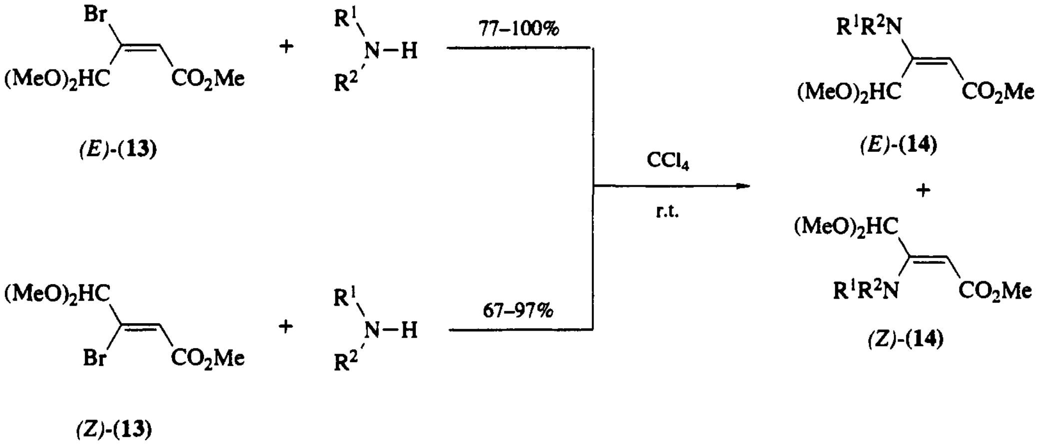


Scheme 8

ary amines proceeded with retention of original alkene configuration, whereas with primary amines (*E*)-isomers were formed as main products, *e.g.* (*E*):(*Z*) = 85:1 to 5:25. When the substitution was carried out with aziridine on the four substrates, (*E*)-(**13**), (*Z*)-(**13**), (*E*)-(**15**) and (*Z*)-(**15**), the reactions proceeded in every case with retention of configuration.[13b,c]



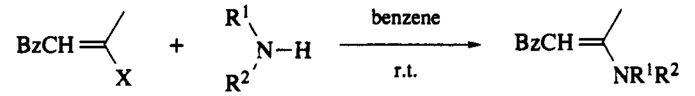
X = Cl, Br; R^1R^2NH = $BnNH_2$, Et_2NH, piperidine, pyrazolidine



R^1R^2NH = Et_2NH, $BnNH_2$, pyrazolidine, perhydro-1,4-oxazine

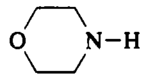
Scheme 9

2-(Alkylthio)- and 2-(alkylsulfinyl)-1-alkenyl ketones (**16a**) and (**16b**) reacted with a variety of amines to give 2-amino-1-alkenyl ketones (**17a**) and (**17b**) (Scheme 10).[14]



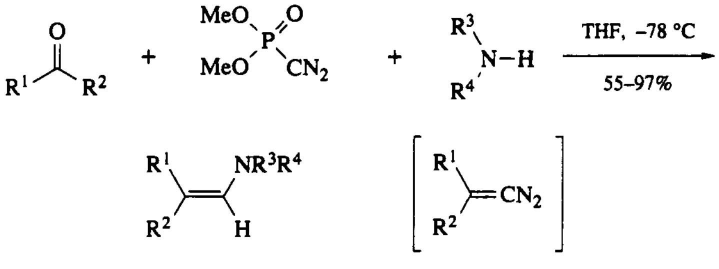
(**16a**) X = SEt
(**16b**) X = S(O)Et

(**17a**) X = SEt
(**17b**) X = S(O)Et

R^1R^2NH	*(17a)*	*(17b)*
	r.t., 15 h, 85%	r.t., 3 h, 99%
$(Me)_2NH$	r.t., 15 h, 65%	r.t., 1 h, 95%

Scheme 10

The Wittig–Horner type reaction of aliphatic ketones with dimethyl diazomethylphosphonate gave the diazoalkenes (**19**), which were trapped by amines thus affording enamines (**18**) of the next higher aldehydes (Scheme 11).[15] For the preparation of allylic amines, the reader is referred to a comprehensive review.[16]

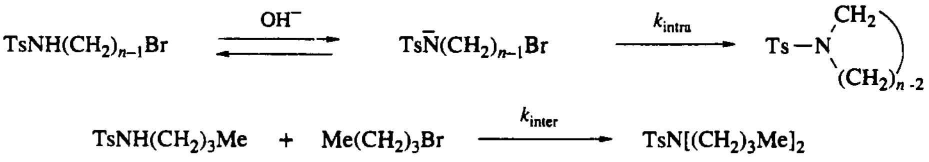


(**18**) (**19**)

Scheme 11

Intramolecular displacement of aliphatic amines having a suitable leaving group also affords cyclic amines. In order to avoid further alkylation, the amino function is protected by appropriate groups. The tosyl group has frequently been utilized to this end, where cyclization proceeds through an anionic displacement reaction.

The rate of cyclization varies with ring size. Kinetic studies of cyclization of a series of anions derived from *N*-tosyl-ω-bromoalkylamines, $TsNH(CH_2)_nBr$ with n = 2–6, in DMSO–H_2O (99:1) have revealed that the rates vary markedly with ring size in the order 5 > 3 > 6 > 7 > 4. First-order rate constants (k_{intra}) for cyclization have been translated into effective molarities (*EM*) with reference to the intermolecular alkylation (k_{inter}) of *N*-tosylbutylamine with butyl bromide (30-fold excess). The results are shown in Scheme 12.[17]



$$TsNH(CH_2)_{n-1}Br \underset{}{\overset{OH^-}{\rightleftharpoons}} Ts\bar{N}(CH_2)_{n-1}Br \xrightarrow{k_{intra}} Ts{-}N\overset{CH_2}{\underset{(CH_2)_{n-2}}{\big)}}$$

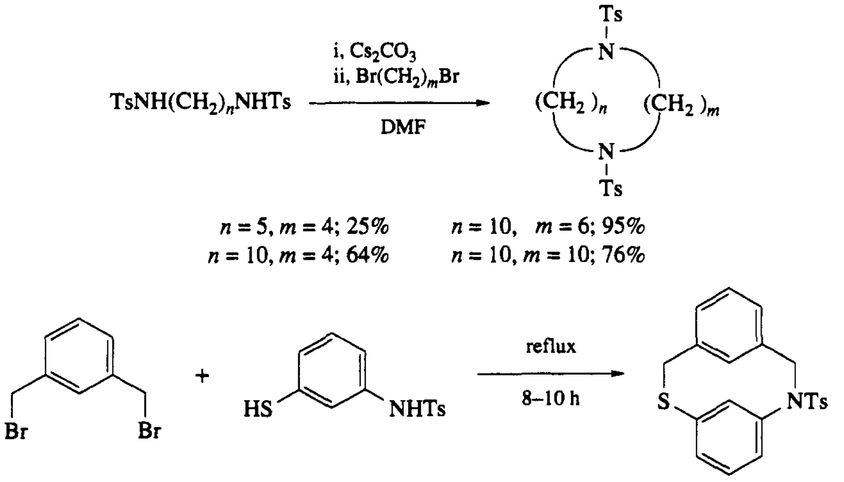
$$TsNH(CH_2)_3Me + Me(CH_2)_3Br \xrightarrow{k_{inter}} TsN[(CH_2)_3Me]_2$$

n	*EM** (mol L^{-1})	*n*	*EM** (mol L^{-1})
3	1.92×10^3	6	2.82×10^2
4	0.59	7	1.36
5	1.38×10^4		

* Calculated as k_{intra} / k_{inter}

Scheme 12

In the preparation of cyclic amines, especially large-membered and strained ones, the use of cesium salts of tosylamides exhibits enhanced reactivity (Scheme 13).[18] The solvent also plays an important role. Macrocyclization can also be successfully carried out under high pressure conditions.[19]

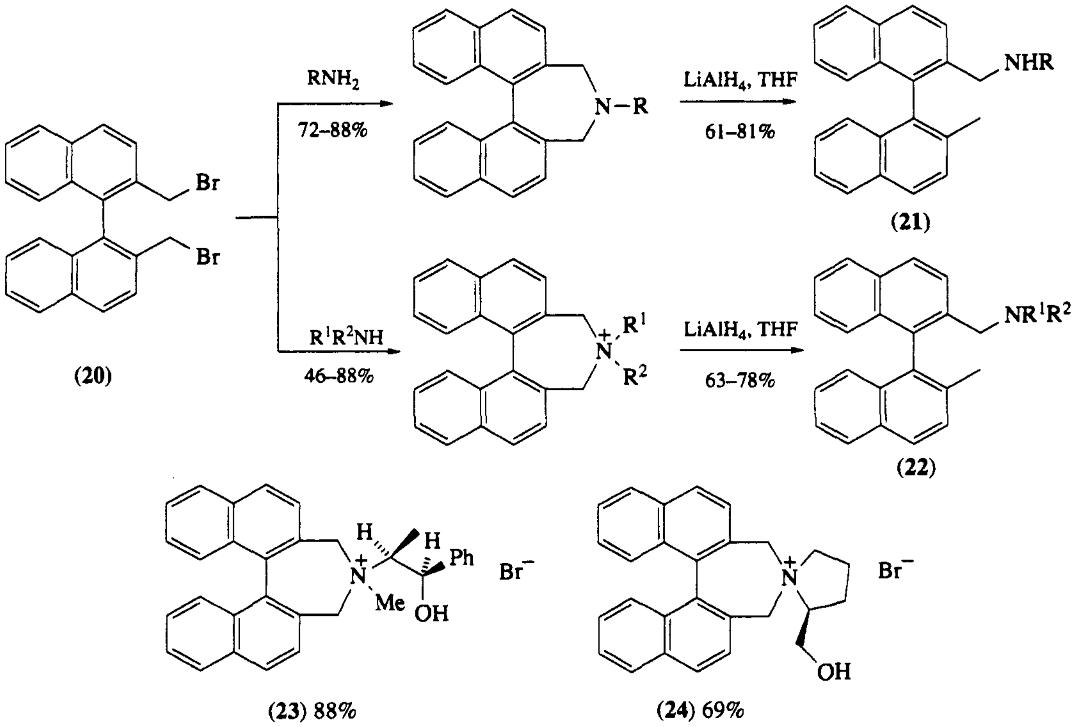


$n = 5, m = 4$; 25% $n = 10, m = 6$; 95%
$n = 10, m = 4$; 64% $n = 10, m = 10$; 76%

CsOH/EtOH–C$_6$H$_6$	9%
CsOH/MeCN	77%
NaOH/MeCN	34%

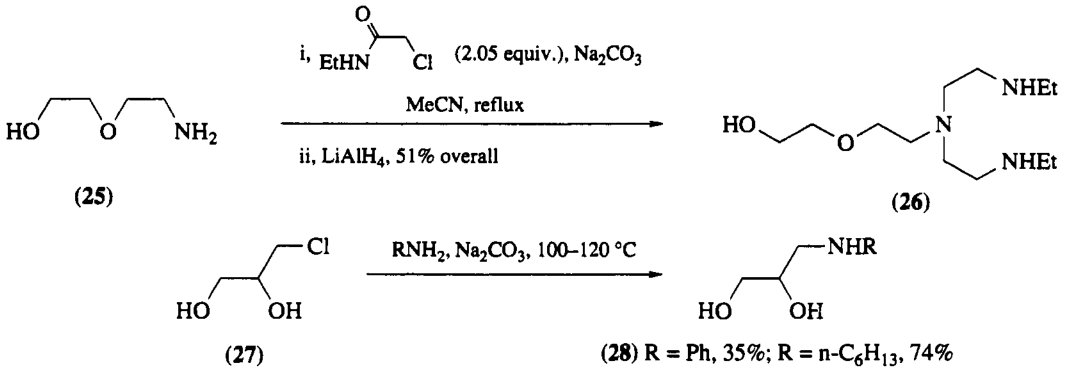
Scheme 13

Dealkylation of tertiary amines and quaternary ammonium salts affords lower substituted amines. Reaction systems that can be utilized to cleave a C—N bond involve sodium amalgam (Emde degradation), LiAlH$_4$, H$_2$/Pd, sodium hydrogen telluride, cyanogen bromide (von Braun reaction) and acyl chlorides.[20] 1,1′-Binaphthyl substituted secondary and tertiary amines (**21**) and (**22**) were synthesized by double alkylation of primary or secondary amines with 2,2′-bis(bromomethyl)-1,1′-binaphthyl (**20**), followed by reduction (Scheme 14). Diaminated binaphthyls of type (R′RNCH$_2$Ar)$_2$ were never formed even when a very large excess of amine is present.[20a]



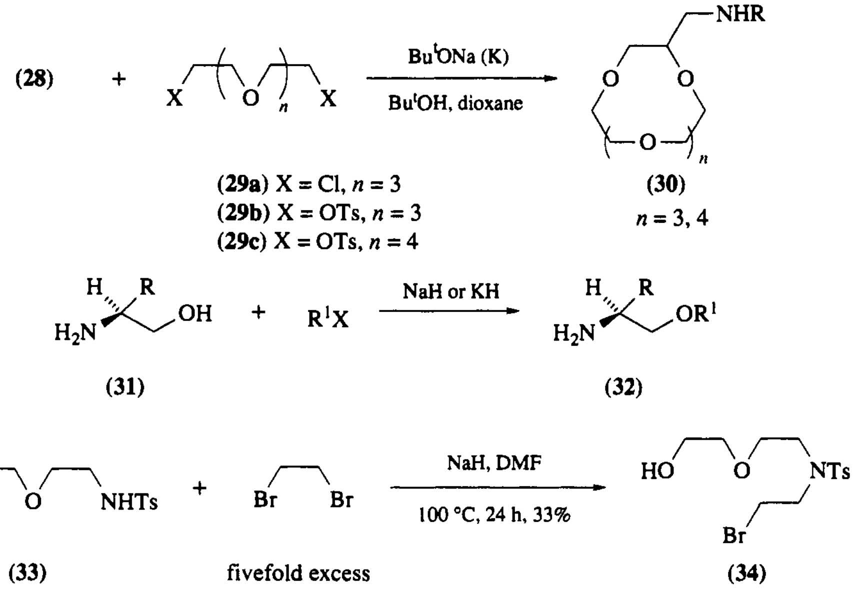
Scheme 14

The reaction of amino alcohols, such as ephedrine or prolinol, with **(20)** took place at the nitrogen atom to give quaternary ammonium salts **(23)** and **(24)** (Scheme 14).[20a] The selective *N*-alkylation was again observed in the reaction of amino alcohol **(25)** with *N*-ethylchloroacetamide (2.05 equiv.) in MeCN in the presence of Na_2CO_3 under reflux. Subsequent reduction of the resulting diamide gave triamine (**26**; Scheme 15).[21a] Chlorohydrin **(27)** reacted with excess primary amines in the presence of Na_2CO_3 or K_2CO_3 to give secondary amines (**28**; Scheme 15).[21b] The chemoselectivity observed can be explained by higher nucleophilicity of the amino group than the hydroxy group; Na_2CO_3 as the base cannot remove the proton from the pendant hydroxy group.



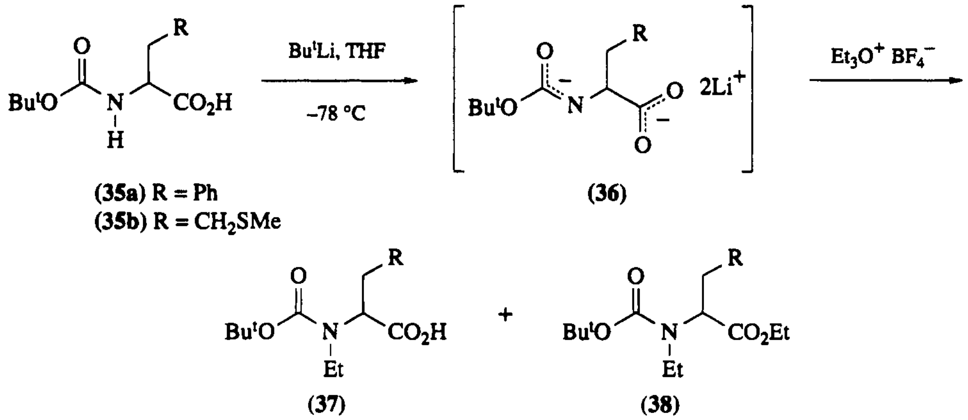
Scheme 15

When the hydroxy group of amino alcohol was converted into alkoxide, alkylation took place at the oxyanion in preference to the nitrogen atom. Thus, the sodium alkoxide derivative of **(28)** reacted with polyethylene glycol ditosylate or dichloride (**29a–29c**) to give the corresponding aminomethyl crown ethers **(30)**.[21b] Chiral amino alcohols **(31)** can be converted into amino ethers **(32)** *via* alkoxides.[22] In contrast, treatment of *N*-tosylamino alcohol **(33)** with NaH, followed by reaction with a fivefold excess of 1,2-dibromoethane afforded (**34**; Scheme 16).[23a]



Scheme 16

Chemoselective *N*-ethylation of Boc-amino acids can be accomplished without racemization *via* the corresponding dianions. Thus, *N*-*t*-butoxycarbonylamino acid **(35)** was converted into dianion **(36)** by treatment with 2 equiv. of Bu^{t}Li, followed by the reaction with 1 equiv. of triethyloxonium tetrafluoroborate to give *N*-ethyl derivative **(37)** along with a trace of ethyl ester **(38)**. On treatment with 2.2 equiv. of the triethyloxonium salt (**36**; R = Ph) gave (**38**; R = Ph) in 95% yield (Scheme 17).[23b]



(35a) R = Ph
(35b) R = CH$_2$SMe

(36)

(37)

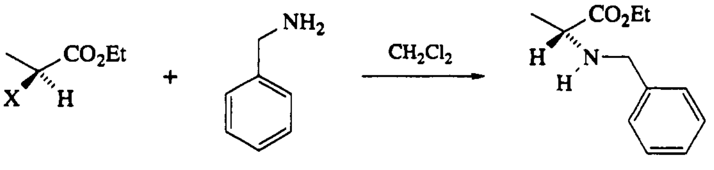
(38)

Scheme 17

1.3.2.2 Alkylation of Amines by Sulfonates and Other Activated Alcohols

Alcohols are readily available in a variety of cyclic and acyclic forms, chain lengths and sense of chirality. Therefore, alcohols have been utilized as versatile starting materials in organic synthesis. In order to prepare amines from alcohols by substitution reactions, the hydroxy group must be converted into a leaving group appropriate to subsequent displacement with nitrogen nucleophiles. Although halogenation is often utilized to this end, introduction of suitable activating groups may be more convenient for the conversion of an alcohol into an alkylating reagent. Of a variety of activated alcohols described in Section 1.2.5, sulfonates are most frequently utilized in the preparation of amines.

A systematic study of the substitution reactions of chiral ethyl propionate derivatives having a leaving group at the α-position (**39a–39e**) with amines reveals that nucleofugacity of the leaving group decreases in the order TfO >> Br > MsO > TsO > Cl and that decreasing reactivity causes increasing racemization and elimination as a consequence of the drastic conditions that are required (Scheme 18 and Table 1). As described in the previous section (Scheme 5), the reaction of (**39d**) with (*R*)-1-phenylethylamine accompanied considerable racemization.[9,24]



(39) a: X = OTf
b: X = OMs
c: X = OTs
d: X = Br
e: X = Cl

(40)

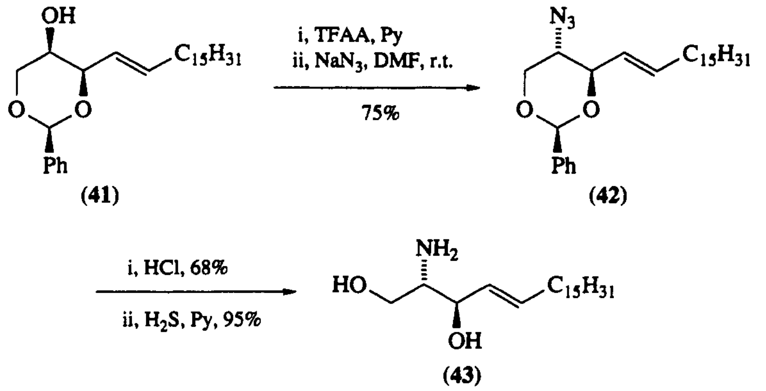
Scheme 18

Table 1 Reaction of (**39a**)–(**39e**) with Benzylamine under Reflux after 0 °C, 20 min and Room Temperature, 75 min (Scheme 18)[9]

(39)	*Yield (%) of (40) after*				
	0.5[a] *h*	*20 h*	*100 h*	*210 h*	*250 h*
a	100				
b		10	30		50
c		10	20		45
d		35	70		
e				trace	

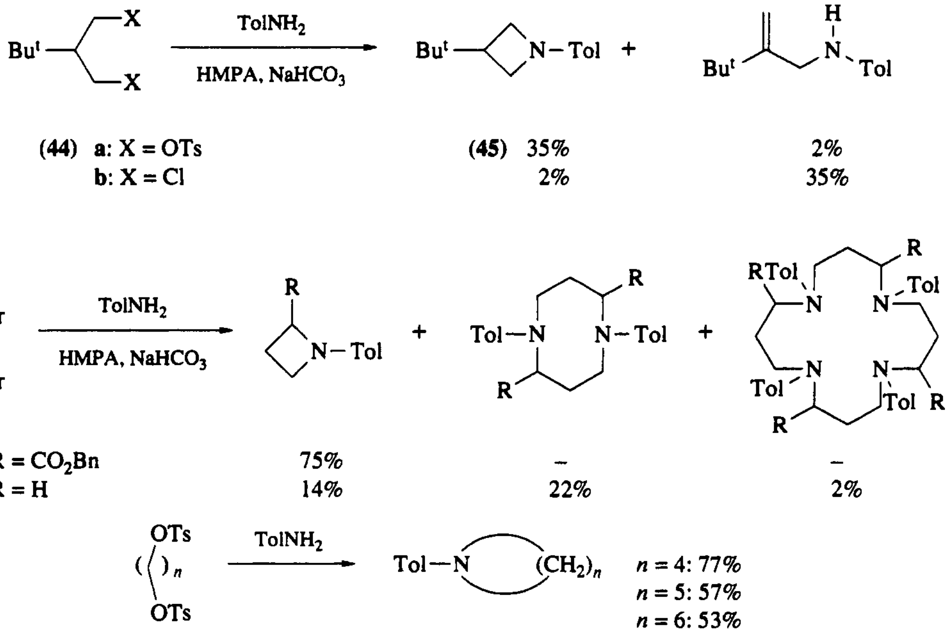
[a] At 0 °C.

The reaction of alcohol (**41**) with TFAA, followed by treatment with sodium azide, gave (**42**) in 75% overall yield. The *p*-toluenesulfonate or methanesulfonate of (**41**) has also been demonstrated to react with sodium azide affording (**42**) but in lower yield. Deprotection and subsequent reduction with hydrogen sulfide gave amine (**43**; Scheme 19).[25]



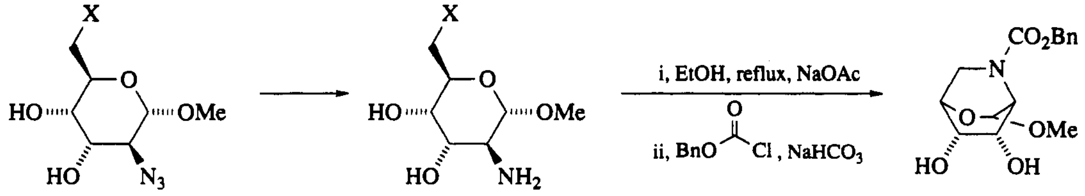
Scheme 19

The displacement of sulfonates with amines or azide ion generally proceeds with inversion of the configuration at the secondary methanol center. As an alkylating reagent, sulfonates are, in general, superior to the corresponding halides. For instance, the alkylation of *p*-toluidine with 2-*t*-butyl-1,3-bis(tosyloxy)propane (**44a**) afforded azetidine (**45**) in 35% yield, while dichloride (**44b**) afforded a lower yield of (**45**) due mainly to competitive elimination (Scheme 20).[26] Dibromides (**46**) and (**47**) reacted with *p*-toluidine giving the corresponding azetidine in 75% and 14% yields, respectively. The reactions shown in Schemes 14 and 20 suggest that the yields of cyclic amines formed by the reaction of bifunctional alkylating reagents with amines are influenced not only by leaving group but also by substitution patterns of the substrates.



Scheme 20

Hydrogenolysis of bromo azide (**48a**) gave bromoamine (**49a**). Cyclization of (**49a**), followed by protection, afforded bicycloamine (**50**) in 59% overall yield. By a similar procedure, tosyl azide (**48b**) afforded (**50**) in 64% overall yield (Scheme 21).[27]



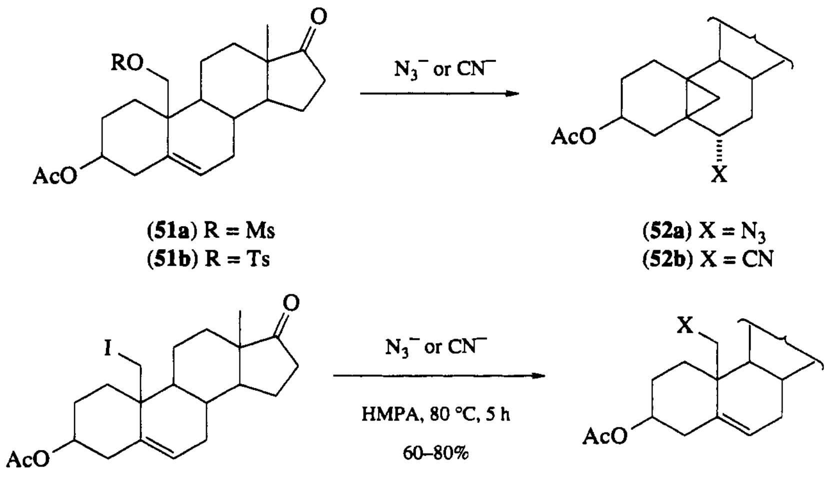
(48a) X = Br
(48b) X = OTs

(49a) X = Br
(49b) X = OTs

(50) 59% (from **48a**)
64% (from **48b**)

Scheme 21

Sulfonates do not necessarily show the same reaction pattern as halides. It has been reported that p-toluenesulfonate (**51a**) and methanesulfonate (**51b**) reacted with azide ion and cyanide ion to give (**52a**) and (**52b**), while iodide (**51c**) gave (**53a**) and (**53b**) (Scheme 22).[28]



(51a) R = Ms
(51b) R = Ts

(52a) X = N_3
(52b) X = CN

(51c)

(52a) X = N_3
(52b) X = CN

Scheme 22

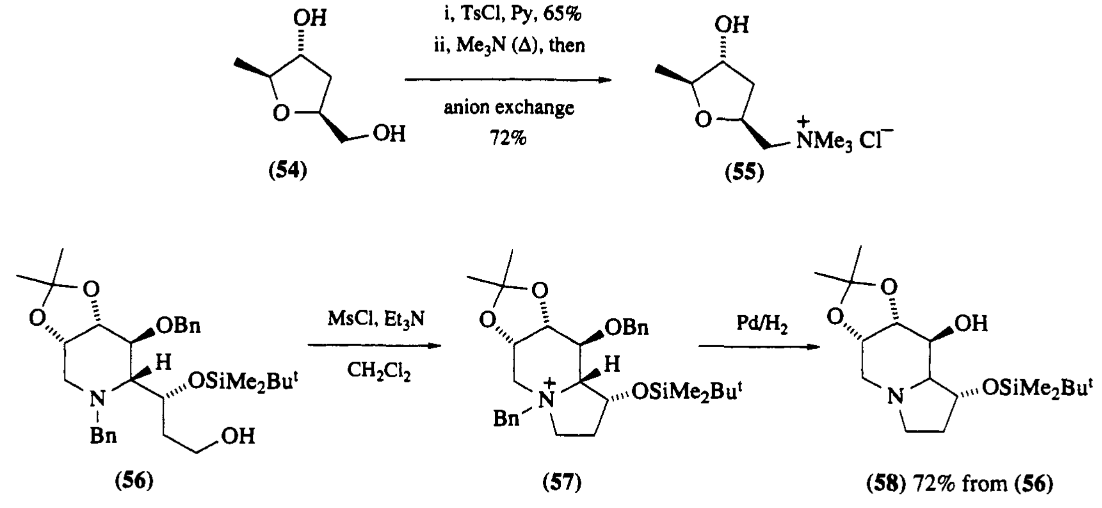
Monosulfonation of primary and secondary diols can generally be accomplished under controlled conditions.[29] The selective tosylation of diol (**54**), followed by reaction with trimethylamine in a sealed tube and ion exchange with Dowex-1(Cl^-) resin gave (+)-muscarine chloride (**55**; Scheme 23).[30] Intramolecular alkylation of cyclic amine (**56**) gave quaternary ammonium salt (**57**); subsequent hydrogenolysis of the benzyl group in (**57**) afforded (**58**; Scheme 23).[31]

Activated alcohols other than sulfonates can also be utilized in the alkylation of amines. For example, *O*-methyl-*N*,*N*′-dicyclohexylisourea reacted with 4-dimethylaminobutanoic acid to give ammonium salt (**59**; Scheme 24).[32,33] *O*-Alkylisourea can also be used in the alkylation of imides.[34a]

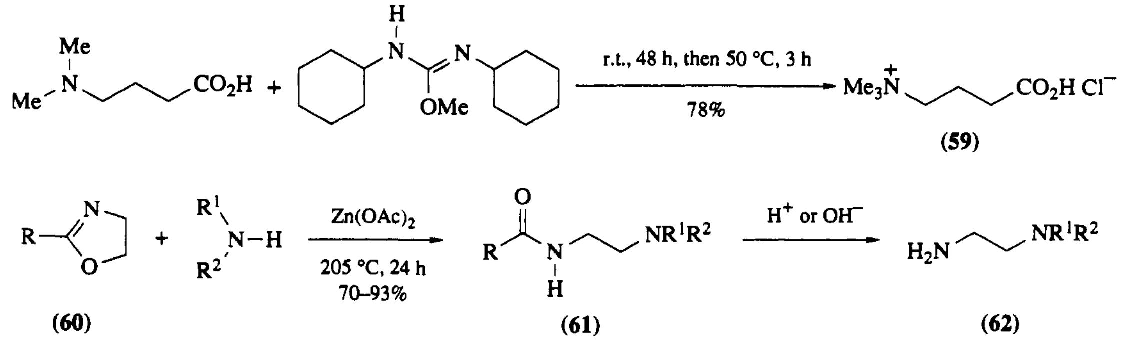
2-Oxazolines (**60**) reacted with secondary amines in the presence of a catalyst to give *N*-(2-aminoethyl)carboxamides (**61**), which were hydrolyzed to unsymmetrically substituted diaminoethanes (**62**). Although reaction conditions are drastic, the yields of products are high (Scheme 24).[34b]

Alkoxyphosphonium salts can also be utilized in the alkylation of amines,[35] where methods of generation of the phosphonium salts are crucial. The reaction of aminophosphonium reagent (**63**) with alkoxides in the presence of amines to be alkylated (80 °C, 1 h in DMF for secondary amines and in benzene for primary amines) afforded the corresponding higher substituted amines in good to excellent yield. Phosphonium amide (**64**) has been proposed as a key intermediate (Scheme 25).[36] Various amines and azides have been prepared by the use of alkoxy[tris(dimethylamino)]phosphonium salts (**65**).[35a]

Reagents formed by combining Ph_3P with CCl_4 and with diethyl azodicarboxylate (DEAD) promote cyclization of amino alcohols to cyclic amines (Scheme 26).[37,38] Various 2-amino alcohols reacted with diethoxytriphenylphosphorane (**66**) to afford the corresponding aziridines in 85–90% yields. The reaction proceeds with retention of the configuration at the amino carbon (C-2) (Scheme 26).[39] In view of

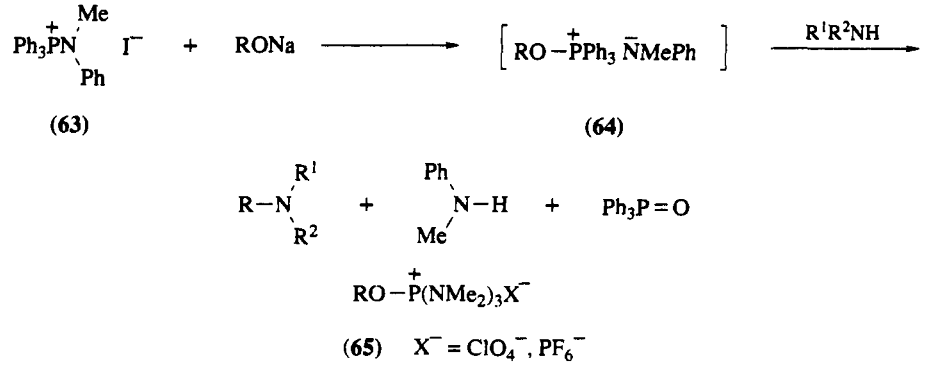


Scheme 23



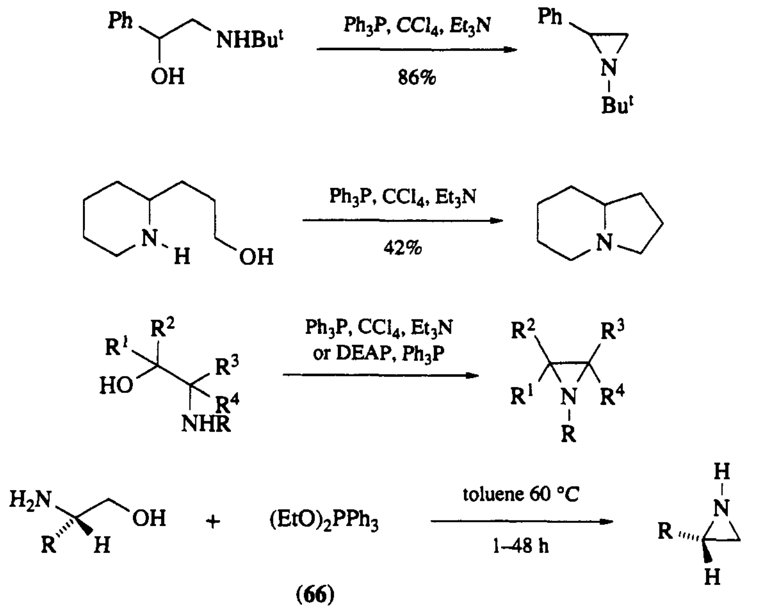
R = Et, $C_{11}H_{23}$, Bu^t, Ph; R^1R^2NH = Et_2NH, Bu_2NH, morpholine, piperidine

Scheme 24



Scheme 25

the availability of the starting materials and the stereochemical outcome of the reaction, the procedure may be one of the most useful methods for the preparation of chiral aziridines.



(66)

R = Bn, 85%; R = Me_2CHCH_2, 90%; R = Me_2CH, 90%

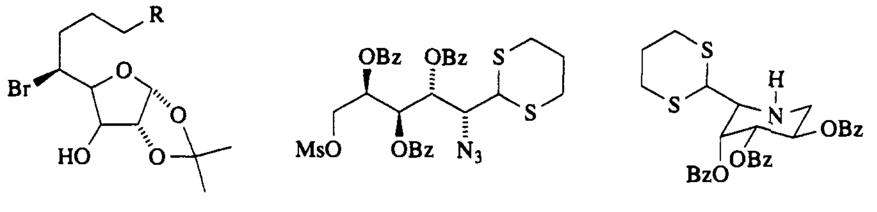
Scheme 26

1.3.2.3 Manipulation of Amino Group Equivalents

1.3.2.3.1 Alkylation of azide ion

Azide anion, which is more nucleophilic than amines, reacts with alkyl halides and activated alcohols giving the corresponding alkyl azides. Phase-transfer conditions can also be utilized.[40] For details, readers are referred to a comprehensive review.[41] Alkyl azides thus formed can be readily transformed into primary amines by a variety of reagents or reaction systems which involve catalytic hydrogenation,[40–42] $LiAlH_4$,[43] $NaBH_4$ under phase-transfer conditions,[44a] $NaBH_4$/THF/MeOH,[44b] Ph_3P or $(RO)_3P/H_2O$,[45] H_2S/Py,[46] Pd–C/HCO_2NH_4/MeOH,[47] NaTeH,[48] nickel boride[49] and $SnCl_2$/MeOH.[50]

The reduction system must be chosen by taking into account the substitution pattern of substrates. For example, azide (**67**) was converted into the amine (**68**) by treatment with $SnCl_2$ in MeOH (64% yield), whereas catalytic hydrogenation or $LiAlH_4$ reduction could not be used due to loss of the 5-bromo group.[51] Azide (**69**) was converted into piperidine (**70**) by the reaction with Ph_3P in $CHCl_3/H_2O$ in 61% yield (Scheme 27).[52] The reaction of azides with PPh_3 gives iminophosphoranes (Staudinger reaction), hydrolysis of which affords primary amines. The procedure has an advantage because the initially formed iminophosphoranes can also be utilized as key intermediates for various nitrogen compounds, such as secondary amines, aziridines, amides, imines, nitro compounds and aminophosphonium salts.[53] Nickel boride generated *in situ* from $NaBH_4$ and nickel chloride does not reduce a ketone, ester, epoxide or a double bond.[49] Sodium hydrogen telluride is inert to unconjugated carbon–carbon double and triple bonds, unconjugated carbonyl, carboxyl, amide, ester, cyano and sulfone groups.[48]



(**67**) R = N_3

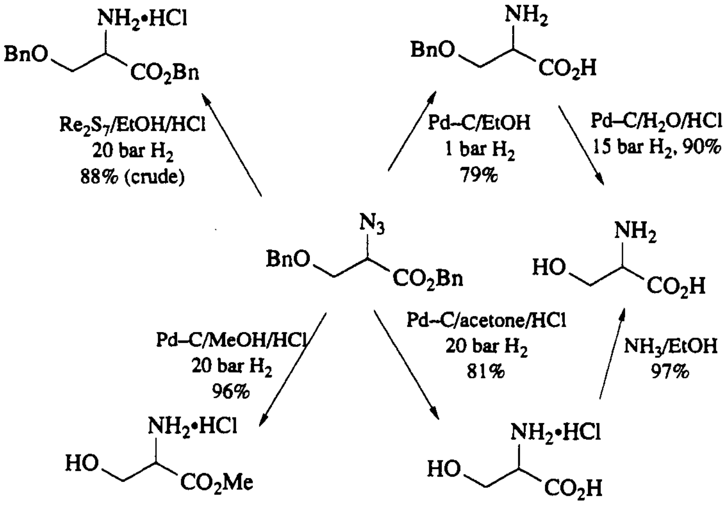
(**68**) R = NH_2

(**69**)

(**70**)

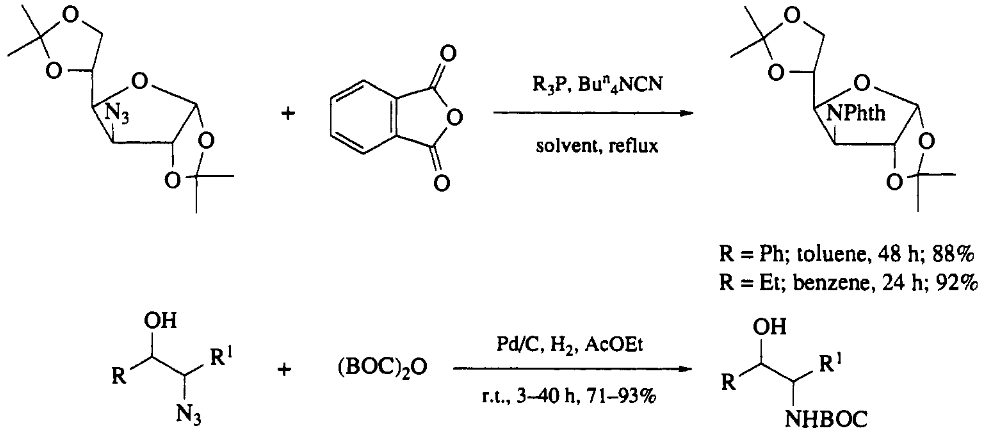
Scheme 27

Benzyl 2-azido-3-(benzyloxy)propionate was converted into (±)-serine and its derivatives by variation of hydrogenation conditions (Scheme 28).[40]



Scheme 28

One-pot procedures for conversion of an azide to an *N*-protected amine have been reported (Scheme 29).[54]



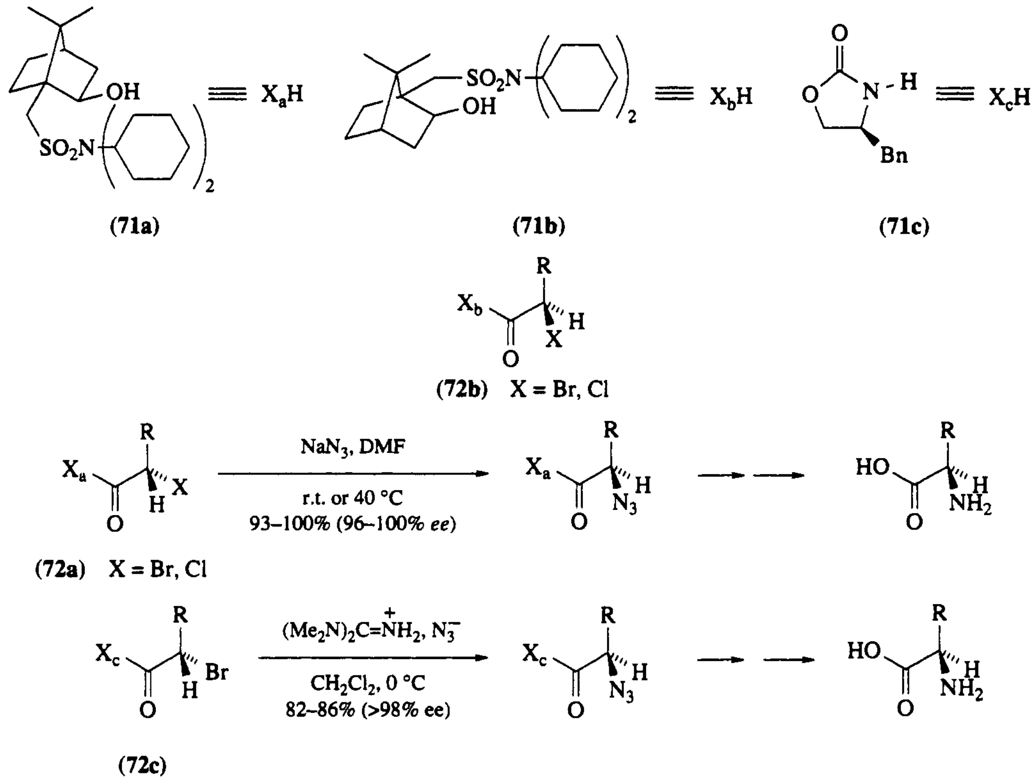
R = Ph; toluene, 48 h; 88%
R = Et; benzene, 24 h; 92%

Scheme 29

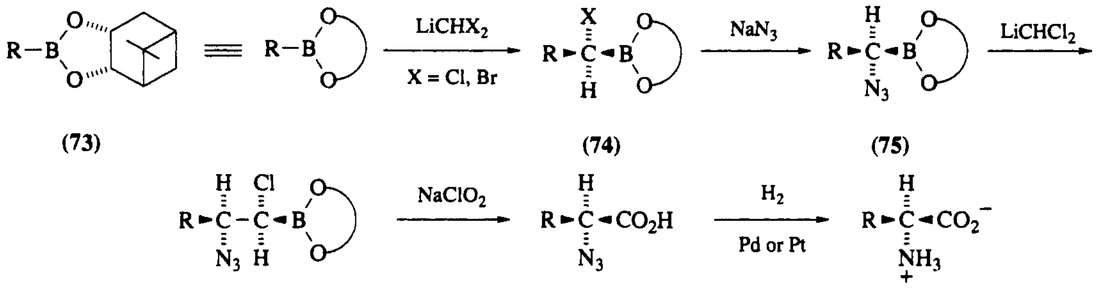
Since the reaction of alkylating reagents with azide ion generally proceeds through an S_N2 process, inversion of the reaction center takes place. Thus, for the synthesis of amines with a definite configuration at the carbon atom to which the amino group is attached, the preparation of enantiometrically pure alkylating reagent is a prerequisite.

Chiral α-halo esters (**72a**) and (**72b**) and α-halo imide (**72c**) have been prepared in high diastereomeric purity by the use of Oppolzer's chiral auxiliary (**71a**) and (**71b**) and Evans' chiral auxiliary (**71c**), respectively. The reactions of (**72a**), (**72b**) and (**72c**) with azide ion proceeded with inversion of configuration (Scheme 30).[55,56] In the latter reaction, the use of NaN_3 (DMF or DMSO, 0 °C) has been reported to afford 2–5% epimerization.[56] The azides thus prepared were transformed into the corresponding amino acids with high chemical and optical yields.

Reaction of chiral boronates (**73**) with (dihalomethyl)lithium afforded (1*S*)-1-haloboronate (**74**), which was converted into (1*R*)-1-azidoboronate (**75**). Homologation of (**75**) with (dichloromethyl)lithium to 1-chloro-2-azidoboronate, oxidation to azido acid and catalytic hydrogenation afforded (–)-amino acids in 32–63% overall yields with 92–96% *ee* (Scheme 31).[57] The procedure has also been applied to the preparation of a chiral *vic*-amino alcohol.[58]

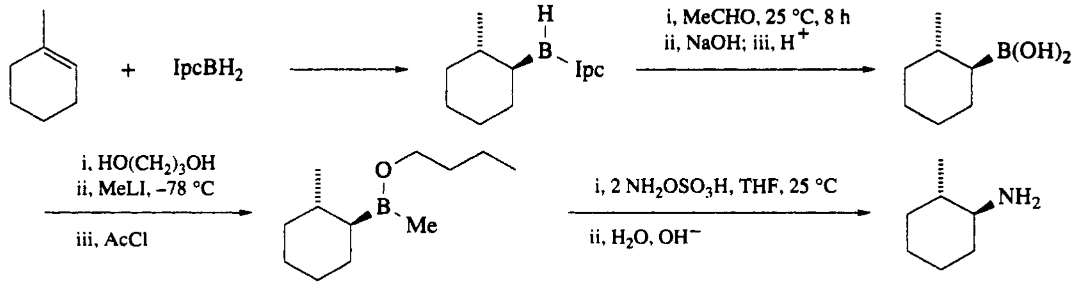


Scheme 30



Scheme 31

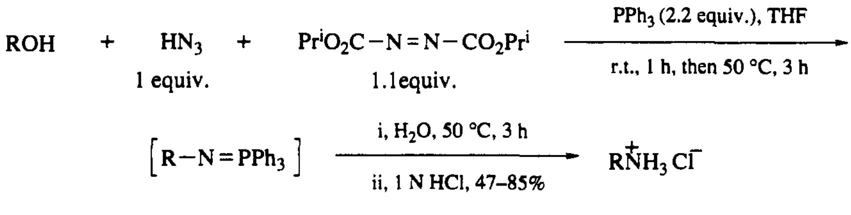
Brown and coworkers have reported chiral organoboron reagent mediated asymmetric synthesis of primary amines of high optical purity (Scheme 32).[59] Stereospecific synthesis of secondary amines and *N*-substituted aziridines by the use of organoboron reagents has also been reported.[60]



Scheme 32

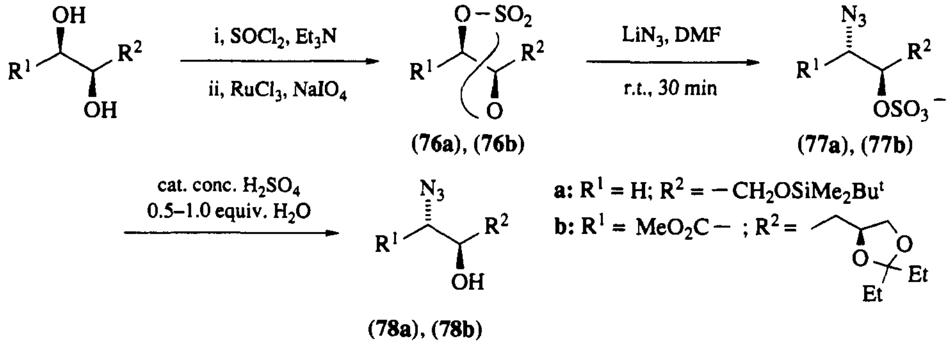
99% *ee*

Alcohols were directly converted into azides by the reaction with HN_3, DEAD and triphenylphosphine.[61] Combination of this procedure with the Staudinger reaction makes it possible to convert alcohols into amines by a one-pot method (Scheme 33).[62]



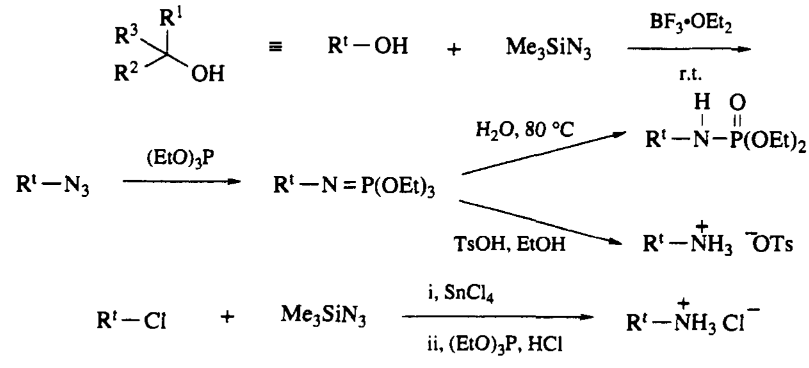
Scheme 33

Regioselective substitution of a hydroxy group of di- and poly-ols by the azido group is an important step for the preparation of amino alcohols. Azidation of polyols *via* an alkoxyphosphonium salt generally takes place at the less-hindered site.[35,61] Nucleophilic opening of cyclic sulfates (**76a**) and (**76b**) with azide ion took place with high regioselectivity to give sulfates (**77a**) and (**77b**), which were converted into azido alcohol (**78a**) and (**78b**) under controlled conditions (Scheme 34).[63]



Scheme 34

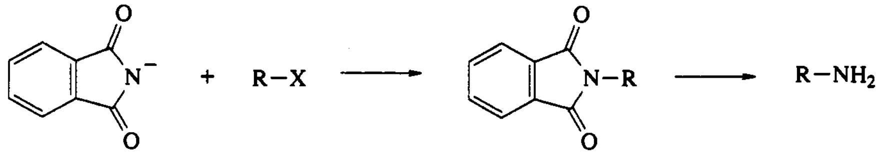
The reaction of tertiary alcohols or tertiary alkyl halides with trimethylsilyl azide in the presence of a Lewis acid ($BF_3{\cdot}Et_2O$ for alcohols and $SnCl_4$ for halides) afforded tertiary alkyl azides (Scheme 35).[45c,64]



Scheme 35

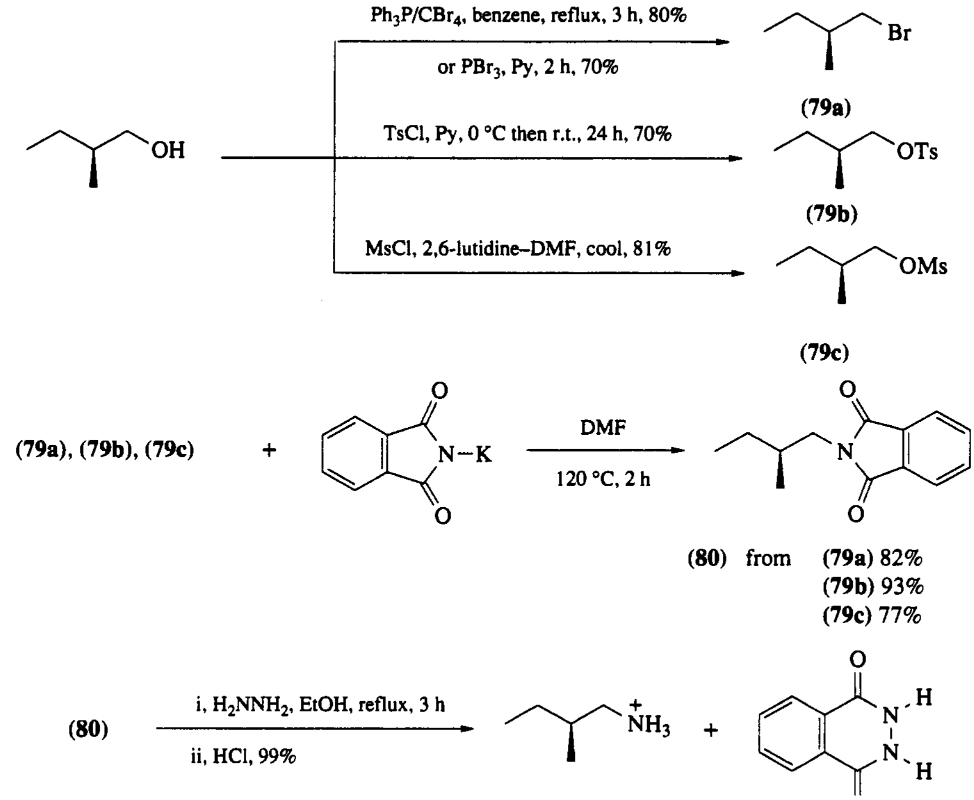
1.3.2.3.2 Gabriel synthesis

The Gabriel synthesis is a classical but still useful procedure for the preparation of primary amines. The method consists of alkylation of phthalimide anion with an appropriate alkylating reagent and subsequent removal of the phthaloyl group to generate primary amines (Scheme 36).[65]



Scheme 36

Alkyl halides and alkyl sulfonates have been generally used as alkylating reagents. An example of the conversion of an alcohol into a primary amine by the Gabriel synthesis is shown in Scheme 37.[66]



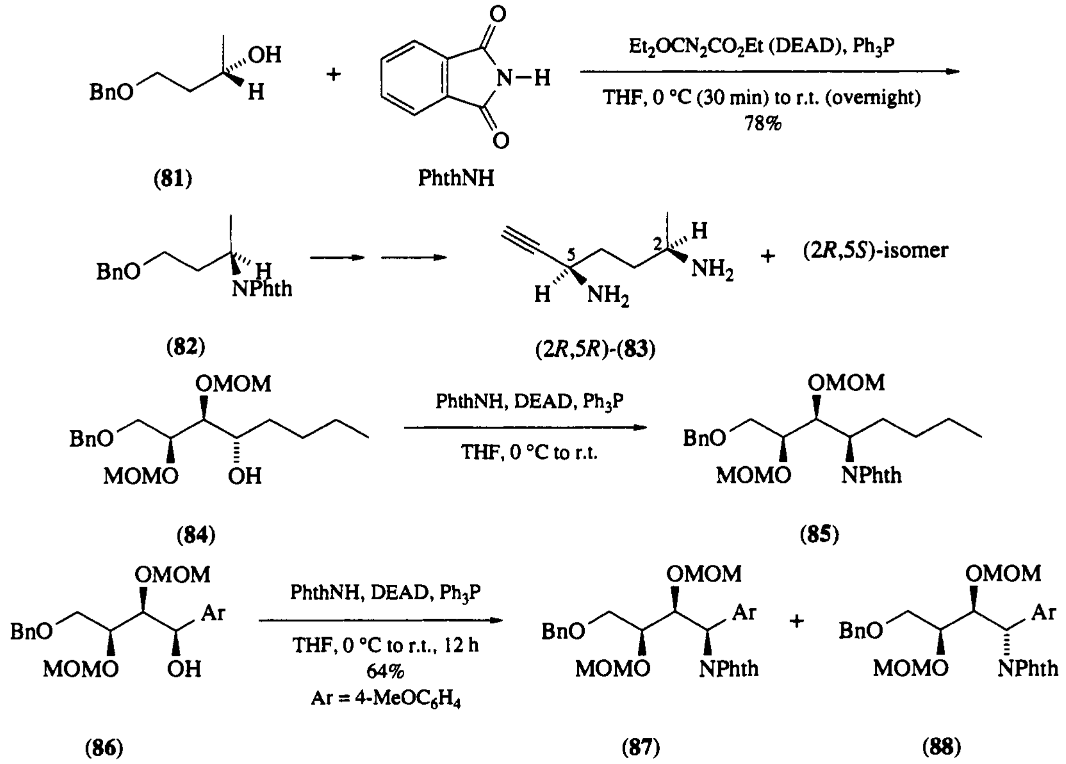
Scheme 37

Alkylation of phthalimide anion can be carried out under solid–liquid phase-transfer conditions, using phosphonium salts[67] or ammonium salts.[68] In the reaction systems using hexadecyltributylphosphonium bromide, alkyl bromides and alkyl methanesulfonate are more reactive than alkyl chlorides. Octyl iodide is less reactive than the corresponding bromide and chloride.[67] (*R*)-2-Octyl methanesulfonate was converted into (*S*)-2-octylamine with 92.5% inversion.[67] Kinetic resolution of racemic ethyl 2-bromopropionate by the use of a chiral quaternary ammonium salt catalyst has been reported.[68] Under liquid–liquid phase-transfer conditions, *N*-alkylation of phthalimide has been reported to give poor results.[68b]

In the presence of [2.2.2]cryptand, the reaction of potassium phthalimide with alkyl halides proceeded smoothly in THF or benzene even at room temperature to give the corresponding *N*-alkylphthalimides in good to excellent yields.[69]

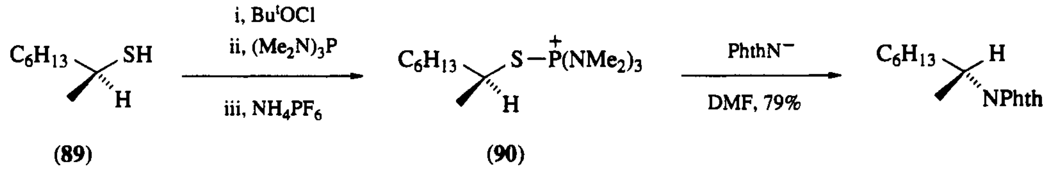
The alkylation of phthalimide can also be accomplished with *O*-alkylisoureas and alkoxyphosphonium salts. Thus, the reaction of *O*-alkyl-*N*,*N'*-cyclohexylisourea with phthalimide afforded *N*-alkylphthalimides in 60–70% yields (DMF, 120 °C, 2–24 h). Starting from (*R*)-2-octylisourea, (*S*)-2-octylamine was obtained in 97.6% *ee*, indicating 98% inversion of the configuration took place.[34a]

The reactions involving alkoxyphosphonium salts are also effective for the *N*-alkylation of phthalimide with virtually complete inversion of the secondary methanol center.[35,61] Thus, the reaction of (*S*)-alcohol (**81**) with phthalimide, DEAD and triphenylphosphine afforded (**82**), which was subjected to a sequence of reactions to yield (2*R*,5*R*)-diamine (**83**) and the (2*R*,5*S*)-isomer in a ratio of 99.4:0.6.[70] The secondary methanol center of alcohol (**84**) was again inverted in the reaction with phthalimide, DEAD and triphenylphosphine giving (**85**).[71] In contrast, alcohol (**86**) afforded *syn*- and *anti*-phthalimide derivatives (**87**) and (**88**) in a ratio of 1:1 under similar conditions (Scheme 38).[72] This result would be explained by assuming intermediacy of a carbonium ion, which is stabilized by an adjacent *p*-methoxyphenyl group.



Scheme 38

Alkylthiophosphonium salts (**90**) prepared from thiol (**89**) can also be utilized as an alkylating reagent for phthalimide. The reaction proceeds with inversion of configuration at the reaction site (Scheme 39).[73]



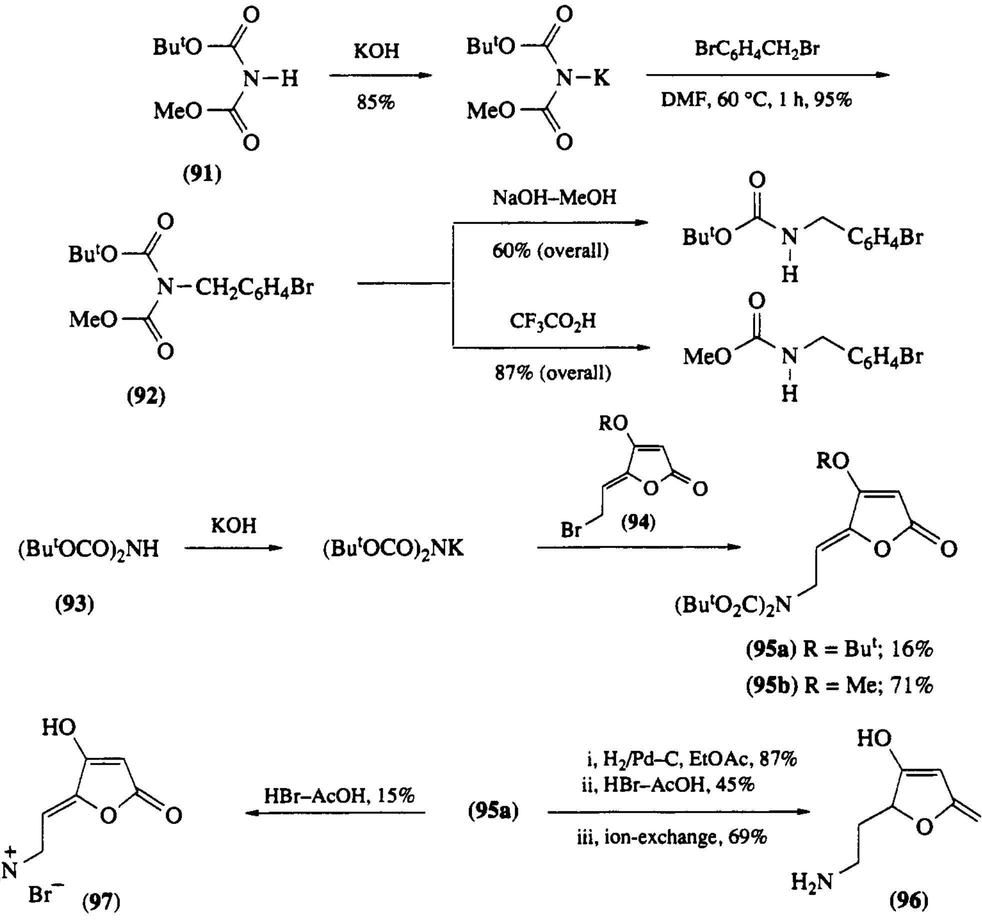
Scheme 39

1.3.2.3.3 Modified Gabriel synthesis

Although alkylation of phthalimide can now be performed under mild conditions as described in the preceding section, the final deprotection step still requires somewhat drastic conditions, *e.g.* the use of strong acid or base, or, alternatively, hydrazinolysis, at elevated temperature, due to the inherent stability of the phthaloyl group.[65] This has prompted investigation of a number of alternatives to phthalimide which afford *N*-alkyl derivatives amenable to milder deprotection.

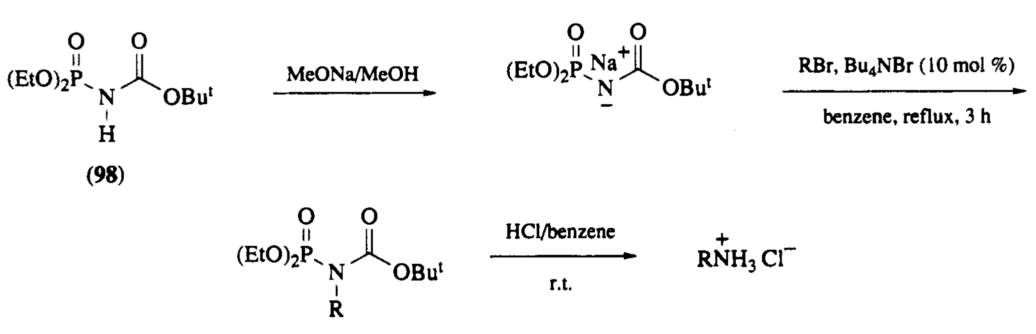
Methyl *t*-butyl iminodicarboxylate (**91**) and di-*t*-butyl iminodicarboxylate (**93**) have been used in a modified Gabriel synthesis.[74–76] Thus, the potassium salt of (**91**) reacted with alkyl halides to give the corresponding *N*-alkylated products (**92**) in 59–95% yields (in DMF or DMSO, 20–60 °C) except for alkylating reagents susceptible to base-catalyzed side reactions. Under basic conditions, (**92**) gave *N*-*t*-butoxycarbonylamines, whereas, with trifluoroacetic acid, *N*-methoxycarbonylamines were obtained (Scheme 40).[74]

The potassium salt of (**93**) reacted with allylic bromides (**94**) to afford protected amines (**95**). Hydrogenolysis of (**95a**), followed by successive treatment with HBr–AcOH and ion exchange resin gave amino alcohol (**96**). Treatment of (**95a**) with HBr–AcOH gave allylamine (**97**; Scheme 40).[76]



Scheme 40

The sodium salt of diethyl *N*-(*t*-butoxycarbonyl)phosphoramidate (**98**) reacted with alkyl halides in boiling benzene in the presence of tetrabutylammonium bromide to give the corresponding *N*-alkyl derivatives (**99**) in 71–95% yields for primary alkyl halides and 38–58% yields for secondary α-halo esters (in MeCN). The phosphoryl and *t*-butoxycarbonyl groups were removed by treatment overnight with benzene saturated with dry HCl (Scheme 41).[77a]

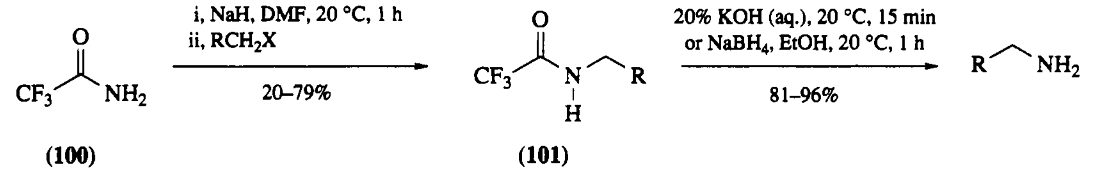


Scheme 41

Alkylation of (**98**) can also be carried out by reaction with alcohols in the presence of DEAD and triphenylphosphine at room temperature. The yields of crude (**99**) were in the range 80–90% for primary alcohols and 70–75% for secondary alcohols with nearly complete inversion of the secondary methanol center.[77b]

Sulfonyl groups can also be utilized to reduce the basicity of amino functions. Inter- and intra-molecular cyclization using bifunctional tosylamides have been widely utilized in the preparation of macrocyclic polyamines (Scheme 13). Trifluoromethanesulfonamide and its derivatives can also be used in the preparation of primary and secondary amines.[78]

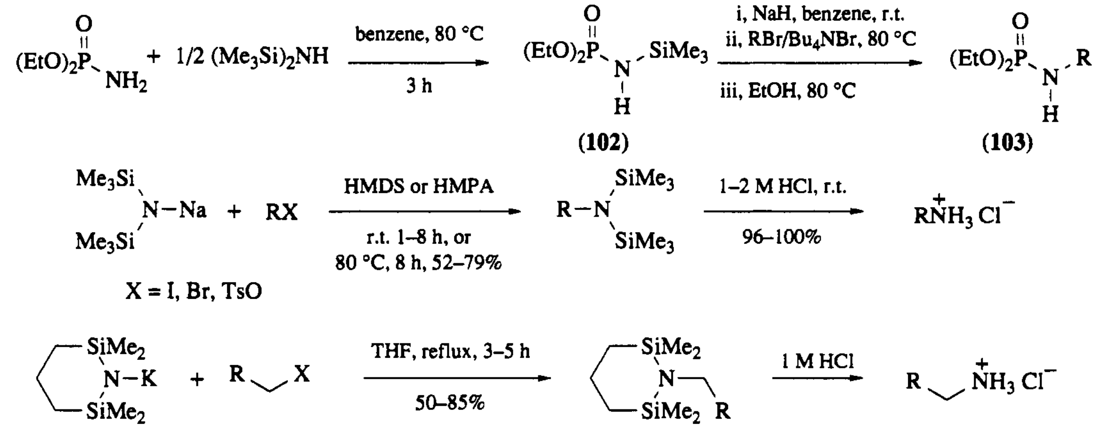
In contrast to the anion of diethyl phosphoramidate or trifluoromethanesulfonamide, which cannot be cleanly monoalkylated,[77,78] the anion of trifluoroacetamide (**100**) was monoalkylated by alkyl halides or alkyl methanesulfonate. The resulting *N*-alkylamides (**101**) were converted into primary amines by alkaline hydrolysis or reduction ($NaBH_4$; Scheme 42). Various primary amines were prepared from (**100**) with primary alkyl iodides or methanesulfonate, benzyl and allyl halides, α-bromocarbonyl compounds and 2,4-dinitrochlorobenzene. However, competitive elimination is a serious side reaction for less reactive primary alkyl chlorides and secondary halides or methanesulfonate. The synthesis of secondary amines from (**100**) has also been reported.[79]



Scheme 42

1.3.2.3.4 *Alkylation of amine synthons having a nitrogen–heteroatom bond*

One of the two hydrogen atoms of phosphoramidates can be temporarily blocked with a trimethylsilyl group. The sodium salt of diethyl *N*-(trimethylsilyl)phosphoramidate (**102**) reacted with alkyl bromides in benzene in the presence of 10 mol % of tetra-*n*-butylammonium bromide to afford, after desilylation, the corresponding *N*-alkyl derivatives (**103**) in 79–95% yields for primary alkyl halides. Secondary alkyl halides gave poor results (Scheme 43). The addition of the quaternary ammonium salt is essential to promote the alkylation reaction.[80] Hexamethyldisilazane and its cyclic analogs can also be utilized in the preparation of amines under moderate conditions (Scheme 43).[81,82]

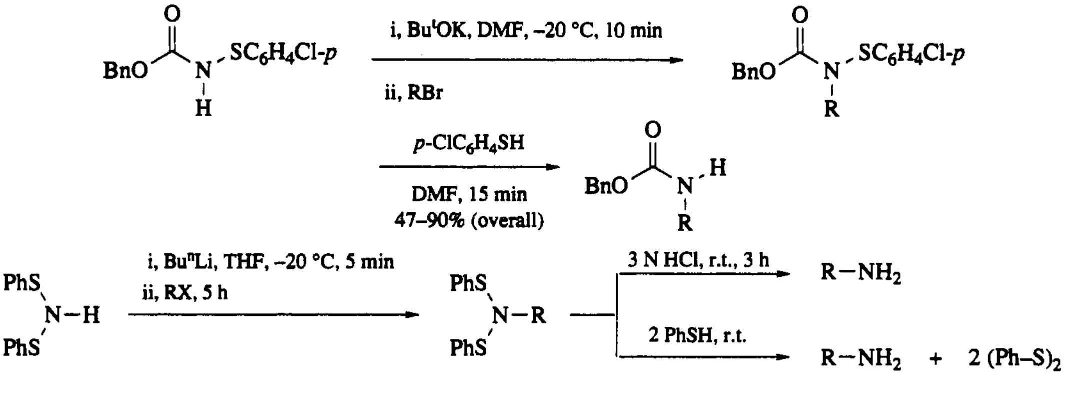


Scheme 43

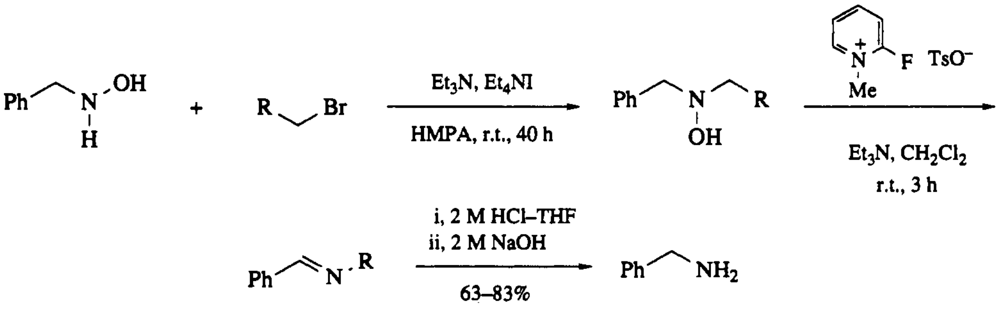
The utility of sulfenimides has been demonstrated.[83] The procedure has the particular advantage of using practically neutral conditions for the final deblocking step (Scheme 44).

N-Alkylation of benzylhydroxylamine by a primary alkyl bromide proceeded smoothly at room temperature. HMPA is the solvent of choice and addition of tetraethylammonium iodide facilitates the reaction. Dehydration of the resulting *N*-alkylhydroxylamines and subsequent acid hydrolysis gave the corresponding primary amines (Scheme 45).[84]

Alkylation of imino or amidine nitrogen and subsequent hydrolysis give rise to amines. For instance, alkylation of imine esters (**104a**) or amidine esters (**104b**) with dimethyl sulfate or methyl triflate, fol-

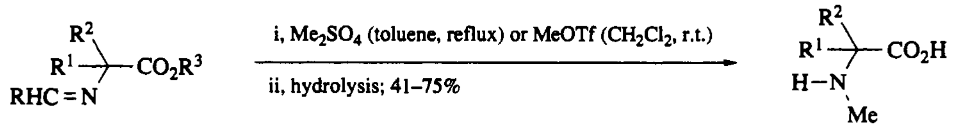


Scheme 44



Scheme 45

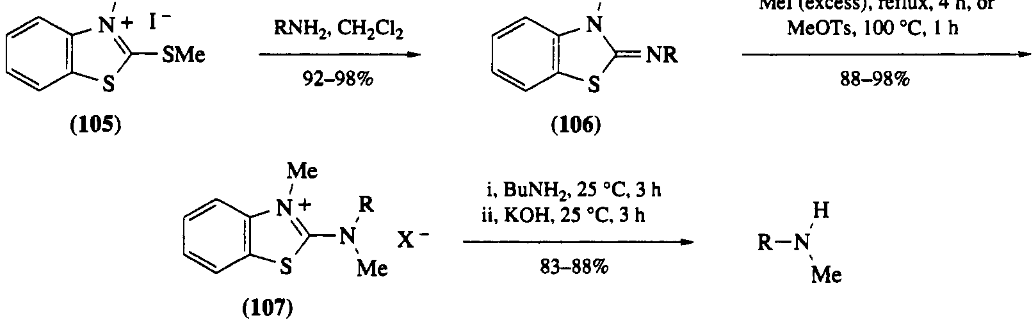
lowed by hydrolysis, afforded the corresponding *N*-methylamino acids with retention of optical activity (Scheme 46).[85]



(104a) R = Ar
(104b) R = Me_2N

Scheme 46

The reaction of benzothiazolium iodide (**105**) with 2 mol of a primary aliphatic amine or 1 mol each of an aromatic amine and triethylamine gave benzothiazolimine (**106**). Methylation of (**106**) and subsequent treatment of the resulting amidinium salts (**107**) with butylamine afforded the corresponding *N*-methylamine (Scheme 47).[86]



(105) **(106)** **(107)**

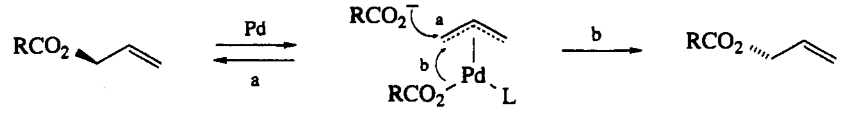
Scheme 47

N-Alkylation of hexamethylenetetramine gave the corresponding quaternary ammonium salts, which were converted into primary amines without concomitant formation of secondary amines (Delépine reaction).[87]

1.3.3 REACTION OF π-ALLYL COMPLEXES WITH NITROGEN NUCLEOPHILES

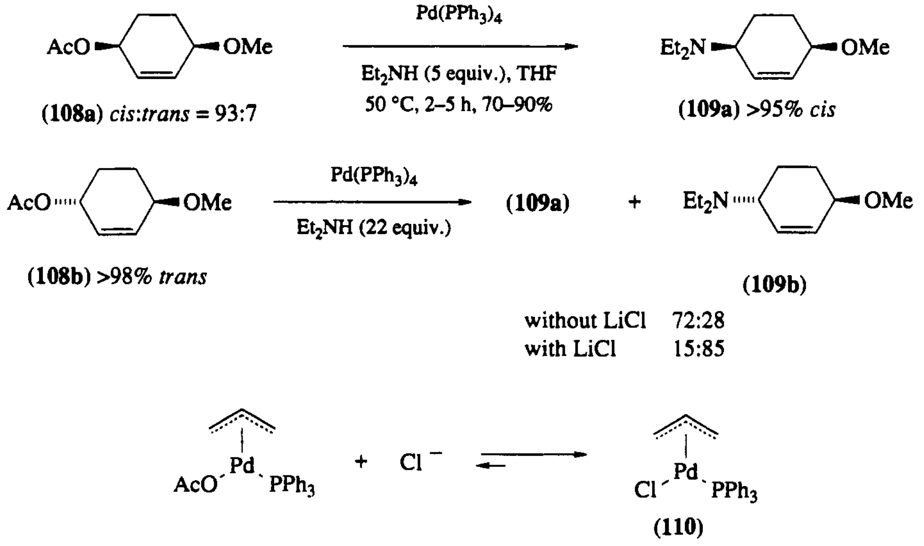
Palladium-catalyzed nucleophilic substitution reactions of allylic substrates have become useful in organic synthesis.[88] As allylic substrates, allyl alcohols, halides, carboxylates, phosphates or vinyl epoxides can be utilized.

Although nucleophiles generally substitute allylic leaving groups with retention of configuration, the substitution of allylic carboxylates sometimes proceeds in a nonstereospecific manner due to palladium-catalyzed isomerization of the substrates (Scheme 48).[89]



Scheme 48

This drawback has been overcome by the use of polymer-supported palladium catalysts.[90] Addition of LiCl also provides remarkably enhanced selectivity without affecting the reaction rate.[89] Thus, the reaction of *cis*-acetate (**108a**) reacted with diethylamine in the presence of Pd(PPh3)4 to give *cis*-amine (**109a**) in good yield, whereas *trans*-acetate (**108b**) afforded (**109a**) and *trans*-amine (**109b**) with the former predominant. However, the addition of LiCl in the reaction system resulted in the formation of (**109b**) as the main product (Scheme 49).[89] The observed effect of LiCl on the stereochemistry of the reaction has been attributed to the formation of intermediate (**110**), where chloride blocks the coordination of acetate (Scheme 49).[89]



(**108a**) *cis*:*trans* = 93:7

(**109a**) >95% *cis*

(**108b**) >98% *trans*

(**109b**)

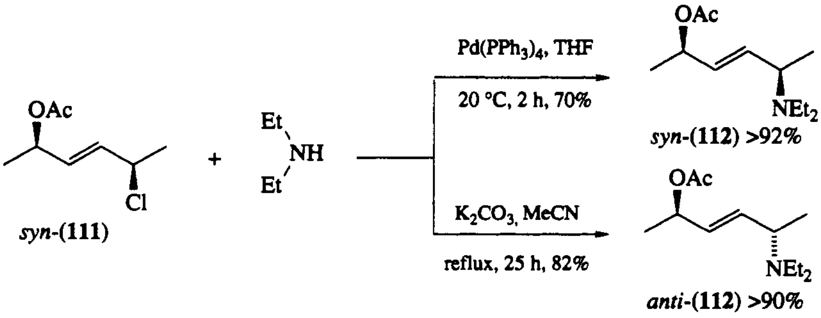
without LiCl 72:28
with LiCl 15:85

(**110**)

Scheme 49

The reaction of (*E*)-(*syn*)-2-acetoxy-5-chloro-3-hexene, *syn*-(**111**), with diethylamine in the presence of a palladium catalyst gave (*E*)-(*syn*)-2-acetoxy-5-(dimethylamino)-3-hexene, *syn*-(**112**). In contrast, the reaction of *syn*-(**111**) with diethylamine under S_N2 conditions afforded the *anti* isomer, (*anti*-(**112**); Scheme 50).[91]

The fugacity of the leaving groups at allylic positions is demonstrated to be in the order —OPO(OEt)2 > —OAc > —OH and —Cl > —OAc > —OH.[92–94] Therefore, chemoselective stepwise substitution of differentially substituted bifunctional allylic substrates is possible as depicted in Scheme 51.[92,94] In the



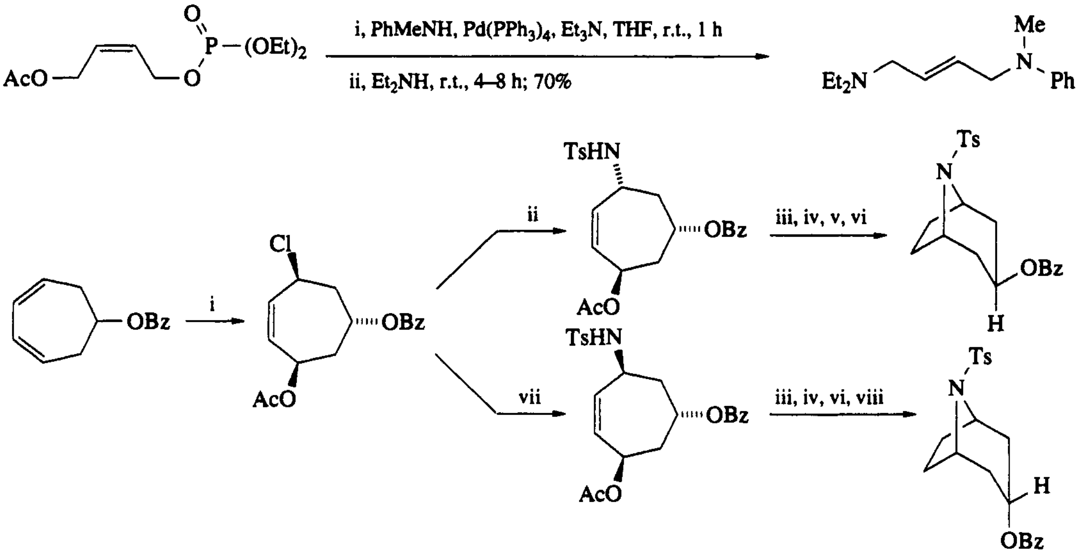
syn-(**111**)

syn-(**112**) >92%

anti-(**112**) >90%

Scheme 50

transformation of acyclic allylic substrates, the resulting amines have, in general, the (*E*)-configuration irrespective of the original alkene geometry.[93,94]



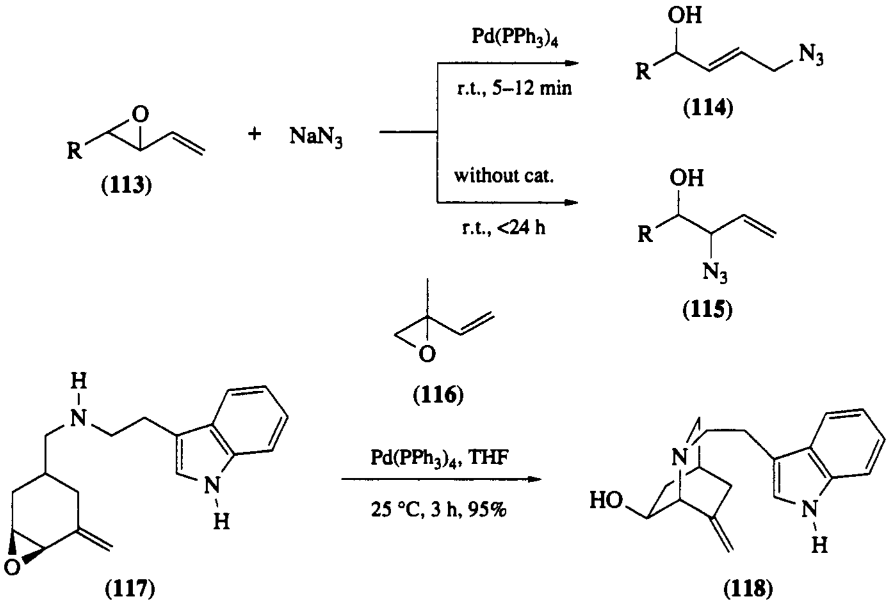
i, $Pd(OAc)_2$, LiCl, LiOAc, *p*-benzoquinone, AcOH (77%); ii, NaNHTs, MeCN–DMSO, 80 °C, 3 h (77%); iii, H_2 (6 atm), $RhCl(PPh_3)_3$, EtOH, 20 °C, 15 h (98%, 95%); iv, NaOH, MeOH–H_2O (98%, 95%); v, MsCl, Et_3N, THF (100%); vi, K_2CO_3, MeOH, 1 h, 20 °C (97%, 90%); vii, NaNHTs, $Pd(PPh_3)_4$, MeCN–DMSO, 20 °C, 12 h (64%); viii, DEAD, $ZnCl_2$, Bu_3P, 20 °C, 3 h (95%)

Scheme 51

Although a variety of primary and secondary amines can be utilized as nitrogen nucleophiles, amination of allylic substrates with ammonia has been reported to be unsuccessful. Therefore, bis(*p*-methoxyphenyl)methylamine,[95] sodium *p*-toluenesulfonamide[96] or sodium azide[97] have been utilized instead of ammonia. In the presence of a palladium catalyst, imides, such as phthalimide, react with allylic esters with the exception of geranyl and linalyl acetates. *O*-Geranyl- and *O*-linalyl-isourea derivatives, however, reacted with phthalimide giving the expected *N*-allylic phthalimides in 65% and 71% yields, respectively.[98]

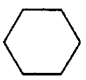
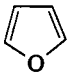
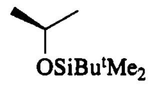
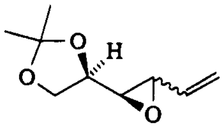
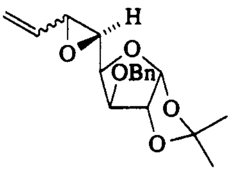
The intermolecular reaction described above has been extended to intramolecular displacement leading to cyclic amines.[99] Reaction of allylic alcohols with morpholine in the presence of a nickel catalyst has also been reported.[100]

In the presence of a palladium catalyst, allyl epoxides (**113**) react with nitrogen nucleophiles at the alkenic carbon atom remote from the oxirane ring to give 1,4-adducts (**114**).[101] In the absence of a palladium catalyst, azide ion attacks the oxirane ring affording 1,2-adducts (**115**; Scheme 52 and Table 2).[101b] Vinyl epoxide (**116**) gave 1,2- and 1,4-azido alcohol in a ratio of 1:1.5 irrespective of the reaction system.[101b] Intramolecular cyclization of vinyl epoxide (**117**) in the presence of a palladium catalyst afforded isoquinuclidine (118; Scheme 52).[101c]



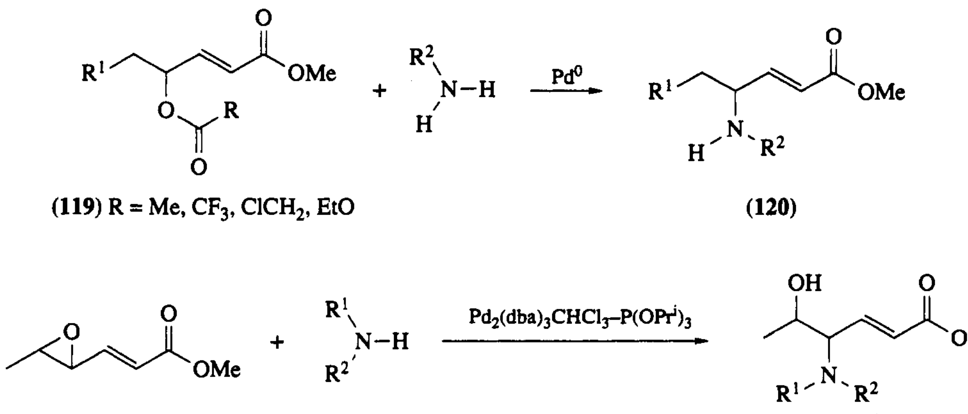
Scheme 52

Table 2 Reaction of **(113)** with NaN_3 in the Presence and Absence of $Pd(PPh)_4$ (Scheme 52)[101b]

(113)	*Yield (%) (syn:anti) with Pd^0* ***(114)***	*Yield^a (%) (syn:anti) without cat.* ***(115)***
R = 	77	NR
R = Ph	81	NR
R = 	68	85 (1:1.5)
R = 	75 (1:1)	NR
 (2:1)	75 (2:1)	88
 (9:1)	82 (9:1)	NR

[a] NR = not recorded.

The palladium-catalyzed reaction of 4-acyloxy-2-alkenoate **(119)** with various primary amines afforded the corresponding 4-amino-2-alkenoates **(120)**. The reactivity of **(119)** strongly depends on the acyl groups at C-4 (Scheme 53).[102] 4,5-Epoxyhex-2-enoate **(121)** hardly reacted with diethylamine, ethyl carbamate and *N*-methylacetamide in the presence of a Pd^0 catalyst, whereas more acidic nitrogen nucleophiles, such as phthalimide, *p*-toluenesulfonamide and benzenesulfonamide, reacted with **(121)** to give γ-*N*-substituted products (**122**; Scheme 53).[103]



(119) R = Me, CF_3, $ClCH_2$, EtO

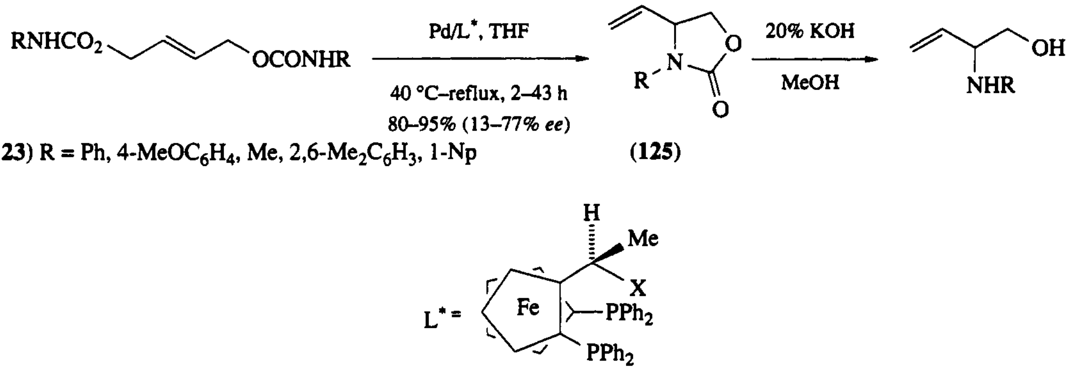
(120)

(121)

(122)

Scheme 53

Cyclization of 2-butene dicarbamate **(123)** in the presence of a palladium catalyst coordinated with chiral ligands **(124)** gave optically active 4-vinyl-2-oxazolidones **(125)**, which were hydrolyzed to optically active 2-amino-3-butenols (Scheme 54).[104]



(123) R = Ph, $4\text{-}MeOC_6H_4$, Me, $2,6\text{-}Me_2C_6H_3$, 1-Np

(125)

(124) X = $NMeCH(CH_2OH)_2$, $NMeCH_2CH_2OH$, NMe_2, OH

Scheme 54

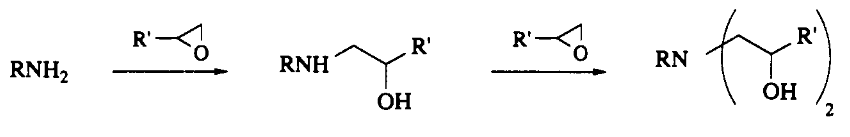
1.3.4 RING OPENING OF SMALL RING HETEROCYCLES BY NUCLEOPHILES

1.3.4.1 Epoxides

Reaction of epoxides with nitrogen nucleophiles affords a variety of β-hydroxyamines and their equivalents. Comprehensive review articles have been published.[105] In conjunction with the development of diastereoselective and enantioselective syntheses of epoxy alcohols, selective oxirane ring cleavage of 2,3-epoxy alcohols and carboxylates by nitrogen nucleophiles has become a versatile route to various amines and their equivalents. For details, the reader is referred to refs. 105c and 105d.

In the reaction with methyloxirane in H_2O at 20 °C, the reactivity of the amines decreases in the order: piperazine > dimethylamine > pyrrolidine > piperidine > morpholine > diethylamine > di-*n*-butylamine > di-*n*-propylamine.[106] Under neutral or basic conditions, nucleophiles generally attack at the sterically less-hindered carbon atom of the oxirane ring.

The simplest method for the preparation of β-amino alcohols consists of heating an amine with an epoxide; limitations sometimes occur with poorly nucleophilic amines and with sensitive epoxides. Another limitation is that the first addition of an amine to an epoxide is often followed by one or more secondary additions (Scheme 55). Therefore, for a primary amine, an excess of the amine is used so that secondary reactions are reduced to a minimum. When a secondary amine is reacted with an epoxide, the product is a tertiary amine and the secondary reaction is insignificant.[106,107]

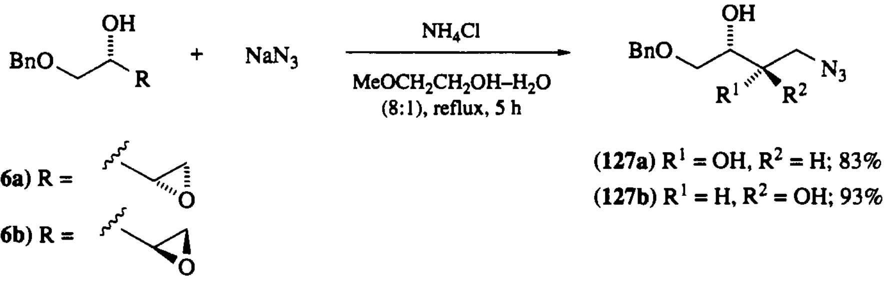


Scheme 55

In order to facilitate the reaction and to improve the regioselectivity of the oxirane ring opening, various procedures have been devised. Cation-exchange zeolites are efficient catalysts for the reaction of amines with epoxides.[108] The advantages of amine-doped alumina over the conventional homogeneous systems have been demonstrated.[109] Moderately acidic and basic zeolites show higher catalytic activity compared to strongly acidic or basic zeolites.[109,110]

Since enantiomerically pure 2,3-epoxy alcohols are readily available by the Sharpless epoxidation procedure,[105,111] the regioselective ring opening of 2,3-epoxy alcohols by nitrogen nucleophiles provides a convenient route to a variety of homochiral amines. A convenient procedure for the conversion of 2,3-epoxy alcohols to 1,2-epoxy-3-alkanols has been developed.[112]

1,2-Epoxy-3-alkanols (**126a**) and (**126b**) reacted with sodium azide to afford 1-azido-2,3-diols (**127a**) and (**127b**) in good yields (Scheme 56).[112]



(**127a**) R^1 = OH, R^2 = H; 83%

(**127b**) R^1 = H, R^2 = OH; 93%

Scheme 56

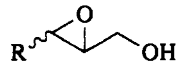
Under basic conditions, 2,3-epoxy alcohols rearrange to 1,2-epoxy-3-alkanols (the Payne rearrangement), resulting in an equilibrium mixture. Therefore, the oxirane ring opening of 2,3-epoxy alcohols with amines under Payne rearrangement conditions (H_2O, base) generally affords three possible isomers with rather poor regioselectivity.[112] Studies on the reaction of a series of 2,3-epoxy alcohols of general formula (**128**) and related compounds with sodium azide under nonisomerized conditions (NH_4Cl, in 2-methoxyethanol/H_2O) have revealed that the ratio of C-3 to C-2 attack is in the range 4:1–C-2 only.[113] In view of the results obtained, it has been demonstrated that, in addition to steric effects, electronic effects can play an important role in regioselectivity of oxirane ring opening reactions.[113] The reaction of epoxy alcohol (**129**) with benzylamine or sodium azide occurred exclusively at the position remote from the free hydroxy group, giving aminodiol (**130**) or azidodiol (**131**) as the sole product (Scheme 57).[114]

The rate and regioselectivity (C-3 attack) of the oxirane ring opening of 2,3-epoxy alcohols by nucleophiles are markedly increased by the addition of $Ti(OPr^i)_4$. Thus, the reaction of 2,3-epoxyhexanol with excess diethylamine in the presence of $Ti(OPr^i)_4$, 1,2-diol (**132**) and 1,3-diol (**133**) were formed in 90% yield in a ratio of 20:1, while, in the absence of the alkoxide, (**132**) and (**133**) were obtained in 4% yields in a ratio of 3.7:1 (Scheme 58).[115]

Regioselective C-2 amination of 2,3-epoxy alcohols can be realized by intramolecular oxirane ring opening of the carbamates prepared by the reaction of the epoxy alcohols with isocyanates.[116,117] In some cases, however, acyl transfer is a serious side reaction (Scheme 59).[117]

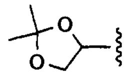
In this connection, intramolecular Michael addition of *O*-carbamates to α,β-unsaturated esters (Scheme 60),[118] iodo cyclization of allylic and homoallylic trichloroacetamidates[119] or aminomercuration of alkenic carbamates[119] has been used for the preparation of amino alcohols.

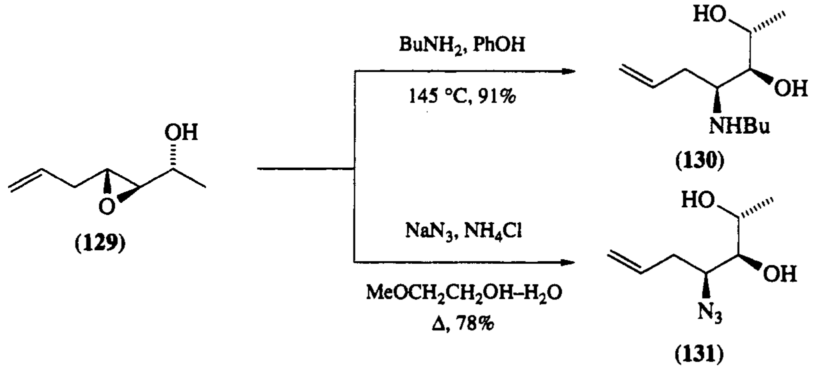
Tetraphenylstibonium triflate (Ph_4SbOTf; **134**) has been reported to be an effective catalyst for oxirane ring opening. Thus, otherwise unreactive cyclohexene oxide reacted smoothly with diethylamine in the presence of (**134**) (CH_2Cl_2, 40 °C, 20 h) to give (*E*)-2-diethylaminocyclohexanol in 75% yield.[120]



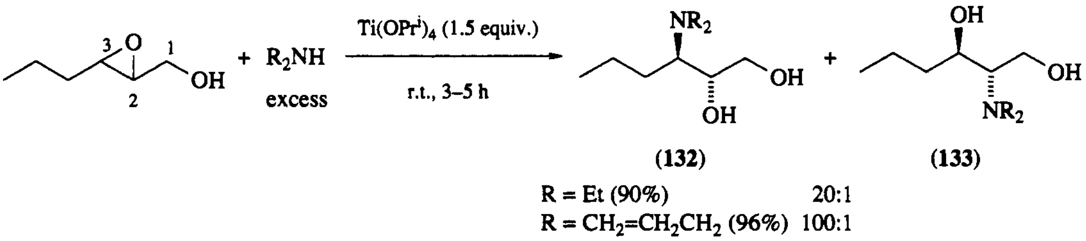
(128)

R = C_nH_{2n+1}, Bn, C_6H_{11}, Bu^t,

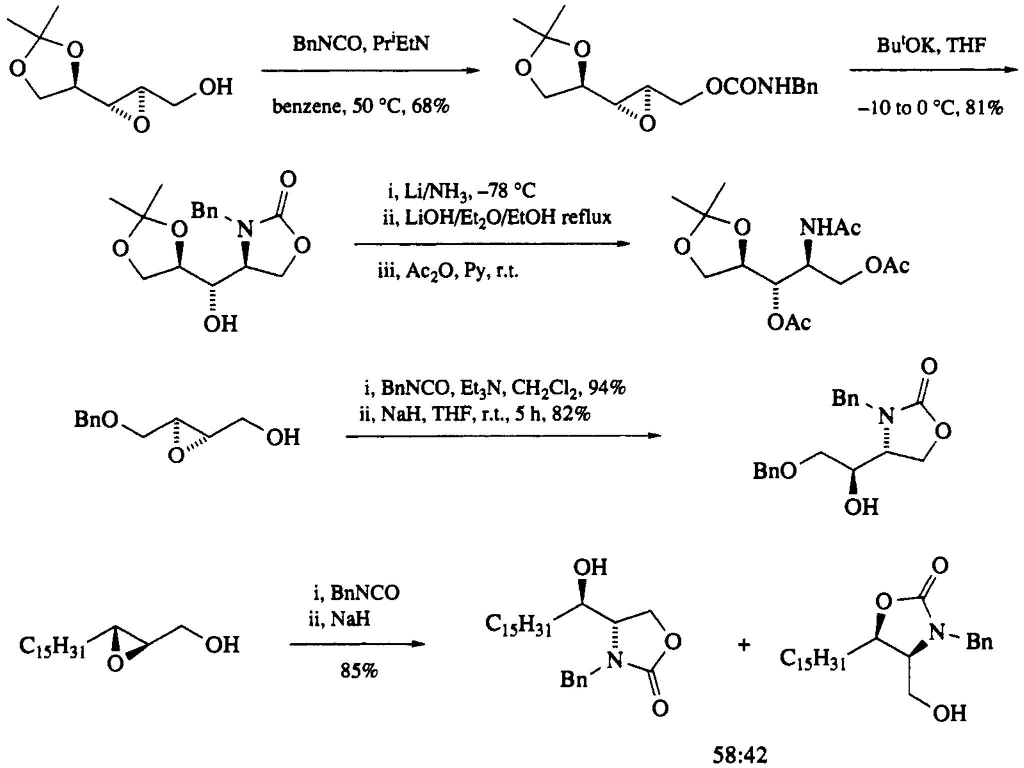




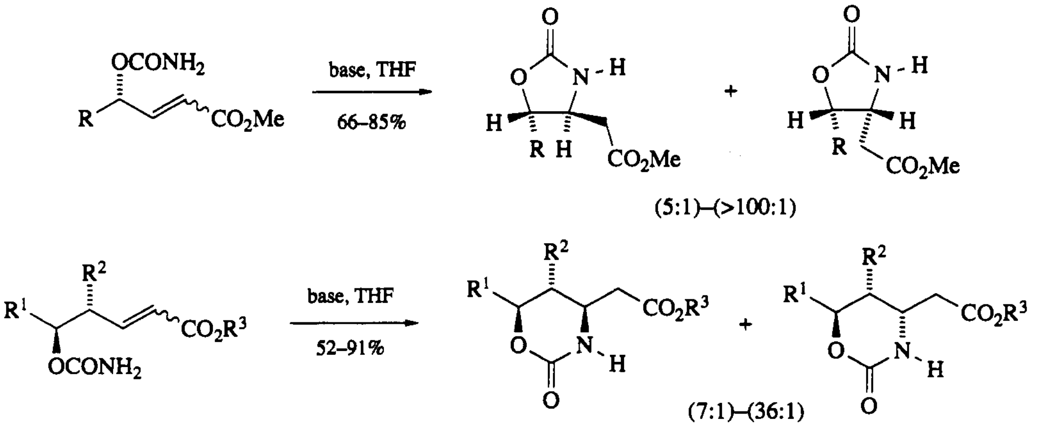
Scheme 57



Scheme 58



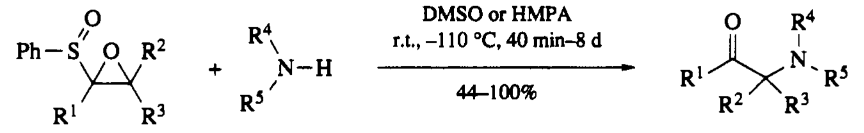
Scheme 59



Scheme 60

Conversion of amines into metal amides is an alternative method to facilitate the oxirane ring opening. The metal amides used are, for example, diethylaluminum amides,[121a] trimethylsilylamides[121b] and halomagnesium amides.[121c]

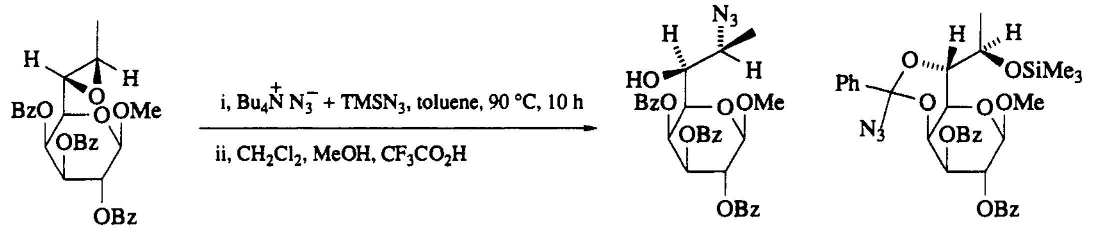
α,β-Epoxy sulfoxides reacted with various amines to afford the corresponding α-amino ketones (Scheme 61).[122]



Scheme 61

Alkali metal azides react with epoxides in a appropriate solvent to give vicinal azidohydrins. Phase-transfer reagents may be used. The reactions usually require high temperatures and/or long reaction times.

Reaction of epoxide (**135**) with tetra-*n*-butylammonium azide in the presence of trimethylsilyl azide (TMSN$_3$) afforded a high yield of azidohydrin (**136**) along with *ortho*-acyl azide (**137**; Scheme 62).[123] It has been reported that omission of TMSN$_3$ in the reaction resulted in extensive acyl transfer. Lewis acid catalyzed oxirane ring opening (ZnCl$_2$/TMSN$_3$) of (**135**) gave (**137**).[123]

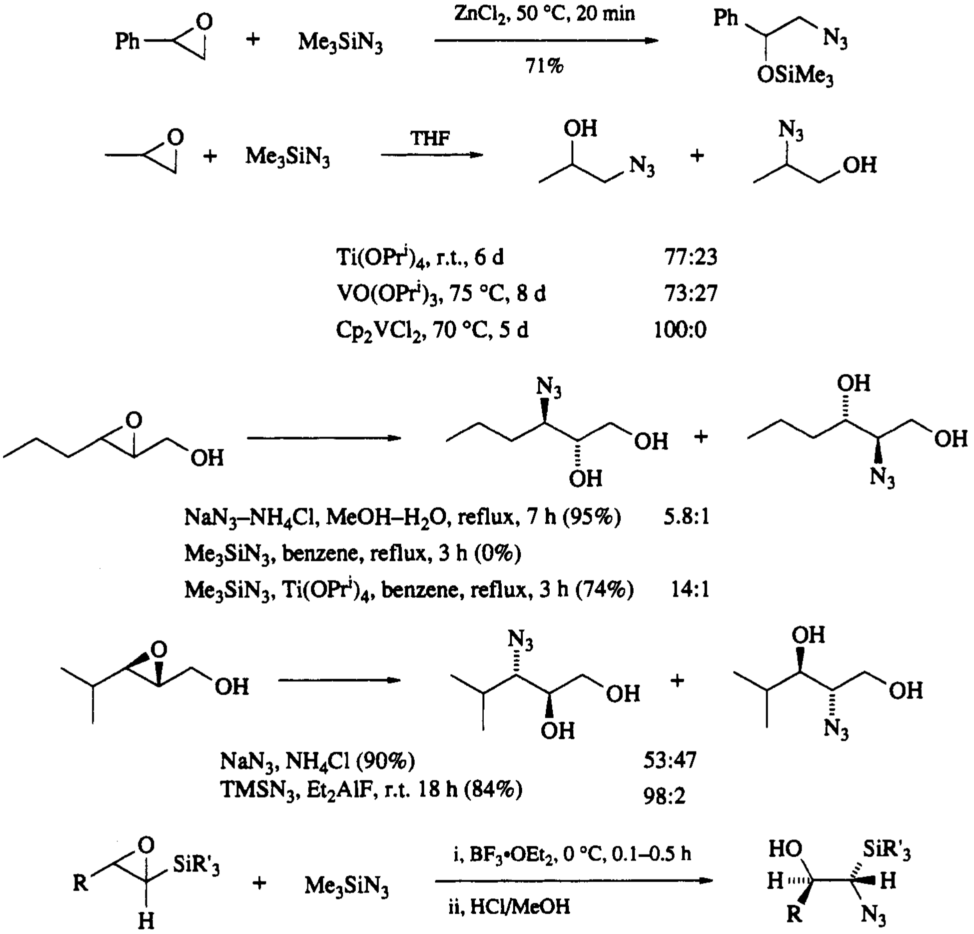


(**135**) (**136**) 78% (**137**) 14%

Scheme 62

TMSN$_3$ can also react with epoxides in the presence of an appropriate catalyst (Scheme 63), such as ZnCl$_2$,[124] Ti(OPr^i)$_4$,[115,125] VO(OPr^i)$_3$,[125a] CpVCl$_2$,[125a] Et$_2$AlF,[126] Al(OPr^i)$_3$[127] or BF$_3$·OEt$_2$.[128,129b]

When 2,3-anhydro-4-*O*-tosyl pyranoside (**138**) reacted with sodium azide, azide ion attacked first at C-4 and then oxirane ring opening took place, giving diazido derivatives (**139a**) and (**139b**).[129a] In contrast, in the reaction of (**138**) with TMSN$_3$ in the presence of BF$_3$·OEt$_2$, only oxirane ring cleavage occurred to give (**140a**) and (**140b**).[129b] Alternatively, 2,3-anhydrotriflate (**141**) reacted with sodium azide affording anhydroazide (**142**; Scheme 64).[129c]



Ti(OPr^i)$_4$, r.t., 6 d 77:23

VO(OPr^i)$_3$, 75 °C, 8 d 73:27

Cp$_2$VCl$_2$, 70 °C, 5 d 100:0

NaN$_3$–NH$_4$Cl, MeOH–H$_2$O, reflux, 7 h (95%) 5.8:1

Me$_3$SiN$_3$, benzene, reflux, 3 h (0%)

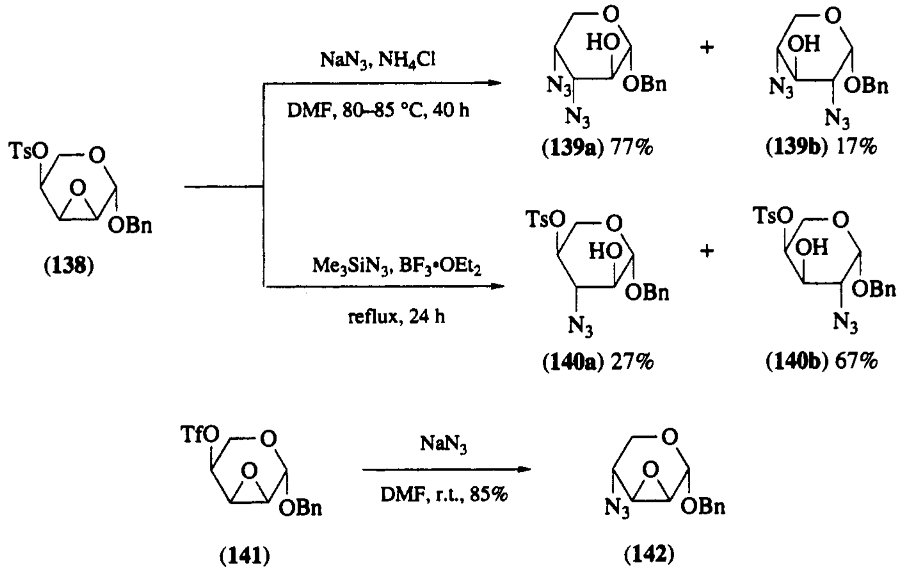
Me$_3$SiN$_3$, Ti(OPr^i)$_4$, benzene, reflux, 3 h (74%) 14:1

NaN$_3$, NH$_4$Cl (90%) 53:47

TMSN$_3$, Et$_2$AlF, r.t. 18 h (84%) 98:2

R = H, R' = Me, 86%; R = 1-hydroxycyclohex-1-yl, R' = Et, 74%

Scheme 63



(138)

(139a) 77%

(139b) 17%

(140a) 27%

(140b) 67%

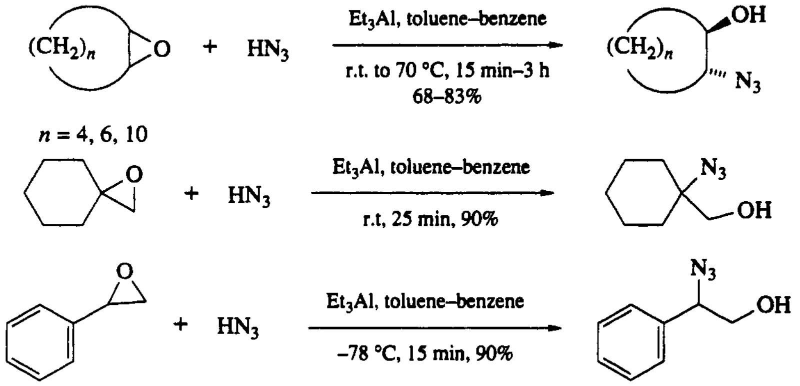
(141)

(142)

Scheme 64

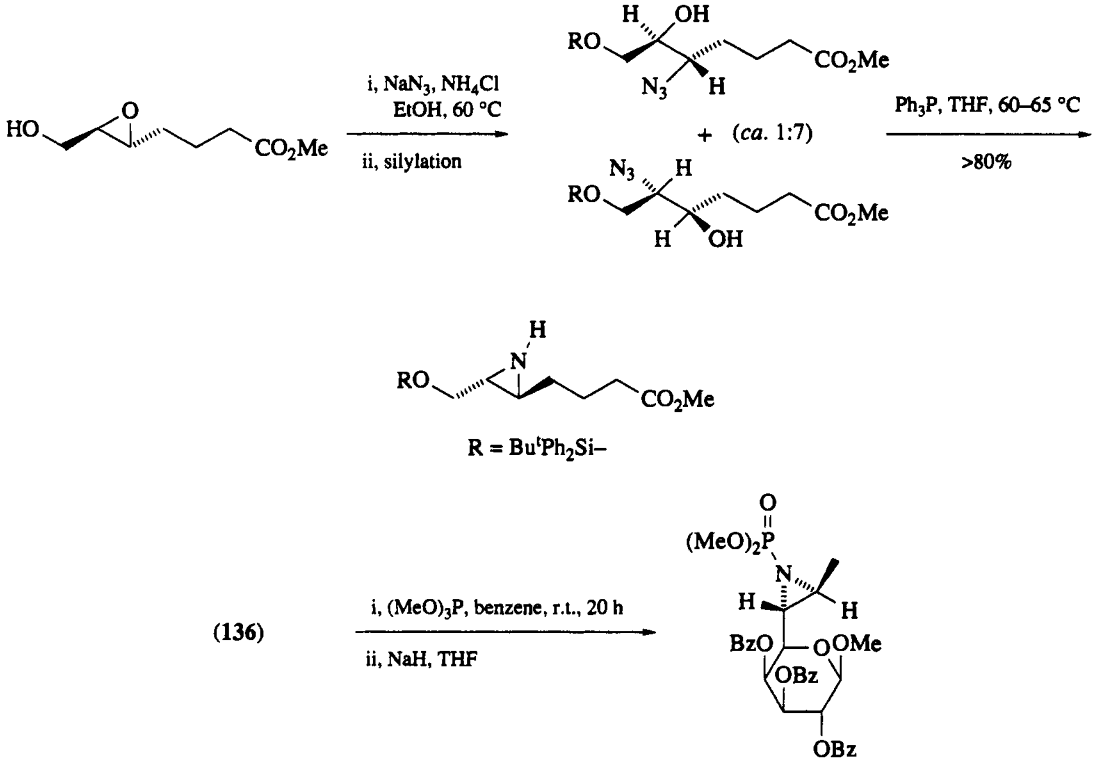
As shown in Scheme 63, the regioselectivity of oxirane ring opening of 2,3-epoxy alcohols is increased in $TMSN_3$–Lewis acid systems compared to conventional systems using sodium azide. It has been reported, however, that sodium azide supported on zeolite CaY facilitates the C-3 attack.[130]

A mild and highly stereoselective transformation of epoxides to azido alcohols by treatment with $Et_3Al–HN_3$ in toluene has been reported (Scheme 65).[131]



Scheme 65

As described above, 1,2-azido alcohols can be stereospecifically prepared from epoxides. 1,2-Azido alcohols thus prepared reacted with triphenylphosphine or trialkyl phosphites to afford aziridines, where inversion of both centers of the original epoxides takes place (Scheme 66).[123,132] Intramolecular oxirane ring opening by nitrogen nucleophiles affords heterocyclic compounds.[133]

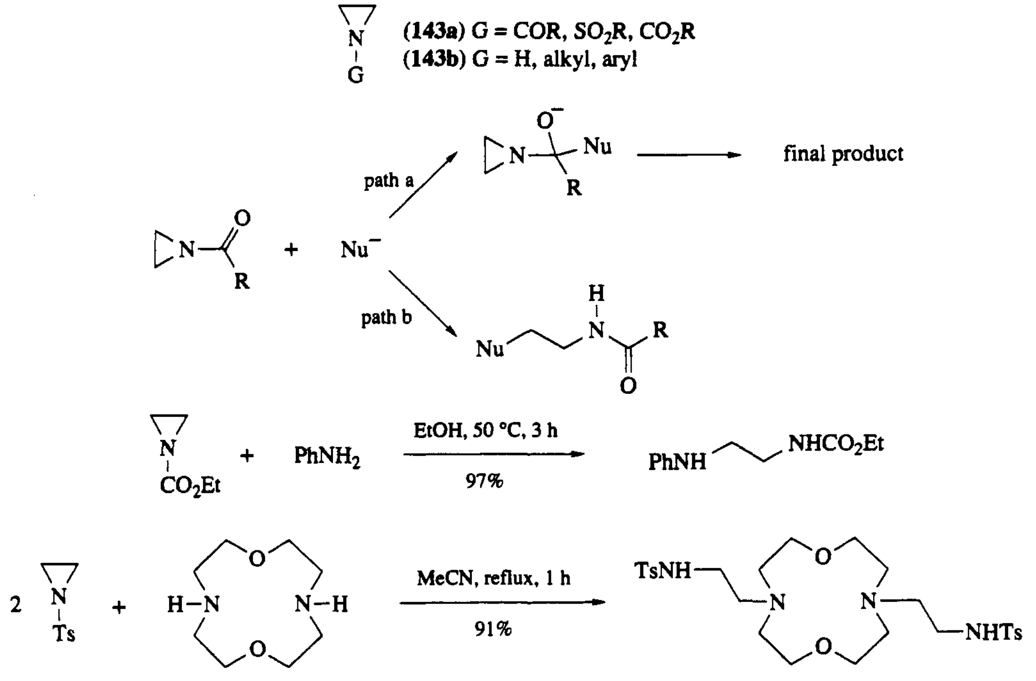


Scheme 66

1.3.4.2 Aziridines

Aziridines can be prepared by various methods which involve dehydration of β-amino alcohols and dehydrohalogenation of β-amino halides.[134] Therefore, the reactions of aziridines with oxygen nucleophiles[135] and halide ions[136] will not be described in this section. A short review article has been published.[137]

Aziridines may be classified into two groups.[138] 'Activated aziridines (**143a**)' contain substituents capable of stabilizing a negative charge developed in the transition state of nucleophilic ring opening. The activated aziridines undergo ring-opening reactions with nucleophiles in the absence of catalysts (Scheme 67),[138,139] while 'unactivated aziridines (**143b**)' generally require acidic catalysts to promote the reaction. Since aziridine activated by a carbonyl group is an ambident electrophile, nucleophiles can attack the carbonyl carbon (Scheme 67, path a) and the ring carbon (Scheme 67, path b).



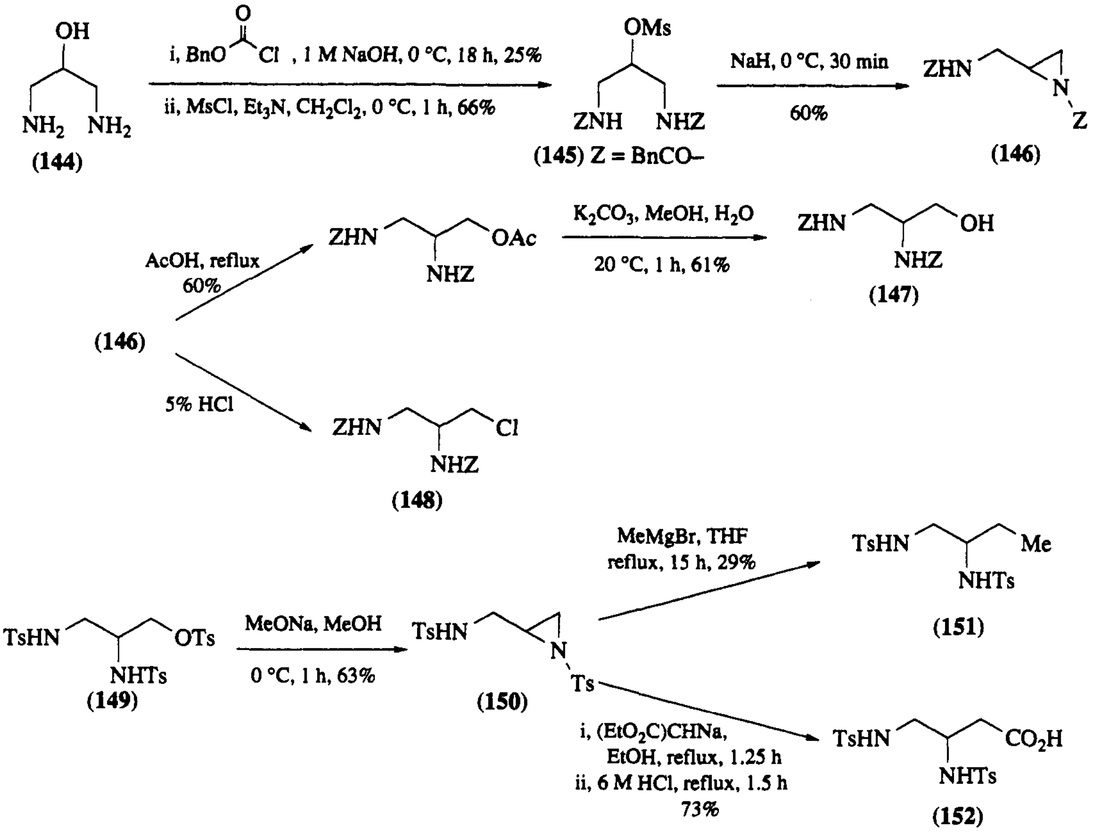
Scheme 67

Transformation of 1,3-diamino-2-propanol (**144**) into vicinal diamines has been reported.[140] Thus, the bis(benzyloxycarbonyl) derivative of (**144**) was mesylated to give (**145**), which was converted into 1-benzyloxycarbonylaziridine (**146**). Acetic acid and HCl reacted at the ring carbon of (**146**) affording 2,3-diamino-1-propanol (**147**) and 1-chloro-2,3-diaminopropane (**148**; Scheme 68). On the other hand, the reaction of (**146**) with Grignard reagents and sodio malonates resulted in the loss of the carbamate protecting group. In contrast, the sulfonamide derivative (**149**) could be converted into diamines (**151**) and (**152**) *via* 1-tosylaziridine (**150**; Scheme 68).

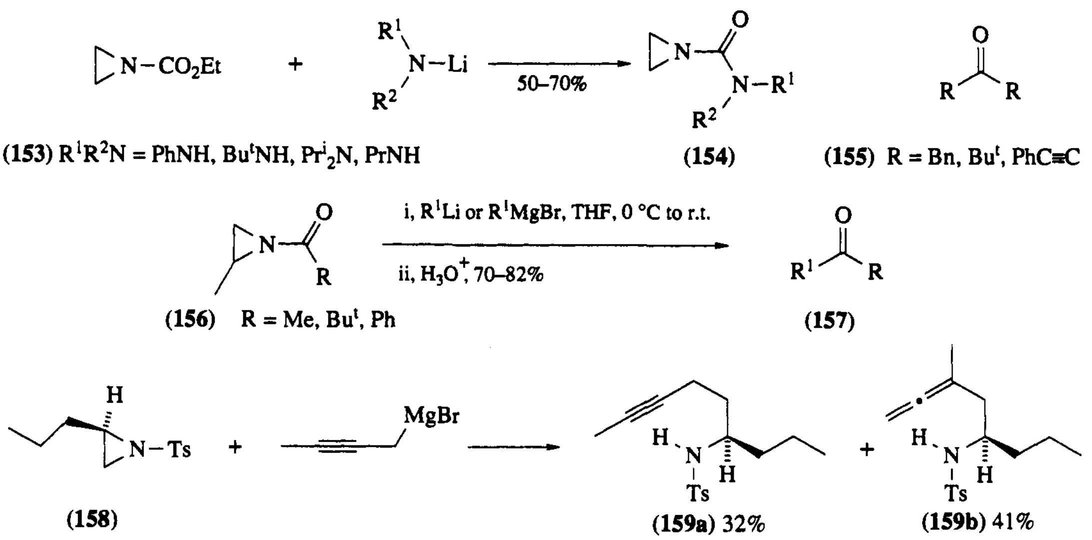
1-Ethoxycarbonylaziridine (**153**) has been reported to react with lithium amides affording carbonyl addition–elimination products (**154**; Scheme 69).[141] The reaction of (**153**) with trityllithium proceeded through path b in Scheme 67, while diphenylmethyllithium gave both 1-(diphenylacetyl)aziridine (path a; 33%) and *N*-(3-diphenylpropyl)carbamate (path b; 66%). Benzyllithium, *t*-butyllithium and lithium phenylacetylide afforded the corresponding symmetrical ketones (**155**).[141] 1-Acylaziridines (**156**) reacted with various organolithium and Grignard reagents to produce ketones (**157**) in high yields (Scheme 69).[142] 1-Tosylaziridine (**158**) reacted with 2-butynylmagnesiumm bromide to give ring-opened products (**159a** and **159b**; Scheme 69).[143]

The studies of the reaction of 1-substituted-2-phenylaziridines (**160a**), (**160b**) and (**160c**) with carbon nucleophiles have revealed that regioselectivity depends on the reagent used and reaction conditions. In general, methyl–metal reagents (MeMgBr, Me_2CuLi and $MeCu{\cdot}BF_3$) tend to attack the C-2 of (**160**) to give (**161**; Scheme 70). 1-Tosylaziridine (**160b**) was found to be more reactive than (**160a**). MeLi caused decomposition of (**160b**) and displacement of the *N*-substituent of (**160a**). 1-Methylaziridine (**160c**) was decomposed by Me_2CuLi or $MeCu{\cdot}BF_3$.[144]

In the reaction with carbon nucleophiles and with nitrogen nucleophiles, the reaction site on 1-substituted-2,2-dimethylaziridines (**163**) depends on the degree of leaving group activation. Thus, highly activated aziridine was attacked at C-3, while less activated aziridines were attacked at C-2 (Scheme 70).[145] The reaction of (**163**; G = Ts—, 2,5-$Cl_2C_6H_3SO_2$—, Bu^{t}C(O)—) with Grignard reagents (RMgX) is



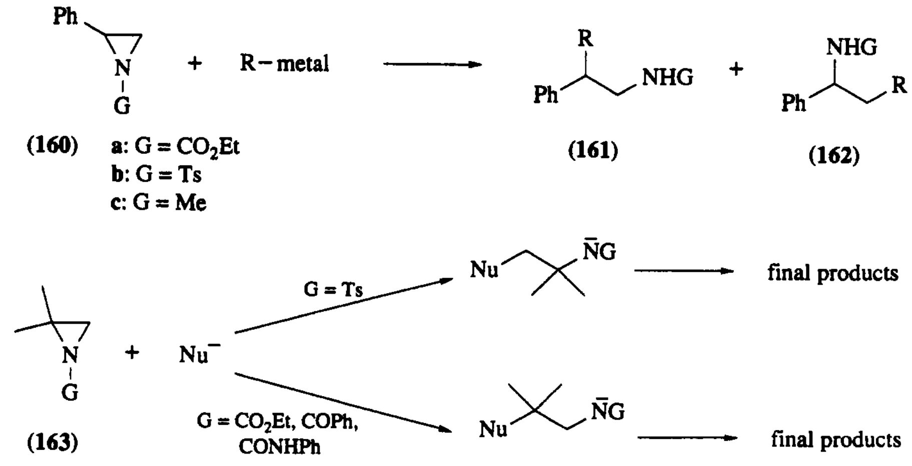
Scheme 68



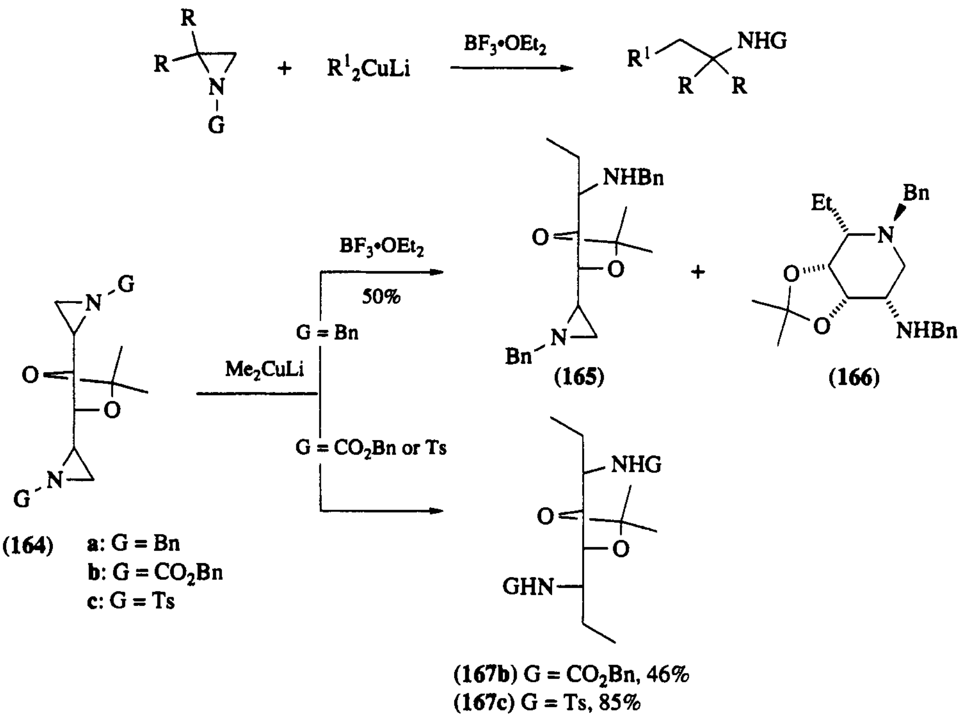
Scheme 69

more complicated; the product distribution depends on the activating group G, R, X and reaction conditions.[146]

Boron trifluoride etherate promotes the nucleophilic ring opening of unactivated aziridines with diorganocopperlithiums leading to both primary and secondary amines (Scheme 71).[147] Reaction of 1-benzyldiaziridine (**164a**) with Me_2CuLi promoted by $BF_3{\cdot}OEt_2$ afforded monobenzylamine (**165**) and piperidine derivative (**166**). When 1-benzyloxycarbonyl- or 1-tosyl-diaziridine (**164b**) and (**164c**) were allowed to react with Me_2CuLi without Lewis acid catalysts, diamine (**167b**) or (**167c**) was obtained (Scheme 71).[132c]



Scheme 70

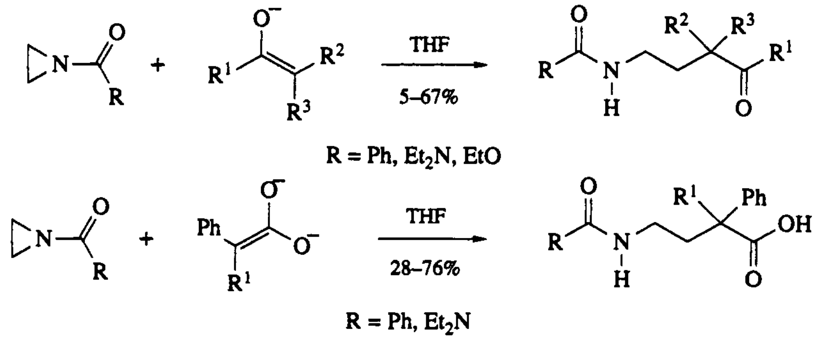


Scheme 71

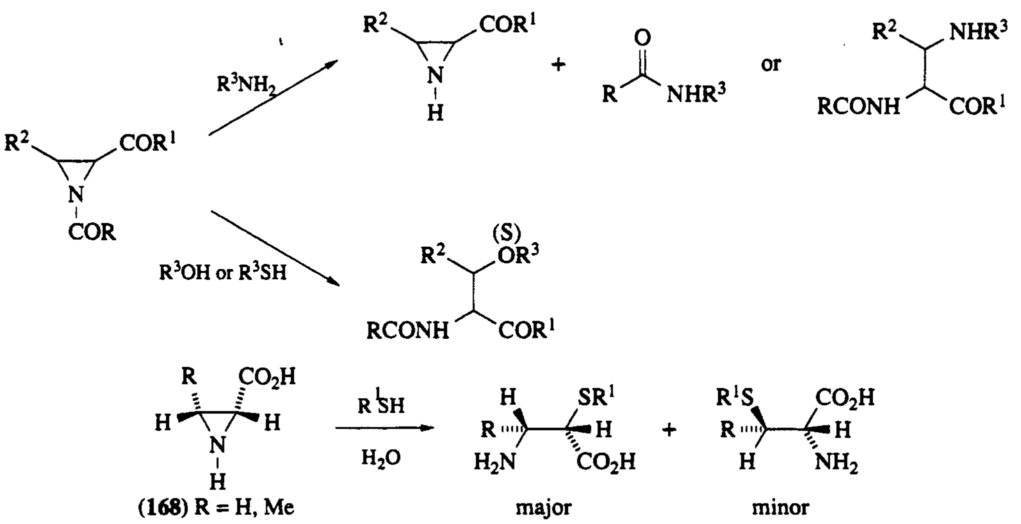
Sodium enolates of ketones and disodium enediolates of substituted phenylacetic acids reacted with activated aziridines to afford γ-amido ketones and γ-amidobutyric acids, respectively (Scheme 72).[148]

Aziridine-2-carboxylic acid esters can be utilized as versatile precursors for amino acid derivatives.[149] Although the product distribution resulting from the reaction of activated aziridine-2-carboxylates with amines depends on the structure of the reactants, the reactions with alcohols or thiols in the presence of acidic catalysts generally gave the α-amino acid derivatives (Scheme 73).[149,150] On the other hand, free 3-methyl-2-aziridinecarboxylic acids (**168**) reacted with thiophenol, cysteine and glutathione to afford β-amino acid derivatives with sulfur substituents at the α-position as the main product (Scheme 73).[151]

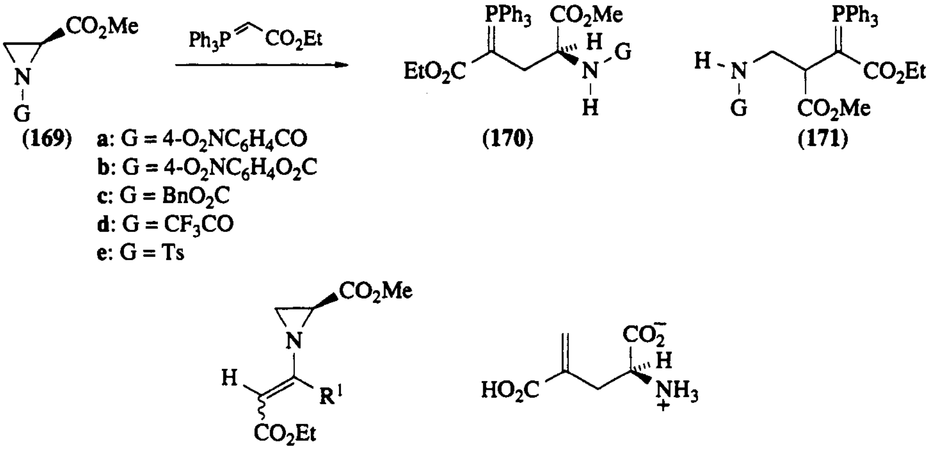
The reaction of activated aziridine-2-carboxylic acid methyl esters (**169**) with ethoxycarbonylmethylenetriphenylphosphorane resulted in the formation of phosphorane (**170**) along with phosphorane (**171**) and aziridine (**172**), with the exception of (**169d**), where (**172d**) was obtained as the sole product (Scheme 74).[152] Phosphorane (**170b**) was converted into 4-methylene-(2*S*)-glutamic acid (**173**).[152]



Scheme 72

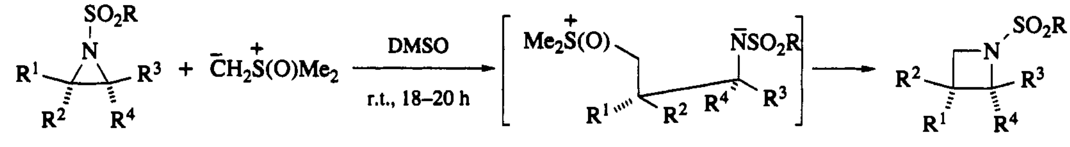


Scheme 73



Scheme 74

The reaction of (*Z*)- and (*E*)-1-arylsulfonylaziridines with dimethyloxosulfoniummethylide proceeded stereospecifically to yield (*E*)- and (*Z*)-azetidines, respectively (Scheme 75).[153]

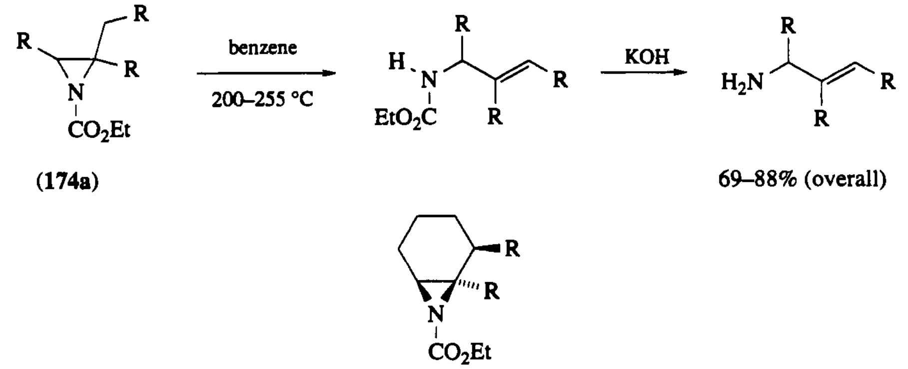


R = Ph, 4-ClC_6H_4, 4-MeC_6H_4

44–80%

Scheme 75

Thermal rearrangement of cyclic and acyclic 1-ethoxycarbonylaziridines (**174a**) and (**174b**) afforded allylic carbamates, which were hydrolyzed to primary allylic amines (Scheme 76).[154]



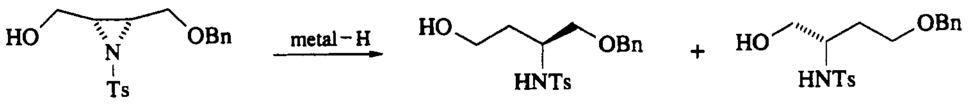
(**174a**)

69–88% (overall)

(**174b**)

Scheme 76

Reaction of 1-acylaziridines with $LiAlH_4$ resulted only in attack at the carbonyl site. In contrast, reduction of (**153**) with $NaBH_4$ in ethanol gave ethyl *N*-ethylcarbamate.[141] Reduction of chiral aziridines (**175**) with various metal hydrides reveals that Red-Al gave the best result (Scheme 77 and Table 3).[132c]



(**175**) (**176**) (**177**)

Scheme 77

Table 3 Reduction of (**175**; Scheme 77)[132c]

Reagent and reaction conditions	*Isolated yield (%)*	*Ratio (176):(177)*
Red-Al, THF, –78 °C	86	>100:1
LAH, THF, –20 °C	80	>100:1
DIBAL-H, THF, –78 °C → r.t.	30[a]	>100:1
DIBAL-H, C_6H_6, 0 °C → r.t.	20[a]	1:1
$NaBH_4/Ti(OPr^i)_4$, C_6H_6, r.t.	No reaction	

[a] Reaction incomplete.

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1.4
Synthesis of Nitroso, Nitro and Related Compounds

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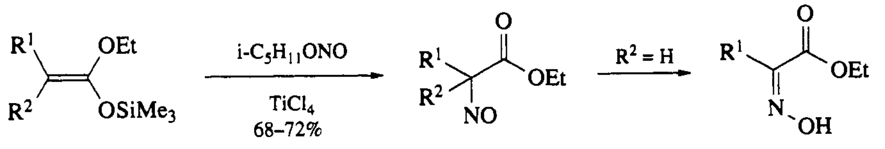
1.4.1 NITROSO COMPOUNDS

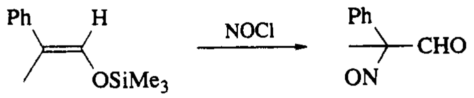
Some comprehensive reviews of the chemistry of *C*-nitroso compounds already exist.[1] Since the latest general review was published, no other relevant new findings on the formation of nitroso compounds by substitution processes have been reported. Reviews of special interest deal with the syntheses and properties of aliphatic fluoronitroso compounds,[2] nitrosoalkenes and nitrosoalkynes,[3] electrophilic *C*-nitroso compounds,[4] α-halonitroso compounds[5] and nitrosation mechanisms.[6]

Indirect replacement of the α-hydrogen atom of carboxylic esters by the nitroso group is remarkable.[7] This procedure uses ketene *O*-alkyl *O'*-silyl acetals (**1**), generated from carboxylic esters, which are treated with nitric oxide or isopentyl nitrite in the presence of titanium(IV) chloride. In the absence of an α-hydrogen α-nitroso esters (**2**) are obtained. α-Nitroso esters with an α-hydrogen undergo isomerization to oximes of α-keto esters (**3**; equation 1). Similarly, silyl enol ethers of aldehydes or ketones can be used instead of the carbonyl compound itself for nitrosation. Thus, treatment of enol ether (**4**) with nitrosyl chloride gives the α-nitroso aldehyde (**5**; equation 2),[8] which is quite stable at 0 °C, but dimerizes at room temperature.



(1)

(**1**) R^1 = Me, Et, Ph; R^2 = Me, Ph (**2**) (**3**)



(2)

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

1.4.2 NITRO COMPOUNDS

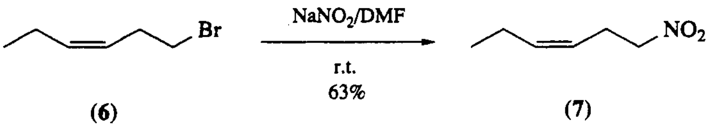
There are several general reviews of this area of chemistry.[9] This section covers mainly novel methods and improvements to established procedures for the preparation of nitro compounds which have been published within the last 10 years.

1.4.2.1 Aliphatic Nitro Compounds

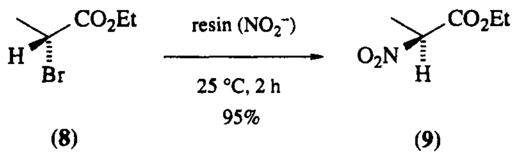
1.4.2.1.1 Nitroalkanes

Substitution of halogen by a nitro group is still one of the most important methods for the laboratory preparation of primary and secondary nitroalkanes. With sodium nitrite, solvents such as dimethylformamide and dimethyl sulfoxide are employed. For example, (*Z*)-1-nitrohex-3-ene (**7**) was prepared from (*Z*)-1-bromohex-3-ene (**6**; equation 3).[10] For the transformation of α-bromo esters into α-nitrocarboxylic esters the use of an anion-exchange resin in anhydrous benzene or ethanol has been recommended. With

(*R*)-ethyl 2-bromopropanoate (**8**) under these conditions the corresponding (*S*)-nitro ester (**9**) is formed with inversion of configuration (equation 4), but it racemizes during the reaction.[11] A short review of the preparation of chiral nitro compounds exists.[12]

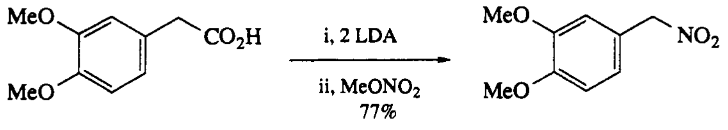


(6) **(7)** (3)



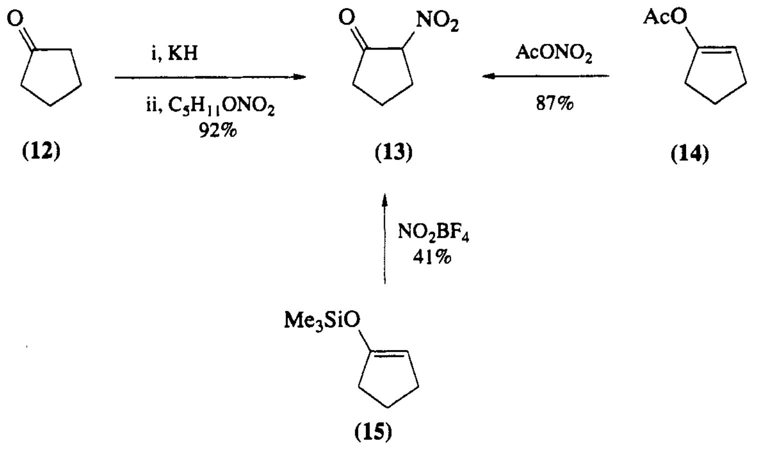
(8) **(9)** (4)

The condensation of dianions of ring-methoxylated phenylacetic acids like (**10**) with methyl nitrate provides a general, one-step procedure to the corresponding phenylnitromethane (**11**; equation 5).[13] Methods for the preparation of nitroacetic esters have been summarized.[14]



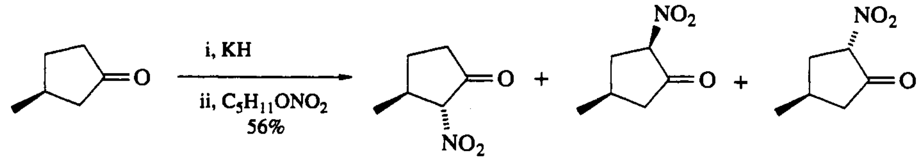
(10) **(11)** (5)

The alkyl nitrate nitration, a reaction of a nitrate ester in the presence of a base with active methylene compounds, enables the introduction of a nitro group at carbons in the α-position to the activating group. This reaction has been applied to a variety of active methylene compounds such as ketones, aliphatic carboxylic esters, amides, lactams, alkane sulfonate esters, activated toluenes and heterocyclic compounds.[15] The preparation of cyclic α-nitro ketones as well as the synthetic utility of these synthetic intermediates has been reviewed.[16] 2-Nitrocyclopentanone has been synthesized by three routes starting with cyclopentanone (**12**; Scheme 1).[17] Treatment of the potassium enolate of cyclopentanone with pentyl nitrate gives 2-nitrocyclopentanone (**13**) in 92% yield. An alternative route to 2-nitrocyclopentanone (**13**) in 87% yield is the nitration of 1-acetoxycyclopentene (**14**) with acetyl nitrate, generated *in situ* from nitric acid and acetic anhydride. Nitration of 1-trimethylsiloxycyclopentene (**15**) with nitronium tetrafluoroborate gives (**13**) in a yield of 41%. Enol ethers (**14**) and (**15**) can be obtained from cyclopentanone.



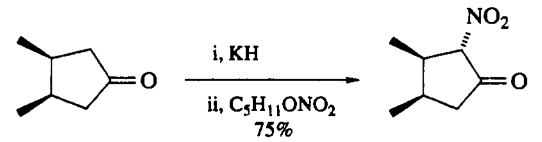
Scheme 1

Generating the enolates of substituted cyclic ketones by using potassium hydride leads to the thermodynamic mixture of enolates, and therefore nitration of potassium enolates often does not allow for a regiospecific synthesis of α-nitro ketones. For example, the potassium enolate of 3-methylcyclopentanone (**16**) gives three isomers in a ratio (**17**):(**18**):(**19**) = 2:1:1 (equation 6). On treatment of the potassium enolate of *cis*-3,4-dimethylcyclopentanone (**20**) with pentyl nitrate *trans*-2-nitro-*cis*-3,4-dimethylcyclopentanone (**21**) is formed diastereoselectively (equation 7).[18]



(**16**) (**17**) 50% (**18**) 25% (**19**) 25%

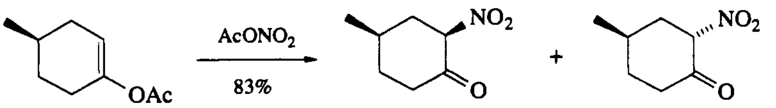
(6)



(**20**) (**21**)

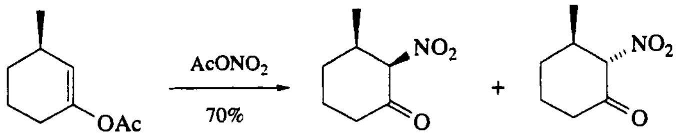
(7)

The nitration of enol acetates with acetyl nitrate is a regiospecific electrophilic addition to the β-carbon of the enol acetate, followed by a hydrolytic conversion of the intermediate to the α-nitro ketone. With enol acetates of substituted cyclohexanones the stereochemistry is kinetically established. So, 1-acetoxy-4-methylcyclohexene (**22**) yields the thermodynamically less stable *trans*-4-methyl-2-nitrocylohexanone (**24**) in greater proportion (*cis*:*trans* = 40:60) (equation 8). This mixture can be equilibrated in favor of the thermodynamically more stable *cis* diastereomer (**23**) (*cis*:*trans* = 85:15). Nitration of 1-acetoxy-3-methylcyclohexene (**25**) leads to *trans*-3-methyl-2-nitrocyclohexanone (**26**), which is also the thermodynamically more stable isomer (equation 9).[19] No stereoselection occurs in the kinetically controlled nitration with acetyl nitrate of 1-acetoxy-5-methylcyclohexene (**27**; equation 10), but the 1:1 mixture of the 5-methyl-2-nitrocyclohexanones can be equilibrated in favor of the *trans* diastereomer (**28**) (*cis*:*trans* = 10:90). 2-Alkyl-2-nitrocyclohexanones cannot be prepared in acceptable yields by nitration of the corresponding enol acetates with acetyl nitrate.



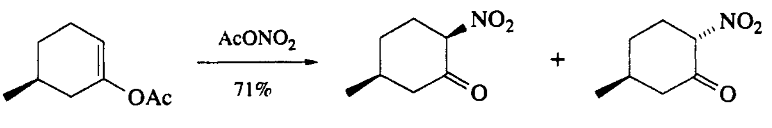
(**22**) (**23**) 40% (**24**) 60%

(8)



(**25**) <1% (**26**) >99%

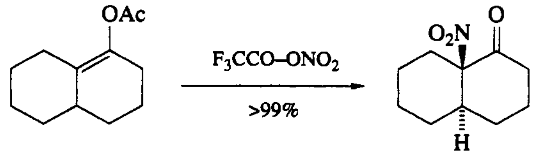
(9)



(**27**) 50% (**28**) 50%

(10)

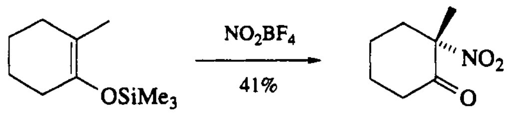
It has been demonstrated that a mixture of ammonium nitrate and trifluoroacetic anhydride is a very effective system for the nitration of enol acetates. It is assumed that trifluoroacetyl nitrate is produced, which is a much more powerful nitrating agent than acetyl nitrate. So, 2-methyl-2-nitrocyclohexanone can be obtained from 2-methyl-1-acetoxycyclohexene in nearly quantitative yield. Also, the enol acetate of decalone (**29**) was quantitatively converted to *trans*-10-nitro-1-decalone (**30**; equation 11).[20]



(29) **(30)**

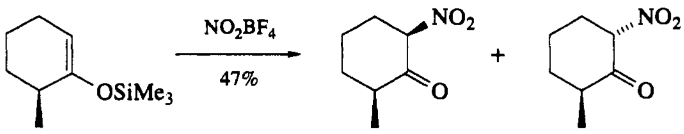
(11)

Nitration of 2-methyl-1-(trimethylsiloxy)cyclohexene (**31**) with nitronium tetrafluoroborate leads to 2-methyl-2-nitrocyclohexanone (**32**; equation 12), while 6-methyl-1-(trimethylsiloxy)cyclohexene (**33**) gives under similar conditions a 30:70 mixture of *cis*- and *trans*-6-methyl-2-nitrocyclohexanone (equation 13).[21] The desilylative nitration of allylsilanes with nitronium tetrafluoroborate proceeds readily. The reaction is considered to pass through initial electrophilic attack of the nitronium ion on the allyl system followed by desilylative elimination. So, on treatment of 1-(trimethylsilyl)but-2-ene (**34**) with nitronium tetrafluoroborate the product is 3-nitrobut-1-ene (**35**) and not 1-nitrobut-2-ene (equation 14).[22]



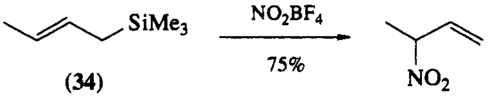
(31) **(32)**

(12)



(33) 30% 70%

(13)



(34) **(35)**

(14)

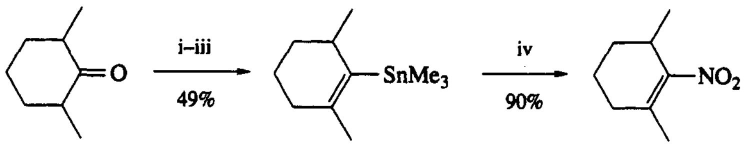
The synthesis of polynitropolycyclic cage molecules has been reviewed.[23]

1.4.2.1.2 Conjugated nitroalkenes

There are reviews dealing with conjugated nitroalkenes in organic synthesis,[24] nitroenamines,[25] the oxyalkylation of carbonyl compounds with conjugated nitroalkenes[26] and the use of conjugated nitroalkenes in the synthesis of heterocyclic compounds.[27] In this section mainly the preparation of nitroalkenes starting from alkenes is described.

In principle nitroalkenes should be available from direct nitration of vinyl carbanions. However, this reaction is not practical due to the potential anionic polymerization. But vinylstannanes obtained from ketones can be used instead of vinyl carbanions. Tetranitromethane is effective in replacing tin by nitro at unsaturated carbon. This method has been used to prepare several alkyl-substituted 1-nitrocyclohexenes and 1-nitrocycloheptenes (Scheme 2).[28]

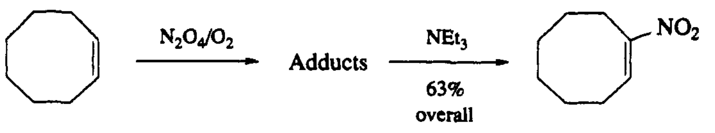
Dinitrogen tetroxide addition to alkenes in the presence of oxygen leads to mixtures of *vic*-dinitro compounds, β-nitro nitrites and nitrates. Nitroalkenes may be prepared without isolation of the adducts by treating the mixture with basic reagents. 1-Nitrocyclooctene (**37**) can be obtained from cyclooctene (**36**) by this route (equation 15).[29] The same reaction sequence has been used for the regioselective and stereoselective preparation of (*E*)-2-nitroethenyltrimethylsilane (**38**; equation 16).[30] In the presence of iodine with alkenes and dinitrogen tetroxide β-nitroalkyl iodides are formed. These give 1-nitroalkenes



i, 2,4,6-triisopropylbenzenesulfonyl hydrazide; ii, Bu^{s}Li; iii, Me$_3$SnCl; iv, C(NO$_2$)$_4$

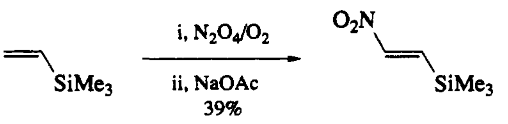
Scheme 2

on dehydrohalogenation. Thus, (*E*)-2-phenylbut-2-ene (**39**) yields (*Z*)-2-nitro-3-phenylbut-2-ene (**40**; equation 17),[31] and methyl acrylate yields methyl (*E*)-3-nitroacrylate.[32]



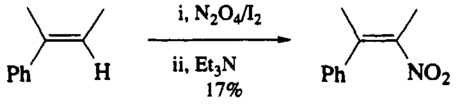
(36) **(37)**

(15)



(38)

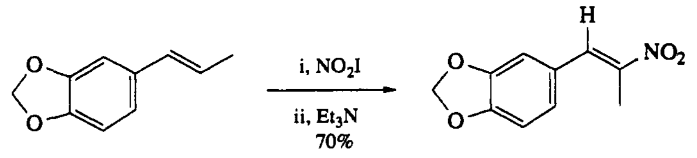
(16)



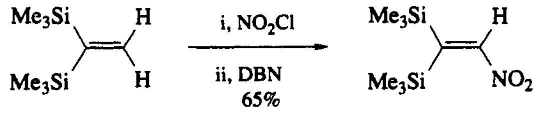
(39) **(40)**

(17)

Nitryl iodide, generated *in situ* by reaction of silver nitrite with iodine, has been used for chemoselective nitration of substituted styrenes (equation 18).[33] Reaction of alkenes with sodium nitrite and iodine in the presence of ethylene glycol provides 1-nitroalkenes without using a base.[34] Nitrovinylsilanes have been prepared by addition of nitryl chloride to a vinylsilane followed by elimination of hydrogen chloride with base from the resulting chloronitrosilane (equation 19).[30,35] In a similar reaction sequence glycals could be transformed to 2-nitroglycals by treatment with nitronium tetrafluoroborate followed by elimination of hydrogen fluoride.[36]

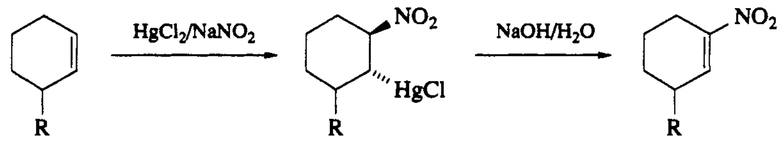


(18)



(19)

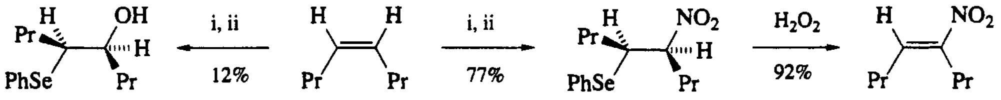
Addition of mercury(II) nitrite, generated *in situ* from mercury(II) chloride and sodium nitrite, provides a general route to 1-nitroalkenes. Thus, on treatment with sodium hydroxide or a tertiary amine the adducts are converted into nitroalkenes in good yields. The clean formation of 2-nitronorbornene from norbornene indicates that carbonium ion rearrangement is not a problem. A further point of interest is the regioselectivity of nitromercuration, illustrated by the nitration of (**42**; Scheme 3).[37] The nitromercuration method has been used for the preparation of 3-nitrocycloalkenones[38] and (*E*)-2-nitroethenyltrimethylsilane.[7]



(41) R = H 80% >98%
(42) R = Me overall 80%

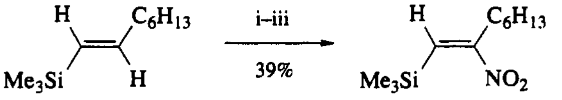
Scheme 3

Another route to conjugated nitroalkenes is based on nitroselenenylation of alkenes. Although the overall yield of nitroalkenes is slightly lower than for nitromercuration, the advantage of nitroselenenylation over nitromercuration is avoidance of aqueous media. Treatment of alkenes with benzene selenyl bromide followed by addition of silver nitrite provides a mixture of 2-nitroalkyl and 2-hydroxyalkyl phenyl selenides. The latter products can be suppressed by addition of mercury(II) chloride. The adducts are converted into conjugated nitroalkenes on oxidation with hydrogen peroxide.[39,40] By using (*E*)- and (*Z*)-oct-4-ene it has been established that the reaction is stereospecific (Scheme 4). Unsymmetrical alkenes give regioisomeric mixtures. Thus on addition, 1-hexene yields Markovnikov product and anti-Markovnikov product in the ratio 78:22.[40] In a similar reaction sequence trialkyl (2-nitro-1-alkenyl) silanes (nitrovinylsilanes) can be prepared starting from vinylsilanes (Scheme 5). In this case the regiochemistry of addition is controlled by the β-effect of the silyl group. This reaction is also stereoselective.[41]



i, PhSeBr; ii, AgNO$_2$/HgCl$_2$

Scheme 4

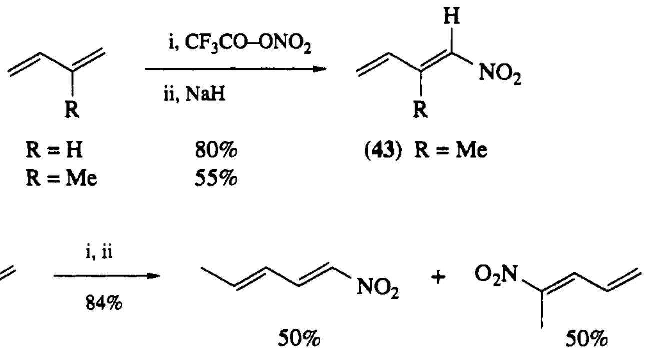


i, PhSeCl; ii, AgNO$_2$/HgCl$_2$; iii, H$_2$O$_2$

Scheme 5

A procedure for the efficient synthesis of 1-nitro-1,3-dienes in two steps involves the *in situ* preparation of trifluoroacetyl nitrate from ammonium nitrate and trifluoroacetic anhydride, and addition to 1,3-dienes to give mixtures of adducts. A mixture of the adducts on treatment with base eliminates to afford 1-nitro-1,3-diene. In the case of isoprene the reaction leads chemo-, regio- and stereo-selectively to (*E*)-2-methyl-1-nitrobuta-1,3-diene (**43**; Scheme 6). In contrast nitrotrifluoroacetoxylation of (*E*)-penta-1,3-diene followed by elimination gives an inseparable mixture of (*E*,*E*)-1-nitropenta-1,3-diene and (*E*)-4-nitropenta-1,3-diene (Scheme 6).[42] Similarly, ethyl vinyl ether has been transformed with acetyl nitrate to ethyl (*E*)-2-nitrovinyl ether.[43]

1-Nitro-2-(trialkylsilyl)alkynes can be synthesized by nitration of bis(trialkylsilyl)alkynes with nitronium tetrafluoroborate or nitronium hexafluorophosphate (equation 20), with nitryl fluoride addition across the triple bond as the major reaction.[44]



i, $CF_3CO-ONO_2$; ii, AcOK

Scheme 6

$$Pr^i_3Si-\equiv-SiMe_3 \xrightarrow[57\%]{NO_2PF_6} Pr^i_3Si-\equiv-NO_2 \qquad (20)$$

1.4.2.2 Aromatic Nitro Compounds

This field has been reviewed recently in a monograph.[45] For syntheses of vicinally substituted nitropyridines an extensive review is accessible.[46] In a recent monograph the preparation of nitroazoles has been discussed.[47] Introduction of a nitro group in an aromatic ring is usually carried out *via* electrophilic aromatic substitution using nitric acid, its metal salts, mixed anhydrides, nitrate esters or nitronium salts.[48–50] Most often these methods require subsequent aqueous work-up. In the case of alkylbenzenes this can be avoided by using a perfluorinated resinsulfonic acid (Nafion-H). So, a number of alkylbenzenes have been nitrated with *n*-butyl nitrate, acetone cyanohydrin nitrate or dinitrogen tetroxide over Nafion-H catalyst.[51]

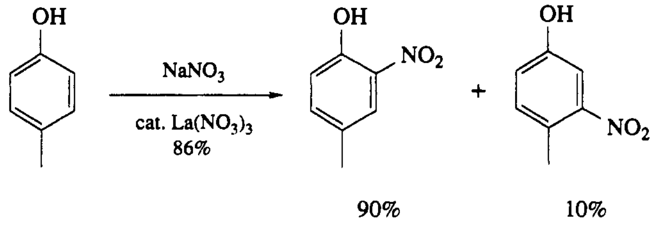
Trifluoroacetic nitrate, prepared *in situ* from ammonium nitrate and trifluoroacetic anhydride, has been used for nitration of aromatic compounds at room temperature with high yields. While benzoic acid gives *m*-nitrobenzoic acid nearly quantitatively, nitrobenzene is not reactive under these conditions. Attack at the *ortho* position rather than the *para* position is observed with activated benzene derivatives like anisole. However, this system oxidizes phenols to quinoid products.[52]

The effect of crown ethers on the selectivity of nitration of aromatic hydrocarbons and anisole has been studied with a mixture of trifluoroacetic anhydride and tetrabutylammonium nitrate as nitration agent. The largest effects on selectivity have been observed with 21-crown-7, which causes *ortho–para*-directing groups to act essentially as *para*-directing groups.[53]

Phenols can be mononitrated in a two-phase system (ether/water) by sodium nitrate and aqueous hydrochloric acid in the presence of a catalytic amount of lanthanum(III) nitrate in yields generally above 80%. Phenol itself gives 2:1 *ortho*:*para* nitration, while phenols substituted in the *para* position give predominantly *ortho* nitration with some *meta* nitration (equation 21). As shown recently nitration of phenols in the two-phase system occurs even without lanthanum(III) nitrate. By use of sodium nitrate, aqueous sulfuric acid and a catalytic amount of sodium nitrite in the two-phase system mononitration of phenols can be achieved in high yields. Under these conditions starting from 3-substituted phenols in addition to the nitro compounds formation of quinones has been observed.[54,55] Polyhydroxy aromatics are typically difficult to nitrate directly. Thus, 4,6-dinitroresorcinol (**45**) has been synthesized from resorcinol diacetate (**44**) with nitric acid or mixed solutions of nitric acid/sulfuric acid containing urea as a nitrous trap (equation 22).[56]

A useful reagent for the regioselective nitration of aromatic amines is urea nitrate in sulfuric acid. *p*-Nitroanilines are formed exclusively. When the *para* position is blocked, nitration occurs to give the *m*-nitroaniline derivative.[57]

Silica gel supported cerium(IV) ammonium nitrate (CAN) has been employed for controlled nitration of some naphthalene derivatives. While treatment of hydroxynaphthalenes and polynuclear arenes with cerium(IV) ammonium nitrate absorbed on silica gel without a solvent affords mononitro derivatives, the reaction of the same substrates with cerium(IV) ammonium nitrate in solution affords a considerable per-



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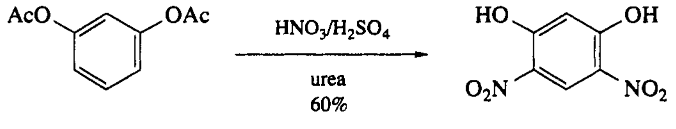
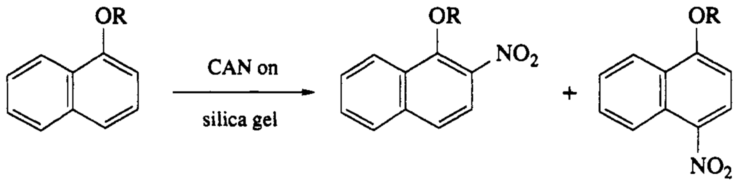


(22)

(44) (45)

centage of dinitro derivatives or quinones. Thus, 1-hydroxynaphthalene (**46**) is converted into a mixture of 4,6-dinitro- and 2,4-dinitro-2-hydroxynaphthalene, when treated with cerium(IV) ammonium nitrate in acetic acid, whereas the 2-nitro- and 4-nitro-naphthalene derivatives (**47**) and (**48**) are obtained when the same nitrating agent on silica gel is used. Under similar conditions 1-methoxynaphthalene (**49**) gives 1-methoxy-4-nitronaphthalene (**50**) exclusively (Scheme 7).[58]



(**46**) R = H	80%	(**47**) 53%	(**48**) 47%
(**49**) R = Me	65%	0%	(**50**) 65%

Scheme 7

Novel reagents consisting of metallic nitrates impregnated on montmorillonite have been introduced in aromatic nitration.[59] With clay-supported copper(II) nitrate in the presence of acetic anhydride it is possible to nitrate toluene quantitatively with a high *para* preference (79% *para*, 20% *ortho*, 1% *meta*).[60] Also, good *para* selectivities have been found on nitration of some other aromatic hydrocarbons with copper(II) nitrate on clay.[61] Halobenzenes are mononitrated with clay-supported copper(II) nitrate in the presence of acetic anhydride. Compared to other methods high *para:ortho* ratios are obtained under these conditions.[62]

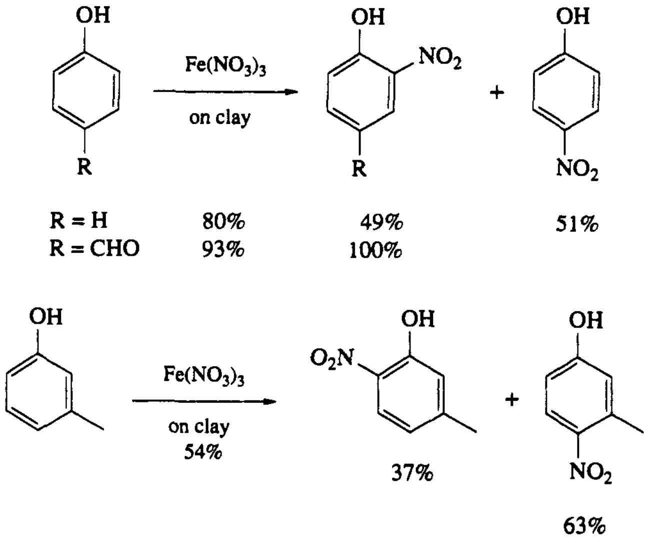
When nitration of phenols is performed with clay-supported iron(III) nitrate at room temperature, exclusively *o*- and *p*-nitrophenols are formed. No *meta* nitration occurs. With *meta*-substituted phenols, one of the *ortho* positions is favored with respect to the other (Scheme 8).[63]

1.4.3 HYDROXYLAMINES

Methods for preparation of hydroxylamine derivatives have been reviewed in detail recently.[64] Here, mainly new developments concerning the synthesis of hydroxylamines by substitution processes with heterobond formation are presented. Reduction of nitro, nitroso, oxime and nitrone derivatives as well as direct oxidation of amines leading to hydroxylamine compounds will not be considered.

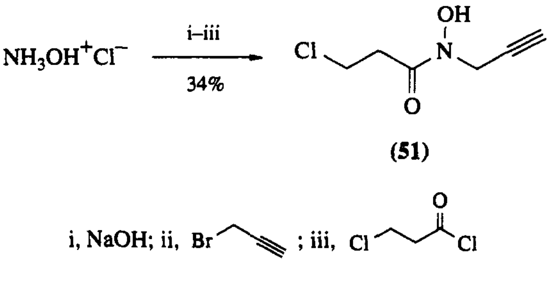
1.4.3.1 Carbon–Heteroatom Linkage with Nucleophilic Heteroatoms

Direct monoalkylation of hydroxylamine is usually not a good preparative method because of the problems with further alkylation on nitrogen. However, in a one-pot procedure hydroxylamine hydro-



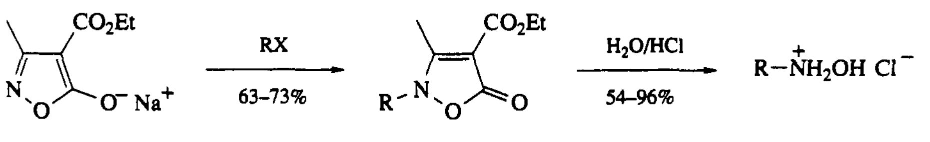
Scheme 8

chloride has been reacted with propargyl bromide followed by addition of 3-chloropropionyl chloride to give the hydroxamic acid derivative (**51**; Scheme 9).[65]



Scheme 9

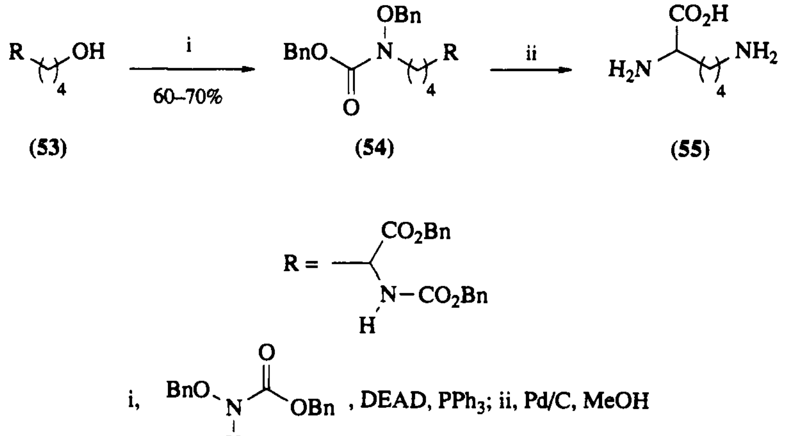
Although several methods have been reported, the synthesis of *N*-monoalkylhydroxylamines from alkyl halides or sulfonates has remained difficult. Relating to this a new preparation of *N*-alkylhydroxylamines is based upon *N*-alkylation of isoxazole derivative (**52**). Besides 2-propyl iodide several primary alkyl halides have been described as the alkylation agent in this procedure (equation 23).[66]



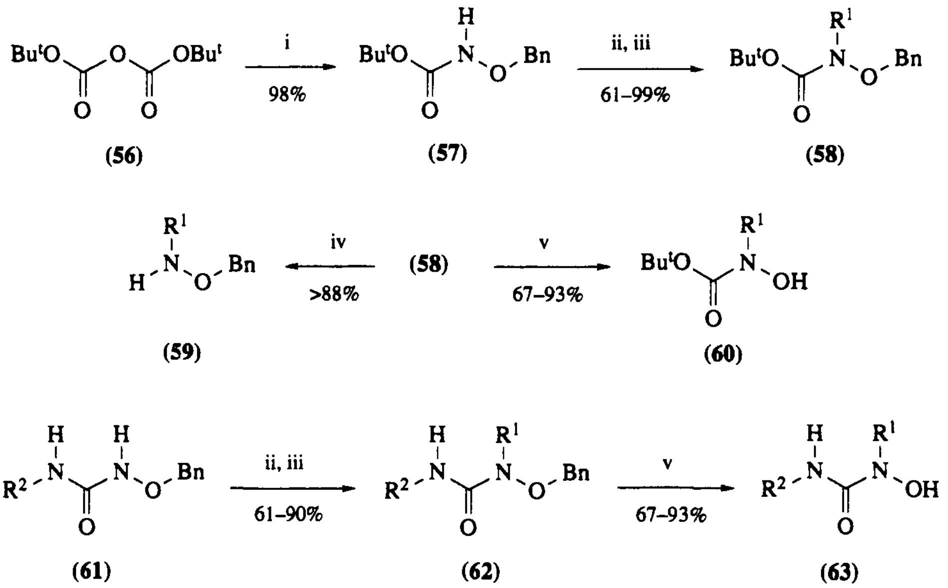
(23)

(**52**)

On application of protecting groups it has to be considered that on deprotection with hydrogen, cleavage of the N—O bond can occur. Thus, the ε-hydroxynorleucine derivative (**53**) was subjected to Mitsunobu reaction with a protected hydroxylamine to yield the *N*-alkylated compound (**54**), but hydrogenolysis gave only lysine (**55**) instead of *N*-hydroxylysine (Scheme 10).[67] Alkylation of the carbamate (**57**), available from di-*t*-butyl dicarbonate (**56**) and *O*-benzylhydroxylamine, with a primary or secondary mesylate or iodide gives carbamates (**58**) in good yields. Similarly, *N*-benzyloxyureas (**61**) have been alkylated exclusively on the benzyloxy-substituted nitrogen to form (**62**). Acidolysis of (**58**) leads to alkylbenzyloxyamines (**59**). Deprotection of (**58**) and (**62**) can be achieved by catalytic transfer hydrogenolysis using ammonium formate and palladium on charcoal (Scheme 11).[68]



Scheme 10

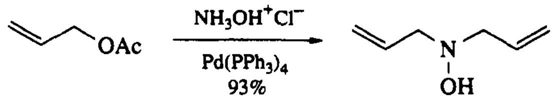


i, $H_2N{-}OBn$; ii, NaH/DMF; iii, R^1X; iv, H^+; v, ammonium formate, Pd/C

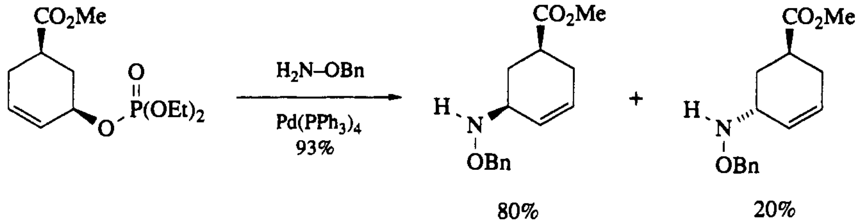
Scheme 11

The palladium(0)-catalyzed reaction of allyl esters with hydroxylamine and substituted hydoxylamines is a valuable route to *N*-allylhydroxylamines (equations 24 and 25). The absolute configuration of the products (equation 25) has not been proved. In other examples the regioselectivity of the reaction has been demonstrated.[69]

A number of syntheses of *N*-hydroxy-α-amino acids and derivatives thereof have been reported.[70] α-Bromocarboxylic acids or their *t*-butyl esters can be treated with hydroxylamine or *O*-alkylated hydroxylamines to give the corresponding hydroxylamine derivatives. *N*-Benzyloxy-L-alanine has been obtained by reaction of (*R*)-α-bromopropionic acid with *O*-benzylhydroxylamine. But due to bromide exchange the optical yield was low.[71] Anchimeric assistance of a suitable attached thio group can bring

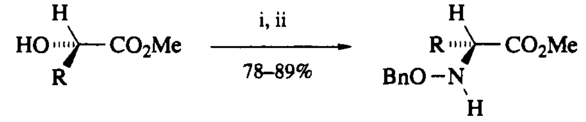


(24)



(25)

problems on reaction of α-bromocarboxylic esters with hydroxylamine.[72] By treating triflates of (*R*)- or (*S*)-α-hydroxy esters with *O*-benzylhydroxylamine *O*-benzyl-*N*-hydroxy-α-amino esters (**64**) can be prepared in good optical yields (Scheme 12).[73] The Mitsunobu reaction of aliphatic α-hydroxy esters with *N*-acylated *O*-benzylhydroxylamines provides a route to protected *N*-hydroxy-α-amino acids.[74] Treatment of α-halo ketones with hydroxylamine leads to α-hydroxylaminooximes.[75]

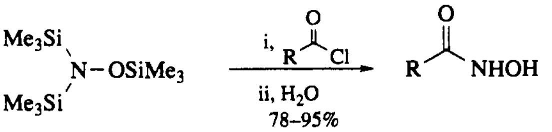


(64) 76–100% *ee*

i, Tf_2O; ii, $BnO–NH_2$

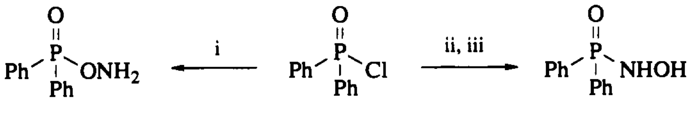
Scheme 12

Hydroxylamines usually react with acid chlorides to give mixtures of *N*-, *O*- and poly-acylated products. In contrast reaction of tris(trimethylsilyl)hydroxylamine (**65**) with aliphatic acid chlorides leads selectively under *N*-monoacylation to the corresponding hydroxamic acids (**66**; equation 26).[76] While diphenylphosphinic chloride (**68**) is attacked by the oxygen of hydroxylamine to yield *O*-(diphenylphosphinyl)hydroxylamine (**67**; Scheme 13), *N*-(diphenylphosphinyl)hydroxylamine (**69**) can be obtained by treatment of diphenylphosphinic chloride with *O*-trimethylsilylhydroxylamine followed by removal of the silyl blocking group (Scheme 13).[77] *O*-Acylation of arylhydroxylamines can be achieved with acyl cyanides.[78]



(26)

(65) **(66)**

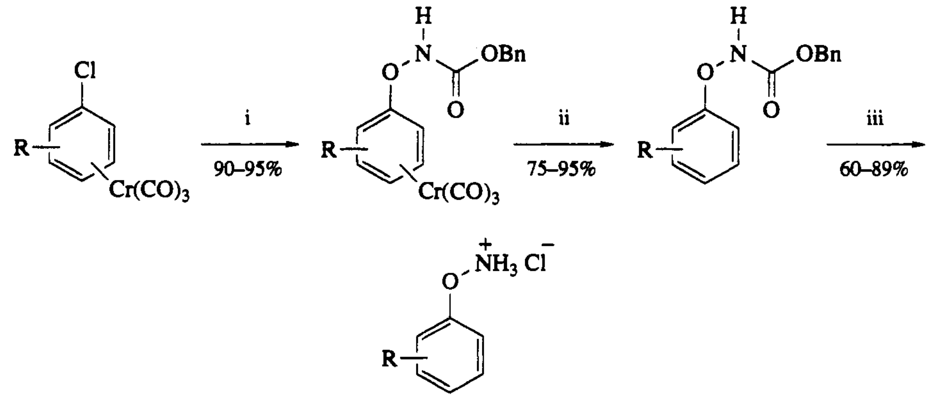


(67) **(68)** **(69)**

i, NH_2OH; ii, NH_2OSiMe_3; iii, MeOH

Scheme 13

The aromatic nucleophilic substitution on tricarbonyl(halogenoarene)chromium complexes with *N*-*t*-butyloxycarbonylhydroxylamine provides a convenient route to *O*-arylhydroxylamine derivatives (Scheme 14).[79]

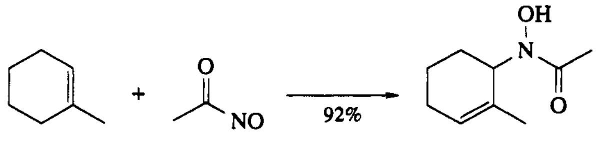


i, HONH–CO$_2$Bu^t, KOH; ii, I$_2$, 0 °C; iii, HCl

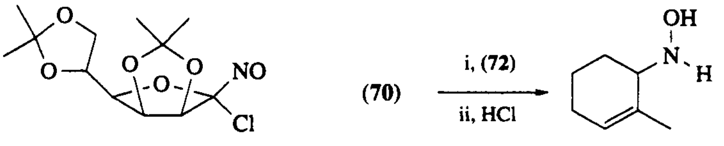
Scheme 14

1.4.3.2 Carbon–Nitrogen Linkage *via* Electrophilic Amination

Both inter- and intra-molecular ene reactions of acylnitroso compounds with alkenes provide *N*-alkylhydroxylamine derivatives. The regiochemistry observed is in agreement with C—N bond formation by electrophilic nitrogen ahead of abstraction of allylic hydrogen by nitroso oxygen. Thus, reaction of 1-methylcyclohexene (**70**) with *in situ* generated nitrosocarbonylmethane yields a single product (**71**; equation 27).[80] The chiral α-chloronitroso derivative (**72**) reacts with several alkenes regio- and diastereo-selectively to give nitrone hydrochlorides, which can be hydrolyzed to optically active allylic hydroxylamines (equation 28). The % *ee* values have not so far been determined.[81]

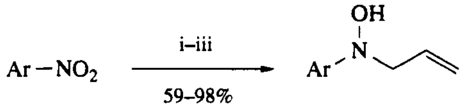


(70) **(71)** (27)



(72) (28)

Bis(silyl)ketene acetals undergo silatropic ene reaction with nitrosobenzene to give *N*-hydroxyamino acid derivatives.[82] When allylmagnesium chloride is reacted with nitroarenes, unstable adducts result. Reduction of these adducts with LAH in the presence of palladium on charcoal leads to *N*-allyl-*N*-arylhydroxylamines (**73**; Scheme 15). With alkyl Grignard reagents this reaction is negligible.[83]



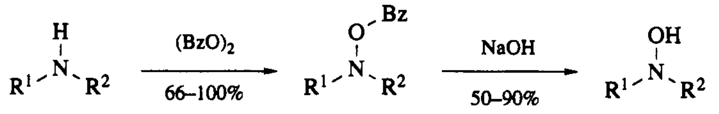
(73)

i, allylMgCl; ii, LAH; iii, NH$_4$Cl

Scheme 15

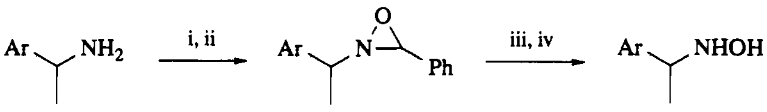
1.4.3.3 Nitrogen–Oxygen Linkage

A two-step procedure for the oxidation of amines to hydroxylamines involves nucleophilic displacement along the peroxide bond of dibenzoyl peroxide and saponification of the intermediate *O*-benzoylhydroxylamine. Primary and secondary amines have been oxidized in this way (equation 29).[84] Related reactions for transformation of amines to *O*-(arylsulfonyl)- and *O*-phosphinyl-hydroxylamines have been described by means of bis(arylsulfonyl)[85] and bis(diphenylphosphinyl) peroxide, respectively.[86,87]



(29)

A method for the synthesis of optically active hydroxylamines from optically active primary amines with retention of configuration is based on the conversion of the amines to corresponding benzylimines followed by oxidation to 3-phenyloxaziridines (**74**). Subsequent hydrolysis leads to hydroxylamines (Scheme 16).[88] This sequence has been extended to the synthesis of optically active *N*-hydroxy-α-amino acid esters.[89]



(**74**) overall 28–46%

i, PhCHO; ii, MCPBA; iii, H_2SO_4; iv, NaOH

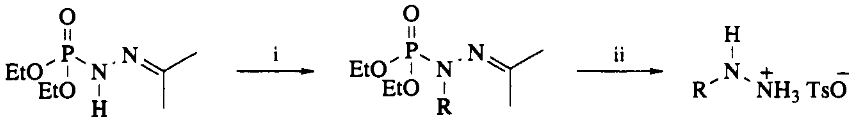
Scheme 16

1.4.4 HYDRAZINO COMPOUNDS

A detailed review of the literature to 1967 is available, as well as several more recent reviews.[90]

1.4.4.1 Carbon–Nitrogen Linkage with Nucleophilic Nitrogen

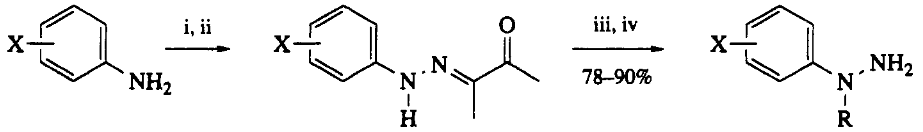
Direct alkylation of hydrazine itself with halides and sulfates usually gives mixtures of mono- and poly-alkylated hydrazines. It is possible to get useful yields of the monoalkylhydrazine by using an excess of hydrazine. Several specific procedures leading to monoalkylhydrazines are based on selective alkylation of hydrazine derivatives with protecting groups attached. So, easily prepared acetone *N*-(diethoxyphosphoryl)hydrazone (**75**) can be used. Phase-transfer catalyzed *N*-alkylation of (**75**), followed by deprotection with *p*-toluenesulfonic acid provides monoalkylhydrazine sulfonates (**76**; Scheme 17).[91] Similarly, *N*-alkyl-*N*-arylhydrazines have been prepared by phase-transfer catalyzed *N*-alkylation of arylhydrazones (Scheme 18).[92] An efficient, one-pot method for the synthesis of a variety of polysilylated hydrazines employs hexamethyldisilane (equation 30).[93] Polysilylated hydrazines were found to react with aldehydes or ketones to give hydrazones under anhydrous conditions. By treatment with triphenylphosphine and diethyl azodicarboxylate primary and secondary alcohols can be converted to hydrazine derivatives (equation 31).[94]



(**75**) overall 47–77% (**76**)

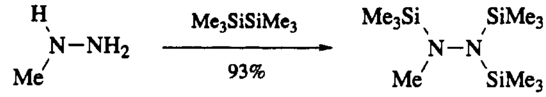
i, RBr, NaOH, $Bu^n_4N^+HSO_4^-$ (0.1 equiv.); ii, TsOH, EtOH

Scheme 17

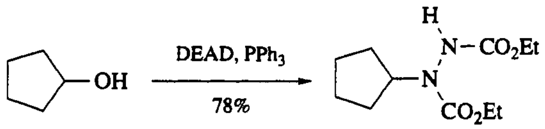


i, $NaNO_2$, HCl; ii, MeCOCHMeCOMe; iii, RBr, NaOH, $BnEt_3N^+Cl^-$; iv, N_2H_4

Scheme 18



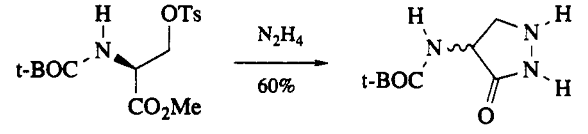
$$MeNHNH_2 \xrightarrow[93\%]{Me_3SiSiMe_3} (Me_3Si)(Me)N{-}N(SiMe_3)_2 \qquad (30)$$



(31)

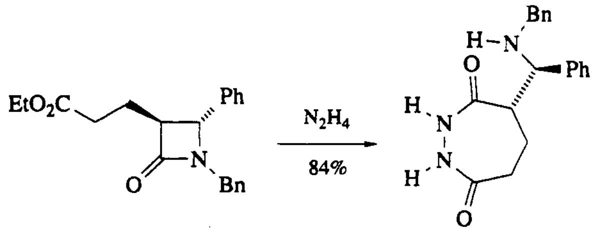
Bidentate alkylating agents may react with hydrazines at both nitrogens to close a ring, if the ring size is suitable. If hydrazine itself is used, further alkylation under formation of a second ring to tetrasubstituted hydrazine derivatives sometimes occurs. In these cases a better procedure is to take an azodicarboxylate derivative and remove the protecting group after alkylation.[95]

Alkylation of hydrazine with α,β-unsaturated carbonyl derivatives or carbonyl derivatives with a leaving group in the β-position provides pyrazole derivatives. For example, treatment of the tosylate (**77**), obtained from L-serine, with anhydrous hydrazine gives racemic pyrazolidinone (**78**). It appears that pyrazolidinone (**78**) or one of the intermediates suffers base-catalyzed racemization (equation 32).[96] Starting from β-lactam (**79**) seven-membered cyclic hydrazine (**80**) has been formed by ring closure in an unusually high (84%) yield (equation 33).[97] Reaction of (π-allyl)palladium complex (**81**) with dimethylhydrazine produces exocyclic diene (**82**) in a modest (29%) yield, but this is still more efficient than the reaction of 2,3-bis(chloromethyl)butadiene (**83**) with dimethylhydrazine (equation 34).[98]



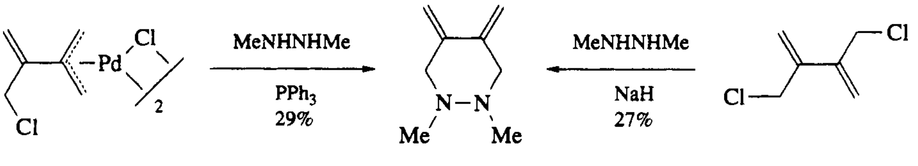
(**77**) (**78**)

(32)



(**79**) (**80**)

(33)

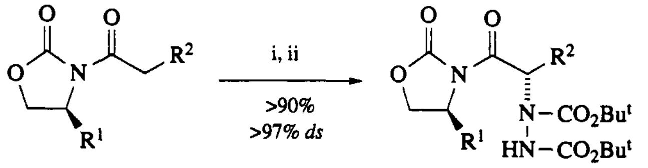


(**81**) (**82**) (**83**)

(34)

1.4.4.2 Carbon–Nitrogen Linkage *via* Electrophilic Amination

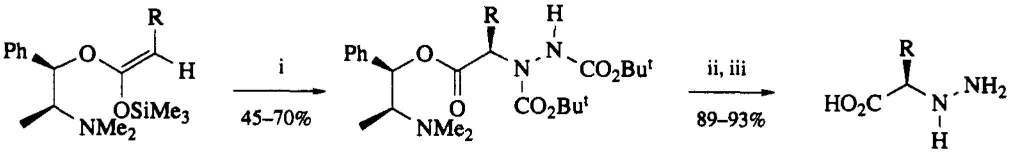
Azodicarboxylate esters are the reagents of choice for electrophilic *N*-amino amination leading to hydrazine derivatives. Besides Grignard reagents[99] and alkyl or aryl lithium compounds,[100] enolates[101] and silyl enol ethers[102] derived from ketones have been aminated by this method. In particular, di-*t*-butyl azodicarboxylate has been reacted with a variety of chiral enolates (Scheme 19)[103,104] and chiral silyl ketene acetals (Schemes 20 and 21)[105,106] to afford α-hydrazino acid derivatives with high diastereoselectivities in good chemical yields. By the same method α-hydrazino-β-hydroxy esters (**84**) with % *ee* values up to 75% have been obtained from α-hydroxy esters (Scheme 22).[107] An even higher stereoselection results by using dioxanone (**85**) instead of the acyclic β-hydroxy ester (Scheme 23).[108]



R^1 = Bn, Pr^i

i, LDA; ii, $(Bu^tO_2CN)_2$

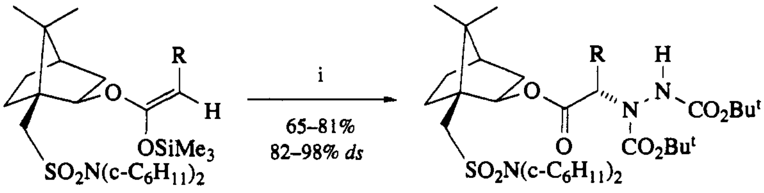
Scheme 19



i, $(Bu^tO_2CN)_2$, $TiCl_4$; ii, TFA; iii, LiOH

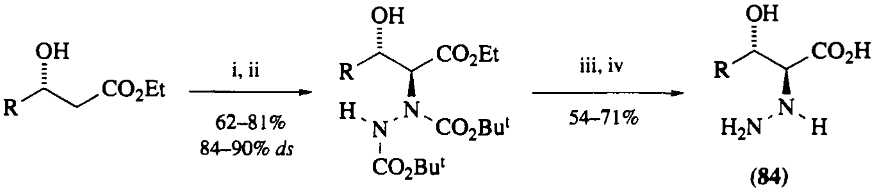
78–91% *ee*

Scheme 20



i, $(Bu^tO_2CN)_2$, $TiCl_4$, $Ti(OPr^i)_4$

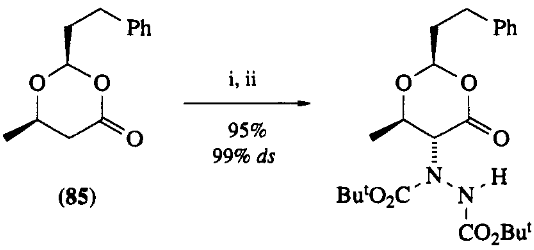
Scheme 21



(**84**)

i, LDA; ii, $(Bu^tO_2CN)_2$; iii, TFA; iv, LiOH

Scheme 22



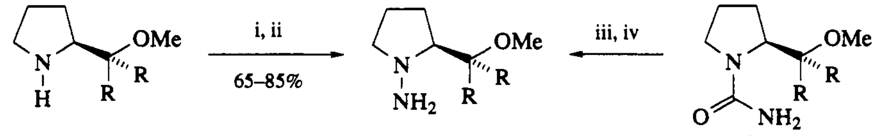
(85)

i, LDA; ii, $\mathrm{(Bu^tO_2CN)_2}$

Scheme 23

1.4.4.3 Nitrogen–Nitrogen Linkage

A widely used method for preparing *N*,*N*-disubstituted hydrazines is the reduction of *N*-nitrosoamines obtained by nitrosation of secondary amines. There are several methods for effecting this reduction based on dissolving metals, low-valent titanium reagents,[109] hydride reagents and catalytic reduction with hydrogen. For example, several chiral auxiliaries derived from (*S*)-proline have been synthesized by reduction of the corresponding *N*-nitrosoamine (Scheme 24).[110] But *N*-nitrosoamines are carcinogenic intermediates. Therefore, an alternative route to (*S*)- and (*R*)-1-amino-2-methoxymethylpyrrolidine ('SAMP' and 'RAMP') (**86**; R = H) has been described. This procedure involves treatment of the urea (**87**) or its enantiomer, obtained from (*S*)- or (*R*)-proline, with potassium hypochlorite followed by elimination of hydrogen chloride with potassium hydroxide (Scheme 24). Yields based on proline range from 50 to 58%.[111]

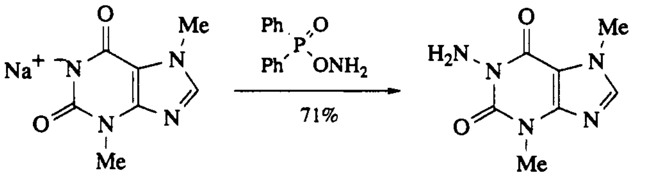


(86) **(87)**

i, $\mathrm{Bu^tONO}$; ii, LAH; iii, KOCl; iv, KOH

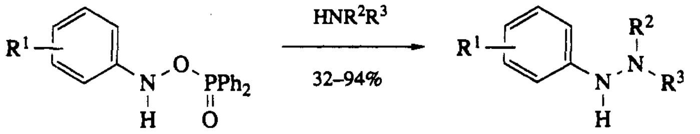
Scheme 24

Electrophilic *N*-aminations have been performed with hydroxylamine-*O*-sulfonic acid (HOSA),[112] *O*-(2,4-dinitrophenyl)hydroxylamine and *O*-mesitylenesulfonylhydroxylamine. The use of HOSA is mainly restricted to aqueous reaction media. Imide sodium salts of some heterocycles such as theobromine (**88**) can be converted to hydrazine derivatives by treatment with *O*-(diphenylphosphinyl)hydroxylamine (equation 35).[113] This reaction has been extended to synthesis of *N*-arylhydrazines, where R^2 and R^3 are hydrogen, alkyl or aryl (equation 36).[114] Similarly, trisubstituted hydrazines can be prepared by the use of *N*-aryl-*O*-acetylhydroxylamines and secondary amines.[115] A recent publication[116] concerning the synthesis of 1-acyl-2-alkylhydrazines from hydroxamic acids and amines in the presence of activating agents has been found to be erroneous; no N—N bond formation occurs under these conditions.[117]



(35)

(88)



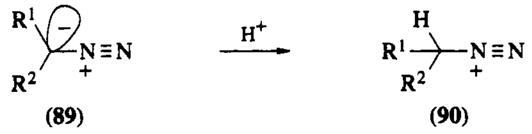
(36)

1.4.5 PREPARATION OF DIAZOALKANES

1.4.5.1 Properties of Diazoalkanes

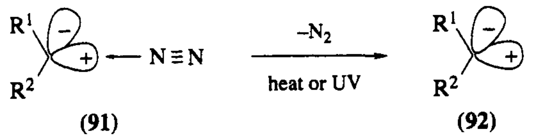
The synthesis and properties of diazo compounds have been covered in an excellent review by Regitz and Maas.[118] This section does not attempt to duplicate that review. Rather, two key areas are covered: the most practical methods for the preparation of diazo-containing compounds, and use of these intermediates in organic synthesis. To understand these areas, however, it is important first to appreciate the structure, bonding and reactivity of the diazo functional group.

One model for bonding in a diazo compound would be the ylide (**89**; equation 37).[119] Unlike many other ylides, diazoalkanes are stable to air and water. With acid, however, protonation can lead to the highly reactive salt (**90**), the functional equivalent of the corresponding carbocation. As the substituents on the diazo group are made increasingly electron withdrawing, the ylide becomes less basic, and thus more stable to acid. Reaction of a diazo compound with a transition metal can also often be understood as proceeding *via* initial donation of electron density by (**89**) to a coordinatively unsaturated metal center.



(37)

The diazo compound can alternatively be viewed as a coordination complex (**91**) between a carbene and N_2 (equation 38).[119] The coordination is weak, so any input of energy, either *via* heating or UV radiation, can lead to N_2 loss, liberation of the free carbene and subsequent reaction.

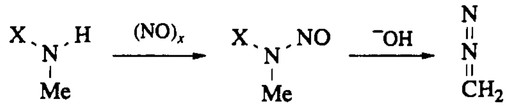


(38)

It should be remembered that many diazo compounds, especially those having electron-withdrawing groups, are quite stable. Ethyl diazoacetate, for instance, can be stored for years. As methods for the preparation of diazo compounds improve, they will become increasingly important in organic synthesis.

1.4.5.2 Diazomethane

The best known and most widely used diazoalkane is diazomethane (**95**; equation 39). Preparative methods for diazomethane involve, in general, the nitrosation of a methylamine derivative (**93**), followed by cleavage under alkaline conditions. Methylamine derivatives used have included the urethanes,[120] ureas,[121] carboxamides,[122] sulfonamides,[123] guanidines[124] and even the methylamine adducts of unsaturated ketones[125] and sulfones.[126] *N*-nitroso-*N*-methyl *p*-toluenesulfonamide (Diazald, Aldrich) is currently the most commonly used diazomethane precursor. Diazomethane is both toxic and explosive. Although in the past it has been purified by codistillation with ether, it is now usually generated, stored and used as an ether solution without distillation.

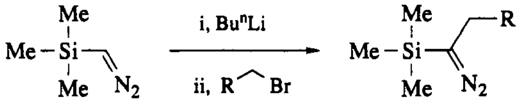


(93) (94) (95)

(39)

1.4.5.3 Trimethylsilyldiazomethane

Trimethylsilyldiazomethane (96), prepared in excellent yield from chloromethyltrimethylsilane,[127] is now commercially available (Petrarch). Trimethylsilyldiazomethane is readily lithiated and alkylated (equation 40).[128] Synthetic applications of the resultant silyldiazoalkanes (97) have not yet been extensively explored. These might, for instance, react smoothly with acid chlorides to give diazoketones (see Section 1.4.6.1).

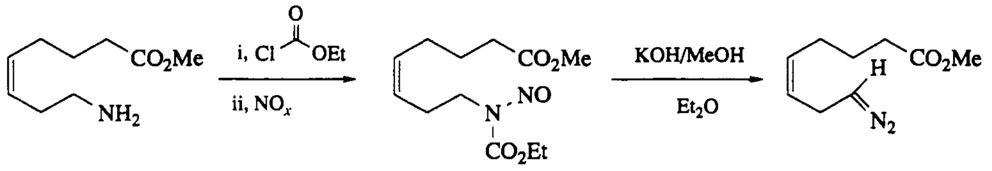


(96) (97)

(40)

1.4.5.4 Higher Diazoalkanes

The synthetic methods outlined above for diazomethane work well, in general, for the higher diazoalkanes. Again, these are usually generated and handled as solutions in diethyl ether. In the special case of the conversion of the amine (98) to diazoalkane (100), the urethane approach proved most effective (equation 41).[129]



(98) (99) (100)

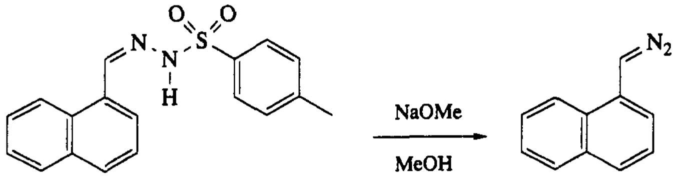
(41)

The N-nitrosation reaction works well for a variety of amine derivatives.[130] The substance to be nitrosated is dissolved in an inert solvent (CCl_4 has classically been used, but diethyl ether works just as well) in which anhydrous potassium acetate has been suspended. The brown vapor generated by addition of concentrated sulfuric acid to sodium nitrite (in a separate flask) is then blown through with a gentle stream of nitrogen. Formation of the N-nitroso derivative (99) is conveniently monitored by TLC. It is usually complete in 1–2 h.

The hydrolysis of (99) to diazoalkane (100) is a little tricky, since the methyl ester is also subject to saponification. It was found that addition of 4 equiv. of methanol to the 50% KOH/ether mixture, stirred rapidly in an ice–water bath, followed by addition of (99), gave optimal yields (30–40%) of (100).[129] The reaction mixture must be kept at ice temperature, as warming leads to emulsification and yield loss.

1.4.5.5 Aryldiazoalkanes

Aryldiazoalkanes are readily prepared by exposure of the arenesulfonylhydrazone to base (Bamford–Stevens reaction).[131] On addition of sodium methoxide, for instance, to a suspension of 1-naphthaldehyde tosylhydrazone (101) in methanol, the solid dissolves, and the solution turns red (equation 42).[132] The diazoalkane (102) can be isolated, as a pink-red solid, by dilution with water, extraction with pentane, drying (Na_2SO_4) and vacuum concentration. Naphthyldiazomethane reacts readily with acids to give the corresponding esters, which have the advantage, for chromatographic purification or analysis, of being UV-absorbing. An aryldiazoalkane can also be easily prepared by MnO_2 oxidation of the hydrazone of the corresponding ketone or aldehyde.[133]

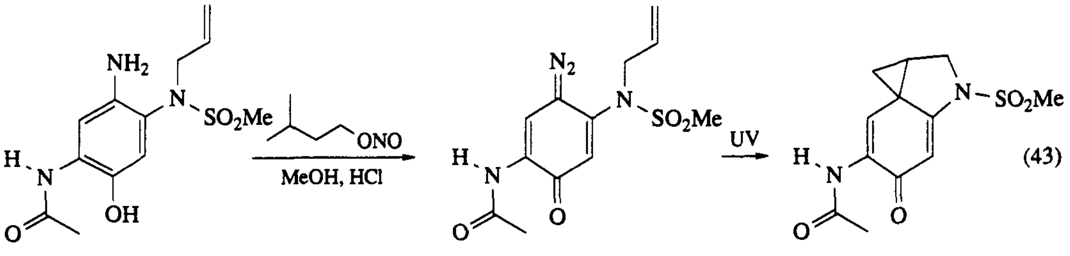


(101) **(102)**

(42)

1.4.5.6 Quinone Diazides

Quinone diazides such as (**104**) are readily prepared by nitrosation of 4-aminophenols.[134] On photolysis, (**104**) smoothly cyclizes to (**105**), a model for the antitumor antibiotic CC-1065 (equation 43).[135]



(103) **(104)** **(105)**

(43)

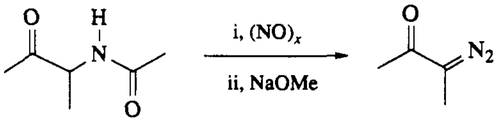
1.4.6 PREPARATION OF α-DIAZO KETONES AND ESTERS

It has not been fully appreciated that α-diazo ketones and esters are easily purified and are quite stable. In the past, such derivatives have been primarily expensive research intermediates. Now, with much better methods available for their preparation, these simple stabilized ylides deserve serious consideration as synthetic intermediates, even on an industrial scale.

1.4.6.1 Acyclic α-Diazo Ketones

1.4.6.1.1 From α-amino ketones

Acylated or sulfonylated α-amino ketones such as (**106**) are smoothly converted *via* *N*-nitrosation to the corresponding α-diazo ketones (**107**; equation 44).[136] A limitation to this approach has been the difficulty of preparing precursors such as (**106**), especially given the instability of the precursor α-amino ketones. A recent report that an azide is smoothly converted to the corresponding carboxamide on exposure to triethylphosphine and a carboxylic acid might nicely sidestep this difficulty.[137]

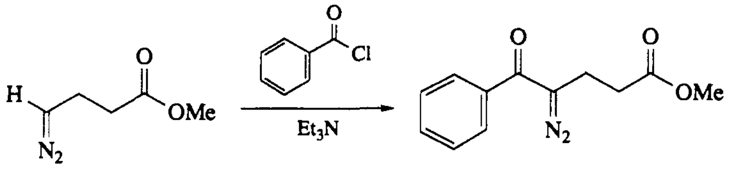


(106) **(107)**

(44)

1.4.6.1.2 From diazoalkanes

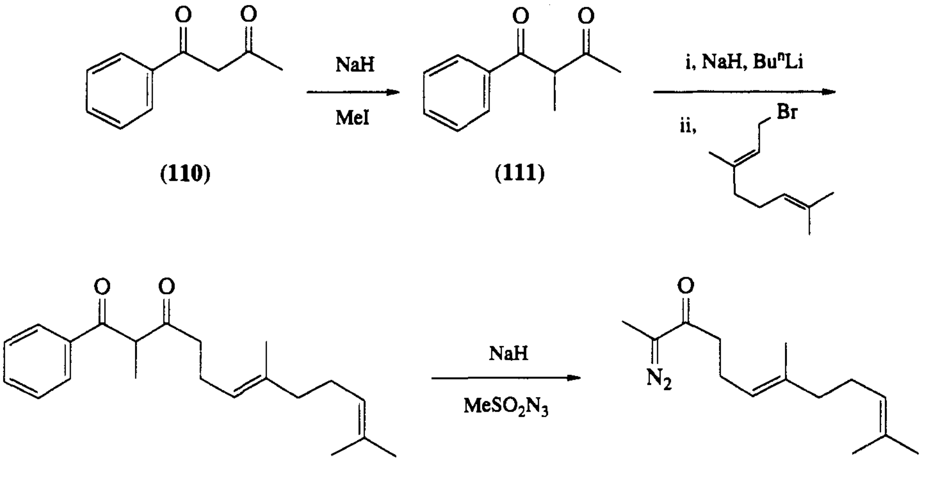
A diazoalkane (**108**) will couple smoothly with an acid chloride or a mixed anhydride to give the corresponding α-diazo ketone (**109**; equation 45).[138] A limitation on this approach is the difficulty of preparing and handling the requisite diazoalkanes (Section 1.4.5.4). Unlike the diazoalkanes, the product α-diazo ketones are stable to silica gel chromatography, and are readily purified.


(108) (109)

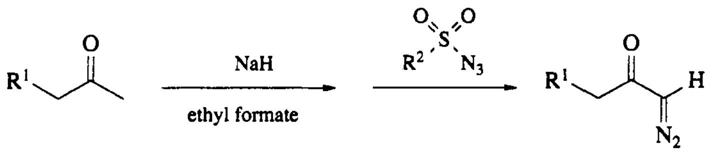
(45)

1.4.6.1.3 *By diazo transfer/cyclization*

Diazo transfer from a sulfonyl azide is well known as a method for the preparation of α-diazo active methylene compounds (see Section 1.4.6.4). Application of this method to an α-alkylated 1,3-diketone leads, *via* fragmentation, to the simple α-diazo ketone. As illustrated for (**112**; Scheme 25) fragmentation can be highly chemoselective, so an unsymmetrical diketone can give a single product. The dianion alkylation approach outlined in Scheme 25 is currently the method of choice for preparing practical quantities of simple α-diazo ketones.[139] It should be noted that the sequence dianion alkylation/diazo transfer is most efficiently carried out in the same reaction vessel. A diazomethyl ketone (**115**) can also be prepared by diazo transfer. Thus, formylation of a methyl ketone (**114**) is usually highly regioselective (equation 46). Addition of a sulfonyl azide to the formylation mixture gives directly the diazomethyl ketone.[140]


(110) (111) (112) (113)

Scheme 25

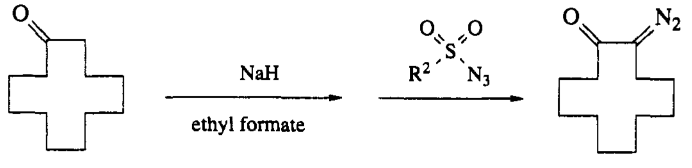

(114) (115)

(46)

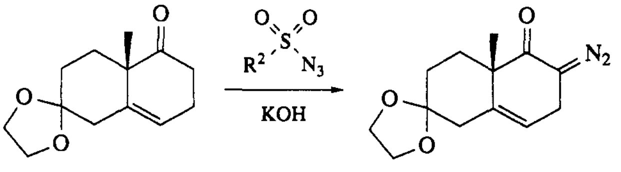
1.4.6.2 Cyclic α-Diazo Ketones

Usually, a cyclic α-diazo ketone such as (**117**) is prepared by formylation/diazo transfer (equation 47).[141] Such diazo ketones can also be prepared by phase transfer reaction of the parent ketone with

2,4,6-triisopropylbenzenesulfonyl azide, as illustrated for the conversion of (**118**) to (**119**) (equation 48).[142]



(**116**) (**117**) (47)

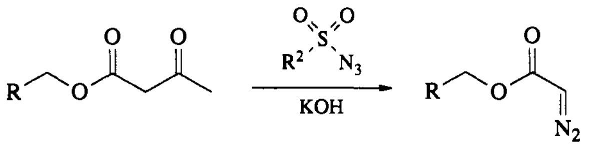


(**118**) (**119**) (48)

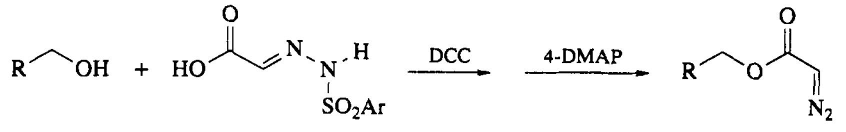
1.4.6.3 α-Diazo Esters

1.4.6.3.1 Esters of diazoacetic acid

Two strategies have been developed for the preparation of esters of diazoacetic acid. If the alcohol is inexpensive, it is first converted (diketene) into the corresponding acetoacetate (**120**; equation 49). Diazo transfer with subsequent deacylation then yields the diazoacetate (**121**).[143] If the alcohol is particularly valuable or sensitive, it may alternatively be esterified with a more direct precursor to diazoacetate. One reagent that has been used for this purpose is glyoxalic acid 2,4,6-triisopropylbenzenesulfonylhydrazone (TIPPS) (**123**; equation 50). Esterification of the alcohol (**122**) with (**123**), using dicyclohexylcarbodiimide followed by addition of 4-dimethylaminopyridine, gives the diazoacetate (**124**).[144]



(**120**) (**121**) (49)

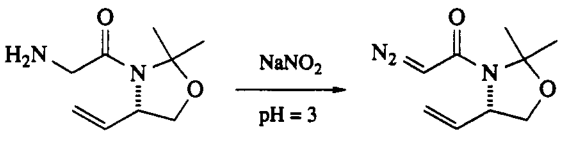


(**122**) (**123**) (**124**) (50)

1.4.6.3.2 Higher α-diazo esters

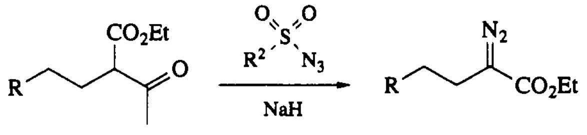
As with diazo ketones, an α-diazo ester (**126**) can be prepared by nitrosation of the corresponding α-amino acid (**125**) or a derivative (equation 51).[145] Alternatively, an α-diazo ester (**128**) can be prepared by diazo transfer to an alkylated acetoacetate (**127**), with concomitant deacylation (equation 52).[139]

To prepare an α-diazo ester from the ester (**129**) itself, formylation is effective. Alternatively, it has been reported that trifluoroacetylation of an ester proceeds smoothly (equation 53).[146] The trifluoromethylacetoacetate (**130**) would be expected to react directly with methanesulfonyl azide and sodium hydride to give the α-diazo ester.



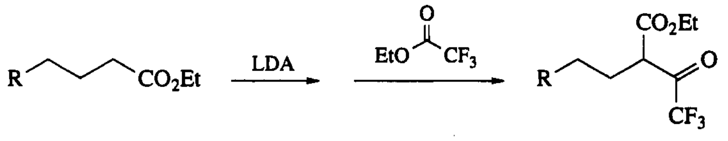
(125) **(126)**

(51)



(127) **(128)**

(52)



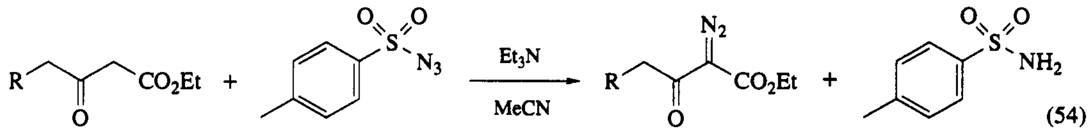
(129) **(130)**

(53)

1.4.6.4 Diazo Transfer to Active Methylene Compounds

1.4.6.4.1 Diazo transfer to β-keto esters

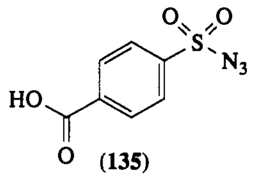
The original Regitz procedure for diazo transfer to a β-keto ester (**131**) used *p*-toluenesulfonyl azide (**132**; equation 54).[143] This reagent works well, and is easy to prepare from the corresponding sulfonyl chloride. A disadvantage of this reagent is that the *p*-toluenesulfonylamide coproduct (**134**), as well as any excess *p*-toluenesulfonyl azide, have to be removed from the product diazo ketone (**133**) before it can be used.



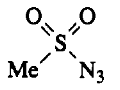
(131) **(132)** **(133)** **(134)**

(54)

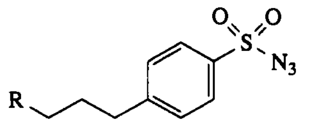
Several alternative sulfonyl azides have been used. Hendrickson introduced *p*-carboxybenzenesulfonyl azide (**135**).[147] Both the coproduced sulfonamide and any excess reagent are readily extractable by aqueous base, so product clean-up is easy. One limitation is that the starting sulfonyl chloride is somewhat expensive. Methanesulfonyl azide is much less expensive, yet still offers the same advantage, that the coproduced sulfonamide and excess reagent are readily removed by extraction with aqueous base.[141] Caution is, however, warranted, since methanesulfonyl azide is potentially explosive. Finally, advantage can be taken of the particular product being prepared. In the Merck thienamycin process, for instance, a lipophilic arenesulfonyl azide (**137**) is used. The product diazo ketone, a polar, highly crystalline β-lactam, is easily separated from this reagent and its coproducts.[148]



(135)



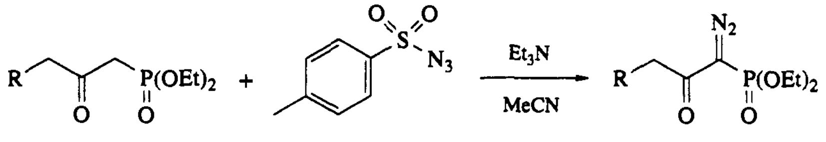
(136)



(137)

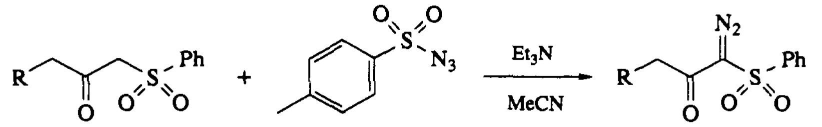
1.4.6.4.2 Diazo transfer to other active methylene compounds

Malonate esters and vinylogous malonates,[149] as well as 1,3-diketones, readily undergo diazo transfer. In addition, the less acidic β-keto phosphonates (**138**; equation 55)[150] and β-keto sulfones (**140**; equation 56)[151] have been shown to participate in this reaction.



(55)

(138) **(139)**



(56)

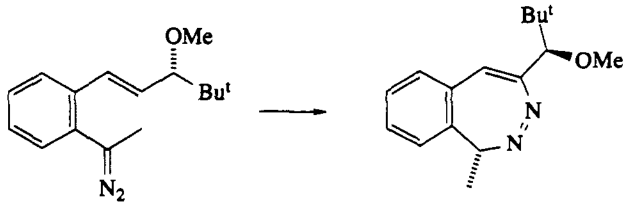
(140) **(141)**

1.4.7 SYNTHETIC APPLICATIONS OF DIAZO COMPOUNDS

Many of the reactions of diazo compounds are covered in detail elsewhere in these volumes. The attempt made here is to briefly highlight the diverse reactivity of the diazo functional group.

1.4.7.1 Dipolar Cycloaddition

Diazoalkanes undergo smooth 1,3-dipolar cycloaddition. For additions to simple alkenes, this is presumably an electrophilic process. In the example illustrated, the overall process of electrocyclization of (**142**) followed by hydride shift proceeds with remarkable diastereoselectivity (equation 57).[152]

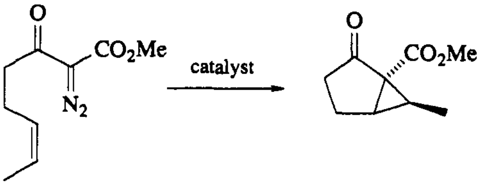


(57)

(142) **(143)**

1.4.7.2 Alkene Insertion to Make Cyclopropanes

An α-diazo ketone or ester such as (**144**) will, *via* metal-mediated nitrogen loss, insert into an alkene to make the corresponding cyclopropane (**145**; equation 58).[153,154] As illustrated, alkene geometry is retained, as would be expected for a concerted process. Cyclopropane construction by diazo insertion is reviewed in detail elsewhere in these volumes.

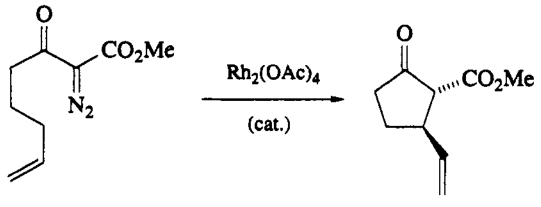


(58)

(144) **(145)**

1.4.7.3 C—H Insertion

An α-diazo ketone or ester such as (**146**) can also, *via* metal-mediated nitrogen loss, undergo 1,5 C—H insertion, to make the corresponding cyclopentane (**147**; equation 59).[155] This process, most efficiently catalyzed by Rh^{II} dimers, is also reviewed in detail elsewhere in these volumes. It is striking that with copper bronze catalyst, (**146**) gives only intramolecular cyclopropanation.[156]

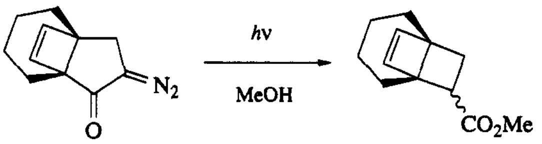


(59)

(**146**) (**147**)

1.4.7.4 Wolff Rearrangement/Arndt–Eistert Synthesis

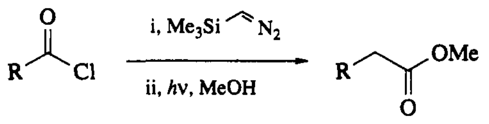
On UV irradiation, an α-diazo ketone such as (**148**), prepared in this case from the parent ketone by formylation/diazo transfer, rearranges with loss of nitrogen to the corresponding ketene (equation 60).[157] In methanol solvent, the methyl ester (**149**) is the product. In aqueous dioxane, the product is the carboxylic acid. It should be noted that substrate (**146**; equation 59), on UV irradiation, gives only the product of Wolff rearrangement, with little trace of either (**147**) or the corresponding cyclopropane.[158] This is significant evidence that both of these latter products are derived from transient organometallic intermediates.



(60)

(**148**) (**149**)

A straight chain diazomethyl ketone will also undergo Wolff rearrangement on irradiation. Such diazomethyl ketones are readily prepared from the corresponding acid chloride (**150**) by exposure to diazomethane or, more conveniently, trimethylsilyldiazomethane (Petrarch).[159] The net one-carbon homologation so effected is known as the Arndt–Eistert synthesis.



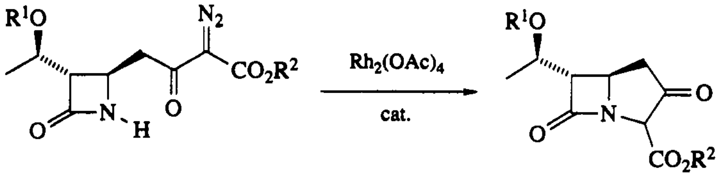
(61)

(**150**) (**151**)

1.4.7.5 Hetero-H Insertion

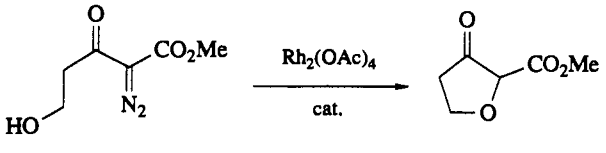
Rh^{II}-mediated hetero-H insertion may proceed by initial coordination of the intermediate metal–carbene complex with the nonbonding electrons of the heteroatom. Proton transfer would then give the observed product. This can be an efficient process both for forming C—N bonds, as in the cyclization of (**152**; equation 62),[148] and for C—O bonds, as illustrated by the construction of ether (**155**; equation 63).[160] Si—H insertion of (**156**) was shown to proceed with retention of absolute configuration, as would be expected for a concerted transition metal carbene mediated process (equation 64).[161]

The reactions illustrated in equations (62–64) are each catalyzed by rhodium acetate. Diazo compounds, especially diazoalkanes, can also react by a simple ionic mechanism. The esterification of a carboxylic acid with diazomethane is a familiar example. The ionic pathway is especially likely when the intermediate carbocation would be stabilized. Thus, diazine (**158**) couples smoothly with phenols, presumably by thermal rearrangement to the corresponding diazo sugar, followed by acid-catalyzed N_2 loss



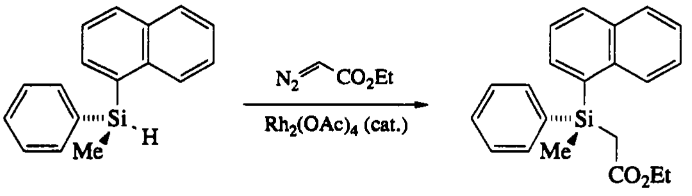
(62)

(152) **(153)**



(63)

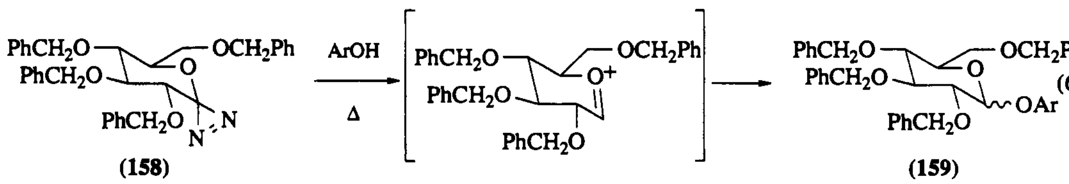
(154) **(155)**



(64)

(156) **(157)**

(equation 65).[162] If conditions for the alternative transition metal mediated coupling can be developed, diazo sugars may turn out to be effective precursors for stereocontrolled glycoside formation.

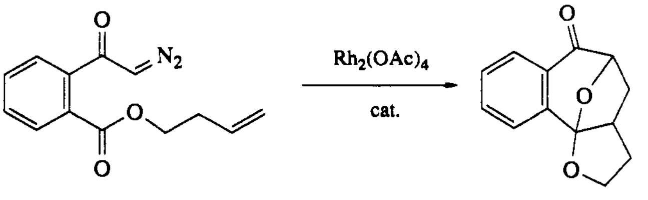


(65)

(158) **(159)**

1.4.7.6 Ylide Formation

In the examples illustrated above (equations 62–64), the heteroatom had an attached proton, which transferred readily. In the absence of such a proton, the initially-formed ylide can undergo other reactions. One of the more interesting of these is 1,3-dipolar cycloaddition, as illustrated by the conversion of (**160**) to (**161**) (equation 66).[163] Rhodium-mediated diazo addition to an ether is currently the method of choice for preparing such oxonium ylides.

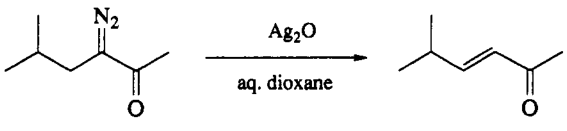


(66)

(160) **(161)**

1.4.7.7 Elimination to Make Alkenes

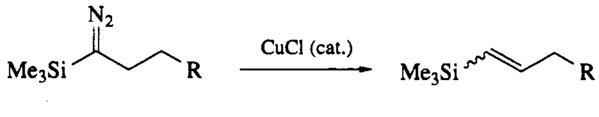
In 1957, Franzen reported that Ag_2O catalyzes the transformation of an α-diazo ketone (**162**) to the corresponding enone (**163**; equation 67).[134] Regitz later made the intriguing observation that for cyclic α-diazo ketones, at least a seven-membered ring is required for efficient conversion to the enone, suggesting that conformational effects may be important.[164] Holt showed that other metallic salts catalyze this transformation, although not as effectively as silver oxide or silver nitrate.[165]



(162) **(163)**

(67)

A silyldiazoalkane (**164**) is converted to the alkene (**165**) under Cu^I catalysis. The silyldiazoalkane (**164**) was prepared by deprotonation and alkylation of trimethylsilyldiazomethane.[166]

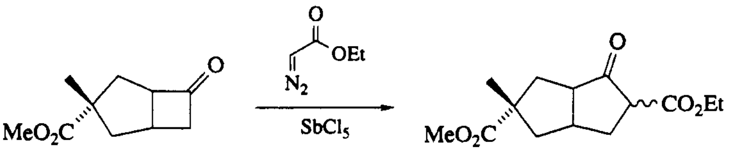


(164) **(165)**

(68)

1.4.7.8 Homologation of Ketones and Aldehydes

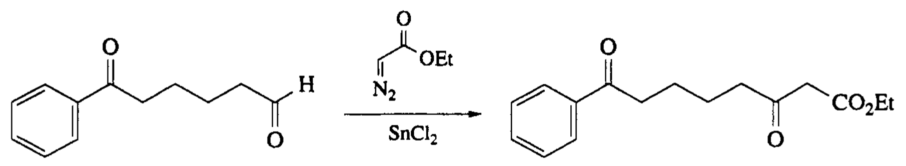
A diazo ester or alkane will react with a ketone, under Lewis acid catalysis, to give the homologated product. This reaction is most often used for one-carbon ring expansion, as illustrated by the conversion of (**166**) to (**167**; equation 69).[167] The regioselectivity of the (**166**) to (**167**) transformation, 98:2 in the example illustrated, was found to depend on both the diazoalkane and the Lewis acid used. With diazomethane and boron trifluoride, a 1:1 mixture of regioisomeric products was observed.



(166) **(167)**

(69)

This homologation reaction most likely proceeds *via* nucleophilic addition of the diazo compound to the Lewis acid complexed carbonyl, followed by 1,2-alkyl migration with concomitant loss of N_2. Application of this reaction to an aldehyde (**168**) gives, *via* 1,2-hydride shift, the corresponding β-keto ester (**169**; equation 70).[168]



(168) **(169)**

(70)

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1.5

Synthesis of Sulfides, Sulfoxides and Sulfones

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1.5.1 INTRODUCTION

During the 1980s, organic sulfur compounds have become increasingly useful and important in organic syntheses. Sulfur incorporated into an organic molecule activates, by its electronegativity, the hydrogen atoms situated on the adjacent carbon atom, increasing their thermodynamic acidity. The acidity of a proton α to a sulfoxide group or to a sulfone group falls between those of a benzylic proton and a proton α to a carboxylate function. It has been demonstrated that sulfur groups exert stabilizing effects on the corresponding carbanions that are much larger than those expected from their polar contributions.[1] The stabilizing resonance effect for the phenyl sulfone group was estimated to be equivalent to 33–75 kJ mol^{-1} (8–18 kcal mol^{-1}), which is comparable with that of a cyano group but somewhat smaller than that of carbonyl or nitro functions. No data are available for a sulfoxide group and, to our knowledge, the extent of such acidification in β-keto sulfoxides or related compounds has not yet been determined. Another report[2] also showed that the presence of a phenylthio group increases the acidity of cyclohexanone by at least 3 pK units, corresponding to a stabilizing effect of the order of 25–42 kJ mol^{-1} (6–10 kcal mol^{-1}).[3] This stabilizing effect was attributed to conjugative effects or polarization effects[4] involving the 3*d*-orbitals of sulfur.

The variety of sulfur compounds generating such carbanion structures permitted the development of several synthetic methods for carbon–carbon bond formation.

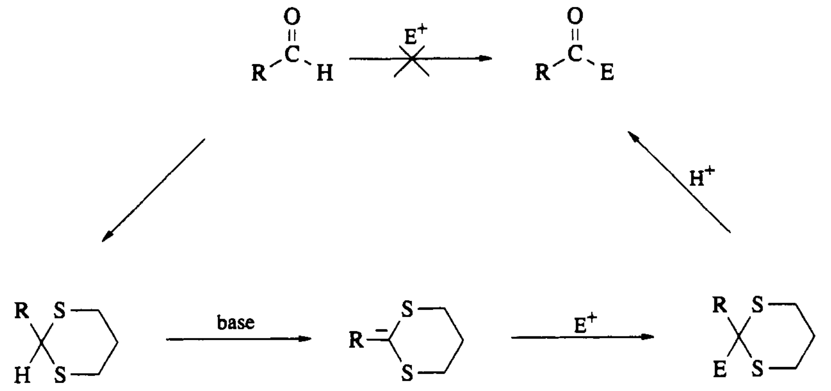
The basic chemistry of organosulfur compounds has already been reviewed in depth in 'Comprehensive Organic Chemistry',[5] so the purpose of this chapter is to outline the important developments in the use of sulfur-containing reagents in organic syntheses since the reviews cited in refs. 6 and 7, which appeared in 1978, were published.

Because of the large variety of sulfur compounds, this chapter will be limited to thioacetals, sulfides, sulfoxides and sulfones. Many examples, selected from recent total syntheses of natural products, will emphasize the selectivity (chemo-, regio-, diastereo- and enantio-selectivity) of these reactions.

1.5.2 SULFIDES

1.5.2.1 Thioacetals

Among organic sulfides, those derived from 1,3-dithiane occupy an important place. The interest in these reagents lies not only in their reactivity with electrophilic substrates but also in the synthetic principles which have been developed from work on these compounds. By masking the aldehyde group by the formation of a dithiane, the carbon atom may participate in nucleophilic additions or substitution reactions and after hydrolysis of the thioacetal, the carbonyl group can then be regenerated (Scheme 1).



Scheme 1

Overall an inversion of polarity of the carbonyl group can thus be achieved; this principle was called 'umpolung' by Seebach.[8] We owe to Corey and Seebach the use of the anions of dithiane, which are more stable than those of noncyclic thioacetals.[9] Although this question was reviewed by Seebach[10] and also by Durst in 'Comprehensive Organic Chemistry',[11] we will briefly comment on the main reactions of the dithiane group.

Dithianes may be prepared by the action of propanethiol on aldehydes or ketones or their acetals in chloroform in the presence of boron trifluoride.[12]

The action of *n*-butyllithium in THF at low temperature leads to the anion. After reaction with an electrophilic compound, the hydrolysis can generally be carried out in polar solvents (acetone, alcohols, acetonitrile) in the presence of mercury(II) chloride or oxide and water.[12–14] In other cases, NBS,[14,15] chloramine T,[16] cerium(IV) ammonium nitrate,[17] *n*-tributyltin hydride,[18] trialkyloxonium tetrafluoroborate,[19] thallium nitrate[20] or photochemistry[21] can be used. Desulfurization by Raney nickel gives hydrocarbons.[22]

Typical examples of the reactions of carbanions α to dithiane are shown in Scheme 2.

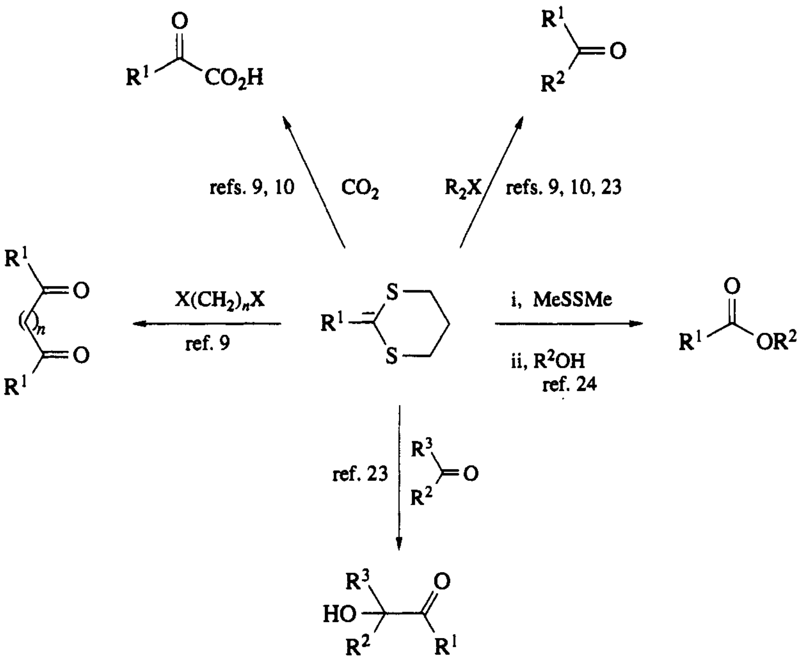
Some noncyclic thioacetals are sometimes used for the preparation of keto acids from aryl halides[25] or keto esters[26] by 1,4-addition on α,β-unsaturated ketones (Scheme 3).

Ketene dithioacetals should also be mentioned; these are readily prepared by dehydrogenation of saturated dithioacetals,[27,28] or dihydrohalogenation of 2-dichloromethyl-1,3-dithiane followed by chain extension (Scheme 4).[29]

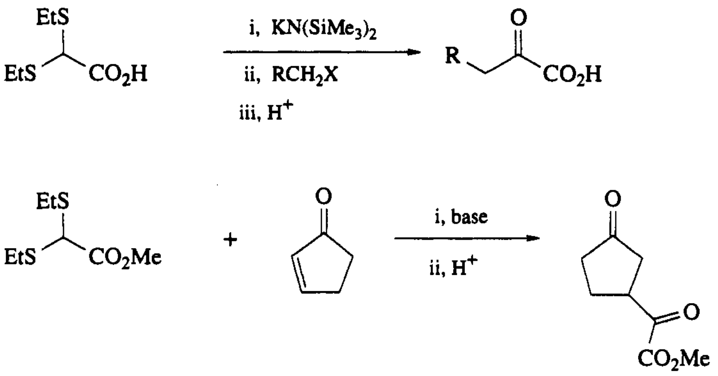
Wittig-type reactions have also been used to prepare ketene dithioacetals (Scheme 5).[30–36]

A variety of complex molecules have been synthesized by methods involving dithioacetal chemistry. Cyclophanediones have been generated by a sequence employing alkylation of the bisdithianyl derivative of isophthalaldehyde (Scheme 6).[37]

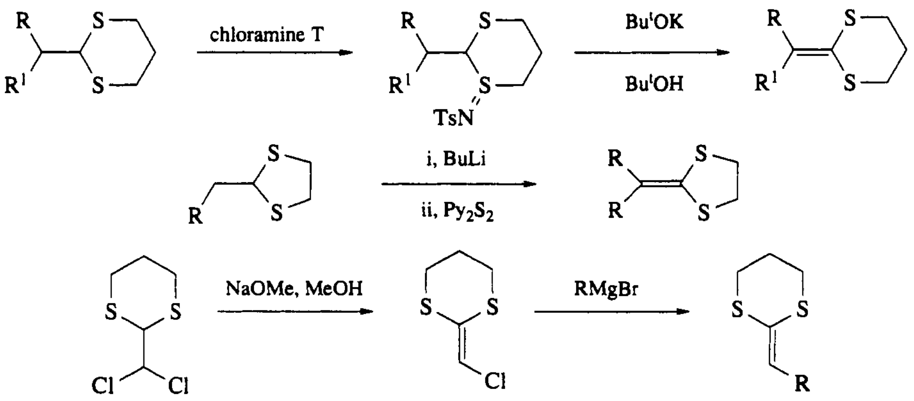
Alnusone, a biphenyl-type natural product, was also synthesized by using a dithianyl reagent to open an epoxide ring (Scheme 7).[38]



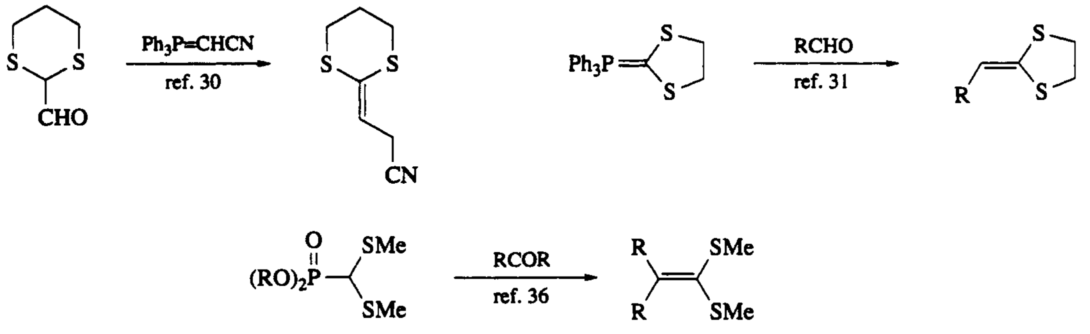
Scheme 2



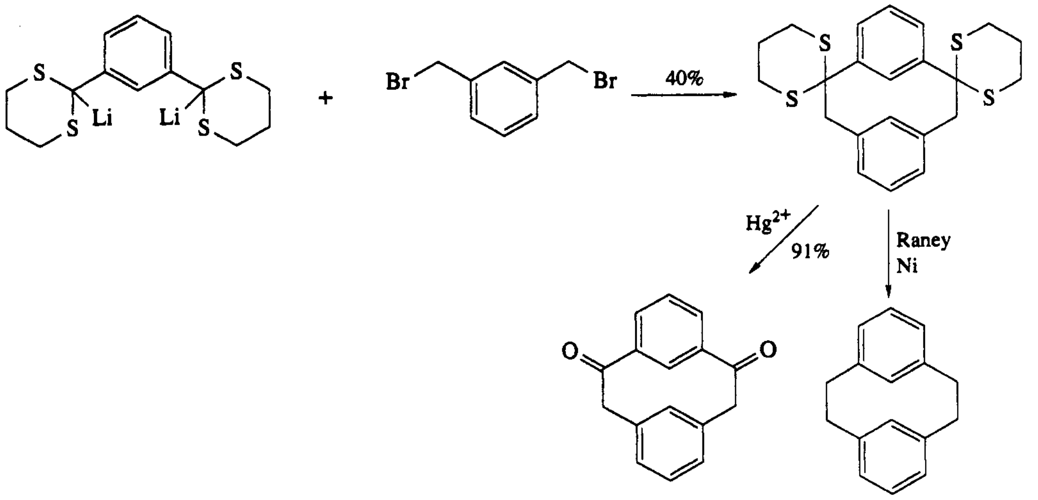
Scheme 3



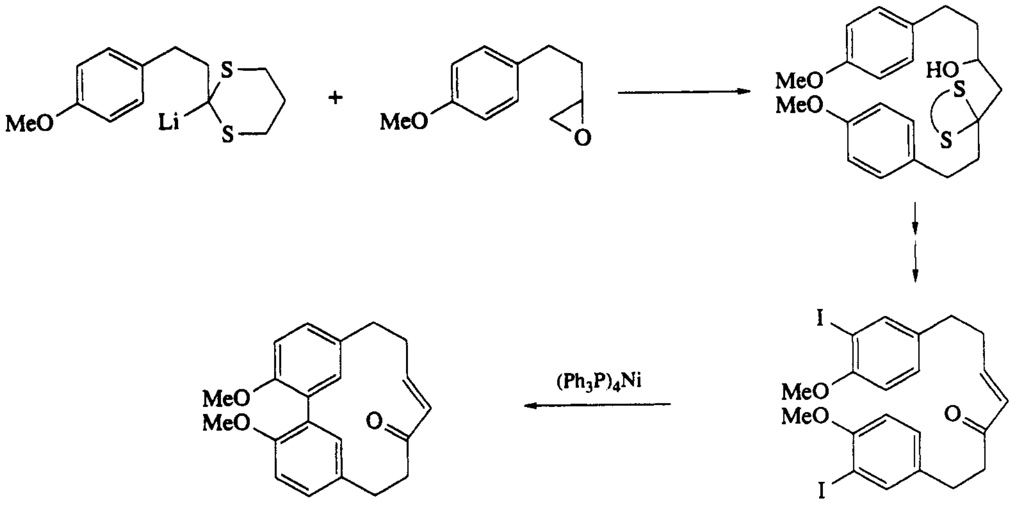
Scheme 4



Scheme 5



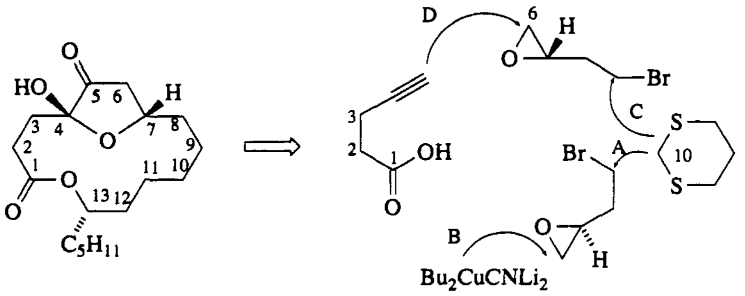
Scheme 6



Scheme 7

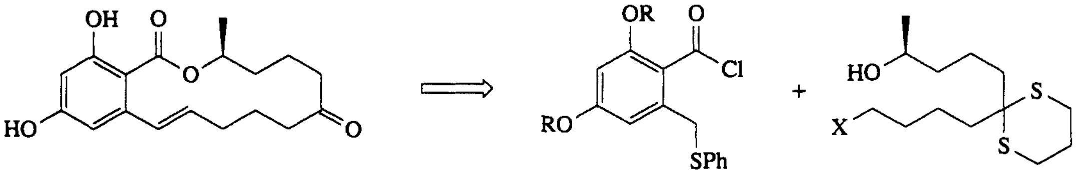
Another relevant example is the total synthesis of the macrolide glacosporone,[39] a germination self-inhibitor from the fungus *Colletotrichum glocosporioides*. The retrosynthetic scheme shows the important role played by the dithiane anion (Scheme 8).

Finally, the recent total synthesis of zearalenone reported by Rao[40] gives a good illustration of the range of reactions available for organosulfur compounds: the macrocyclization reaction, the formation of the double bond and the introduction of the ketone group were made possible by using sulfur-containing

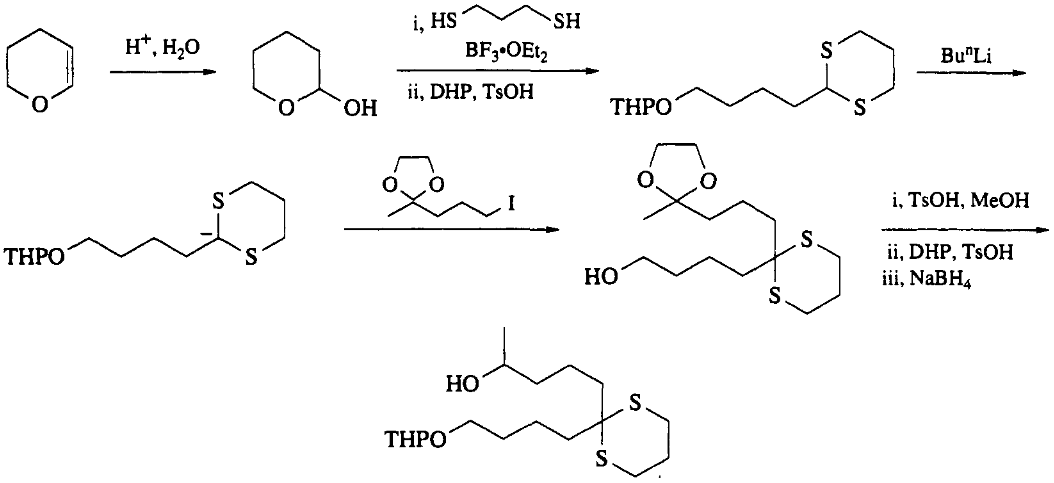


Scheme 8

reagents as shown on the retrosynthetic scheme (Scheme 9). The nonaromatic part of the molecule was readily made from dihydropyran *via* thioacetal formation from the corresponding hemiacetal, followed by alkylation of dithiane carbanion (Scheme 10).



Scheme 9

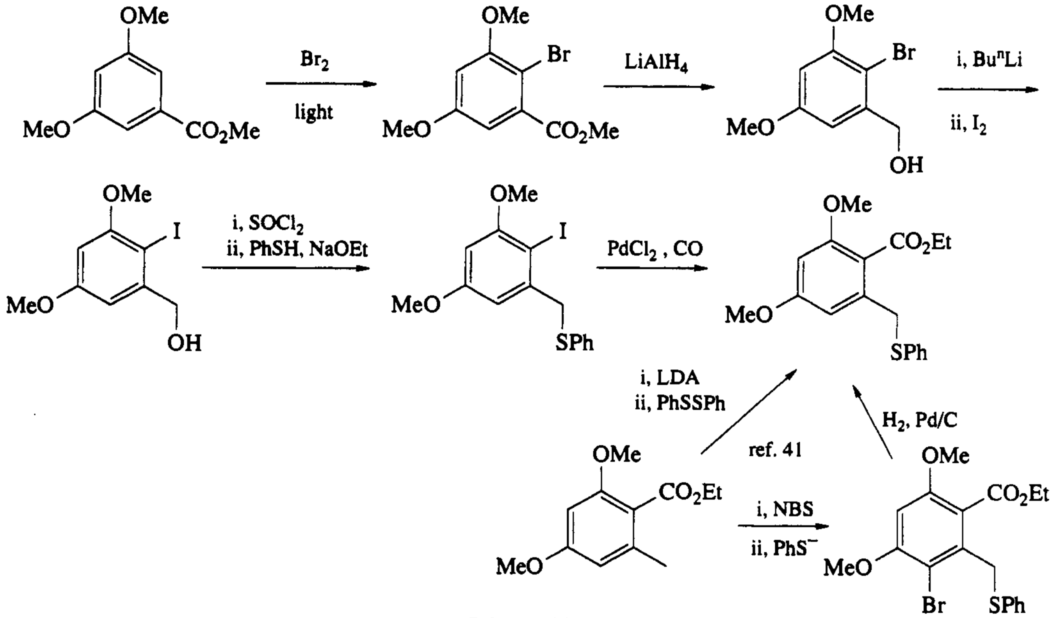


Scheme 10

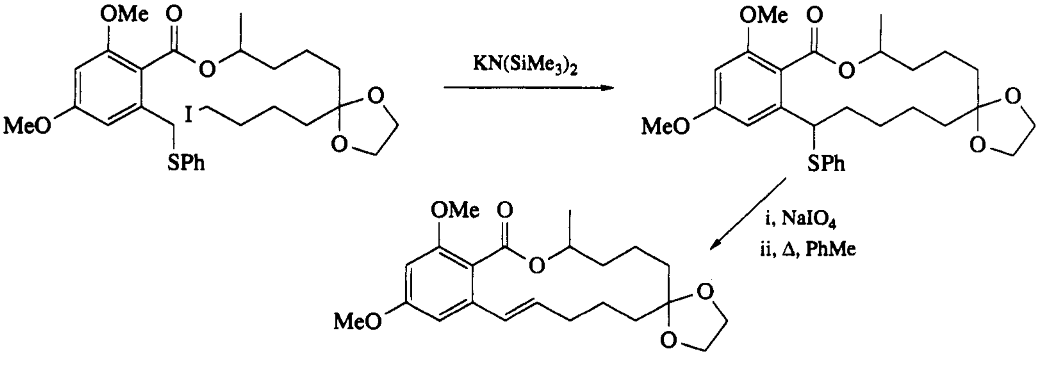
Although benzylic sulfides will be treated later in a separate section, the synthesis of zearalenone gives the first opportunity to mention their synthetic use. The introduction of sulfur to build the aromatic part of zearalenone was done in two different ways:[41,42] displacement of a benzylic bromide by benzenethiol or reaction of diphenyl disulfide with benzylic carbanion (Scheme 11).

Finally, zearalenone was obtained[43] by intramolecular alkylation of the carbanion α to the benzylic sulfide, which occurs readily with potassium hexamethyldisilazane. After cyclization, the double bond was created by oxidation of sulfide to sulfoxide followed by pyrolytic elimination, a technique described in more detail in the next section (Scheme 12).

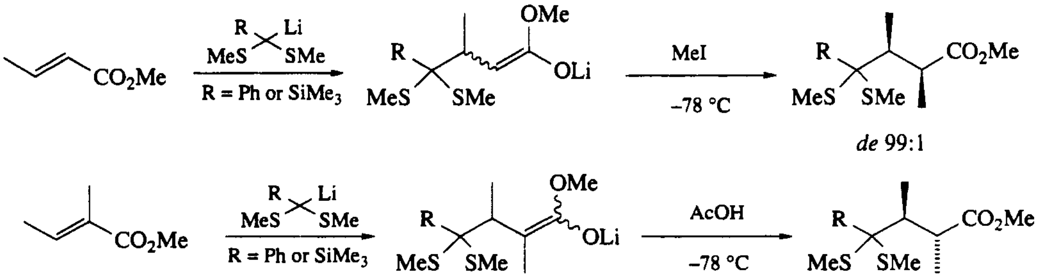
Recently, Koga[74] found a novel use of dithioacetal as a stereocontrolling unit during alkylation of acyclic α,β-unsaturated esters. Conjugate addition of lithiated dimethyl thioacetals to α,β-unsaturated esters in THF at low temperature, followed by subsequent methylation of the corresponding enolate gave only a single isomer. Alkylation and protonation take place with the electrophile attacking *anti* to the bulky dithioacetal for steric reasons (Scheme 13).



Scheme 11



Scheme 12



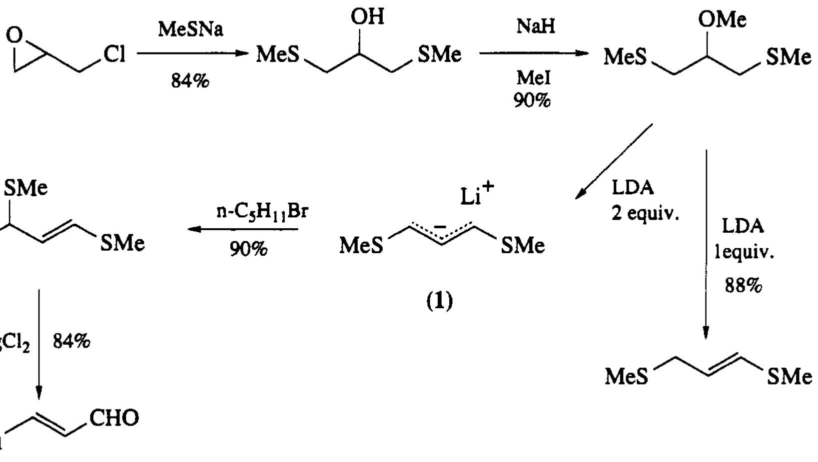
Scheme 13

1.5.2.2 Other Sulfides

Benzylic and allylic sulfides have very important applications in organic syntheses.

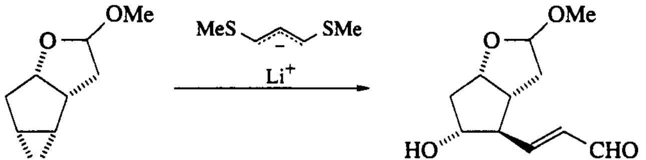
One of the first papers was published by Corey[44] on the use of bis(methylthio)allyllithium (**1**; Scheme 14) for the synthesis of α,β-unsaturated aldehydes from alkyl halides. The generation of the carbanion as the lithio derivative was readily accomplished by a simple three-step sequence from epichlorohydrin.

Reaction of epichlorohydrin with sodium methanethiolate gave 1,3-bis(methylthio)-2-propanol, which was converted to the sodio derivative and methylated to afford 1,3-bis(methylthio)-2-methoxypropane. Finally, treatment with LDA (1 equiv.) resulted in elimination of methanol to give 1,3-bis(methylthio)propene, whereas reaction with 2 equiv. of LDA gave bis(methylthio)allyllithium, which reacted with 1-bromopentane furnishing 1,3-bis(methylthio)-1-octene, which in turn was converted by hydrolysis with mercury(II) chloride to *trans*-2-octenal (Scheme 14).



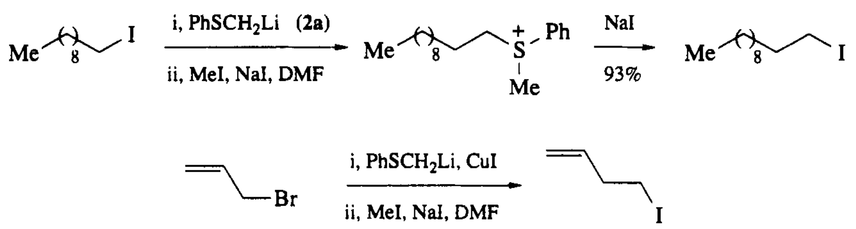
Scheme 14

The application of the lithio reagent (**1**) to the conversion of the oxidoacetal to the corresponding hydroxy aldehyde as a key step in a total synthesis of prostaglandin $F_{2\alpha}$ has been described (Scheme 15).[45]



Scheme 15

Phenylthiomethyllithium (**2a**) was used for the homologation of primary halides[46] in a two-step sequence: first halogen displacement by reagent (**2a**) or the organocuprate derivative (in the case of allylic compound) and then replacement of the phenylthio group by iodo by heating the sulfide with a large excess of methyl iodide in 1 M sodium iodide solution in DMF (Scheme 16).

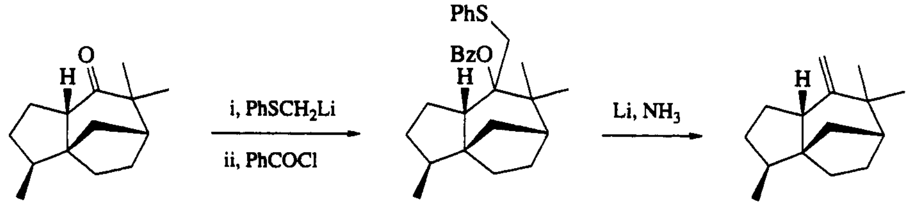


Scheme 16

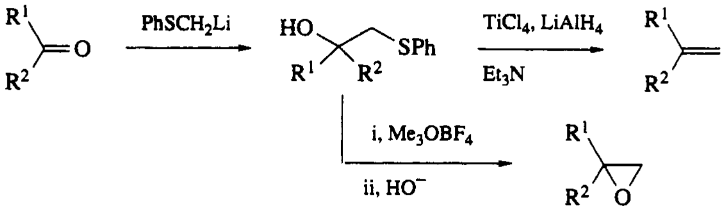
Phenylthiomethyllithium was also used for ketone methylenation,[47,49] mainly in the case of hindered ketones which do not react with the usual Wittig reagent. This is a three-step sequence: the reagent (**2a**) is added, then the resulting alcohol is acylated, and finally the exocyclic methylene is formed by reduction with lithium in ammonia (Scheme 17).

The phenylthiomethyl adduct could also be transformed in one step to methylene with $TiCl_4/LiAlH_4$[48] or to epoxide[50] *via* the corresponding sulfonium salt (Scheme 18).

α-Phenylthiomethyltrimethylsilane (**2b**) was shown to react with alkyl halides or epoxides giving in two steps the corresponding aldehyde.[51-53] This method is interesting because the α-phenylthioalkyl-

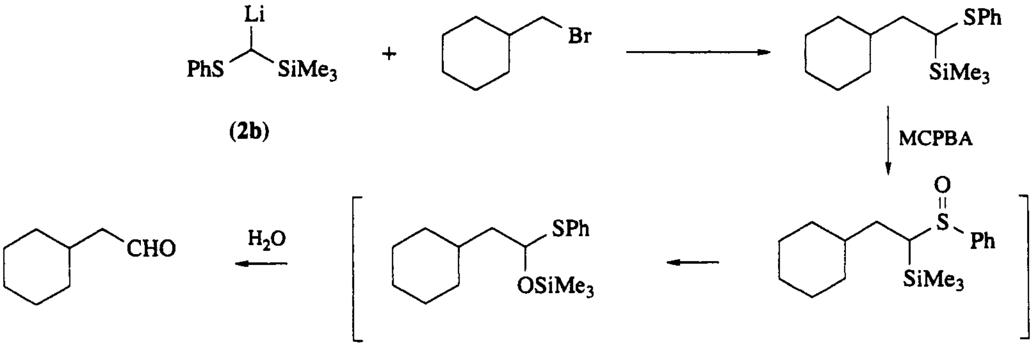


Scheme 17



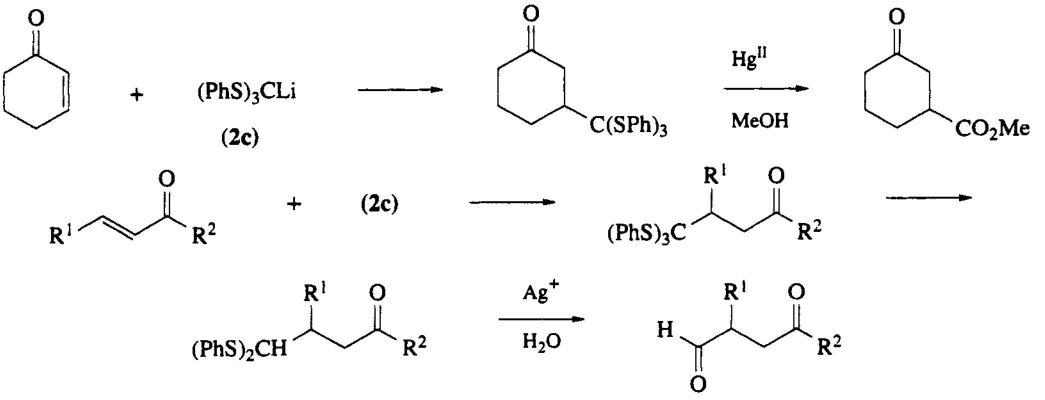
Scheme 18

trimethylsilane obtained in the first step can be oxidized to the corresponding sulfoxide, which undergoes a silyl-Pummerer rearrangement[54,55] giving an *O*-trimethylsilyl hemithioacetal, which is readily hydrolyzed to the aldehyde (Scheme 19).



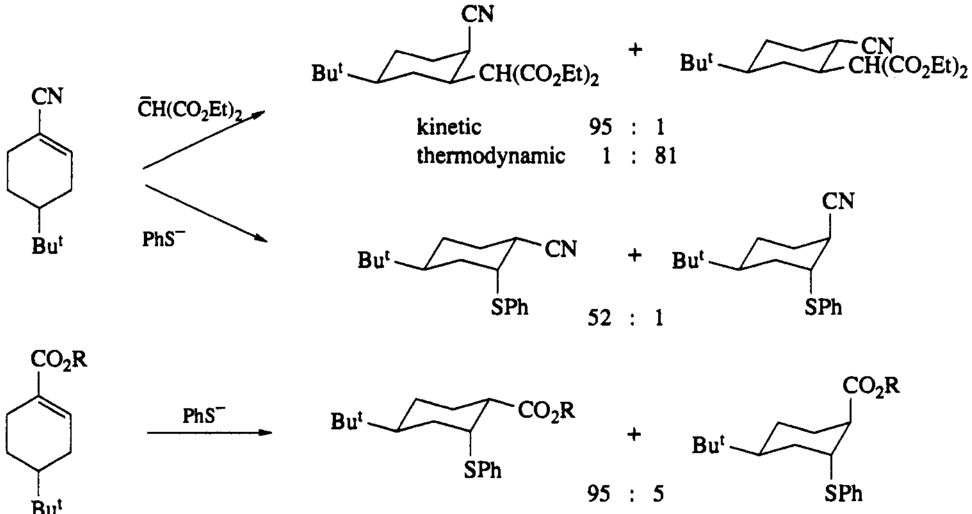
Scheme 19

Tris(phenylthio)methyllithium (**2c**) adds in conjugate fashion to a number of enones,[56,57] and the resulting adduct could then be hydrolyzed into a carboxylic acid ester or aldehyde (Scheme 20).



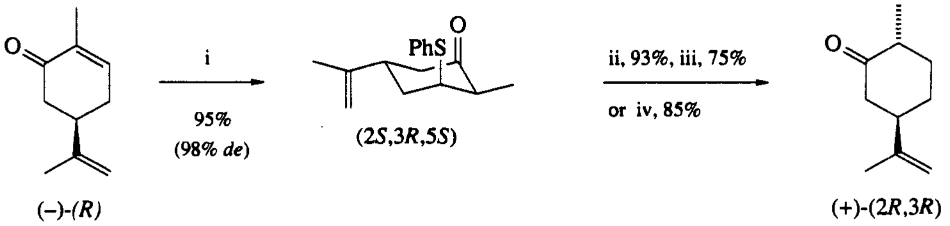
Scheme 20

Michael addition of benzenethiolate to 4-*t*-butyl-1-cyanocyclohexene gives only products containing an axial PhS$^-$ group;[60] the same result was obtained from ethyl 4-*t*-butylcyclohexene-1-carboxylate.[61] In contrast, the addition of diethyl sodiomalonate gave only the equatorial malonate group under thermodynamic or kinetic control (Scheme 21).[58,59] Similar results were observed with the addition of tris(phenylthio)methyllithium (**2c**) on carvone.[62a]



Scheme 21

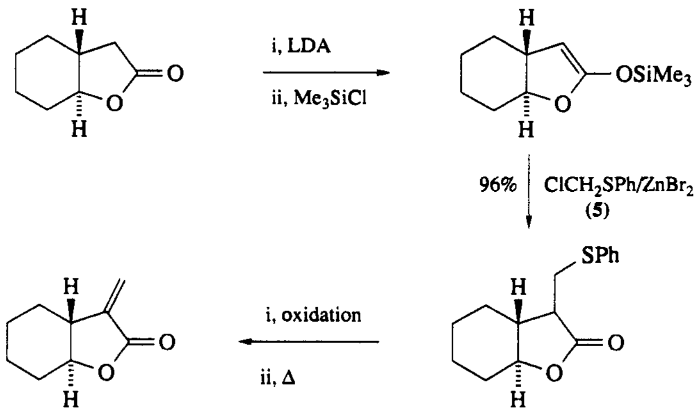
The same diastereoselectivity was obtained during the addition of benzenethiol to (–)-carvone;[62b] this was then applied to the preparation of (+)-(2*R*,5*R*)-dihydrocarvone (Scheme 22).



i, PhSH, Et_3N, *n*-hexane, 0 °C; ii, $LiAlH_4$; iii, Li/Pr^{n}NH$_2$; iv, PDC/DMF

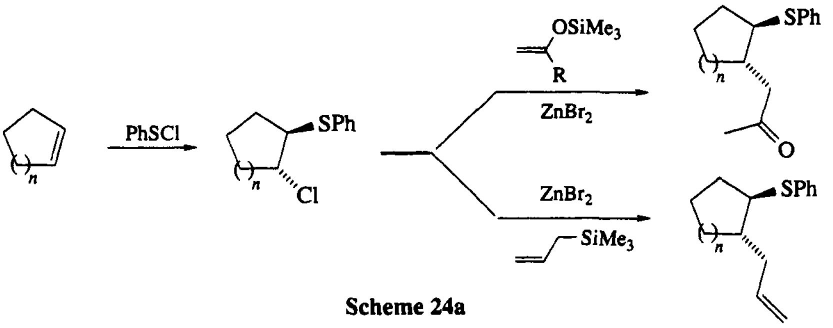
Scheme 22

Chlorosulfides are often used for vicinal functionalization of alkenes. Silyl enol ethers can react with α-chloromethyl phenyl sulfides (**5**) in the presence of $ZnBr_2$[63] or $TiCl_4$[64] to give the corresponding β-keto sulfide, which could be easily transformed into the α-methylene ketone *via* sulfide oxidation to sulfoxide, followed by pyrolytic elimination (Scheme 23).

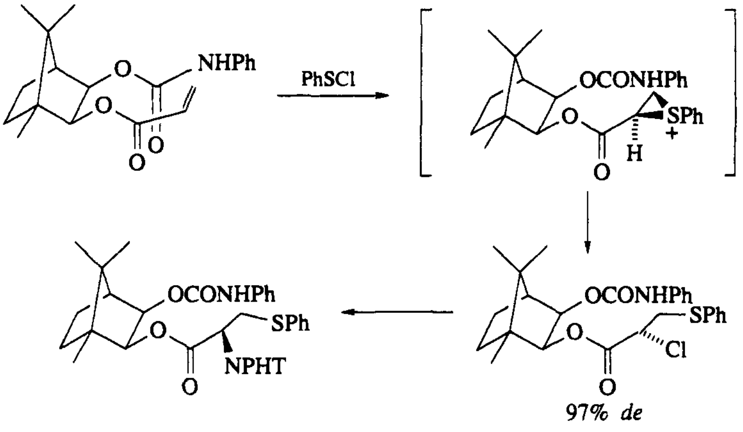


Scheme 23

Cyclic α-chloro sulfides are easily made from the corresponding alkenes and PhSCl. They have also been reacted with *O*-silylated enolates or allyltrimethylsilanes (Scheme 24a).[65a] A stereoselective synthesis of α-chloro sulfide was also reported[65b] on a camphor derivative (Scheme 24b). A complete review on organic synthesis with α-chloro sulfides was recently published by McKervey.[66]

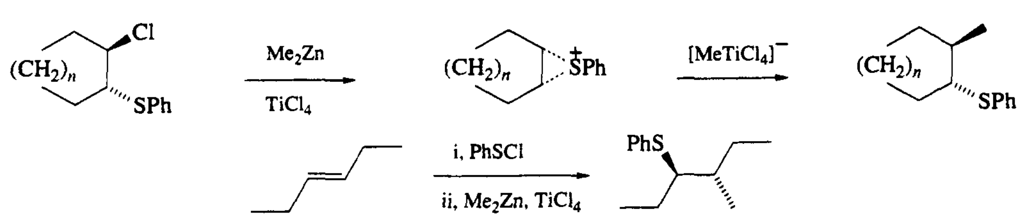


Scheme 24a



Scheme 24b

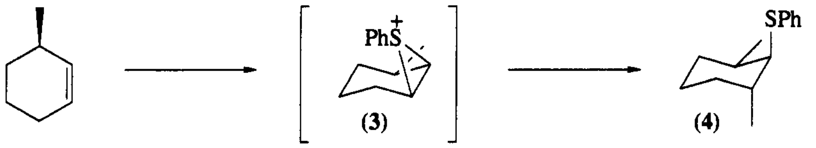
Recently Reetz[67] reported on the regio- and stereo-selective carbosulfenylation of alkenes.[67] When *trans*-β-chloro sulfides obtained from cyclic alkenes are allowed to react in a one-pot process with dimethylzinc in the presence of 20 mol % TiCl$_4$, the C—C coupling products are formed with complete retention of configuration. The same is true of noncyclic alkenes. The mechanism should probably proceed by the formation of an episulfonium ion, which is attacked by the complex [MeTiCl$_4$]$^-$ (Scheme 25).

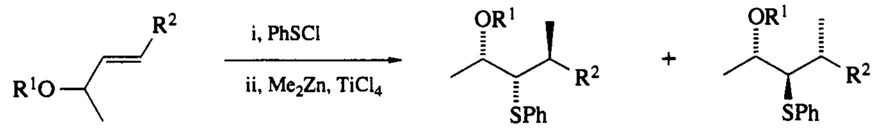


Scheme 25

Finally, the regioselectivity as well as the 1,2-asymmetric induction were investigated. In the case of optically active 2-methylcyclohexene the regioselectivity was 85%, giving mainly compound (4) with 99% diastereofacial selectivity (Scheme 26). For stereoelectronic reasons only (3) undergoes a *trans*-1,2-diaxial ring opening to give (4) in the chair conformation.

In the case of acyclic alkenes, the carbosulfinylations are likewise regio- and, depending on the nature of the protective group on oxygen, stereo-selective (large protecting groups give smaller 1,2-asymmetric induction; Scheme 26).

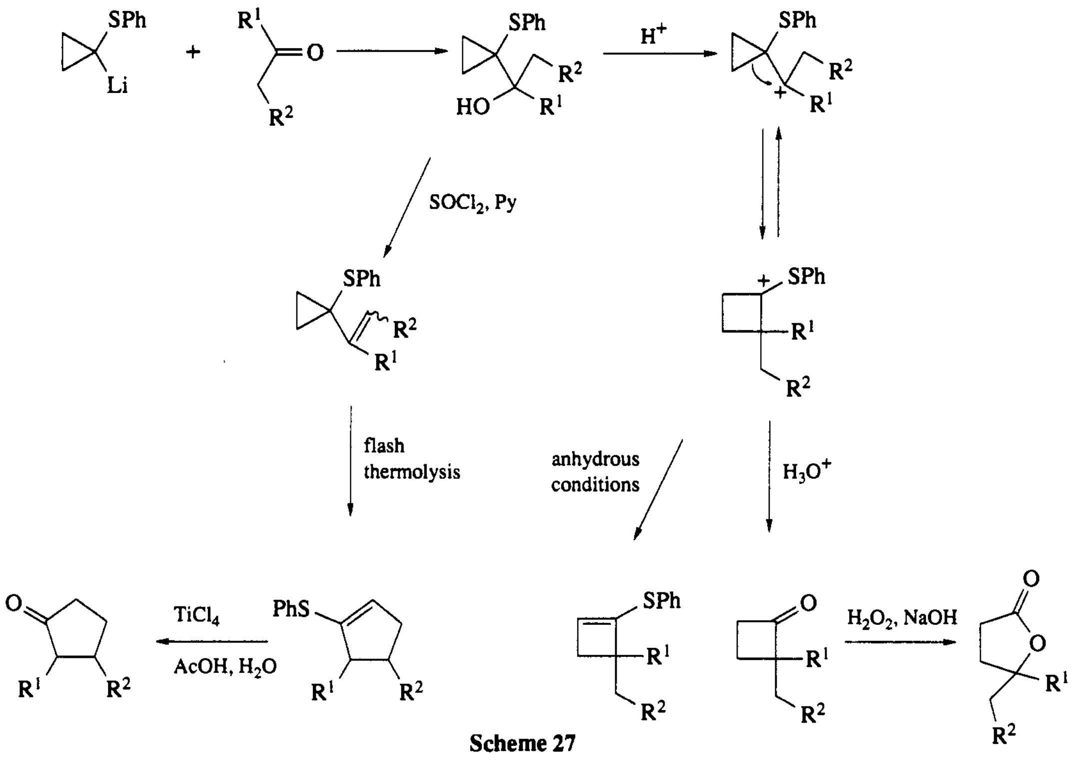




$R^1 = Me$	99	:	1
$R^1 = CH_2Ph$	85	:	15
$R^1 = SiMe_3$	84	:	16
$R^1 = SiMe_2Bu^t$	60	:	40

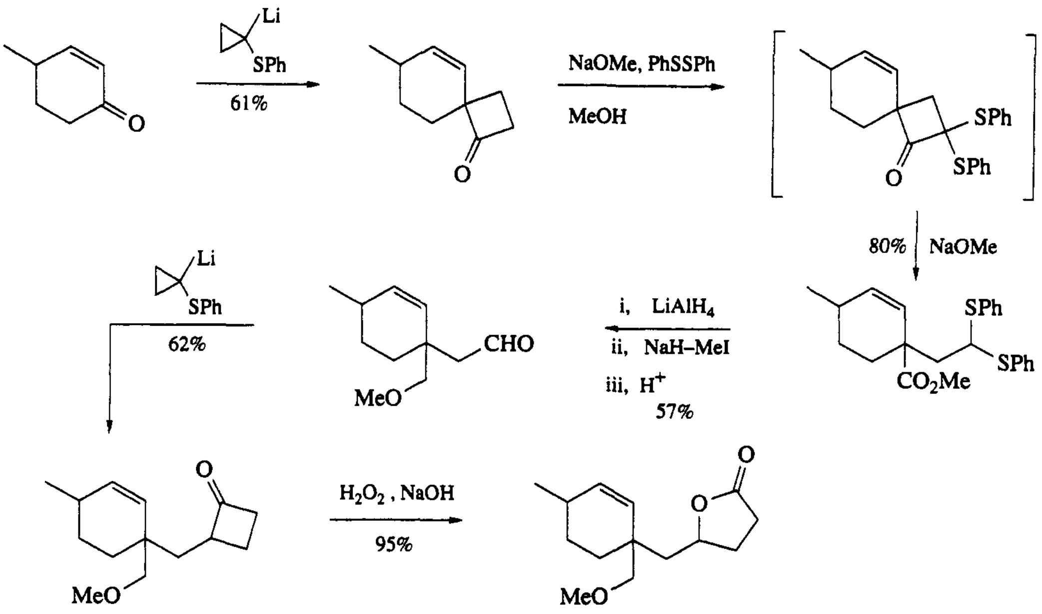
Scheme 26

Treatment of cyclopropyl phenyl sulfide with *n*-butyllithium gives α-lithio(phenylthio)cyclopropane, which reacts with electrophilic reagents to give adducts that undergo a variety of transformations, many of which are difficult to achieve by more conventional methodology. Perhaps the most interesting chemistry of cyclopropyl phenyl sulfide involves its reaction with carbonyl compounds,[68,69] giving cyclobutanones or 1-phenylthiocyclobutenes[70] through carbocation rearrangements. After dehydration of the adduct, the resulting vinylcyclopropane could be transformed into cyclopentanone by a known thermal rearrangement (Scheme 27).[71]



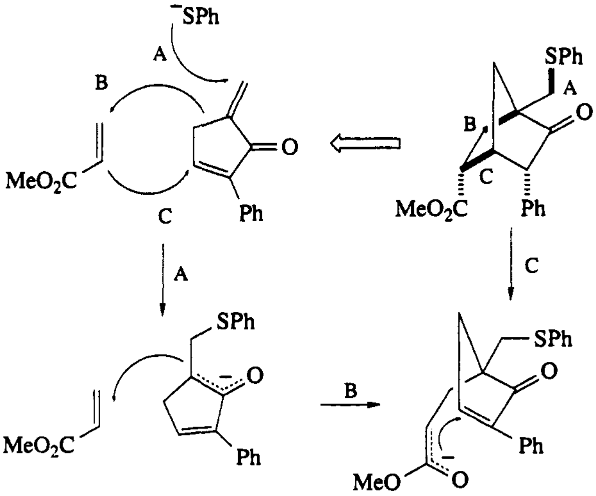
Scheme 27

Trost also found[72] that treatment of these cyclobutanones with sodium methoxide and diphenyl disulfide leads to *in situ* bisulfenylation and ring cleavage (secosulfenylation). This was applied to the total synthesis of verrucarol, a complex tetrahydrochromanone substituted at the ring junction by a hydroxymethyl substituent. The synthetic strategy[73] twice used the cyclobutanone formation from 1-lithiocyclopropyl phenyl sulfide and a ketone, followed by the secosulfenylation process and Baeyer–Villiger type rearrangement of cyclobutanone. Only this part of the synthesis is described in Scheme 28.



Scheme 28

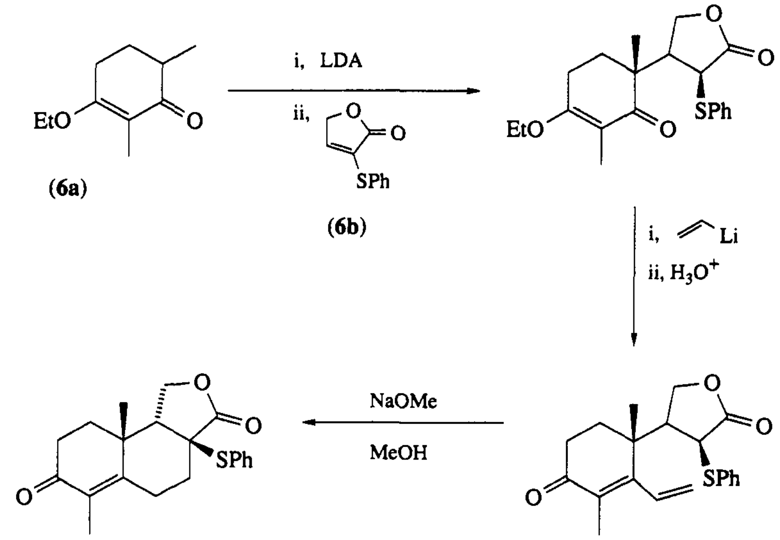
Sulfides were also involved in a unique three-component, stereospecific Michael addition.[75] The reaction described in Scheme 29 can be explained as follows: regiospecific addition of the nucleophile to the exocyclic double bond of the α-methylenecyclopentenone, followed by trapping of the resulting enolate by methyl acrylate, and attack of the anion thus formed on the endocyclic double bond of the cyclopentenone moiety to result, after protonation, in the bicyclo[2.2.1]heptan-6-one as a single stereoisomer (68% overall yield; Scheme 29).



Scheme 29

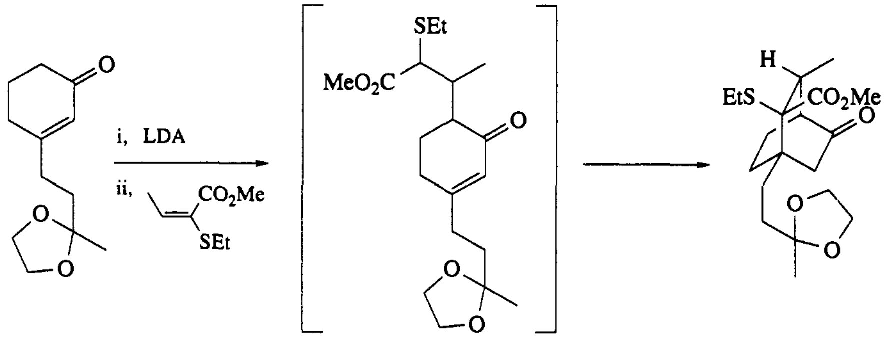
Sulfide has also been involved in a new two-step annulation method which featured stereospecific formation of three contiguous asymmetric centers.[76] It was found that the lithium dienolate of the vinylogous ester (**6a**) reacts rapidly with the α-thiophenyl butenolide (**6b**) to provide the corresponding adduct as a single diastereoisomer. Subsequent addition of vinyllithium, acidification and cyclization gave the tricyclic lactone (Scheme 30).

A similar highly stereoselective Michael addition has been reported by Uda.[77] The enolate of a substituted cyclohexenone reacted rapidly in a Michael-type addition with methyl α-thiophenylmethacrylate



Scheme 30

to provide the corresponding adduct, which, by an intramolecular Michael addition, leads to the substituted [2.2.2]octanone as a single stereoisomer (Scheme 31).



Scheme 31

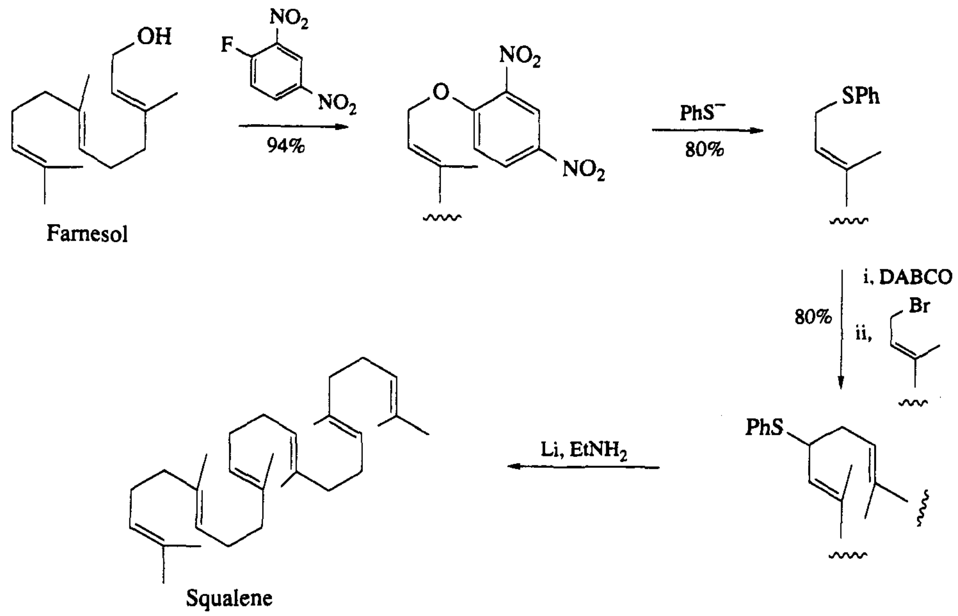
Allylic sulfides can be coupled with allylic bromides in a process which was first described by Biellmann and applied to the squalene synthesis.[78] Farnesyl sulfide was prepared from 2,4-dinitrophenylfarnesyl oxide and benzenethiolate. Finally, the allylic thiocarbanion was coupled with farnesyl bromide to give, in 82% yield, squalene sulfide, easily transformed to squalene with Li/$EtNH_2$ (Scheme 32).

Several applications of this method appeared in the literature. Furaterpenes can be synthesized in this way; *e.g.* dendrolasin was made from *trans*-ω-chloroperillene and the carbanion of prenyl phenyl sulfide (Scheme 33).[79] Elemol has been synthesized by an intramolecular variant of Biellmann's method (Scheme 34).[80]

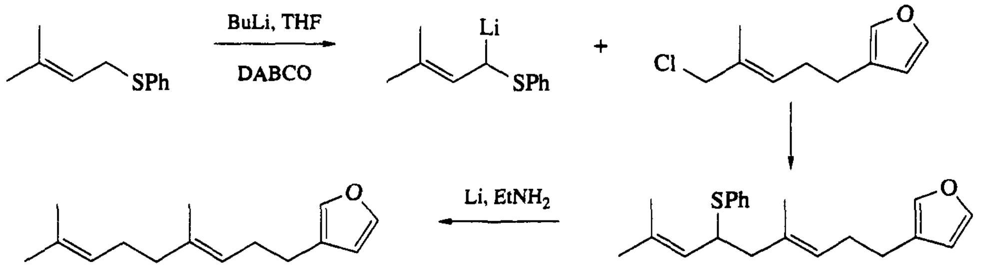
Until now, α-lithio ethers were nearly always prepared by deprotonation of an α-carbon atom of an ether having a special anion-stabilizing feature (carbonyl, cyano, phenylthio). An interesting report by Cohen[81] showed that a variety of types of unstabilized and stabilized α-lithio ethers can be readily prepared from α-(phenylthio) ethers by reductive lithiation with lithium 1-(dimethylamino)naphthalenide or lithium naphthalenide. What makes this method one of considerable generality is the ready availability of various types of α-(phenylthio) ether substrates or their vinylogues as shown in Scheme 35.

An example of this method is given by the synthesis of brevicomin.[81] The desired α-(phenylthio) ether (7) was made by Diels–Alder addition of phenyl vinyl sulfide and methyl vinyl ketone. Treatment of (7) with lithium 1-(dimethylamino)naphthalenide, followed by trapping of the anion with propionaldehyde and ring closure to an acetal during the acidic work-up, afforded a mixture of *endo* and *exo* isomers of brevicomin (Scheme 36).

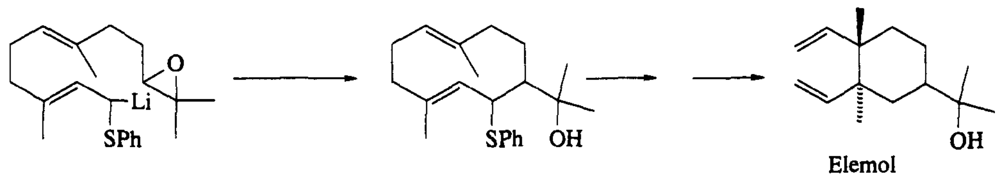
Several other applications of this method have been published. Reductive lithiation of 1-(trimethylsilyl)cyclopropyl phenyl sulfide gives α-lithio(trimethylsilyl)cyclopropane, which reacts with carbonyl



Scheme 32



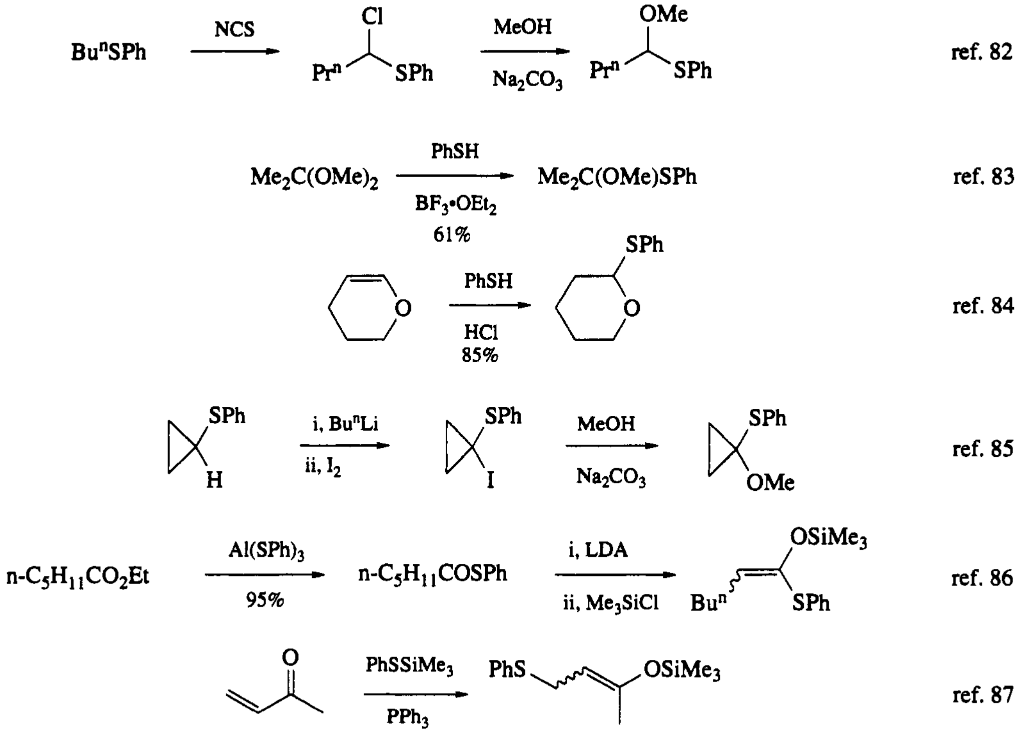
Scheme 33



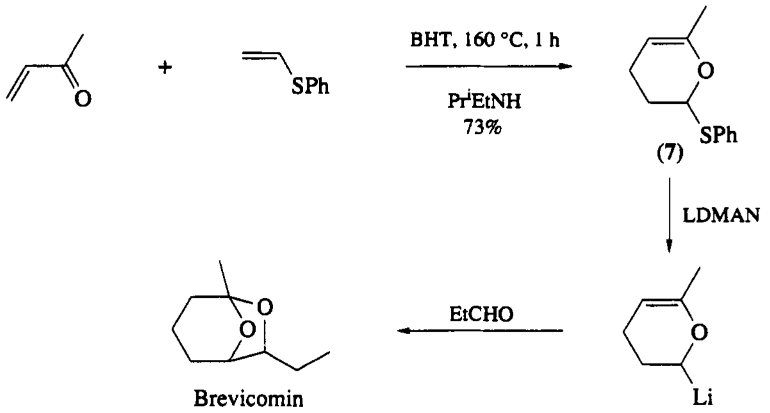
Scheme 34

compounds to give 1-(trimethylsilyl)cyclopropylethylenes. Pyrolysis of these compounds provides a new cyclopentane annulation procedure. A unique feature of this process is that the double bond in the vinylsilane is formed in the more highly substituted position (Scheme 37).[88]

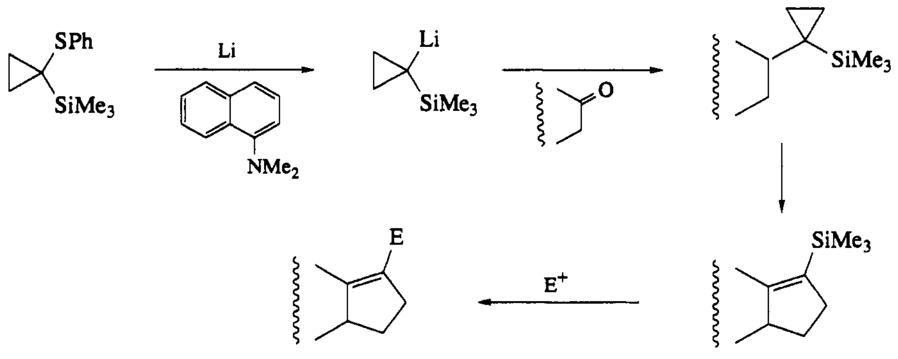
The synthesis of (–)-β-selinene from the commercially available (–)-perillaldehyde used a reductive lithiation of 1-methoxycyclopropyl phenyl sulfide, condensation to an aldehyde, acid-catalyzed rearrangement to a vinylcyclobutanone and finally basic 1,3-sigmatropic rearrangement of the corresponding cyclobutanol to cyclohexenol (Scheme 38a).[89a] 1-Phenylthio-1-(trimethylsiloxy)cyclopropane was prepared *via* the silyl-Pummerer rearrangement with high stereoselectivity (Scheme 38b).[89b] (1-Methoxy-1-phenylthio)cyclopropane was also obtained from alkenes *via* Pummerer rearrangement.[89c] 2-Methoxy-3-phenylthiobuta-1,3-diene was also shown to be a novel annelating agent *via* a Diels–Alder reaction (Scheme 38c).



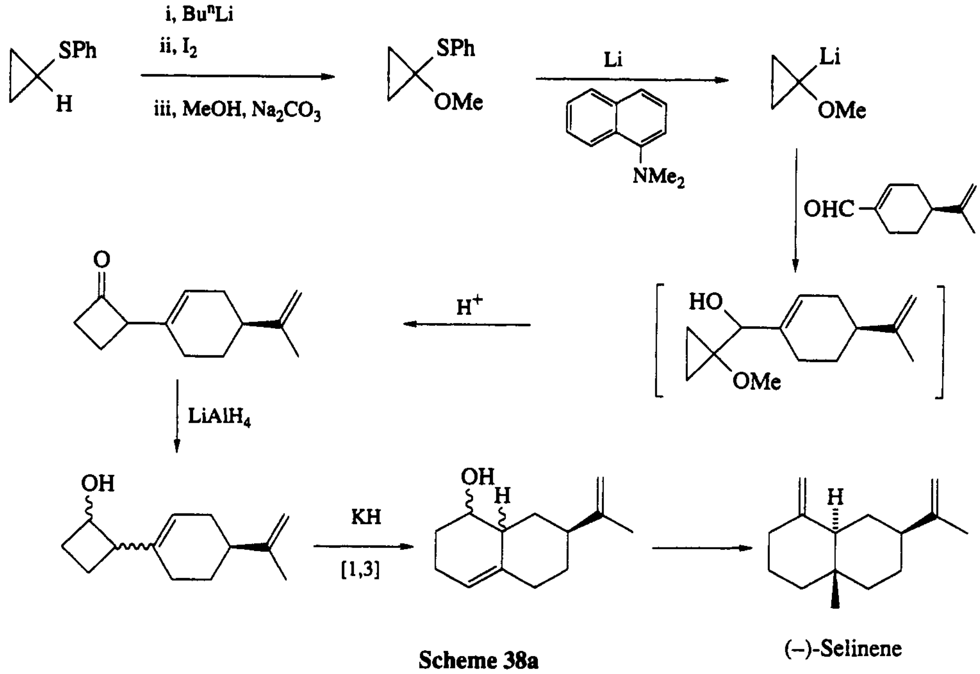
Scheme 35



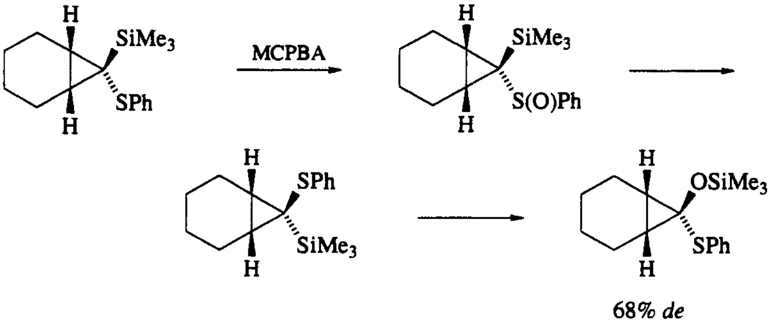
Scheme 36



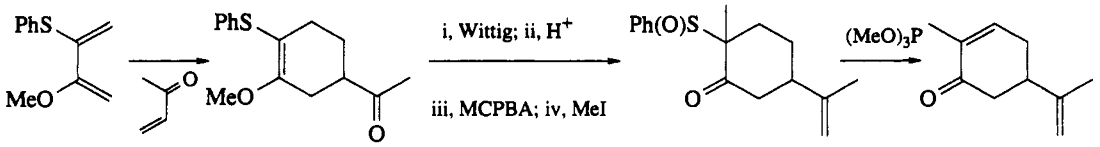
Scheme 37



Scheme 38a



Scheme 38b

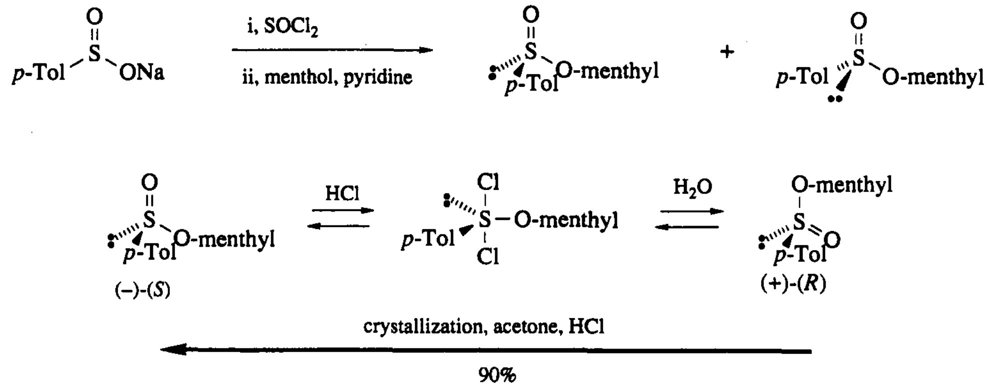


Scheme 38c

1.5.3 SULFOXIDES

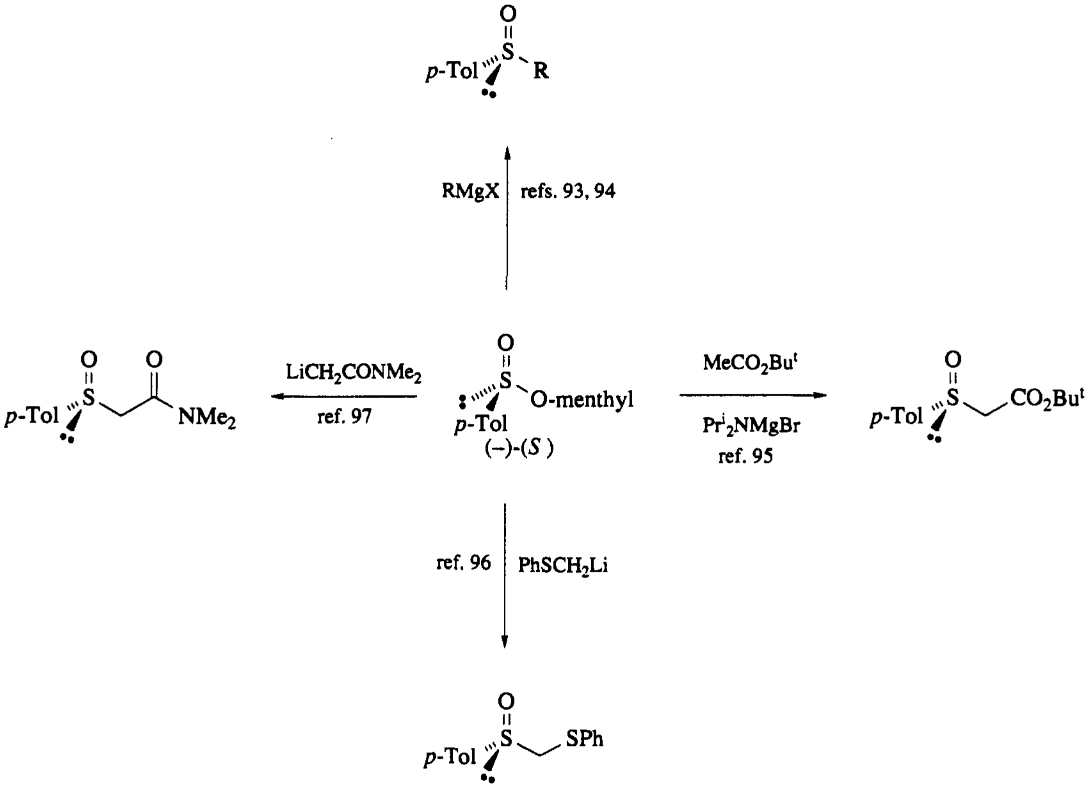
This part concentrates mainly on the utility of chiral sulfoxides in asymmetric synthesis. The main advantage of sulfoxides over the other sulfur functions which are described in this review is indeed their chirality. Sulfoxides are chiral groups which are easy to introduce, easy to remove and give high asymmetric induction in many reactions.[90]

The best way to prepare large quantities of optically active sulfoxides makes use of optically active menthyl sulfinate. By esterification of *p*-toluenesulfinic acid with l-menthol, a mixture of diastereoisomeric menthyl sulfinates is obtained. This esterification reaction shows no particular stereoselectivity and therefore a mixture of the two diastereoisomeric esters was obtained. However, it is possible to equilibrate these diastereoisomers in acidic media and to shift the equilibrium towards the less soluble isomer, (–)-(*S*)-menthyl *p*-toluenesulfinate, which was obtained in 90% yield from the starting *p*-toluenesulfinic acid (Scheme 39).[91]



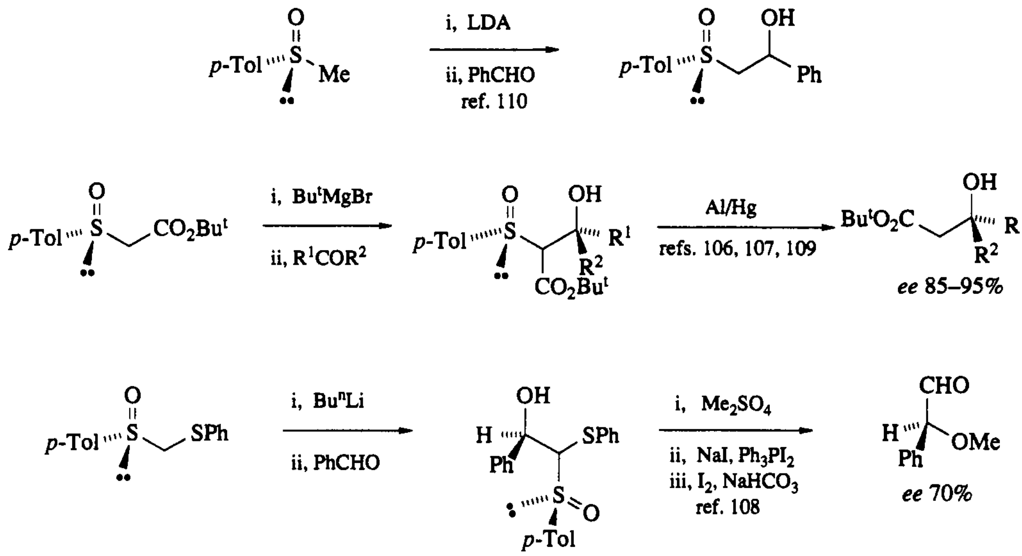
Scheme 39

Optically active sulfoxides are readily obtained from menthyl sulfinate by a Grignard reaction. This reaction was originally proposed by Gilman[92] and applied to optically active products by Andersen:[93,94] this is a pure S_N2 reaction at sulfur with displacement of the menthoxy group by the Grignard. A great variety of sulfoxides have been prepared by this method;[90,95–105] other organometallics have also been used. A few examples are shown in Scheme 40.



Scheme 40

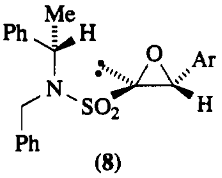
If optically active sulfoxides such as methyl *p*-tolyl sulfoxide give a poor diastereoselectivity when such an α-sulfinyl carbanion is added to a carbonyl,[90] the presence of another function such as ester, sulfide or amide, which has a chelating effect in the transition state, makes optically active α-sulfinyl esters, sulfides or amides very useful in asymmetric aldol-type condensation (Scheme 41).[97,106–109]



Scheme 41

Optically active sulfoxides can also be prepared by asymmetric oxidation of sulfides. However, numerous papers have reported very low enantioselectivity.[111] Only one report,[112–113] using a modified Sharpless reagent, $H_2O/Ti(OPr^i)_4$/diethyl tartrate/Bu^tOOH, described asymmetric oxidation of alkyl aryl sulfoxides with good enantiomeric excesses: 75 to 95%.

It should also be mentioned that optically active 2-sulfamyloxaziridines (**8**) afforded high asymmetric induction[114a] for the oxidation of nonfunctionalized sulfides to sulfoxides (53–91% *ee*). The enantioselectivities exhibited by these reagents are comparable to, or in some cases better than, the modified Sharpless reagent reported by Kagan.



(8)

Several papers have also reported asymmetric oxidation of chiral sulfides having a structure derived from camphor.[114b,c]

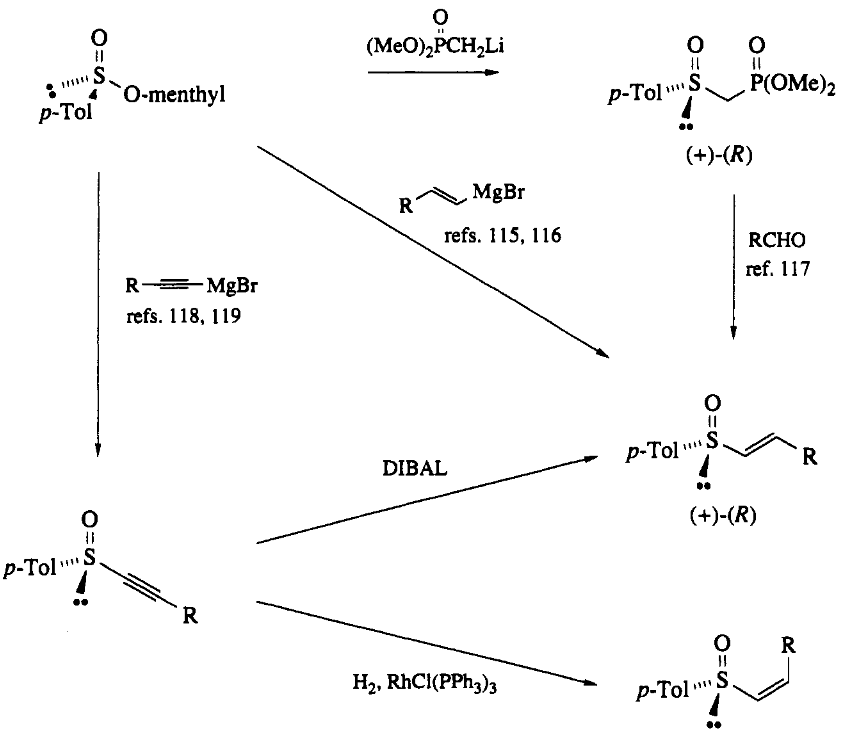
Optically active vinylic sulfoxides can be prepared by the Andersen synthesis, using (–)-menthyl (–)-(*S*)-*p*-toluenesulfinate and vinylic Grignards,[115,116] or by the Wittig–Horner procedure, using carbonyl compounds and the anion of dimethyl (*R*)-*p*-toluenesulfinylmethanephosphonate, easily made from the corresponding menthyl sulfinate.[117] However, applicability of the former method depends on the availability of stereochemically pure 1-alkenyl halides for preparing Grignard reagents and the latter usually leads to a mixture of (*E*)- and (*Z*)-vinylic sulfoxides. Therefore, it is sometimes easier to prepare the corresponding alkynyl sulfoxide by the Andersen method from alkynyl Grignards and then reduce stereospecifically the triple bond into a *trans* double bond with DIBAL or a *cis* double bond by catalytic hydrogenation using the Wilkinson catalyst (Scheme 42).[118,119]

Vinylic sulfoxides have been used successfully in several Michael-type asymmetric syntheses.[120–124] One typical example is given by the asymmetric synthesis of (–)-methyl jasmonate (Scheme 43).[123]

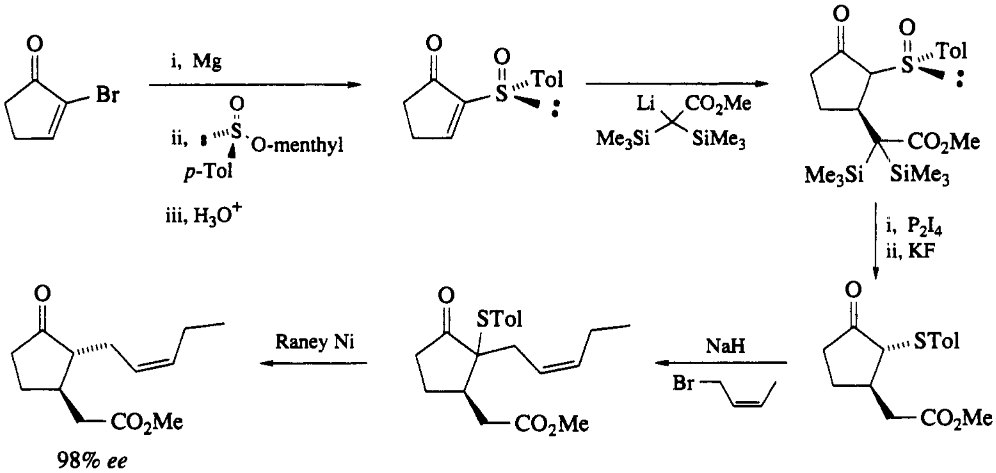
The CD rings of steroids were synthesized by the same method in high enantiomeric purity.[124]

Vinylic sulfoxides have also been used in asymmetric Diels–Alder reaction.[125–130] A very high diastereoselectivity was observed with optically active sulfinylacrylates. One example[126] is given in Scheme 44.

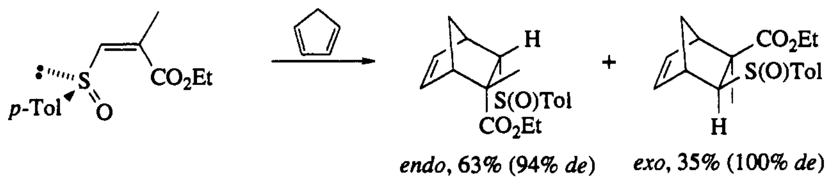
An interesting observation was reported by Posner who showed that α-pyrone substituted by a sulfoxide[131] or a sulfone[132] reacts rapidly with vinyl ethers, giving a diastereoselective [2 + 4] cycloaddition (Scheme 45). Racemic sulfide, sulfoxide or sulfone was introduced on α-pyrone *via* 3-cuprio-



Scheme 42



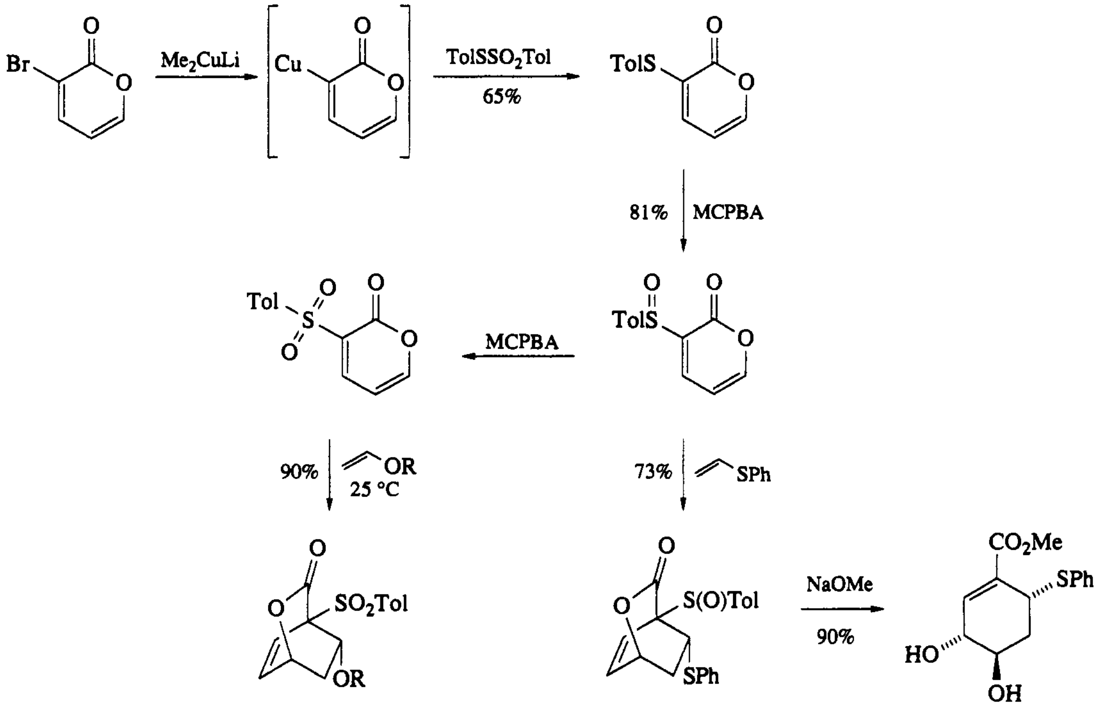
Scheme 43



Scheme 44

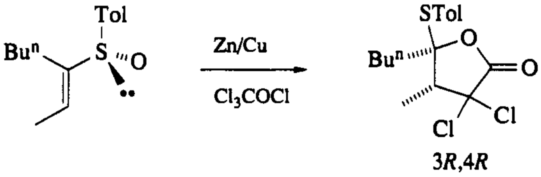
2-pyrone.[133] However, optically active pyrone sulfoxide was prepared from (–)-(*S*)-dihydropyrone sulfoxide by dehydrogenation with MnO_2 in low yield.[131]

Vinylic sulfoxides can undergo additive Pummerer rearrangement when they are treated with trichloroacetyl chloride and a zinc/copper couple in refluxing ether giving optically pure γ-butyrolactone

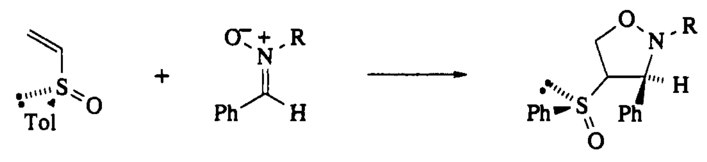


Scheme 45

(Scheme 46).[134,135] Vinyl sulfoxides also exhibited high chiral induction in the 1,3-dipolar cycloaddition with typical nitrones (Scheme 47).[136]



Scheme 46



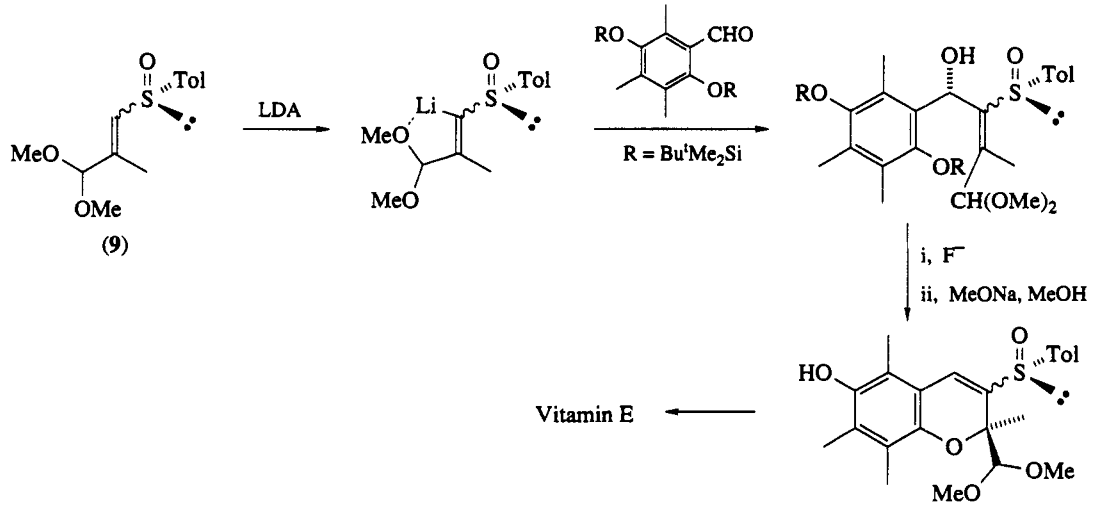
de > 90%

Scheme 47

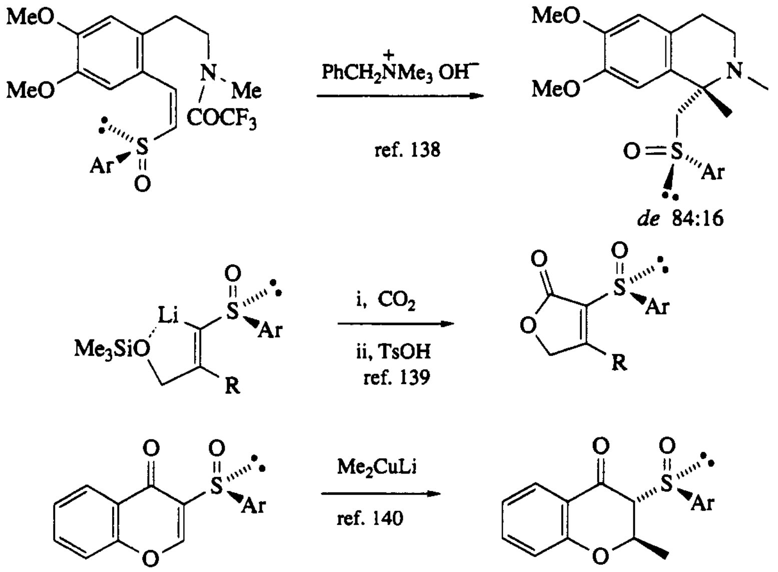
They can also be used as vinylic carbanion species as shown by the asymmetric synthesis of the chroman ring of vitamin E.[137] The (*E*)/(*Z*) mixture of chiral sulfoxide (**9**) was readily isomerized into the (*E*)-isomer with LDA in THF (the exclusive formation of the (*E*)-isomer was due to the chelation of lithium with an oxygen of the acetal). Condensation to trimethylhydroquinonecarbaldehyde gave only one diastereoisomer and then the cyclization in presence of sodium methoxide was also fully stereoselective (the stereochemistry of the cyclization being controlled by that of the allylic hydroxy group which is eliminated during the cyclization; Scheme 48).

A few other examples are listed in Scheme 49: intramolecular addition of amine giving a good synthesis of (*R*)-(+)-carnegine,[138] synthesis of chiral butenolides by carbonation of vinylic carbanions[139] and conjugate additions of cuprates yielding chiral chromans.[140]

Allylic sulfoxides are also of interest mainly because of the possible sulfoxide/sulfenate rearrangement described by Mislow[141] when he observed that allyl *p*-tolyl sulfoxide racemized in a temperature range

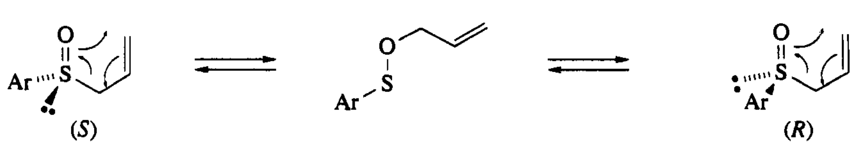


Scheme 48



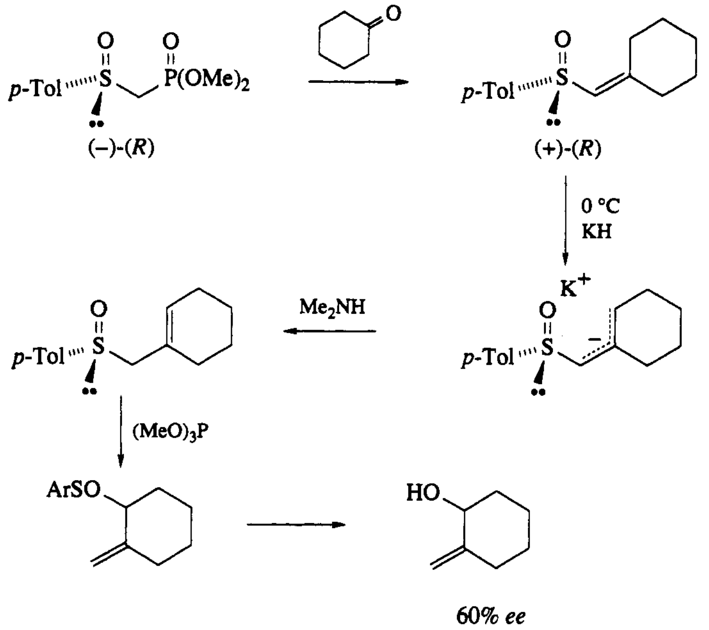
Scheme 49

(50–70 °C) significantly below the usual racemization temperature of sulfoxides (150 °C and higher; Scheme 50).



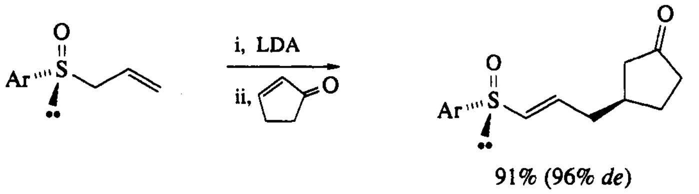
Scheme 50

This 2,3-sigmatropic shift has been of substantial utility since Evans[142] and Hoffmann[143] realized that allyl alcohols can be obtained by intercepting the sulfenate with thiophilic agents. One possible way of preparing optically active allylic sulfoxides, which started to racemize even at 0 °C was the isomerization of the corresponding vinylic sulfoxide followed by the sulfenate rearrangement in the presence of trimethyl phosphite (Scheme 51).[143,144]



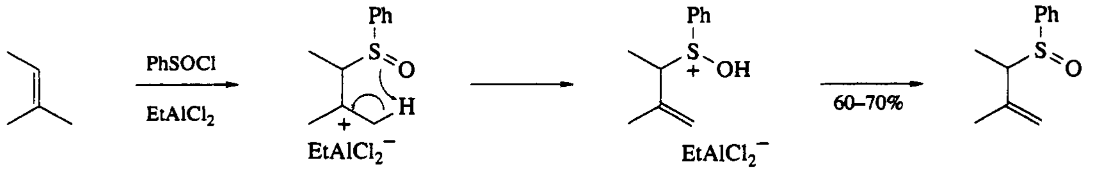
Scheme 51

The carbanions of allylic sulfoxides undergo kinetically controlled conjugate additions to give vinylic sulfoxides as a single diastereoisomer (Scheme 52).[145,146]



Scheme 52

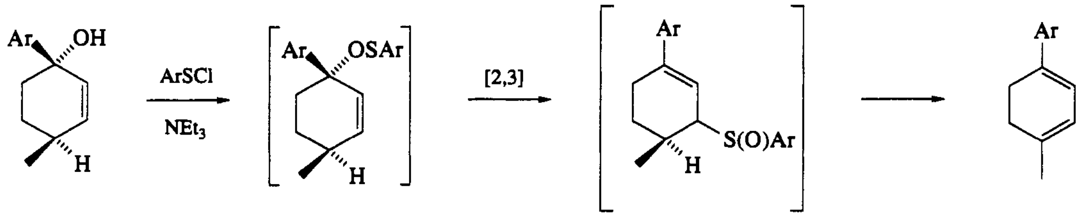
(*E*)- and (*Z*)-allylic sulfoxides bearing alkyl groups at C-3 also undergo highly stereoselective conjugate additions to cyclic enones to give *syn*- and *anti*-vinylic sulfoxides.[146c] Racemic allylic sulfoxides can also be obtained from alkenes by an $EtAlCl_2$-catalyzed ene reaction with *p*-toluenesulfinyl chloride (Scheme 53).[147]



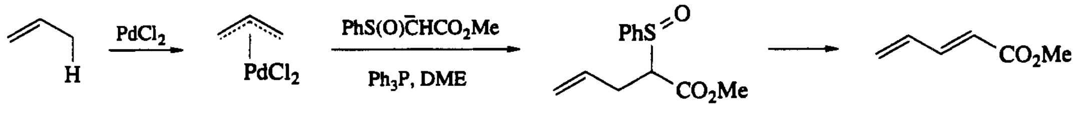
Scheme 53

Allylic alcohols can be converted to 1,3-dienes by sequential sulfenate–sulfoxide 2,3-sigmatropic rearrangement and *syn* elimination (Scheme 54).[148] The last step used the pyrolytic elimination of sulfoxide, a *cis* elimination discovered by Cram.[149] A paper published by Trost[150] documented this topic in detail.

A useful synthesis of functionalized dienes from alkenes used the initial formation of a stable π-allyl palladium complex, followed by reaction with α-sulfinyl ester enolate and pyrolytic sulfoxide elimination (Scheme 55).[151]

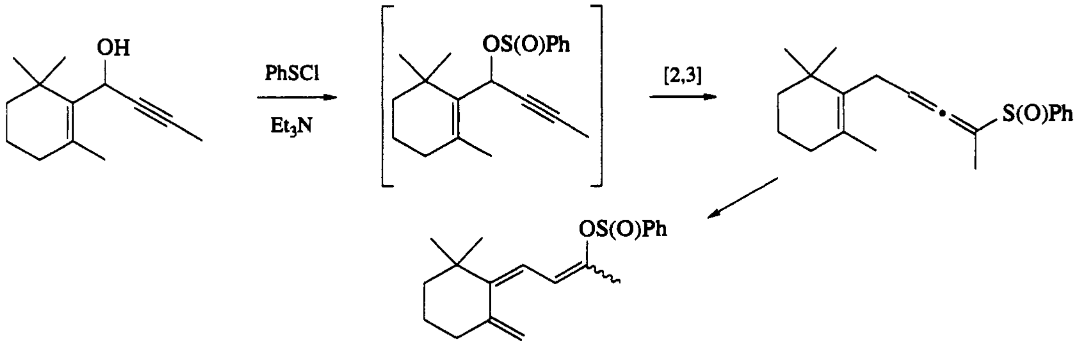


Scheme 54

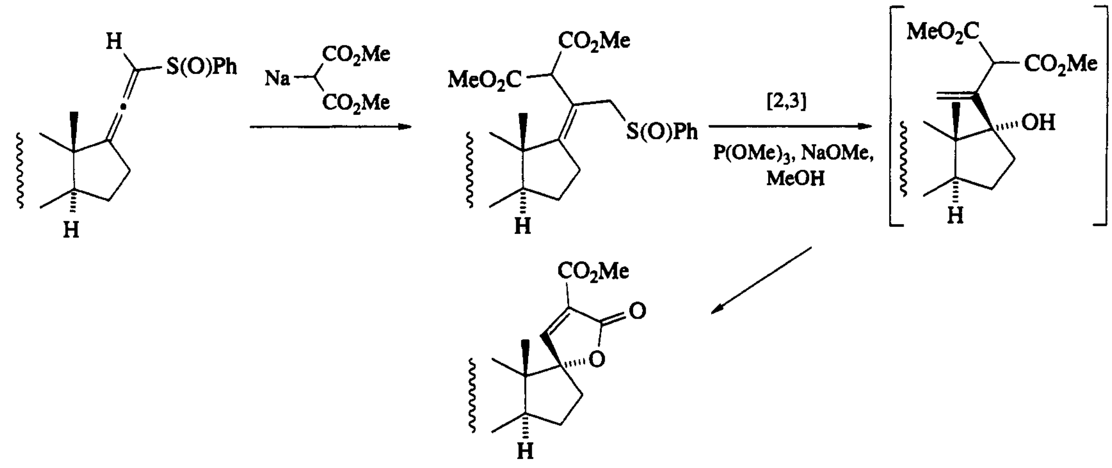


Scheme 55

Allenic sulfoxides can be made from propargylic sulfenates by a 2,3-sigmatropic shift. In the example reported,[152] the product is not stable at room temperature and undergoes a 1,5-sigmatropic hydrogen shift (Scheme 56). These allenic sulfoxides can react as Michael acceptors (Scheme 57).[153]

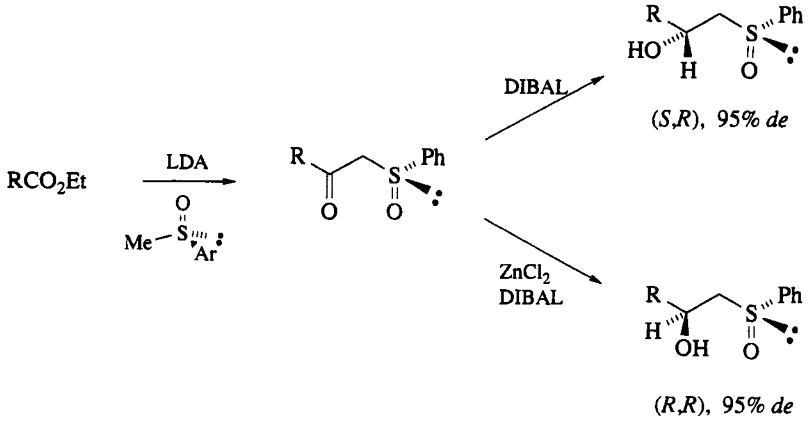


Scheme 56



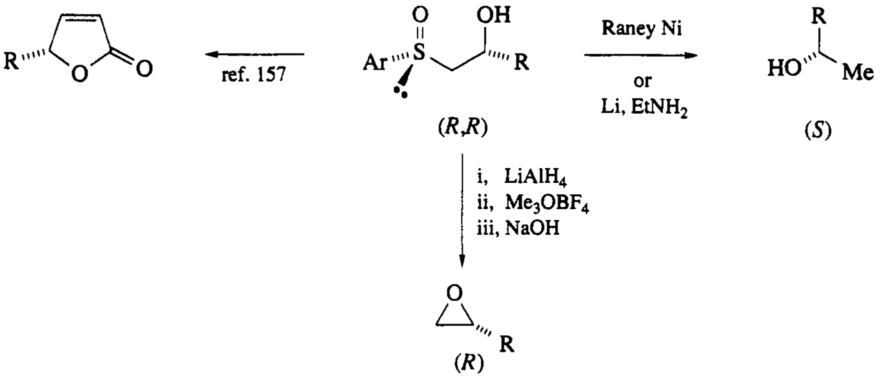
Scheme 57

Optically active β-keto sulfoxides are readily available from esters and methyl *p*-tolyl sulfoxide. The ketone function can be reduced with metal hydrides (DIBAL and $ZnCl_2$/DIBAL) giving, with very high diastereoselectivity, opposite configurations in the resulting β-hydroxy sulfoxides (Scheme 58).[154,155]



Scheme 58

Chiral β-hydroxy sulfoxides are very good intermediates for the synthesis of optically active alcohols,[156] epoxides[155] or butenolides (Scheme 59).[157]



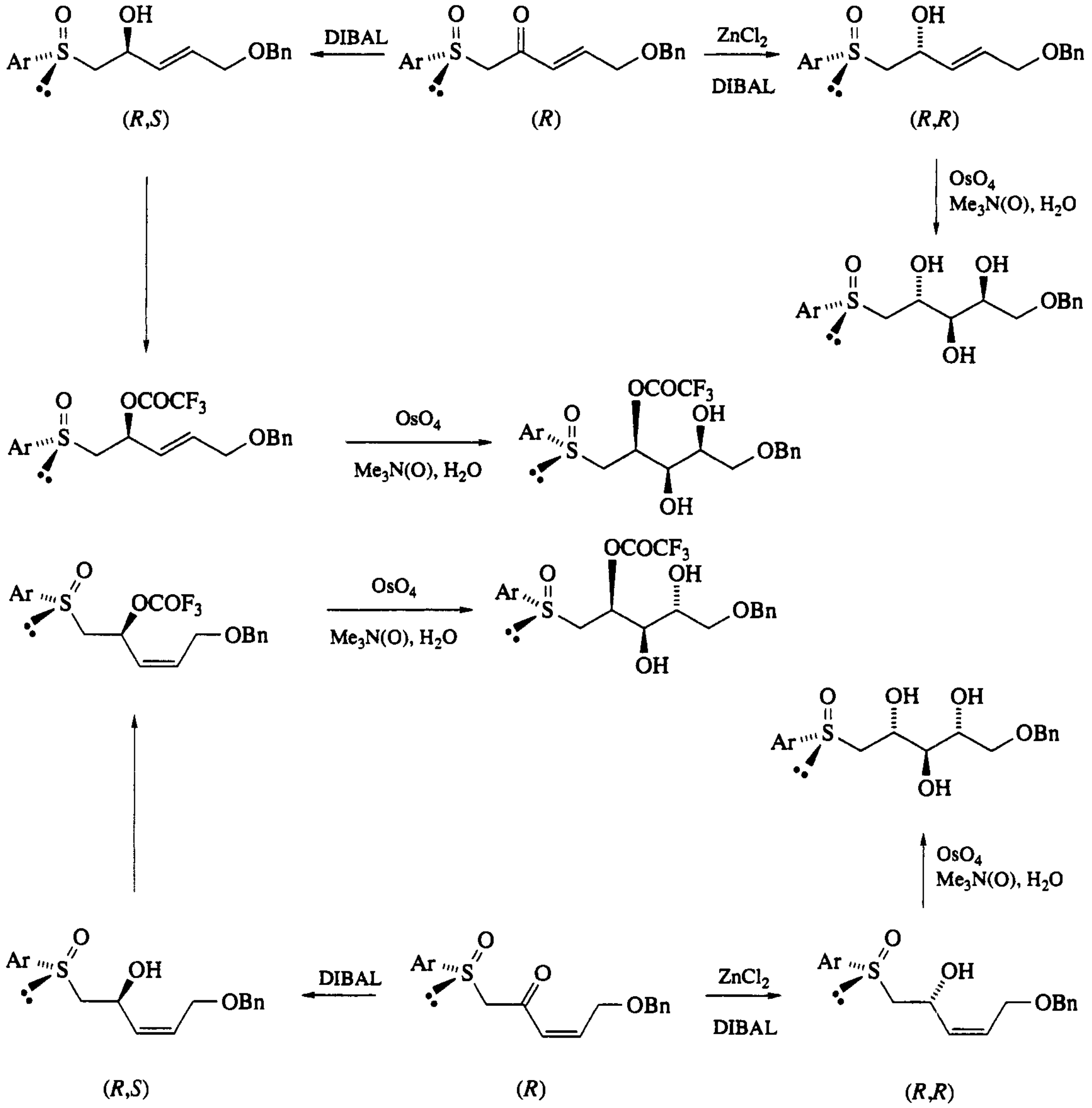
Scheme 59

Allylic and propargylic β-keto sulfoxides could be reduced as well as saturated compounds. Optically active allylic β-hydroxy sulfoxides present some specific interest because of the possible hydroxylation of the double bond leading to vicinal triols. The osmium tetroxide catalyzed hydroxylation reaction of the double bond in the presence of trimethylamine *N*-oxide is highly stereoselective:[158,159] the (*R*,*R*)-β-hydroxy sulfoxide gave only one diastereoisomeric triol as a result of a *cis* hydroxylation of the double bond and a symbiotic effect of the two chiral centers in the asymmetric induction (the (*S*,*R*)-isomer gave a lower *de*).

In the case of the (*S*,*R*)-β-hydroxy sulfoxide, the OH group has to be protected by a trifluoroacetyl group before hydroxylation, which was highly stereoselective and fully controlled by the chiral sulfoxide group.[160] Very similar results were obtained in the case of allylic β-hydroxy sulfoxides having a (*Z*)-geometry on the double bond.[160] Trihydroxy sulfoxides in all possible configurations can therefore be made by this method (Scheme 60).

These trihydroxy sulfoxides are useful molecules in total synthesis because of the possible transformation of the sulfoxide into aldehyde by a Pummerer rearrangement.[159,161] Homoallylic β-hydroxy sulfoxides have also been prepared from β-epoxy sulfoxides, readily obtained from methyl monochloroacetate (Scheme 61a).[162a]

Optically active α-chloro sulfoxides have recently been obtained by a very practical procedure[162b] using NBS and potassium carbonate with the expected inversion of configuration at sulfur. Chloro sulfoxides were shown to be very useful in the synthesis of epoxides[162c] and for α,β-unsaturated ketone homologation (Scheme 61b).[162d]



Scheme 60

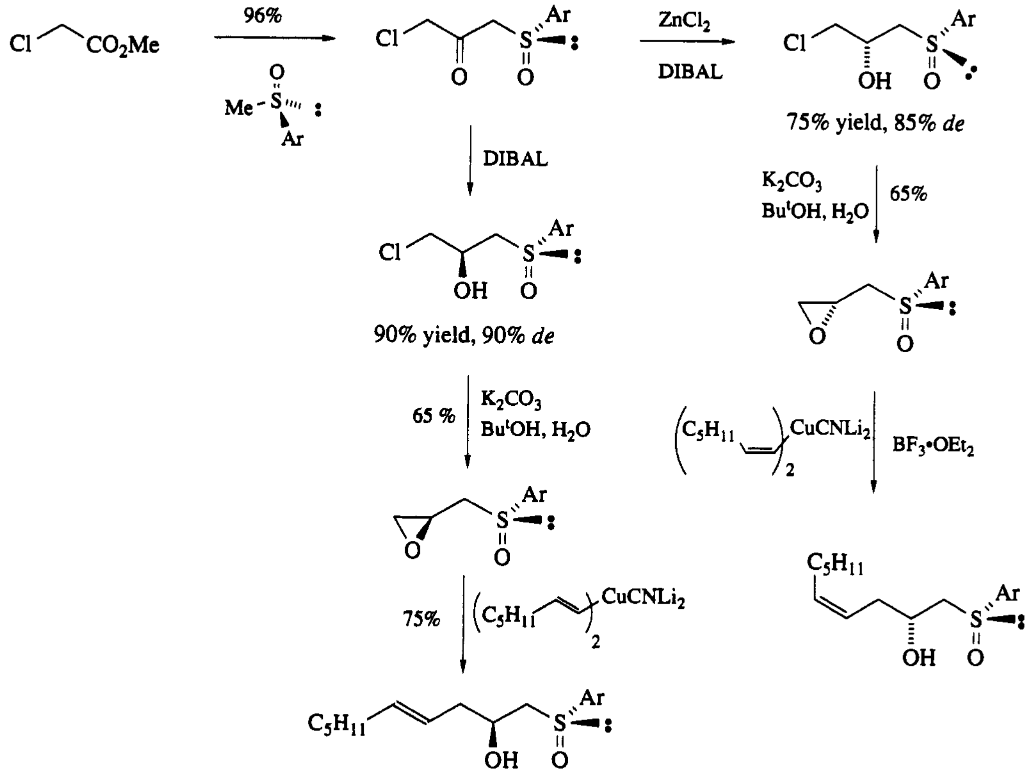
1.5.4 SULFONES

Although Kohler and Tishler[163] reported the metallation of benzyl sulfones in 1935 and Field[164] later used benzyl sulfones in Grignard reactions, the use of new bases and the easy introduction of a sulfonyl group into a molecule *via* alkyl halides and sodium sulfinate resulted in a major development by Julia[165-170] of the synthetic use of sulfones.

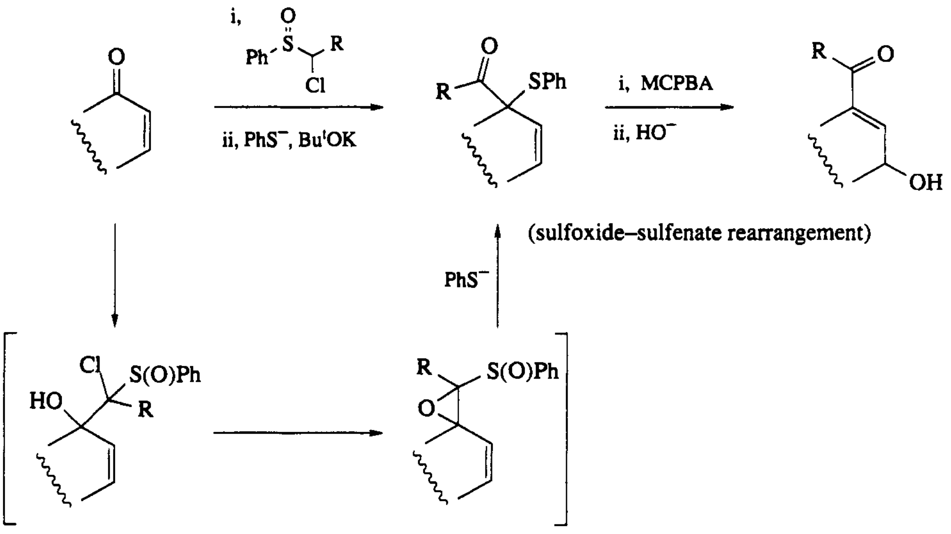
The preparation of 3,7-dimethyl-2-*trans*-4-*trans*-6-*trans*-octatrienoic acid (Scheme 62)[165,166] is a good example of the introduction of a sulfonyl group from sodium sulfinate, of the coupling reaction of a sulfonyl carbanion and allylic bromide and finally of the elimination of the sulfonyl group in basic medium giving the all-*trans* compound. The same method was used for vitamin A synthesis (Scheme 63).[168,170]

In a similar way, Grieco[171] reported the synthesis of *trans*-squalene from *trans*-farnesyl acetate and the corresponding sulfone and Liu[176] prepared difluororetinal analogs.

A modification of vitamin A synthesis was reported recently,[172] using addition of allylic sulfone carbanion to aldehyde followed by a basic double elimination[173] of the resulting β-alkoxy sulfone with excellent stereocontrol (Scheme 64).



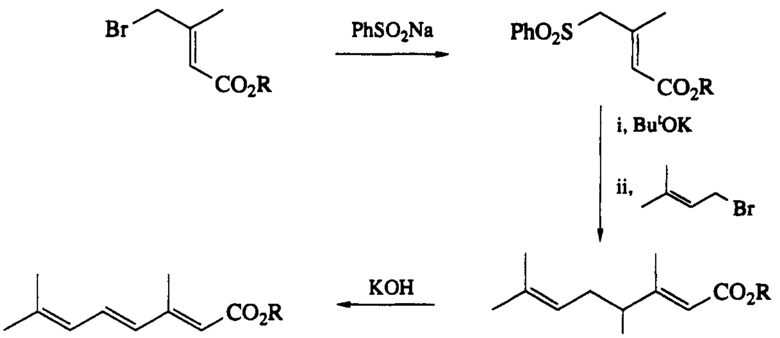
Scheme 61a



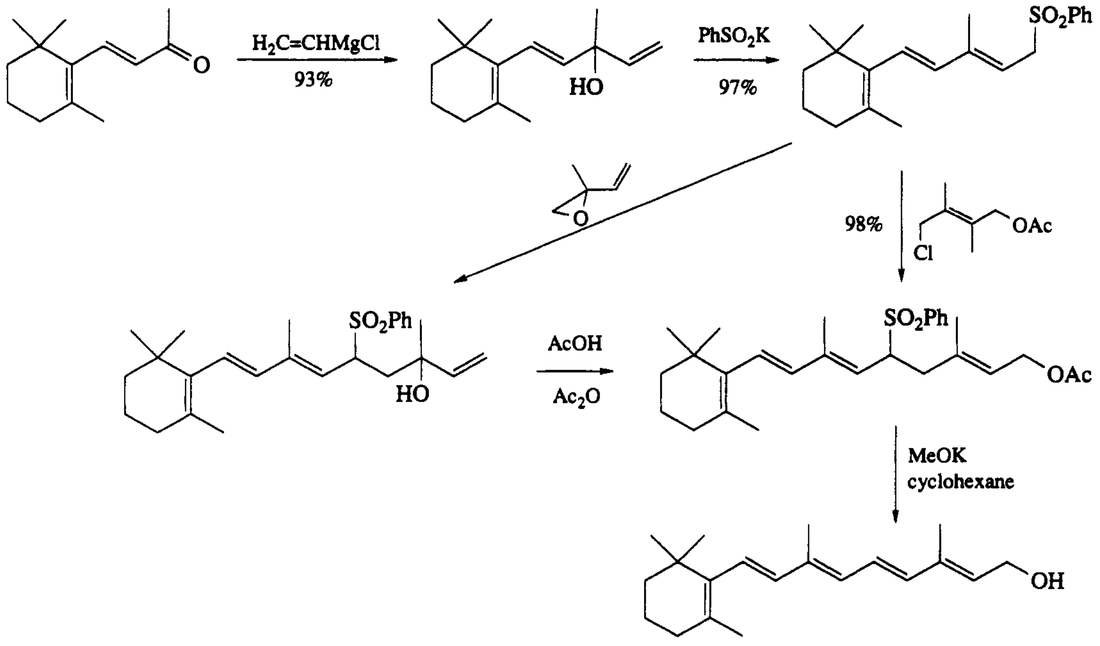
Scheme 61b

Other applications of carbanions α to a sulfone in total syntheses have recently been reported. Most of them used allylic sulfones or allylic halides. Two examples are reported here. In the synthesis of a precursor of cembranolides,[183] a sulfone derived from geranyl bromide was coupled with an allylic alcohol epoxide (Scheme 65). An interesting point was that the coupling reaction gave high yields only when the lithiated sulfone was allowed to react with the epoxymagnesio alkoxide (the lithium salt of the epoxy alcohol did not react at all with the lithiated sulfone).

In the synthesis of an ionophore antibiotic,[184] a bicyclic sulfone made by oxidation of the corresponding sulfide with $PhSeSePh/H_2O_2$ to avoid double bond oxidation was coupled with an allylic bromide in 97% yield and high stereoselectivity. The sulfonyl group was finally eliminated in basic medium to create a *trans*-diene (Scheme 66).

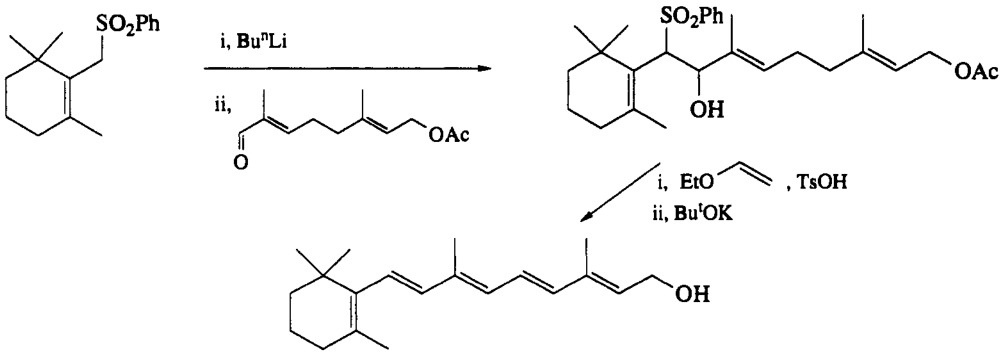


Scheme 62



Vitamin A

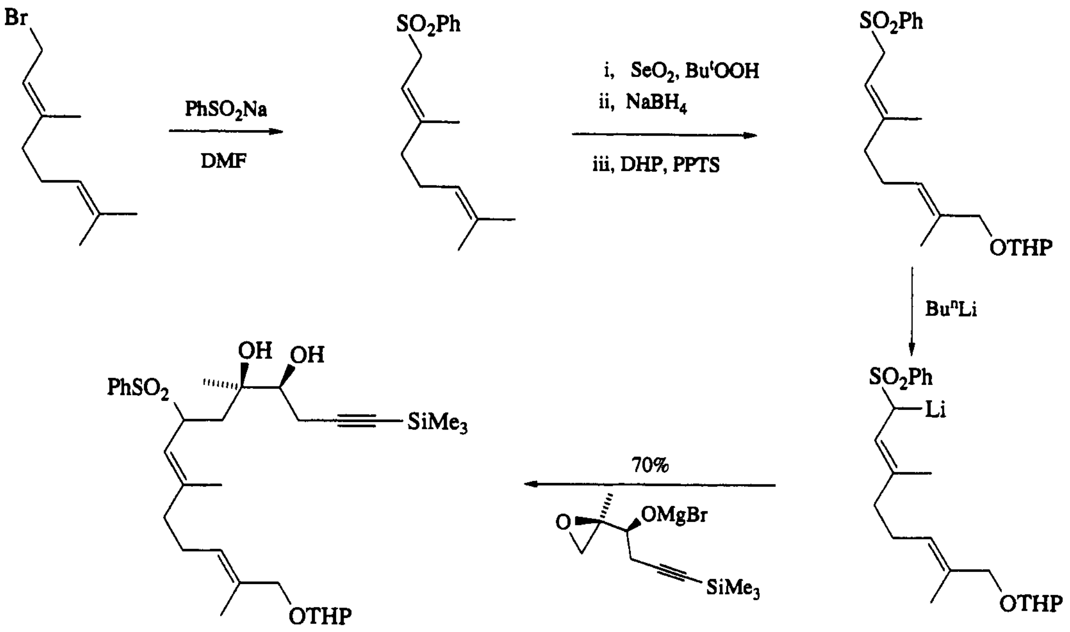
Scheme 63



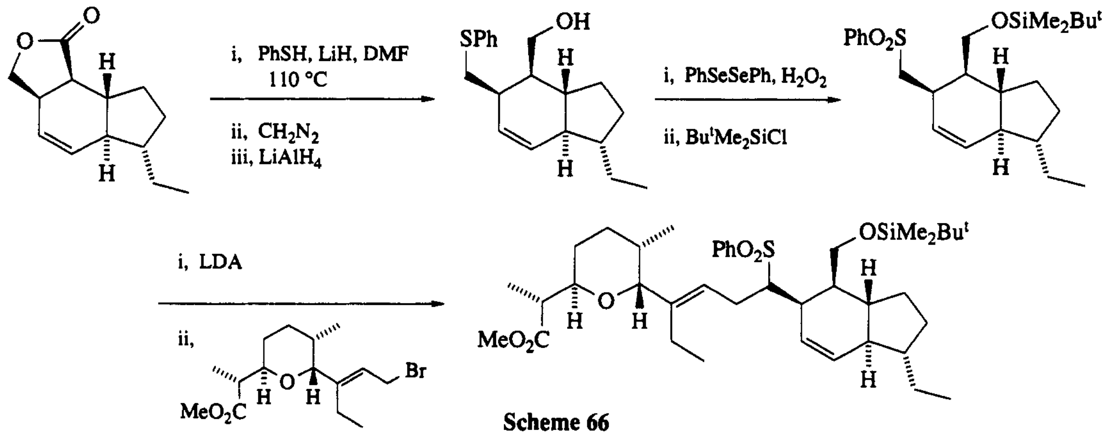
Vitamin A

Scheme 64

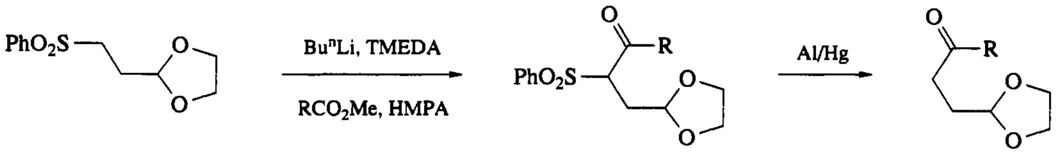
γ-Oxo sulfone acetals can be acylated with esters giving, after reductive desulfonylation, a convenient route to γ-keto aldehydes or 1,4-diketones (Scheme 67).[174] The intermolecular acylation of α-sulfonyl carbanions was also used to synthesize γ-butyrolactones.[175]



Scheme 65

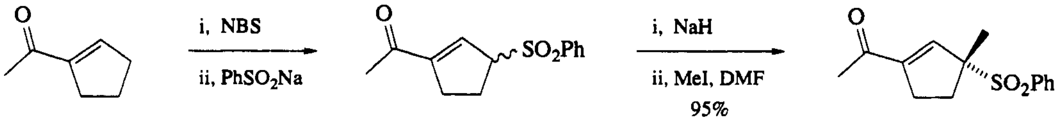


Scheme 66



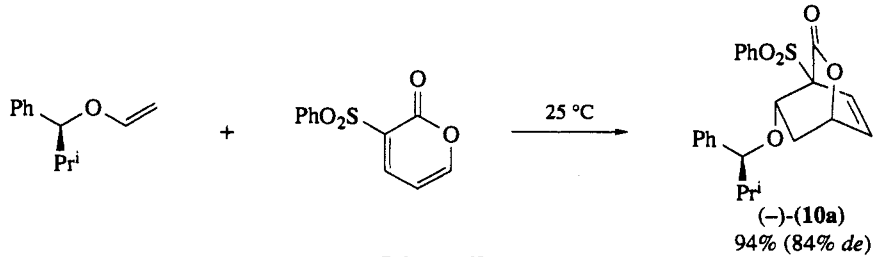
Scheme 67

The introduction of a sulfonyl group on cyclic compounds allowed γ-alkylation of α,β-unsaturated ketones (Scheme 68).[177]

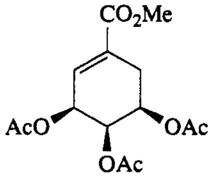


Scheme 68

α-Pyrone sulfone[132,178a] is indeed, as we have already shown, very reactive in Diels–Alder reactions. The chiron (–)-(**10a**) was obtained with very high diastereoselectivity from α-pyrone sulfone and optically active vinyl ether (Scheme 69). This lactone was later used[178a] in the asymmetric synthesis of (–)-methyltriacetyl-4-epishikimate (**10b**). β-Sulfonylnitroalkenes were also shown to be reactive alkyne equivalents in Diels–Alder reactions.[178b]

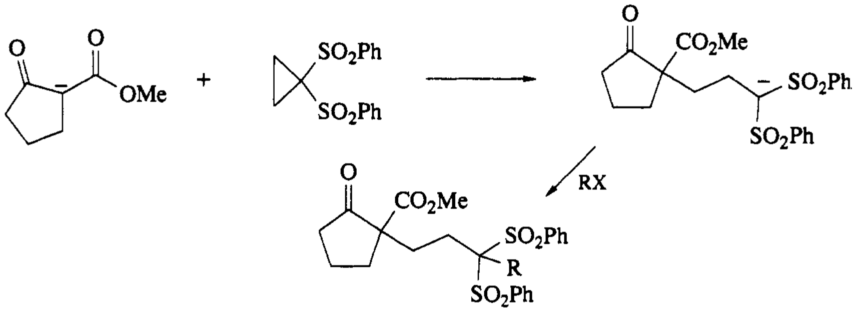


Scheme 69



(**10b**)

1,1-Bis(benzenesulfonyl)cyclopropane[179] presents several advantages in organic synthesis: the electron-withdrawing groups on the cyclopropane facilitate its opening by nucleophiles and, since each sulfone can be cleaved to create a carbanionic center, various electrophilic substitutions can be performed. One example is given in Scheme 70.

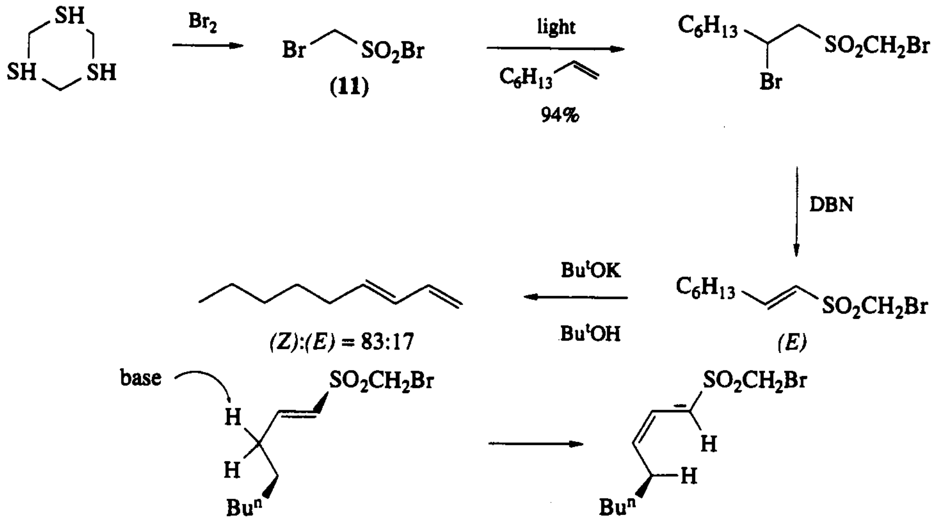


Scheme 70

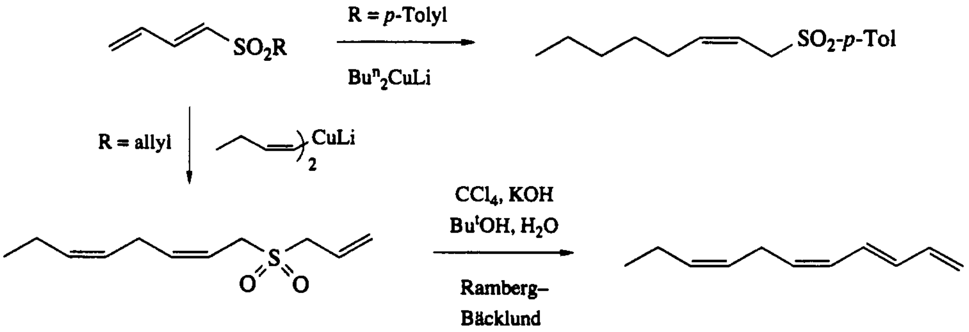
The Ramberg–Bäcklund reaction is a synthetically useful process in which α-haloalkyl sulfones afford alkenes upon treatment with base.[180] Bromomethanesulfonyl bromide (**11**) is a very useful reagent for such reactions with unusual stereochemical features of the reaction with base.[181,182] Adducts between (**11**) and alkenes are formed in nearly quantitative yield by a light-catalyzed free radical addition. Direct treatment of these adducts with DBN afforded vinylic sulfones, which on treatment with Bu^{t}OK gave a highly stereoselective elimination to the corresponding diene, probably *via* a base-catalyzed isomerization to the corresponding allylic sulfone (Scheme 71).

(*E*)-1,3-butadienyl tosyl sulfone was found to react with dialkylcuprates; the alkyl group was added to the terminal double bond and the newly formed double bond has exclusively (*Z*)-geometry (Scheme 72).[185] It is interesting that starting from butadienyl allyl sulfone, the stereochemistry of the double bonds was maintained during the Ramberg–Bäcklund sulfur extrusion.

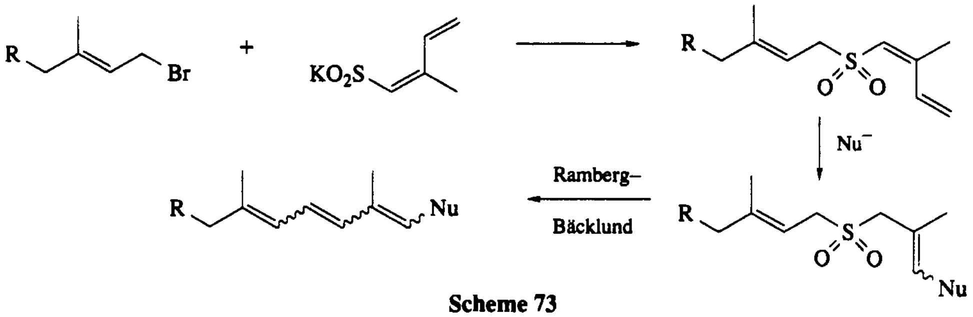
In similar work, Julia[186] prepared allyl dienyl sulfones from (*Z*)-2-methyl-1,3-butadienylsulfinate. Addition of various nucleophiles to the diene and Ramberg–Bäcklund reaction then yielded isoprenoid compounds (Scheme 73).



Scheme 71

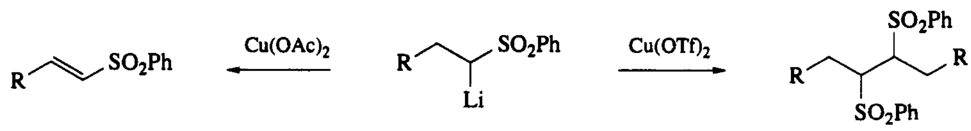


Scheme 72



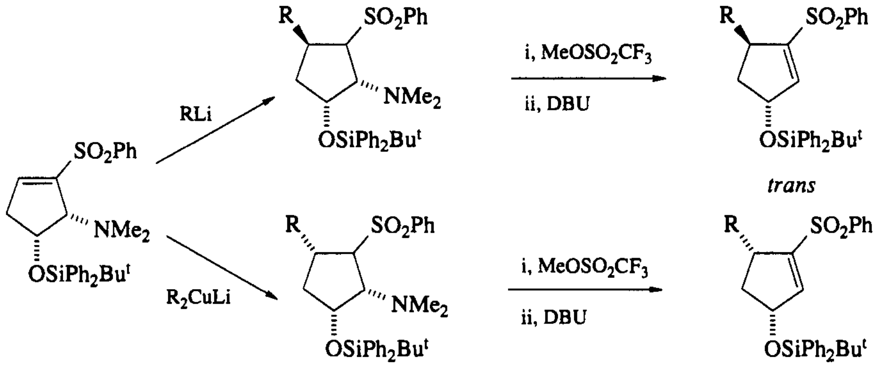
Scheme 73

Oxidation of α-sulfonyl carbanions with copper(II) trifluoromethanesulfonate gives dimers of the original sulfone,[187] while with copper(II) acetate vinylic sulfones were obtained (Scheme 74).[188]



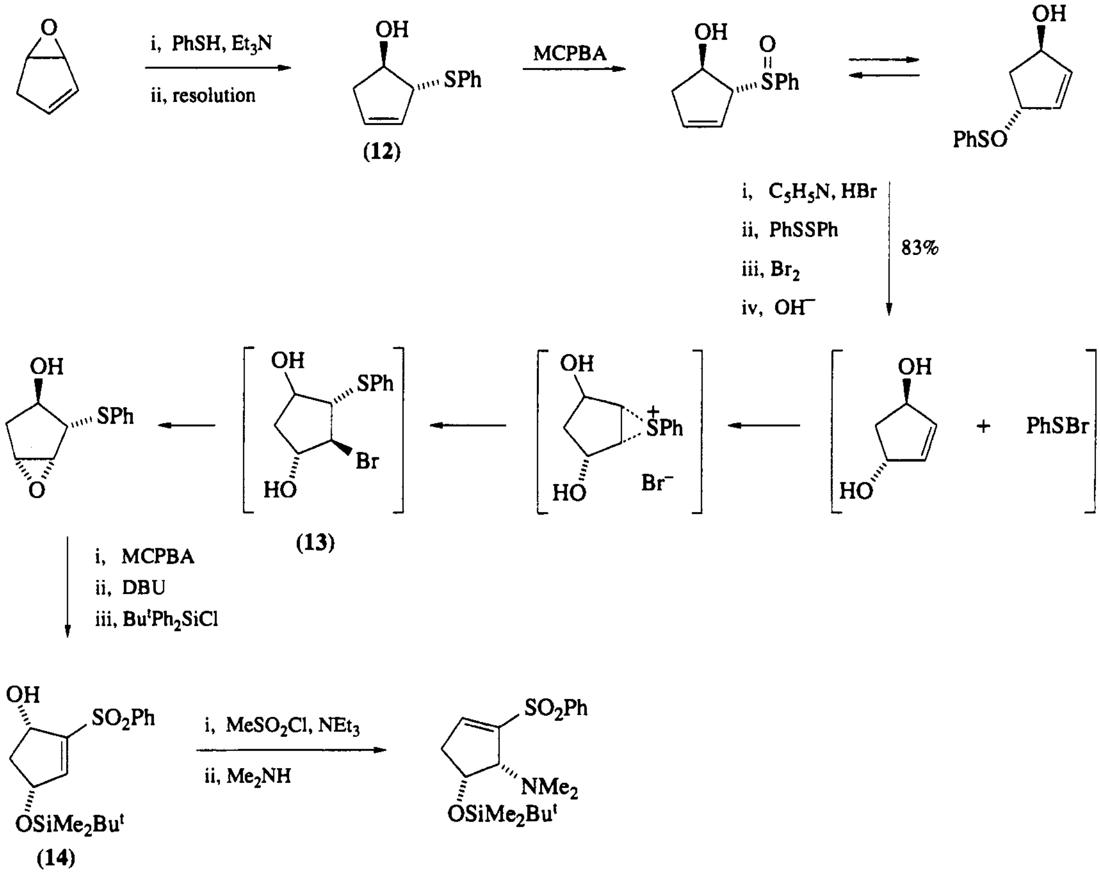
Scheme 74

Vinyl sulfones can be easily functionalized in a highly regio- and stereo-selective way: organolithium reagents undergo conjugate addition to afford *trans* adducts in high yield,[189] while organocuprate reagents undergo an amine-directed conjugate addition to afford the *cis* adduct (Scheme 75).[190,191]



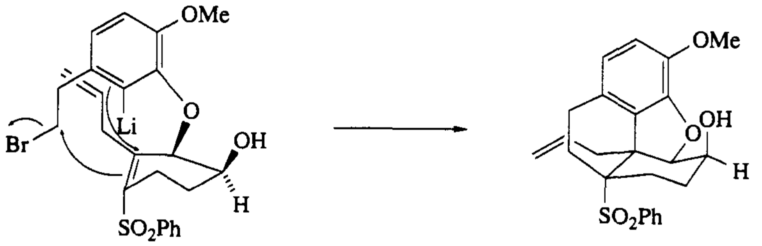
Scheme 75

The synthesis of the preceding vinyl amino sulfone offers a very good example of a stereospecific sulfide-directed epoxidation (Scheme 76).[192] Oxidation of optically active sulfide alcohol (**12**; readily made from epoxycyclopentadiene[193] and resolved) with MCPBA affords the corresponding sulfoxide, which is in equilibrium with the sulfenate ester. Treatment with pyridine hydrobromide and then phenyl disulfide and bromine gives the bromodiol (**13**), which is simply cyclized to the epoxide with aqueous sodium hydroxide solution (83% overall yield from the sulfoxide). Treatment of the β-epoxy sulfone with DBU followed by *in situ* silylation with *t*-butyldiphenylsilyl chloride affords an 86% yield of vinyl sulfone (**14**). Mesylation of the alcohol moiety followed by immediate treatment with dimethylamine produces the amino vinyl sulfone *via* a *syn* S_N2' substitution.[189]

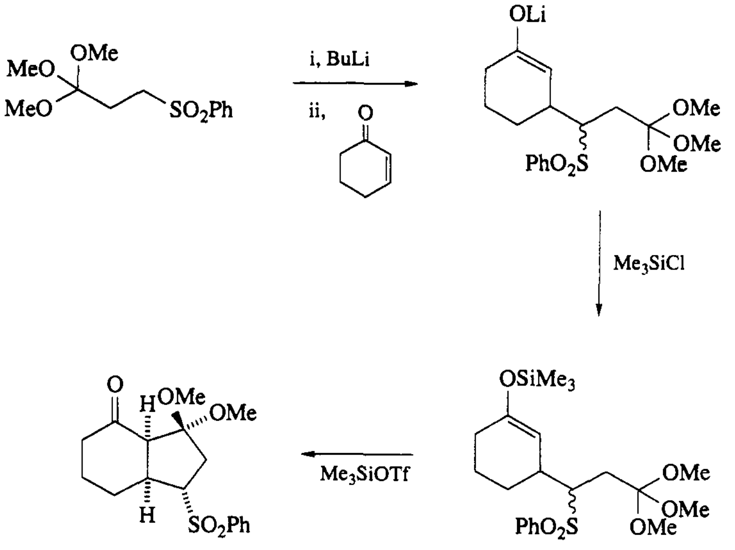


Scheme 76

In a recent total synthesis of (±)-morphine,[194] the key step was a cyclization step induced by intramolecular Michael addition on a vinylic sulfone followed by bromide displacement (Scheme 77). The entire process was highly stereoselective. Methyl-3-phenylsulfonyl orthopropionate was shown to be a good reagent for cyclopentannulation (Scheme 78).[195]

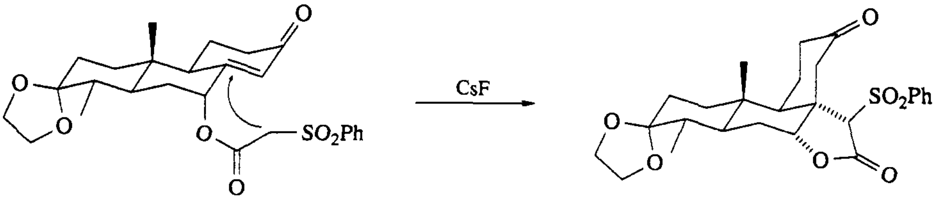


Scheme 77



Scheme 78

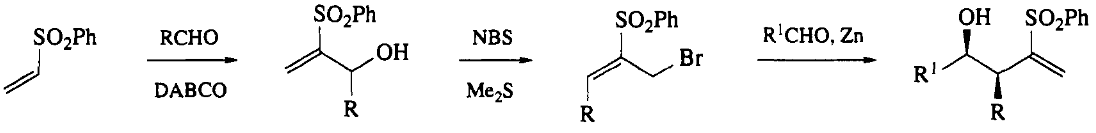
During the total synthesis of an antileukemia agent, control of the stereochemistry of the c ring formation has been established by a cesium fluoride mediated intramolecular conjugate addition of an α-face α-sulfonyl ester to an α-chloroenone (Scheme 79).[196]



Scheme 79

2-Phenylsulfonic allylic bromide (**15**) reacts with aldehydes in the presence of zinc in high yield and high diastereoselectivity giving *syn*-hydroxy sulfones (Scheme 80).[197,198]

A good example of acyclic diastereoselection was reported by Isobe[199] during 'heteroconjugate addition' on vinylic sulfone. The 'heteroalkene' is indeed a vinylic sulfone with an α-chiral center and a hydroxy group in the allylic or homoallylic position. In the allylic case, a complete *syn* diastereoselection was observed during methyllithium addition. This high stereoselectivity can be explained by the following: the nucleophilic carbanion should coordinate with the oxygen atom by a chelation effect through the

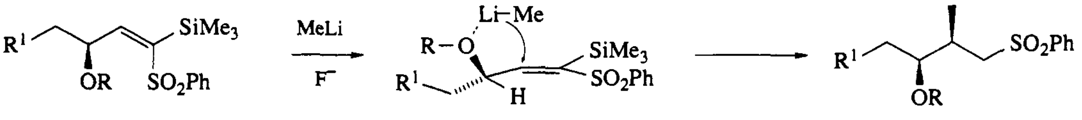


(15)

syn (*de* 90%)

Scheme 80

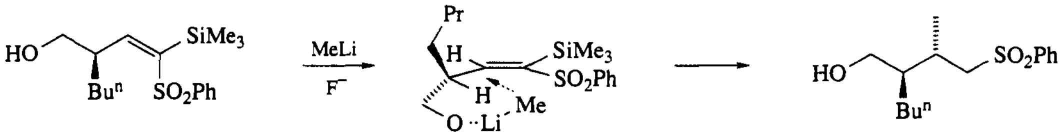
lithium cation so that the nucleophile will have a higher opportunity for attacking the alkene from the oxygen face than from the nonchelating carbon face (Scheme 81).



syn

Scheme 81

The *anti* diastereoselectivity can be achieved by coordination of the nucleophile to the opposite face of the α-oxygen atom. This was the case with the homoallylic system (Scheme 82).

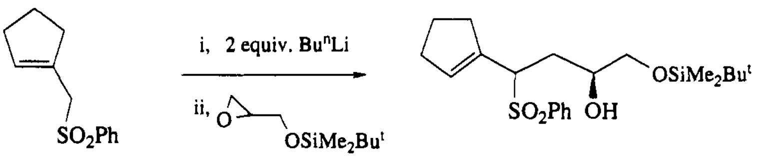


anti

Scheme 82

The heteroalkenes were prepared by Peterson-type alkenation of the corresponding aldehydes with bis(trimethylsilyl)phenylthiomethyllithium [$PhS(Me_3Si)_2CLi$] followed by oxidation to sulfones.

Remarkable diastereocontrol was also reported by Trost[200] during alkylation of allylic sulfones with epoxide. A very high kinetic diastereoselectivity was observed in the case of terminal epoxide and branching on the vinyl carbon proximal to sulfone (Scheme 83).



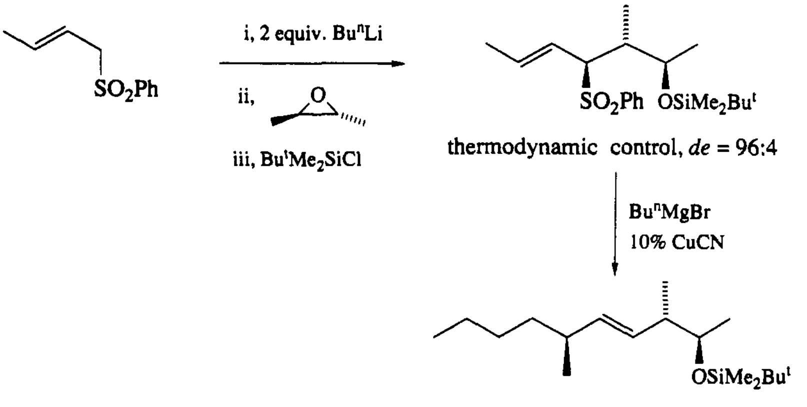
kinetic control, *de* = 97:3

Scheme 83

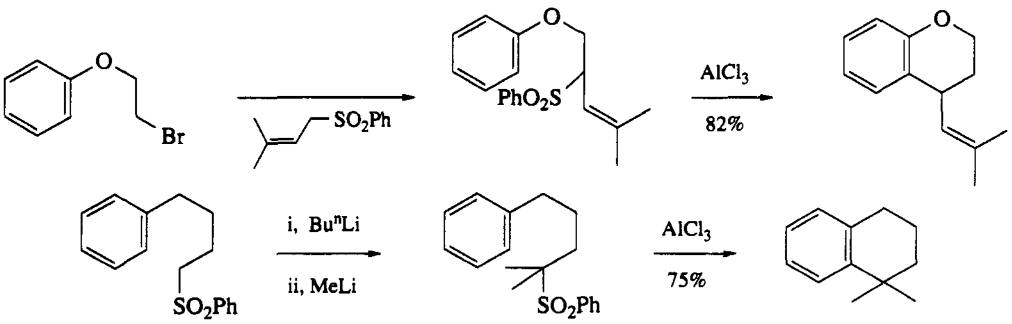
In the other cases, the diastereoselectivity was higher under thermodynamic control. The remarkable ability to obtain γ-hydroxy sulfones with high diastereoselectivity offers the flexibility to transfer stereocontrol to carbon–carbon bond formation by substitution of the sulfone. This is illustrated by the copper cyanide catalyzed coupling of Grignard reagents (Scheme 84).

Sulfones can also be used in Friedel–Crafts-type cyclizations.[201] One example is shown in Scheme 85, where the cyclization in the presence of aluminum chloride of the allylic sulfone occurred in high yield, showing that sulfones can also become electrophiles. Since a tertiary carbanion has about the same stability as a simple allylic cation, tertiary sulfones can also be cyclized (Scheme 85). These last examples illustrated the 'umpolung' provided by the sulfone since carbanion chemistry was used to introduce the 2-methyl groups.

Sulfonyl group substitutions can also be observed with organoaluminum reagents.[202] They proceed with remarkable ease and good chemo- and regio-selectivity and with a strong bias for formation of an axial C—C bond in cyclohexenyl systems. The unique advantage of the sulfone as a leaving group stems from the ease of alkylation α to the sulfone prior to the substitution. The chemoselectivity of this method was tested by its ability to employ carbonyl adducts. Initial complexation of the free alcohol with

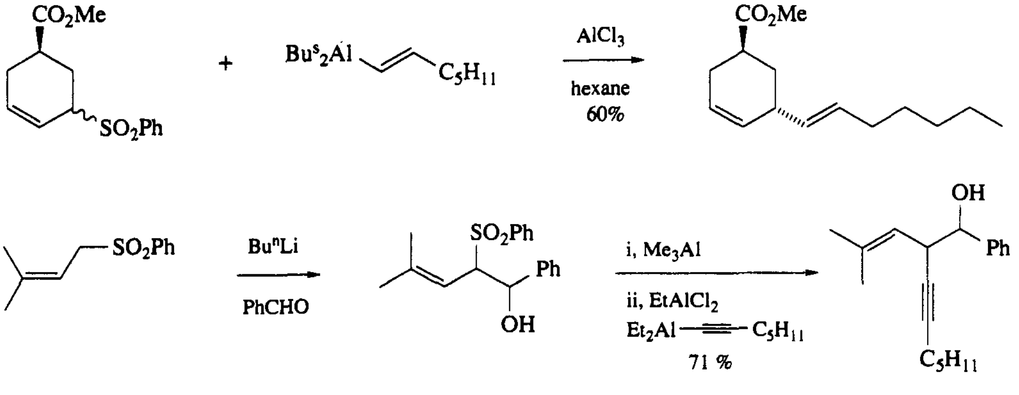


Scheme 84



Scheme 85

trimethylaluminum, followed by addition of the alkynylalane using ethylaluminum chloride as the Lewis acid gives only the product of substitution of the allylic sulfone with formation of the new C—C bond at the secondary carbon (Scheme 86). The high selectivity for transfer is particularly noteworthy: only alkynyl or vinyl systems are transferred, never alkyl groups.



Scheme 86

1.5.5 CONCLUSION

The variety and number of examples listed in the literature show the efficiency of sulfur-containing molecules in organic synthesis. In the mid-1960s, organic sulfur chemistry was an area for specialists, but currently almost every organic chemist, in some way or another, encounters organosulfur compounds. It was not, of course, possible to review in this chapter all of the literature work in which sulfur-containing groups serve an important auxiliary function in synthetic sequences. It has, however, been attempted to describe most of the reports which have important applications in selective organic synthesis.

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1.6

Synthesis of Phosphonium Ylides

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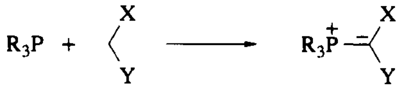
1.6.1 ALKYLIDENEPHOSPHORANES

1.6.1.1 Synthesis from Tertiary Phosphines and Various Compounds

Tertiary phosphines (especially triphenylphosphine) react with various compounds giving rise to the formation of alkylidenephosphoranes.[1–5] By the addition of carbenes and carbenoids, respectively, to tertiary phosphines especially, alkylidenephosphoranes are available which carry one or two halogen atoms at the α-carbon atom (equation 1).



(1)

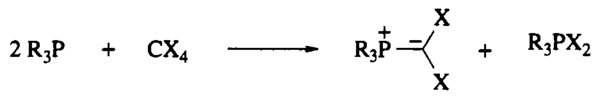
The necessary carbene or carbenoid species are generated from di- or tri-halomethanes with bases (organolithium compounds or alkoxides) or by decomposition of sodium trihaloacetates in the presence of a tertiary phosphine. The resulting haloalkylidenephosphoranes are usually not isolated but react with added carbonyl compounds to give alkenes. The *in situ* formation of dichloromethylenetriphenylphosphorane as well as the analog methylthiochloro compound can be achieved in aqueous sodium hydroxide solution under phase transfer conditions.[6] Bis(phenylthio)- and bis(phenylseleno)-methylenetriphenylphosphorane have also been synthesized by the carbenoid method.[7]

Aliphatic diazo compounds may also be used as a source for carbenes, which combine subsequently with tertiary phosphines to give phosphonium ylides. The reaction requires the presence of Cu^I salts, otherwise phosphazines are formed from the diazo compounds and the phosphines.

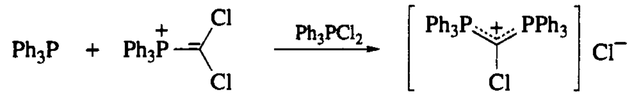
Alkylidenephosphoranes containing the bis(aryl/alkylsulfonyl)methylene functionality may be obtained from aryliodonium ylides and triphenylphosphine, a carbene mechanism presumably being involved.[8]

Ylide formation by capture of electrophilic carbenes with tertiary phosphines has been shown to be a symmetry-breaking allowed pathway.[9] The reverse process, dissociation of a phosphonium ylide into carbene and phosphine,[10] is in agreement with the concept of phosphonium ylides as phosphine–carbene complexes.[11]

Dihalomethylenephosphoranes are easily available from tetrahalomethanes and tertiary phosphines, especially triphenylphosphine (equation 2). From mixed tetrahalomethanes preferably difluoro- and dichloro-methenylenephosphoranes are formed. The primarily resulting dihalomethylenephosphorane may undergo subsequent reaction giving rise to the formation of a semi-ylide salt (equation 3).[12,13]



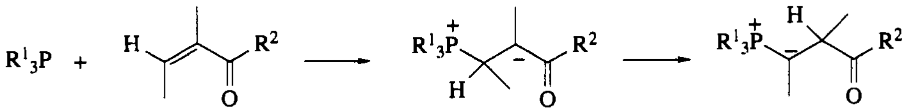
(2)



(3)

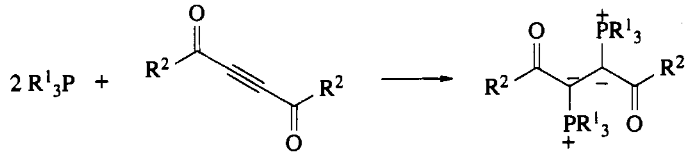
In contrast to triphenylphosphine alkyldi(*t*-butyl)phosphines react with carbon tetrachloride or tetrabromide to give *P*-halo ylides.[14] Usually dihalo ylides are generated *in situ* in the presence of an aldehyde or a ketone whereby the simultaneously formed dihalotriorganophosphorane reacts with a second mole of the carbonyl compound to give dichloroacetals. The addition of zinc dust proved to be favorable in the synthesis of the difluoro-,[15,16] dibromo-,[17,18] and diiodo-methylenetriphenylphosphoranes.[19] Analogous to tetrahalomethanes trihaloacetates react with triphenylphosphine yielding alkoxycarbonylhalomethylenetriphenylphosphoranes.[5] Also 2,2-dichlorohexafluoropropane seems to react with triphenylphosphine by formation of the corresponding ylide.[20]

Phosphonium ylides are also available from the reaction of trivalent phosphorus compounds with activated C—C multiple bonds.[21–23] Phosphines add to the activated C=C double bond of α,β-unsaturated ketones or carboxylic acid derivatives. The zwitterionic intermediate (generally a phosphonioenolate) undergoes 1,2-prototropic shift giving rise to the formation of an alkylidenephosphorane (equation 4). Ylides generated according to this method *in situ* from acrylic acid derivatives[24,25] are difficult to prepare otherwise, because of the easily occurring Hofmann degradation. Several alternative routes for the stabilization of the zwitterionic intermediate leading to other compounds than the desired ylide have been observed.[23]



(4)

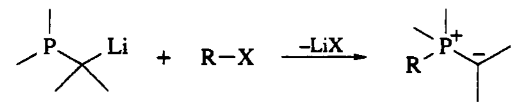
Alkynes having activated C≡C triple bonds react with tertiary phosphines in the molar ratio 1:2 giving rise to the formation of 1,2-bisylides (equation 5).[23] Beyond that some rather complex reactions between phosphines and alkynes are known; however, these are of no preparative importance as unambiguous routes to ylides.



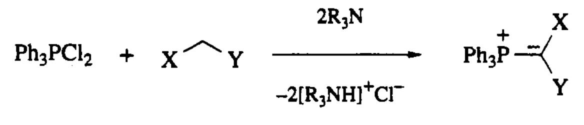
(5)

In addition to the synthetic routes described, tertiary phosphines react with miscellaneous compounds (epoxides, nitrilimines, sulfuranes, amidines) leading to phosphonium ylides.[26] These reactions, however, seem not to represent generally applicable methods for the synthesis of phosphonium ylides.

α-Lithiated tertiary phosphines undergo reaction with electrophiles at phosphorus rather than carbon and thus provide a route to a variety of *P*-substituted phosphonium ylides (equation 6).[26–28]


(6)

Dihalotriorganophosphoranes react with activated methylene compounds in the presence of triethylamine yielding stabilized ylides in good yields (equation 7).[29]


(7)

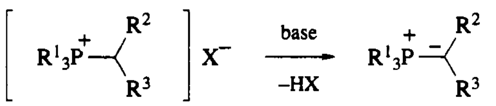
X, Y = CN, SO_2R, CO_2R, COR, *etc.*

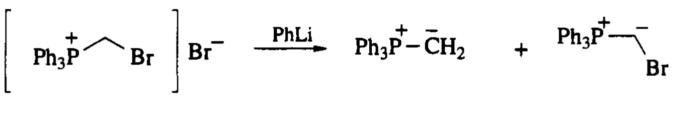
The generation of an ylide from a phosphine oxide and an alkyne is of interest because it represents the reversal of the known intramolecular Wittig reaction of acylated alkylidenephosphoranes.[30]

1.6.1.2 From Phosphonium Salts

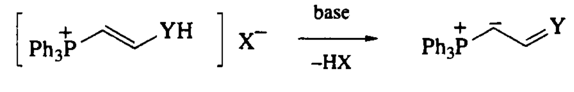
1.6.1.2.1 Generation with bases

The most important method of preparing phosphonium ylides is deprotonation of the corresponding phosphonium salts with suitable bases (equation 8).[31–36] In some instances an alternative ylide may be formed instead of that by deprotonation, if the phosphonium salt is carrying another positively charged substituent in the α-position (*e.g.* equation 9).[35,37–40]


(8)


(9)

An alternative route to ylide synthesis *via* α-deprotonation is the abstraction of a proton from the γ-position of a vinylphosphonium salt (equation 10).[41–43] Complications may arise, however, if the phosphonium salt carries a good leaving group in the β-position so that a vinylphosphonium salt may be formed, or if a β-proton is so acidic that a Hofmann elimination is favored.[35,44–47]


(10)

While triphenylalkylphosphonium salts as ylide precursors unambiguously lead to alkylidenetriphenylphosphoranes, in the case of tetraalkylphosphonium salts ylide formation may take place principally at different α-positions relative to the phosphorus.[48–50] Furthermore an intramolecular transylidation process causes the ligands at the phosphorus in methylenetrialkylphosphoranes to exist alternately as alkyl or as alkylidene substituents, thus giving rise to the formation of isomeric ylides.

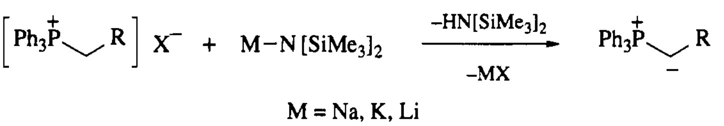
The choice of the appropriate base/solvent system for the ylide generation depends on the acidity of the corresponding salt, the stability of the resulting ylide in the reaction medium and the intended application of the ylide. Thus phosphonium salts with electron-withdrawing groups on the α-carbon, which are capable of stabilizing a negative charge, are deprotonated by relatively weak bases, such as dilute aqueous alkali or ammonia. If there are electron-donating substituents on the α-carbon, stronger bases, such as alkyllithium, are required. Highly reactive phosphonium ylides are usually generated in an aprotic medium and mostly are not isolated but reacted *in situ*.[51]

For many reactions with ylides it is very important to use 'salt-free' solutions. This is especially true for lithium salts because they can affect decisively the course of many ylide reactions, especially the stereochemical course of subsequent Wittig reactions.[52–55]

A great variety of bases has been used to generate ylides from the corresponding phosphonium salts: various nitrogen bases, alkoxides, alkali metal hydrides, carbanionic bases, alkali metal hydroxides and carbonates, ethylene oxides, basic ylides and others.[31,35,36]

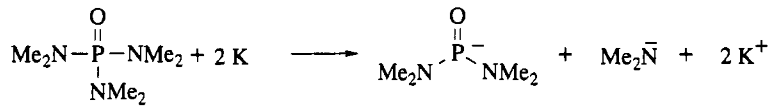
The use of sodium amide proved to be very successful in the synthesis of nonstabilized ylides free from lithium salts.[35,56] The reaction is usually carried out in liquid ammonia, but also a suspension of sodium amide in benzene or THF can be used. Whereas alkyltriarylphosphonium salts are deprotonated in liquid ammonia, in the case of the corresponding tetraalkyl compounds boiling THF is necessary.[48] Mixtures of dry phosphonium salt and powdered sodium amide can be stored indefinitely and hence provide 'instant ylide' mixtures.[57] Upon addition of an ethereal solvent the ylide is quantitatively generated.

Conversion of phosphonium salts to salt-free solutions of ylides can also be effected with sodium bis(trimethylsilyl)amide.[58] As it is soluble in many solvents, and easy to handle and to weigh out, sodium bis(trimethylsilyl)amide is preferred to sodamide in liquid ammonia in many cases (equation 11).[59] The corresponding potassium and lithium compounds can also be used.[60]



(11)

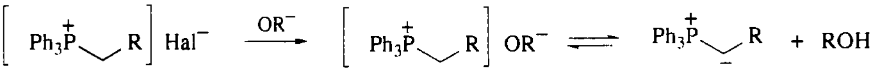
The anions resulting from dissolving potassium in HMPT are also suitable for generating reactive ylides from their corresponding salts, HMPT also turning out to be a favorable solvent for many ylide reactions (equation 12).[61]



$$\mathrm{Me_2N{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle NMe_2}{|}}{P}}{-}NMe_2} + 2\,\mathrm{K} \longrightarrow \mathrm{Me_2N{-}\overset{\overset{\displaystyle O}{\|}}{P^-}{-}NMe_2} + \mathrm{Me_2\bar{N}} + 2\,\mathrm{K^+} \qquad (12)$$

Apart from the bases mentioned a series of other nitrogen bases (ammonia, triethylamine, pyridine, cyclic amidines, lithium diethylamide, lithium diisopropylamide, lithium piperidide, *etc.*) have been used to deprotonate phosphonium salts.

Many alkoxides (especially sodium methoxide, sodium ethoxide, potassium *t*-butoxide and others) can be used as bases in ylide syntheses (equation 13).[35] The reaction is carried out in the corresponding alcohol or another inert solvent. The alkoxide method has some advantages: alkoxide bases are easy to handle, ylide generation may be effected in a homogeneous phase and phosphonium salts carrying corresponding alkoxycarbonyl groups are not cleaved at the alkoxy function. Since, however, ylides may be quenched by the alcohol produced from the base, they are usually generated in the presence (the temperature playing an important factor[38]) of a carbonyl compound to undergo a Wittig reaction. It seems that among alkoxides potassium *t*-butoxide and sodium as well as potassium *t*-pentylate are most suitable for the generation of reactive ylides.[38,62–64] Alkoxide bases are less suitable for the deprotonation of phosphonium salts carrying activated H atoms in the β-position since alkoxides favor cleavage into a phosphine and an alkene.

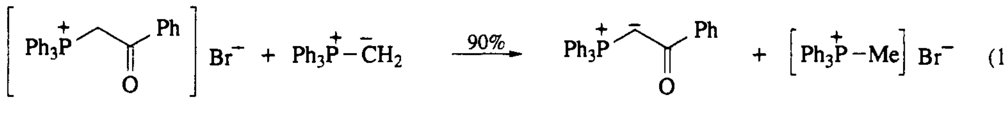


(13)

Very often phosphonium ylides are generated with organolithium compounds (in particular phenyl-, methyl-, *n*-butyl- and *t*-butyl-lithium) as bases.[31,32,34,35] However difficulties may be attached to this method in some cases. When alkyllithium compounds are used, ligand exchange at phosphorus may occur, thus giving rise to the alternative or additional formation of a second ylide. To avoid this phenomenon in the case of triphenylphosphonium salts phenyllithium has to be used as base. Ligand exchange may also be suppressed if one uses, instead of *n*-butyllithium for example, the more bulky tertiary compound.[65] From phosphonium salts carrying halogen at the α-carbon both a proton or a positively charged halogen may be split off and also displacement of an α-halogen by the carbanionic substituent of the lithium compound may occur. β-Substituted phosphonium salts may undergo Hofmann elimination under the influence of organolithium reagents giving rise to the formation of vinyl salts, which subsequently may add a second mole of base at the β-position. Attack of alkyllithium directly at the β-substituent has also been observed.[66] Ylides generated by organolithium compounds may be attacked by excess base yielding metallated ylide species,[39,67] which can act as a more reactive alternative to methylene ylides.[67a,b] Ylides, especially alkylidenetrialkylphosphoranes form complexes with lithium salts,[67f,68] from which the ylide sometimes can be released only at elevated temperatures.

Other carbon bases that have been used successfully to convert phosphonium salts into ylides include sodium methylsulfinate and the corresponding potassium compound[69] (prepared from alkali metal hydride and DMSO), tritylsodium, sodium acetylide and other strongly basic ylides.

Deprotonation of a phosphonium salt by an ylide is a 'transylidation' reaction,[56] which is of importance especially in those cases where ylides are reacted with electrophiles (see Section 1.6.1.3), but may also be applied to isolated phosphonium salts.[35] For an unequivocal reaction the two involved ylides must differ sufficiently with respect to their base strength (as for example in equation 14).

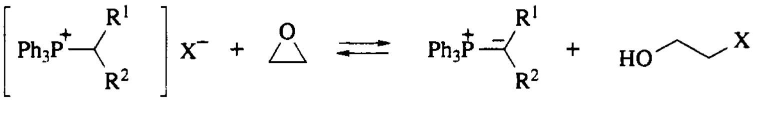


(14)

Aqueous alkali metal hydroxides and carbonates are suitable for the generation of ylides from phosphonium salts, which carry strongly electron-withdrawing groups (*e.g.* acyl, alkoxycarbonyl, cyano, 9-fluorenyl, nitrophenyl and others) at the α-carbon. The resulting stabilized ylides are usually sufficiently stable to be unreactive in water. The above mentioned bases may also be applied to the synthesis of reactive ylides, if the reaction is carried out under phase transfer conditions[46,70–74] in the presence of an aldehyde, which undergoes a Wittig reaction with the *in situ* generated ylide.

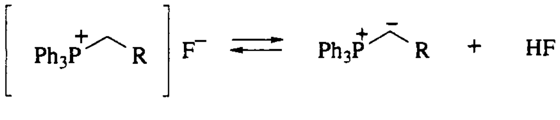
Sodium hydride itself, not only its reaction product with DMSO, is also suitable for deprotonation of phosphonium salts and preference has been given to this base over sodium ethoxide.[75]

Ethylene oxide or 1,2-epoxybutane may also be used for the synthesis of ylides.[76] The resulting ylide is in equilibrium with its conjugated salt (equation 15). The use of ethylene oxide offers some advantages over more conventional bases used in Wittig reactions. The application is simple since ylides and most often also phosphonium salts (from phosphine and alkyl halide) need not to be prepared separately. The reaction medium is neutral, so that base-induced side reactions fail to appear. The method is however less applicable to weakly acid phosphonium salts, since deprotonation requires high temperatures (150 °C).



(15)

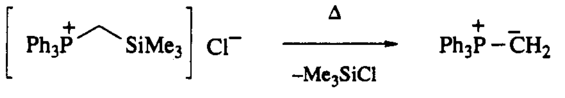
Another ylide synthesis avoiding basic conditions starts from phosphonium fluorides.[77–79] Fluoride ions are basic enough to play the role of the usually added external base, giving rise to the formation of a phosphonium salt/ylide equilibrium (equation 16).



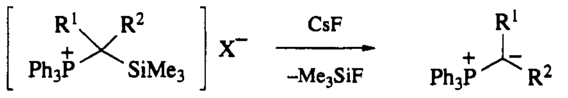
(16)

Ylide generation on alumina or potassium fluoride supported on alumina is of interest since the use of a solvent is unnecessary.[79]

In addition to the generation of phosphonium ylides from phosphonium salts by deprotonation with bases in some instances ylides may result from pyrolysis of phosphonium salts,[80] especially silylated salts (equation 17). Similar fluoride ion induced desilylation (equation 18) of phosphonium salts proved to be a very useful alternative for the synthesis of ylides which are difficult to synthesize by the conventional salt method (as in the case of R^1, R^2 = alkyl).[81,82] The most effective fluoride source is cesium fluoride and the reaction proceeds at room temperature.



(17)

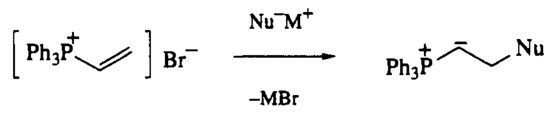


(18)

Phosphonium salts may also be converted to ylides by electrochemical procedures.[80,83] The preparative applicability of these methods, however, seems to be limited.

1.6.1.2.2 By addition of nucleophiles to vinyl- and cyclopropyl-triphenylphosphonium salts

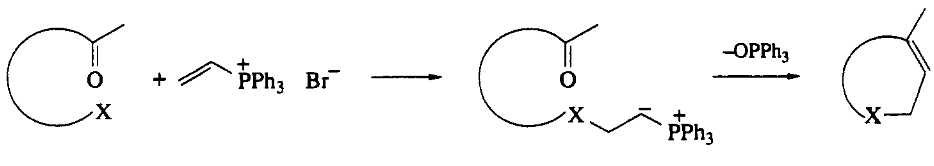
Vinylphosphonium salts are susceptible to nucleophilic attack at the terminal vinyl carbon, thus providing 2-substituted ethylidenephosphoranes (equation 19).[84] This method, developed by Schweizer, has been successfully employed in the addition of a variety of anionic derivatives from alcohols, thiols, amines and others to vinylphosphonium salts, especially to the commercially available vinyltriphenylphosphonium bromide ('Schweizer's reagent').[84–101] The analogous reaction involving alkyl- or aryllithium reagents proceeds in poor yields only, obviously because of ligand exchange processes and a competing elimination reaction transforming the vinyl salt to triphenylphosphine and acetylene. However, when the less basic organolithium cuprates are used as a source of carbanions the desired addition takes place readily.[101] Stabilized carbanions, especially enolate anions, are also well suited as nucleophiles.[92–100]



(19)

M = metal; Nu = OR, SR, NR_2, CR_2, CR_3, *etc.*

Ylides generated according to the vinyl salt method are usually not isolated but are quenched *in situ* with a carbonyl compound. Vinylphosphonium salts are most often reacted with nucleophiles containing suitable adjacent carbonyl groups yielding carbonyl substituted ylides, which provides an elegant method for the synthesis of a great variety of cyclic compounds by a subsequent intramolecular Wittig reaction (equation 20). The reaction principle may also be applied to the conjugate addition of a nucleophile to 1,3-butadienyl- and 1,3,5-trienyl-phosphonium salts, leading to the corresponding ylides (*e.g.* equation 21).[84,102,103]



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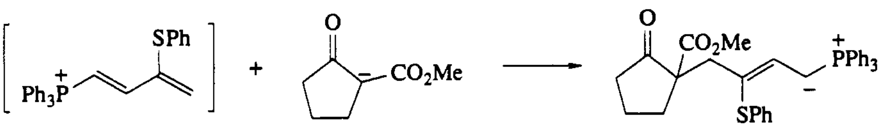
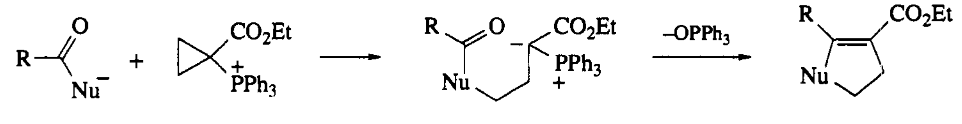


(21)

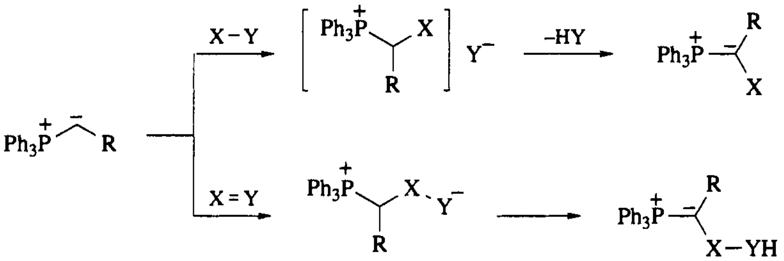
Ylides may also be generated by nucleophilic ring opening of cyclopropylphosphonium salts (equation 22).[84,104,105] The resulting ylide undergoes intramolecular Wittig reaction if the attacking nucleophile is carrying a carbonyl group.


(22)

1.6.1.3 From Conversion of Other Phosphonium Ylides

1.6.1.3.1 By substitution of a proton at the ylide carbon atom

Phosphonium ylides carrying at least one proton at the α-carbon atom react with various electrophilic reagents with formation of α-substituted phosphonium salts or zwitterionic intermediates, from which α-substituted ylides are generated by deprotonation or proton migration, the former reaction being more important (equation 23).[4,106–112]


(23)

If the reaction provides a salt whose acidity is greater than that of the starting phosphorane precursor (for example in the case of X = acyl), a second mole of the starting ylide reacts with the intermediate phosphonium salt in a transylidation reaction[56] (*cf.* equation 14) giving rise to the formation of an α-substituted ylide and the conjugated salt of the original ylide. If the proton of the phosphonium salt generated in the first step is not sufficiently acidic for this proton transfer to occur, the phosphonium salt formed in the first step can be isolated and has to be deprotonated by an external base.

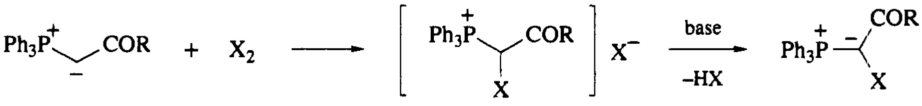
Reactions of ylide anions with electrophiles lead directly to substituted ylides.[109,113]

(i) Substitution by heterofunctional groups

α-Heterosubstituents influence the stability of phosphonium ylides markedly since σ-donors and π-acceptor groups, *e.g.* electropositive elements, stabilize ylides, whereas π-donors and σ-acceptors, *e.g.* electronegative elements, destabilize them.[9a]

(a) Substitution by halogen

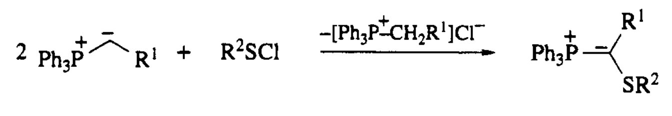
Halogenation of strongly basic ylides with free halogen is accompanied by side reactions and is not suitable for preparative application. Stabilized ylides, *e.g.* acyl- or alkoxycarbonyl-methylenephosphoranes, react with free halogen or various halogen carriers to give halogenated phosphonium salts.[114–118] Subsequent α-halo ylide formation may occur *in situ* by a second mole of the original ylide (transylidation), a base added to the reaction mixture at the beginning, or after isolation of the intermediate salt by an external base (equation 24). Suitable halogen carriers are bromo cyanide (in the presence of triethylamine), dichloro- and difluoro-iodobenzene, chloramine T, iodo bromide and perchloryl fluoride.


(24)

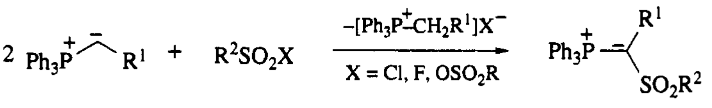
X = Cl, Br, I; R = alkyl, aryl, *O*-alkyl

(b) Substitution by elements of Group 6

Stabilized, as well as basic ylides, react with sulfenyl chlorides in a transylidation reaction to give alkylthiomethylenephosphoranes (equation 25).[119] In methylenetriphenylphosphorane both α-protons may be substituted by sulfenyl groups. The phenylthio and the methylthio group may also be introduced by *N*-methyl-*N*-phenylthioacetamide and dimethylsuccinimidosulfonium chloride, respectively. These methods avoid the disadvantage of requiring two moles of starting ylide as in the reaction with sulfenyl chlorides.


(25)

1-Sulfonylalkylidenephosphoranes are available from simple ylides and sulfonic acid halides or anhydrides in a transylidation reaction (equation 26).[119a] With aromatic sulfonyl chlorides halogenation and sulfenation may occur instead of sulfonation. Aliphatic sulfonyl chlorides give only poor yields of 1-alkanesulfonylalkylidenephosphoranes. Aromatic and aliphatic sulfonyl fluorides are very suitable for the introduction of sulfonyl groups into the α-position of ylides. However, as a consequence of the reaction mechanism (presumably *via* sulfenes) in addition to the expected ylide a rearranged byproduct may be formed (equation 27). 1-Sulfinylalkylidenephosphoranes are synthesized analogously with sulfinyl halides.[119a]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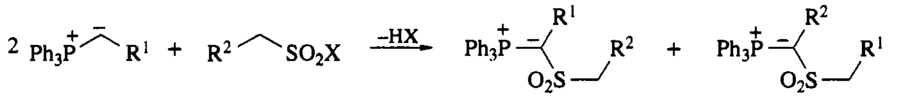
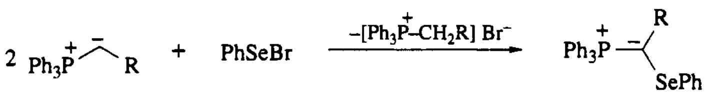
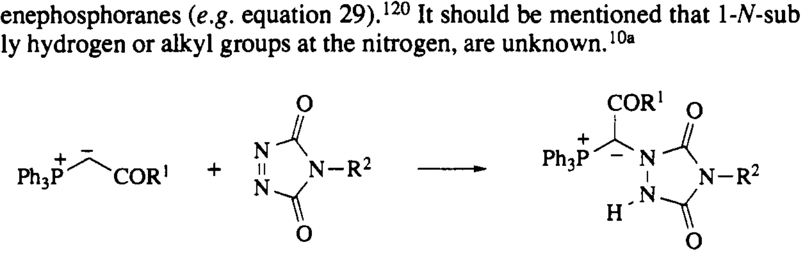

(27)

The transylidation reaction of phenylselenyl bromide with two moles of alkylidenetriphenylphosphorane yields 1-phenylselenoalkylidenetriphenylphosphoranes (equation 28).[119]

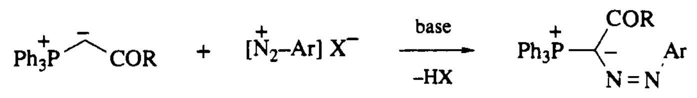

(28)

(c) Substitution by elements of Group 5

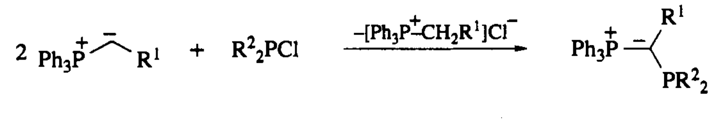
Acyl ylides add to N═N double bonds of azo compounds giving rise to the formation of 1-*N*-substituted alkylidenephosphoranes (*e.g.* equation 29).[120] It should be mentioned that 1-*N*-substituted ylides, which carry only hydrogen or alkyl groups at the nitrogen, are unknown.[10a]


(29)

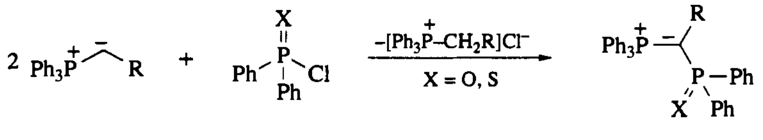
Coupling of aromatic diazonium salts with stabilized methylenephosphoranes leads to arylazomethylenephosphoranes (equation 30).[121]


(30)

1-Phosphino-substituted ylides are available from simple ylides and chlorodialkyl- or chlorodiarylphosphines (equation 31).[122,123] It depends upon the conditions of the reaction whether the substituted phosphonium salt or the corresponding ylide can be isolated. Methylenetriphenylphosphorane may undergo double phosphinylation. Phosphino-substituted ylides have also been synthesized using 1-alkyl-2-vinylphosphiranes as reagents.[124]


(31)

Diphenylphosphinyl chlorides and simple ylides yield 1-diphenylphosphinylalkylidenephosphoranes in a transylidation reaction; the introduction of the thiophosphinyl group may be carried out analogously (equation 32). Synthesis of diethoxy- and diphenoxy-phosphinomethylenetriphenylphosphoranes may be achieved with the corresponding phosphoro chloridates (equation 33).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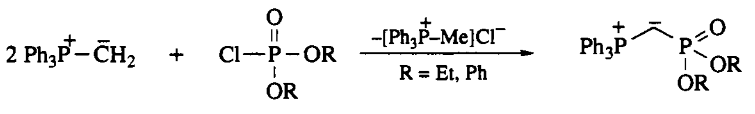
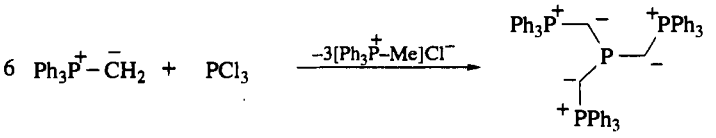
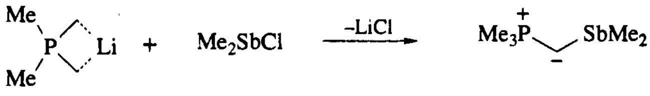

(33)

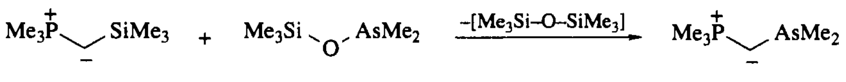
Apart from the mentioned phosphorus halogen compounds also dichlorophenylphosphine, phosphorus(III) trichloride, phosphorus(III) oxychloride and its thio analog have been reacted with methylenetriphenylphosphorane generating the corresponding phosphorus(III) substituted ylides (*e.g.* equation 34).


(34)

The dimethylstibino group has been introduced by the reaction of lithiated ylide with chlorodimethylstibine (equation 35).[125a] Bis(diphenylstibino)methylenetriphenylphosphorane results from chlorodiphenylstibine and methylenetriphenylphosphorane in a transylidation reaction.[125b]

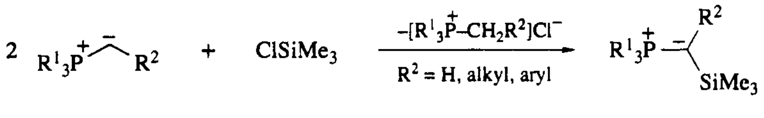

(35)

1-Dimethylarsinomethylenetrimethylphosphorane is available by desilylation of the corresponding 1-trimethylsilyl compound (*cf.* Section 1.6.1.3.2)

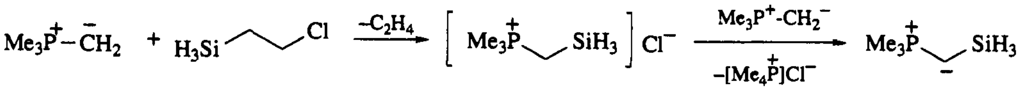

(36)

(d) Substitution by various element–organic substituents

α-Silylated alkylidenephosphoranes can be synthesized from simple alkylidenephosphoranes and chlorosilanes (especially chlorotrimethylsilane) by transylidation, since the silyl group stabilizes the resulting ylide (equation 37).[81,126,127]


(37)

From methylenephosphoranes (R^2 = H) both mono- or bis-silylated products may result.[128] Schmidbaur *et al.* have used a variety of compounds for the silylation of ylides.[126] α-Silylated alkylidenephosphoranes are also formed in the reaction of simple ylides with 2-chloroethylsilane (equation 38), chloromethylsilane (equation 39), siletanes, 1,3-disiletanes (equation 40) and the highly strained hexamethylsilirane (equation 41).[129]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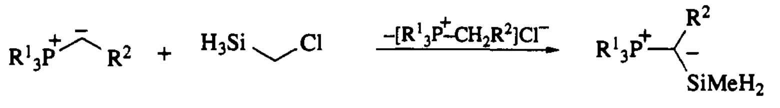
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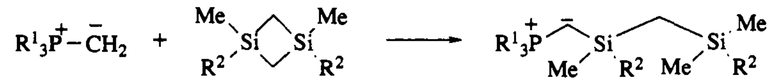
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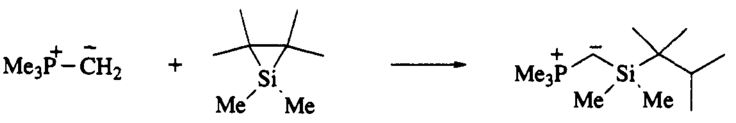
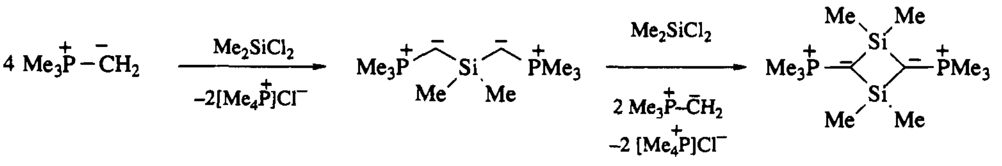

(41)

Reaction of simple ylides with dialkyldihalosilanes leads in a twofold transylidation to the formation of Si-bridged bisphosphoranes (equation 42), which can undergo consecutive reactions with excess starting materials leading to cyclic products. Bis(chlorodimethylsilyl)methane also reacts with dilithiomethylenetrimethylphosphorane to give a methylenephosphorane with an exocyclic ylide function (equation 43).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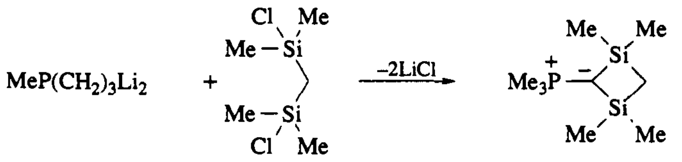
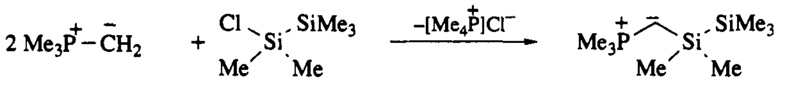

(43)

Analogously to the silyl group the Si—Si unit may be introduced into the α-position of methylenephosphoranes using chlorodisilanes (equations 44 and 45).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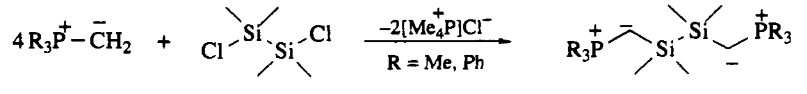
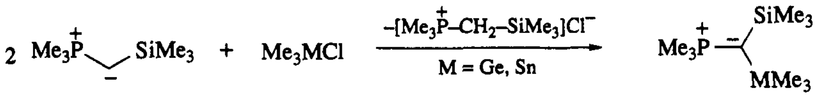

(45)

Germanyl- and stannyl-substituted ylides may be synthesized starting from ylides and germanyl and stannyl chlorides (*e.g.* equation 46).[126] Methylenetriphenylphosphorane is converted into the corresponding disubstituted ylide (equation 47). The monosubstituted derivatives are available by desilylation of 1-trimethylsilylmethylenephosphorane (*cf.* equation 36).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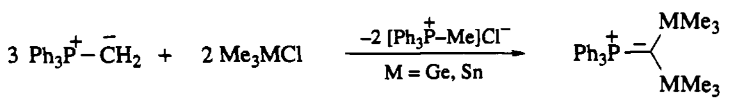
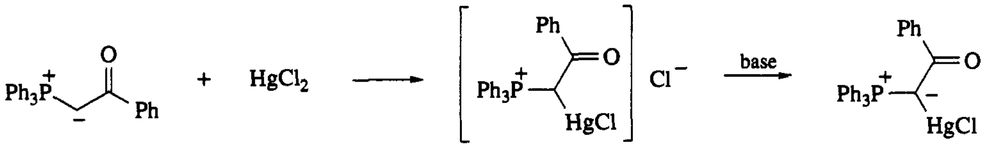
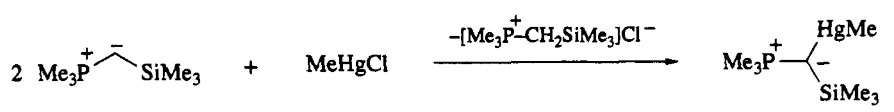
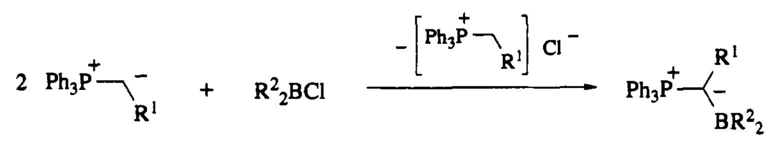

(47)

Stabilized ylides react with mercury(II) chloride giving salts, which can be deprotonated to the corresponding mercury substituted ylides (equation 48).[126] Among reactive ylides only the trimethylsilylmethylenetrimethylphosphorane can be transformed into its mercurated derivative (equation 49).


(48)


(49)

Dialkylboron-substituted phosphonium ylides have been prepared by reaction of dialkylchloroboranes with alkylidenephosphoranes (equation 50).[130] The reaction of phosphonium ylides with alkyldichloroboranes leads to the formation of boron-bridged 1,3-bisylides (equation 51).[131]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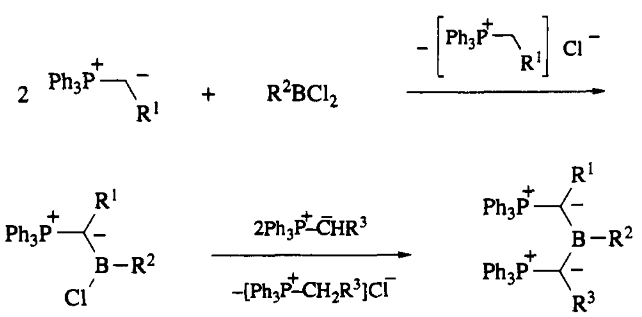
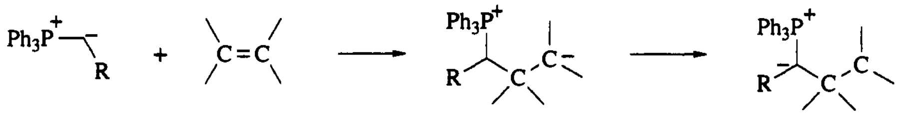

(51)

(ii) Substitution by carbon substituents

(a) By alkyl groups

Substitution of an α-proton in alkylidenephosphoranes by an alkyl group can be achieved by two alternative routes:[106–108,110–112,132] (a) Michael addition to activated C=C double bonds (equation 52); (b) reaction with alkylating reagents to give phosphonium salts, which are subsequently deprotonated by a second mole of the original ylide (transylidation) or an external base (equation 53). Ylide synthesis according to method (a) is restricted to some special cases.[132] Concerning method (b) it should be mentioned that in some instances the second mole of ylide causes β-elimination (Hofmann degradation) instead of α-elimination (transylidation) of the initially formed salt.[110,111,133]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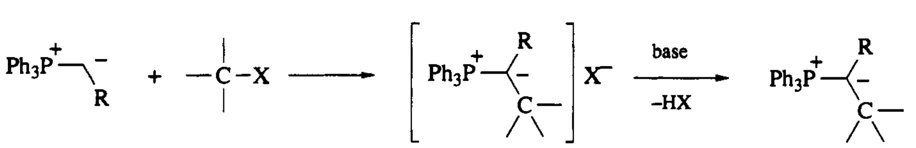
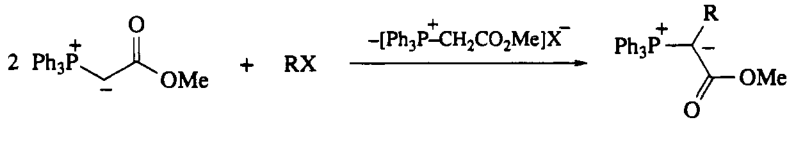
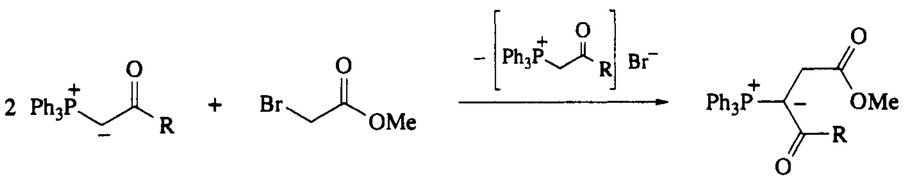

(53)

The reaction of ylides with saturated aliphatic alkyl halides (like methyl iodide, ethyl iodide *etc.*) usually stops at the stage of the alkylated salt because the *+I* effect of the aliphatic substituent causes the resulting salt to be a weaker acid than the conjugated salt of the original ylide (which would result in the course of a transylidation reaction).[56,133,134] However since partial transylidation also occurs between alkylidenephosphoranes and phosphonium salts with equal or not very different base and acid strength,[135] mixtures may result from the reaction with saturated aliphatic alkyl halides. At this point it should be mentioned that the synthesis of dialkylated ylides *via* the salt method is also difficult since the preparation of the necessary phosphonium salt is accompanied by β-elimination. The successful synthesis of dialkylated ylides may be achieved by fluoride ion induced desilylation of α-trimethylsilylphosphonium salts (see equation 18). There is no doubt about the course of ylide alkylation in cases where the inductive effect of the new substituent leads to complete transylidation (*e.g.* equation 54).[134]


(54)

R = $CH_2CH{=}CH_2$, CH_2CO_2Me, CH_2CN, CH_2Ph, $CH_2CH{=}CHPh$

Ylides with ambident character, like 1-formyl- or 1-acyl-methylenephosphoranes, may be attacked by alkylating reagents (the same is true for acylation) at the α-carbon or at the O atom.[85,136] Bromomethyl acetate *C*-alkylates acylmethylenetriphenylphosphoranes in a transylidation reaction (equation 55).[137] Recently cyanomethylenetriphenylphosphorane has been successfully alkylated *via* its ylide anion, the substituted cyano ylides being accessible more readily in greater variety than previously (equation 56).[113]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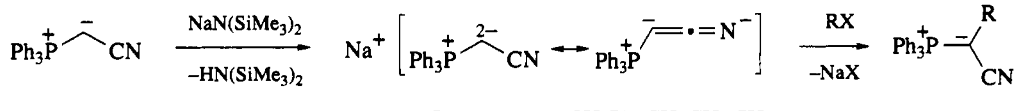
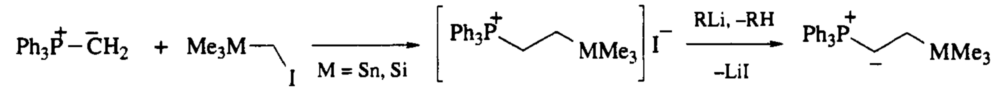

(56)

R = Me, Bu^n, CH_2SiMe_3, CH_2Ph, $CH_2CH{=}CH_2$

Syntheses of complex ylides by alkylation of simple ylides have been achieved in great variety,[110,111,132] using not only alkyl halides (usually containing another functional group) but also other alkylating reagents (Mannich bases,[138] strained cyclic compounds like epoxides,[113b,139] aziridines[140] and siletanes,[141] pyrylium salts[142] and others). Equations (54)–(56), (57),[66] (58),[143] (59),[138] (60)[139a] and (61)[140] give some selected examples.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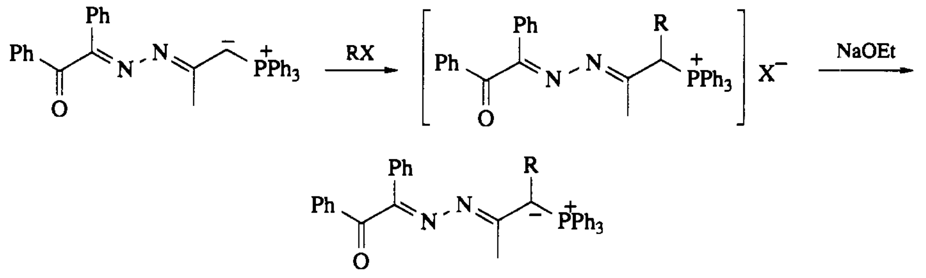
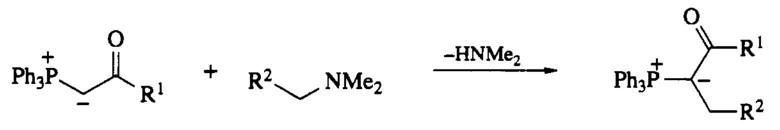


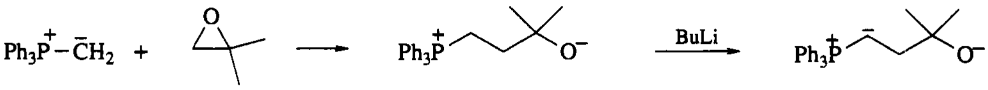
(58)

R = Me, $CH_2CH{=}CH_2$, CH_2Ph

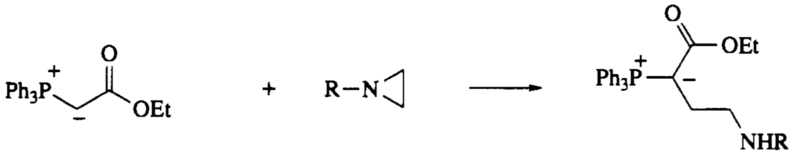


(59)

R^1 = OEt, Ph; R^2 = Ar, CH_2CH_2Ar

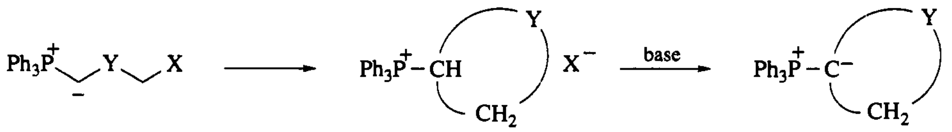


(60)



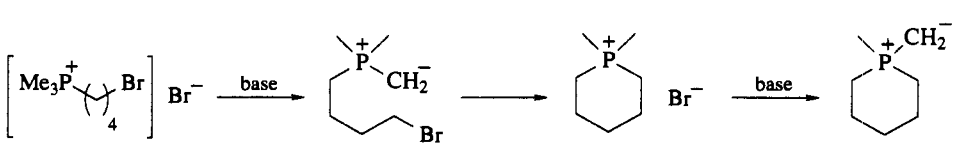
(61)

ω-Haloalkylidenetriphenylphosphoranes undergo intramolecular *C*-alkylation giving rise to the formation of an exocyclic phosphonium salt, which can be deprotonated by a second base (original ylide or an external base) to yield the corresponding exocyclic ylide (equation 62).[144–147]



(62)

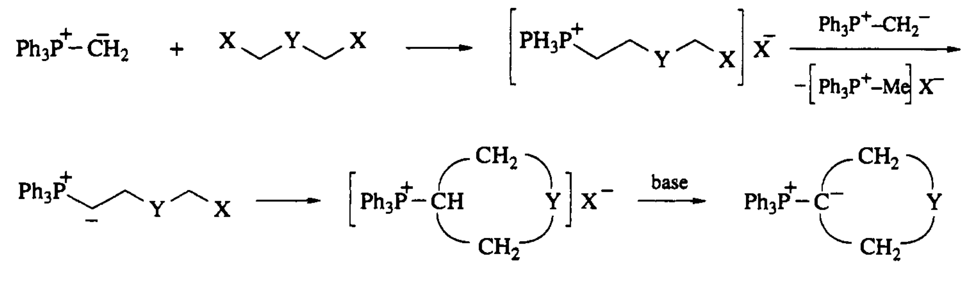
Differing from this course of reaction, in the case of the analogous trialkyl compounds the P atom may be incorporated into the ring system (equation 63).[148]



(63)

For a successful intramolecular *C*-alkylation of alkylidenetriphenylphosphoranes it is required that the conjugated salt of the starting ylide can be synthesized from triphenylphosphine and a 1,ω-dihalide. As a consequence of this fact intramolecular *C*-alkylation often fails in the aliphatic series with Y = $(CH_2)_n$, with the exception of $n = 1, 2$. This difficulty can be overcome by the combination of the inter- and intramolecular *C*-alkylation of ylides (equation 64).[144–146]

Two moles of methylenetriphenylphosphorane are reacted with one mole of a dihalogen compound. In the first step methylenetriphenylphosphorane is *C*-alkylated yielding an ω-halophosphonium salt, which subsequently reacts with a second mole of methylenetriphenylphosphorane forming a transylidation equilibrium with methyltriphenylphosphonium halide and an ω-halogenated ylide. This compound undergoes intramolecular *C*-alkylation, in the course of which the resulting exocyclic phosphonium salt



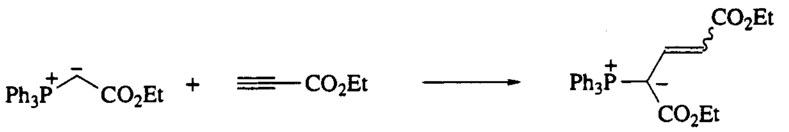
(64)

is formed and precipitates together with the methyltriphenylphosphonium halide (from the transylidation step) from the benzene solution. As a consequence of the precipitation the transylidation equilibrium is permanently disturbed so that the reaction takes place with complete formation of both phosphonium salts. These can be separated by recrystallization from water. From the resulting cycloalkyltriphenylphosphonium salt the corresponding cycloalkylidenetriphenylphosphorane may be generated with a base. Deprotonation may sometimes occur immediately under the influence of a third mole of methylenetriphenylphosphorane. Usually the exocylic alkylidenetriphenylphosphoranes synthesized are not isolated but reacted *in situ*, mostly in a Wittig reaction.

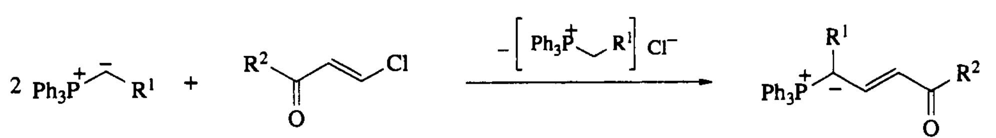
The efficiency of this method is impressively proved by the synthesis of the skeleton of shikimic and chinic acid starting from an open chain sugar derivative and the synthesis of optically active cyclopentanediol synthetic building blocks from tartaric acid.[149]

(b) By alkenyl and alkynyl groups

The alkenylation of alkylidenephosphoranes may be achieved, by analogy to the alkylation, either by Michael addition to conjugated alkynes and allenes or by reaction with alkenylating reagents.[110,111,132b,150,151] Michael addition is restricted to stabilized ylides (*e.g.* equation 65); however, in one case the resulting product has been observed to fragment in a retro-Michael reaction.[152] More reactive alkylidenephosphoranes and alkynes give rise to the formation of four-membered adducts, which undergo ring opening to yield alkenyl-substituted ylides in which the original P—C function has been cleaved.[150] 4-Oxo-2-alkenylidenetriphenylphosphoranes can be prepared from reactive or stabilized ylides and 2-chlorovinyl ketones in a transylidation reaction (equation 66).[150a]



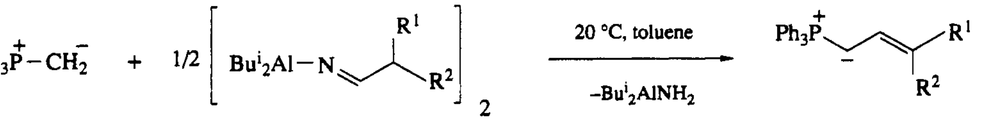
(65)



(66)

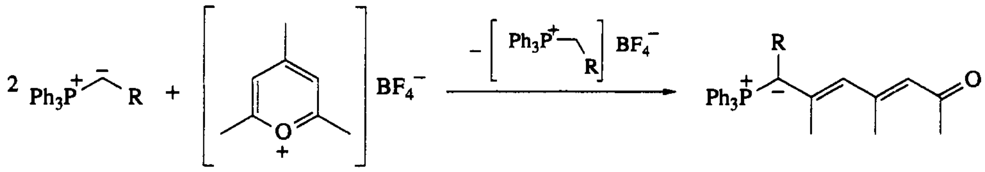
R^1 = CO_2Et, COMe, SPh, Ph, CH_2Ph, CH=CHMe R^2 = alkyl, phenyl

Methylenetriphenylphosphorane reacts with alkylideneaminodialkylaluminum compounds (available from diisobutylaluminum hydride and nitriles) to give allylidenetriphenylphosphoranes (equation 67). In the case of R^1 = *n*-alkyl, R^2 = H, predominantly (*Z*)-allylidenephosphoranes are formed; branching of R^1 leads to an increasing portion of (*E*)-isomer. The method has also been applied to the synthesis of cyclic and acyclic bisallylidenephosphoranes.[153]



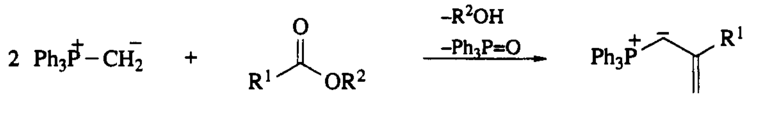
(67)

2,4-Alkadienylidenephosphorane can be synthesized from simple ylides and pyrylium or pyridinium salts (*e.g.* equation 68).[150a] The resulting ylides may undergo spontanous intramolecular Wittig reaction.



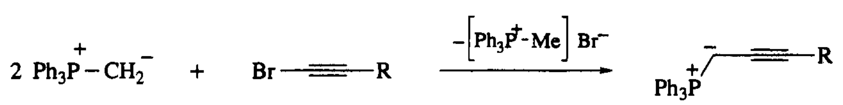
(68)

Esters of aromatic acids react with an excess of methylenetriphenylphosphorane giving rise to the formation of allylidenephosphoranes (equation 69).[150a]



(69)

Alkynyl substituted alkylidenetriphenylphosphoranes are available from the transylidation reaction of methylenetriphenylphosphorane with bromoalkynes (equation 70) or alternatively with 1,1-dibromoalkenes in the presence of a third mole of original ylide.[154]

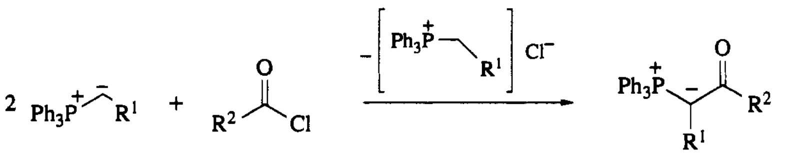


(70)

(c) By acyl groups and their derivatives

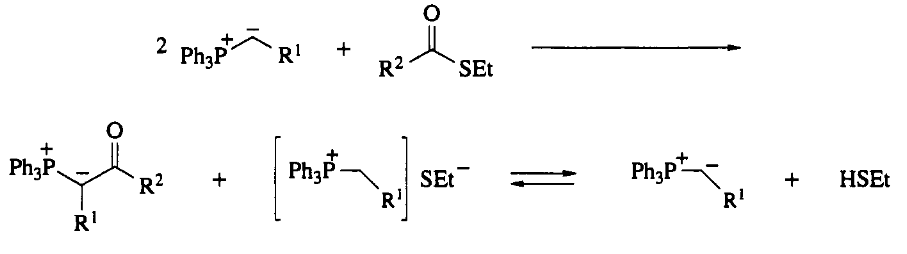
Acyl halides, activated esters, carboxylic anhydrides and *N*-acylimidazoles react with alkylidenephosphoranes to yield acylated ylides.[106,110,111,155–157]

Acid chlorides react readily with alkylidenephosphoranes. Owing to the strongly electron-withdrawing effect of the acyl group, the initially formed salt is a sufficiently strong acid to undergo transylidation very easily with a second mole of starting ylide (equation 71). The method has been applied to reactive[158–160] as well as to resonance-stabilized (especially ester-stabilized) ylides,[121d,143,161–164] β-ketoalkylidenephosphoranes however usually yield *O*-acylated products. The second mole of starting ylide necessary for a transylidation may be substituted by triethylamine if the amine is a stronger base than the ylide, as is usual in the case of stabilized phosphoranes.[156,165] Under the influence of the added amine or the original ylide hydrogen chloride may be eliminated from acid chorides containing activated α-hydrogen. The ketenes so formed may react with ylides to give allenes.[166] Acid fluorides have also been used for the acylation of ylides.[167]



(71)

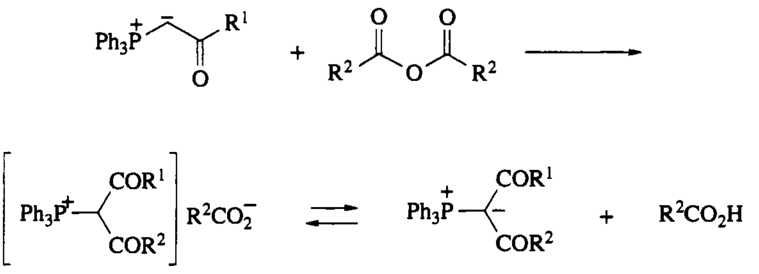
A disadvantage of the acylation method with acid halides is the requirement of two moles of starting ylide, one acting as a base to deprotonate the initially formed acylated phosphonium salt (although the precipitating salt may be used for the regeneration of the starting ylide). This disadvantage can be removed by the use of thiocarboxylic acid *S*-ethyl esters as acylating reagents (equation 72).[156] The phos-



(72)

phonium thiolate initially formed by transylidation eliminates mercaptan thus generating the second mole of starting ylide and removing it from the equilibrium by reaction with further thioester. This method usually supplies purer products and better yields than the acid chloride acylation.

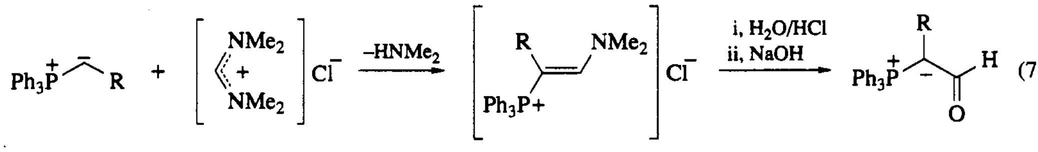
In general, salt-free solutions of ylides do not react with methyl or ethyl esters of carboxylic acids. Better results can be obtained when activated esters (*e.g.* phenyl or pyridyl esters) are used for acylation.[121d,166c] Acylation with carboxylic acid anhydrides also requires only one mole of starting ylide (equation 73).[156,163]



(73)

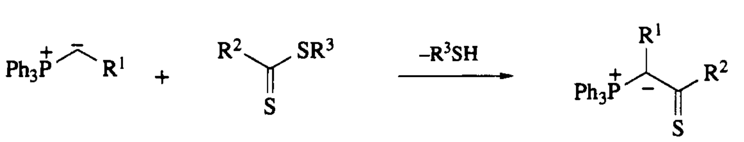
This route proved to be advantageous in the case of resonance-stabilized ylides since there are no problems in separating the acylated ylide from a phosphonium salt resulting from transylidation, and *O*-acylation does not occur when β-keto ylides are used as starting materials. The acylated ylide is generated from the initially formed phosphonium carboxylate by heating or with an alkali metal hydroxide. Cyclic anhydrides, like succinic or glutaric anhydrides, may also be used as acylating reagents which give rise to the introduction of an ω-carboxy substituted acyl group.[168]

Formylation of alkylidenetriphenylphosphoranes has been achieved with formic esters, *N*-formylimidazole, formyl acetate, chloromethylenedimethylammonium chloride and tetramethylformamidinium chloride. The formamidinium compound leads primarily to vinylphosphonium salts which can be easily hydrolyzed without isolation thus providing a very efficient route to formylalkylidenephosphoranes (equation 74).[169] The preparation of α-formyl substituted ylides with formic ester could be improved by adding tertiary butoxide to the starting ylide before admixture of ethyl formate as formylating reagent, thereby circumventing the necessity for transylidation and increasing the yield drastically.[170]



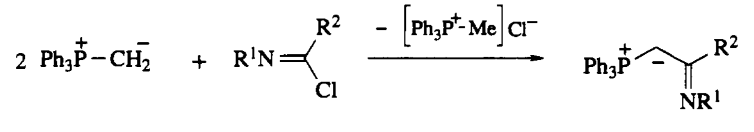
(74)

The introduction of the thioacyl group may be achieved by analogy to the acylation using dithiocarboxylic acid esters (equation 75), however side reactions may occur.[171]



(75)

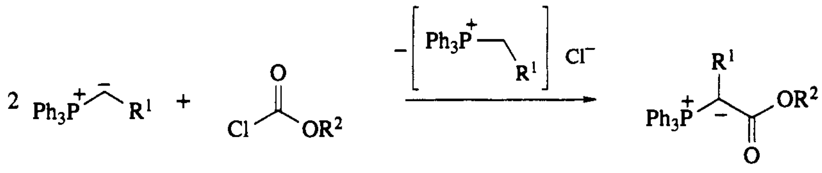
2-Iminoalkylidenetriphenylphosphoranes result from the transylidation reaction of methylenetriphenylphosphorane with imidoyl chlorides (equation 76),[172a] or from Michael addition of ylides to the C=C bond of ketenimines[172b] (formed from carbodiimide and ylides in the initial step).



(76)

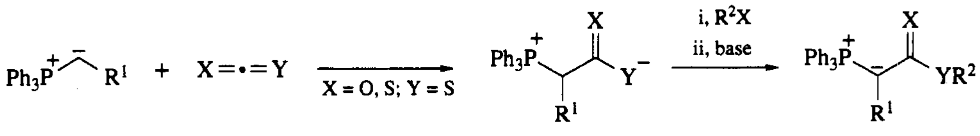
(d) By derivatives of the carboxy group

Ylides carrying α-substituents derived from the carboxy group (alkoxycarbonyl, alkylthiocarbonyl, alkylthiothiocarbonyl, cyano) have been synthesized by different routes.[173,174] Ester-substituted ylides are prepared from simple ylides and alkyl chloroformates in a transylidation reaction (equation 77). Using two moles of potassium bis(trimethylsilyl)amide (one for the generation of the starting ylide from its salt, the other for the deprotonation of the substituted salt) permits efficient carbalkoxylation with only one equivalent of valuable starting ylide.[175]



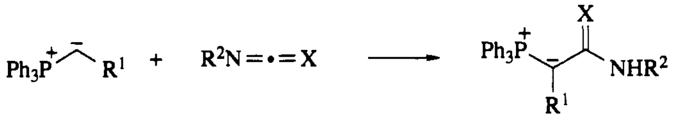
(77)

The synthesis of ylides which are α-substitued with a derivative of the carboxy group can also be achieved *via* the addition of simple ylides to heteroallenes. The reaction with carbon oxysulfide gives rise to the formation of betaines from which alkylthiocarbonylalkylidenephosphoranes may be generated by alkylation and subsequent deprotonation (equation 78; X = O, Y = S).[176] Carbon disulfide reacts in a similar way yielding (alkylthio)thiocarbonyl-substituted ylides (equation 78; X = S, Y = S).[177] These compounds are also available from the reaction of simple ylides with trithiocarbonates or dithiochlorocarbonates in analogy to the acylation of ylides (see equations 71 and 72).[173]



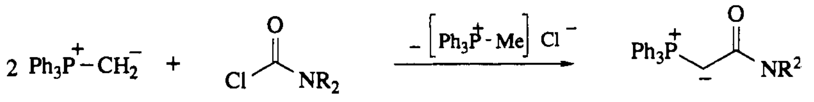
(78)

Alkylidenephosphoranes which carry a carbamoyl or thiocarbamoyl group in the α-position are formed from ylides and isocyanates or thioisocyanates (equation 79).[164,173] If the starting ylide has no activated α-H atom the reaction with thioisocyanates stops at the betaine intermediate (see equation 78) which can subsequently be alkylated and transformed into the corresponding substituted ylide with an external base.



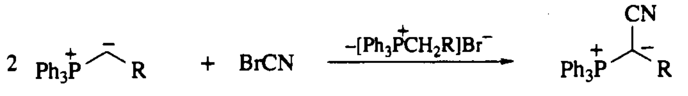
(79)

Carbamoylmethylenephosphoranes can also be synthesized from methylenetriphenylphosphorane and carbamoyl chlorides in a transylidation reaction (equation 80).[158]

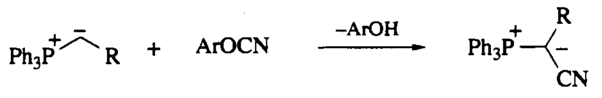


(80)

The cyano group may be introduced into the α-position of ylides by bromocyanide (equation 81) or with cyanic acid aryl esters (equation 82).[173,174]



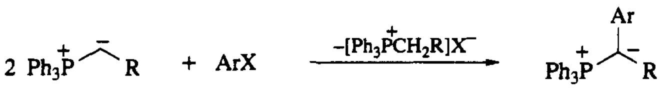
(81)



(82)

(e) By aryl and heteroaryl groups

The substitution of a H atom at the α-C atom by an aryl group may be achieved with chloropolynitrobenzenes or hexafluorobenzene, whereby transylidation takes place (equation 83).[178,167] A variety of heteroaryl groups can be introduced in an analogous manner.

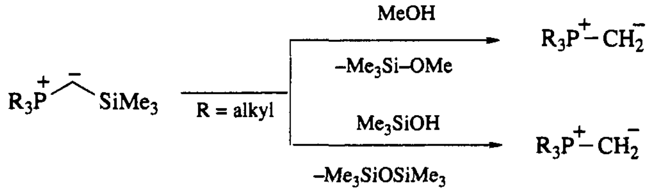


(83)

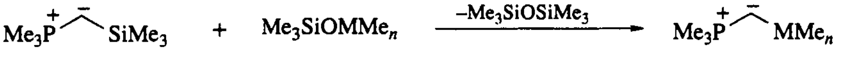
1.6.1.3.2 *By substitution of a heterosubstituent at the ylide carbon atom*

Besides protons a series of heteroligands in the α-position of phosphonium ylides can also be substituted, giving rise to the formation of new alkylidenephosphoranes.[179] Halogen atoms have been substituted by carbon groups (with lithium organyls or acyl chlorides) or another halogen. Reaction of α-lithiated ylides (see equation 35) or ylide anions[113] with electrophiles may be considered as substitution of an alkali metal substituent at the ylide carbon atom.

Most important is the substitution of the trimethylsilyl group.[179,180] In this way phosphonium ylides have been generated which could not, or only with difficulties, be synthesized by other methods. Desilylation may be achieved using methanol or trimethylsilanol (substitution of trimethylsilyl by hydrogen), heterosiloxanes (substitution of trimethylsilyl by element–organic groups), acid chlorides, thioesters, anhydrides and trimethylsilyl esters (acylation),[149b,181] and halogenosilanes (transsilylation). Equations (84)–(87) give some examples.

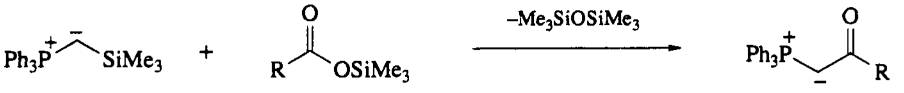


(84)

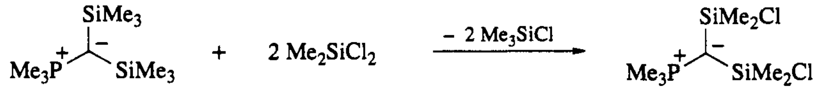


(85)

$n = 2$, M = As; $n = 3$, M = Ge, Sn, Pb



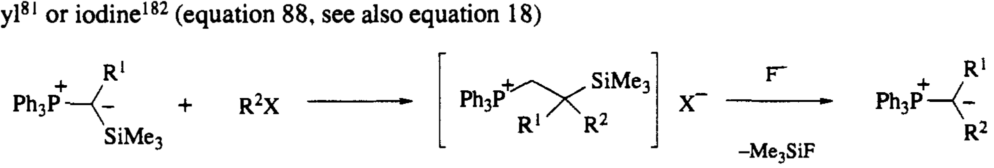
(86)



(87)

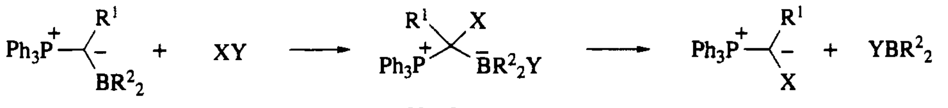
Ylides add to heteroallenes (see equations 78 and 79). In the case of silyl-substituted ylides the initially formed betaine stabilizes by silyl group migration instead of proton migration.[179]

α-Trimethylsilylalkylidenephosphoranes can be transformed into α-trimethylsilylphosphonium salts which can be desilylated by fluoride ions, thus providing a method of substituting trimethylsilyl by alkyl[81] or iodine[182] (equation 88, see also equation 18)



(88)

Dialkylborylalkylidenetriphenylphosphoranes react with polar or polarizable compounds *via* onium complexes to give new ylides, in which the dialkylboryl group has been substituted, and the corresponding organoboron compounds (equation 89).[183]



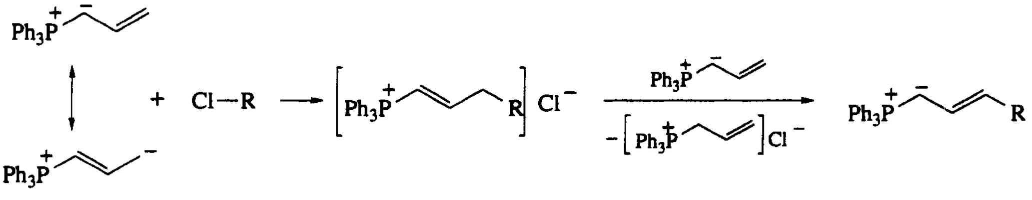
(89)

XY = Br_2, DOMe

1.6.1.3.3 From reactions which do not take place at the ylide carbon atom

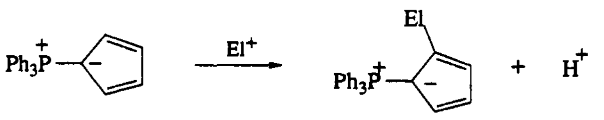
Many alkylidenephosphoranes can be transformed into new phosphonium ylides by reactions which take place in the side chain of a parent ylide, the α-C atom of the ylide group not being involved.[184]

Allylidenetriphenylphosphoranes react with a series of chloro compounds (alkyl chloroformates, acyl chlorides, 3-chloroacrylates, 2-chlorovinyl ketones, phosphorus chlorides) and other electrophilic compounds at the γ-C atom.[184–188] Abstraction of a proton from the γ-position of the resulting phosphonium salts by a second mole of starting ylide (or proton migration) gives rise to the formation of γ-substituted derivatives of the original allylidenephosphoranes (equation 90).



(90)

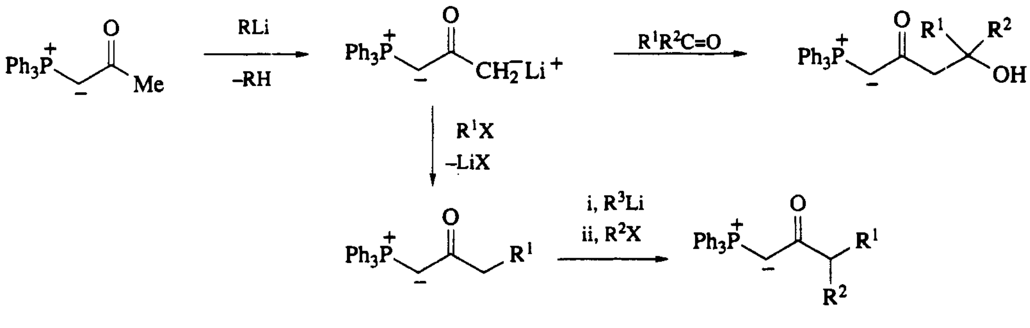
The extremely stable cyclopentadienylidenetriphenylphosphorane and its derivatives are too inactive to undergo typical ylide reactions. The cyclopentadienyl ring, however, may be substituted by a variety of electrophiles in the 2-position (equation 91).[184]



(91)

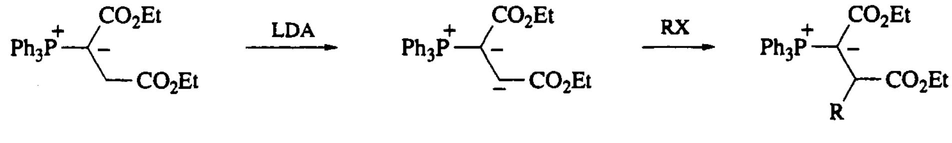
El = alkyl, acyl, azo, nitro *etc.*

Treatment of acetylmethylenetriphenylphosphorane with *n*-butyllithium or lithium diisopropylamide results in abstraction of a methyl proton to form an ylide anion. Reactions of the 1,3-dicarbanion with electrophilic compounds including alkyl halides, aldehydes, ketones and benzoate esters occurs at the terminal carbanion site to afford a variety of substituted β-ketophosphonium ylides (equation 92).[184,189,190]



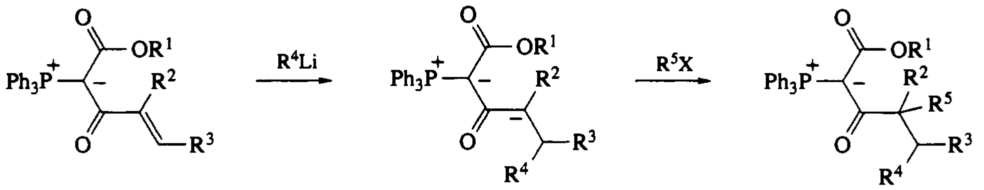
(92)

Converting the resulting monosubstituted ylide into the corresponding secondary ylide anion followed by another alkylation may give rise to the formation of disubstituted 2-oxoalkylidenephosphoranes. The diacetylmethylenetriphenylphosphorane can be deprotonated selectively at one or both methyl groups. Subsequent treatment with an alkyl halide leads to the corresponding mono- or di-alkylated ylide. Ylide anion formation followed by alkylation could also be achieved with the ylide which is readily available from the addition of triphenylphosphine to diethyl fumarate (equation 93).[191]



(93)

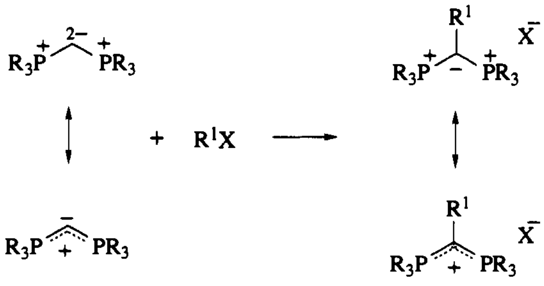
Another route to substituted ylides *via* ylide anions involves charge-directed addition of a wide range of carbon nucleophiles to γ,δ-unsaturated acylphosphoranes yielding intermediate anions which further react with electrophiles, mostly alkyl halides (equation 94).[161,184,192]


(94)

Generally alkylidenephosphoranes that carry in addition to the ylidic function another reactive site (*e.g.* a second ylide function, an additional phosphonate group, a halogen or a silyl substituent) may react at this additional functional group thus providing a derivative of the original ylide.[184,193–195]

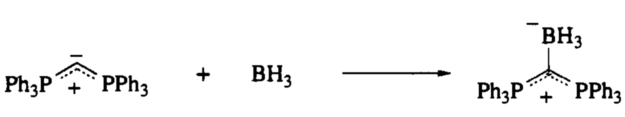
1.6.1.3.4 From carbodiphosphoranes

Carbodiphosphoranes (*cf.* Section 1.6.2.1) react with a series of halogen compounds including bromine, hydrogen chloride, alkyl halides, acyl chlorides, sulfenyl chlorides, diorganohalogenophosphines and silyl chlorides, giving rise to the formation of semi-ylide salts which formally contain an ylidic function, being however best described as salts of diphosphaallyl cations (equation 95).[196–201] Phenylcarbodiphosphoranes are converted by water into stable 1-phosphinylmethylenephosphoranes (equation 96).[196–198]

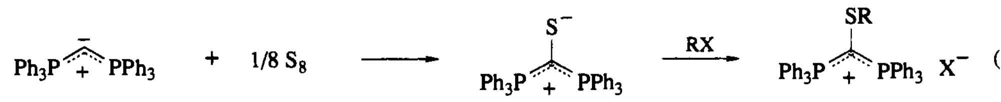

(95)


(96)

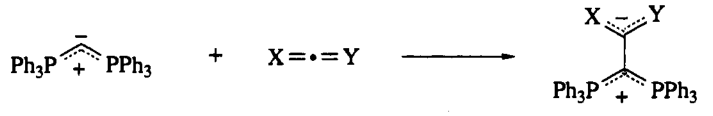
Borane yields zwitterionic compounds with partial ylide structure (equation 97).[199,201]


(97)

The reactions with sulfur or selenium result in the formation of betaines, which can be alkylated to give semi-ylide salts (equation 98).[202] The reactions of hexaphenylcarbodiphosphorane with a series of heteroallenes also lead to betaines which on thermolysis yield new cumulated ylides (equation 99, *cf.* equation 120).


(98)

The bridging oxygen in aromatic carboxylic anhydrides may be exchanged by the ylide function in the reaction with hexaphenylcarbodiphosphorane (*e.g.* equation 100).[203]



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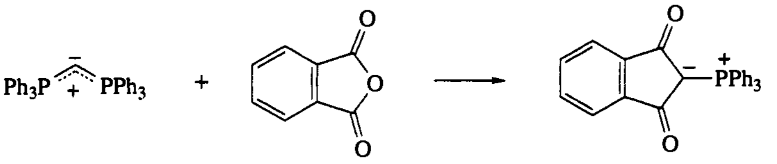


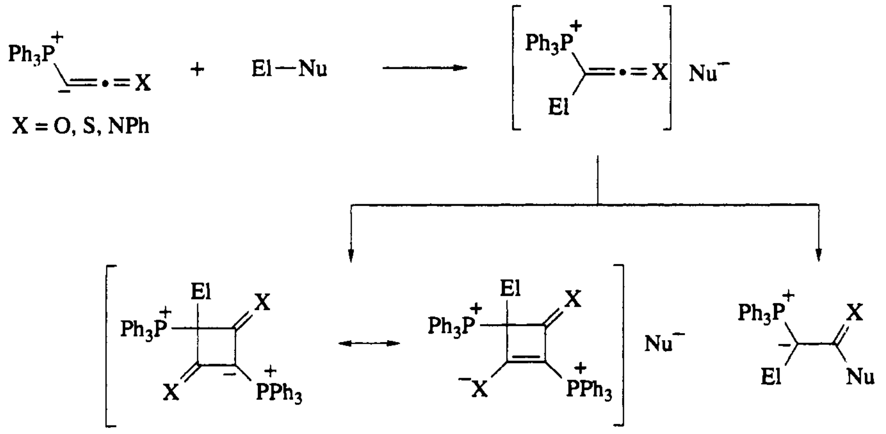
(100)

1.6.1.3.5 From vinylidenephosphoranes

'Simple' alkylidenephosphoranes can be synthesized from vinylidenephosphoranes by various routes.[204,205]

(i) By nucleophilic substitution

Addition of an electrophile to the lone pair of oxo-, thioxo- and imino-vinylidenephosphoranes transforms the nucleophilic π^4–π^4 system into the dipolar π^4–π^2 system of a ketene. The resulting phosphonium salt becomes a true dipolar ketene which, as such, reacts in a known manner (equation 101). Whenever the anion Nu^- is a stronger nucleophile than the original cumulated ylide, the new alkylidenephosphorane will be formed, in which compound ElNu has added to the parent vinylidenephosphorane. If the starting phosphacumulene ylide is a stronger nucleophile than Nu^-, the intermediate salt always reacts with a second molecule of unreacted ylide in a [2 + 2] cycloaddition to give 1,3-cyclobutanedione derivatives.



(101)

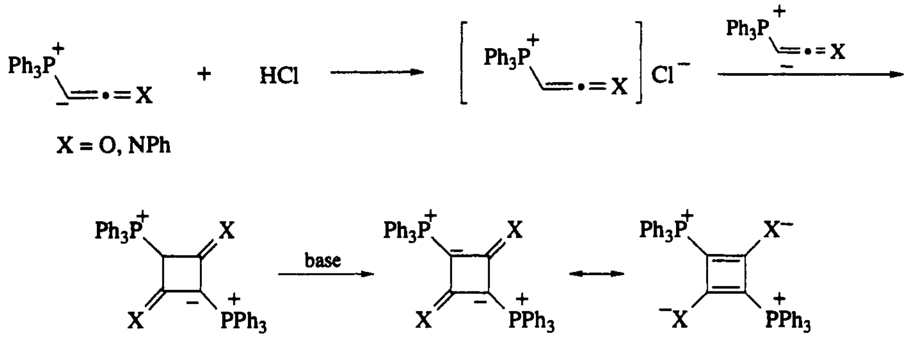
(a) From reaction with halogen compounds

Oxovinylidene- and iminovinylidene-triphenylphosphoranes react with hydrogen chloride in the molar ratio 2:1, leading to 1,3-dioxo- and 1,3-diimino-cyclobutane derivatives, which can be converted into stable exocyclic bisalkylidenephosphoranes by sodium bis(trimethylsilyl)amide (equation 102).

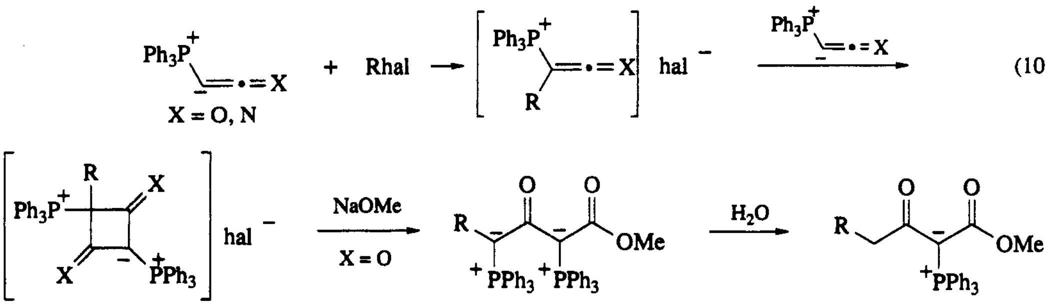
The resulting dimers of the original phosphacumulene ylides are of particular interest because one of their resonance forms represents another type of 'push–pull' cyclobutadiene.

Reactions of oxo- and imino-vinylidenetriphenylphosphoranes with alkyl halides also proceed *via* nucleophilic substitution, which is followed by a [2 + 2] cycloaddition yielding four-membered ylide phosphonium salts (equation 103), which can also be generated from the previously mentioned dimers and alkyl halides. Ring opening of the resulting ylide phosphonium salts with sodium methoxide gives bisylides. Since the ylide flanked by two carbonyl groups in the bisphosphoranes is much more inert than that adjacent to only one CO group, these compounds are easily hydrolyzed by water to monoylides.

The reaction of oxovinylidenetriphenylphosphorane or its dimer with aromatic carboxylic acid chlorides leads not to cyclobutanedione derivatives but to pyrone compounds, which can be converted to open chained bisphosphoranes with sodium methoxide (equation 104).[205] If the acid chlorides carry an

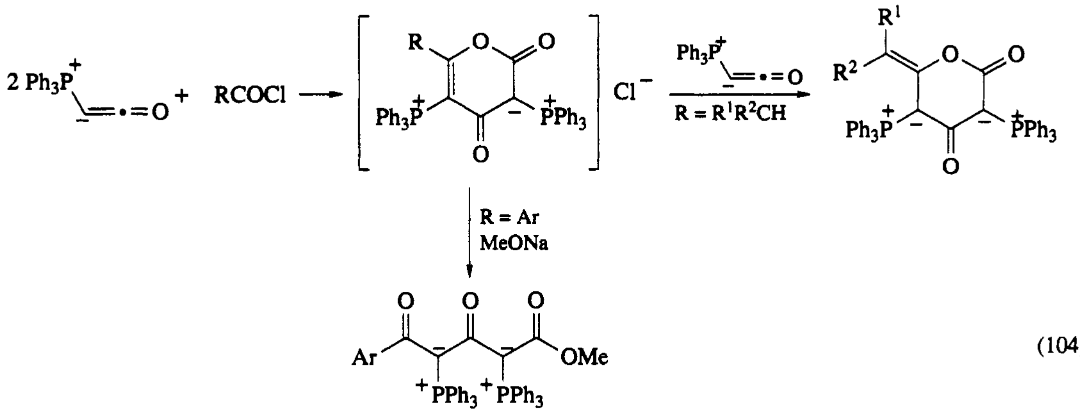


(102)



(103)

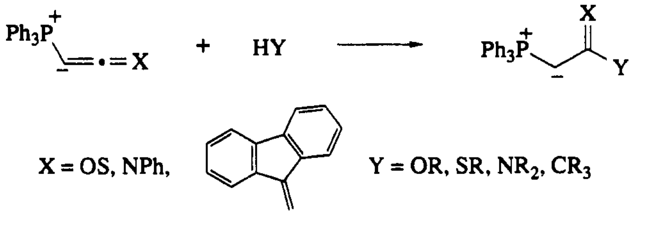
α-H atom, the resulting ylide phosphonium salts are deprotonated at the vinyl position by excess starting ylide yielding exocyclic bisylides.



(104)

(b) From reactions with acidic compounds

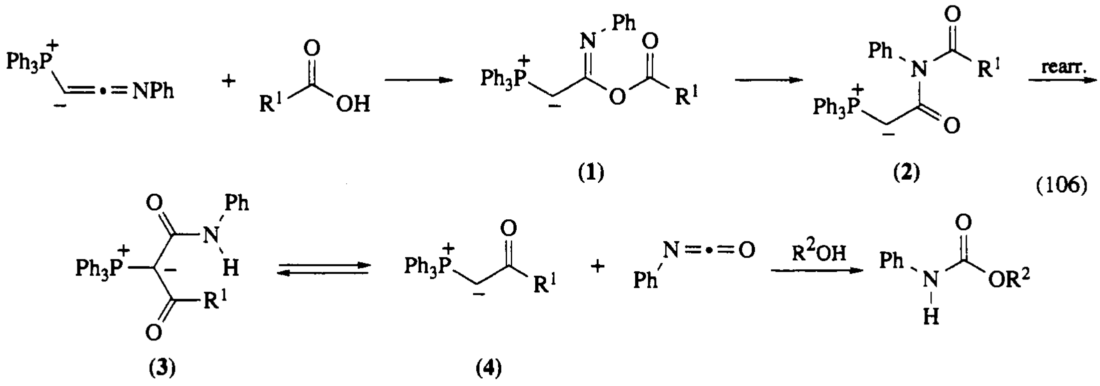
In the reaction of OH-, NH-, SH- and CH-acidic compounds with phosphacumulene ylides the anion Nu⁻ of the initially formed phosphonium salt (*cf.* equation 101) is so nucleophilic, that addition of the anion to give a new alkylidenephosphorane is faster than cycloaddition of a second mole of starting ylide (equation 105).[204,206]



(105)

According to the difference of the ylides in nucleophilicity (NR > O > S) iminovinylidene- and oxovinylidene-phosphorane smoothly add alcohols, thiols and acidic NH compounds, while thioxovinylidenephosphorane reacts readily with thiols and phenols, less rapidly with aliphatic alcohols and does not react with NH-acidic compounds. Strongly activated CH_2 groups add readily to iminovinylidenephosphoranes, less rapidly to oxovinylidenephosphorane and not at all to thioxovinylidenephosphorane. (The fluorenylidene derivative is less reactive than iminovinylidenetriphenylphosphorane and more reactive than the oxovinylidene and thioxovinylidene compounds.) By this method a great variety of alkylidenephosphoranes carrying α-substituents derived from the carboxy group can be synthesized.[206]

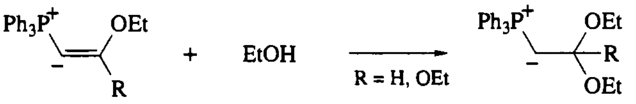
Carboxylic acids react with phenyliminovinylidenetriphenylphosphorane (equation 106) *via* the intermediates (**1**) with formation of the alkylidenephosphoranes (**2**), which, on heating, rearrange in an intramolecular acyl migration to ylides (**3**). By heating (**2**) in the presence of an alcohol the acyl ylides (**4**) and *N*-phenylurethanes are formed.[206,207] The reaction sequence allows the replacement of the OH group in carboxylic acids by the ylide function.



(106)

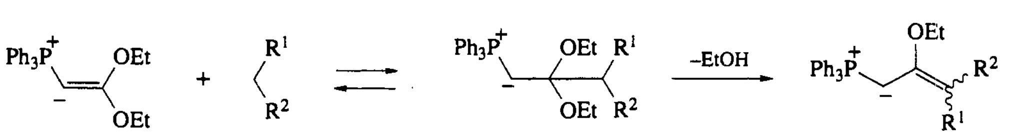
The addition of acidic compounds to phosphacumulene ylides yielding substituted alkylidenephosphoranes is of particular interest in the reaction of those acidic molecules which carry, besides the Y—H bond, a group capable of cyclization with the ylide function formed by addition.[208-215]

Ethoxy- and diethoxy-vinylidenetriphenylphosphorane add alcohols to the C═C bond according to the general scheme described above yielding orthoester phosphoranes (equation 107).[85,216,217]



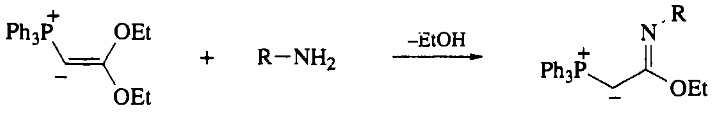
(107)

Because of its enhanced reactivity, diethoxyvinylidenetriphenylphosphorane adds a variety of CH acids, even those which do not react with oxo-, thioxo- and imino-vinylidenetriphenylphosphorane. Irreversible loss of ethanol from the initially formed Michael adduct gives phosphoranes which are vinylogs of β-keto ylides if the starting material is an acidic carbonyl compound (equation 108).[204,216] CH-acidic carbonyl compounds also may add to diethoxyvinylidenetriphenylphosphorane *via* the enolate oxygen, thus leading to orthoester phosphoranes which can undergo intramolecular Wittig reaction.[218]



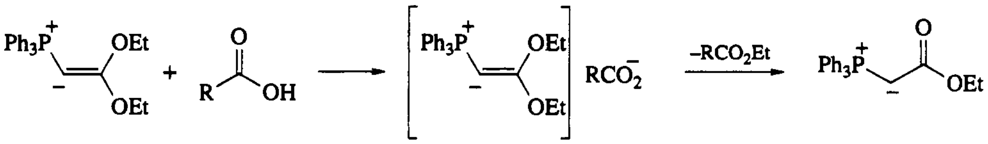
(108)

NH-acidic amines react like CH-acidic compounds. The initially formed Michael adduct loses ethanol giving rise to the formation of ethoxyiminocarbonylmethylenephosphoranes (equation 109).[206]



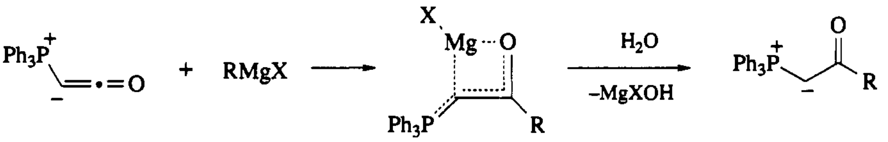
(109)

Strongly CH-acidic compounds, carboxylic acids and thiols react with diethoxyvinylidenetriphenylphosphorane not in the described manner but are ethylated by the ylide (*e.g.* equation 110).


(110)

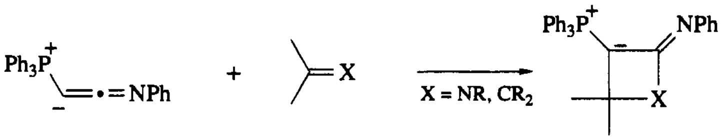
(c) From reaction with Grignard compounds

In the reaction of halogen compounds with oxovinylidenetriphenylphosphorane the initially formed phosphonium salt undergoes cycloaddition with a second molecule of the starting ylide. Umpolung of the reactivity of alkyl halides by transformation into the corresponding Grignard compounds, however, results in the reaction type which occurs in the reaction of acid compounds with oxovinylidenetriphenylphosphorane. Grignard compounds and oxovinylidenetriphenylphosphorane yield addition compounds from which, on subsequent hydrolysis, acyl ylides are formed (equation 111).[219,220]


(111)

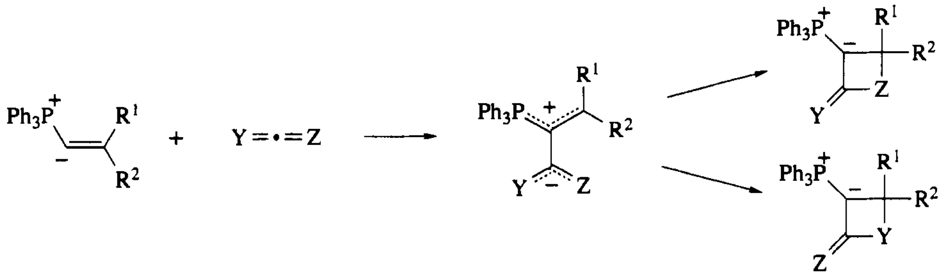
(ii) By cycloaddition reactions

A variety of compounds may undergo cycloaddition at the C═C bond of vinylidenephosphoranes yielding exocyclic ylides.[204,221] [2 + 2] Cycloadditions of *N*-phenyliminovinylidenetriphenylphosphorane to electron poor double bonds of alkenes and imines lead to the formation of four-membered ylides (equation 112).[204,221]

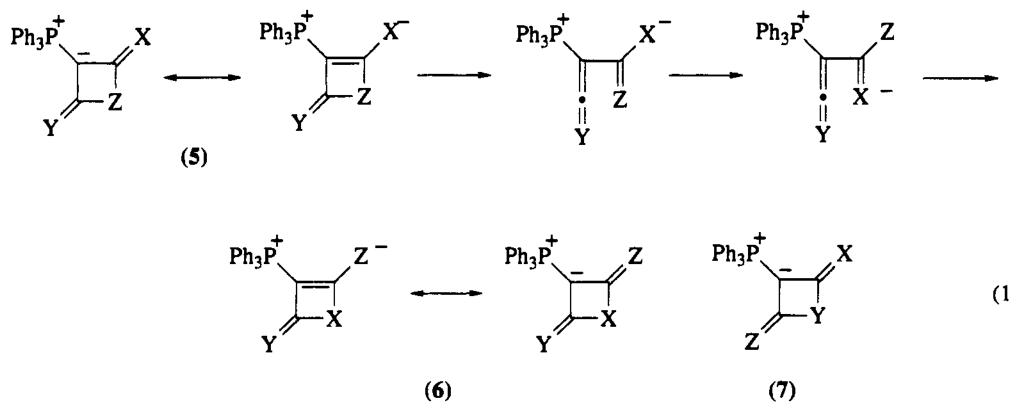

(112)

Alkynes however add to the P–C bond of vinylidenephosphoranes. The initially formed phosphacyclobutenes undergo electrocyclic ring opening to afford open chain ylides.[204,221]

Heteroallenes (*e.g.* carbon disulfide, carbon dioxide, carbon oxysulfide, isocyanates, isothiocyanates, ketenes, ketenimines) and vinylidenephosphoranes can form polar intermediates from which two isomeric products may result in a 1,4-cycloaddition (equation 113).[204,221] The direction of the ring closure depends decisively upon the nucleophilic character of Z compared with that of Y.


(113)

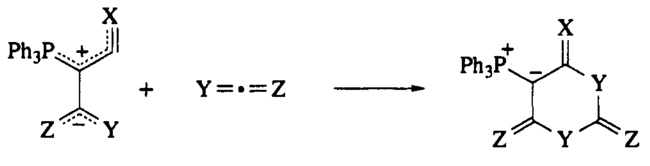
In the reaction of oxo-, thioxo- and imino-vinylidenetriphenylphosphorane the initially formed cycloadduct (5) may undergo electrocyclic ring cleavage followed by a second ring closure thus affording the rearranged isomer (6). The overall reaction sequence amounts to exchange of the exocyclic substituent X with the ring member Z. The isomer (7) may rearrange analogously. In one case cycloreversion of the four-membered ring occurred (see preparation of thioxovinylidenetriphenylphosphorane).



(5) (6) (7)

(114)

Sometimes [4 + 2] cycloaddition of the dipolar 1:1 intermediate with a second molecule of heteroallene proceeds faster than the 1,4-cyclization, thus leading to six-membered rings (equation 115). Obviously this type of reaction especially occurs if the lifetime of the dipolar intermediate is sufficiently long owing to stabilization of the positive charge. While phenyliminovinylidenetriphenylphosphorane reacts with heteroallenes only in the molar ratio 1:1 the corresponding oxo, thioxo and diethoxy compounds can react both in 1:1 and 1:2 ratio.

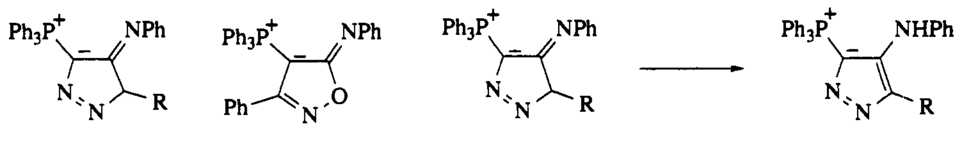


(115)

Diethoxy- and bis(ethylthio)-vinylidenetriphenylphosphorane differ in some instances in their behavior towards heteroallenes from the other vinylidenephosphoranes. The dipolar 1:1 intermediates from diethoxyvinylidenephosphorane and carbon dioxide or carbon disulfide stabilize by migration of an ethyl group to the negative substituent (*cf.* equation 113, R^1, R^2 = OEt; Y, Z = O or S); on the other hand the 1:2 adducts from the bis(ethylthio) ylide and isocyanates or isothiocyanates do not form six-membered but five-membered rings, which lose triphenylphosphine and hence yield no ylides.[222]

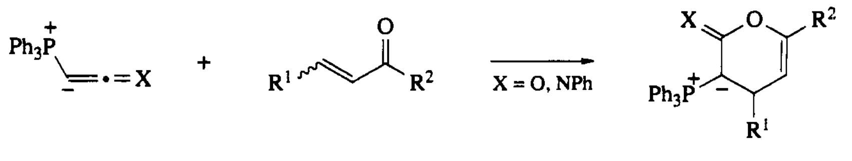
The [2 + 2] cycloaddition and the [4 + 2] addition of vinylidenephosphorane with heteroallenes have been applied to the synthesis of a great variety of four- and six-membered heterocyclic compounds carrying an exocyclic ylide function.[204,221,223]

1,3-Dipolar compounds (*e.g.* azides, nitriloxides and diazo compounds) add to the C=C bond of vinylidenephosphorane, affording five-membered ylidic heterocycles, *e.g.* those based on the 1,2,3-triazole, 1,2-oxazole and pyrazole skeleton from the reactions with *N*-phenyliminovinylidenetriphenylphosphorane (equation 116).



(116)

[4 + 2] Cycloaddition of α,β-unsaturated ketones, acyl ketenes, acyl, thioacyl, imidoyl and vinyl isocyanates, as well as the corresponding isothiocyanates, to the C=C bond of vinylidenephosphoranes leads to the formation of six-membered heterocycles carrying an exocyclic ylide function (*e.g.* equation 117).[204,212,224] In some instances the mentioned thioisocyanates, however, may undergo [2 + 2] cycloaddition at the C=S bond. Interestingly *N*-aryliminovinylidenetriphenylphosphoranes dimerize in a [4 + 2] cycloaddition on heating alone.[225]



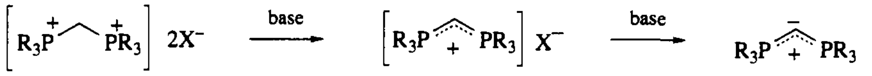
(117)

1.6.2 CUMULATED PHOSPHORANES

1.6.2.1 Carbodiphosphoranes

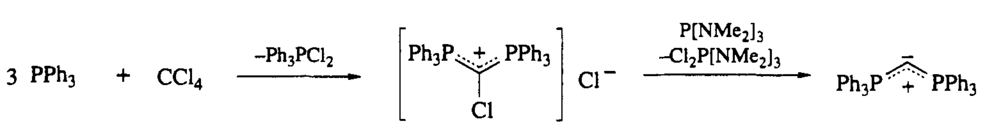
Carbodiphosphoranes (bistriorgano)phosphoranylidenemethanes, hexaorganocarbodiphosphoranes) may be generated from suitable phosphonium salt precursors by dehydrohalogenation or dehalogenation.[226] Since the first synthesis of hexaphenylcarbodiphosphorane, a series of symmetrical, unsymmetrical, mixed alkyl/phenyl, cyclic and difunctional carbodiphosphoranes have been prepared. Compounds synthesized until 1984 have been listed.[227]

Stepwise deprotonation of methylenebis(triorgano)phosphonium salts with bases yields carbodiphosphoranes *via* intermediate semi-ylide salts, which may also be accessible by alkylation or phosphinolation of corresponding alkylidenephosphoranes (equation 118).[226–228] It depends on the starting phosphonium salt and the base whether the intermediate ylide salts can be isolated or not. Suitable bases are sodium amide, alkali metal hydrides, alkylidenetrialkylphosphoranes, potassium and lithium organyls. For the synthesis of hexaphenylcarbodiphosphorane improved methods have been reported by which this compound may be generated without isolation of the ylide salt and on a large scale.[201,229]



(118)

Hexaphenylcarbodiphosphorane and other carbodiphosphoranes are also available by dechlorination of phosphonium salts (*e.g.* equation 119).[198,226]



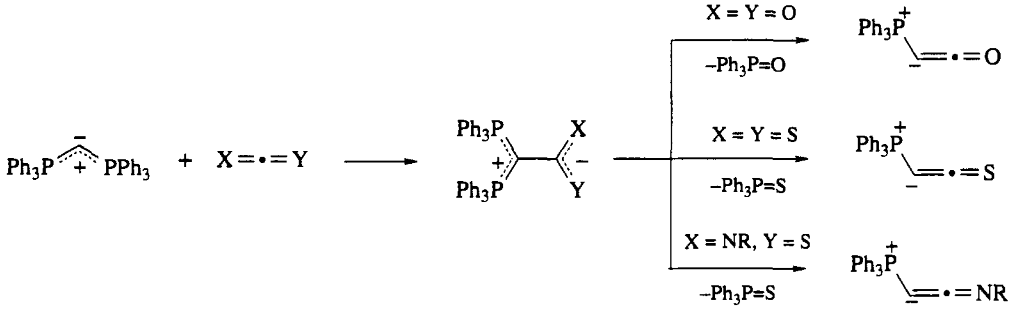
(119)

Hexaphenylcarbodiphosphorane may be stored as a stable adduct formed with sulfur or trimethylchlorosilane, from which it may be regenerated with triethylphosphine or by thermolysis, respectively.[201,202]

As a consequence of their astonishingly high tendency of formation carbodiphosphoranes spontaneously result in some instances from other bisylide precursors by skeletal rearrangement.[227,230] The stability of carbodiphosphoranes is markedly influenced by the nature of the substituents attached to the phosphorus and in the case of cyclic species also in particular by ring strain. As a consequence of these facts carbanion-stabilizing substituents and ring strain effects may cause prototropic rearrangements to afford conjugated isomeric double ylides.[199,231–234]

1.6.2.2 Vinylidenephosphoranes

Hexaphenylcarbodiphosphorane reacts with carbon dioxide, carbon disulfide and isothiocyanates to give betaines whose thermolysis affords oxovinylidene-, thioxovinylidene- and iminovinylidene-triphenylphosphoranes (equation 120).[204,235] The corresponding 2,2-di(trifluoromethyl) compound is obtained when the 1,2-oxaphosphetane resulting from hexaphenylcarbodiphosphorane and hexafluoroacetone (equation 121) is heated.



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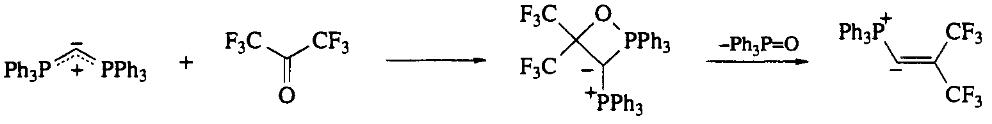
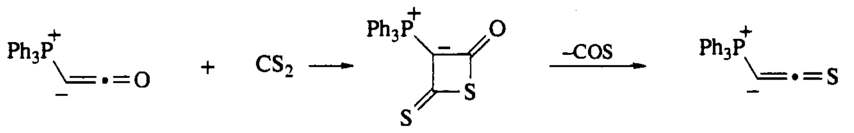
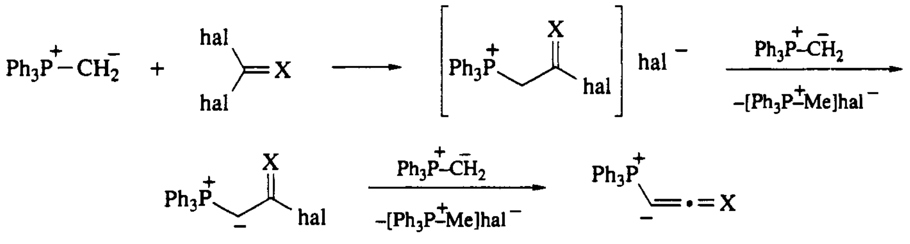

(121)

Thioxovinylidenetriphenylphosphorane is formed when the cycloaddition compound from oxovinylidenetriphenylphosphorane and carbon disulfide decomposes in a cycloreversion (equation 122).[204,235]

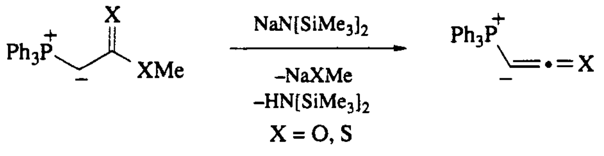

(122)

Methylenetriphenylphosphorane reacts with geminal dihalo compounds (isocyanide dichlorides, thiophosgene and 1,1-dihalo-1-alkenes) in the molar ratio 3:1. The initially formed phosphonium salt undergoes transylidation affording the conjugated ylide from which a third molecule of methylenetriphenylphosphorane removes hydrogen halide thus leading to thioxovinylidene-, iminovinylidene- and 1,2-alkadienylidene-phosphoranes, respectively (equation 123).[204,235] The reaction with 1,1-dihalo-1-alkenes requires electron-accepting substituents R^1 and R^2. The method is not suitable for the synthesis of oxovinylidenetriphenylphosphorane starting from phosgene. Attempts to generate cumulated species $R_3P{=}C{=}SiR_2$ by dehydrohalogenation of the corresponding β-halogenated ylide precursor were not successful.[67i]


(123)

X = S, NR, CR^{1}R^2; hal = Cl, Br

Reaction of sodium bis(trimethylsilyl)amide with methoxycarbonylmethylenetriphenylphosphorane or its dithio analog leads to β-elimination and formation of oxovinylidene- and thioxovinylidene-triphenylphosphorane, respectively (equation 124).[204,235] The analogous reaction of sodium bis(trimethylsilyl)amide with 2-ethoxyallylidenetriphenylphosphoranes resulting from 2,2-diethoxyvinylidenetriphenylphosphorane and CH acids gives rise to the formation of stable propadienylidenephosphoranes (equation 125).[235]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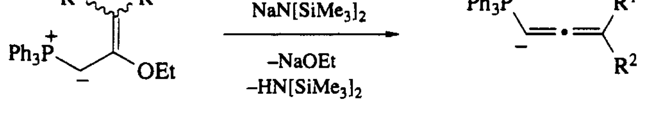
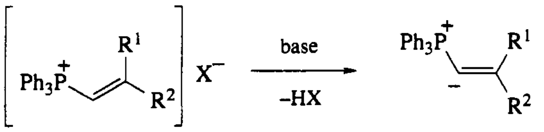

(125)

Finally vinylidenephosphoranes are accessible by α-deprotonation of vinylphosphonium salts with suitable bases, *e.g.* sodium amide, sodium ethoxide or sodium bis(trimethylsilyl)amide (equation 126).[169,204,235]



(126)

a, $R^1 = R^2 = OEt$; b, $R^1 = H$, $R^2 = OEt$; c, $R^1 = S$-alkyl, $R^2 = S$-alkyl; d, $R^1 = H$, $R^2 = NMe_2$

Propadienylidenephosphoranes have been generated by dehydrohalogenation of 2-halogeno-2-propenyl and propargyl phosphonium salts.[235,236]

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1.7

Synthesis of Halides

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Schering AG, Berlin, Germany

1.7.1 NUCLEOPHILIC HALOGENATION

The formation of halides by the nucleophilic substitution of leaving groups is commonly used in the synthesis of more elaborate structures. The synthesis of inexpensive bulk chemicals like solvents, however, is mostly done by oxidation or addition reactions. Halides are either used as intermediates or are valuable end products. Authors of publications, especially patent literature, often claim one reaction for three or even four halogens. In practice, this rarely holds true and each of the halogens quite often requires different conditions. The usual order of halide nucleophilicity is $I^- > Br^- > Cl^- > F^-$. In dimethylformamide the reverse order $Cl^- > Br^- > I^-$ is observed.[1] This order goes along with the order of the basic strength of the halogens. Thus in some cases the choice of the proper solvent will be the answer to a synthetic problem.

The following chapter deals with the individual halogens separately. A recent survey of the most important methods of preparation of halogen compounds[2] organizes the material in a similar way. This former review also includes tables[3] correlating halogenating agents with the starting materials and halogenated products.

The development in the field of halogenation is not very rapid. Consequently the now almost 30 years old, thoroughly written Volumes 5/3[4] and 5/4[5] of *Houben–Weyl* are still very useful. Fluorination procedures in organic chemistry are developing considerably faster and the field has been reviewed more recently.[6,7]

1.7.2 CHLORINATION

The C—Cl bond is less stable than the C—F bond but more stable than the C—Br and the C—I bonds. This means that chlorinated products normally do not suffer from the often undesired instability of bromides or iodides. On the other hand, more severe conditions are normally required to transform the C—Cl bond later in the synthesis when the chloride is not the desired final functionality. If this is no problem, the chloride is the first choice intermediate functionality because chlorine is by far the least expensive and most ready available of all halogens.

1.7.2.1 Chlorination of Alkyl Alcohols

The displacement of hydroxy groups by chlorine is of great importance in synthesis.[8] The reaction of hydrochloric acid with tertiary alkyl alcohols proceeds at room temperature within minutes,[9] while secondary alcohols react more slowly and primary alcohols are the least reactive (Scheme 1). A catalyst, usually zinc chloride[10] or phase transfer conditions,[11] is required if the reaction is too slow. Alternatively the use of HMPA as solvent gives good yields of primary halides.[12] Primary alcohols undergo mainly S_N2 and tertiary undergo mainly S_N1 reactions. The formation of rearrangement and elimination products is a drawback of this reaction. In addition to that problem, chiral alcohols give different degrees of racemization (S_N1), inversion (S_N2) or retention of configuration. For these and other reasons inorganic acid chlorides like $SOCl_2$, PCl_3, PCl_5 and Ph_3PCl_2 are often employed, as rearrangement products with these reagents are formed only to a small extent.

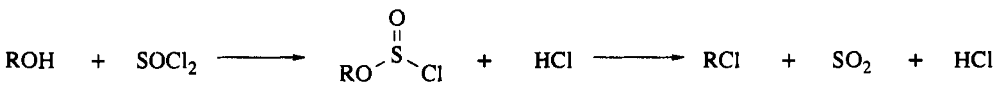
$$\mathrm{ROH} + \mathrm{HCl} \longrightarrow \mathrm{RCl}$$

R = primary
secondary ↓ increasing rate of reaction
tertiary

Scheme 1

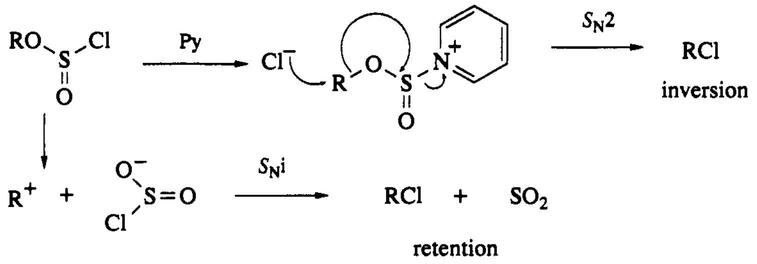
$SOCl_2$ is used extensively in the preparation of chlorides (Scheme 2)[13] although this reaction can give a variety of by-products.[14] Yields are typically in the 70–90% range. In the absence of base retention of configuration is the rule (Scheme 3). This has been explained by an S_N1 mechanism or by participation of the solvent.[15] The fact that the secondary chlorosulfite (**1**) gives, on heating, the tertiary chloride (**3**), indicates that an intramolecular single step mechanism is ruled out and an ion pair (**2**) may be involved (Scheme 4).[16] If the reaction is done in the presence of one equivalent of pyridine, inversion (S_N2) is likely to occur.[17,18]

$SOCl_2$, like PCl_3, still can give products of rearrangement,[19] especially with allylic alcohols. Less rearrangement is observed if DMF[20–23] or HMPA[19] is added. DMF and $SOCl_2$ give the Zollinger reagent (**4**), as in equation (1). Reaction of tertiary alcohols with PCl_5 under mild conditions as in equation (2) is a good special method for the synthesis of tertiary chlorides with retention of configuration.[24]

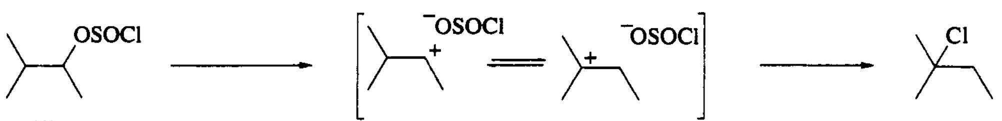


$$\mathrm{ROH} + \mathrm{SOCl_2} \longrightarrow \mathrm{RO{-}S(=O){-}Cl} + \mathrm{HCl} \longrightarrow \mathrm{RCl} + \mathrm{SO_2} + \mathrm{HCl}$$

Scheme 2



Scheme 3



(1) (2) (3)

Scheme 4

(4) (1)

$$ROH + PCl_5 \longrightarrow RCl + POCl_3 + HCl \qquad (2)$$

For other phosphorus reagents good yields, less rearrangement or both are claimed. The reaction of neopentyl alcohol with Ph_3PCl_2 gives 92% yield (Scheme 5).[25,26] The use of oxyphosphonium[27] and phosphorus(III)[28] reagents for the replacement of alcoholic hydroxy groups has been reviewed. The system $Ph_3P–CCl_4$ (Scheme 6)[29–31] allows the transformation of labile alcohols like geraniol, lincomycines or sugars. Addition of imidazole to Ph_3PCl_2 and to the $Ph_3P–CCl_4$ system improves the selectivity and reactivity, respectively.[32] With this technique primary hydroxy groups in carbohydrates are selectively substituted, as exemplified in equation (3). Ph_3P–hexachloroacetone is another reagent for the formation of chlorides in high yields, with no rearrangement.[33]

$$R_3P + Cl_2 \longrightarrow R_3PCl_2 \xrightarrow{R'OH} R'Cl + HCl + R_3PO$$

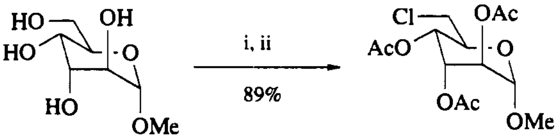
R = Ph, R' = neopentyl; 92%

Scheme 5

$$Ph_3P + CCl_4 \longrightarrow Ph_3\overset{+}{P}Cl\ ^{-}CCl_3 \xrightarrow{ROH}$$

$$HCCl_3 + Ph_3\overset{+}{P}OR\ Cl^{-} \longrightarrow RCl + Ph_3PO$$

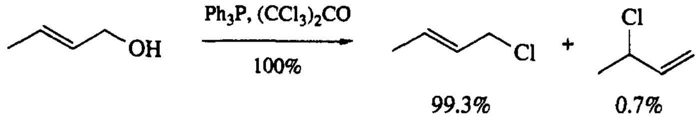
Scheme 6



(3)

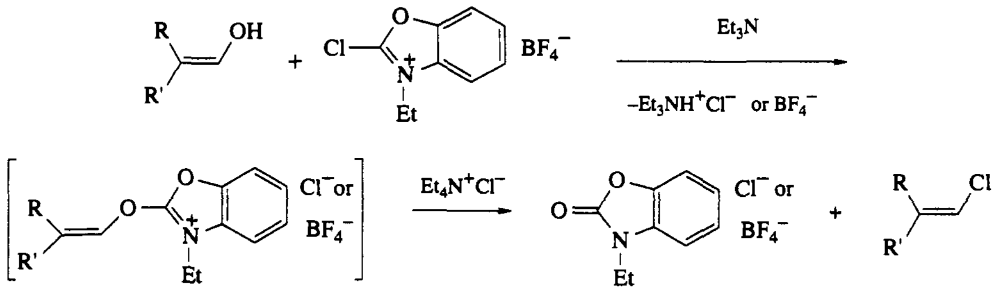
i, Ph_3PCl_2, imidazole; ii, Ac_2O, pyridine

The conversion of allylic alcohols into chlorides is complicated by the competition of S_N2 and S_N2' reactions (equation 4). $SOCl_2$ and PCl_3 give mainly S_N2' reactions.[34] With $Ph_3P–CCl_4$[35] or $MeSO_2Cl/LiCl$[36] mainly normal S_N2 products are formed.



(4)

Alkyl alcohols[37] or enolizable aldehydes are converted in a stereospecific manner to alkyl chlorides or vinyl chlorides in good yields on treatment with a Mukaiyama-type chlorobenzoxazolium salt (Scheme 7).[38] The very good activation of hydroxy groups by the Mitsunobu procedure may be useful in some difficult cases (Scheme 8).[39–42]



Scheme 7

$$\mathrm{ROH} \xrightarrow{\text{i, ii}} \mathrm{RCl}$$

i, $EtO_2CN{=}NCO_2Et$, Ph_3P; ii, Cl^-

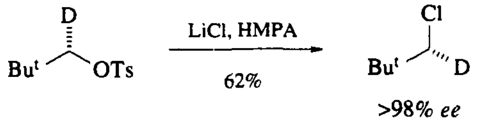
Scheme 8

The leaving group is not OH^- but H_2O or OR^-. It is a common feature of all the above reactions that the activated species is not isolated. Chlorination of isolated activated alcohols is the subject of the next section.

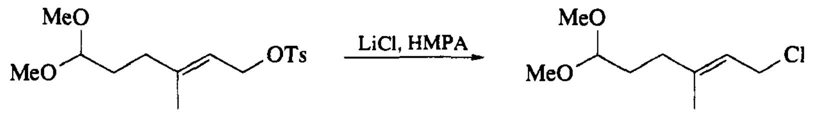
1.7.2.2 Chlorination of Alkyl Alcohol Derivatives

OH^- is not a satisfactory leaving group. A sufficient activation is needed to allow nucleophilic displacements. Tosylates, mesylates, triflates, sulfates and other esters of sulfuric and sulfonic acids are suitable leaving groups for this purpose. They are generally easy to make and stable enough for isolation or purification. Isolation of a stable intermediate often gives cleaner reactions and products.

Neopentyl tosylate reacts with LiCl in HMPA and gives the chloride with clean inversion without rearrangement (equation 5).[43] Another example of this reaction is the conversion of allylic tosylates to chlorides without rearrangement or reaction of the sensitive acetal (equation 6).[44] Dimethylaminopyridine is a useful catalyst for the transformation of hydroxy compounds to chlorides with tosyl chloride.[45]

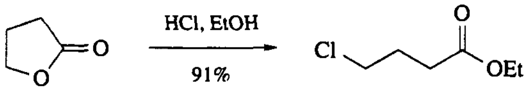


(5)



(6)

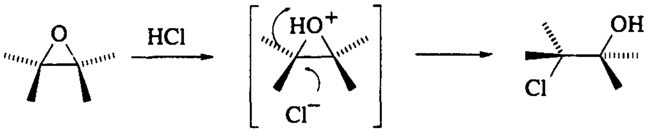
The opening of γ-lactones with alcoholic hydrogen chloride (equation 7) is a useful example of the otherwise rare cleavage of carboxylic esters to alkyl chlorides.[46]



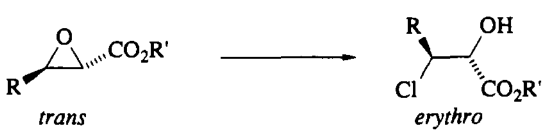
(7)

1.7.2.3 Chlorination of Epoxides

The cleavage of dialkyl ethers with hydrogen chloride is rarely successful. A special case is the cleavage of epoxides (Scheme 9), which, due to ring strain, are much more reactive than open chain or larger ring ethers. The mechanism is S_N2. This results in formation of a *threo*-chlorohydrin from a *cis*-epoxide and an *erythro* product from a *trans*-epoxide. The regioselectivity of the reaction is satisfactory if one of the two carbon centers can stabilize a positive charge better than the other. An example for good regioselectivity is the opening of epoxy esters (Scheme 10). In the absence of strong electronic effects, hard to predict mixtures of the two possible chlorohydrins are formed.

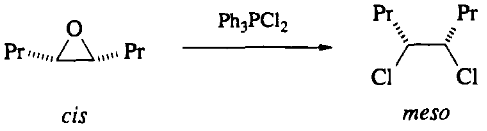


Scheme 9



Scheme 10

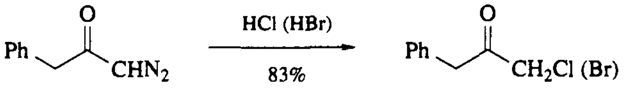
The conversion of epoxides to vicinal dichlorides has been done with $SOCl_2$ and pyridine,[47] $Ph_3P–CCl_4$[48] or Ph_3PCl_2.[49] Symmetric *cis*-epoxides give *meso*-dichlorides (equation 8), and the corresponding *trans*-epoxides give D,L-dichlorides. This is a two-step mechanism involving an intermediate chlorohydrin. Two S_N2 reactions give inversion at both carbon atoms.



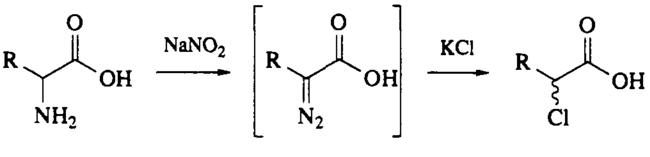
(8)

1.7.2.4 Chlorination of Diazo Ketones

Diazo ketones give α-chloro ketones on treatment with hydrogen chloride (equation 9).[50] Diazotization of α-amino acids in the presence of an excess of chloride gives α-chloro acids (Scheme 11).[51] The configurational identity of the amino acids is lost with the achiral diazo intermediate. The reaction becomes useful in cases where the amino acid is easily available and the chloride is not.



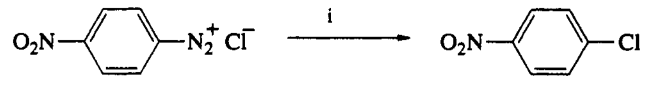
(9)



Scheme 11

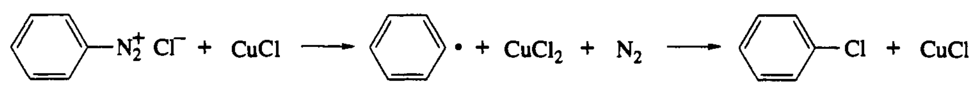
1.7.2.5 Chlorination of Diazonium Salts

Phenolic hydroxy groups undergo S_NAr reactions only if the aromatic ring is activated by electron-withdrawing substituents. The replacement of nitrogen in aromatic diazonium salts with hydrogen chloride is by far more common.[52] If the catalyst is copper(I) or copper(II) chloride it is called the Sandmeyer reaction. With copper as catalyst it is called the Gattermann reaction. The choice of catalyst and conditions influences the yields (equation 10).[53] The scope of the reaction is wide. These reactions are useful not only for the formation of aryl chlorides but also of aryl bromides (see Section 1.7.3.5). The synthesis permits the introduction of chlorine with good yields in positions where direct chlorination fails. The mechanism (Scheme 12) is believed to involve a reduction of the diazonium ion to an aryl radical by the copper(I) ion. In the next step the aryl radical reduces copper(II) chloride with aryl–chlorine bond formation.[54]



(10)

i, CuCl, acid, 60% or $CuCl_2$, neutral, 85%

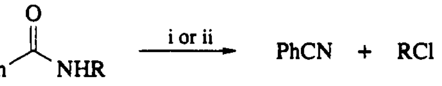


Scheme 12

The isolation of the diazonium salt is not always necessary. Several procedures allow the preparation of aryl chlorides from aromatic amines in one step.[55–57]

1.7.2.6 Other Chlorinations

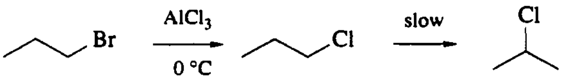
N-Alkylamides form alkyl chlorides upon treatment with PCl_5[58] or $SOCl_2$.[59] Benzamides give better results than aliphatic amides (Scheme 13), with yields sometimes in the region of 80%.



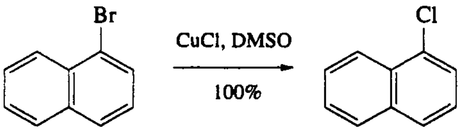
i, PCl_5; ii, $SOCl_2$

Scheme 13

The replacement of other halogens by chlorine is in most cases a devaluation of the more valuable starting material. If necessary (*e.g.* isotopic labeling), it can be done with LiCl,[60] $AlCl_3$ (equation 11)[61] or copper(I) chloride (equation 12).[62]

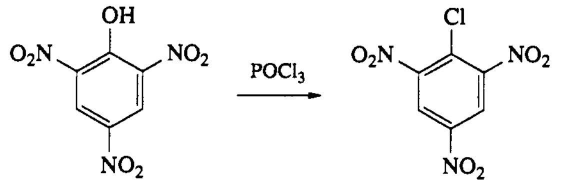


(11)



(12)

Substitution of phenolic hydroxy groups is possible if the aromatic ring is activated by electron-withdrawing substituents, as in picric acid (equation 13).[63] The intermediate pyridinium picrate reacts with $POCl_3$ in an S_NAr mode.



(13)

1.7.3 BROMINATION

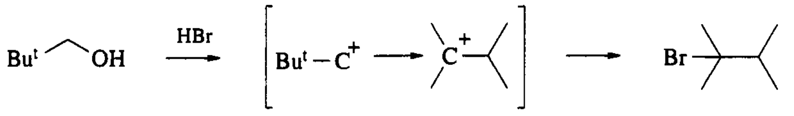
The C—Br bond is less stable than the C—Cl and C—F bonds. Only the C—I bond is weaker. Organic bromine chemistry is strongly related to organic chlorine reactions. On average brominated compounds are two orders of magnitude more reactive than the chlorinated analogs. Brominated intermediates are often not stable enough for storage or even isolation. On the other hand much milder reaction conditions are required for further transformations of the C—Br bond. In laboratory scale preparations the higher reactivity is often more important than storage or cost considerations. Moreover, smaller brominated molecules have a higher boiling temperature than the chlorinated analogs, so the former are often more easy to handle at atmospheric pressure. Distillation of the less stable bromine compounds may be more critical.

Brominated derivatives are especially useful as precursors for organometallic compounds or free radicals.

1.7.3.1 Bromination of Alkyl Alcohols

The substitution of alcoholic hydroxy groups with hydrogen bromide appears to be more common than that with hydrogen chloride.[8] Hydrogen bromide is used as a 48% aqueous solution with[64] or without[65] conc. H_2SO_4 in acetic acid,[66] or gaseous.[67]

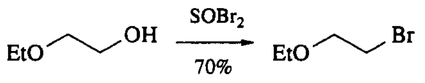
Primary alcohols prefer an S_N2 mechanism. When this mechanism is hindered by steric bulk, the Wagner–Meerwein rearrangement competes with substitution (Scheme 14). Secondary and tertiary alcohols follow an S_N1 pathway. The intermediate carbonium ion has the tendency to isomerize to a more stable cation.



Scheme 14

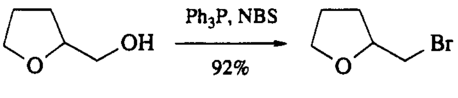
The use of PBr_3[68] avoids rearrangement to some extent, but PBr_3 is less easily available than hydrogen bromide. PBr_5 can also replace hydroxy groups with bromine. It is, however, even more expensive and difficult to handle than PBr_3.

The use of $SOBr_2$ is comparatively much less common than the use of the analog $SOCl_2$. $SOBr_2$ is expensive and less stable than $SOCl_2$, but it gives clean reactions with primary alcohols (equation 14).[69]



(14)

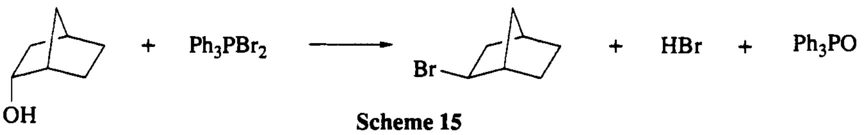
An alternative to the above-mentioned reagents is the combination of NBS or 1,3-dibromo-5,5-dimethylhydantoin with Ph_3P in DMF (equation 15).[70] In carbohydrate chemistry this reagent gives primary bromides in >70% yield.



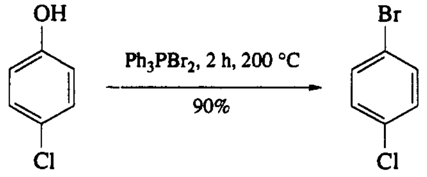
(15)

Ph_3P forms with Br_2 the very useful brominating reagent Ph_3PBr_2. This can replace aliphatic hydroxy groups without rearrangement or elimination (Scheme 15).[71] Another remarkable reaction of this reagent is the substitution of phenolic hydroxy groups, even if they are not activated (equations 16 and 17).[25,72] The high temperature required for this substitution limits the scope of this reaction, however.

$$Ph_3P + Br_2 \longrightarrow Ph_3PBr_2$$



Scheme 15



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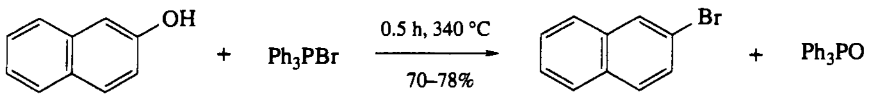
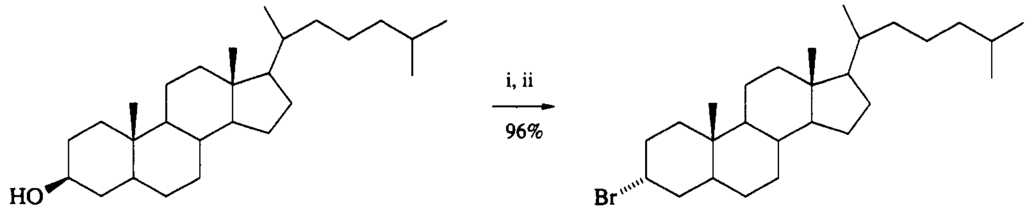


(17)

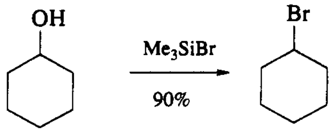
The system of Ph_3P–diethyl azodicarboxylate–hydroxy compound–LiBr allows the formation of alkyl bromides under mild conditions (equation 18).[40–42] An S_N2-type displacement of an intermediate alkoxyphosphonium species is generally assumed. Hindered alcohols such as menthol do not give bromides with the Mitsunobu procedure.



(18)

i, Ph_3P, $EtO_2CN{=}NCO_2Et$; ii, LiBr, 20 °C

Good yields of alkyl bromides result from the treatment of alcohols with Me_3SiBr (equation 19)[73] or Me_3SiCl and LiBr.[74,75]

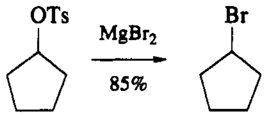


(19)

1.7.3.2 Bromination of Alkyl Alcohol Derivatives

The above-mentioned reactions for the introduction of bromine always involve an activation of the alcohol as the first step. In some cases it can be useful to isolate the activated intermediate. The reactions of alkyl mesylates or tosylates with $MgBr_2$ give alkyl bromides under mild conditions with good yields (equation 20).[76] Neopentyl tosylate with LiBr in HMPA gives neopentyl bromide in 67% yield (equation 21).[43] Complete inversion with little or no rearrangement is observed in this difficult case.

Cleavage of dialkyl ethers with Me_3SiBr is strongly catalyzed by 0.1 equiv. of IBr (equation 22).[77] This makes possible synthetic applications which were previously ruled out by low reactivity.



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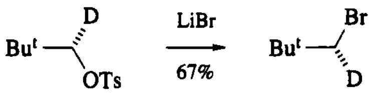

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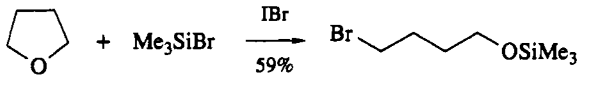
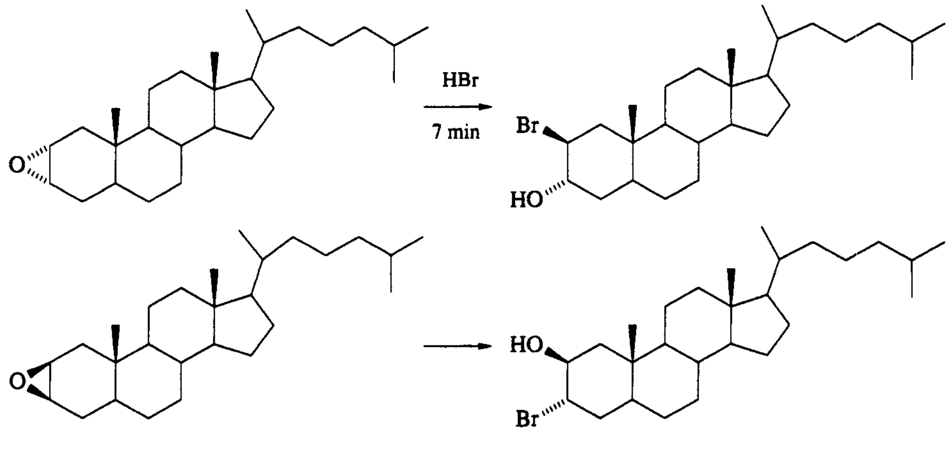


(22)

1.7.3.3 Bromination of Epoxides

The reaction of epoxides with hydrogen bromide gives bromohydrins. The mechanism is S_N2 as for the analogous chlorination (see Section 1.7.2.3). The cleavage of epoxy cholestanes with hydrogen bromide (Scheme 16) demonstrates the stereochemical features of the reaction.[78] Diaxial opening of the epoxide ring following the Fürst–Plattner rule is the preferred reaction. Bromohydrins formed this way with excellent stereospecificity can undergo further bromination to dibromides. The replacement reactions are most favored when the centers of the reaction are coplanar.



Scheme 16

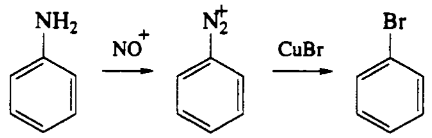
1.7.3.4 Bromination of Diazo Ketones

Diazo ketones are transformed to α-bromo ketones on treatment with hydrogen bromide (equation 9).[79]

1.7.3.5 Bromination of Diazonium Salts

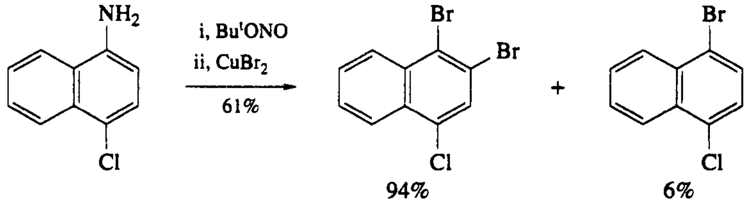
The replacement of phenolic hydroxy groups with Ph_3PBr_2 (equations 16 and 17) requires 200 °C or more (see Section 1.7.3.1). The transformation of anilines to bromides *via* diazonium salts is a much more general reaction.[52] Copper(I) or copper(II) bromide is the catalyst in case of the Sandmeyer reaction. If copper is used, the reaction is called the Gattermann reaction. These reactions are also known with the analogous chlorine reagents (see Section 1.7.2.5). Yields are in the 90% range and the scope of the reaction is wide. The mechanism is believed to be analogous to the formation of chlorides (Scheme 17).[54]

Isolation of the intermediate diazonium salt can be avoided in many cases. Treatment with *t*-butyl nitrite followed by $CuBr_2$ can give oxidative bromination in addition to replacement of the diazo group



Scheme 17

(equations 23 and 24).[57,80] Several other procedures have been described for the preparation of aryl bromides from aromatic amines in one step.[55]



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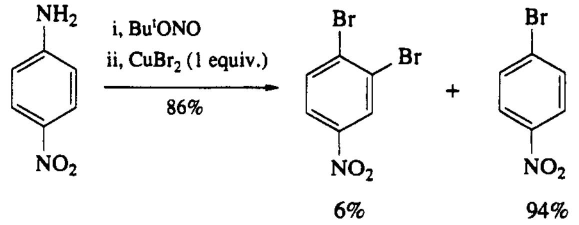


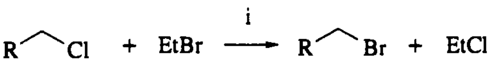
(24)

1.7.3.6 Other Brominations

Brominated compounds are more reactive than the analogous chlorinated compounds. Accordingly it is sometimes necessary to exchange chlorine for bromine. This can be achieved by an equilibrium process, called the Finkelstein reaction, if it is possible to shift the equilibrium to the brominated product (Scheme 18). Primary alkyl chlorides react with ethyl bromide in the presence of *N*-methyl-2-pyrrolidone and metal bromides to give alkyl bromides (Scheme 19).[81] Alkyl iodides do not exchange with HBr under normal conditions. The equilibrium is pushed to the alkyl bromide if I^- is selectively removed from the reaction by oxidation with HNO_3 to I_2 (Scheme 20).[82] An equimolar mixture of HCl and HBr in the presence of HNO_3 gives the alkyl bromide as the major product.

$$\mathrm{RCl} + \mathrm{Br}^- \rightleftharpoons \mathrm{RBr} + \mathrm{Cl}^-$$

Scheme 18



i, *N*-methyl-2-pyrrolidone, MBr

Scheme 19

$$\mathrm{RI} + \mathrm{Br}^- \rightleftharpoons \mathrm{RBr} + \mathrm{I}^-$$

$$\mathrm{HNO_3} + \mathrm{I}^- \longrightarrow 0.5\,\mathrm{I_2}$$

Scheme 20

Tertiary amines are cleaved with BrCN to give an alkyl bromide and a disubstituted cyanamide (Scheme 21). This process is called the von Braun reaction. Many examples have been reviewed.[58,83] Tertiary amines with different R groups cleave so that the most reactive alkyl bromide is formed. Benzyl and allyl cleave better than alkyl, lower alkyl cleaves better than higher alkyl and aryl is not cleaved at all. The mechanism involves an intermediate *N*-cyanoammonium species, which is substituted by bromide anions (Scheme 22).[84]

$$R_2NR' + BrCN \longrightarrow R'Br + R_2NCN$$

Scheme 21

$$R_3N + BrCN \longrightarrow [Br^- + R_3\overset{+}{N}CN] \longrightarrow RBr + R_2NCN$$

Scheme 22

1.7.4 IODINATION

The C—I bond is very unstable and more reactive than C—Br, C—Cl and C—F bonds. Iodine is the most expensive of the common halogens and is much less frequently used in synthesis than bromine, chlorine or fluorine. Organometallic reactions proceed with iodinated aliphatic or aromatic compounds more easily than with the other halogens. Noble metal catalysis with palladium complexes is most effective with iodinated compounds. A useful synthetic procedure is the facile reduction of iodinated derivatives under mild conditions. Replacement of iodine by hydrogen at an sp^3 carbon is an exothermic reaction with $\Delta H = -25$ kJ mol^{-1}.

Selective reactions of iodide are possible in the presence of other functional groups, including other halides.

1.7.4.1 Iodination of Alkyl Alcohols

Alcohols are converted to iodides with HI in good to high yields (Scheme 23).[8] HI is often prepared *in situ* from potassium iodide and phosphoric acid.[85] The substitution reaction competes with reduction of the alkyl iodide to the alkane.[86] Another problem, namely rearrangement, is common to all acid-catalyzed reactions of alcohols; HI is no exception to this rule.

$$ROH \xrightarrow{HI} RI$$

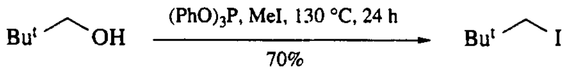
Scheme 23

A method to avoid unwanted rearrangements involves the use of PI_3, which is normally generated from white or red phosphorus and I_2 (Scheme 24).[87] This method also suffers from the reducing power of iodide as an alternative pathway.

$$ROH \xrightarrow{\text{red P, } I_2} RI$$

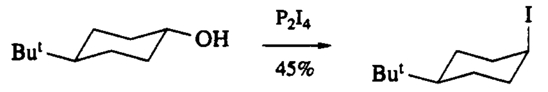
Scheme 24

Phosphite diiodide converts alcohols to iodides.[88] This reagent has been used much less often than the corresponding dibromides or dichlorides. Phosphite methiodides give better yields of iodides in the reaction with primary, secondary and tertiary alcohols and are simple to use.[89] Neopentyl iodide is isolated in 70% yield from the reaction of triphenyl phosphite, neopentyl alcohol and methyl iodide (equation 25). This reaction is remarkable considering the severe steric bulk of the neopentyl group which often makes rearrangement become the major process.



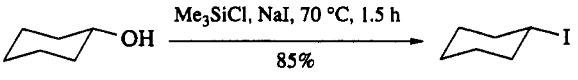
(25)

Diphosphorus tetraiodide is a valuable reagent for the regioselective synthesis of iodoalkanes from alcohols. The reaction occurs stereoselectively in the case of secondary alcohols (equation 26).[90]



(26)

Trimethylsilyl iodide converts alcohols to iodides.[91] The disadvantage of this method is the expensive reagent, which is avoided if trimethylsilyl chloride and sodium iodide are used instead (equation 27).[92,93] Trimethylsilyl polyphosphate (PPSE), which is prepared from hexamethyldisiloxane and phosphorus pentoxide, also activates alcoholic hydroxy groups for substitutions with iodide anions (equation 28).[94]



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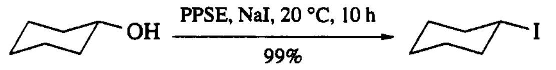
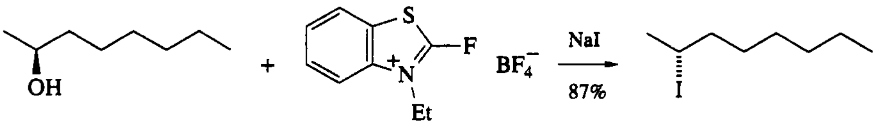


(28)

Activation of alcohols with fluorobenzothiazolium[95] or fluoropyridinium salts,[96] as well as with carbodiimidinium iodide,[97] allows the nucleophilic substitution with iodide to occur under mild conditions with inversion of configuration (equation 29).

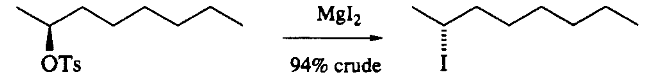


(29)

1.7.4.2 Iodination of Alkyl Alcohol Derivatives

Iodide is a very effective nucleophile, although it is still not able to substitute the hydroxy group without activation. The activated intermediates are not isolated in most cases. The iodinated products, however, suffer sometimes from a low stability which limits the period of storage. In such and other cases it may be best to use activated derivatives of alcohols as the stable intermediate.

A general method for the synthesis of alkyl iodides is the reaction of tosylates or methanesulfonates with sodium iodide in acetone or magnesium iodide in diethyl ether (equation 30).[98] The reaction is not always a clean S_N2 process. Stereoselectively deuterated neopentyl tosylate, for example, gives with NaI in HMPA only low yields (34%) of the racemic iodide (equation 31).[43] This is in contrast to analogous reactions with bromide and chloride (see Sections 1.7.3.2 and 1.7.2.2), where better yields with complete inversion are observed.



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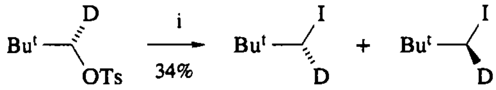


50% 50%

i, NaI, HMPA, 100 °C, 4 h, 80% conversion

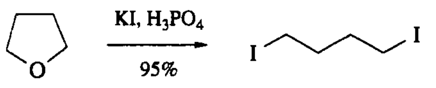
(31)

1.7.4.3 Iodination of Ethers and Epoxides

Ethers are cleaved by HI faster than by HBr and HCl (Scheme 25). To prevent the undesirable reducing action of the reagent, KI and phosphoric or polyphosphoric acid are used to generate HI *in situ* (equation 32).[99,100] The ether bond is also cleaved by trimethylsilyl iodide (equation 33).[74]

$$\text{ROR}' + \text{HI} \longrightarrow \text{RI} + \text{R}'\text{OH}$$

Scheme 25



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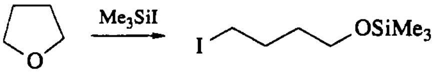
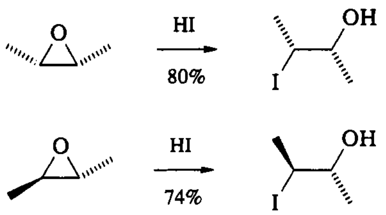
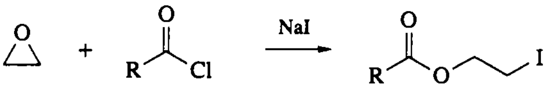


(33)

The release of ring strain in epoxides is probably responsible for the high reactivity of these special ethers. HI opens epoxides under mild conditions stereospecifically to iodohydrins (Scheme 26).[101] The mechanism is similar to the reaction of bromide with epoxides (see Section 1.7.3.3). It should be noted, however, that reduction of epoxides to alkenes may occur if vicinal diiodides are intermediately formed, which can lose I_2 under the reaction conditions. With the combination of acyl chloride and NaI unstable diiodides are avoided and 2-iodoethyl esters are formed from oxiranes (Scheme 27).[102]



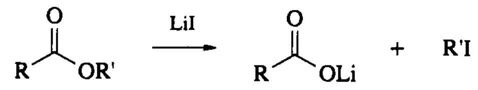
Scheme 26



Scheme 27

1.7.4.4 Iodination of Carboxylic Esters

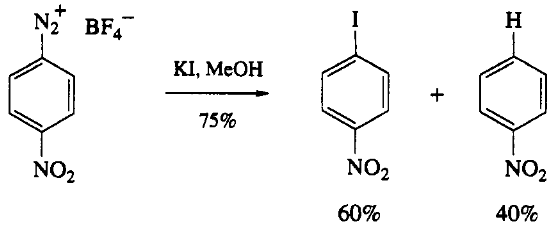
LiI in boiling pyridine or other weak nucleophilic bases can cleave alkyl esters to alkyl iodides and lithium carboxylates (Scheme 28). The reaction is mainly used for mild, aprotic cleavage of esters to carboxylates. The high degree of dissociation for LiI and the nucleophilic strength of the iodide ion explain the reaction with esters, which is not useful with the other halides. Trimethylchlorosilane and sodium iodide also give alkyl iodides from esters.[93]



Scheme 28

1.7.4.5 Iodination of Diazonium Salts

The transformation of aryl diazonium salts by aryl iodides does not require catalysis by copper or its salts (see Sections 1.7.2.5 and 1.7.3.5). A drawback is unwanted reduction with removal of functionality (equation 34).[103] Diazo ketones are reduced to ketones with HI and do not give halogenated products (Scheme 29).[104]



(34)

Scheme 29

1.7.4.6 Other Iodinations

Halide exchange from the lower halides to iodine is often desirable due to the higher reactivity of iodides in nucleophilic substitutions, reductions, organometallic or radical reactions (Scheme 30). Conversion of chlorides and bromides to iodides with sodium iodide in acetone is called the Finkelstein reaction. This halide exchange is an equilibrium process, which is shifted to the iodinated products due to precipitation of the less soluble sodium bromide or chloride from acetone. Best results are obtained when the reaction mixture is free of water.

$$RX \xrightarrow{I^-} RI$$

Scheme 30

1.7.5 FLUORINATION

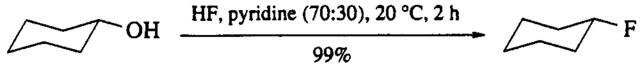
The C—F bond has a very high dissociation energy (>450 kJ mol^{-1}) and it is accordingly seldom used as an intermediate functionality. Poly- and per-fluorinated hydrocarbons are useful due to their inertness and physical properties. Monofluorinated analogs of biologically important compounds often show very different activities to the parent compounds. Fluoroacetic acid, for instance, is highly toxic with an estimated lethal dose of 2–5 mg kg^{-1} and is used as a rodenticide.[105] The discovery that fluorinated cortisol is 10 times more potent than the natural parent compound[106] came totally unexpectedly and was a contradiction to the belief that the natural hormone has the highest achievable potency. Fluorine has several interesting properties which make it a potentially useful substituent in drug molecules. The steric requirements of fluorine and hydrogen are very similar. The metabolism of fluorinated drugs is often inhibited due to the strong C—F bond. The electronegativity of fluorine compared with hydrogen may increase receptor affinity. A recent review[7] focuses on the preparation of biologically active organofluorine compounds.

Formation of the C—F bond mostly requires conditions different from all other carbon–halogen bond formations.

1.7.5.1 Fluorination of Alkyl Alcohols

Hydrogen fluoride is only of limited value for the conversion of alcohols to fluorides.[107] Anhydrous HF is a dangerous low boiling liquid (b.p. 19.5 °C), which can cause painful injuries if traces of the acid come into contact with the skin. Only tertiary and secondary alcohols give fluorides, accompanied by elimination products and ethers. Olah's reagent, a mixture of 70% HF and 30% pyridine, is much more convenient to use and often gives better yields (equation 35).[108] The reagent contains a poly(hydrogen fluoride) species, in which each fluorine atom is surrounded by four hydrogen atoms. The poly(hydrogen fluoride) is in equilibrium with some monomeric hydrogen fluoride. The reagent is stable up to 55 °C and often overcomes the need to carry out reactions with corrosive and hazardous anhydrous HF under pressure. The mechanism of the reaction is not clear. In steroid chemistry retention, inversion and scrambling of configuration is observed in related cases with tertiary alcohols (Scheme 31).[109]

SF_4 and diethylaminosulfur trifluoride (DAST) give alkyl fluorides not only from tertiary and secondary, as with HF, but also from primary alcohols (equation 36). Reactions with gaseous, corrosive SF_4 (b.p. −38 °C) usually require temperatures of 20–100 °C. The special equipment needed for reactions with toxic gases under pressure make the use of SF_4 inconvenient. The introduction of DAST has removed the handling problems. DAST is a liquid reagent made from SF_4 and trimethylsilyldiethyl-



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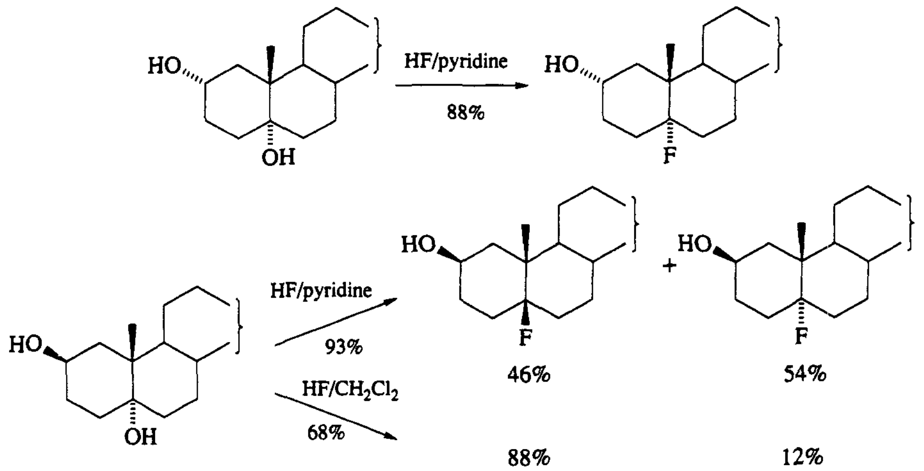
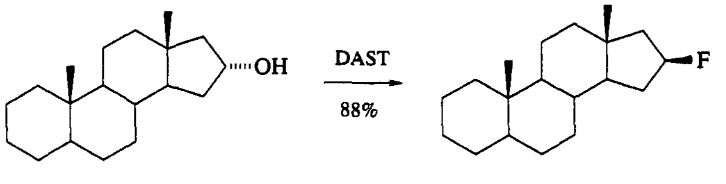


Scheme 31

amine. It gives fluoroalkanes from alcohols at lower temperatures (–50 to –78 °C) than SF_4 and is safe below 40 °C.[110] Carbenium ion type rearrangement and elimination appear less problematic with DAST than with HF reagents. The stereochemistry of the reaction, however, is still not uniform. In the absence of other directing factors an S_N2-type mechanism with inversion of configuration is often observed (equation 37).[111,112] Neighboring group participation, however, results sometimes in retention of configuration (equation 38).[111]

$$n\text{-}C_8H_{17}OH \xrightarrow[90\%]{\text{DAST, -50 °C}} n\text{-}C_8H_{17}F \qquad (36)$$



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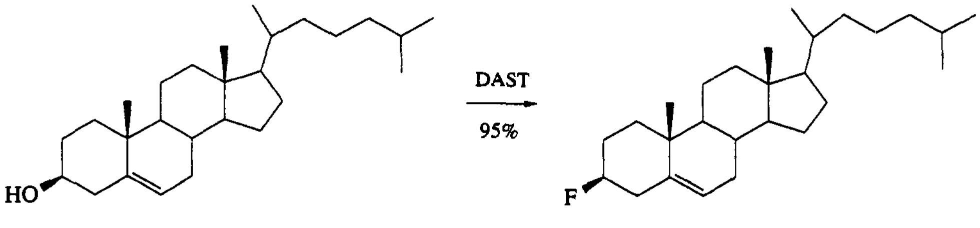
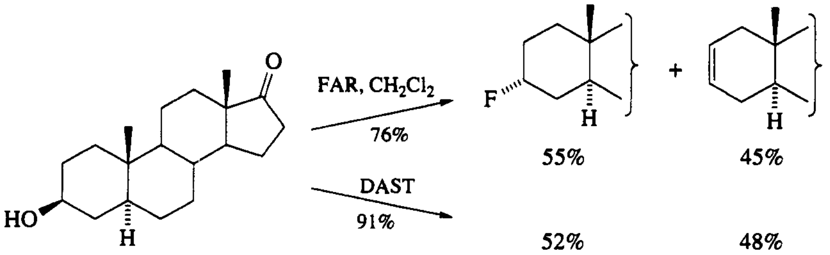


(38)

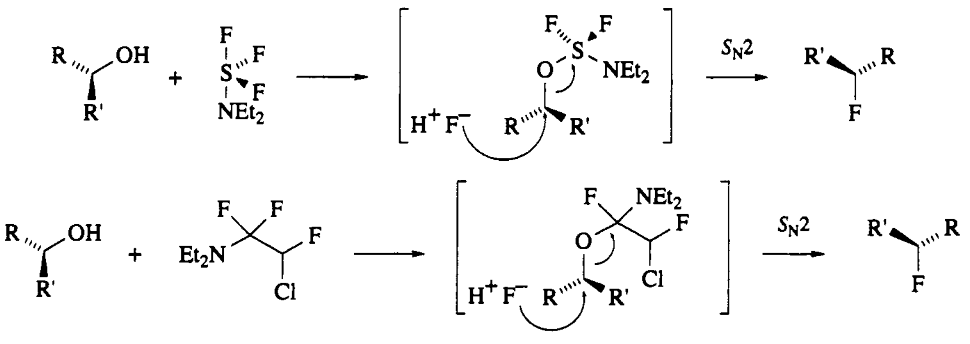
The fluoroalkylamine reagent (FAR) 2-chloro-1,1,2-trifluorotriethylamine gives alkyl fluorides from alcohols in one step and is known as the Yarovenko reagent.[113] This reagent is less reactive than DAST but was used intensively before the introduction of DAST. Rearrangement and elimination are similar with FAR and DAST (equations 39 and 40).[112,114] This may be explained by the similar mechanism. Activation of the alcohol by intermediate formation of ester-type derivatives is followed by S_N2-type displacement by fluoride ion (Scheme 32).

A related group of reagents to FAR and DAST is the phenylfluorophosphoranes. The mechanism is believed to be similar but the reactivity increases with the degree of fluorination. While the di- and trifluorophosphoranes require 150 °C for the conversion of primary alcohols to primary fluorides (equation 41),[115,116] tetrafluorophosphorane converts cholesterol to fluorocholesterin with inversion of configuration at 20 °C (equation 42).[117]



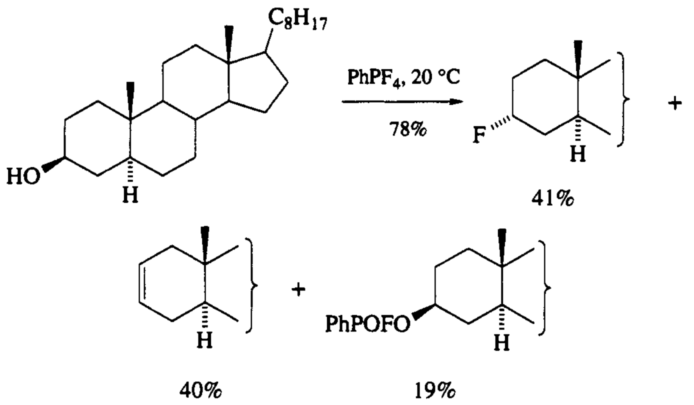
(39)

(40)



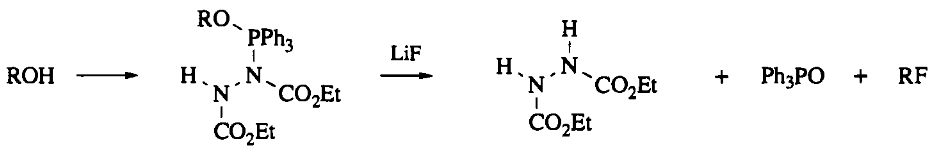
Scheme 32

$$\text{n-C}_8\text{H}_{17}\text{OH} \xrightarrow[78\%]{\text{Ph}_3\text{PF}_2,\ 150\ ^\circ\text{C}} \text{n-C}_8\text{H}_{17}\text{F} \qquad (41)$$



(42)

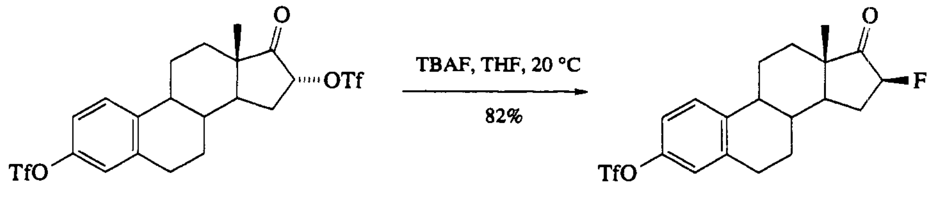
A preformed complex of diethyl azodicarboxylate/Ph_3P activates primary and secondary alcohols sufficiently for S_N2-type reactions with LiF (Scheme 33).[42] This Mitsunobu procedure is a rare example of a reaction useful with all four halogens.



Scheme 33

1.7.5.2 Fluorination of Alkyl Alcohol Derivatives

The fluoride ion is only a weak nucleophile in water, due to high solvation. Aprotic solvents, however, do not solvate fluoride as readily. Accordingly fluoride is a strong nucleophile in aprotic solvents in the absence of water. Tetrabutylammonium fluoride (TBAF) is a commercial product, which transforms triflates to fluorides with inversion of configuration (equation 43).[118] Triflates react even with the commercial TBAF, although this is not free of water. Partial removal of water from TBAF results not only in a more potent source of nucleophilic fluoride but also in a more potent base; elimination may then become the dominant reaction.[119] If complete removal of water is attempted, the strong base properties cause *E*2 elimination, which decomposes the reagent itself (Scheme 34).[120] With metal fluorides like CsF the reagent itself is perfectly stable.



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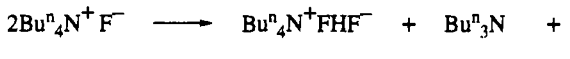
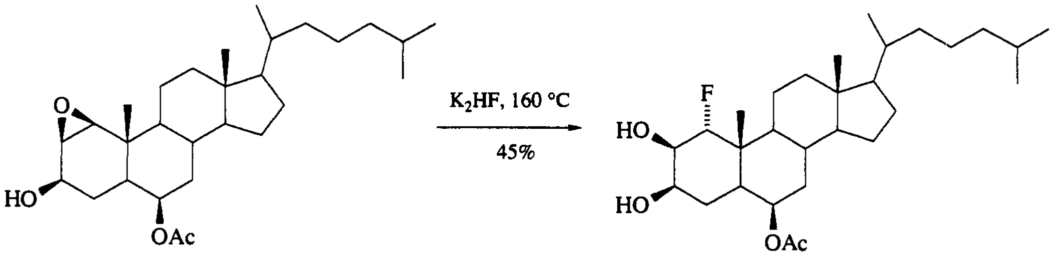


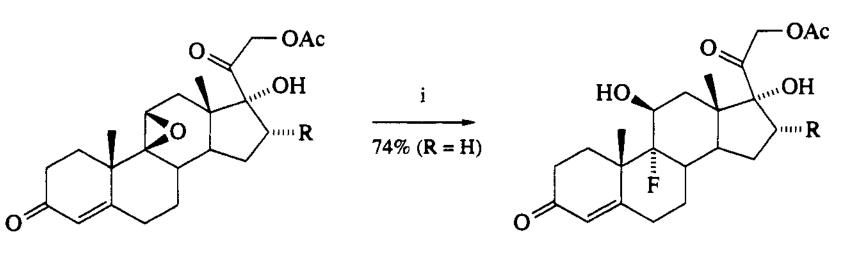
Scheme 34

1.7.5.3 Fluorination of Epoxides

Open chain ethers are not cleaved by HF or other fluoride sources. Epoxides, however, are easily opened by HF or KHF_2 to fluorohydrins. The reaction has been widely used in steroid chemistry (equation 44).[121] Dexamethasone is still a practical, important corticoid, which is synthesized on an industrial scale with the help of an epoxide-opening reaction (equation 45).[122,123] The low temperature needed for rigid steroidal epoxides and the high regio- and stereo-selectivity are remarkable. HF/pyridine is even more convenient for the opening of rigid epoxides. Side reactions often predominate with nonrigid, less reactive epoxides.[124]



(44)



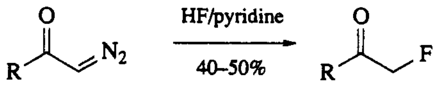
(45)

i, HF, THF/$CHCl_3$, −30 °C, 4 h

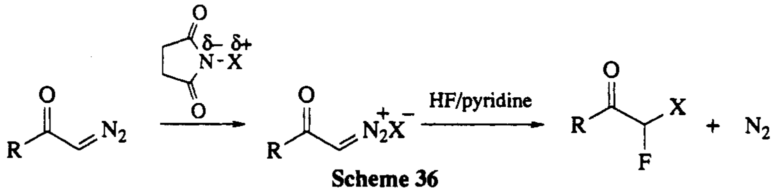
(Dexamethasone: Δ^1, R = Me)

1.7.5.4 Fluorination of Diazo Ketones

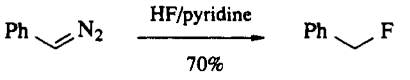
Diazo ketones react with HF/pyridine to give the corresponding fluoro ketones (Scheme 35).[108] Reactions in the presence of *N*-halosuccinimides result in the formation of geminally dihalogenated compounds. The mechanism involves initial attack by electrophilic halogen followed by nucleophilic displacement of nitrogen by fluoride ion (Scheme 36). Diazo alkanes give fluoro alkanes with HF/pyridine in good yields (equation 46).



Scheme 35



Scheme 36



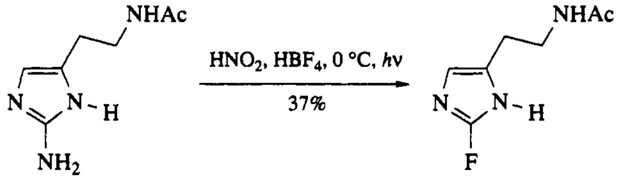
(46)

1.7.5.5 Fluorination of Diazonium Salts

Selective introduction of fluorine into an aromatic ring is often achieved by thermal decomposition of diazonium fluoroborates, which is called the Balz–Schiemann reaction (Scheme 37).[125,126] The scope of the reaction is wide and includes heterocyclic compounds (equation 47).[127] The BF_4^- salts are unusually stable for diazonium salts and yields are usually high. In some cases, however, use of PF_6^- or SbF_6^- salts gives improved yields.[128]

$$\mathrm{ArN_2{}^+BF_4{}^-} \xrightarrow{\Delta} \mathrm{ArF} + \mathrm{N_2} + \mathrm{BF_3}$$

Scheme 37

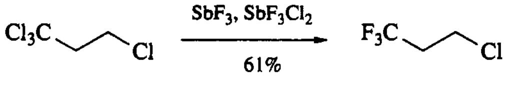


(47)

The mechanism involves a positively charged intermediate, which is attacked by BF_4^- rather than fluoride. The decomposition follows a first-order law, so it is probably of S_N1 type.[129]

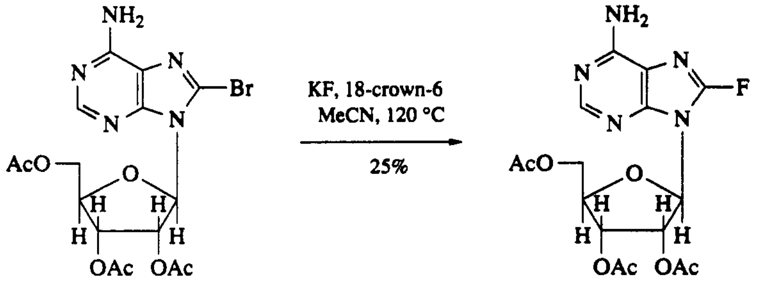
1.7.5.6 Other Fluorinations

The classical route to fluorinated organic compounds is the metathetical halogen–fluorine exchange. Polychloroalkanes are converted to polychlorofluoroalkanes with anhydrous HF. Reactions are carried out in autoclaves at temperatures of 50–150 °C in the presence of catalysts like antimony tri- or pentachloride. Chlorofluorocarbons are produced worldwide in large quantities by this method and used as refrigerants and foamers for plastics. For small scale preparations metal fluorides are more convenient to use. SbF_3 gives similar products as anhydrous HF and is activated by the addition of catalysts like chlorine, bromine or $SbCl_5$ (equation 48).[130] The replacement of halogens in polyhalogenated compounds becomes more difficult with increasing fluorination. The formation of perfluoro compounds by replacement of the last fluorine requires severe conditions.



(48)

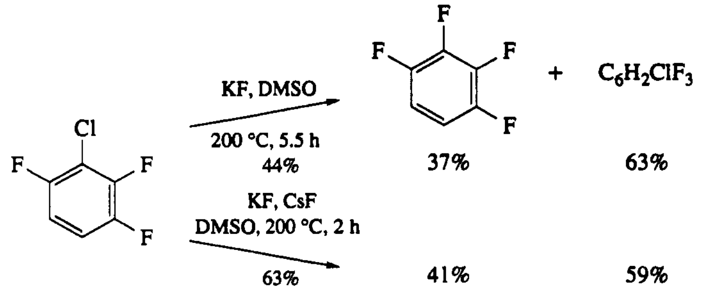
SbF_3 does not exchange single halogens at sp^3 or sp^2 carbon centers. A more general reagent for the metathetical reaction is KF. Even aromatic (equation 49)[117] or primary alkyl (equation 50)[131] halides are exchanged to fluorides if phase transfer catalysts are used.[132] The classical conditions for a similar reaction give lower yields (equation 51).[133] Addition of CsF to KF results in faster reactions with higher yields (equations 52 and 53).[134]



(49)

$$\text{n-}C_8H_{17}Cl \xrightarrow[82\%]{\text{aq. KF, }(C_{16}H_{33})Bu_3PBr\text{, 160 °C, 7 h}} \text{n-}C_8H_{17}F \qquad (50)$$

$$\text{n-}C_6H_{13}Cl \xrightarrow[54\%]{\text{KF, glycol, 180 °C}} \text{n-}C_6H_{13}F \qquad (51)$$



(52)

(53)

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1.8

Synthesis of Pseudohalides, Nitriles and Related Compounds

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1.8.1 NITRILES

1.8.1.1 Introduction

Nitriles comprise one of the classical functional groups of organic chemistry. The present review deals with useful preparative methods for the synthesis of nitriles by displacement reactions. In view of the extensive current activity in this area, it is necessary to be selective rather than comprehensive. A series of outstanding review articles[1–6] will guarantee rapid acquaintance with the field and some complementary accounts,[7,8] not repeatedly cited, inform of recent developments.

1.8.1.2 By Replacement of a Halogen Substituent

1.8.1.2.1 Alkyl halides

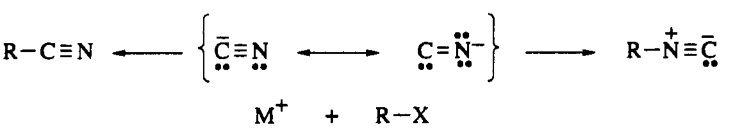
(i) General remarks

The transformation of alkyl halides with cyanides (equation 1) represents not only the 'classical' route to nitriles, but, if modified properly, is still of very great practical importance even today. A whole series of review articles[1–6] stress the scope and value of this reaction. Although the substituent 'R' may be varied to a large extent, the primary as well as the benzylic halides generally give higher yields than secondary and tertiary ones, as, with the latter, the formation of alkenes gains in importance. This side reaction as well as the undesired formation of alcohols and ethers, which sometimes takes place in aqueous media or with alcohols as solvent, is of course due to the basicity of the cyanide ion. Under deleterious conditions one may even observe carboxylic acids, which result from the hydrolysis of the nitriles.[2,9] Some of these undesired side reactions may be avoided by the use of CuCN instead of sodium or potassium cyanide.[2]

$$\mathrm{R{-}X} \;+\; \mathrm{MCN} \longrightarrow \mathrm{R{-}CN} \;+\; \mathrm{M{-}X} \qquad (1)$$

$$\mathrm{X} = \text{halogen}$$

As cyanide ions operate as ambident nucleophiles, alkylation reactions may generate isonitriles as well as nitriles (equation 2). A whole range of parameters is responsible for the outcome of reactions of this type and their particular role together with special counter influences is not easily evaluated. There is a large and growing number of papers on this topic, but one can concentrate here on a few selected review articles.[10,11] Suffice it to say that Kornblum's seminal article[12] from 1955 is still of special importance in this field. Pearson's principle of soft and hard acids and bases (HSAB) proved to be particularly helpful in the interpretation of experimental results.[11,13,14]



$$\mathrm{R{-}C{\equiv}N} \longleftarrow \left\{ \mathrm{\bar{C}{\equiv}N} \longleftrightarrow \mathrm{C{=}\ddot{N}^{-}} \right\} \longrightarrow \mathrm{R{-}\overset{+}{N}{\equiv}\bar{C}} \qquad (2)$$

$$\mathrm{M^{+}} \;+\; \mathrm{R{-}X}$$

$$\mathrm{X} = \text{halogen}$$

Of particular preparative value is the observation that ambident anion alkylations, by appropriate choice of reaction conditions, may be manipulated to operate preferentially in one direction. The results of Guillemard's classical work in this area have been reviewed by Kurtz.[2] Although most of the modern investigations do not deal in particular with the nitrile/isonitrile problem, the following rules can be summarized.

(i) Given kinetically controlled reactions, an S_N1-type transformation of alkyl halides with cyanide ions should favor the formation of isonitriles. In a charge-controlled reaction the ambident cyanide nucleophile will tend to attack the carbon of the alkyl halide with the more electronegative nitrogen, the center of greater charge density. With S_N1 substitutions there will also be a comparatively high positive charge density on the carbon atom of the alkyl halide, although this does not necessarily mean the existence of a discrete cationic intermediate. Even a partially charged carbon atom, according to Pearson's classifications, has to be considered a relatively hard electrophile and should therefore interact most easily with the nitrogen atom of the cyanide ion, which does represent the harder base in this combination,[13] to generate the isonitrile. In Section 1.8.2 the synthetic possibilities will be discussed in detail.

(ii) Accordingly S_N2 substitution conditions will favor the formation of nitriles. In an orbital-controlled transformation the less electronegative, but more nucleophilic carbon atom of the CN^- ion will attack the alkyl halide in an S_N2-type reaction. The halide-substituted carbon of R—X (X = halogen) may be considered a soft electrophile, thus classifying the formation of nitriles as a soft–soft interaction. Primary halides should therefore be the best candidates for the formation of nitriles and Table 1 proves this for a large number of examples.

If a particular nitrile is being aimed at, there will be no possibility of changing the nature of R in order to promote an S_N2 process. Therefore it may be of interest that the nature of the transition state may also be influenced by other parameters. So, important consequences may be expected from changing the

Table 1 Alkyl Cyanides from the Reaction of Alkyl Halides with CN^- Ions

$$R{-}X \ + \ MCN \longrightarrow R{-}CN \ + \ M{-}X$$

R	*X*	*MCN*	*Solvent*	*Approx. reaction time* (h)	*Temp.* (°C)	*Yield* (%)	*Ref.*
Pr^i	Br	NaCN	Glycol	24	60–180	39	3
Pr^i	Br	Et_4NCN	DMSO	18	50	72	3, 21
Bu^n	Cl	NaCN	MeOH	48	?	45	3
Bu^n	Cl	NaCN	DMSO	0.3	90–160	93	3
Bu^n	Cl	KCN	DMSO	10	120–140	69	3
Bu^n	Cl	NaCN/reversed micelles		Overnight	100	75	22
Bu^n	Br	KCN	PEG[a]	3	110	90	19
Bu^n	Br	NaCN	DMSO	0.6	60–90	92	3
Bu^n	Br	$NaCN/Al_2O_3$	Toluene	24	90	93	3
Bu^i	Cl	NaCN	DMSO	0.5	80–140	88	3
Bu^i	Br	NaCN	DMSO	2	70	62	3
Bu^s	Cl	NaCN	EtOH	70	?	24	3
Bu^s	Cl	KCN	DMSO	24	120–140	42	3
Bu^s	Cl	NaCN	DMSO	3	90–160	69	3
Bu^s	Br	NaCN	Glycol	22	70–180	0	29
Bu^s	Br	NaCN	DMSO	6	70–160	41	3
Bu^t	Cl	NaCN	Glycol	6	46	10	3
Bu^t	Cl	NaCN	DMSO	4	130	0	3
Bu^t	Cl	$TMS\text{-}CN/SnCl_4$	CH_2Cl_2	36	20	64	23
Bu^t	Br	NaCN	Glycol	3	70–180	Low	29
$n\text{-}C_5H_{11}$	Cl	NaCN	DMSO	0.3	90–160	97	3
$n\text{-}C_5H_{11}$	Br	Et_4NCN	CH_2Cl_2	2.5	35	80	3, 21
Bu^tCH_2	Br	Et_4NCN	MeCN	24	50	55	3, 21
$Me_2C(Et)$	Cl	$TMS\text{-}CN/SnCl_4$	CH_2Cl_2	36	20	75	23
Cyclopentyl	Cl	NaCN	DMSO	3	125–130	70	3
$n\text{-}C_6H_{13}$	Cl	NaCN	DMSO	0.3	90–160	91	3
$n\text{-}C_6H_{13}$	Cl	KCN/crown[a]	MeCN	2.2	83	91	3
$n\text{-}C_6H_{13}$	Cl	NaCN/reversed micelles		Overnight	100	87	22
1-Me-cyclopentyl	Cl	$TMS\text{-}CN/SnCl_4$	CH_2Cl_2	32	20	75	23
$n\text{-}C_7H_{15}$	I	A 26 CN[a]	Benzene	6	80	92	3
Benzyl	Cl	NaCN	DMSO	2.5	35–40	92	3
Benzyl	Cl	A 26 CN[a]	Benzene	2	80	87	3
Benzyl	Cl	KCN/crown[a]	MeCN	0.4	20	94	3
Benzyl	Cl	LiCN	THF	6	65	100	20
Benzyl	Br	LiCN	THF	2	65	92	20
Benzyl	Br	NaCN/reversed micelles		Overnight	100	87	22
$PhCH_2CH_2$	Cl	NaCN/reversed micelles		Overnight	100	85	22
$n\text{-}C_8H_{17}$	Cl	NaCN/reversed micelles		Overnight	100	92	22
$n\text{-}C_8H_{17}$	Cl	$NaCN/R_4P\,Br$	Water	2	80–100	94	3
$n\text{-}C_8H_{17}$	Br	KCN	PEG[a]	3	110	94	19
$n\text{-}C_8H_{17}$	I	NaCN or KCN	THF	15	65	0	20
$n\text{-}C_8H_{17}$	I	LiCN	THF	1	65	90	20
2-Octyl	Cl	NaCN	DMSO	1	90–160	70	3
Cyclooctyl	Cl	$TMS\text{-}CN/SnCl_4$	CH_2Cl_2	32	20	76	23
Cyclooctyl	Cl	LiCN	THF	6	65	100	20
$n\text{-}C_{10}H_{21}$	Cl	NaCN	DMSO	0.3	90–160	94	3
$n\text{-}C_{10}H_{21}$	Cl	NaCN/reversed micelles		Overnight	80	85	22
$Me_2C(Ph)CH_2$	Cl	NaCN	DMSO	24	120	26	3

[a] Abbreviations: A 26 CN, Amberlyst A 26 + KCN; crown, 18-crown-6; PEG, polyethyleneglycol.

leaving group. As the polarity of the bond between the leaving group and the carbon atom increases, as shown in equation (3), the likelihood of an S_N1 process occurring increases. Within certain limits even the countercation will be able to influence the S_N1/S_N2 ratio: with AgCN for instance (sometimes zinc cyanide, CuCN or HgCN have also been used) the initial formation of silver halides ionizes the alkyl halide to a large extent, thus imposing a comparatively high positive charge on the carbon atom. In the transition state there will be a higher positive charge at this center, which, by enhancing the S_N1 character, will favor the formation of isonitriles. On the other hand, alkali metal cyanides will be used, if the corresponding nitriles are required. A practical application resulting from these considerations is the optimized preparation of ethyl isocyanide from iodoethane and silver cyanide, as described in *Organic Synthesis*.[15]

$$\xrightarrow[\text{increasing } S_N1 \text{ character}]{X = I,\ Br,\ Cl,\ OSO_2R} \qquad (3)$$

It should be mentioned briefly that solvation phenomena should also influence the outcome in the case of ambident nucleophiles, at least to the extent to which these reagents are sensitive to solvent effects. With an ambident anion, which is not manipulated by countercations (formation of ion pairs), the more electronegative center should attack preferentially. The more this area is blocked by hydrogen bridges formed in protic solvents, or shielded by countercations, the more likely it is that the less electronegative end will react. If dipolar aprotic solvents are used, which can only solvate the cations, a preferential attack of the nonshielded more electronegative center is to be expected. It must be realized, however, that in substitution reactions employing cyanide ions, dipolar aprotic solvents have not been reported to enhance the formation of isonitriles.[16–18]

Assessing the relative importance of the various factors, which also has to include steric effects, is a complicated task. As already mentioned, nitrile formation in general is favored in these substitution reactions (equation 1), and as isonitriles are normally formed to only a very small extent, they can easily be removed by extraction with diluted mineral acids.

(ii) Preparative possibilities

As will be shown, a whole range of variations and modifications is known for the reaction of alkyl halides with cyanide ions (equation 4). Without trying to cover every detail, an attempt will be made to mention the most important procedures and to give a few typical examples (see Tables 1 and 2). Despite the diversity of the reaction conditions, a general comparison of their synthetic importance is useful.

$$\mathrm{R{-}X} \;+\; \mathrm{MCN} \;\longrightarrow\; \mathrm{R{-}CN} \;+\; \mathrm{M{-}X} \qquad (4)$$

R = alkyl, X = halogen

Table 2 Dinitriles or Halonitriles from Aliphatic Dihalides

n	*X*	*Y*	*MCN*	*Solvent*	*Approx. reaction time* (h)	*Temp.* (°C)	*Z*	*Yield* (%)	*Ref.*
2	Cl	Cl	NaCN	DMSO	0.3	90–160	CN	56	16
2	Cl	Cl	NaCN/reversed micelles		Overnight	80	CN	86	22
2	Br	Br	Et_4NCN	CH_2Cl_2	2.5	40	CN	70	21
3	Cl	Cl	NaCN	DMSO	0.5	90–160	CN	67	16
3	Cl	Cl	KCN/crown	MeCN	1.5	83	CN	97	3
3	Br	Br	NaCN	$EtOH/H_2O$	1.5	80–100	CN	86	30
3	Cl	Br	KCN	$EtOH/H_2O$	1.5	80–100	Cl	47	31
3	F	Br	NaCN	Glycol	1	100	F	81	32
4	Cl	Cl	NaCN	DMSO	0.5	90–160	CN	88	3, 16
4	Cl	Cl	KCN/crown	MeCN	0.7	83	CN	95	3
4	Br	Br	NaCN/reversed micelles		Overnight	80	CN	92	22
4	F	Cl	NaCN + NaI	$EtOH/H_2O$	12	80–100	F	76	32
4	F	Br	NaCN	$EtOH/H_2O$	7.5	80–100	F	82	32
5	Cl	Cl	NaCN	DMSO	0.5	90–160	CN	75	16
5	Br	Br	Et_4NCN	CH_2Cl_2	2.5	40	CN	90	21

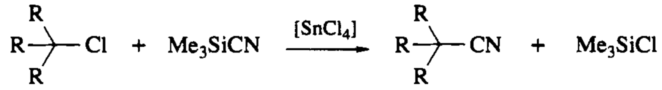
The transformation of alkyl halides into alkanenitriles with cyanide ions has frequently been carried out in protic solvents such as methanol or ethanol, sometimes with the addition of water or acetone, and often at elevated temperatures. Under these conditions reaction rates decrease in the order iodides, bromides, chlorides, as would be expected. Accordingly iodide ions have a catalytic effect and increase reaction rates.[2,4] The use of anhydrous ethylene glycol or di- and poly-ethylene glycols and their corresponding ethers allows the use of higher temperatures, which means better solubility of the alkali metal cyanides.[2,4,19] There is probably additional help from the extensive solvation of the countercations by some of these hydroxy polyethers. While for primary halides yields for nitriles range up to 90% (Table 1), they drop sharply with secondary and tertiary halides.[3]

Particularly good results have been reported (Table 1) with dipolar aprotic solvents like DMSO, DMF, formamide or HMPA,[3,4] which exclusively solvate cations and thus generate highly reactive 'naked' cyanide anions. As a consequence a remarkable increase in reaction rates is observed. The most impressive results were seen with DMSO. Under these conditions even alkyl bromides and chlorides are very useful starting materials and not only primary, but also secondary halides can give rise to high yields if there is not too much steric hindrance (Table 1). Tertiary halides even under these conditions are poor substrates. The cation also may, even if one focuses on alkali metal cyanides, sometimes have a strong influence on reaction rates. With sterically hindered halides for instance, NaCN seems to be superior to the potassium salt in DMSO.[3] Another modification is the use of LiCN in boiling THF; NaCN and KCN fail under these conditions. There has also been a very thorough investigation of the use of tetraalkylammonium cyanides and quite good results were obtained with the tetraethyl or tetrabutyl derivative.[21] Using these highly soluble cyanides, one can run the reaction not only in many polar solvents, *e.g.* acetonitrile, but also in comparatively nonpolar solvents such as CH_2Cl_2 and THF, or even benzene or toluene, and at high concentrations. Slowly reacting compounds will again be used in DMSO.[21] Even neopentyl bromide yields 55% of the corresponding nitrile, if treated with tetraethylammonium cyanide in acetonitrile.

Phase transfer catalysis and the use of crown ethers are also of particular advantage in alkanenitrile synthesis (Table 1). Usually quaternary ammonium and phosphonium salts serve quite well as catalysts.[3] Another modification is represented by the use of a solid catalyst, which is insoluble in the two-phase system, for instance alumina or anion-exchange resins (triphase catalysis).[3,7] Crown ethers again capture the cations and generate 'naked' cyanide ions in fairly nonpolar solvents, leading to exceptionally mild reaction conditions.

The use of 'reversed micelles' for the preparation of nitriles is a particularly interesting modern development.[22] Some examples can be found in Table 1.

As discussed above, the classical procedures for the transformation of alkyl halides fail with tertiary derivatives. Trimethylsilyl cyanide (TMS-CN)[23] recently turned out to be the reagent of choice in this case. It may easily be obtained from trimethylchlorosilane,[24–28] but is also available commercially. In this way various *t*-alkyl and cycloalkyl chlorides can be converted to the corresponding nitriles in the presence of a catalytic amount of $SnCl_4$ at room temperature and in solvents such as CH_2Cl_2 (equation 5). The yields range between 64 and 80% (Table 1). A sharp drop in yields is observed with educts, however, which have an electron-withdrawing group (EWG) in the neighborhood of the reaction center, as was noticed with 1,1,1,2-tetrachloro-2-methylpropane (yield < 5%) or methyl 2-chloro-2-methylpropanoate (<5%). Isonitriles are not observed in the course of the reaction, although they may play a crucial role in the reaction sequence. A number of observations led to the following mechanism (Scheme 1).[23]

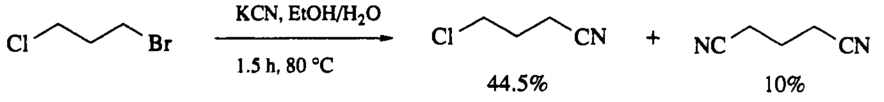


(5)

$$\begin{aligned}
&R_3C{-}Cl \;+\; SnCl_4 \;\rightleftharpoons\; R_3C^+\,SnCl_5^-\\
&R_3C^+\,SnCl_5^- \;+\; Me_3Si{-}CN \;\rightleftharpoons\; R_3C{-}\overset{+}{N}{\equiv}C{-}SiMe_3\;\; SnCl_5^-\\
&R_3C{-}\overset{+}{N}{\equiv}C{-}SiMe_3\;\; SnCl_5^- \;\rightleftharpoons\; Me_3SiCl \;+\; SnCl_4 \;+\; R_3C{-}\overset{+}{N}{\equiv}\underset{\bullet\bullet}{C^-}\\
&R_3C{-}\overset{+}{N}{\equiv}\underset{\bullet\bullet}{C^-} \;+\; R_3C^+\,SnCl_5^- \;\rightleftharpoons\; R_3C{-}\overset{+}{N}{\equiv}C{-}CR_3\;\; SnCl_5^-\\
&R_3C{-}\overset{+}{N}{\equiv}C{-}CR_3\;\; SnCl_5^- \;\rightleftharpoons\; R_3C{-}CN \;+\; R_3C^+\,SnCl_5^-
\end{aligned}$$

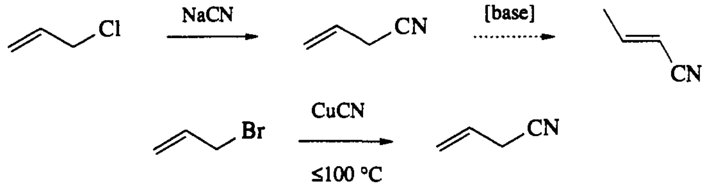
Scheme 1

By using displacement reactions even nitriles that carry a number of functional groups may be prepared. Dinitriles may also be obtained by this method; in the case of ω-chloroalkyl bromides, the bromine atom is exchanged preferentially (equation 6).[2] Dichloro compounds may also be converted into the corresponding dinitriles. This is done mainly in dipolar aprotic solvents such as DMSO or with the help of phase transfer catalysis or crown ethers (Table 2).[3] Generally, the generation of dinitriles does not create any special problems. It should be mentioned that even in γ-halocarboxylic acids a smooth halogen/nitrile exchange is possible.[2]

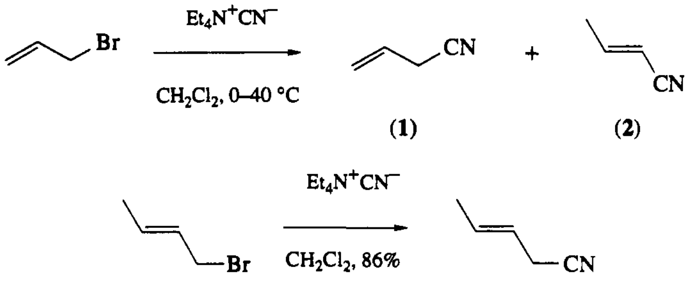


(6)

β,γ-Unsaturated alkanenitriles may often be generated quite easily from allyl halides and cyanide ions. Unfortunately, the preparation of pure compounds suffers sometimes from the formation of rearrangement products (Scheme 2).[2,4] In this case the use of CuCN is expected to be of advantage.[2,4] An 80–84% yield of allyl cyanide may be obtained on treatment of neat allylic bromide with CuCN (Scheme 2).[33] A quite remarkable influence of the reaction conditions is observed, for instance, in the reaction of tetraethylammonium cyanide with allylic bromide.[21] If the cyanide, dissolved in CH_2Cl_2, is slowly added to a cold solution of allylic bromide in the same solvent, the main product, allylic cyanide (**1**), will dominate in a 15:1 ratio against crotononitrile (**2**), while the addition of allylic bromide to a boiling solution of the ammonium cyanide in methylene chloride provides 70% (**2**), which is accompanied by only 8% of compound (**1**). On the other hand, 1-bromo-2-butene gives rise to 1-cyano-2-butene exclusively, independent of reaction conditions (Scheme 3).[21] A great number of patents on this topic have been reviewed by Kurtz.[2]

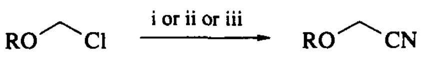


Scheme 2



Scheme 3

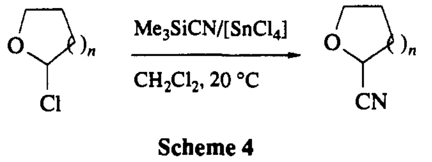
α-Cyano ethers may be obtained from the corresponding halogen precursors (which are quickly destroyed in aqueous or alcoholic solution) with NaCN in DMF or DMSO.[4] Earlier papers recommend the use of CuCN, sometimes without any solvents.[2,4] Good results are reported again for the transformation of α-chloro ethers with tetraethylammonium cyanide in CH_2Cl_2,[23] or with TMS-CN/$SnCl_4$ (Scheme 4).[23] In the carbohydrate series nitriles are often prepared by reaction of the corresponding bromo derivative with $Hg(CN)_2$. No special care has to be taken in the formation of alkoxynitriles, where the ether moiety is separated from the nitrile group by at least two carbon atoms.[2]



i, $Et_4N^+ CN^-$, CH_2Cl_2, ≤20 °C (ref. 7); R = Me, 67%; R = n-C_5H_{11}, 87%

ii, NaCN, DMF, 20 °C; R = Me, 62%

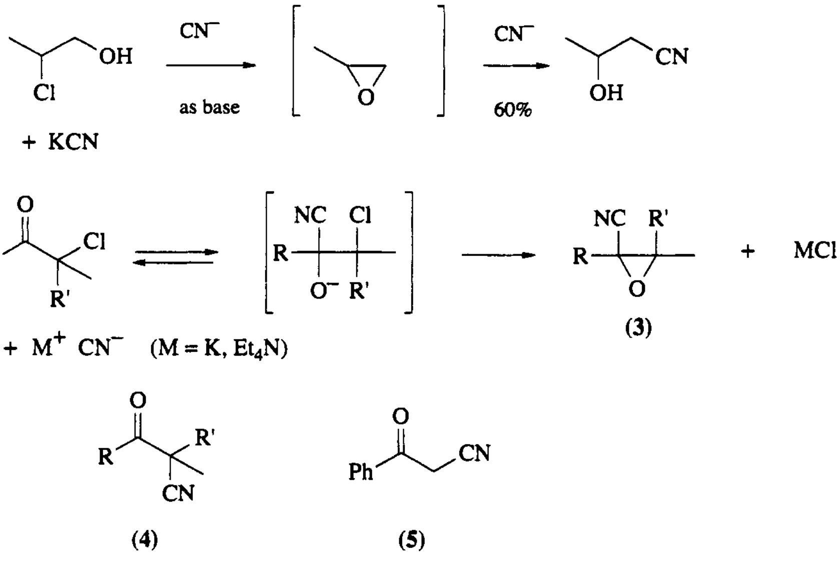
iii, CuCN, Et_2O or C_6H_6 ; R = Pr^n, 55%; R = Et, 83%



n = 1, 84%
n = 2, 90%

Scheme 4

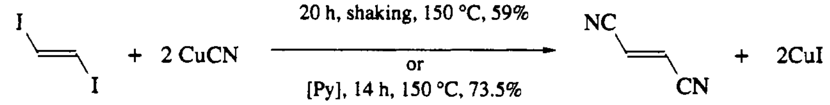
In the reaction of 2-hydroxyalkyl halides with cyanide ions the intermediate formation of oxiranes can give rise to rearrangement products. Epoxides may also be encountered if CN^- ions are reacted with α-halo ketones (Scheme 5).[2,3] On heating with quaternary ammonium halides in acetonitrile or DMSO at 80–130 °C these cyanooxiranes (**3**) are converted into 2-cyano ketones (**4**).[21] Phenacyl bromide, in contrast, gives rise to 3-oxo-3-phenylpropionitrile (**5**) on treatment with cyanide ions.[21] Not much is known about the reaction of the corresponding α-halo sulfides with cyanide;[34] ethylthioacetonitrile was obtained from the chloro sulfide by treatment with $Hg(CN)_2$.[35]



Scheme 5

1.8.1.2.2 Vinyl and aryl halides

The low reactivity of vinyl halides in nucleophilic displacement reactions is well known. For preparative procedures the use of CuCN, sometimes in the presence of bases like pyridine, at temperatures higher than 200 °C (closed vessel) is recommended.[2,4] This technique may be used to prepare maleonitrile and fumaronitrile from *cis*- and *trans*-1,2-diiodoethylene (equation 7).[2,4]

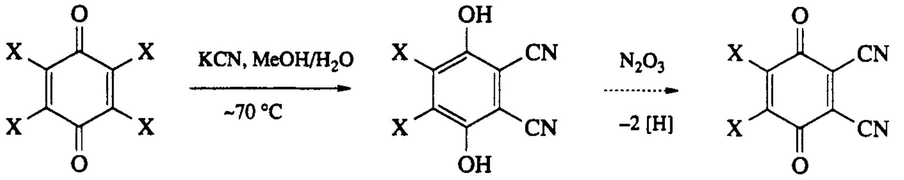


(7)

The reaction of haloquinones with cyanide ions in aqueous ethanol, which yields cyanohydroquinones (Scheme 6),[2] formally represents the same type of reaction. The synthesis of vinyl cyanides from the corresponding halides with KCN in the presence of crown ethers and a Pd^0 catalyst can be run under much milder conditions (60–100 °C) in benzene or pyridine as the solvent.[3] The transformations turn out to be nearly stereospecific. Comparable results are obtained at 50 °C with a Ni^0 catalyst, prepared *in situ* from bis(triphenylphosphine)bromonickel(II) on treatment with zinc and triphenylphosphine in DMF or DMSO. The stereospecificity is only slightly inferior to the Pd^0 catalyst.[3] With both systems yields of more than 90% can be reached. A series of examples is given in a table by Grundmann.[3]

Although the preparation of aryl cyanides from the corresponding halogen compounds is described by the very simple equation (8), the process does not correspond to a simple aromatic substitution reaction. In a series of comprehensive articles[2,3,8,36] various aspects of this transformation are discussed. An excellent review, written by Ellis and Romney-Alexander,[36] should be mentioned in particular, as it provides the literature leading into the modern status of the field.

As a 'classical' technique for the synthesis of aromatic cyanides treatment of the corresponding halides with CuCN has to be cited (Rosenmund–von Braun reaction).[1–4] It is carried out at 150–250 °C, either without any solvent at all, or using pyridine or quinoline, which also operate as complexing agents for the CuCN. Other heavy metal cyanides or hexacyanoferrates have been used in principle, but their



X = Cl, 24% 85%
X = Br, 43.5% 80%
X = I, 71% 80%

Scheme 6

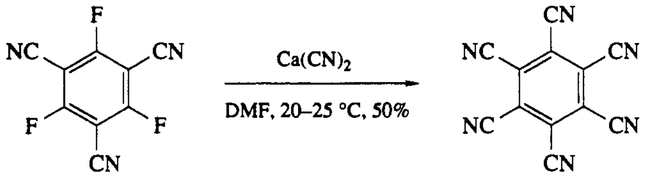
$$\mathrm{Ar{-}X} + \mathrm{CN^-} \xrightarrow{\Delta} \mathrm{Ar{-}CN} + \mathrm{X^-} \tag{8}$$

X = halogen

practical importance seems to be low. In recent years DMF, HMPA, NMP or tetramethylurea proved to be very useful solvents. As the reactions with these dipolar aprotic solvents can be run using comparatively mild conditions, it has also been possible to apply this transformation to quite sensitive and nonactivated educts.[3,4,36]

Although aryl iodides represent the most reactive substrates, a very large number of reactions have been run with the bromides, as these are more easily available and still offer satisfactory reactivity. From chloroaryl iodides the corresponding chloronitriles may be obtained with remarkable selectivity. Many heteroaromatic halogen compounds have been transformed into the corresponding nitriles in an analogous manner.[3,4,36]

The substitution pattern of the aromatic ring tends to influence the reaction rates, but the relationship is not very clear cut. Chloro ligands in the 2-position as well as nitro and carboxy groups in the 2- or 4-position seem to increase the reaction rates. There are additional successful transformations with the following substituents: primary amino, tertiary amino, alkoxy, alkylthio, hydroxy, alkyl, formyl, acyl, carboxy, alkoxycarbonyl and nitro groups. Polyhalogenated educts give rise to polynitriles.[8] Starting from 2,4,6-trifluorotricyanobenzene even hexacyanobenzene may be obtained (equation 9).[37]



(9)

For work-up of the reaction mixtures, reagents which destroy the nitrile–copper cyanide complexes, for instance $\mathrm{Fe^{III}}$/HCl (oxidation of $\mathrm{Cu^{I}}$ to $\mathrm{Cu^{II}}$, followed by extraction of the nitrile), ethylenediamine (complexation of Cu ions) or an excess of aqueous NaCN (formation of the soluble $\mathrm{NaCu(CN)_2}$), proved to be particularly useful.[38] With appropriate *ortho* substituents, such as carboxy groups, cyclization reactions may be observed under the reaction conditions.[4] If treated at higher temperatures with CuCN, *o*-dihalides often provide phthalocyanines.

The mechanism of of these substitution processes, in spite of numerous investigations, is not completely (or not for all variants) solved in detail. As reaction conditions differ very much, one may not even expect a simple homogeneous mechanism. The crucial role of Cu complexes is, however, widely accepted. A very thorough discussion of all aspects can be found in some comprehensive accounts.[36,39]

An excellent overview with numerous tables, providing details on the reaction conditions and disclosing scope and limitations of all transformations of aromatic halogen compounds with CuCN, is provided by Grundmann[3] as well as Ellis and Romney-Alexander[36] (more than 200 examples, some of them with preparative variations). They list various reaction conditions, so that it is not necessary to discuss individual examples here.

Under remarkably mild conditions aromatic cyanides can be prepared from halogen compounds with alkali metal cyanides in the presence of transition metal complexes.[3,36] Complexes of palladium and nickel are particularly useful, for instance tetrakis(triphenylphosphine)palladium(0) (**6**), tris(triphenylphosphine)nickel(0) (**7**) or *trans*-dichlorobis(triphenylphosphine)nickel(II) (**8**; Scheme 7).

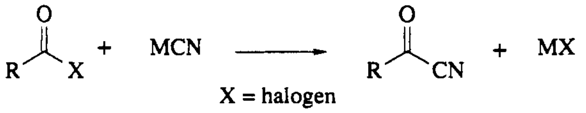
$(Ph_3P)_4Pd$	$(Ph_3P)_4Ni$	$Cl_2Ni(PPh_3)_2$
(6)	**(7)**	**(8)**

Scheme 7

Various cobalt complexes have also been used. While the use of these complexes is more expensive and needs more demanding reaction conditions (oxygen must be strictly excluded), the transformations can be done at comparatively low reaction temperatures. Very often high yields will be obtained at 50–60 °C, and in some cases reactions have even been run at 30 °C. Yields of up to 80–90% are not unusual. The addition of crown ethers proved to be quite helpful in various cases. Instead of alkali metal cyanides, acetone cyanohydrin can also be used.[36] A discussion of relevant mechanistic aspects can be found in eview articles.[3,36,40] Again the aromatic ring may carry various substituents, although *ortho* - ligands tend to give rise to lower yields.[36] Another drawback seems to be the interaction of nitro groups with the catalysts. Depending on the stability of the catalytic system under investigation, one may in principle decide on various polar or nonpolar solvents and details on this matter can again be found from reaction tables provided in the literature.[36] The reaction of aryl iodides with TMS-CN/$(Ph_3P)_4Pd$ in boiling triethylamine was studied recently.[41]

1.8.1.2.3 Acyl halides

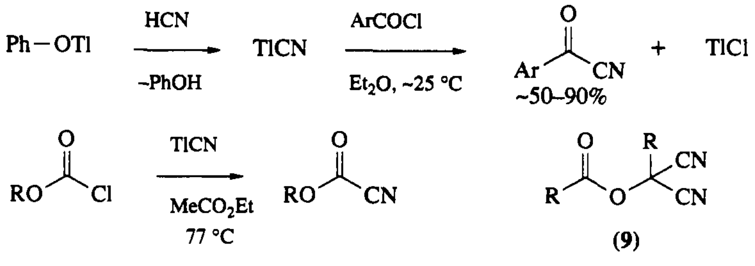
The preparation of benzoyl cyanide on distillation of benzoyl chloride and HgCN, which was reported by Liebig and Wöhler in 1832,[42] has to be regarded as a cornerstone in nitrile chemistry, as this documents the first synthesis of an organic nitrile. Today numerous methods for the preparation of these important acylnitriles are known (equation 10). A number of review articles[2,3,7,43–45] provide quick access to the original papers, the very broad patent literature included.



(10)

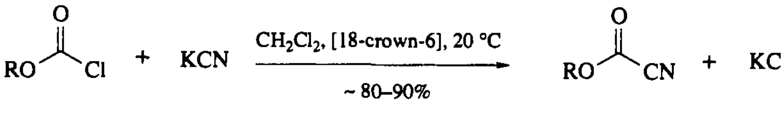
The most favored technique for quite a while was the transformation of the, compared to acyl chlorides, much more reactive acyl bromides with AgCN or CuCN at elevated temperatures.[2,3,7,45] A whole range of phosphorus compounds may be used as catalyst.[4] Dry alkali metal cyanides were for some time considered to be useless, probably because of their poor solubility in solvents like benzene. Aqueous solvents and alcohols are of course useless, as they react very quickly with the starting material as well as with the product. At this stage the particular sensitivity of acylnitriles to protic solvents and basic or acidic reagents should be mentioned.[2,4] Recently very good results were reported in many cases from the transformation of acid chlorides and CuCN in acetonitrile, which may also operate as a complexing ligand.[3,45] In another modification, aroyl chlorides are treated with CuCN in the presence of LiI in solvents such as diethyl ether.[46] An interesting technique makes use of the reaction of the (difficult to obtain) TlCN with an aroyl chloride in ether or ethyl acetate at room temperature (Scheme 8); high yields of aroyl cyanides are described.[3,45] One cannot apply this method, however, to the preparation of the corresponding aliphatic acyl cyanides, as dimers such as (**9**) are mainly formed under the reaction conditions. If this dimerization is blocked by steric hindrance, it may be possible to isolate the desired acylnitriles. The preparation of 3,3-dimethyl-2-oxobutyronitrile, which was obtained in 45% yield, provides an example of this method.[3] Even cyanoformates can be prepared from chloroformates and TlCN in acceptable yields (Scheme 8).[3] An often quite useful modification, which permits the synthesis of sensitive acyl cyanides, uses the reaction of acyl iodides (which can be generated *in situ* from acid chlorides on treatment with NaI in acetonitrile) with CuCN.[3,47] Although the corresponding isonitriles could well be intermediates, this question is not dealt with by the author[47] (but see also ref. 45). In CH_2Cl_2 or acetonitrile good yields are obtained under mild conditions. In the same manner α,β-unsaturated acyl halides and phenyl iodoformate can be transformed into the corresponding nitriles.

Now even alkali metal cyanides are used for the preparation of acylnitriles. The transformation of chloroformates with KCN using phase transfer catalysis can be achieved under very mild conditions. The yields, however, are frequently much lower than those from the TlCN technique.[3,45,48] Probably these deficits may be compensated for by the very convenient operations under phase transfer conditions ($Bu_4N^+Br^-$ in water/CH_2Cl_2). The reaction of numerous chloroformates with KCN/18-crown-6 in CH_2Cl_2 (equation 11) is reported to give excellent yields.[3,45,49]



R = alkyl

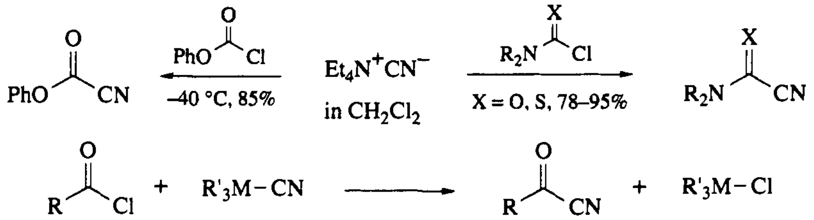
Scheme 8



(11)

The recent application of sonochemistry to the reaction of aroyl chlorides with KCN in acetonitrile is very interesting.[3] Aromatic acyl cyanides could also be prepared by reaction of aroyl chlorides with KCN impregnated onto XAD resins.[50] A number of patents describe the results of the two-phase interactions of alkali metal cyanides with a solution of acyl halides or anhydrides in aprotic organic solvents, which in general run in the presence of Cu^I salts.[45]

Due to its excellent solubility in CH_2Cl_2, triethylammonium cyanide also serves extremely well in this reaction. The transformation of phenyl chloroformate and (thio)carbamoyl chlorides yields the corresponding nitriles (Scheme 9).[3,21,45] Alkyl chloroformates fail under these conditions as a result of decarboxylation. Trimethylsilyl cyanide (TMS-CN) has also proved to be a very useful reagent for the preparation of acyl cyanides (Scheme 9)[3,45] but see also ref. 47b. The TMS-Cl formed in the process (Scheme 9) is said to be a catalyst in this transformation. The reaction may also be catalyzed by small amounts of other Lewis acids such as ZnI_2 or, particularly for aroyl halides, $SnCl_4$. Unsaturated as well as haloalkanoyl chlorides or dicarboxylic acid dichlorides may be transformed in a similar fashion with very satisfactory results. It has to be mentioned, however, that highly reactive or enolizing acylnitriles may suffer from subsequent transformations.[3] In a further modification acylnitriles can also be prepared by reaction of various acid chlorides with cyanotributylstannane,[3,45] although primary and secondary acyl chlorides give rise to acyloxymalodinitriles (**9**).



$R'_3M = Me_3Si, Bu_3Sn$

Scheme 9

1.8.1.3 Exchange of Oxygen or Sulfur Functionality

The formation of alkanenitriles from alcohols and HCN is of no interest for laboratory preparations. However, a large number of publications, particularly patents, have appeared, which deal with technical applications of this procedure. A few review articles[2–4] serve very well as introductions to this field. Under particularly mild conditions allyl and propargyl alcohols can be transformed into the corresponding nitriles with hydrogen halides in the presence of Cu^I salts.[2,4] The possibility of generating nitriles from alcohols *via* the analogous halides needs no further treatment at this stage.

An attractive procedure for the direct transformation of alcohols into nitriles operates with TMS-CN, generated *in situ* from TMS-Cl and NaCN with catalytic amounts of NaI.[51] The reaction (Scheme 10) is run in DMF/acetonitrile at about 60 °C and leads to good or even excellent yields with primary, secondary and also tertiary alcohols. With 3-β-cholestanol 85% of the nitrile (+ 6% cholest-2-ene) is formed with inversion.[51] Decisive, mechanistically relevant intermediates could be the nitrilium ion (**10**) as well as the oxonium ion (**11**; Scheme 10).[51] The preparation of nitriles from alkanols with KCN, triphenylphosphine and CX_4 (X = halogen) in the presence of crown ethers at room temperature (Scheme 11) is restricted to primary alcohols.[52] A second version (Scheme 11), which operates on primary and secondary alcohols, particularly in the carbohydrate series, makes use of triphenylphosphine, tetrachloromethane and DMSO at 90 °C under anhydrous conditions.[3] In the conversion of *o*- and *p*-hydroxybenzyl alcohols to the corresponding arylacetonitriles (NaCN, DMF, 110 °C) quinone methides are discussed as intermediates.[3]

$$\mathrm{ROH} + 2\,\mathrm{NaCN} + 2\,\mathrm{Me_3SiCl} \xrightarrow{[\mathrm{NaI}]} \mathrm{RCN} + \mathrm{HCN} + (\mathrm{Me_3Si})_2\mathrm{O} + 2\mathrm{NaCl}$$

R = $PhCH_2$	98%	R = Bu^t	64%
R = c-$C_6H_{11}CH_2$	93%	R = 1-Me-cyclohexyl	80%
R = n-$C_6H_{13}CHMe$	75%	R = 1-adamantyl	91%

$$\mathrm{Me_3SiCl} + \mathrm{MeCN} \xrightarrow{[\mathrm{I^-}]} \underset{\textbf{(10)}}{\mathrm{Me{-}C{\equiv}\overset{+}{N}{-}SiMe_3}}\ \mathrm{I^-} + \mathrm{Cl^-}$$

$$\mathrm{Me_3SiCl} + \mathrm{ROH} \xrightarrow[\mathrm{-HCl}]{} \mathrm{R{-}O{-}SiMe_3}$$

$$\mathrm{Me{-}C{\equiv}\overset{+}{N}{-}SiMe_3}\ \mathrm{I^-} + \mathrm{R{-}O{-}SiMe_3} \longrightarrow \mathrm{MeCN} + \underset{\textbf{(11)}}{\mathrm{R{-}\overset{+}{O}(SiMe_3)_2}}\ \mathrm{I^-}$$

$$\mathrm{R{-}\overset{+}{O}(SiMe_3)_2}\ \mathrm{I^-} + \mathrm{CN^-} \xrightarrow{-\mathrm{I^-}} \mathrm{R{-}CN} + (\mathrm{Me_3Si})_2\mathrm{O}$$

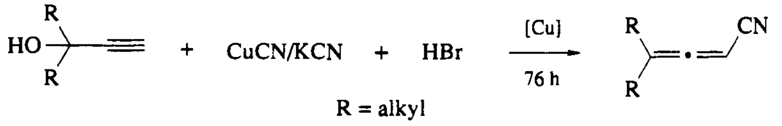
Scheme 10

$$\mathrm{RCN} \xleftarrow[\text{[18-crown-6]}]{\mathrm{NaCN,\ Bu_3P/CCl_4}} \mathrm{ROH} \xrightarrow[\text{boiling temp.}]{\mathrm{KCN,\ Ph_3P/CCl_4/DMSO}} \mathrm{RCN}$$

R = n-C_8H_{17},	76%	R = Bu^n,	85%
R = $PhCH_2$,	82%	R = 2-octyl,	70%
R = $Ph(CH_2)_2$,	75%		

Scheme 11

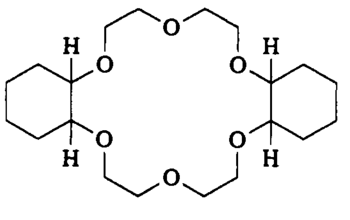
One should briefly mention the preparation of cyanoallenes from substituted 2-propynols, KCN and HBr in the presence of CuCN and copper (equation 12).[3] For a mechanistic discussion see ref. 53. In another route to cyanoallenes, the corresponding halides are first prepared from the alcohol and then treated with CuCN.[3]



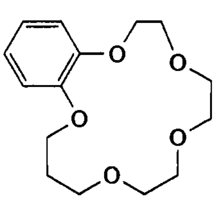
(12)

Various sulfuric and phosphoric acid esters have sometimes been used instead of alcohols as starting materials for the preparation of nitriles.[2,4] Of more general importance are sulfonates, particularly from methane- or *p*-toluene-sulfonic acid, which react in an S_N2-type substitution with cyanide ions. The most common starting materials are, as described in Section 1.8.1.2.1, alkyl halides, and if their preparation creates problems, the use of sulfonates may be advantageous.[3] The addition of crown ethers or the application of 'classical' phase transfer conditions may enhance the efficiency of this transformation.[51] The reaction of *n*-octyl methanesulfonate with a saturated aqueous KCN solution, in the presence of crown ether (**12**) at 100 °C, which gives rise to an 80% yield of the corresponding nitrile (Scheme 12), may serve as an example.[54] For the reaction of *n*-octyl bromide with NaCN and crown ether (**13**) for 24 h at 100 °C, a complete failure is reported.[54] The corresponding sulfonate, however, gave rise to 1-cyanooctane on treatment with LiCN in boiling THF.[20] According to literature reports,[3] sulfonic acid aryl and benzyl esters are not converted to nitriles under mild conditions. Carboxylic esters are not useful starting materials for the preparation of nitriles.[2,3] In contrast to this, γ-lactones give rise to the salts of γ-cyanocarboxylic acids without problems. Following a 'classical' procedure,[2] KCN is used without any solvent at 180–200 °C (equation 13). In spite of these forcing conditions, yields tend to be high.[2] There seems to be a possibility for milder reaction conditions by using DMSO as the solvent.[3]

$$\text{n-}C_8H_{17}\text{-}OSO_2Me \quad + \quad KCN \xrightarrow{H_2O/[(12)]} \text{n-}C_8H_{17}CN \quad + \quad MeSO_3^- \; K^+$$

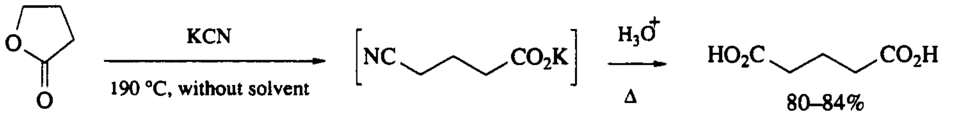


(12)



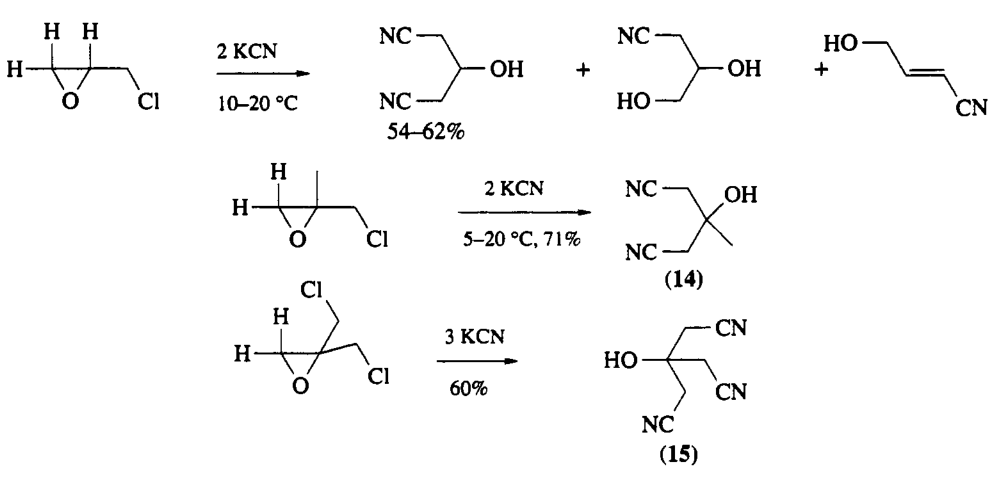
(13)

Scheme 12



(13)

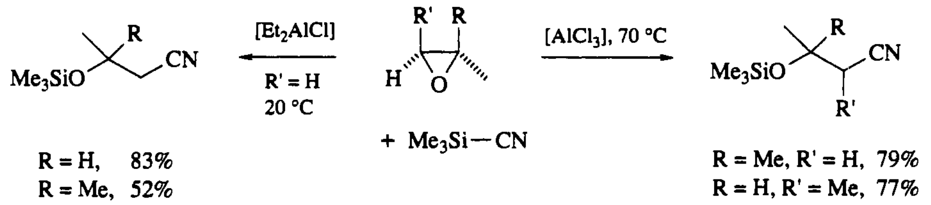
The generation of 3-hydroxypropionitrile from ethylene oxide and HCN in a closed vessel was described in 1878.[55] As the reactivity of epoxides exceeds that of acyclic ethers considerably, oxiranes do represent useful starting materials for hydroxynitriles and their derivatives.[2] For laboratory preparations, the use of alkali metal cyanides (Scheme 13)[56,57] instead of HCN will be more convenient.[3,4] The syntheses of (**14**) and (**15**) (Scheme 13)[57] were accomplished in a buffered ($MgSO_4$) aqueous solution at about pH 9.5. The intermediate formation of epoxides on treatment of 2-halo alcohols with CN^- ions has already been mentioned in Section 1.8.1.2.1.ii.



Scheme 13

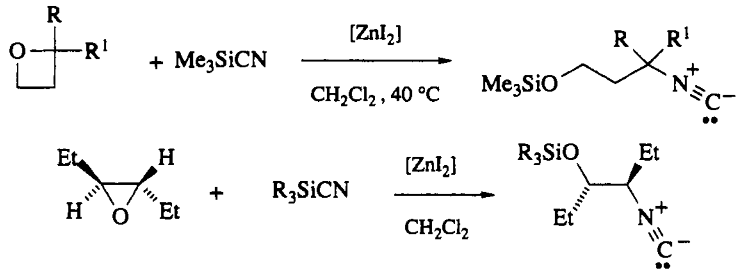
For the synthesis of *trans*-β-cyanohydroxy steroids from the corresponding epoxides treatment with HCN/triethyl aluminum or with diethyl aluminum cyanide proved to be particularly useful.[3]

Recently the transformation of oxiranes with TMS-CN in the presence of Lewis acids, which actually play a major role in this sequence, was investigated in detail. A few examples (Scheme 14)[58,59] were chosen to illustrate the topic.[3]



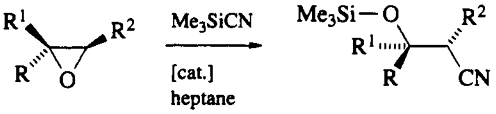
Scheme 14

The same reaction products are obtained from epoxides and TMS-CN in the presence of aluminum alkoxides,[60] samarium, cerium or lanthanum chlorides[61] as well as titanium tetraisopropanoate,[62,63] which may all be considered comparatively 'hard' Lewis acids. On the other hand various groups demonstrated[60,64,65] that 'softer' Lewis acids like zinc, tin and palladium dichloride may give rise to isocyanides (Scheme 15).



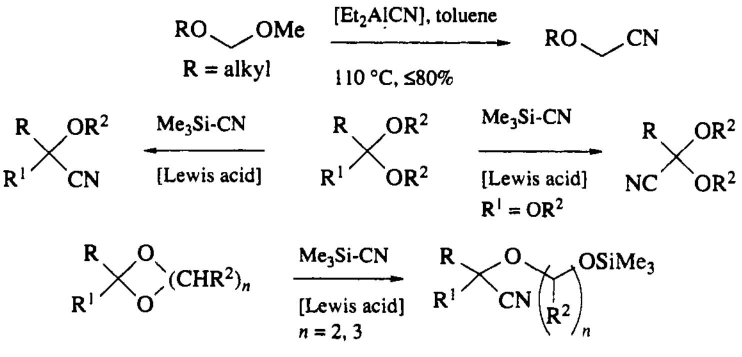
Scheme 15

According to a recent report[66] oxiranes yield β-trimethylsilyloxynitriles on treatment with TMS-CN in heptane in the presence of inorganic bases like calcium or magnesium oxide, hydroxyapatite or calcium fluoride, with high regioselectivity (equation 14).



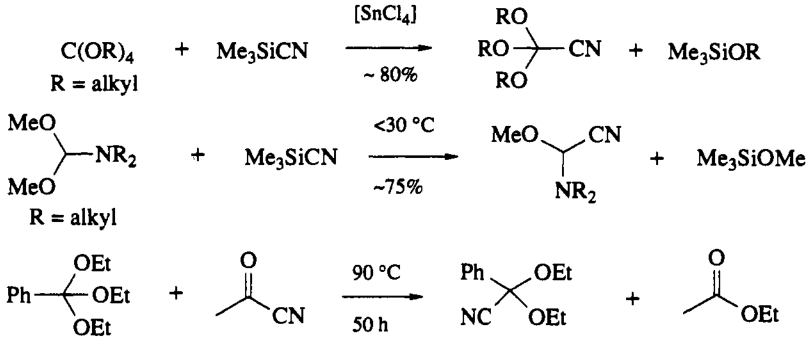
(14)

The exchange of alkoxy groups for the cyanide function can also be achieved in acetals (cyclic types like dioxolanes and 1,3-dioxane derivatives included), *S*,*N*-acetals and ortho esters with the combination of TMS-CN/Lewis acids,[3,67–69] or under neutral conditions with transition metal salts as catalysts (Scheme 16).[70] Furanose derivatives may be treated with TMS-CN in a similar way.[3,67,68]



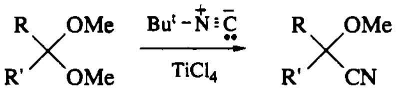
Scheme 16

Orthocarbonates and their analogs do exchange just one alkoxy group with TMS-CN/$SnCl_4$ (Scheme 17). In earlier papers even the direct reaction with HCN and $ZnCl_2$ at room temperature was reported to give (after several days or even some weeks) high yields.[2,4] Treatment with acetyl cyanide (Scheme 17) represents another possibility for transforming orthoesters into bisalkoxynitriles.[71]



Scheme 17

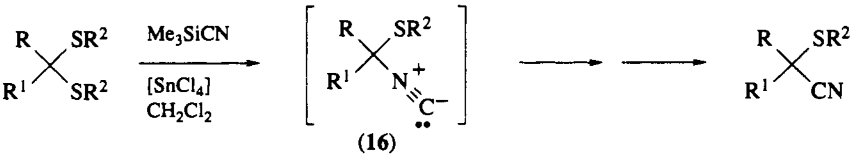
An elegant procedure for generating α-cyano ethers from acyclic or cyclic acetals and ketals is their reaction with *t*-alkyl isocyanides in the presence of an equimolar amount of $TiCl_4$ (Scheme 18).[3,72] The exchange of alkoxy groups against cyanide functions proved to be very important for the preparation of cyanoquinones.[73]



R	*R'*	*Yield*
Bu^n	H	81%
Ph	H	96%
$-(CH_2)_4-$		86%
$-(CH_2)_5-$		92%

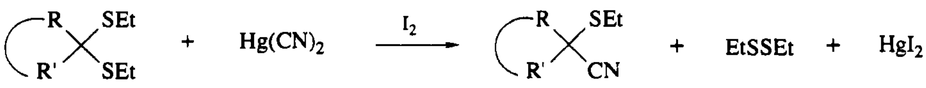
Scheme 18

As with oxiranes, ring opening with TMS-CN/$AlCl_3$ can also be carried out with thiiranes.[74] Dialkylaminotrialkylstannanes react with episulfides without anyLewis acid catalysis.[74] For the synthesis of α-cyano sulfides from thioacetals or thioketals with TMS-CN (Scheme 19), $SnCl_4$ proved to be the best catalyst.[34] For the mechanistic interpretation the authors favor the isonitrile (**16**) as a key intermediate. An additional technique for preparing alkylthionitriles uses $Hg(CN)_2$ in the presence of I_2, thus reaching yields of up to 80%.[75]



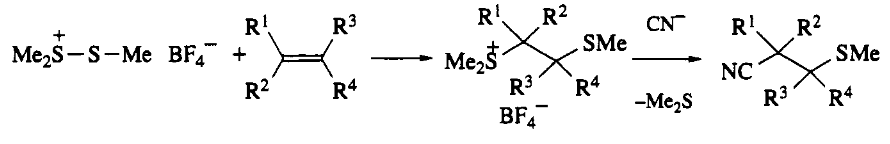
(**16**)

R	*R¹*	*R²*	*Yield*	*R*	*R¹*	*R²*	*Yield*
Pr^i	H	Et	93%	Ph	H	Et	84%
Bu^t	H	Et	81%	Tol	Me	Et	70%
c-C_6H_{11}	H	Et	85%	Et	Et	Ph	78%



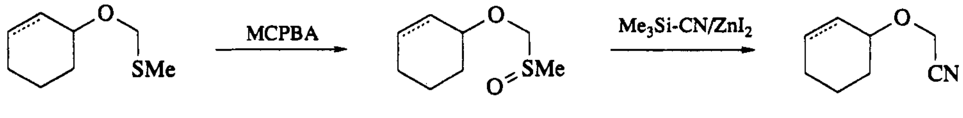
Scheme 19

The synthesis of α-methylthionitriles in high yield by 'cyanosulfenylation', *i.e.* addition of dimethyl(methylthio)sulfonium tetrafluoroborate to alkenes, followed by reaction with a CN donator, *e.g.* alkali metal cyanide/HBF_4 or TMS-CN (equation 15), was recently described by Trost.[76]



(15)

Sulfoxides may also be used for the preparation of nitriles: alkoxymethyl methyl sulfide, easily obtained from DMSO/acetic anhydride and primary alcohols, gives rise to the corresponding sulfoxides on treatment with MCPBA. By reaction with TMS-CN and ZnI_2, 2-alkoxyacetonitriles in good to excellent yields were obtained (Scheme 20).[77]

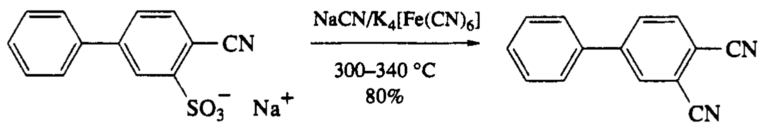


cyclohexenyl	85%	67%
cyclohexyl	100%	100%

Scheme 20

The thermal reaction between sulfonates and alkali metal cyanides (equation 16) or potassium hexacyanoferrate is more of historical value.[2,4] The finely powdered, dry and thoroughly mixed starting materials (equation 17) are heated up to 400 °C. For more efficient heat exchange the addition of mineral oil, sand, iron turnings or iron oxide is recommended. In spite of the quite forcing reaction conditions, yields of up to 80% are given in certain cases.[2]

$$ArSO_3M + MCN \xrightarrow{\Delta} Ar-CN + M_2SO_3 \qquad (16)$$



(17)

1.8.1.4 Exchange of Other Nitrogen Functionality

A quite important process for the preparation of aromatic nitriles is certainly the substitution of diazo groups by a cyanide function (equation 18). Following this route, the nitro or a primary amino group is, in principle, replaced by a CN ligand. The most important procedures are summarized in review articles[2,4] and in some shorter accounts.[78]

$$Ar-\overset{+}{N_2}\ X^- + CN^- \xrightarrow[\Delta,\ -N_2]{[CuCN]} Ar-CN \qquad (18)$$

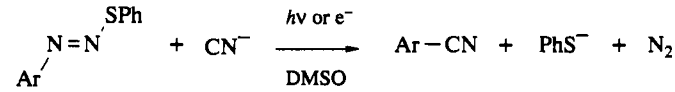
The first examples reported by Sandmeyer date back to 1884. The many various preparative procedures differ mainly in the type and the preparation of the copper–cyanide complex which is used.[2,4] In the 'Gattermann procedure' KCN in the presence of Cu powder is used. Generally one tries to avoid the formation of HCN on the addition of alkali metal cyanide to the acidic medium by neutralizing the diazonium salt solution in advance with sodium or barium carbonate. Cyanogen, which is formed from CN^- ions on treatment with Cu^{II} salts, is also a harmful by-product. In this case the addition of sodium hydrogen sulfite (equation 19) proved to be of great value.

$$2\,CuSO_4 + 2\,CN^- + HSO_3^- + H_2O \longrightarrow 2\,CuCN + 3\,HSO_4^- \qquad (19)$$

Better yields were often also obtained by use of the complex copper salt (**17**), prepared *in situ* from KCN and $CuSO_4$ in the presence of NH_3 (equation 20). In a thorough investigation Japanese workers[79] recently treated a series of aromatic amines with sodium nitrite in a mixture of polyethylene glycol and CH_2Cl_2 with HCl in a little water at 0 °C. After addition of the crystalline complex salt (**17**) the corresponding arenenitriles were obtained in high yield.

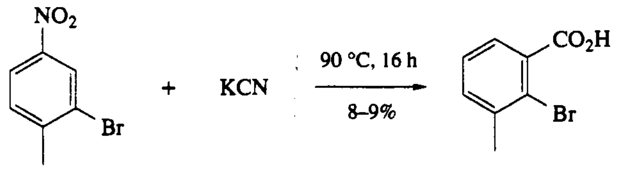
$$CuSO_4 + 4\,KCN + NH_3 \longrightarrow \underset{(\mathbf{17})}{K_2[Cu(NH_3)(CN)_4]} + K_2SO_4 \qquad (20)$$

The preparation of aromatic nitriles by an $S_{RN}1$ process was described recently.[80] Suitably substituted diazo sulfides, either isolated or only generated *in situ*, reacted with tetrabutylammonium cyanide under photon or electron stimulation (equation 21), leading to aryl cyanides with yields that are comparable with those of the Sandmeyer reaction. Bromo- and chloro-substituted aryl diazo sulfides afforded the corresponding dinitriles in high yields.



$$Ar{-}N{=}N{-}SPh + CN^- \xrightarrow[\text{DMSO}]{h\nu \text{ or } e^-} Ar{-}CN + PhS^- + N_2 \qquad (21)$$

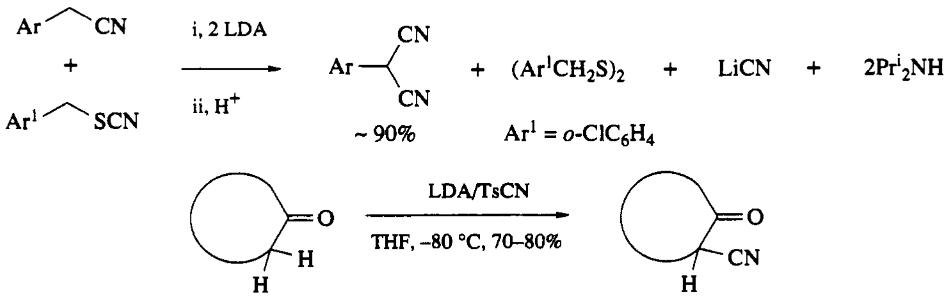
The thermally triggered transformation of aromatic nitro halides with KCN is known as the 'von Richter rearrangement'.[3,4,81] The process is illustrated in equation (22). In principle the nitro group is replaced by a cyano group by *cine* substitution, and a carboxylic acid is isolated, but with the carboxy group taking the *ortho* position to the former nitro substituent. The carboxy function is not formed by simple hydrolysis of the nitrile, as was believed for quite a period of time. A number of authors contributed to a better understanding of the reaction mechanism;[81–83] the details of the rearrangement, which involves heterocyclic intermediates, cannot be covered here. The yield of this reaction is generally rather low.



(22)

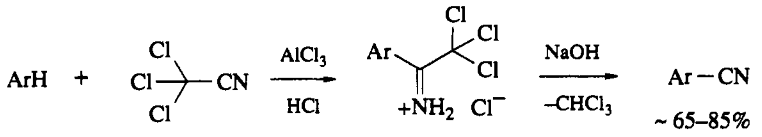
1.8.1.5 Exchange of a Hydrogen

The preparation of nitriles by (formal) exchange of a proton in alkyl-substituted aromatic and heteroaromatic systems, activated methylene compounds *etc*., for a cyanide group, using cyano halides, cyanogen, or aryl cyanates, is described mainly in the patent literature. Operating on contact times of a few seconds, reaction temperatures as high as 1000 °C are proposed.[2–4] The treatment of benzyl cyanide, deprotonated by LDA, with *o*-chlorobenzyl thiocyanate is, owing to mild reaction conditions and high yields, considered to be of some preparative value (Scheme 21).[3] Cyclic 2-cyano ketones may be obtained from the corresponding enolates on treatment with *p*-toluenesulfonyl cyanide.[3]



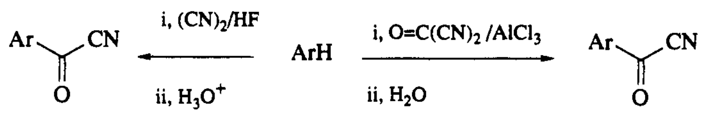
Scheme 21

A closer look has to be taken at the transformation of arenes into cyano derivatives. Aromatic starting materials may for instance be converted into nitriles under Friedel–Crafts conditions. Although a number of variations have been described,[2-4] the preparative value of this process seems to be quite low. The method of Houben and Fischer[2-4] gives rise to quite acceptable yields, but the work-up is very tedious (equation 23).[2]



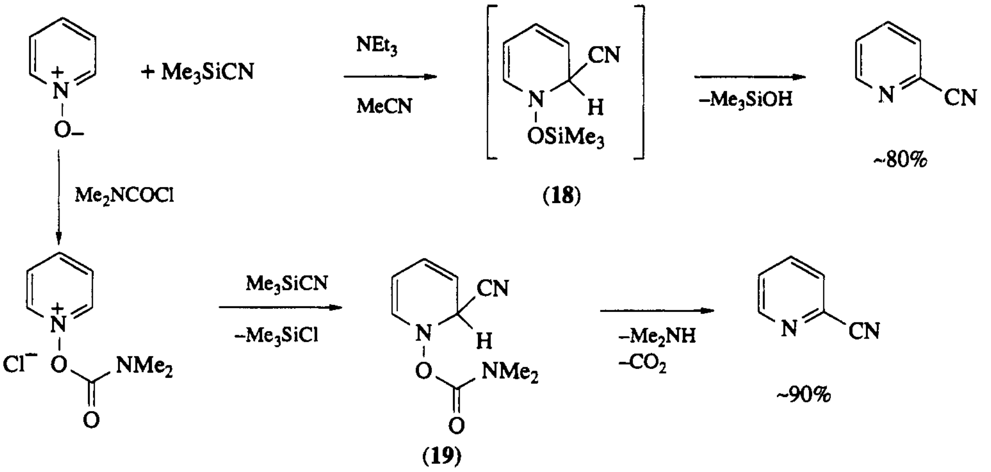
(23)

Aroyl cyanides may be obtained from substrates which are not too electron poor on treatment with cyanogen and HF, when the reaction temperature is slowly raised from –30 to 50 °C.[3] Instead of cyanogen, carbonyl cyanide may also be used,[3] but preparation and handling of this reagent is problematic (equation 24).[3]



(24)

High yields of α-cyanoazines are obtained from pyridine, quinoline or isoquinoline *N*-oxides and TMS-CN in acetonitrile/triethylamine or in DMF, and also in THF in the presence of tetrabutylammonium fluoride.[3] In another variation TMS-CN together with dimethylcarbamoyl chloride is used. Mechanistically these transformations should be similar to the Reissert reaction and may run through intermediates of type (**18**) and (**19**; Scheme 22).[3]



Scheme 22

1.8.1.6 Nitriles From Organometallic Compounds

As many organometallic compounds are prepared from the corresponding halides, their transformation into nitriles may in a way be considered as a substitution reaction.[2-4] Of special use is the treatment of aliphatic or aromatic Grignard compounds with cyanogen or halocyanogen. Aryl cyanates also react with Grignard reagents and usually give excellent yields of the corresponding nitriles (Scheme 23).[3] The reaction of lithium arenes and lithium heterocyclic compounds with *N*-methyl-*N*-phenylcyanamide is probably of only limited value (Scheme 23).[3] It should be mentioned that aluminum compounds may also serve for the preparation of acrylonitrile derivatives.[3]

$$\underset{X = \text{halogen}}{\text{R-MgX}} \xrightarrow[\text{ii, } H_3O^+]{\text{i, X'CN}} \text{R-CN} \xleftarrow[\text{ii, } H_3O^+]{\text{i, ArOCN}} \text{R-MgX}$$

$$\text{ArLi} \xrightarrow[\text{ii, } H_3O^+]{\text{i, PhNMeCN}} \text{ArCN}$$

Scheme 23

1.8.2 ISONITRILES

A series of papers from Gauthier and Hofmann, which are cited in nearly every review article on isocyanides,[84–92] is considered the real beginning of scientific work on this class of compounds. Lieke,[88,93] however, seems to have encountered isonitriles earlier. This author reports on 'cyanallyl', which was obtained from mercury cyanide with 1 equiv. of allyl iodide in a sealed tube at 100 °C. This 'cyanallyl' has a highly penetrating and most unpleasant smell'. Opening a vessel of the compound will pollute the air inside a room for several days, which is the reason why all work with this material was done in the open air. Hydrolysis of the compound with alcoholic KOH yielded (after acidification) formic acid and not, as the author had expected, crotonic acid. Lieke finishes: 'There was no more material for further investigations and no possibility of preparing more, as there were complaints about the infernal stink from all over the neighborhood'.[93]

Treatment of alkylating agents with metal cyanides should in principle be the method of choice for preparing isocyanides (equation 25). But as the cyanide ion again represents an ambident nucleophile, the well-known problems already discussed will arise (Section 1.8.2.1.i). It remains to be stated that simple alkylation of alkali metal cyanides with halogen compounds or dialkyl sulfates is not useful for the preparation of isonitriles. The formation of nitriles always prevails and isocyanides are at best obtained in yields of up to 25%.[85–88] The prospects are much better in the alkylation of heavy metal cyanides, if the reaction is done under conditions which initially give rise to isocyanide–transition metal complexes (equation 26). These will then be transformed into isonitriles by treatment with KCN. Under optimized conditions this technique yielded 55% of ethyl isocyanide.[15]

$$\text{R}{-}\text{X} + \underset{\bullet\bullet}{\text{N}}{\equiv}\underset{\bullet\bullet}{\text{C}}^{-}\,\text{M}^{+} \longrightarrow \text{R}{-}\overset{+}{\text{N}}{\equiv}\underset{\bullet\bullet}{\overset{-}{\text{C}}} + \text{MX} \tag{25}$$

$$\text{EtI} \xrightarrow[\text{ii, KCN/}H_2O]{\text{i, AgCN, 100 °C}} \text{Et}{-}\overset{+}{\text{N}}{\equiv}\underset{\bullet\bullet}{\overset{-}{\text{C}}} \tag{26}$$

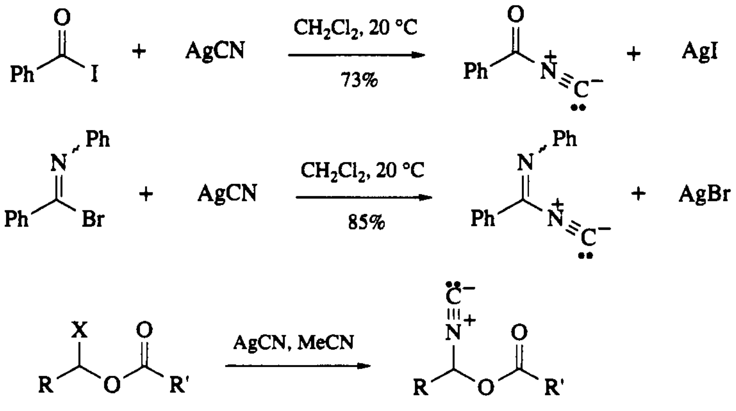
In general, these transformations are run at about 80–100 °C. For preparative use, alkyl iodides proved to be the most useful alkylating agents. CuCN may be used instead of AgCN, in experiments with zinc, cadmium and nickel cyanides; however, a serious decrease in yields was observed.[85–88] Although hexacyano-ferrates and -cobaltates have been recommended in a few cases,[85,88,92] their general use may be rather limited. Remarkable results have, however, been obtained with tetraalkyl- or tetraaryl-ammonium, -phosphonium or -arsonium dicyanoargentates in acetonitrile (Scheme 24).[94] In the diaryl- and triarylmethyl series the bromides or chlorides can be used instead of iodides. The reaction fails, however, with *p*-nitrophenyl derivatives, and aryl iodides and acyl chlorides are not attacked by oniumargentates.

$$2\,\text{MeI} + \text{Ph}_4\text{As}^+[\text{Ag(CN)}_2]^- \longrightarrow 2\,\text{Me}\overset{+}{\text{N}}\overset{-}{\text{C}} + \text{Ph}_4\text{As}^+[\text{AgI}_2]^-$$

$$2\,\text{PhCH}_2\text{Br} + \text{Me}_4\text{N}^+[\text{Ag(CN)}_2]^- \longrightarrow 2\,\text{PhCH}_2\overset{+}{\text{N}}\overset{-}{\text{C}} + \text{Me}_4\text{N}^+[\text{AgBr}_2]^-$$

Scheme 24

The quite labile acyl isocyanides on the other hand may be obtained from acyl iodides with AgCN in CH_2Cl_2; similarly imidoyl bromides give rise to imidoyl isocyanides (Scheme 25).[95,96] Both types of compounds decompose quite easily under comparatively mild conditions. Acyloxy isocyanides are well known too.[97]



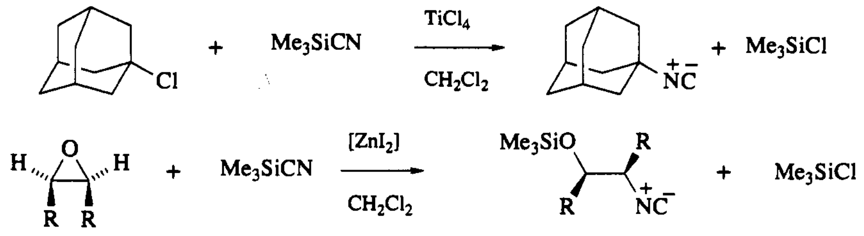
R = Me, X = I, R' = Ph; 79%

R = Ph, X = Br, R' = Bu^t; 72%

Scheme 25

Silver cyanide is also very useful for the preparation of glycosylisonitriles.[91] Although respectable yields are reported, the reaction is accompanied by anomerization.

In addition to its use in the preparation of nitriles, trimethylsilyl cyanide (TMS-CN) is also becoming a very useful reagent for the preparation of isocyanides. 1-Chloroadamantane, for instance, gives rise to 78% of the corresponding isonitrile in the presence of catalytic amounts of $TiCl_4$ (Scheme 26). Of special interest is the remarkably regioselective and stereoselective synthesis of trimethylsilyloxyalkyl isocyanides (Scheme 26) from oxiranes and TMS-CN in the presence of, for example, zinc halides (see also Section 1.8.1.3).[60,64,65]



Scheme 26

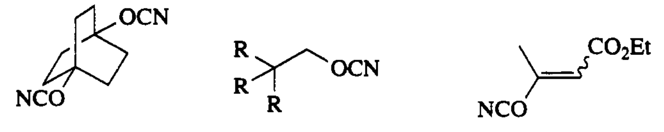
Finally, it should be remembered that isonitriles are not only obtained by substitution processes, but also by alternate routes, which may be of high value. In particular the various techniques for the dehydration of formamides, or the phase transfer version of the classical 'carbylamine' reaction should be noted.[84–92]

1.8.3 CYANATES

Attempts to prepare cyanates date back to 1857,[98] but remained unsuccessful for more than 100 years, so that eventually the existence of cyanic esters was questioned. The decisive breakthrough was achieved only about 30 years ago by Stroh and Gerber,[99] when they succeeded in preparing the sterically strongly shielded 2,6-bis(*t*-butylphenyl) cyanate. Today numerous alkyl and aryl cyanates are available and a series of review articles[100–105] provide an excellent overview of the chemistry of this class of compounds. Several tables listing numerous cyanates and the yields from different preparative procedures can be found.[100,103] Discussion of individual examples therefore seems to be unnecessary here. Suffice is to say that, while at the beginning steric protection was believed to be of utmost importance for the stability of the cyanates, it was later realized that sticking to exactly defined reaction conditions is a key measure in preventing secondary reactions.

While aromatic cyanates in their pure state tend to be quite stable compounds, their aliphatic counterparts very often prove to be extremely unstable molecules with an accordingly low preparative value.

Alkyl cyanates are obtained from sterically crowded alcohols or bridgehead derivatives *via* the corresponding alcoholates by treatment with cyanohalides in quite modest yields (Scheme 27). Higher yields and more stable products may be obtained from polyhalogenated alcohols or certain enols. These cyanates show properties comparable to the aromatic series discussed earlier.[106–108]



41% R = Me, 4.4%; R = Cl, 93% 73%
R = F, 80%; R = Br, 85%

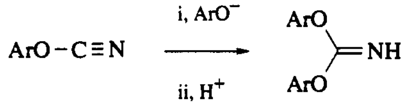
Scheme 27

Further reaction procedures leading to alkyl cyanates[102,103] cannot be discussed here. Mention has to be made, however, of the sometimes particularly useful thermal degradation of 5-alkoxy-1,2,3,4-thiatriazoles, which are often only prepared in solution.[102,103]

The aromatic cyanates are of much more importance. If phenols are treated with cyano halides in such a way as to definitely prevent an excess of the corresponding phenolate, aryl cyanates can be isolated in up to quantitative yields. To achieve this, triethylamine is slowly added to an equimolar mixture of the phenol and the cyano halide in a nonprotic solvent, preferably acetone or *n*-pentane/diethyl ether (equation 27).[109] Heteroaromatic hydroxy compounds can be treated in the same way. The method fails, however, if various electron-attracting substituents are present, as for instance with 2,4-dinitrophenol or polyhalophenols.[108]

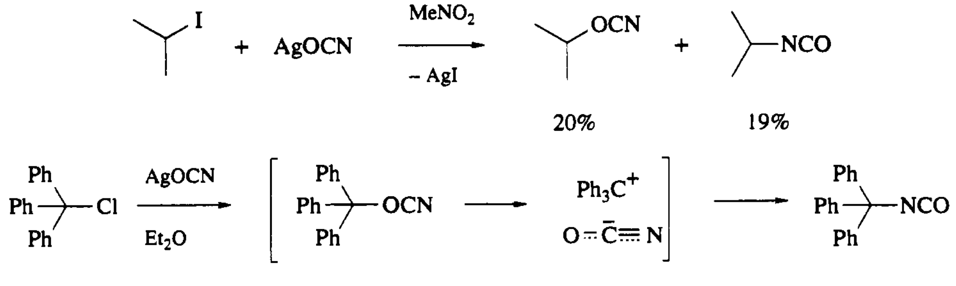
$$\mathrm{ArOH} \xrightarrow[\mathrm{NEt_3}]{\mathrm{ClCN}} \mathrm{ArO{-}CN} + \mathrm{Et_3\overset{+}{N}H\ Cl^-} \qquad (27)$$

Martin *et al.*[110] report investigations on the kinetics and the mechanism of aryl cyanate formation from cyanogen bromide and phenols in the presence of different tertiary aliphatic amines. According to Vowinkel,[111] the use of diethyl ether as the solvent at –10 °C raises the yields and various patents describe how the amines can be replaced by sodium hydroxide. There are even reports on work in aqueous solution under phase transfer conditions.[103] With all synthetic variants it is crucial to avoid a surplus of the phenolate as only under these conditions can the often quite fast formation of imino carbonates be prevented (equation 28).



$$\mathrm{ArO{-}C{\equiv}N} \xrightarrow[\mathrm{ii,\ H^+}]{\mathrm{i,\ ArO^-}} \mathrm{(ArO)_2C{=}NH} \qquad (28)$$

Treatment of alkyl halides with alkali metal or silver cyanate is of no preparative value for the synthesis of cyanates.[103,112,113] As cyanate ions do represent ambident nucleophiles, Holm and Wentrup[114] tried to reach cyanates under well-defined S_N1 conditions (Scheme 28). But even treatment of isopropyl iodide with silver cyanate in nitromethane provided only a very low yield of a 1:1 mixture of isopropyl cyanate and the corresponding isocyanate, and from a reaction of silver cyanate with triphenylchloromethane they isolated only triphenylmethyl isocyanate, although the cyanate may have been an intermediate in this transformation.[114]



Scheme 28

1.8.4 AZIDES

1.8.4.1 General Remarks

The history of the azides starts in 1864 with the first report on phenyl azide by Griess.[115] In 1990, the first preparation of hydrazoic acid by Curtius had its 100th anniversary.[116] There are many reports on aliphatic and aromatic azides in the literature. In a very recent and thorough review[117] Scriven and Turnbull present a highly impressive list of review articles which have appeared in the 20 years since 1970. Out of the many possibilities for preparing all types of azides, substitution reactions are of special importance. Here again a series of recent review articles[117–123] will guarantee a quick orientation in the field.

1.8.4.2 Azides from Halogen, Sulfonate and Sulfate Derivatives

1.8.4.2.1 Alkyl azides

The reaction of halides or sulfonates with alkali metal azides, mostly NaN_3, offers a simple and high yield access to alkyl azides.[118,119] For the preparation of the most simple ones, *e.g.* methyl and ethyl azide, the corresponding sulfates were for a long time considered the only useful starting materials.[118,119] The preparation of azidoethane in ether solution from ethyl iodide and NaN_3 was reported recently (Scheme 29).[124] Alkane- and *p*-toluene-sulfonates are well-established starting materials for the preparation of azido carbohydrates.[117,119] Their particular importance rests mainly on the possibility for reductive generation of amino sugars. The crucial role of alkanesulfonates for the generation of alkyl azides is demonstrated by Scriven and Turnbull[117] with numerous examples.

$$\mathrm{R{-}X} \quad + \quad \mathrm{N_3^-} \longrightarrow \mathrm{R{-}N_3} \quad + \quad \mathrm{X^-}$$

$$\mathrm{X = halogen,\ OSO_2R',\ OSO_2OR'}$$

$$\mathrm{EtI} \quad + \quad \mathrm{NaN_3} \xrightarrow[\mathrm{Et_2O/H_2O}]{\mathrm{Bu_4N^+\,BF_4^-}} \mathrm{EtN_3} \quad + \quad \mathrm{NaI}$$

Scheme 29

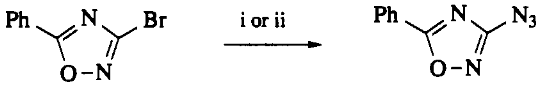
If alkyl halides are used as starting materials, one is not restricted to iodides, as bromides and chlorides may also be used. So-called activated NaN_3[118,119,125] or AgN_3 is only necessary in special cases, and may then, however, prove to be of particular advantage.[118] Besides primary alkyl halides, secondary ones may also be considered as starting materials and even some tertiary azides were prepared this way.[117] Some experimental details can be found in Grundmann's review;[118] tables with numerous examples[118,119] provide a very good impression of the scope of this transformation. The high tendency for explosions of many azides, particularly the lower ones, is a good reason to generate and transform these compounds, whenever possible, in solution only.

For a long time protic solvents like methanol or water at temperatures between 60 and 100 °C were considered best. 2-Alkoxyethanols ('carbitols') with their higher boiling points have in the meantime become quite popular.[118,119] Of course dipolar aprotic solvents like DMSO, DMF and also nitrobenzene may be used for the preparation of azides too, although the isolation of reaction products may sometimes be difficult here.[117] Given slowly reacting substrates, the higher solubility of LiN_3 may in certain cases provide advantages compared to other alkali metal azides.[117] A combination of NaN_3 and $ZnCl_2$ is often recommended, particularly for the generation of tertiary azides.[117,126]

The various phase transfer techniques also led to very good results in azide synthesis. Excellent yields of alkyl azides were secured, for instance, when alkyl bromides were treated with alkali metal azides in the presence of catalytic amounts of tetrabutylammonium bromide or 'aliquat 336' (equation 29).[117,127] The use of crown ethers has been described as well.[117]

A very impressive example consists of the preparation of 3-azido-1,2,4-oxadiazole, which after a series of failures was eventually obtained from the corresponding bromo compound with LiN_3 in dry DMF or with KN_3 in the presence of 18-crown-6 (Scheme 30).[128]

$$\underset{R = \text{alkyl}}{R{-}Br} + NaN_3 \xrightarrow[\sim 90\%]{H_2O/\text{aliquat } 336} R{-}N_3 + NaBr \qquad (29)$$



no reaction with:
NaN_3, DMF/H_2O, 100°C;
NaN_3/NaI, 50 °C;
LiN_3, MeOH, 65 °C;
$Bu_4N^+N_3^-$, MeCN, 83 °C

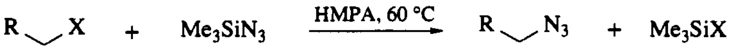
i, KN_3, DMF, 18-crown-6, 72 h, 90 °C, 50%; ii, LiN_3, DMF, 45 h, 90 °C, 50%

Scheme 30

The acceleration of substitution reactions with azides using ultrasound techniques (Scheme 31) has not yet been investigated in detail.[129] Activated primary halides react with trimethylsilyl azide (TMS-A) under particularly mild and absolutely neutral conditions (Scheme 31).[117] Secondary and tertiary cyclic halides were treated with TMS-A/$SnCl_4$ in CH_2Cl_2 or $CHCl_3$ to yield the corresponding azido compounds.[117] Very impressive results with yields of about 90% were in this case reported in the adamantane and diamantane series.[117] High solubility in organic solvents is also noticed with acetyl azide, which, prepared *in situ*, has also been used for azide syntheses. The scope of this reaction has still to be determined, however.[117] Hassner[130] noticed nearly quantitative yields of azides when alkyl halides (or tosylates) were treated with polymeric quaternary ammonium azides.

$$R{-}X + NaN_3 \xrightarrow{H_2O,\ \text{ultrasound}} R{-}N_3 + NaX$$

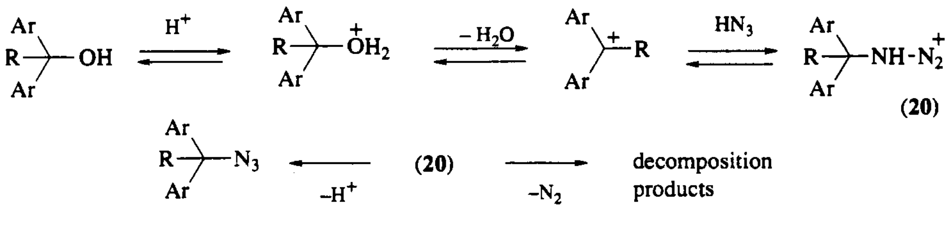
R = $HC{\equiv}CCH_2$, X = Br; 88%
R = $NCCH_2$, X = Cl; 64%
R = $H_2C{=}CHCH_2$, X = Br; 91%
R = $H_2C{=}C(Cl)CH_2$, X = Cl; 81%
R = Et, X = Br; 20%



R = $ArCH_2$, $R'_2C{=}CHCH_2$, $NCCH_2$, EtO_2CCH_2; 60–87%

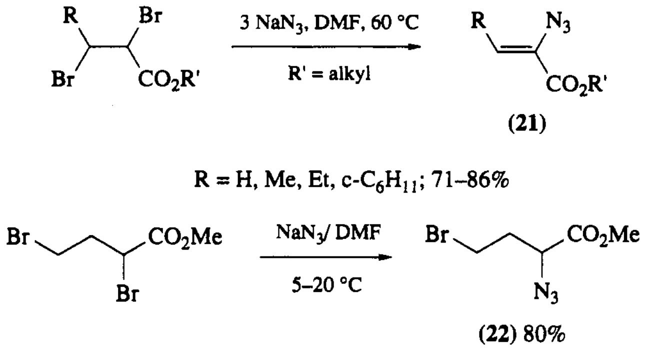
Scheme 31

Mechanistically most of these transformations correspond to *S*N2-type substitutions; chiral substrates react with inversion. In certain cases, however, azides may also be obtained under *S*N1 conditions.[118,119,126b] Some di- and tri-arylmethanols for instance (Scheme 32) react with HN_3 in the presence of trichloroacetic acid *via* the corresponding carbenium ions. Sulfuric acid seems to be inferior for these transformations.[118,119] Under highly acidic conditions the intermediate (**20**) obviously tends to decompose with the elimination of nitrogen (*cf.* Schmidt reaction[117]). *S*N1 substitution is also highly probable in the reaction of α-halo ethers and sulfides with azide ions.[118,119] In some cases even *S*RN1-type substitution was observed for the halogen/azide exchange.[117]



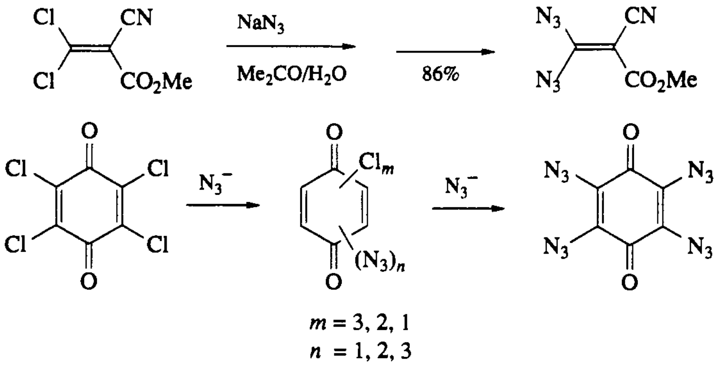
Scheme 32

By starting from the corresponding dihalides, diazides may also be obtained with ease. A list of numerous examples is given by Grundmann.[118] The high tendency of some diazides to explode, has to be mentioned here. For a demonstration of the strong influence of structural parameters on the reactivity of dihalides with azide ions[117] two examples will suffice (Scheme 33): in a sequence of elimination, addition (Michael acceptor) and substitution steps, followed by another β-elimination, 2,3-dibromocarboxylic esters give rise to high yields of the vinyl azides (**21**) with 3 equiv. of NaN_3; on the other hand, methyl 2,4-dibromobutanoate yields 80% of the monoazido ester (**22**) with only a very small amount of the corresponding bisazido compound.[131]



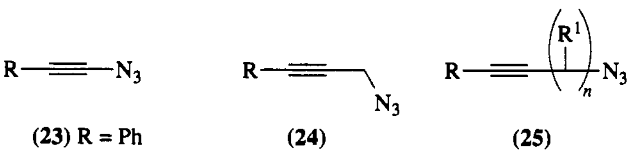
Scheme 33

Vinyl azides are generally prepared from 2-azido halides by elimination,[118,119,132,133] while vinylogous acid chlorides and similar systems may be treated with azide ions directly in an addition–elimination sequence (Scheme 34). With haloquinones smooth transformations into azidoquinones are also observed.[118,119,134,135] Thus all four chloro substituents of chloranil can be successively exchanged with azide ions (Scheme 34).



Scheme 34

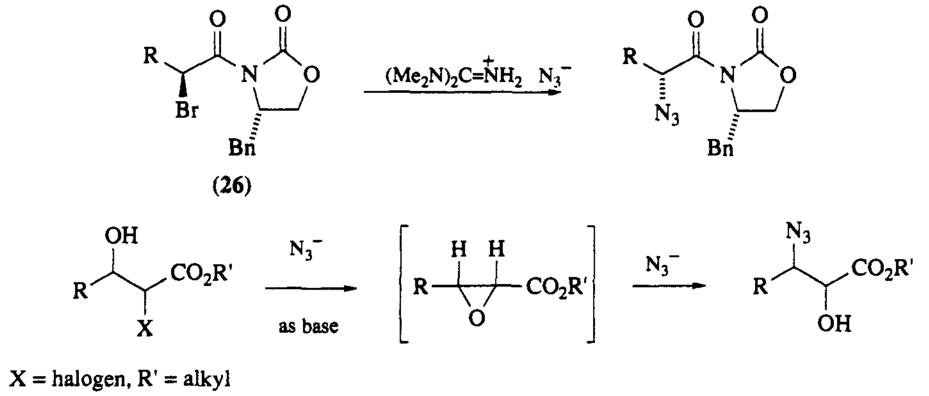
There is still no successful approach to 1-azidoalkynes, although the corresponding phenyl derivative (**23**; Scheme 35) is thought to be a short-lived intermediate in the reaction of chlorophenylacetylene with azide ions.[117,118] In contrast to this, propargylic azide (**24**) and its higher homologs (**25**) can be obtained in the usual way.[117] The formation of these compounds is sometimes accompanied by rearrangements, which also very often take place with azidoallene derivatives; their chemistry was intensively studied recently by Priebe[117] and Banert.[136]



Scheme 35

Mechanistically, there is a range of possibilities for the reaction of allylic halides with azide ions, with many details still open for discussion.[117,119] Besides simple substitution reactions, depending on the structure of the starting materials and the experimental conditions, allylic rearrangements as well as equilibration reactions may be observed.[117,119]

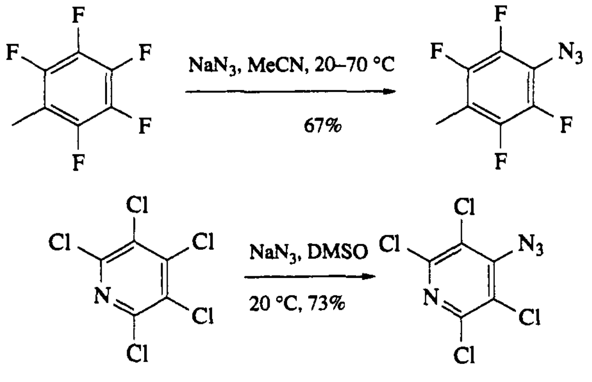
Nucleophilic substitution of functionalized halides may also lead to azides, carrying further functional groups, not only in the 'periphery' of the molecule, but also in the very close neighborhood (α-position). A few examples have been mentioned already. Quite well known are, for instance, α-azido-alkylamines, -carboxylic acid derivatives, ethers, sulfides and ketones, which can be quite simply obtained from the corresponding halo compounds.[117,118] The observation that the chiral substrate (**26**) undergoes the substitution reaction, if tetramethylguanidinium azide is used, with less than 1% epimerization (Scheme 36)[137] merits special interest. In the interaction of azide ions with 3-hydroxy-2-halocarboxylic esters, a rearrangement *via* oxiranes may take place (Scheme 36).[118] Aiming at a stereoselective synthesis of the corresponding amines, a series of azide steroids was prepared,[117,119] starting from the halo derivatives or the corresponding sulfonates. In most cases an S_N2-type process, leading to stereochemically well-defined products, was observed.



Scheme 36

1.8.4.2.2 Aryl azides

The synthesis of aromatic azides (Scheme 37) from aryl halides with azide ions (S_NAr) is particularly successful with systems that carry an activating substituent, an electron-withdrawing group, either in the *ortho* or the *para* position relative to the potential leaving group.[118,119] A table with numerous examples can be found in the literature.[119] Fluoride ion as a leaving group is superior to the other halides. Dipolar aprotic solvents, such as DMF for instance, have their special merits in these transformations, too. The reaction of 2,4- or 2,6-dinitroaryl halides with azide ions was shown to be accelerated in micelles or in the presence of quaternary ammonium salts.[117]

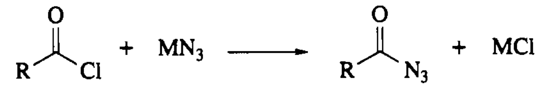


Scheme 37

Various perhalo aromatic compounds as well as a series of heterocyclic precursors, such as, for instance, chloro-pyridazine or -triazine derivatives, gave rise to the corresponding azides, too.[117,119,121]

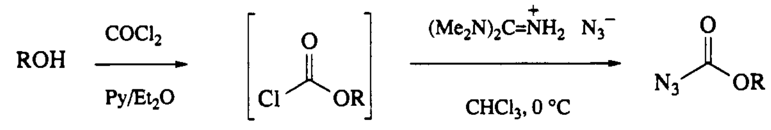
1.8.4.2.3 *Acyl azides*

The preparation of acyl azides by substitution is presented in connection with the Curtius rearrangement in a series of review articles.[117-121,125,138] The most important synthetic methods are discussed in the sequel. The routine technique for the generation of various acyl azides by substitution starts from acyl chlorides and azide ions (equation 30).[119-121,125] The reactions are generally run by mixing an aqueous solution of the azide, mostly NaN_3, with a solution of the acid chloride in a water-miscible solvent such as acetone, alcohols, dioxane, HOAc or DMF. The competing solvolysis of the acyl chloride with alcohols must be considered. In certain cases the use of tertiary amines or amine oxides as catalysts is recommended.[120] If suspensions of NaN_3 in organic solvents such as pyridine, toluene, xylene or nitrobenzene are used, reaction temperatures often have to be used that lead to the Curtius rearrangement of the required acyl azide.[119,120] In this case the use of 'activated' NaN_3 is recommended.[118] Advantages are seen by using LiN_3 in DMF,[139] mainly due to its better solubility, and the same holds for a series of tetraalkylammonium azides, which in many cases are thermally quite stable, too.[120] DMSO cannot be used as the solvent here, as it reacts with acyl chlorides quite vigorously at room temperature.[119]



(30)

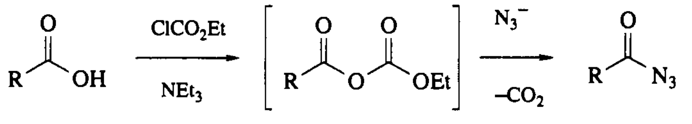
The reaction of acid chlorides with tetramethylguanidinium azide also proceeds under very mild conditions.[140] Using this technique even *t*-alkyl azidoformates may be prepared (Scheme 38). Quantitative yields of acyl azides (in solution) are reported for the interaction of acid chlorides in toluene with HN_3/pyridine at 0 °C. Even sterically hindered educts are smoothly converted into acyl azides.[121] If tetraalkylammonium azides are used, the use of hazardous hydrazoic acid is avoided.[120,121]



R = Bu^t, ~100%; R = *t*-amyl, 84%; R = Ph, 97%

Scheme 38

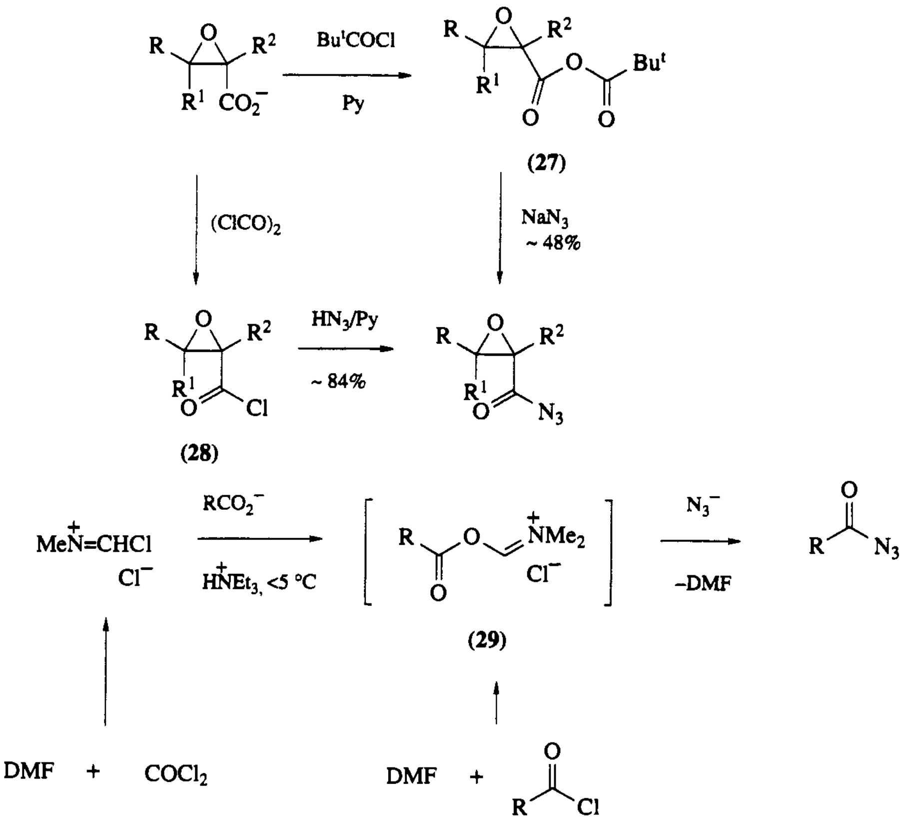
It should be mentioned at this stage that instead of acyl chlorides, mixed anhydrides may also be used for the synthesis of acyl azides. From carboxylic acids and chloroformates/triethylamine, mixed anhydrides are formed, which can directly react with azide ions. Sterically hindered acids fail in this procedure (equation 31).[119-121] The similar synthesis of *t*-butyl azidoformate by reaction of *t*-butylcarbonic diethylphosphoric anhydride with KN_3 is described in *Organic Syntheses*.[141]



(31)

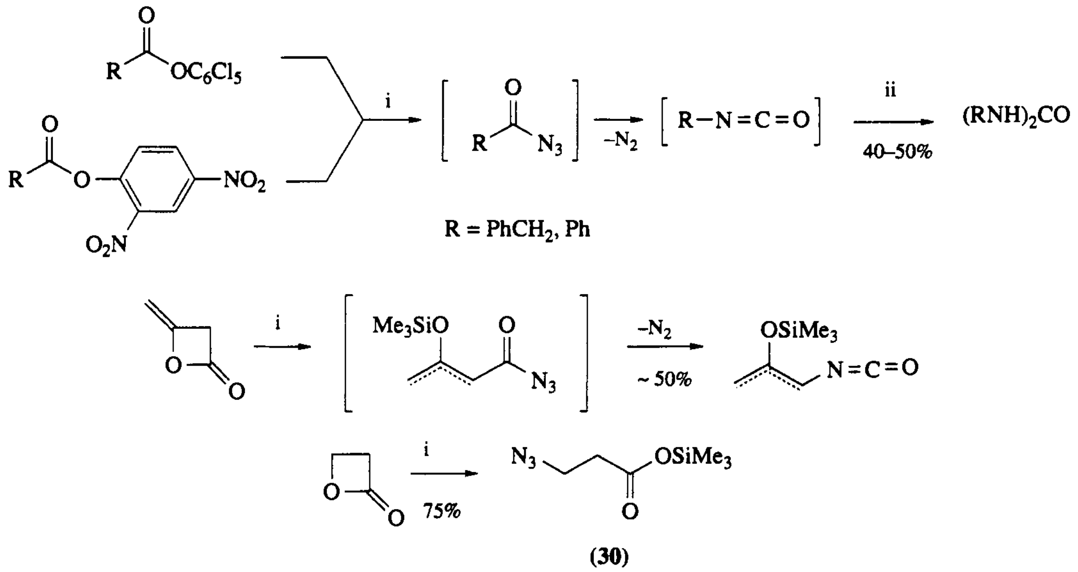
In synthesizing α,β-epoxyacyl azides Zwanenburg *et al.*[142] noted that treatment of the acid chloride (**28**) with HN_3/pyridine is superior to the reaction of mixed anhydrides (**27**), prepared *in situ*, with NaN_3 (Scheme 39). Another version of this process uses the transformation of acyloxyiminium salts of type (**29**) (again prepared *in situ*) with NaN_3 (Scheme 39).[143] The authors did not isolate the azido derivatives, but used them in a subsequent Curtius rearrangement in boiling toluene. After a final treatment with aniline, yields of the corresponding ureas were between 60 and 80% with alkyl compounds and 86–100% for aryl systems. Palomo *et al.*[144] used a very similar procedure and were able to isolate the azides.

Trimethylsilyl azide (TMS-A) in the presence of catalytic amounts of pyridine turned out to be very useful in the preparation of acyl azides, as this reagent will not only transform acyl chlorides and mixed anhydrides into azides, but also works with reactive esters and lactones (Scheme 40).[121,145] Many of these reactions have, however, been run under conditions which will lead to the Curtius rearrangement of the azide intermediates. Pyridine as a catalyst can be replaced by the combination KN_3/18-crown-6.[121] Diazidodiphenylsilane, which was investigated as well, will probably not become a standard reagent.[145]



Scheme 39

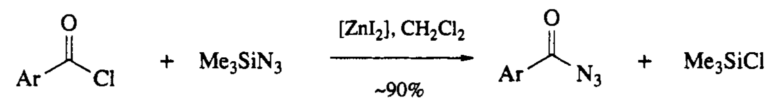
A slight deviation from the routine mechanism is found in the reaction of TMS-A with β-propiolactone (Scheme 40), which generates 75% of the azidosilyl ester (**30**).[144]



i, Me_3SiN_3, [Py], dioxane, 100 °C; ii, RNH_2

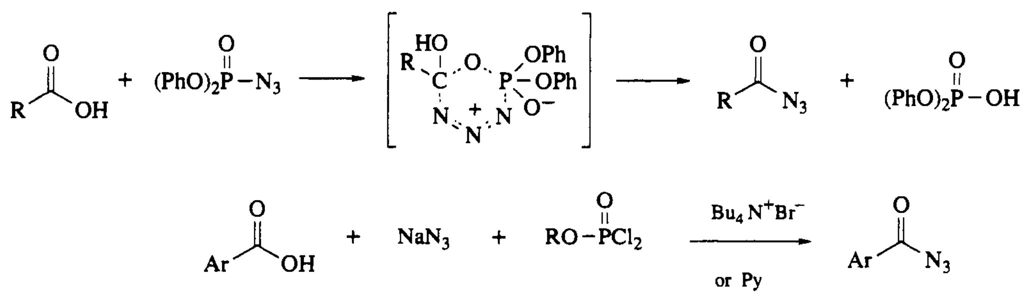
Scheme 40

The transformation of aroyl chlorides with TMS-A can be run at 0 °C if a catalytic amount of ZnI_2 is used in CH_2Cl_2 (equation 32). This provides a simple and high-yielding route to aroyl azides, which may be isolated in a pure state.[146] Electron-donating groups in the aryl group retard the reaction, without, however, influencing yields.



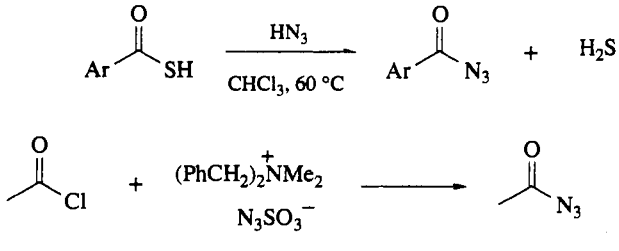
(32)

In a direct route from carboxylic acids to acyl azides diphenyl phosphorazidate is used;[121] probably the reaction passes through a cyclic transition state (Scheme 41). With aromatic and heteroaromatic educts, yields as high as 75% may be obtained.[147] If aliphatic acids are treated under the same conditions, the corresponding azides are, however, immediately transformed into urethanes *via* isocyanates.[148] Aroyl azides can also be obtained in excellent yields by reaction of carboxylic acids with NaN_3 and phenyl dichlorophosphate in the presence of tetrabutylammonium bromide or pyridine (Scheme 41).[149]



Scheme 41

The preparation of acid azides from thiocarboxylic acids/HN_3 or from acyl chlorides with dibenzyldimethylammonium azidosulfonate[119] has not yet found broad application (Scheme 42).

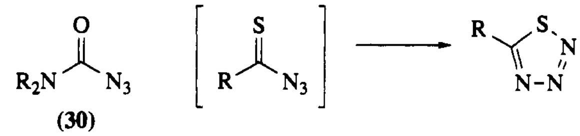


Scheme 42

There are great differences in the thermal stabilities of acyl azides. While the aromatic derivatives are considered to be comparatively stable, their aliphatic counterparts very often decompose close to room temperature. As in the course of this destruction the preparatively most useful Curtius rearrangement will take place, this instability is not necessarily a disadvantage.

Owing to the unpredictable tendency of most azides to explode suddenly, it is essential in the preparation of acyl azides to pay strict attention to the necessary precautions.

As demonstrated above, azidoformates, which, like the very similar carbamoyl azides (**30**; equation 33),[119,120,150] play an important role in peptide chemistry and as nitrene precursors,[119,120] can be generated in the usual way. Their thermal stability is generally higher than that of alkanoyl and aroyl azides. The tendency of acyl azides to form 1,2,3,4-oxatriazoles in a cyclization process is extremely low. In contrast to this thioacyl azides, which are only generated on treatment of thioxohydrazides with nitrous acid, seem to be only very short-lived intermediates, which immediately form 1,2,3,4-thiatriazoles as stable end products.[120]

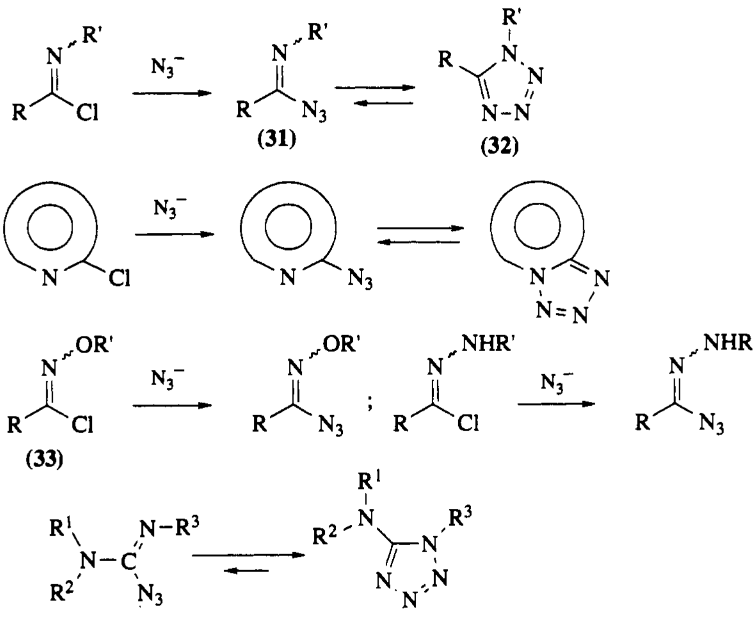


(30)

(33)

1.8.4.2.4 *Further azides of the type RC(=X)N$_3$*

In the reaction of imidoyl halides with azide ions, imidoyl azides (**31**) are obtained, which caused some interest on account of their ring–chain tautomerism (**31**)/(**32**) (Scheme 43).[119,120] It is not possible, however, to discuss this point in detail here.[117,120,151] The final elucidation of a series of dubious structural assignments had to wait until the advent of modern spectroscopic methods. As expected, the position of this equilibrium is influenced by the nature of substituents R/R′ as well as by temperature and solvents. Electron-withdrawing ligands seem to favor the formation of the tetrazole isomer (**32**). The equilibrium (**31**)/(**32**) does not always operate — there are a number of cases known which show a comparatively high activation barrier.[120] The same problems are encountered with the reaction products from 2-halo-azoles and -azines with azide ions.[118–120]



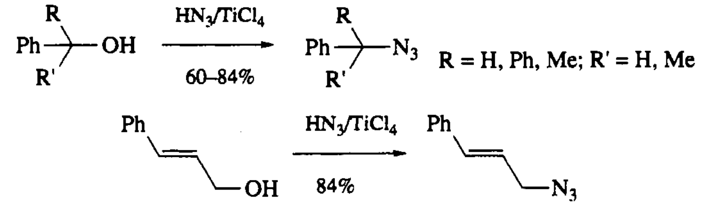
Scheme 43

In a similar way to azidoazomethines, the corresponding azido oximes and hydrazides may be obtained (Scheme 43). The formation of cyclic tautomers seems to play only a minor role here.[117,119,120,152] The stereochemical aspects of the transformation of *O*-acylhydroxamoyl chlorides (**33**; R = $^-$Ac) with N$_3$ ions have been studied by Hegarty.[153] Further systems such as the interesting pairs guanyl azides (**34**)/5-aminotetrazoles, are comprehensively discussed by Lwowski.[120]

1.8.4.3 Azides by Exchange of Oxygen or Sulfur Functionality

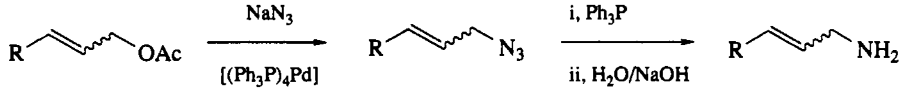
Alcohols may be used in various ways as starting materials for azides. The well-known transformations *via* alkyl halides and sulfonates need not be discussed at this stage again (see Section 1.8.4.2.1). The activation of alcohols *via* phosphonium salts has found application in the carbohydrate series.[117]

The S_N1-type transformation of secondary and tertiary alkanols with the help of trichloroacetic acid and hydrazoic acid has also been mentioned in Section 1.8.4.2.1. Several azides, *e.g.* of the adamantane and diamantane series, have been obtained on treatment of the corresponding alcohols with NaN$_3$ and sulfuric acid.[154] As expected, this procedure lends itself particularly well to the formation of tertiary azides.[117] Treatment of tertiary carbinols with HN$_3$ and BF$_3$ or other Lewis acids represents another route to tertiary azido compounds.[117] On the other hand, with primary alcohols this procedure only succeeded when benzylic or allylic alcohols were used (Scheme 44), an observation which, together with the partial racemization noticed in the case of chiral educts, hints at carbenium ion intermediates.[117]



Scheme 44

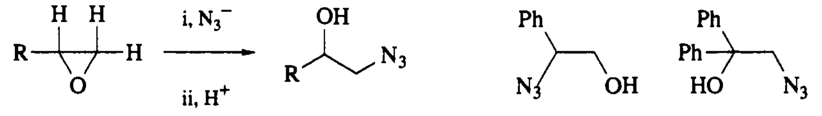
Walden inversion, on the other hand, is observed in the reaction of alkanols with diethyl azodicarboxylate, triphenylphosphine and HN_3 (*cf.* the Mitsunobu reaction).[117,155] There is also some interest in the Pd-catalyzed transformation of allyl acetates into the corresponding azido derivatives.[156] Primary amines can be generated in a one-pot procedure without isolation of these azides, by further treatment with Ph_3P and subsequent hydrolysis (Scheme 45).



Scheme 45

The direct transformation of carboxylic acids into azides and the ring fission of β-lactones have been discussed in Section 1.8.4.2.3.

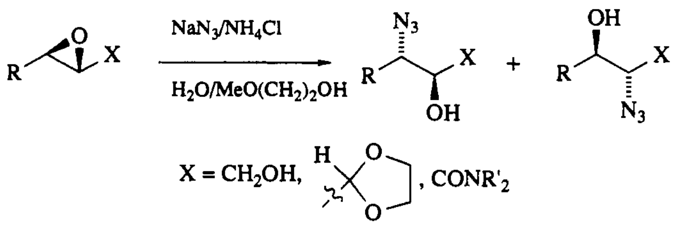
Opening of epoxides with azide ions represents a very interesting route to azidocarbinols. The large number of examples quoted in the literature proves the broad scope of this technique.[117-119,157] On treatment of nonsymmetrically substituted oxiranes, the products expected from an S_N2 process are usually obtained. In boiling aqueous dioxane, cyclohexene oxide gives rise to 61% of *trans*-2-azidocyclohexanol. The reported formation of (**35**; Scheme 46) with styrene oxide is unexpected,[158b] particularly if the formation of (**36**) from the analogous diphenyl precursor is considered.[158]



(**35**) 63% (**36**) 73%

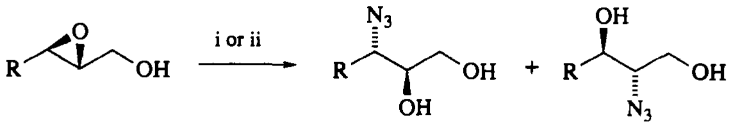
Scheme 46

In a recent very thorough investigation, Behrens and Sharpless studied the possibilities for the selective transformation of 2,3-epoxy-carbinols, -acetals and -amides into azidoalkanols (Scheme 47).[159] The regioselectivity of this process turned out to be strongly dependent on steric as well as electronic parameters; it is not possible to discuss details here.



Scheme 47

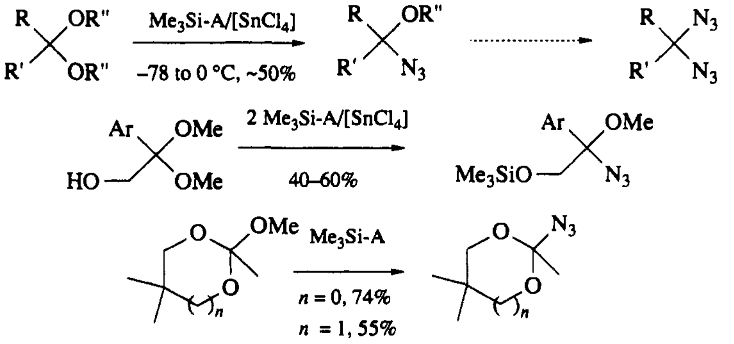
The special merits of solid-supported sodium azide reagents were intensely investigated recently. Under well-defined reaction conditions very high regioselectivity may be achieved with nonsymmetrically substituted oxiranes.[160] A new approach to an especially mild and selective synthesis of 3-azidodiols was recently described, which involves a highly regio- and stereo-selective ring fission of epoxy alcohols, using TMS-A and Et_2AlF (Scheme 48).[161] For comparison, some results with NaN_3/NH_4Cl are also included.



i, $Me_3Si\text{-}A/Et_2AlF$; R = Pr^i, 81%, 98:2; R = n-C_7H_{15}, 84%, 98:2;
ii, NaN_3/NH_4Cl; R = Pr^i, 78:22; R = n-C_7H_{15}, 90%, 53:47

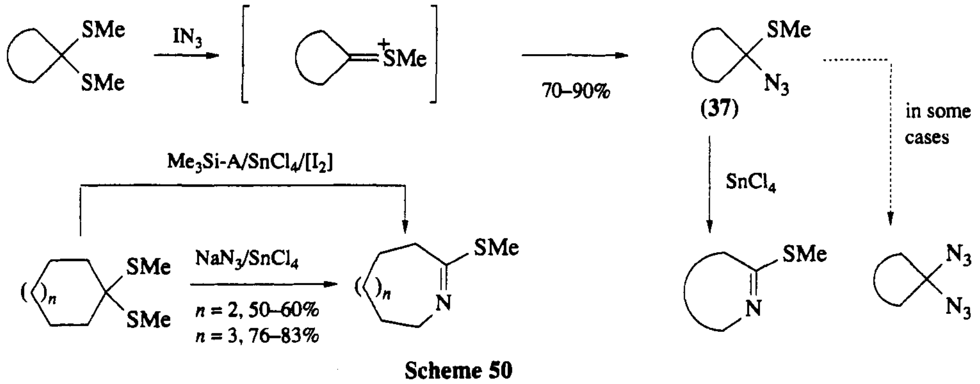
Scheme 48

α-Azido ethers or even diazides can be obtained on treatment of acetals with TMS-A/$SnCl_4$ (Scheme 49).[162,163] TMS-A proved also to be the best reagent for the transformation of orthoesters (cyclic ones included) into the corresponding azido derivatives.[164] Cationic species are considered as intermediates.



Scheme 49

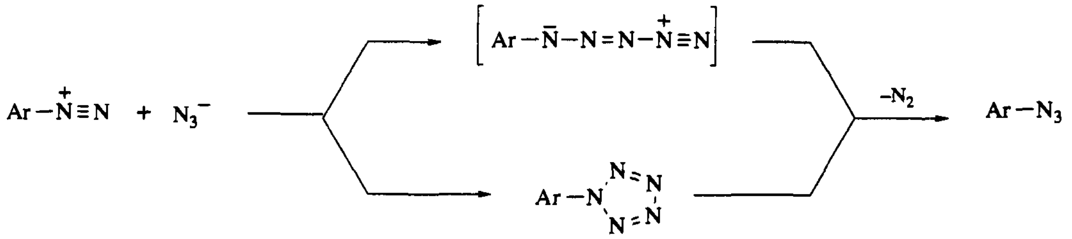
Thioketals reacted with IN_3 to give α-azido sulfides or 1,1-diazides.[165] Treatment of the azido sulfides (**37**) with $SnCl_4$ led to the corresponding imino sulfides; these were also available directly from the thioketals (probably *via* azido sulfides) by reaction with $NaN_3/SnCl_4$ or with TMS-A/$SnCl_4$ and a catalytic amount of iodine (Scheme 50).



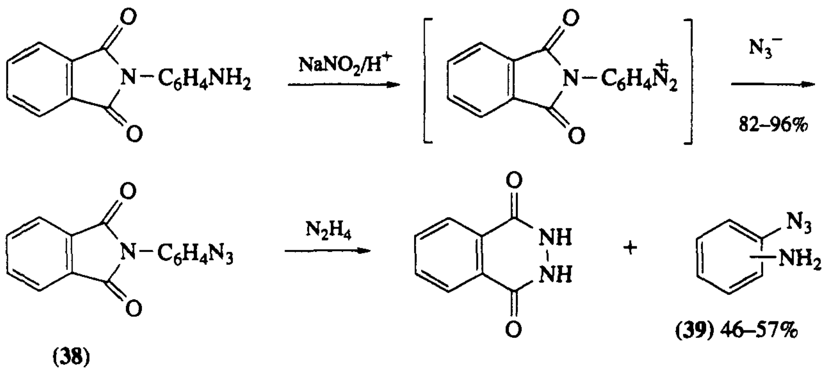
Scheme 50

1.8.4.4 Azides by Exchange of Nitrogen Functionality

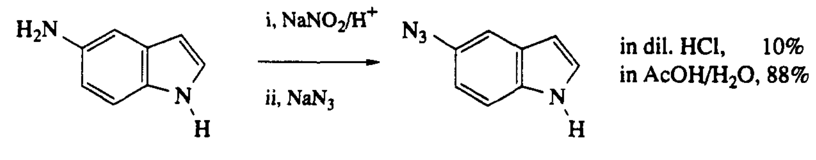
In an interesting technique for the preparation of aromatic azides, aryl diazonium salts are treated with azide ions.[117-119] At least in a very formal sense, one can consider this reaction as a substitution process, although the real mechanism of this transformation is much more complicated.[166] An excellent discussion of the mechanistic aspects of the reaction sequence is presented by Biffin *et al.*[119] Without going into details, Scheme 51 illustrates the chemistry involved. The preparative significance becomes obvious from a published table with about 15 examples; sometimes yields of more than 90% were obtained.[119] The aromatic ligand may carry a number of further functional groups and di- or tri-azides can be formed as well as heterocyclic azides. Starting with *N*-(aminophenyl)phthalimide, the azido derivative (**38**) is obtained *via* diazotization, followed by reaction with HN_3. Hydrazinolysis of the protecting phthaloyl group (Scheme 52) yields the otherwise inaccesible azidoanilines (**39**).[119] With the 4-, 5- or 6-aminoindoles a remarkable increase of azide yields was noticed when the formation of the diazonium salts was performed in 80% HOAc instead of diluted mineral acids (Scheme 53).[167]



Scheme 51



Scheme 52



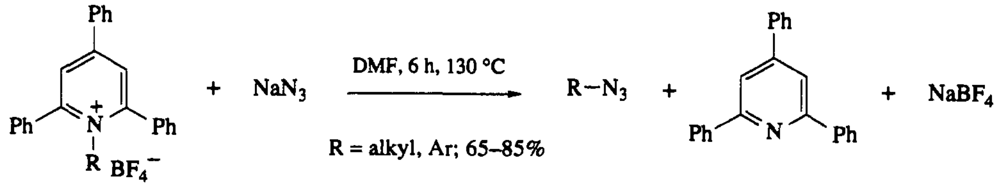
Scheme 53

Provided the starting materials are easy to obtain, the interesting reductive substitution of aromatic nitroso compounds (Scheme 54) is also a useful preparative technique.[118,119,168] The mechanistic aspects of the reaction sequence have been discussed.[119]

$$\mathrm{Ar{-}N{=}O} \xrightarrow{HN_3} \left[\mathrm{Ar{-}N{=}N{-}OH}\right] \xrightarrow[-N_2]{HN_3} \mathrm{Ar{-}N_3}$$

Scheme 54

N-Alkyl and -benzyl substituents can be displaced from 2,4,6-triphenylpyridinium tetrafluoroborates by reaction with azide ions (Scheme 55). This method enables the conversion of primary alkyl- or benzyl-amines to the corresponding azides.[169]



Scheme 55

1.8.4.5 Azides by Azide Transfer Reactions

The synthesis of various azido compounds with arene sulfonyl azides has, at least in a formal sense, to be considered as an electrophilic substitution of hydrogen by an azide function.[117,119,122] By this route a number of amines, cyclic derivatives and bridgehead compounds included, after deprotonation with NaH or Grignard reagents, could be transformed into azides in high yield on treatment with arene sulfonyl azides.[117,170] Details cannot be given here. Enolates can also be converted into azido derivatives in a very similar way, *via* triazene intermediates.[117] Evans *et al.*[171] did recently investigate the influence of the countercation, the structure of the transfer azide and work-up conditions on this process.

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1.9

Ritter-type Reactions

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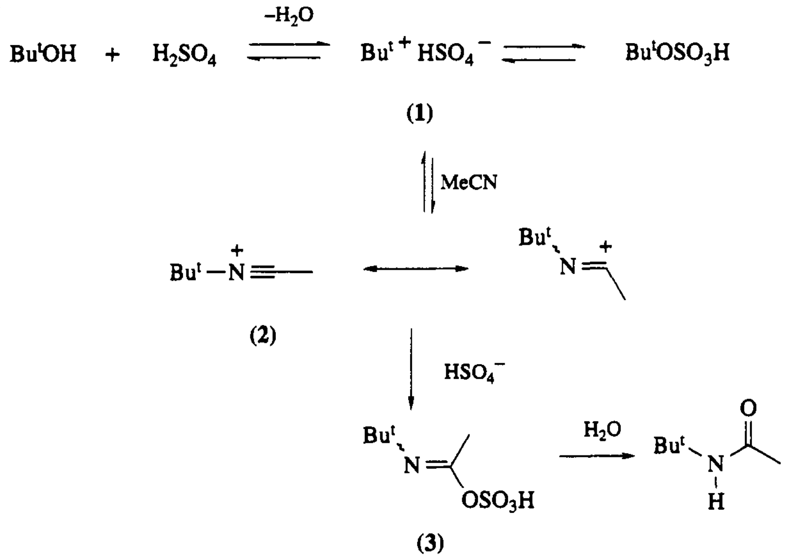
1.9.1 THE RITTER REACTION

The process now known as the Ritter reaction was first described in detail in two papers[1,2] published in 1948. Strongly acidic conditions were used to generate a carbenium ion which underwent nucleophilic attack by a nitrile, and further events leading to the isolated product. In its original and most familiar form, hydrolytic work-up produced an amide. However, later investigations showed that in suitable cases intramolecular cyclization could occur, affording a wide range of heterocyclic materials. Although this very general reaction is justly named for Ritter, who recognized and explored its considerable potential, it is not surprising that a few special cases of Ritter-type processes are described in earlier independent reports.[3–7] Early work on the Ritter reaction is well served by a number of review articles,[8–14] that by Krimen and Cota[12] being especially valuable in the present context.

1.9.1.1 Reaction Mechanism

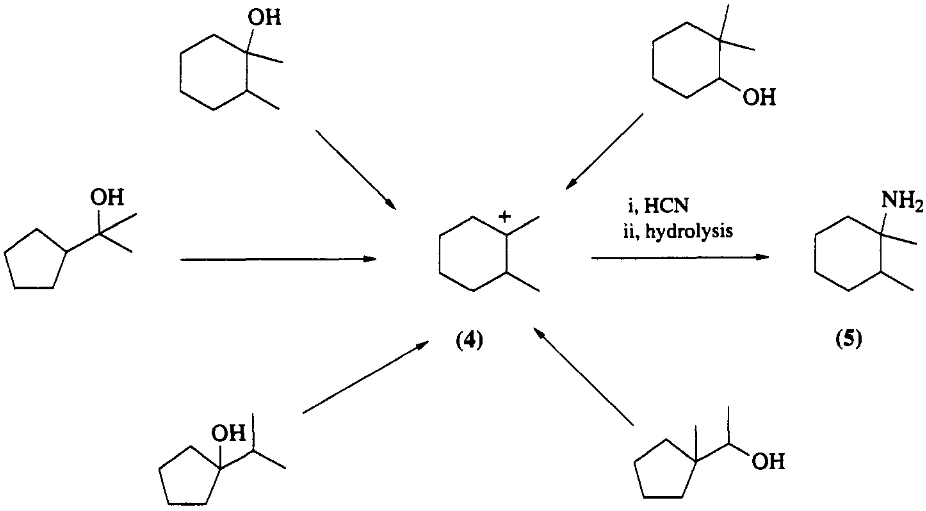
The mechanism of the reaction is illustrated in Scheme 1 for the conversion of *t*-butanol, using sulfuric acid and acetonitrile, into *N*-*t*-butylacetamide. Three intermediates are involved. Firstly, a carbenium ion (**1**) is produced under strongly acidic conditions. This reacts with the nitrile to produce a resonance-stabilized nitrilium ion (**2**), which in turn is converted into the corresponding imidate (**3**). Finally, the latter is hydrolyzed to the amide. Since all three events occur in a one-pot process, frequently in high yield, the Ritter reaction is a simple, efficient and general synthetic procedure.



Scheme 1

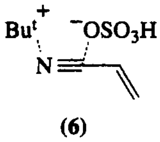
As an alternative to amide formation, intramolecular cyclizations involving the nitrilium ion lead to a variety of heterocyclic systems (Section 1.9.2). Since carbenium ions, or their equivalents, may be produced by means other than strong acid, a number of valuable extensions of the original reaction are possible (Section 1.9.3). In addition, nitrilium and imidate species are also available through other processes, implying that the Ritter reaction has close mechanistic relationships with other well-established reactions and with the chemistry of the isonitriles. These aspects are explored in Section 1.9.4.

The essential details of the reaction mechanism were originally proposed by Ritter and his collaborators,[2,15] and only a brief description of the work supporting this reaction pathway will be presented here. Replacement of the nitrile with the corresponding amide resulted in failure of the reaction, demonstrating that addition of the amide and carbenium ion was not involved.[1] As part of a detailed study using oleic acid, Roe and Swern[16] were not only able to use a variety of acidic media to obtain amide products, but evidence of isomerization due to carbenium ion intermediates was also presented. This expected feature of the above mechanism was thoroughly investigated by Christol, a good illustration[17] of such rearrangement being formation of cation (4), and subsequent isolation of the amine (5), from each of the five alcohol precursors shown in Scheme 2.



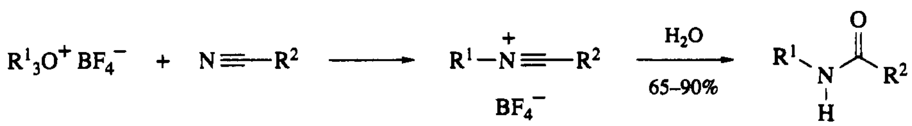
Scheme 2

Kinetic measurements on the reaction between *t*-butanol and acrylonitrile in 20–69% sulfuric acid showed it to be first order with respect to both reagents. This led Deno[18] to suggest that the transition state involved nucleophilic attack by the nitrile on the protonated alcohol. However, the latter might better be regarded as a weakly solvated carbenium ion and the process as an 'S_N intermediate' reaction.[19] In a later related study (isobutene and acrylonitrile) Glikmans[20] concluded that the reaction involved an ion pair and that the nitrile was associated with both partners in the transition state (**6**). Nitriles are only about half-protonated in 89–100% sulfuric acid and, therefore, nucleophilic behavior presents no difficulty.[21] Retro-Ritter reaction can occur when an *N*-*t*-alkylamide is treated with dehydrating agents such as thionyl chloride or phosphorus(V) oxide.[22] Carbenium ions generated by nonacidic routes also react with nitriles and yield amides on hydrolytic work-up (Section 1.9.3).



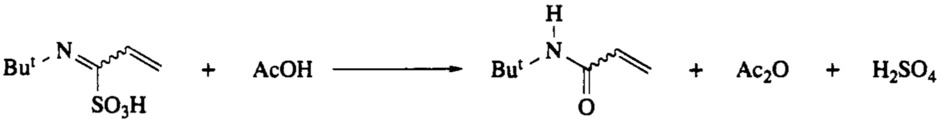
(6)

Evidence supporting the involvement of nitrilium ion intermediates is available from the large number of heterocyclic derivatives obtained by intramolecular trapping reactions.[14] Furthermore, independently generated nitrilium salts[23] undergo hydrolysis to Ritter products (Scheme 3).



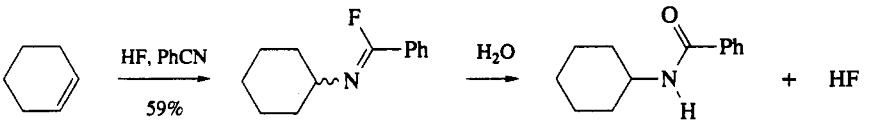
Scheme 3

Definitive evidence for the imidate intermediate was provided by Glikmans[24] in 1966. Reaction between isobutene and acrylonitrile in anhydrous acetic acid containing 100% sulfuric acid allowed isolation and characterization of (**7**), which was readily hydrolyzed to the corresponding amide by dehydration of acetic acid (equation 1). Subsequent work by Norell[25] on reactions of alkenes with nitriles in anhydrous liquid hydrogen fluoride allowed isolation of imidoyl fluorides such as (**8**) for the first time. Such materials, obtained pure and fully characterized, react instantly with water to yield the amide (Scheme 4).



(**7**)

(1)



(**8**)

Scheme 4

1.9.1.2 Reaction Conditions

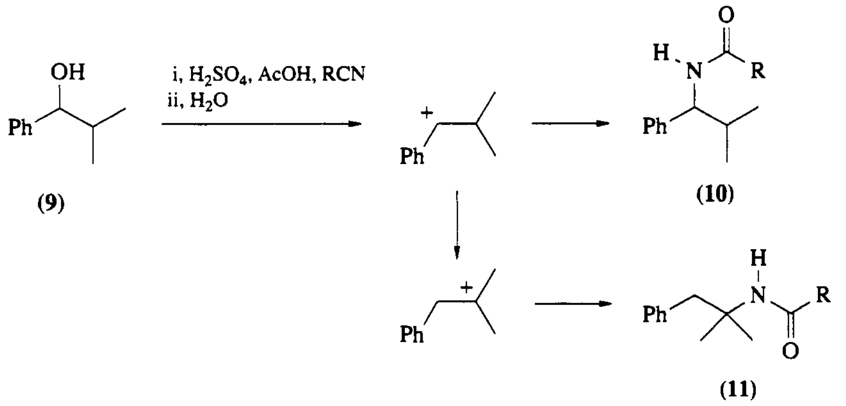
The precise experimental conditions used can greatly influence the efficiency, or even the course, of the Ritter reaction. Representative procedures are available, along with a comprehensive tabular survey to 1966, in the article by Krimen and Cota.[12] Optimum reaction times (typically 1–24 h) and temperatures (typically 20–50 °C) depend very much on the particular cases. Typical temperatures of 0–10 °C are used when hydrogen cyanide or hydrogen fluoride are employed. Benzenesulfonic, fluoroboric, formic, hydrofluoric, methanesulfonic, perchloric, phosphoric, polyphosphoric, sulfuric, toluenesulfonic and trifluoromethanesulfonic acids are amongst those used to generate the carbenium ion. However, the majority of workers favor sulfuric acid and, in cases where comparative studies have been carried out,[16,24,26] this reagent generally gave the best yields. This may reflect participation of the hydrogensulfate ion during attack by the nitrile reagent.

The best acid concentration depends on the type of substrate[26] but usually 85–90% sulfuric acid is employed. Similarly, for hydrofluoric acid the optimum concentration was 90–100% for linear alkenes and 60–75% for branched alkenes.[27] The function of the water present may be to suppress side reactions by enabling rapid hydrolysis of the imidate to the stable amide product. However, it will also increase the solvent polarity, which is known to enhance the nucleophilicity of the nitrile through solvation and polarization effects.[28] Frequently the reaction is performed using just the nitrile and acid as solvents, but any additional diluent should be polar. Glacial acetic acid is most commonly used, although acetic anhydride, di-*n*-butyl ether, nitrobenzene and dioxane have also found favor. Nonpolar solvents such as carbon tetrachloride or hexane give poor yields,[28] and the reaction fails in the presence of methanol or ethanol.[24] Although acetic acid is the best diluent, formation of acetates can be a significant side reaction,[24,29] and in other cases dilution prevents reaction.[15]

Lewis acids such as tin(IV) chloride,[30] boron trifluoride-acetic acid[16] and boron trifluoride–etherate,[31] are also effective in promoting the Ritter reaction. In general, the original technique is more efficient, but use of Lewis acids can sometimes significantly influence the proportions of products in a mixture and has advantages when relatively sensitive substrates are present.

In reactions where rearrangement is likely, a rule of thumb is that the most stable available carbenium ion will lead to the product. Such thermodynamic control may be used deliberately to carry out complex rearrangements in high yields for suitable cases.[12] When the potential carbenium ions are of similar energy, for example in Ritter reactions of unsaturated fatty acids or esters, then mixtures of products are likely. In such cases, mass spectrometry has proved to be a particularly useful analytical technique.[32,33]

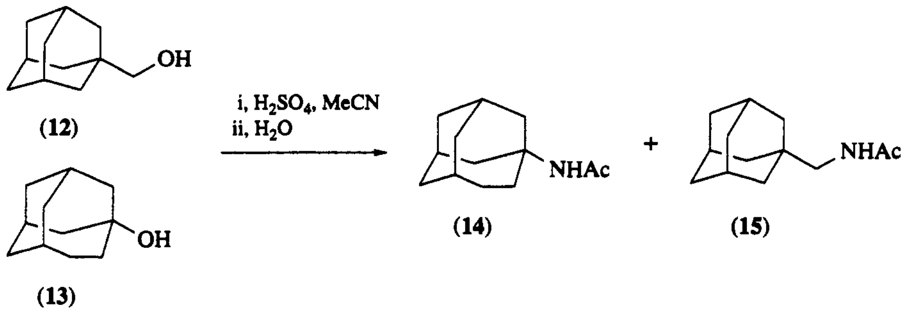
The outcome of the Ritter reaction can also be determined by kinetic control. For example, conflicting reports have appeared in the literature regarding the behavior of alcohol (**9**), the alternative products (**10**)[34] or (**11**)[35] both having been reported. These differences result from the order of addition of the reagents.[36] The amides (**10**) result if the alcohol is mixed first with the nitrile and acetic acid, the sulfuric acid being added last. In this instance (kinetic control), the initial cations are reacted to (**10**) as they are produced. Conversely, if (**9**) is mixed first with the acids, and then the nitrile is added, the products (**11**) result. In this case (thermodynamic control) carbenium ion rearrangement precedes Ritter reaction (Scheme 5). For less clear-cut cases, the use of less acidic conditions and/or lower temperature results in greater isomer selectivity, but at the cost of lower overall yields.[27]



Scheme 5

A good illustration of the interplay of reaction conditions with product formation is provided by the work of Sasaki *et al.*[37] on reactions of 1-hydroxymethyladamantane (**12**) and 3-homoadamantanol (**13**) with sulfuric acid and acetonitrile (Scheme 6). Under a variety of experimental conditions, both alcohols gave a mixture of the acetamides (**14**) and (**15**), but in quite different proportions and total conversions. A selection of these data is present in Table 1. For each entry, a mixture of the alcohol (1.2 mmol) and acetonitrile (76.5 mmol) was added to stirred sulfuric acid (1.5 ml). For the later experiments, $AlCl_3$ (0.6 g) or $BF_3–Et_2O$ (1.5 ml) were added first to the H_2SO_4.

The results without Lewis acid demonstrate that the homoadamantane (**14**) is the kinetic product and that the adamantane (**15**) is the thermodynamic product. Addition of Lewis acid to either alcohol decreased the yield of amides. However, while aluminum chloride increased the proportion of the kinetic product, the use of boron trifluoride etherate boosted the proportion of the thermodynamic product.



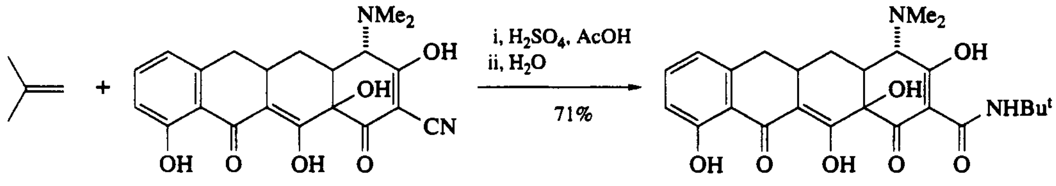
Scheme 6

Table 1 Correlation of Reaction Conditions for Alcohols (**12**) and (**13**) with the Resulting Kinetic (**14**) and Thermodynamic (**15**) Amide Products[37]

Reagent(s)	*Conditions*		*Total yield of amides* (%)	*Relative yields* (%)	
	Temperature (°C)	*Time* (h)		*(14)*	*(15)*
(**12**)	15	1	20	66	34
(**12**)	15	24	42	10	90
(**12**)	50	1	40	2.9	97.1
(**12**)	50	24	92	0.2	99.8
(**13**)	15	24	93	16.5	83.5
(**13**)	50	24	98	10	90
(**12**), $AlCl_3$	15	24	23	92	8
(**12**), $AlCl_3$	15	96	42	17	83
(**13**), $AlCl_3$	15	24	72	31	69
(**13**), BF_3-Et_2O	15	24	76	3	97

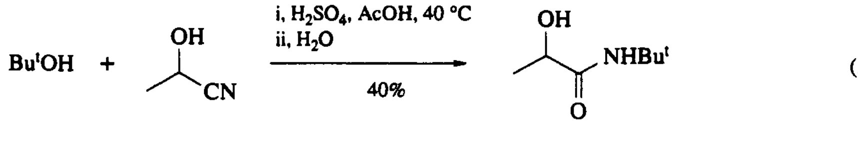
1.9.1.3 The Nitrile Component

In general, most compounds containing a nitrile group undergo reaction with carbenium ions.[1] Not only are hydrogen cyanide, aliphatic nitriles and aromatic nitriles all effective reagents but the process also occurs with varying degrees of efficiency for nitrile derivatives such as cyanamide, cyanogen and dicyandiamide. Nitriles bearing other functional groups undergo efficient Ritter reaction provided the materials are acid stable, a striking illustration being the tetracycline derivative (**16**; equation 2).[38] Cyanohydrins also undergo Ritter reaction without interference from the hydroxy substituent (equation 3).[39]



(**16**)

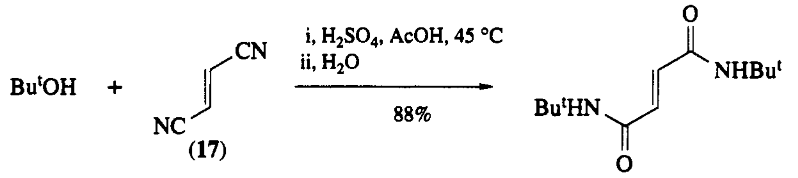
(2)



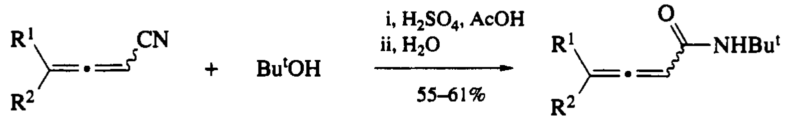
(3)

Conjugated unsaturated nitriles such as acrylonitrile[1] or fumaronitrile (**17**; equation 4)[39] are effective Ritter reagents. More recent work has shown that this is also true of conjugated allenic[40] and alkynic nitriles,[41] as shown in equation (5) and Scheme 7, respectively. Suitably functionalized propiolamides such as (**18**) are readily cyclized, allowing facile preparation of the oxazoline (**19**).[41,42]

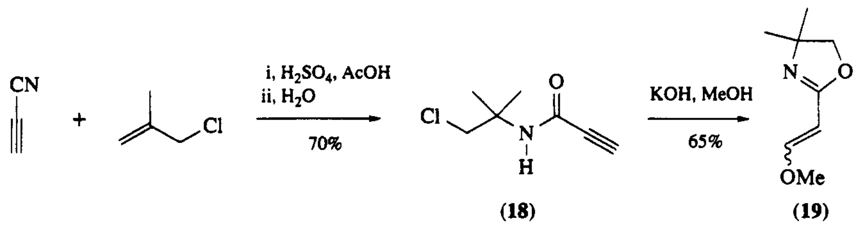
Dinitriles such as (**17**) can be used to prepare bisamides or, alternatively, can provide an excellent source of polyamides if glycol, diene,[43] or aldehyde[44,45] carbenium ion sources are utilized.



(4)

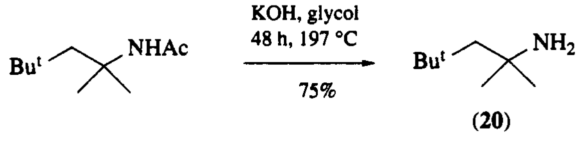


(5)

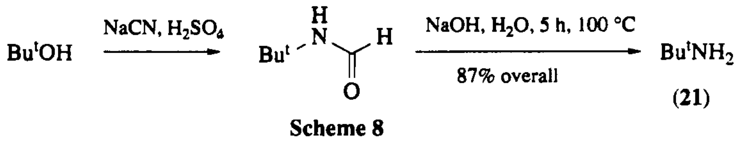


Scheme 7

Hydrogen cyanide, used either directly or generated from cyanide ion *in situ*, is an especially important nitrile source because the *N*-*t*-alkylformamide products can be readily hydrolyzed to the corresponding *N*-*t*-alkylamines.[2] Such materials, frequently of pharmacological interest,[46] could be obtained in principle by either basic or acidic hydrolysis of *N*-*t*-alkylamides. However, alkaline hydrolysis of these compounds can be surprisingly difficult to carry out in some cases.[16] For example, Ritter and Minieri[1] found that *N*-*t*-octylacetamide required prolonged reflux with 0.4 M potassium hydroxide in ethylene glycol to obtain the optimum yield of amine (**20**; equation 6). Under the same conditions, only a 27% conversion of *N*-*t*-amylacetamide was achieved. In contrast, preparation of *N*-*t*-butylamine (**21**) *via* the formamide route (Scheme 8) was possible with shorter reaction time, lower temperature, and in higher yield.[1] Although reagents such as hydrazine,[47] diisobutylaluminum hydride,[48] lithium diethylamide[49] and triethyloxonium tetrafluoroborate[50] have been used in hydrolysis of recalcitrant amides, such difficulties are best avoided by use of the formamide where possible.



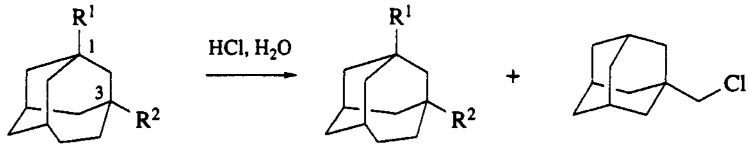
(6)



Scheme 8

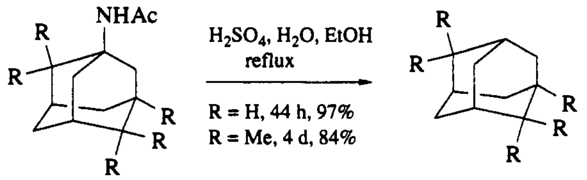
Although *N*-*s*-alkylamides are hydrolyzed to the corresponding amines under acidic conditions,[51] the *N*-*t*-alkyl derivatives usually undergo alkyl–nitrogen fission, producing alkene or alcohol fragments.[52] Hydrolysis of 3-acetamidohomoadamantane (**22a**) using hydrochloric acid produced a mixture of the compounds (**23a**) and (**24**), while the 1-acetamido isomer (**22b**) gave only chloride (**23b**; equation 7). The absence of amine products from these reactions[53] once again indicates the ease of *A*AL1 hydrolysis[52] to the carbenium ion. If the acidic hydrolysis is conducted in the presence of ethanol, then adamantyl- and homoadamantyl-amides undergo ready deamidation. In this process, illustrated by equation (8), the ethanol acts as a hydride donor, reducing the cation to the hydrocarbon.[54]

A mechanistic limitation of the Ritter reaction is that, while *N*-alkylformamides (and thence primary amines) are readily available, further direct substitution on nitrogen is ruled out. However, simple *N*-alkylation of the formamide may be performed utilizing phase-transfer catalysis. This provides a conven-



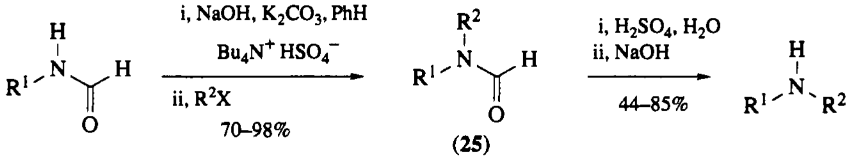
(7)

(22) **a**: $R^1 = H, R^2 = NHAc$ **(23)** **a**: $R^1 = H, R^2 = OH$, 50% **(24)** 49%
b: $R^1 = NHAc, R^2 = H$ **b**: $R^1 = Cl, R^2 = H$, 98%



(8)

ient indirect route to the *N*,*N*-dialkylformamides (**25**) and the corresponding secondary amines (Scheme 9).[55]



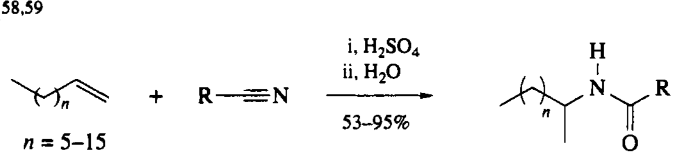
(25)

Scheme 9

1.9.1.4 The Carbenium Ion Source

In principle, any functionality capable of producing a carbenium ion under strongly acidic conditions will be able to participate in a Ritter-type reaction. Such classes of compounds include alcohols, aldehydes, alkanes, alkenes, alkyl halides, carboxylic acids, dienes, epoxides, esters, ethers, glycols, ketones, *N*-methylolamides and oximes. Consequently, an enormous number of examples is reported and only a representative selection can be presented here. A comprehensive listing of examples reported up to 1966 is provided in the review by Krimen and Cota.[12]

Despite the range of sources available, the majority of reactions described have used alcohol or alkene precursors. This reflects both the availability of such materials and their ease of reaction. Typical examples of alkene reagents are shown in equations (9),[56] (10),[30] (11)[24] and (12).[57] When two reactive groups are in close proximity in the substrate it is possible to combine transannular cyclization with Ritter reaction (equation 13).[58,59]



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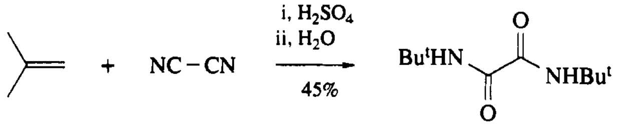

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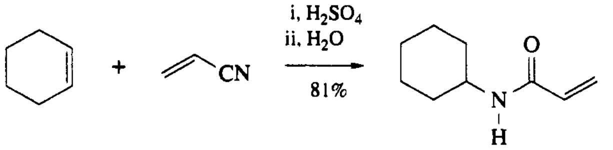

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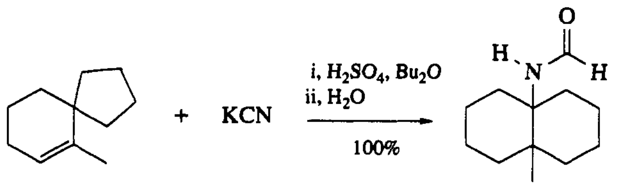

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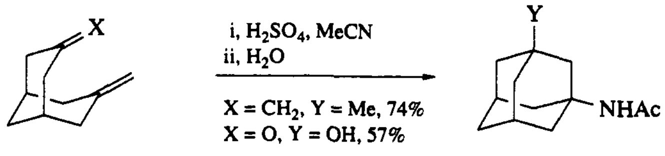
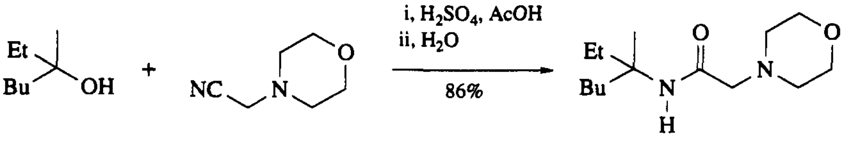


(13)

Tertiary alcohols tend to react without rearrangement while secondary alcohols are liable to do so, equations (14)[60] and (15),[28] as discussed in Section 1.9.1.2. Primary alcohols normally fail to react with nitriles even under severe conditions,[15] but this restriction does not apply to benzylic examples (equation 16).[29] In appropriate cases,[61] the Ritter reaction can be stereoselective (Scheme 10). Either alcohol isomer, separately or as a mixture, gave identical mixtures of the two amine products, showing that axial attack on the cation was predominant.



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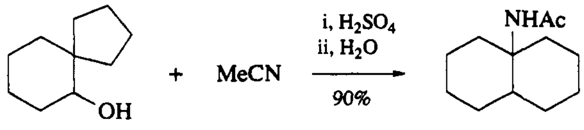

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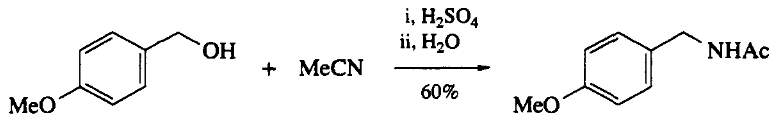

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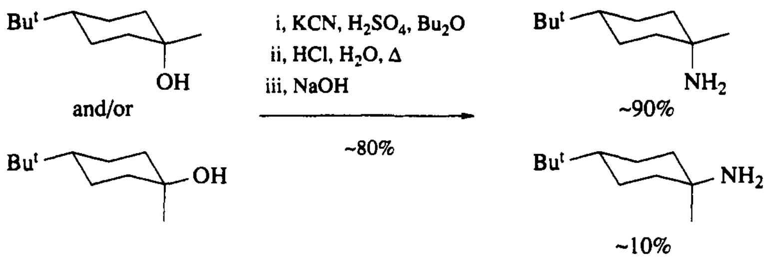
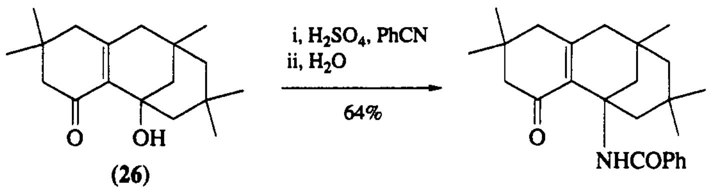


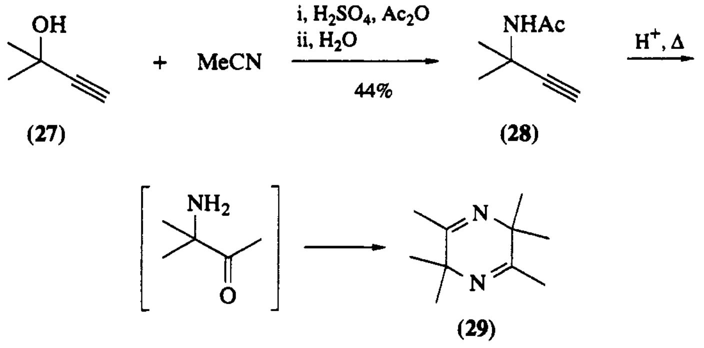
Scheme 10

In cases where more than one functional group is present in the substrate, it is usually an alcohol group which is preferred for Ritter reaction, although there are exceptions such as ricinoleic acid.[33] Examples shown here are the diisophorane derivative (**26**; equation 17)[62] and the alkynic alcohol (**27**; Scheme 11).[63] The latter compounds undergo Ritter reaction in only moderate yields because of competing Meyer–Schuster rearrangement to the unsaturated ketone in some cases. Hydrolysis of the product provides either the alkynic amine or, in the case of (**28**), the amino ketone, which undergoes selfcondensation to the dihydropyrazine (**29**). Combination of these processes into a one-pot reaction gives the latter in 54% overall yield.[64]

Similarly, *N*-methylolamides[7] (equation 18)[65,66] and substituted oximes (Scheme 12)[67,68] react specifically through their hydroxy group. Hydroxy esters afford either amido esters[69] or amido acids[70] (equation



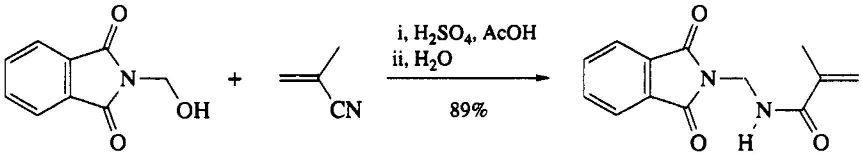
(17)



Scheme 11

19), depending on the conditions used. Increased substitution in the starting material results in lower yields due to competing elimination processes.[71,72] Esters of *t*-alcohols should be avoided since these may be regarded as masked *t*-carbenium ions and can participate in Ritter reactions in their own right. Thus, triphenylmethyl formate[73] or *t*-butyl acetate[20,74] produce excellent yields of *N*-*t*-alkylamides when heated with nitriles in the presence of sulfuric acid (equations 20 and 21).

Magat[75] first reported the use of *t*-alkyl halides as Ritter reaction substrates but, in general, these were less satisfactory than the use of the corresponding alcohol or alkene analogs. This process has since come into its own for polycyclic systems, where simple methods of generating bridgehead halides are often available. An early example is Stetter's conversion[76] of 1-bromoadamantane to the acetamide (30), there-



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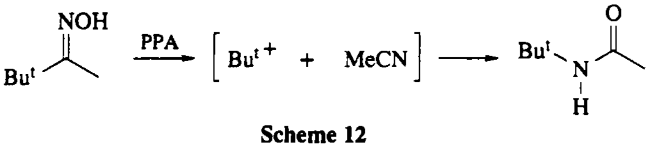
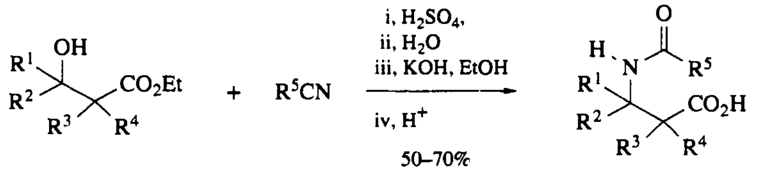


Scheme 12



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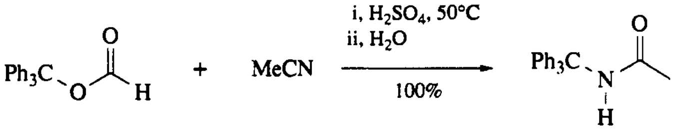

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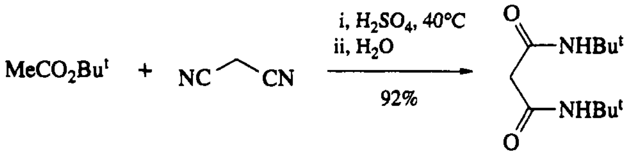
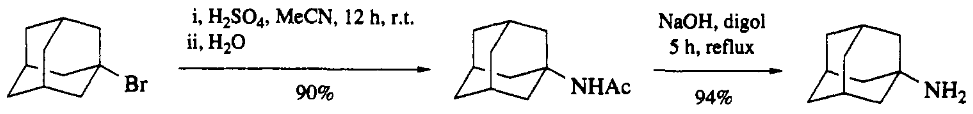


(21)

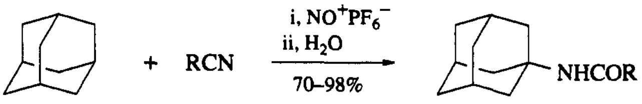
by providing a simple route to 1-aminoadamantane (**31**; Scheme 13). The discovery that (**31**) alleviates symptoms of Parkinsonism and exhibits antiviral behavior against influenza A[77] has led to considerable interest in the synthesis and testing of related polycyclic amino compounds. A number of these also show significant antiviral activity.



(**30**) (**31**)

Scheme 13

Saturated hydrocarbons capable of yielding a *t*-carbenium ion can participate directly in the Ritter reaction[78] provided a suitable hydride acceptor is present, or more efficiently using nitrosonium hexafluorophosphate (equation 22).[79] More recently, Inamoto[80] has described an elegant process whereby bridgehead bromination and Ritter reaction are performed in one step. This procedure is highly efficient for the functionalization of a number of tricyclic hydrocarbons, including conversion of 4-homotwistane (**32**) directly into its 3-acetamido derivative (**33**; equation 23). Although most halides used have been bromides, a recent report[81] indicates that this is not essential. Although the fluorotrishomocubane (**34a**) required more forcing conditions than its bromo analog (**34b**), the yields of amide obtained were identical (equation 24).



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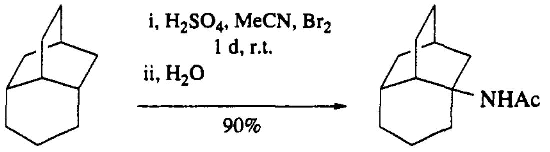
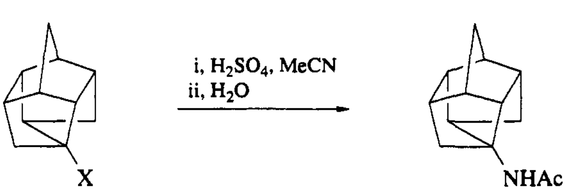


(**32**) (**33**)

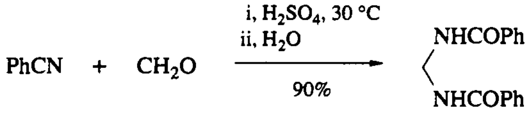
(23)



(24)

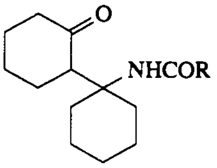
(**34**) **a**: X = F; 5 h, 95 °C, 61%
b: X = Br; 12 h, 20 °C, 62%

In 1876 Hepp and Spiess[3,4] reported that aldehydes react with nitriles under acidic conditions to yield geminal bisamides (equation 25). This process proceeds by a mechanistic pathway which is essentially two consecutive Ritter reactions.[26] In general, ketones do not yield similar products; however, Kozlov[82] has recently obtained a low yield of the geminal bisamide from camphor and acetonitrile. High yields of analogous products from cyclopentanone and cyclohexanone have also been reported.[83]



(25)

More typical behavior of ketones is a condensation process yielding β-acylamino ketones. This process was first reported by Bruson *et al.*[84] who reacted cyclohexanone and nitriles in the presence of anhydrous aluminum chloride and obtained products now known[44] to have the structure (**35**). Such reactions were later studied in more detail by Khorlin[85] using conventional Ritter conditions. β-Acylamino ketones were obtained only from ketones capable of undergoing condensations to produce α,β-unsaturated ketones or ketols, suggesting the intermediacy of such structures in the reaction. This process is shown for acetophenone in Scheme 14. It is well established that α,β-unsaturated acids, esters and ketones yield similar products under Ritter reaction conditions.[69,70]



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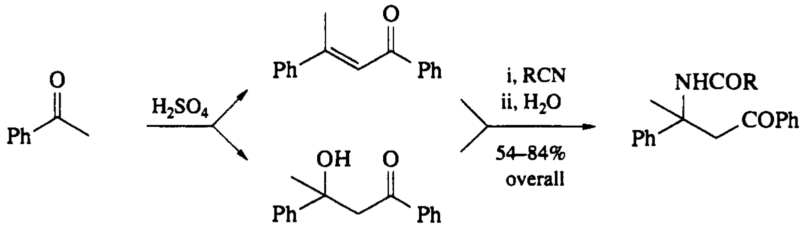
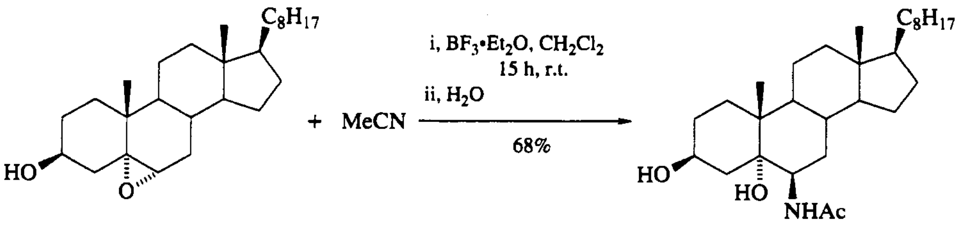


Scheme 14

Epoxides react efficiently with nitriles in the presence of either mineral or Lewis acids. Much of this work has been carried out on steroidal systems, which has allowed ready stereochemical analysis of the process. Such reactions yield specifically the *trans*-diaxial α-amido alcohol product, examples from the cholestanol series being shown in equations (26)[86] and (27).[87] Similar stereospecific results can also result from suitable aliphatic cases, as demonstrated by the reaction of methyl *trans*-2-epoxystearate yielding only the *erythro* isomer (**36**; equation 28).[88]

As final examples of the versatility of the Ritter reaction, bridged hemiacetals react by means of their acyclic form in solution to afford amido ketones in good yield (equation 29),[89] while halohydrins give α-amido halides, which are readily cyclized to oxazoline derivatives in an overall stereospecific process.[90]



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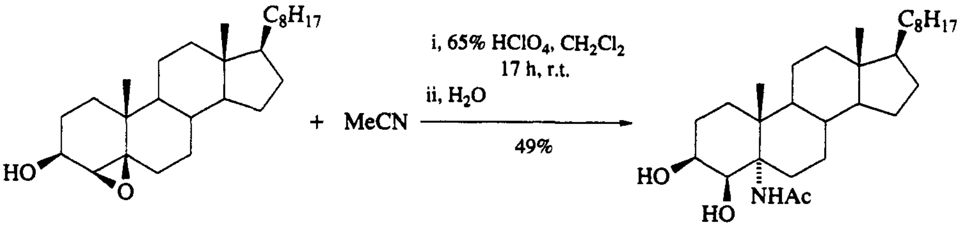

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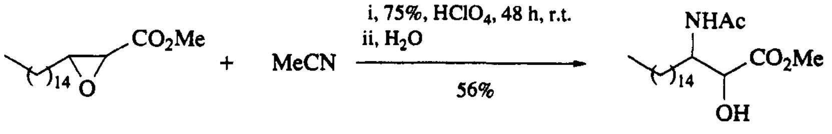
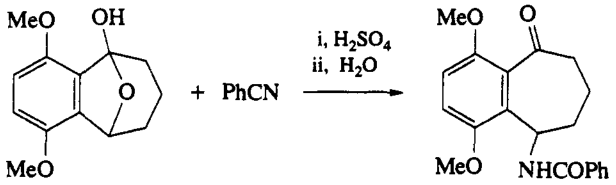


(28)

(36)



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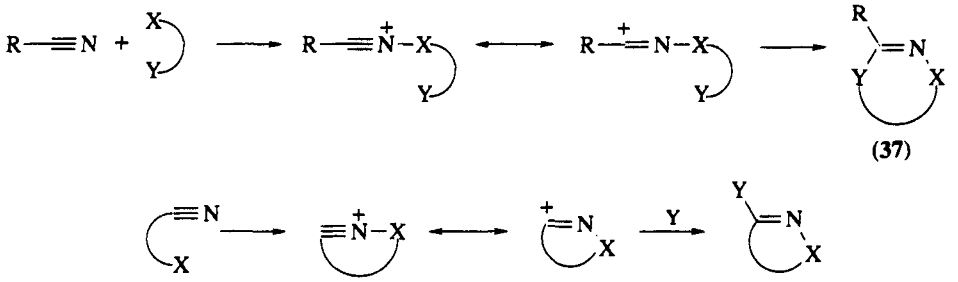
1.9.2 THE INTRAMOLECULAR RITTER REACTION

The pathways by which nitrile groups can be utilized in the construction of heterocyclic systems have been reviewed by Meyers and Sircar.[14] Two of these routes constitute intramolecular variants of the Ritter reaction and, therefore, are discussed here in detail.

The more common process commences in the normal way, with addition of nitrile and carbenium ion generating a nitrilium species. However, the latter now undergoes intramolecular cyclization with a nucleophilic group in the same molecule to produce a heterocycle of structure (37; Scheme 15). The less common reaction involves initial intramolecular formation of a cyclic nitrilium ion which is then quenched by an external nucleophile, giving products of type (38).



(37)

(38)

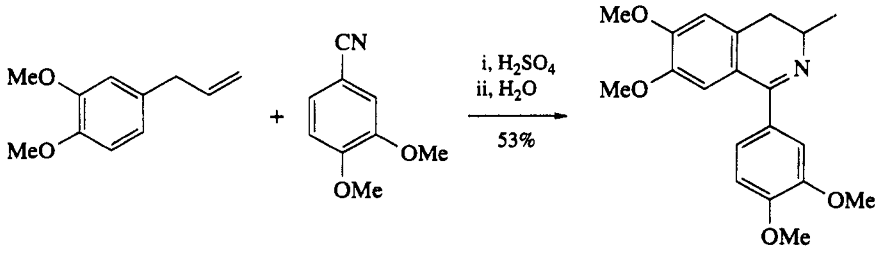
X = schematic electrophilic group; Y = schematic nucleophilic group

Scheme 15

Only specific ring sizes are available from these procedures since they are constrained by the configuration of the nitrilium intermediate (Section 1.9.4), in addition to the usual factors influencing intramolecular reactions.

1.9.2.1 Intramolecular Cyclization of the Nitrilium Ion

In 1952, Ritter and Murphy[91] reported cases of intramolecular Ritter behavior resulting in formation of dihydroisoquinolines from reactions of methyleugenol with nitriles such as veratronitrile (equation 30). Such reactions involve nucleophilic attack by the aromatic ring on the nitrilium ion and are enhanced by the use of Lewis acids. Meerwein[23] reacted a wide range of nitrile–Lewis acid complexes with alkyl and acyl halides, obtaining nitrilium salts such as (**39**) which were readily hydrolyzed to the corresponding amide. A significant advantage of this approach, as illustrated in Scheme 16, is that this Ritter-type process is no longer restricted just to *N*-*t*-alkyl derivatives.



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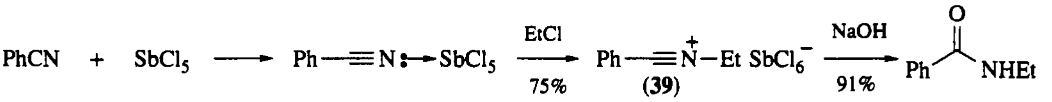
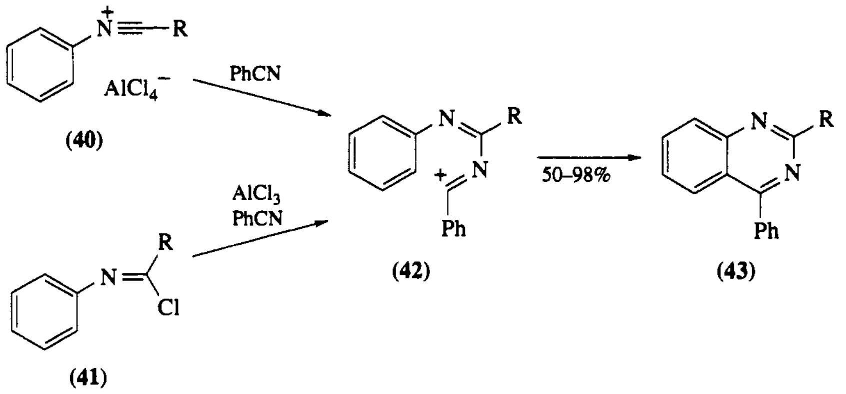
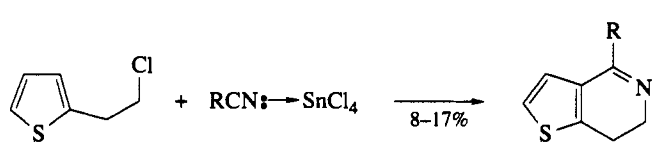


Scheme 16

Reaction[92] of aryl nitrilium ions (**40**) or imidoyl chlorides (**41**) with benzonitrile produced the nitrilium species (**42**), which underwent Friedel–Crafts reaction yielding the quinazoline system (**43**; Scheme 17). Generation and cyclization of nitrilium species using Friedel–Crafts reagents has since found widespread favor in heteroaromatic synthesis and such procedures have been reviewed in detail.[10,93] An illustration of its use for a nonbenzenoid aromatic system is given in equation (31).[94]



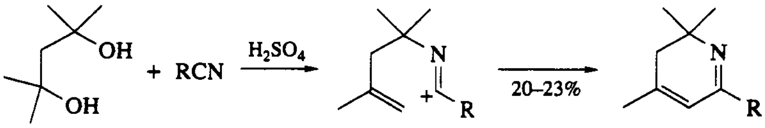
Scheme 17



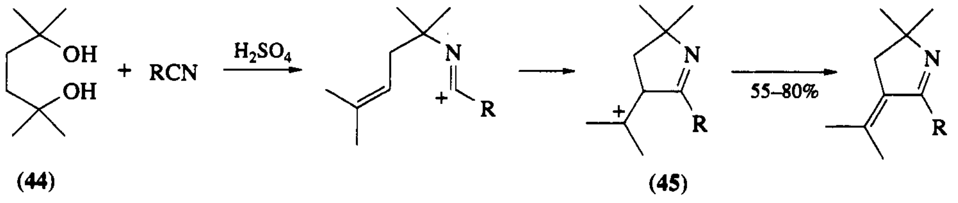
(31)

If the internal nucleophile is an alkenic group, then 5,6-dihydropyridine (Scheme 18)[95–97] or 1-pyrroline (Scheme 19)[95] rings are produced. In a recent development[98] of the latter process, the diol (**44**) follows the same sequence to yield the carbenium ion (**45**; R = Bn). However, this now cyclizes onto the aromatic group originating from the nitrile component and produces the tetrahydrobenz[*f*]indole (**46**) in good yield, with the conventional pyrroline structure (**47**) now being only a minor product. Compound (**46**), present as a tautomeric mixture, was rapidly autoxidized to (**48**; Scheme 20). A further unusual variant of this process is the production of small quantities of the 3-azabicyclo[3.3.0]octanes (**49**) and (**50**) from Ritter reaction of 1-vinylbicyclo[2.1.1]hexane (equation 32).[99]

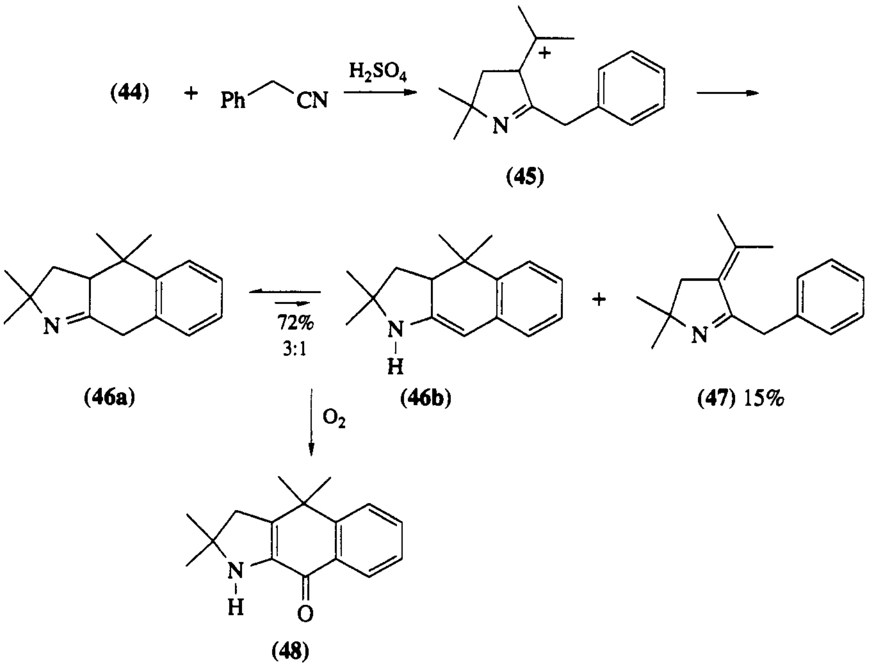
In 1957 Tillmanns and Ritter reported that reaction of diol (**51**) with nitriles led to dihydro-1,3-oxazine products (**52**)[100,101] instead of yielding bisamides (Scheme 21). In this process the tertiary alcohol group



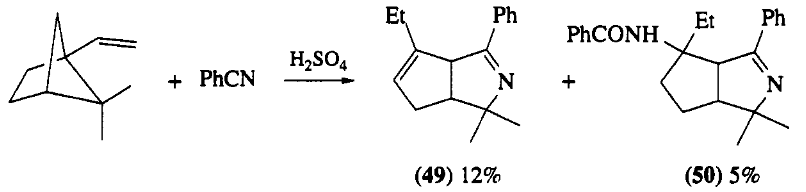
Scheme 18



Scheme 19



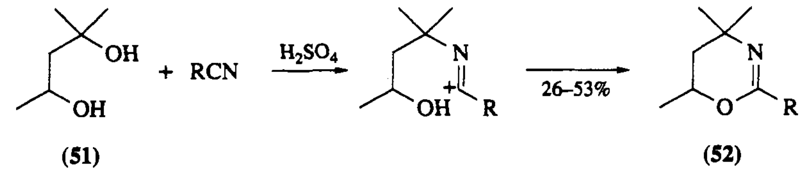
Scheme 20



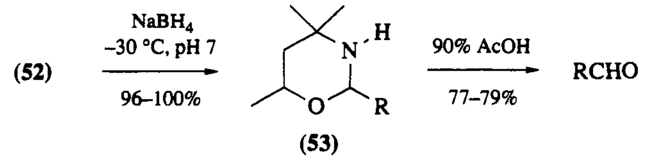
(32)

is converted to a carbenium ion, whereas the secondary alcohol is retained and later acts as the nucleophile which quenches the nitrilium intermediate. Use of a hydroxy group as the internal nucleophile is the most widespread practice and invariably leads to 1,3-oxazine or oxazoline derivatives.

The dihydro-1,3-oxazine route has been extensively investigated by Meyers. Controlled reduction to the tetrahydro derivative (**53**), followed by hydrolysis, gave good yields of the corresponding aldehyde or deuteriated aldehyde, R—CDO (Scheme 22).[102] Further development of this concept has subsequently given rise to convenient routes to acyclic,[103] α,β-unsaturated,[104] alicyclic,[105] γ-hydroxy[106] and γ-oxo aldehydes.[106] Full synthetic details of these and other variants of the Meyers aldehyde synthesis have been published.[107]

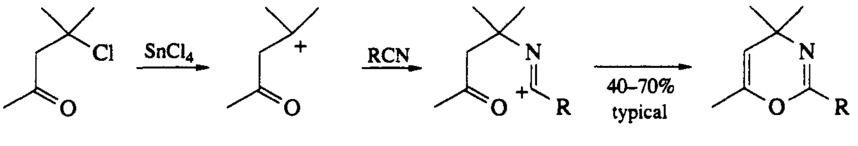


Scheme 21

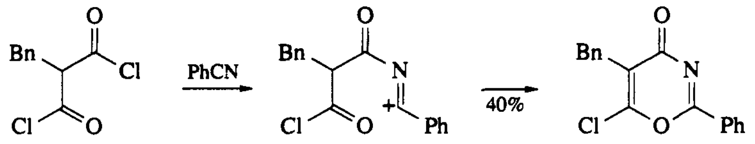


Scheme 22

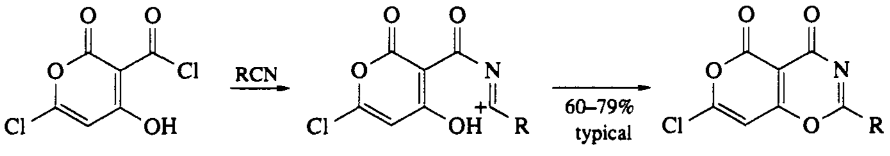
Other processes yielding 1,3-oxazine derivatives include the reaction of chloro ketones with Lewis acids (Scheme 23)[108] and reactions of nitriles directly with malonyl chlorides (Scheme 24)[109,110] or related acid chlorides (Scheme 25).[111,112] These processes are also all believed to involve reaction of nitrilium species with an internal oxygen nucleophile.



Scheme 23

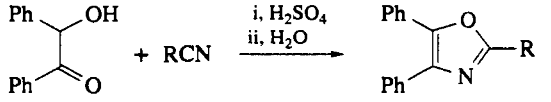


Scheme 24

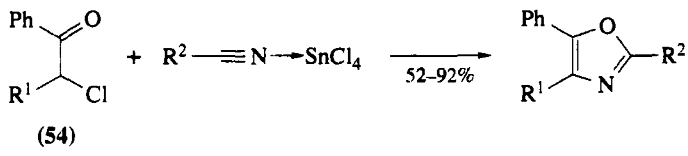


Scheme 25

The isolation of oxazole derivatives from Ritter-type reactions dates back to 1893, when Japp and Murray[5] reported that benzoin and sulfuric acid reacted with nitriles (equation 33). Better yields of such products are obtained from reaction of chloro ketones (**54**) with nitrile–$SnCl_4$ complexes (equation 34).[113] Likely mechanisms for these processes have been discussed by Meyers and Sircar.[14]

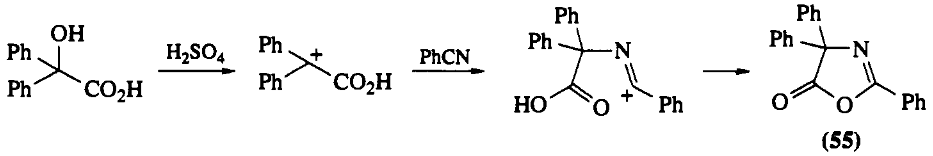


(33)

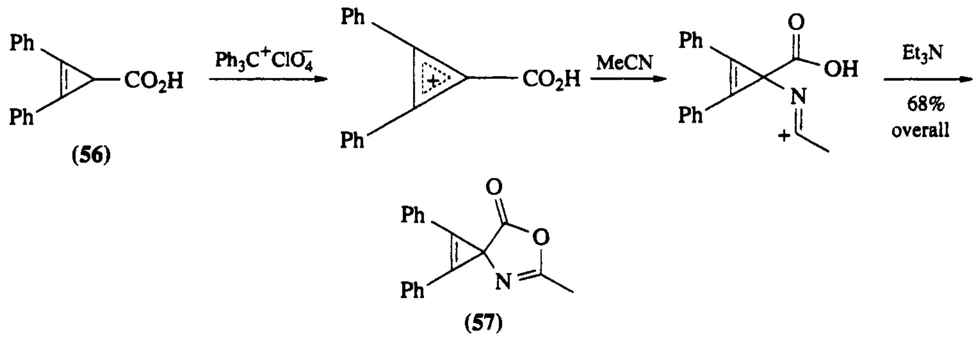


(34)

Japp also found that benzilic acid gave a triphenyloxazolone product with benzonitrile,[114] and later work[115,116] demonstrated that this material was (**55**; Scheme 26). The internal nucleophile in this case is the carbonyl oxygen. More recently, extensions of this type of reaction have been applied to the synthesis of sterically hindered peptides.[117] A further interesting oxazolone synthesis[118] from (**56**) involves nucleophilic attack by the nitrile on a cyclopropenium intermediate and leading ultimately to formation of the spiro derivative (**57**; Scheme 27).



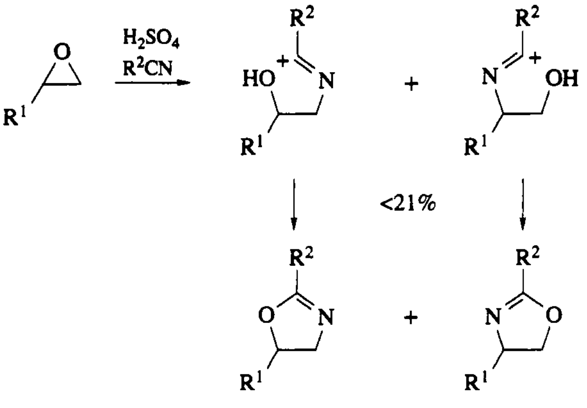
Scheme 26



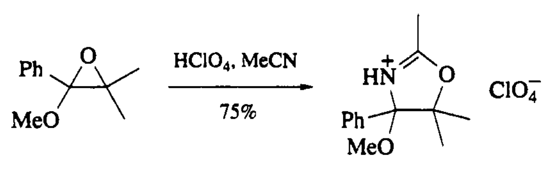
Scheme 27

The reaction of epoxides, nitriles and sulfuric acid results in generally poor yields of oxazoline derivatives, and mixtures of isomers may also result (Scheme 28).[119] These difficulties are overcome by the use of epoxy ethers (equation 35).[120,121] As shown in equation (36), oxetanes undergo analogous reactions to afford dihydro-1,3-oxazines in excellent quantities.[122]

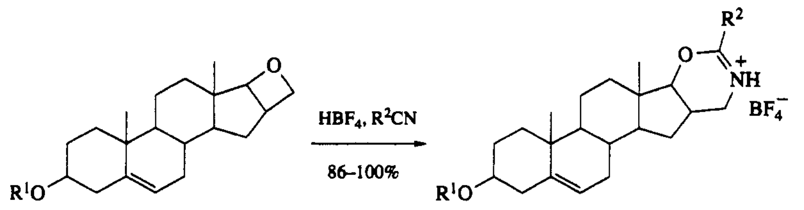
When sulfur species act as the internal nucleophile, then thiazoline (**58**) and thiazine (**59**) products result. These processes are analogs of previously discussed oxygen examples,[95] and typical cases are



Scheme 28

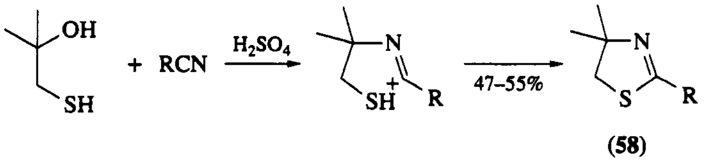


(35)



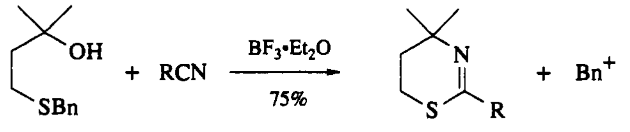
(36)

shown in Scheme 29[123] and equation (37).[124] Episulfides undergo stereospecific ring expansion to thiazoline products in typical yields of 30–80%. Reaction occurs with inversion of configuration,[125,126] as shown in Scheme 30.



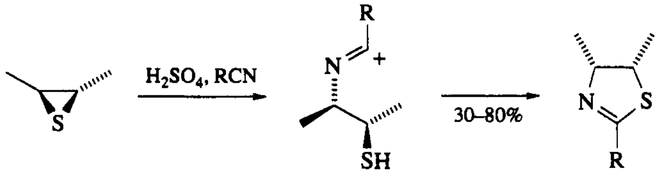
(58)

Scheme 29



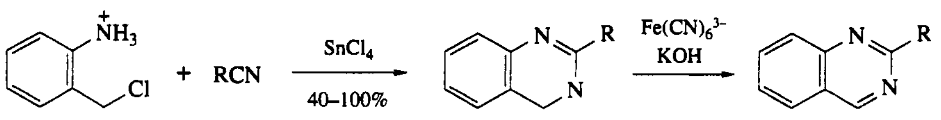
(59)

(37)



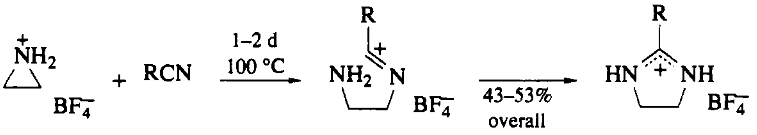
Scheme 30

Nitrogen derivatives may also be used to trap nitrilium ions and produce heterocycles. This has been used[127] to produce the 3,4-dihydroquinazoline system (**60**) and the corresponding aromatic derivatives (**61**; Scheme 31; *cf.* Scheme 17[92]). Most examples, however, involve three-membered nitrogen species. Nitriles readily attack aziridinium salts,[128,129] *e.g.* (**62**), producing imidazoline salts (**63**; Scheme 32). Aziridines (Scheme 33) and azirines undergo similar ring expansion under Ritter conditions.[121]



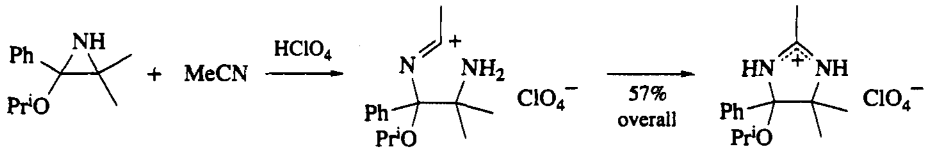
(60) **(61)**

Scheme 31



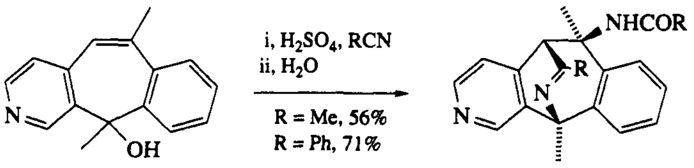
(62) **(63)**

Scheme 32



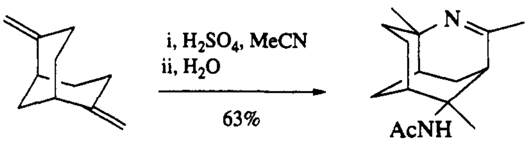
Scheme 33

Until recently, the intramolecular cyclization procedure had been used only to synthesize fused heterocyclic structures. The first report[31] of a bridged product, in 1978, involved only a minor amount (9%) of an azabicyclo[3.3.1]nonane derivative obtained from the reaction of *cis*-carveol with acetonitrile and BF$_3$–Et$_2$O. However, several effective examples are now known. These all involve reaction of the nitrilium intermediate with an internal alkenic nucleophile to yield a 1-azacyclohexene ring and a new carbenium ion which undergoes conventional, but stereospecific, Ritter reaction from the least hindered face. Such reactions are typified by formation of the multicyclic structures (**64**; equation 38)[130] and (**65**; equation 39),[131] and have considerable potential in the synthesis of complex nitrogen heterocyclic systems since suitable optically pure substrates should undergo completely stereospecific conversions. This has been confirmed by Marschoff[132] in an elegant study on (*R*)-(+)-limonene (**66**) and (1*S*)-(−)-β-pinene (**67**), which produced opposite enantiomers of the bicyclic amide (**68**; Scheme 34).



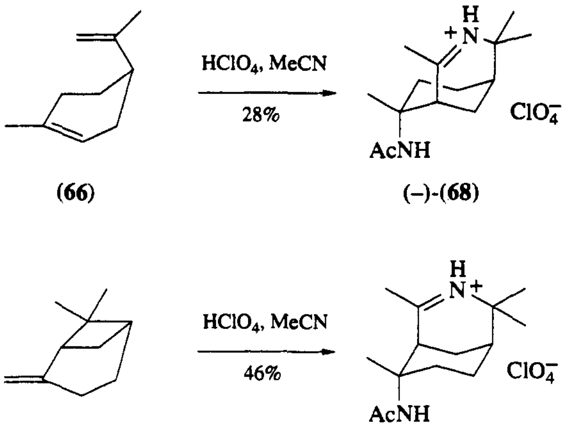
(**64**)

(38)



(**65**)

(39)



(**66**) (−)-(**68**)

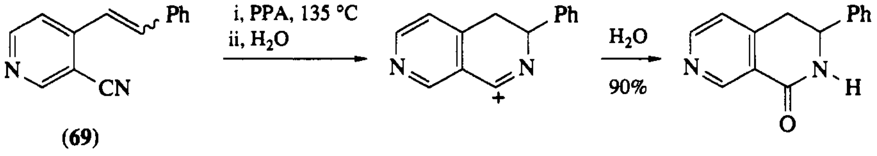
(**67**) (+)-(**68**)

Scheme 34

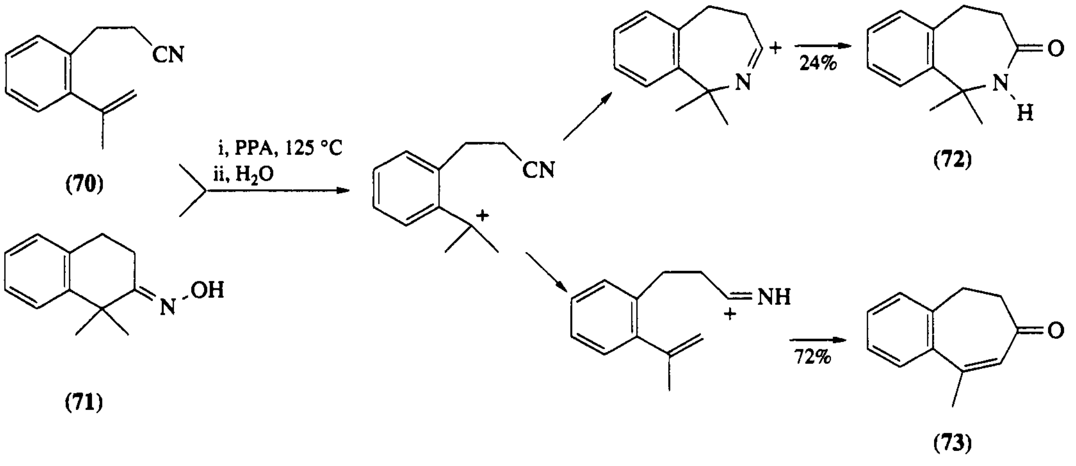
1.9.2.2 Intramolecular Formation of the Nitrilium Ion

Intramolecular reaction of a nitrile group and a carbenium ion can produce a cyclic nitrilium intermediate leading to Ritter-type products after reaction with an external nucleophile (Scheme 15). Geometrical considerations determine that six-membered rings are the smallest available by this mechanism. The carbenium ion is most commonly generated from an alkene, oxime, ketone or a second nitrile group.

Conversion of 3-cyano-4-stilbazole (**69**) into a tetrahydrocopyrine derivative illustrates the use of an alkenic group as the cation precursor (Scheme 35).[133] Such processes are frequently less clear-cut; for example, reaction of either the unsaturated nitrile (**70**) or oxime (**71**) resulted[134] in competitive cyclizations to the minor Ritter product (**72**) and the major Hoesch product (**73**; Scheme 36). Similar competing processes have been observed for spirocyclohexanone oximes,[135] but in other cases no cyclic products were produced at all.[136]

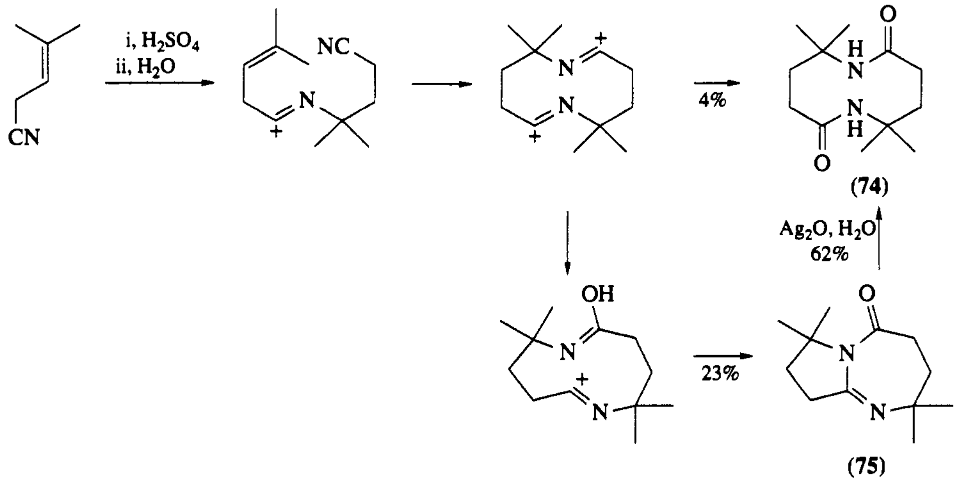


Scheme 35



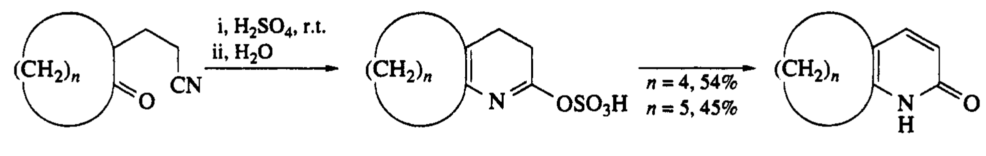
Scheme 36

Reports of five-membered ring formation involving this mechanism remain unauthenticated. Formation of an oxazolidinone product from Ritter reaction of cyclohexanone and cyclohexanone cyanohydrin[137] has been shown by Ducker[138] to result from an alternative pathway. Although 4-methyl-3-pentenonitrile did undergo intramolecular cyclization, this did not involve pyrrolidone formation.[139] Rather a novel dimeric process took place, leading to formation of a monocyclic (**74**) and a bicyclic (**75**) product. The latter was readily ring opened to (**74**) using silver oxide and water (Scheme 37).

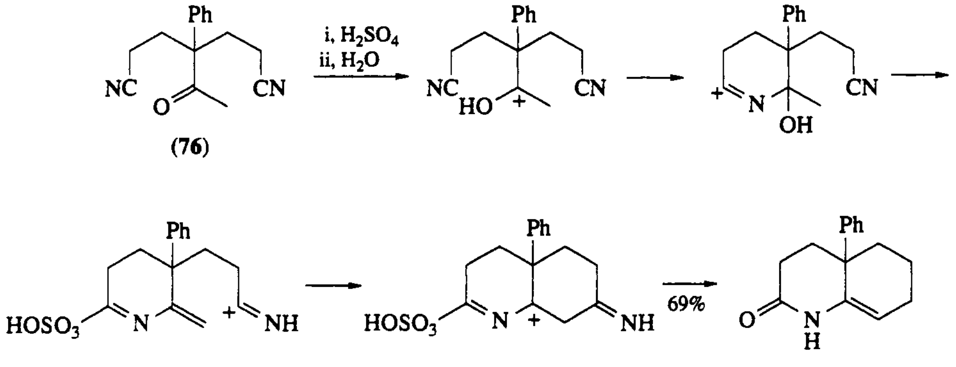


Scheme 37

It has been known for many years that δ-ketonitriles produce 2-pyridone derivatives under acidic conditions,[140] and such processes have been reviewed by Meyers.[14] Such reactions generally yield reduced derivatives, but in some cases (*e.g.* Scheme 38) *in situ* oxidation produces the aromatic compounds directly.[141] A further interesting example is conversion of the pimelonitrile derivative (**76**) into the bicyclic product (**77**) by means of sequential Ritter and Hoesch processes in a one-pot reaction (Scheme 39).[142]



Scheme 38



(**76**)

(**77**)

Scheme 39

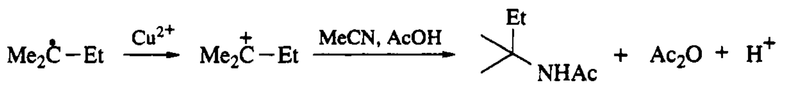
Cyclization of α,ω-dinitriles under acidic conditions has been reviewed thoroughly by Johnson and Madronero.[10] Anhydrous hydrogen halides are favored for such reactions and a wide range of five-, six- and seven-numbered heterocyclic systems are produced.

1.9.3 EXTENSIONS OF THE ORIGINAL REACTION

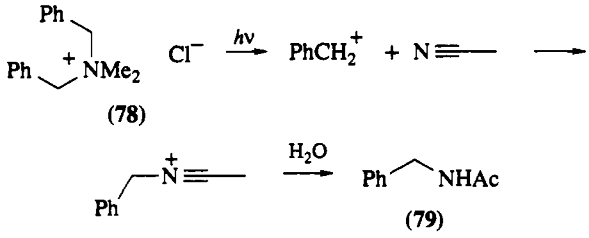
The Ritter reaction as originally reported involved generation of a carbenium ion intermediate under strongly acidic conditions, followed by reaction with the nitrile component. Not surprisingly, other means of generating the carbenium ion, or related chemical species, also result in Ritter-type processes. These newer developments have greatly added to the overall synthetic versatility of the reaction over recent years.

1.9.3.1 Physical Techniques

Carbenium ions generated by nonacidic routes also react with nitriles and yield amides on hydrolytic work-up. Such experiments[143] have included oxidation of free radicals (Scheme 40) using Cu^{2+}. Similarly, Cacace *et al.*[144] produced carbenium ions including s-$C_3H_7^+$, s-$C_4H_9^+$ and t-$C_4H_9^+$ by radiolysis, and observed reaction with nitriles and water leading to *N*-alkylamides. Ritter-type products have also been isolated from a number of organic photochemical reactions carried out in nitrile solvents. For example, photolysis of dibenzyldimethylammonium chloride (**78**) in acetonitrile resulted[145] in a mixture of products including toluene, dibenzyl, benzyl chloride and *N*-benzylacetamide (**79**). The small amounts of amide produced were postulated to result from the sequence shown in Scheme 41.

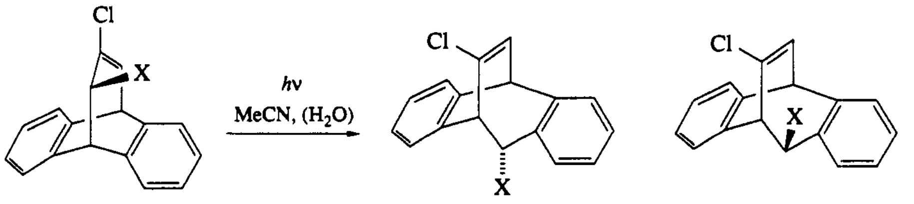


Scheme 40



Scheme 41

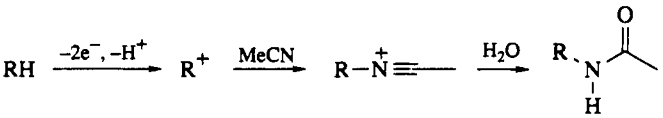
Cristol has carried out photochemical studies on a range of cyclic halogenated substrates which yield Ritter-type products.[146] Irradiation of the dihalides (**80**) in acetonitrile normally affords a mixture of the isomeric products (**81**) and (**82**; X = halogen), plus polar material. However, when the solvent was switched to 5% aqueous acetonitrile, significant amounts of the additional products (**81**; X = OH; 15%) and (**81**; X = NHAc; 16%), plus traces of (**82**; X = NHAc) were isolated (equation 40). These new substances are believed to result from nucleophilic attack by water or acetonitrile on a ground state carbenium ion-like intermediate. A number of further, closely related reactions of this type have been described.[147–149] These photolyses consistently yield amide products but, unfortunately from the synthetic viewpoint, mixtures are often produced, and overall yields of the amides are not generally high.



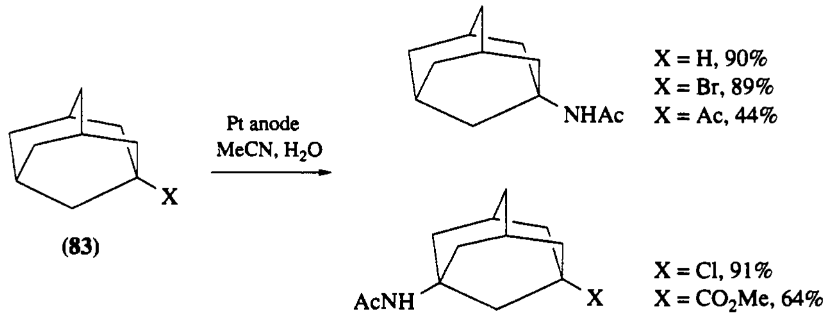
(40)

(**80**) X = Cl, Br (**81**) (**82**)

The physical technique with the greatest potential for synthetic applications of Ritter-type reactions is electrochemistry. A selection only of examples is discussed here. Synthetic chemists unfamiliar with this technique will find the review by Eberson and Nyberg[150] an informative and entertaining introduction to this area. Electrochemical Ritter reactions may be performed through anodic substitution of a hydrogen by the nitrile, followed by hydrolysis of the nitrilium ion intermediate, as shown in Scheme 42. The majority of reactions investigated have been anodic acetamidations using hydrocarbons, alkyl halides, esters or ketones as the substrate. In some cases, such as reaction of the adamantane derivatives (**83**),[151] the yields of amide product are excellent (Scheme 43).

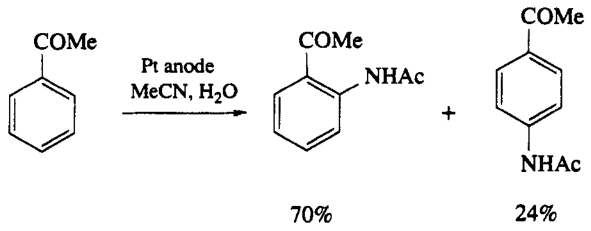


Scheme 42

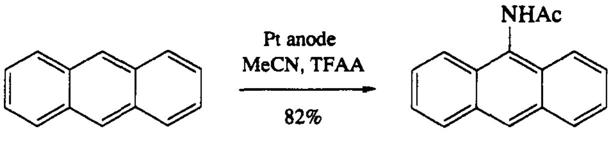


Scheme 43

Anodic oxidation of *n*-alkanes in acetonitrile results in mixtures of *N*-*s*-alkylacetamides but skeletal rearrangement of the intermediate *s*-carbenium ions is not observed.[152] Aromatic compounds can undergo direct acetamidation in the ring. Thus, acetophenone, which normally undergoes electrophilic aromatic substitution at the *meta* position, affords the *o*- and *p*-acetamides (Scheme 44).[153] Anthracene is cleanly converted into the acetamide (**84**) when the reaction is performed in the presence of TFAA as water scavenger (equation 41).[154]



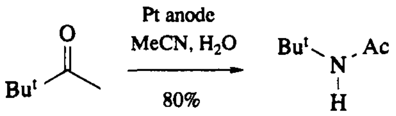
Scheme 44



(**84**)

(41)

Generally, α-branched ketones undergo α-cleavage followed by acetamidation (equation 42),[155] while unbranched or remotely branched ketones result in substitution at remote (γ, δ and ε) positions (equation 43).[156] These modes of reaction are direct analogs of behavior in ketone photochemistry (Norrish Type I and II processes) and mass spectrometry (α-cleavage and McLafferty rearrangement). However, the electrochemical intramolecular hydrogen abstraction is much less selective, which detracts from the synthetic opportunities in being able to functionalize unactivated hydrocarbon groups at remote sites. On the other hand, acyclic esters tend to be more selective than the ketones, generally providing ω-1-substituted products (equation 44).[157]



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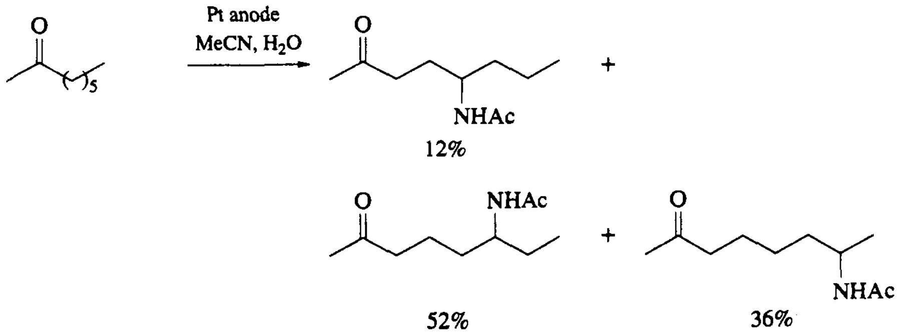

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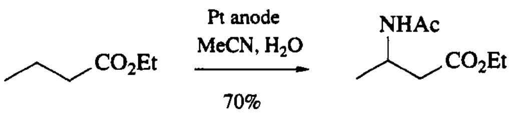
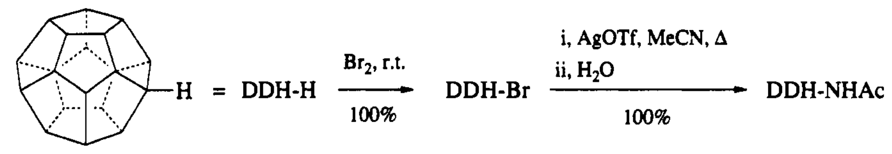


(44)

1.9.3.2 Metallic Reagents

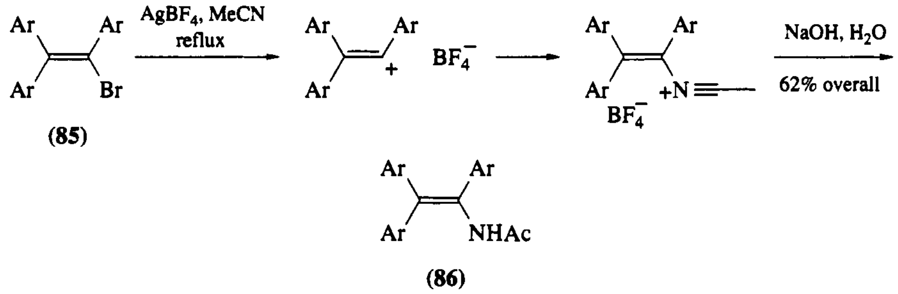
The scope of the Ritter reaction can also be extended by avoiding strong acid as the carbenium ion initiator. In at least one case it is possible to omit this reagent entirely because of the facility of S_N1 reaction. Thus, reflux of *t*-butyl bromide in acetonitrile or propionitrile for 24 h led to formation of *N*-*t*-butylamide products.[158] Less commonly used initiators have included cation exchange resins[159] and clayfen.[160] In this latter case, the clay-supported iron(III) nitrate is believed to give rise to nitrosonium ions, which react with the alkyl halide substrate to produce a carbenium ion. Yields of amide from this technique are generally modest (21–35%).

Earlier mention has been made of the use of Lewis acid and Friedel–Crafts reagents as initiators of carbenium ion formation. Another versatile device is to employ a metal to assist in generation of the carbenium ion. In its simplest form, addition of silver(I) ion to an alkyl halide is an excellent technique for encouraging reaction by means of the S_N1 pathway. This process was first applied to the Ritter reaction by Cast and Stevens,[161] but yields obtained were modest. A recent elegant application of this technique is the two-step conversion of dodecahedrane into its acetamide derivative (Scheme 45).[162]

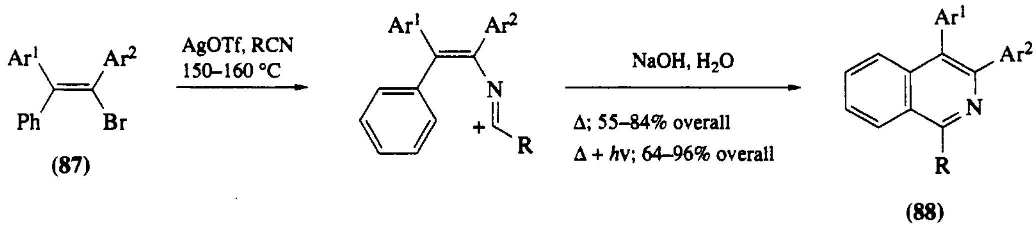


Scheme 45

Silver-assisted solvolysis of the trianisylvinyl bromide (**85**) produces a vinyl cation, which then undergoes Ritter reaction, yielding the amide (**86**; Scheme 46).[163] Other less reactive triarylvinyl bromides (**87**) required much higher temperatures for generation of the cation, and silver triflate proved a better reagent.[164] Under these conditions the intermediate nitrilium ion performed an intramolecular electrophilic aromatic substitution, producing the highly substituted isoquinolines (**88**). This conversion may also be carried out photochemically at low temperature, but in variable yield (12–77%) since the vinyl radical initially produced can carry out hydrogen abstraction reactions in competition with being oxidized to the vinyl cation. Superior yields were obtained by combining the procedures and performing sequential thermal and photochemical steps (Scheme 47).[164]

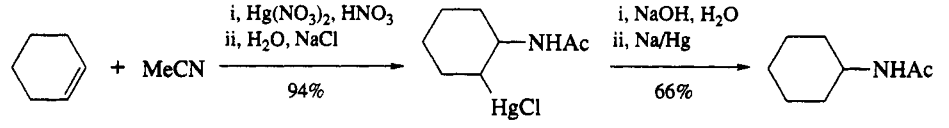


Scheme 46



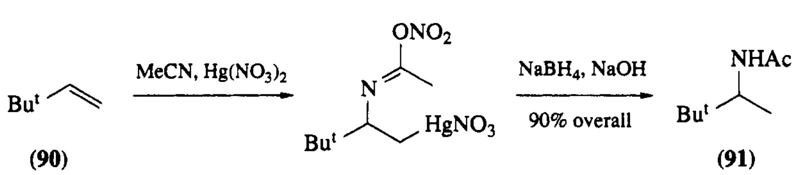
Scheme 47

Some years ago it was reported that cyclohexene reacted with mercury(II) nitrate and acetonitrile in nitric acid to give the metallic derivative (**89**), which, in turn, underwent demercuration with sodium amalgam, producing the corresponding amide (Scheme 48).[165] Later investigators[166–168] found that less severe conditions were adequate, requiring only a solution of anhydrous mercury(II) nitrate in the nitrile, and sodium borohydride, respectively. This process is analogous to the more familiar procedure developed by Brown for the hydration of alkenes using mercury(II) acetate.[169] It shares the advantage of that process in that it proceeds *via* a bridged mercurinium ion rather than a carbenium ion and, therefore, it is less prone to rearrangement. Thus, for example, the alkene (**90**) is converted into amide (**91**) in excellent yield and without formation of isomeric side products (Scheme 49).[167] Unfortunately, many alkenes fail to react in this process due to steric effects resulting from the bulky mercury reagent. When this does occur, reduction of the organomercurial intermediate produces β-amido radicals which may be coupled with electron-deficient alkenes to produce nitrogen heterocyclic products.[170,171]



(89)

Scheme 48



Scheme 49

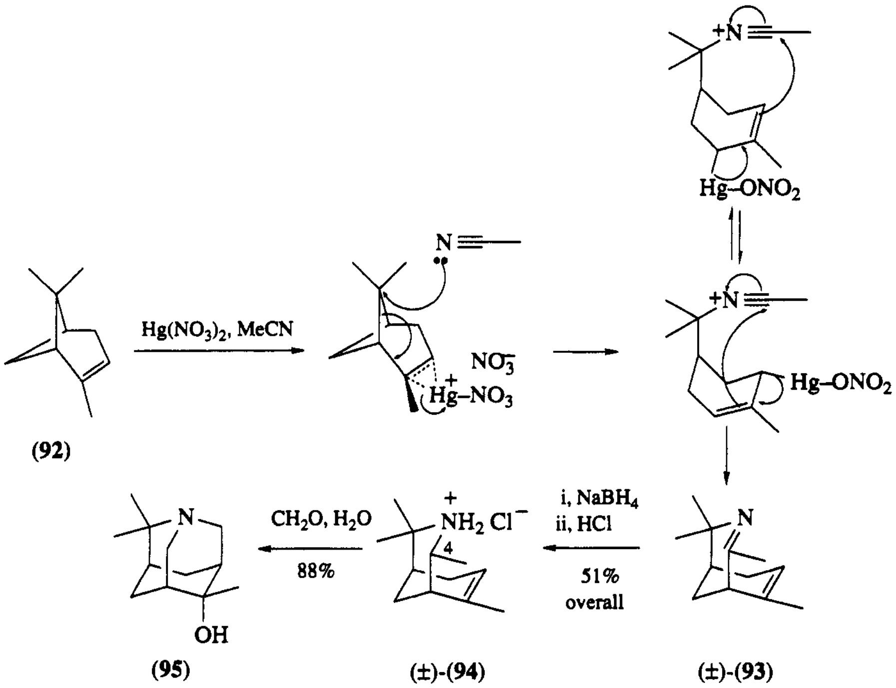
When Delpech and Khuong-Huu[172] applied this procedure to a trisubstituted steroidal alkene, they obtained four isomeric unsaturated amide products. In crowded cases the mercuration can therefore proceed by means of an allylic oxidation pathway with concomitant rearrangement.[173] In contrast, the reaction of (–)-α-pinene (**92**) with acetonitrile and mercury(II) nitrate gave a good yield of either of the racemic 3-azabicyclo[3.3.1]nonene derivatives (**93**) or (**94**), depending on the work-up conditions used.[174] The mechanism proposed (Scheme 50) involves an intramolecular nitrilium ion cyclization similar to those discussed in Section 1.9.2. Reaction of (**94**) with aqueous formaldehyde produced the azaadamantanol (**95**) *via* another novel pathway involving loss of the C(4)-methyl group of (**94**) as acetaldehyde. Replacement of water by alternative nucleophiles allows access to a range of substituted azaadamantanes, avoiding previous multistep procedures.

This mercuration reaction has been adapted by Stevens and Kenney[175] to perform elegant stereospecific syntheses of the *Aristotelia* indole alkaloids (+)-makomakine (**97**) and (+)-aristoteline (**98**) from (–)-β-pinene and indol-3-ylacetonitrile (**96**) in only two and three steps, respectively (Scheme 51). A similar procedure from (+)-α-pinene yielded racemic hobartine (**99**) in 11% overall yield. Enantiospecificity is not observed in this reaction for the same reasons encountered during the preparations of (**93**) and (**94**).[174]

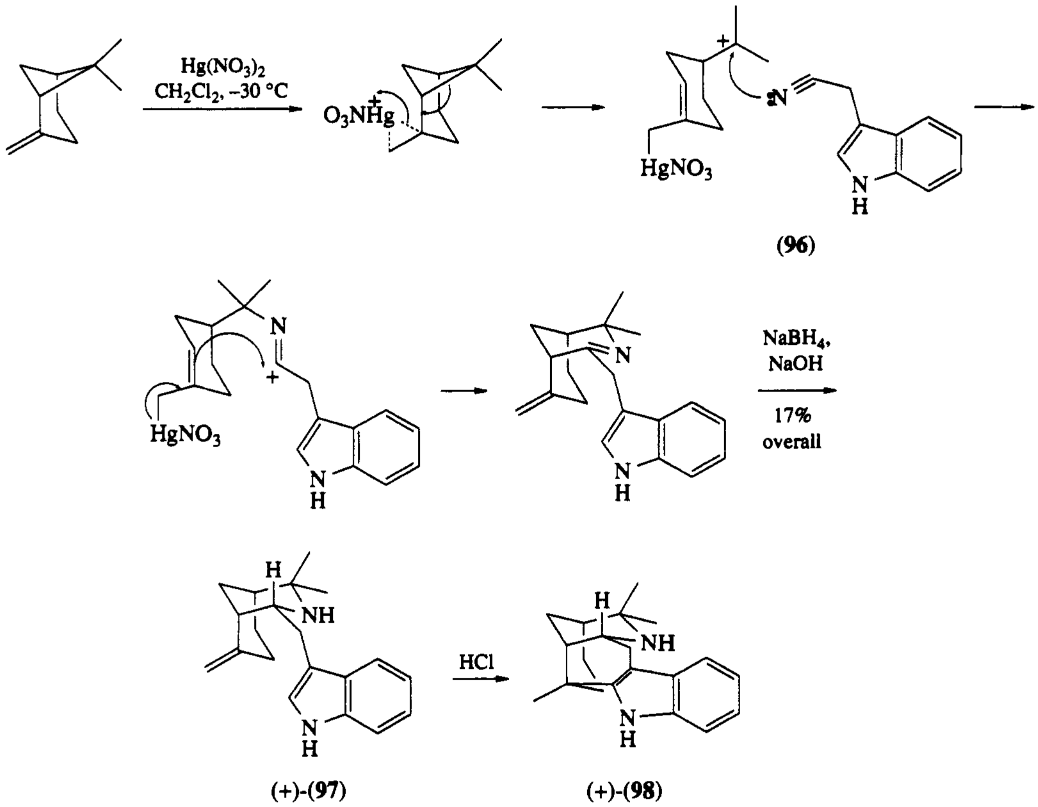
Whereas palladium(II) salts frequently react with aromatic substrates causing direct palladation, the strongly electrophilic complex (**100**) is known to interact with alkenes and induce reactions involving incipient carbenium ions. Hegedus[176] has recently demonstrated that reaction of (**100**) with a variety of alkenes can be followed by nucleophilic attack by nitriles in a palladium-assisted version of the Ritter reaction. This process is illustrated (Scheme 52) for the reaction of (**100**) with *N*-allylskatole in nitrile solvents. Initial reaction yields the σ-alkylpalladium(II) complex (**101**), which is stabilized by chelation. On reduction with sodium borohydride stereospecific reduction to the *syn*-1,2,3,4-tetrahydropyrazino[1.2-*a*]indoles (**102**) occurs, or work-up using benzylamine affords the pyrazinoindole (**103**). Alternatively, treatment of (**101**) with carbon monoxide leads to insertion, producing the acylpalladium complex (**104**) and leading to isolation of the esters (**105**).

Other examples from this study indicate that the reaction path followed by the nitrilium ion depends very much on the nature of the nucleophiles present. Thus, the allylindole (**106**) produced the imidate (**107**) through reaction of the nitrilium ion with methanol in preference to the electron-rich heterocyclic system (equation 45). In contrast, alcohol (**108**) underwent effective intramolecular cyclization (equation 46).

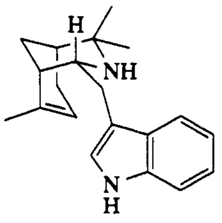
It is also reported that palladium(II) chloride is a suitable catalyst for Ritter reactions conducted at elevated temperature and pressure.[177]



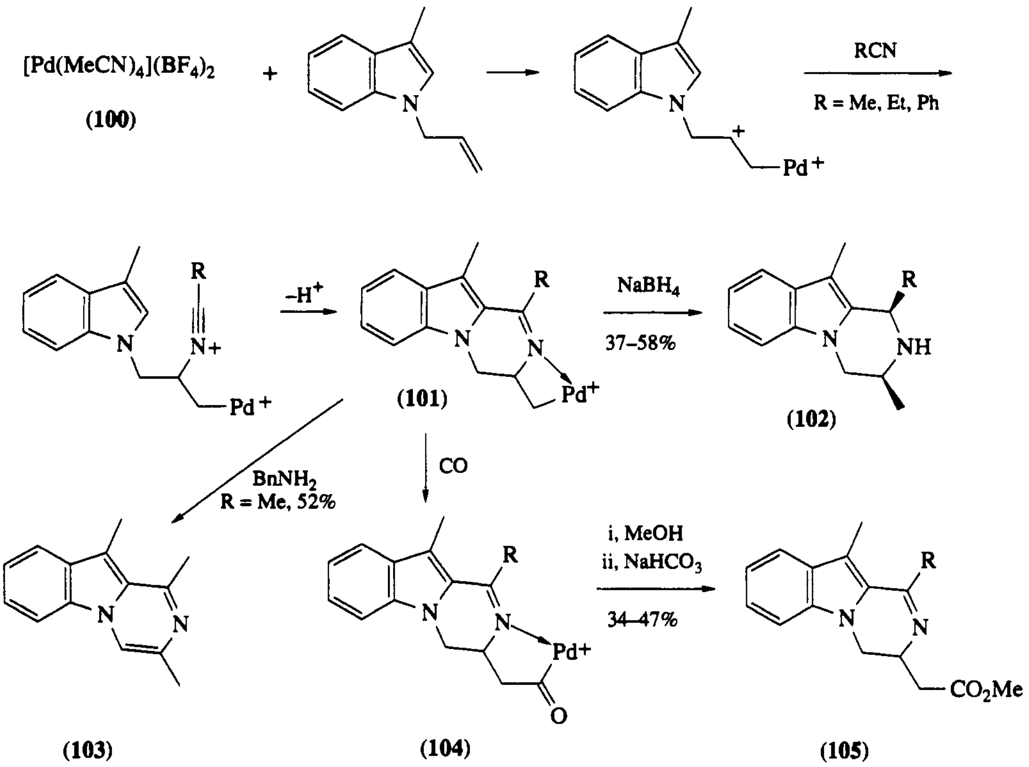
Scheme 50



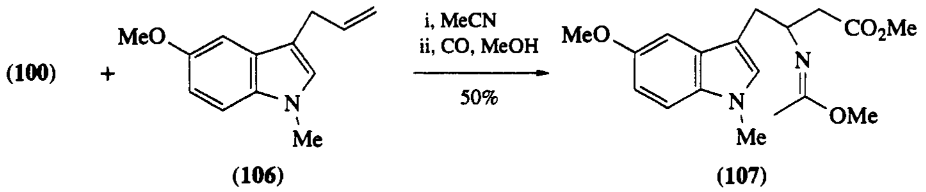
Scheme 51



(±)-(99)



Scheme 52



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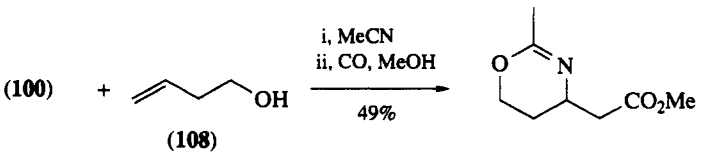
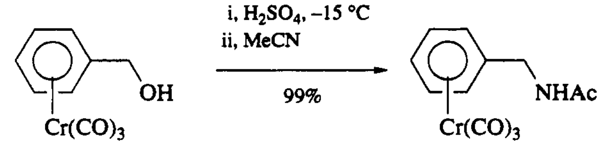


(46)

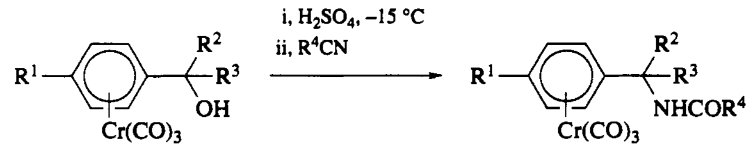
Top and Jaouen[178,179] have found that an effective means of controlling carbenium ion reactivity is to employ temporary stabilization of the ion by means of a suitable organometallic complex. Thus, while benzyl alcohol gives a 48% yield of *N*-benzylacetamide under conventional conditions,[29] the use of

(η^6-benzyl alcohol)tricarbonylchromium (**109**) gave more than double that yield of the complexed acetamide (**110**; equation 47).



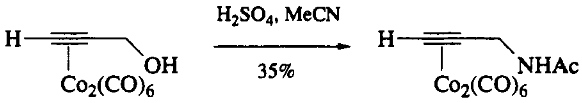
(**109**) (**110**) (47)

Similarly, several nitriles (such as $ClCH_2CN$ and *o*-MeC_6H_4CN) which tend to react poorly in the conventional reaction now reacted most efficiency (98 and 83%, respectively) with the stabilized benzyl cation. Tertiary carbenium ions were so stabilized that no Ritter reaction took place and the behavior of secondary ions depended on the particular case (Scheme 53). Complexed propargyl alcohol (**111**) was converted into the complexed acetamide (**112**) without encountering the customary acid-catalyzed rearrangement problems (equation 48).



R^1	R^2	R^3	$R^4 = Me$	$R^4 = Ph$
p-MeO	Me	H	99%	84%
H	Ph	H	82%	0%
H	Me	Me	0%	0%

Scheme 53



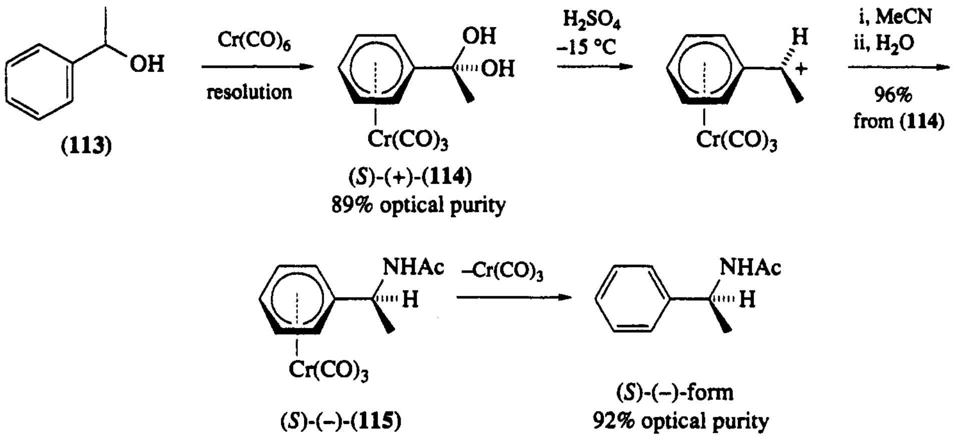
(**111**) (**112**) (48)

Complexation of the $Cr(CO)_3$ group to an aromatic ring imparts a three-dimensional structure to the molecule which can be exploited in asymmetric syntheses.[179,180] Reaction of alcohol (**113**) with $Cr(CO)_6$ was followed by resolution. Complex (**114**) underwent Ritter reaction in acetonitrile yielding the complexed amide (**115**; Scheme 54). Decomplexation gave the free chiral amide whose optical purity (92%) indicated that this process took place with almost complete retention. In contrast, the indanol complex (**116**) was transformed into the Ritter product (**117**) with complete inversion of configuration (equation 49). Convincing explanations of these different stereochemical results have been provided.[179,180] These results are significant in foreshadowing future possibilities for the synthesis of chiral amides and amines by Ritter-type reactions.

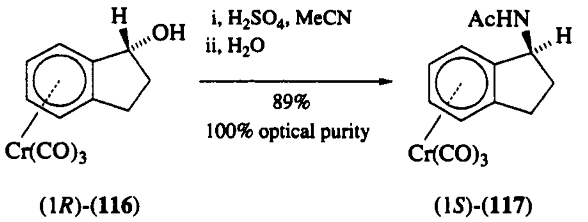
1.9.3.3 Generation of Onium Intermediates

Electrophilic attack of alkenic groups provides a variety of cationic species available for Ritter-type reaction with nitriles, but avoiding strongly acidic conditions. Such processes involving bridged onium ions are also subject to the usual regio- and stereo-chemical factors in the ring-opening step.

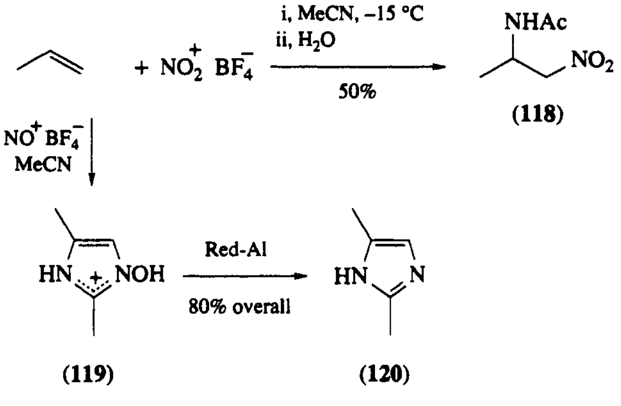
Both nitronium and nitrosonium salts are effective initiators but with quite different results. Thus, propene and nitronium fluoroborate react[181] to produce the secondary α-nitrocarbenium ion which undergoes Ritter reaction with acetonitrile to yield amide (**118**). Under similar conditions, nitrosonium fluoroborate leads to heterocyclic products.[182,183] Intramolecular reaction of the nitroso and nitrilium groups, followed by prototropic shifts, affords the *N*-hydroxy imidazolium salt (**119**). This may be either neutralized to produce the *N*-oxide or reduced to the imidazole (**120**; Scheme 55).



Scheme 54

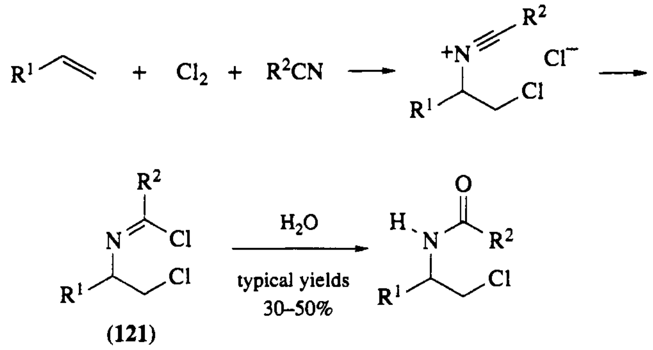


(49)

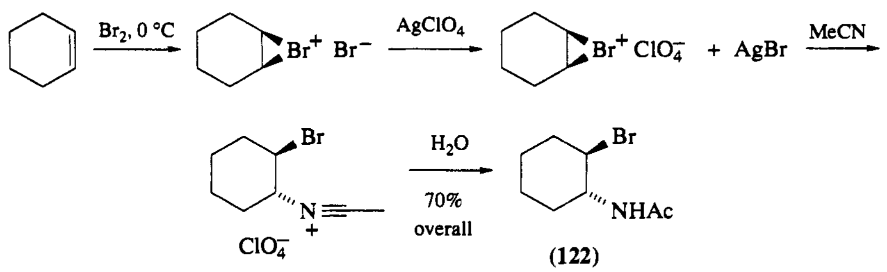


Scheme 55

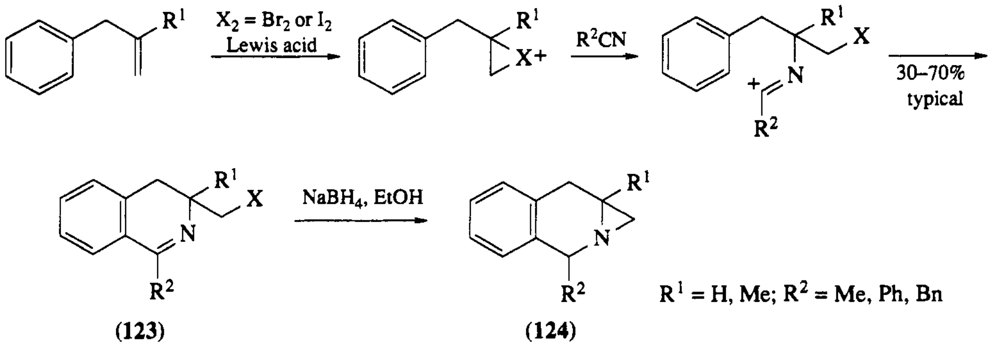
Cairns[184] demonstrated that, as initiator, chlorine provided a convenient synthesis of *N*-(2-chloroalkyl)amides (Scheme 56). In cases where the intermediate imidoyl chloride (**121**) was formed from a nitrile with no α-hydrogen atoms, then this material could be separated from the vicinal dichloride side product by distillation. Otherwise, loss of hydrogen chloride and further reaction was likely, making immediate hydrolysis to the amide desirable. One example of the use of bromine, with cyclohexene and acetonitrile, was also described, producing *N*-(2-bromocyclohexyl)acetamide (**122**) in 26% yield. Hassner[185] has since reported that this type of reaction is best carried out in the presence of silver ion, which removes bromide from solution, thus suppressing the competing formation of vicinal dibromide. Amide (**122**) was now obtained in 70% overall yield (Scheme 57). The use of alkenes, halogen and nitriles or nitrile derivatives (R—SCN, R_2N—CN, Cl—CN, R—OCN) has been extensively studied by Beger as a synthetic route to imidate species and derived five-membered heterocyclic systems.[186–190] This methodology can also be combined with that of the intramolecular Ritter process to synthesize 3,3-disubstituted isoquinoline derivatives (**123**) not available by Bischler–Napieralski reaction (Scheme 58).[191] Reduction affords the fused aziridines (**124**). Utilization of aziridinium species in Ritter-type processes has already been discussed (Section 1.9.2.1).[128,129]



Scheme 56



Scheme 57



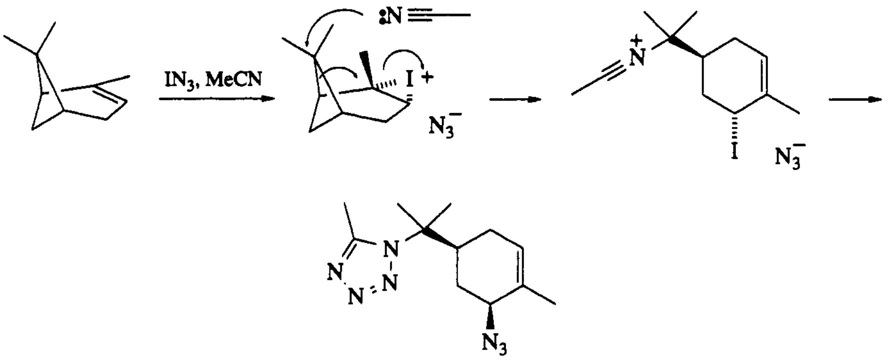
Scheme 58

Generally, iodine azide adds to an alkene by an ionic pathway, yielding a *trans* addition product;[192] however, in a few cases nitrile reagents compete successfully with azide ion in attacking the iodonium intermediate. Thus, α-pinene was converted into tetrazole (**125**) in a one-pot reaction in near quantitative yield (Scheme 59).[193] This type of process is far from general.

More recently, these concepts have been extended to include a range of elegant amidoselenation processes. Alkenes react with benzeneselenenyl chloride and nitriles to yield β-amido phenyl selenides in excellent yield.[194,195] Oxidative elimination of the latter provides the corresponding allylic amides (Scheme 60). Since the reaction proceeds *via* an episelenonium intermediate, the amido selenides are formed with *trans* stereospecificity. However, when applied to nonsymmetrical alkenes (equation 50)[195] it only proceeds with regioselectivity.

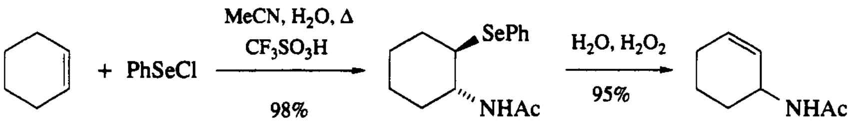
An alternative approach[196] is to use the readily available β-hydroxy phenyl selenides as Ritter substrates. Amide formation occurs with retention of configuration, indicating that fission of the carbon–oxygen bond is assisted by the neighboring phenylseleno group (Scheme 61). Diphenyl diselenide and iodine react with 1,5-dienes to give carbocyclic products. Initial formation of the episelenonium ion is followed by intramolecular attack and subsequent Ritter reaction (Scheme 62).[197]

Vankar and Rao[198] have shown that the cationic intermediate (**126**) in the Pummerer reaction can be intercepted by nitriles producing the amido sulfides (**127**). The moderate yield of these novel products is a consequence of competition with the normal Pummerer process (Scheme 63).

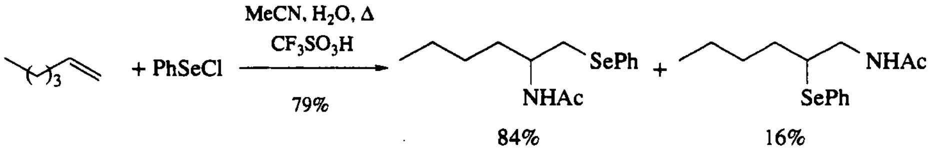


(125)

Scheme 59



Scheme 60



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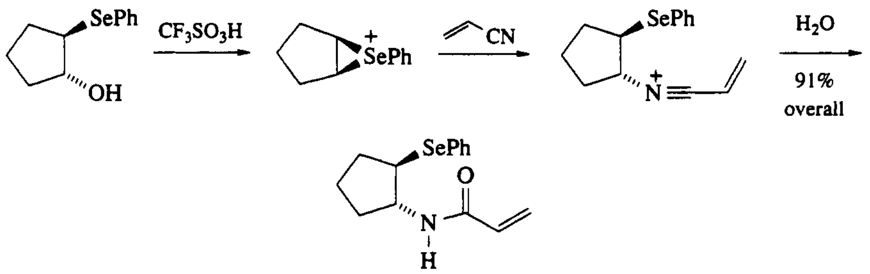
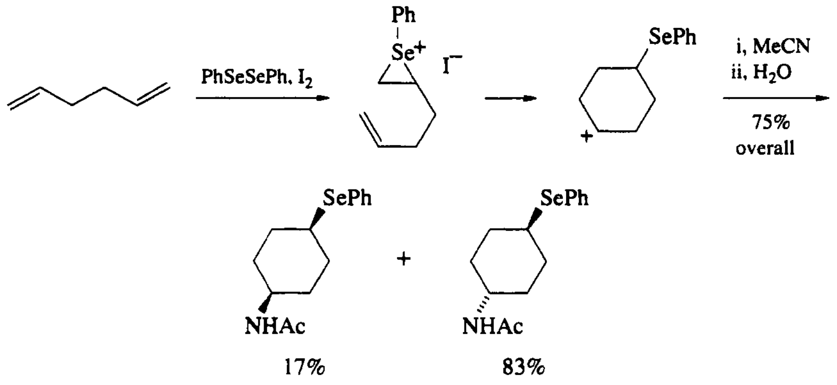
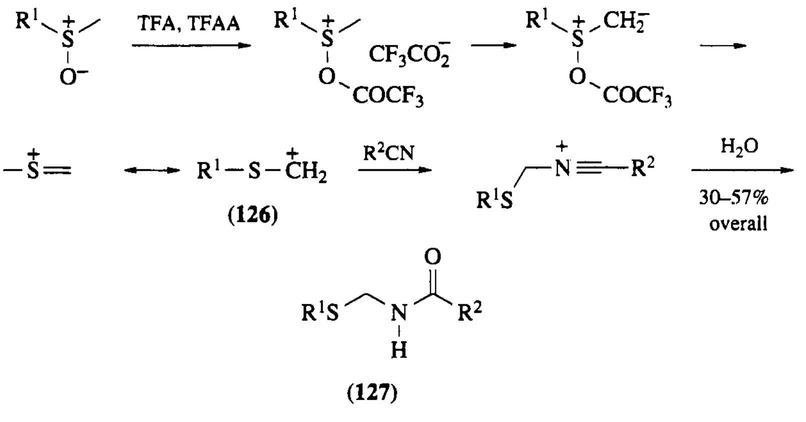


Scheme 61



Scheme 62



Scheme 63

1.9.4 RELATED PROCESSES

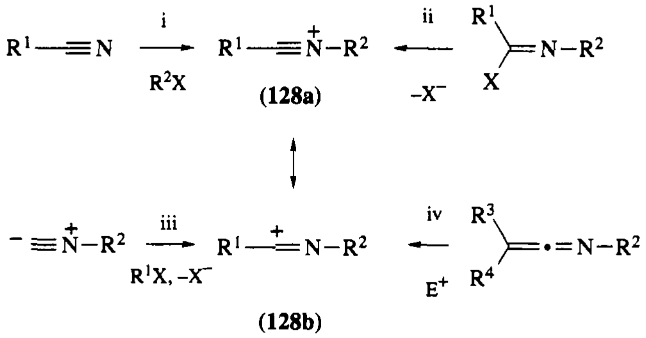
1.9.4.1 Relationship of Ritter and Other Reactions

Over recent years it has become clear that certain organic reactions share common intermediates and therefore have a closer relationship than previously suspected. The first step of the Ritter reaction is production of a carbenium ion, as originally reported under strongly acidic conditions, where Wagner–Meerwein rearrangements are liable to be encountered. As discussed in Section 1.9.3, alternative means of generating carbocationic species have resulted in a resurgence in Ritter-type chemistry. The recent report[199] that carbenium and nitrilium ions may be generated under mild conditions in the absence of strong electrophiles is therefore of considerable interest. Related carbenium ion reactions are those with thiocyanates yielding *N*-alkyl thiocarbamates,[200,201] and with carbon monoxide followed by hydrolysis yielding carboxylic acids (the Koch–Haaf reaction).[202] The relationship between the latter reaction and the Ritter process has been examined in detail.[203]

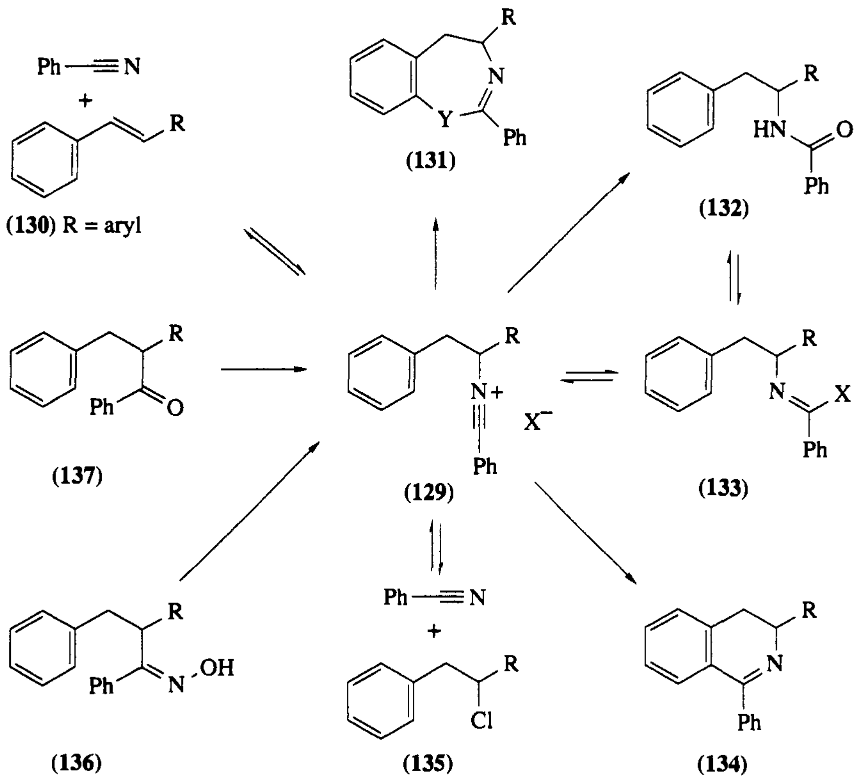
Trapping of the carbenium ion by a nitrile produces a nitrilium ion (**128**). Although such species were proposed by Hantzsch[204] in 1931, chemical syntheses did not become available for some time.[23,205] Major routes to such species now include: (i) alkylation of nitriles; (ii) reaction of imidoyl halides with Lewis acid;[206] (iii) 1,1-addition to isonitriles;[207] and (iv) reaction of ketenimines with electrophiles (Scheme 64).[208] From ^{1}H, ^{13}C and ^{15}N NMR data, Olah and Kiovsky[209] concluded that nitrilium ions and protonated nitriles had a linear structure. This is supported by low temperature X-ray studies on *N*-(2,6-dimethylphenyl)acetonitrilium tetrafluoroborate where the angles R^1—C—N (179.2°) and C—N—R^2 (177.4°) were found. The C—N bond length of 1.15 A° indicated that form (**128a**) is the major contributor to the structure. However, CNDO/2 calculations revealed that, while the positive charge was spread over the entire acetonitrilium group, the carbon atom derived from the nitrile carried the most density. This may be largely due to polarization effects involving the tetrafluoroborate counterion.[210] More recently, the crystal structure of an organometallic nitrilium ion derived from *t*-butyl isocyanide has been obtained. This is significantly bent at nitrogen (169.5°), indicating a contribution from the ketenimine resonance form.[211]

Nitrilium chemistry ranges far beyond hydrolysis to an amide (Ritter reaction) or cyclization (intramolecular Ritter reaction). The generation of nitrilium triflate salts, often in high yield (72–95%),[212] has permitted detailed study of such processes.[213–215] In particular, evidence for the intermediacy of the nitrilium ion in the Beckmann rearrangement,[216,217] von Braun amide degradation[218] and Bischler–Napieralski reaction[219] has been presented. Fodor and Nagubandi[206,220,221] have done much to clarify the interplay of these previously unrecognized relationships of named reactions,[222] as illustrated in Scheme 65 for structures (**129**)–(**137**). This summary may readily be extended to include analogs of the Bischler–Napieralski reaction such as the Pictet–Gams isoquinoline synthesis and Pictet–Hubert (Morgan–Walls) phenanthridine synthesis, as well as offshoots incorporating carbenium ion and imidate chemistry.

It has been shown[208,223] that appropriately substituted nitrilium ions undergo stereospecific attack by nucleophiles to produce only the (*Z*)-isomer (**138**), *i.e.* approach of nucleophile Y^- is concomitant with development of the *trans*-nitrogen lone pair (Scheme 66). While this stereospecificity may be completely general, it can only be proven for cases where addition is faster than nitrogen inversion in (**138**). The



Scheme 64



KEY: **Reaction name**: functional group conversion; steps involved; typical reagents

Ritter reaction: alkene *(etc.)* into amide, sequence **(130)** → carbenium ion → **(129)** → **(133)** → **(132)** or **(130)** → **(129)** → **(132)**; H_2SO_4 then H_2O ($X = SO_3H$).

Retro-Ritter reaction: amide into alkene; reverse sequence to above; $SOCl_2$ or P_4O_{10}.

Intramolecular Ritter reaction: alkene *(etc.)* into heterocycle; sequence **(130)** → carbenium ion → **(129)** → **(131)** (where Y is a nucleophilic substituent); H_2SO_4 then H_2O.

Bischler–Napieralski reaction: β-phenethylamide into 3,4-dihydroisoquinoline; sequence **(132)** → **(133)** → **(129)** → **(134)**; P_4O_{10} or $POCl_3$ plus Lewis acid.

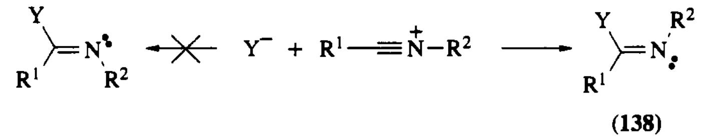
Beckmann rearrangement; ketoxime into amide; sequence **(136)** → **(129)** → **(132)**; PCl_5.

Schmidt reaction: ketone *(etc.)* into amide; sequence **(137)** → **(129)** → **(132)**; HN_3 and H_2SO_4.

von Braun reaction (modified): amide into alkyl halide and nitrile; sequence **(132)** → **(133)** → **(129)** → carbenium ion → **(135)**; PCl_5.

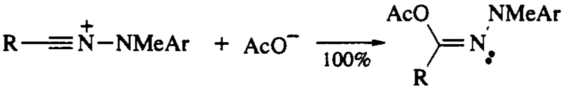
Scheme 65 Schematic summary of some major nitrilium ion reaction pathways major cases studied have therefore employed substituents (R^2 = OR, NR_2, $N{=}CR_2$ and SR) which retard inversion of the imidoyl nitrogen atom. Consequently, previously unknown materials such as *O*-acylisoamides (**139**) may be readily obtained (equation 51).[224] Such *O*-acylated products may be generated in the presence of amines as *in situ* acyl transfer reagents for peptide synthesis.[225] It seems likely that these stereochemical considerations are a major factor in the success of intramolecular Ritter cyclizations (Section 1.9.2.1).

As an extension of the amidoseleniation processes discussed previously,[194–197] imidates (the third Ritter intermediate) may be utilized as precursors for the synthesis of cyclic amides (Scheme 67)[226] and lactams (equation 52).[227] Such combination of imidate and onium ion processes has much potential for further extension of Ritter-type chemistry.



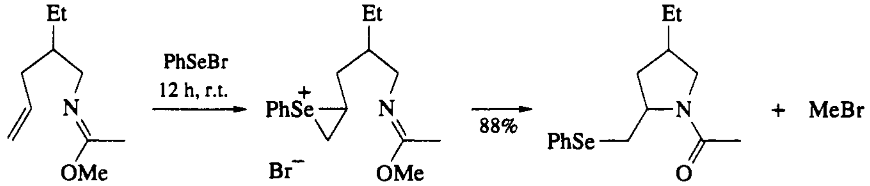
(138)

Scheme 66

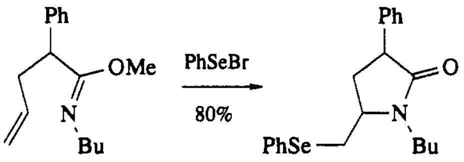


(139)

(51)



Scheme 67

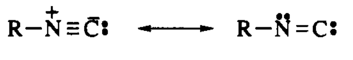


(52)

1.9.4.2 Isonitriles and Ritter-type processes

Although the isomeric nitrile (R—CN) and the isonitrile (R—NC) functional groups have structural characteristics leading to their own unique chemistry,[207,228,229] the two have much in common. They share properties such as a linear configuration, triple bonding between carbon and nitrogen, low steric demand, polarizability and similar bond strengths. Both have large and similar dipole moments, for example 3.9 D for benzonitrile and 3.5 D for phenyl isocyanide.[230] Not surprisingly, there are therefore occasions when their chemistry becomes closely related.

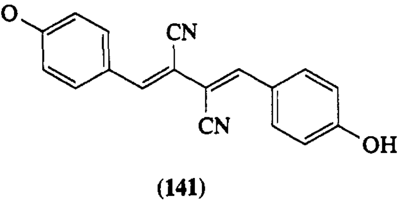
In valence bond terms, the isonitrile (isocyanide) group requires representation as two resonance structures (**140a**) and (**140b**), but physical properties indicate that the dipolar contribution (**140a**) is the major one. The isonitrile structure involves divalent carbon,[230] a property shared only with carbon monoxide and fulminates (R—O—NC) as isolable entities. Since the latter are notoriously reactive materials, this singles out the isonitriles as the only stable family of organic compounds which are formally divalent.



$$R{-}\overset{+}{N}{\equiv}\overset{-}{C}{:} \longleftrightarrow R{-}\ddot{N}{=}C{:}$$

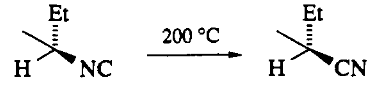
(140a) **(140b)**

Formerly, isonitriles were perhaps best known to many chemists through the indescribably vile odor[231] of volatile members of the series encountered during the Hofmann carbylamine test for primary amines.[232] Over recent years, however, isonitriles have come into their own as versatile synthetic reagents. Several reliable preparative methods now allow ready access to this family of substances and their remarkable chemistry.[207,233] Biological pathways to isonitriles are also known, the first such substance isolated being the antibiotic xanthocillin (**141**), isolated from *Penicillium notatum*.[234,235] Isonitrile compounds are also isolated fairly frequently from marine sources.[236]



(141)

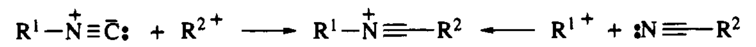
It has been known for many years that on strong heating isonitriles isomerize to nitriles[237] in an exothermic, unimolecular process. For example,[238] kinetic work on *p*-tolyl isocyanide demonstrated that clean isomerization to *p*-tolunitrile took place in solution at 200 °C with an energy of activation of 154 kJ mol^{-1}. Cyclobutyl isocyanide underwent rearrangement to cyclobutanenitrile without ring-contraction or ring-opening side products being formed.[239] Furthermore, the homochiral isonitrile (**142**) underwent rearrangement (equation 53) with almost complete retention of configuration. It is therefore believed that the thermal isomerization process is a concerted reaction.[240] However, more recently, evidence for a competing radical process in solution reactions has been presented.[241,242] At the lower reaction temperatures normally employed in organic synthesis, these isomerization processes are not a complicating factor.



(142) (53)

A further bridge between the chemistry of the two functional groups is formation of nitrilium ions. Nucleophilic attack on a carbenium ion by the carbon atom of an isonitrile produces a nitrilium ion (**143**) identical in all respects with that resulting from Ritter reaction (Scheme 68). In practice this process is less common than might be expected since the procedure for generating carbenium ions for Ritter reaction is through use of strong acid which would destroy the isonitrile. Thus, the tropylium ion reacts with isonitriles (Scheme 69)[243] to give a nitrilium intermediate which is hydrolyzed to the corresponding amide in traditional Ritter fashion. In a related process (Scheme 70) the benzyne precursor (**144**) reacts with cyclohexyl isocyanide to produce the amide (**145**). Here, nucleophilic attack on benzyne was followed by dehydration of the *t*-butanol solvent to yield the stable products.[244] A further interesting example[245] involves reaction of the cyclobutadiene complex (**146**) with cyclohexyl isocyanide (Scheme 71).

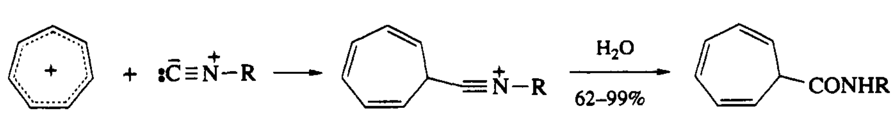
Acidic hydrolysis of isonitriles proceeds in two steps to the *N*-formamide and subsequently to the amine derivatives in common with nitrilium ions produced in the Ritter reaction using hydrogen



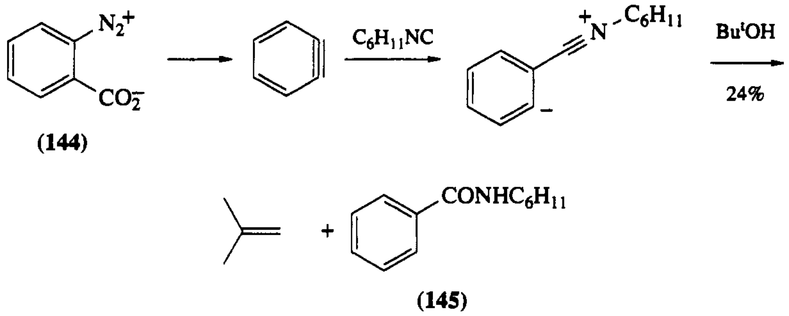
$$R^1-\overset{+}{N}\equiv C\!: + R^{2+} \longrightarrow R^1-\overset{+}{N}\equiv R^2 \longleftarrow R^{1+} + :N\equiv R^2$$

(143)

Scheme 68



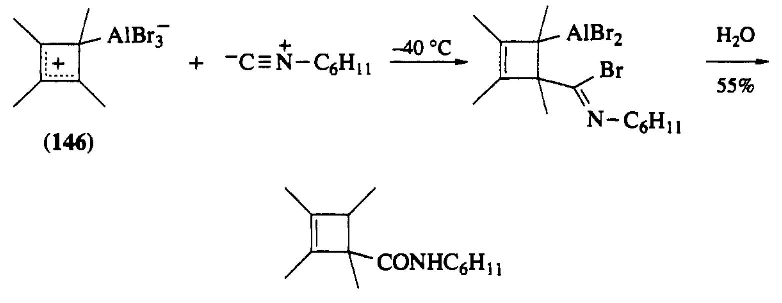
Scheme 69



(144)

(145)

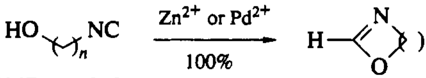
Scheme 70



(146)

Scheme 71

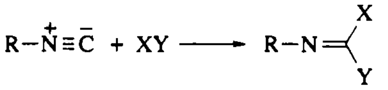
cyanide.[246] In another parallel with chemistry discussed earlier, isonitriles may also be employed in aldehyde syntheses, including production of C(1)-labeled derivatives.[247,248] Coordination of an isonitrile to a metal leads to a rich range of chemistry.[207,249] In the presence of catalytic amounts of metal ion, the hydroxyalkyl isocyanides (**147**) are cyclized in quantitative yield to the 2-oxazoline and dihydro-1,3-oxazine derivatives (equation 54).[250] This process is analogous to the intramolecular Ritter process.



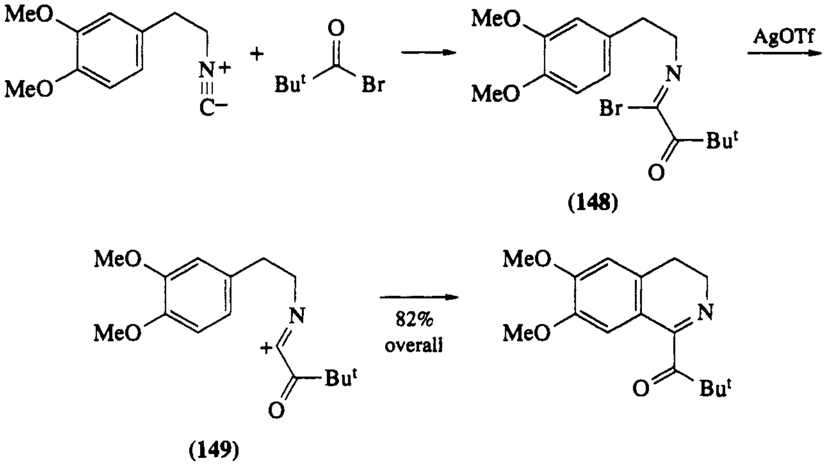
(**147**) $n = 2, 3$ (54)

A major reaction of isonitriles is α-addition of a reagent XY to the formally divalent carbon atom (equation 55), thereby yielding imidate or imidoyl products[251] and providing a further direct connection with Ritter-type reactivity. Indeed, on occasion, isonitriles have been obtained from Ritter reactions *via* such intermediates.[25,27] Recent elegant work by Livinghouse[252–254] illustrates how isonitrile chemistry is intermeshed with Ritter-type processes. Isonitriles react with acyl halides (Scheme 72) to produce ketoimidoyl halides, *e.g.* (**148**), from which the acylnitrilium ion (**149**) may be generated through reaction with silver salts. In this example, the reactive intermediate cyclizes readily and in high yield to the corresponding dihydroisoquinoline. A range of nitrogen heterocyclic systems has been synthesized using this methodology.

Isonitriles can otherwise attain tetravalent respectability by participating in cyclization reactions,[207,255] and in multicomponent condensations such as the Passerini[207] (3-component) and Ugi (4-component) reactions.[207,256] Nitrilium-type intermediates are implicated in many of these processes. These isonitrile reactions of major synthetic importance are discussed in detail elsewhere in this compendium.



$$\mathrm{R{-}\overset{+}{N}{\equiv}\overset{-}{C}} + \mathrm{XY} \longrightarrow \mathrm{R{-}N{=}C}\begin{smallmatrix}\mathrm{X}\\ \mathrm{Y}\end{smallmatrix} \qquad (55)$$



Scheme 72

1.9.5 REFERENCES

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2.1

Synthesis of Acid Halides, Anhydrides and Related Compounds

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2.1.1 INTRODUCTION

Activation of the carbonyl group is the major purpose for the generation of the carboxylic acid derivatives treated in this chapter. They are of importance as intermediates in the preparation of other functionalized organic molecules. The electronic character of the substituents at the carbonyl group of the carboxylic acid increases the electrophilicity of the carbonyl C atom and, therefore, facilitates the attack by nucleophiles. The different electron-withdrawing power of the halogen atoms, the acyl group in anhydrides or the cyano group in α-ketonitriles allows a fine tuning of the electronic character of the carbonyl C atom. This can be used successfully for adapting the reactivity in the desired direction. Although acid chlorides represent the biggest number of acyl derivatives and, therefore, are used preferentially for synthetic purposes, it is sometimes of advantage to rely on other acyl compounds. α-Ketonitriles form a separate class of acid derivatives. Besides being mild acylating agents they can undergo a number of useful synthetic reactions.

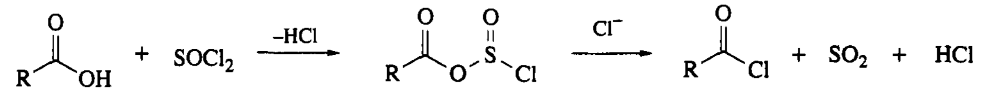
The preparation of the acid derivatives is organized according to their precursors. The synthetic method of choice in a particular case will depend on a number of factors of which the presence of other functional groups in the molecule under study is not the least important. The methods will be evaluated with respect to their scope of application. The chemistry of acid halides has been reviewed.[1] Methods of preparation are treated in Houben–Weyl[2] as well as in other reference books.[3,4] This applies also to acid anhydrides[5] and α-ketonitriles.[6]

2.1.2 ACID HALIDES

No explicit subdivision according to the type of halide will be made, *i.e.* the preparation of acid fluorides, chlorides, bromides and iodides will be treated simultaneously.

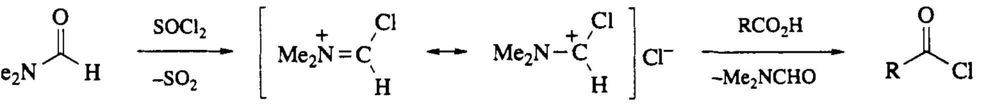
2.1.2.1 Acid Halides from Carboxylic Acids

The most widely used synthesis of acid chlorides is based on the reaction of a free carboxylic acid with thionyl chloride. A number of examples of this reaction can be found.[7] The mechanism seems to involve an intermediate chloro sulfite, which is transformed to the acid chloride (equation 1).[8] Polar solvents normally increase the reaction rates.[9]



(1)

The reactions can be catalyzed effectively by various additives. It has been shown that dimethylformamide constitutes an effective catalyst in many cases, the reaction being thought to proceed *via* an intermediate imidoyl chloride (equation 2).[10] The catalytic effect may be so pronounced that otherwise unreactive carboxylic acids can be transformed to their acid chlorides. An example is trichloroacetic acid which reacts only in the presence of *N*,*N*-dimethylformamide with thionyl chloride.[10] Interestingly, this reaction can also be accomplished in the presence of an alkali metal chloride.[1] Other catalysts being used include pyridine[11] and triphenylphosphine.[12] The latter converts iso- and tere-phthalic acid quantitatively to the corresponding acid dichlorides.

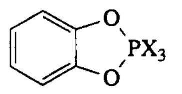


(2)

The nature of the catalyst seems to be important if additional functional groups are present. Thus, a complicating factor may be that double bonds in a molecule add the evolving hydrogen chloride. By using hexamethylphosphoramide and thionyl chloride at low temperature (–20 °C) this side reaction can be suppressed and in the case of acrylic acid, acryloyl chloride is formed in 80% yield.[13] The reactivity towards thionyl chloride is such that there is a correlation with the acidity of the acids: the stronger the acid the less reactive it is. A rate acceleration can be achieved in strongly polar solvents.

Phosphorus chlorides, PCl_3, PCl_5 and $POCl_3$, are common reagents for preparing acid chlorides of a variety of carboxylic acids. A comprehensive discussion of these reagents has been given by Ansell.[1] In these cases the reaction conditions, with regard to relative amount of phosphorus halide, solvent, temperature *etc.*, are important parameters for successful applications, *i.e.* tolerable yields. The often sluggish reactions with these phosphorus halides do not recommend them as reagents. Side reactions, *e.g.* oxidations at higher temperatures, and difficulties in the handling of PCl_5 have led to their replacement by other reagents.

Modified phosphorus halides, which allow more controlled reaction conditions, have been developed more recently. Thus 2,2,2-tribromo- and 2,2,2-trichloro-1,3,2-benzodioxaphospholes (**1a**) and (**1b**),[14–16] as well as dichloro- and dibromo-phosphoranes (**2a**) and (**2b**)[17] have been used successfully in the preparation of a number of aromatic and aliphatic acid halides. These reactions can be carried out at room temperature or slightly above and convert carboxylic acids or anhydrides in good yield to the acid halides. Also, unsaturated acids tolerate these reaction conditions. In many cases products can be isolated by distilling the acid halide directly from the reaction mixture. An advantage of these reagents is their solubility in organic solvents like diethyl ether, chloroform or benzene. Some examples are given in Table 1.



Ph_3PX_2

(**1a**) X = Cl
(**1b**) X = Br

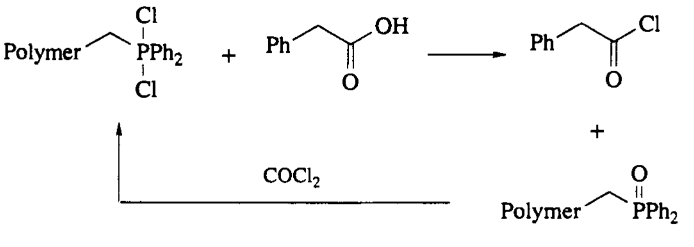
(**2a**) X = Cl
(**2b**) X = Br

Table 1 Acid Chlorides and Acid Bromides from Free Carboxylic Acid and Reagents (**1a**) and (**1b**)

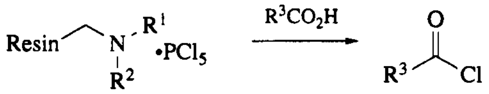
Acid	*Reagent*	*Product*	*Yield (%)*	*Ref.*
$MeCO_2H$	(**1a**)	$MeCOCl$	67	15
$ClCH_2CO_2H$	(**1a**)	$ClCH_2COCl$	77	15
$ClCH_2CO_2H$	(**1b**)	$ClCH_2COBr$	80	16
$EtCO_2H$	(**1b**)	$EtCOBr$	78	16
$PhCO_2H$	(**2a**)	$PhCOCl$	63	14
$Me_2C{=}CHCO_2H$	(**2b**)	$Me_2C{=}CHCOBr$	50	17
$PhCH{=}CHCO_2H$	(**2b**)	$PhCH{=}CHCOBr$	76	17
$C_6H_{11}CO_2H$	(**2b**)	$C_6H_{11}COBr$	71	17

Problems of isolation which may arise for higher boiling or temperature sensitive acid halides can be circumvented by the use of polymer-bound phosphorus halides. Thus, a suspension of trisubstituted phosphine dichlorides, chemically connected to cross-linked polystyrene, reacted with carboxylic acids in methylene chloride almost quantitatively according to equation (3).[18]

Product isolation is very simple as only the solvent has to be removed after separation from the polymer. The polymer can be returned to the active chlorinating agent by reaction with carbonyl chloride. A variation of this procedure does not require polymer-bound phosphorus halide but uses Lewis acid–Lewis base complexes between anion-exchange resins, such as Amberlite IRA 93, and phosphorus pentachloride (equation 4).[19] Again, isolation of the resultant acid chloride is simple and the exhausted polymer can be regenerated for further use by simply washing it with aqueous acidic and basic solutions. Yields range from 51% for crotonic acid chloride to 86% for decanoic acid chloride.

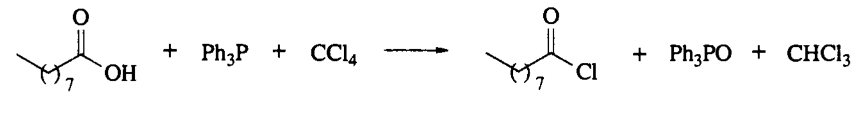


(3)



(4)

The reactions of thionyl chloride and phosphorus halides, also in their polymer-modified form, involve the formation of hydrogen halide and cannot, therefore, be applied without complications to acid sensitive compounds. The combination of triphenylphosphine and tetrachloromethane as reagent provides conditions under which, for instance, pelargonic acid can be converted to the acid chloride in good yield according to equation (5).[20] This method has been recently applied to polymer-bound triphenylphosphine.[21] Table 2 lists some examples of acids treated in this manner.



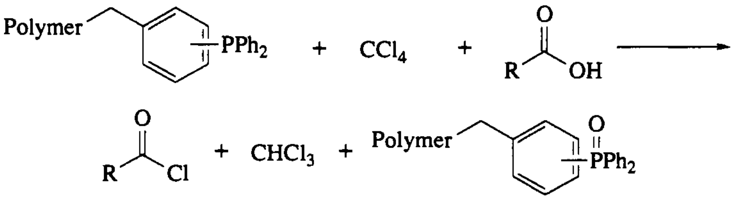
(5)

Table 2 Conversion of Acids to Acid Chlorides by Treatment with Phosphine Resin[a] (2 equiv.) in Carbon Tetrachloride under Reflux for 4 h

Acid	*Yield (%)*
n-Octanoic	63
Phenylacetic	50
Stearic	82
Phenoxyacetic	50
Cinnamic	77
Benzoic	90
β-Naphthoic	84
α-Furoic	82

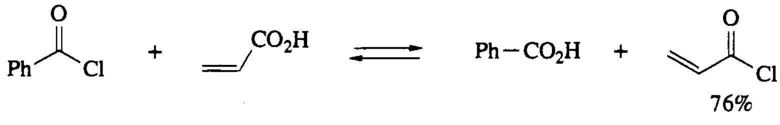
[a] 1% cross-linked polymer containing 2.50 mmol of phosphine per g.

Whereas the need to prepare the polymer might count against this technique, the commercial availability of a polymer obtained from polymerization of diphenyl-*p*-styrylphosphine would make this procedure more attractive (equation 6).[22] The process has also been tried successfully for the conversion of alcohols to alkyl chlorides. There are, however, limitations in the fact that the starting material cannot be regenerated for the reaction with carbon tetrachloride. In this respect the above mentioned reagent of Relles and Schluenz might prove superior even though it has the drawback of acidic conditions.[18]



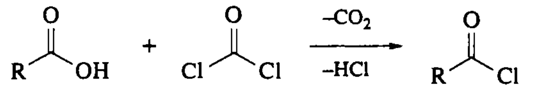
(6)

For acid-sensitive carboxylic acids it may sometimes be advantageous to use easily accessible acid halides of other carboxylic acids as halogen transfer agents. In this case an equilibrium is established between the carboxylic acid, its acid halide, the halogenating agent and its reaction product, respectively. This procedure is of particular interest if the desired product has a lower boiling point than the reagent.[23] Thus, acrylic acid can be converted to its acid chloride in 76% yield by use of benzoyl chloride as reagent (equation 7).[24] If higher boiling acid chlorides are desired then phthaloyl chloride may be a suitable reagent.[25,26] In this way maleic anhydride gives in the presence of $ZnCl_2$ *ca.* 90% fumaryl chloride. Benzenesulfonyl chloride has also been used in this context.[27] Polymer-bound aroyl chloride may be an alternative.[28]

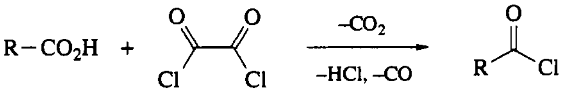


(7)

An extension of this methodology which, however, again involves the generation of hydrogen halide is the application of carbonyl chloride and oxalyl chloride (equations 8 and 9). As in the case of thionyl chloride only gaseous byproducts are formed, thus facilitating the isolation of the products. These reagents are in many cases a true alternative to the thionyl halides, sometimes giving even better yields and requiring less drastic reaction conditions. For a thorough discussion see Ansell.[1] Large scale syntheses in high yield either continuously or in batches seem to be possible by these procedures. A variety of catalysts has been applied successfully. For a list of references see Houben–Weyl.[2]



(8)



(9)

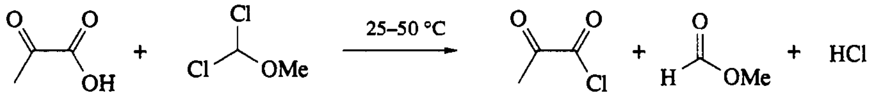
A method for converting carboxylic acids under neutral conditions to the corresponding acid chlorides is available with α-halogenated ethers as reagents. Thus it has been shown that 2-chlorodioxin can give acid chlorides of a variety of acids in good yield.[29] The method, however, has not received wide application. Instead α,α-dichloromethyl methyl ether, which can be prepared easily,[30] has replaced other α-haloethers as reagents.[31] In Table 3 some examples are listed.

Table 3 Acid Chlorides from the Reaction of Dichloromethyl Methyl Ether[a] with Carboxylic Acids

Acid	*Product*	*Yield (%)*
Cl_3CCO_2H	Cl_3CCOCl	88
$CH_2(CO_2H)_2$	$CH_2(COCl)_2$	88
$(CH_2CH_2CO_2H)_2$	$(CH_2CH_2COCl)_2$	96
$PhCO_2H$	$PhCOCl$	96
$PhCH_2CO_2H$	$PhCH_2COCl$	92

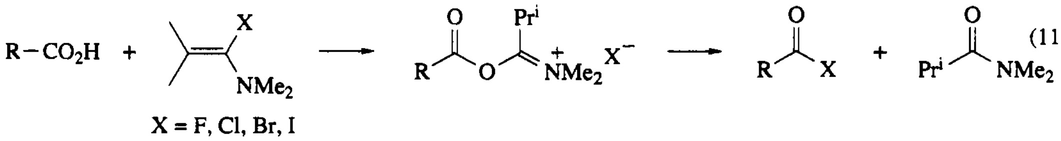
[a] The reagent is used in 25% excess in the presence of 0.001 mol % $ZnCl_2$.

Sometimes the addition of a small amount of $ZnCl_2$ as a catalyst is recommended, *e.g.* succinic acid is transformed to the dichloride only in the presence of this catalyst. It has to be noticed, however, that under these conditions hydrogen chloride is evolved and, therefore, acid sensitive compounds cannot be taken. *N*-acylamino acid chlorides[32] and chlorides of fully acetylated sugar acids[33] are also obtainable in yields of 70% or more. Whereas most reagents seem to be unsuited to the preparation of acid halides of α-keto acids, dichloromethyl methyl ether is successful in this reaction (equation 10).[34] Pyruvyl chloride can now be made in *ca.* 50% yield.[35] In some examples the corresponding α,α-dibromomethyl methyl ether has also been tested.[36]



(10)

There are as shown a number of reagents for the preparation of acid chlorides; acid bromides are also produced by similar reactions, *e.g.* with thionyl bromide.[37] A general approach to obtain acid halides of fluorine, chlorine, bromine and iodine has been described by Ghosez *et al.* (equation 11).[38] 1-Dimethylamino-1-chloro-2-methylpropene, which is accessible from *N,N*-dimethylisobutyroamide,[39] is a generally applicable reagent for this purpose. The other halo derivatives can be formed by halogen exchange. Under very mild conditions, *i.e.* at room temperature or below in dichloromethane as solvent, the acid halides are obtained in high yield (Table 4). No hydrogen halide is evolved, so acid labile compounds



(11)

Table 4 Preparation of Acyl Halides RCOX[a] According to equation (11)

R	*X*	*Yield (%)*[b]
Cl_3C	Cl	100
Bu^t	Cl	100
$H_2C{=}CH$	Cl	96
MeCO[c]	Cl	100
Pyrrol-2-yl	Cl	100
Furan-2-yl	Cl	100
H[d]	Cl	94
Cl_3C	F	100
Bu^t	F	100
H	F	100
Bu^t	Br	100
$H_2C{=}CH$	Br	100
H	Br	100
Me	I	100
Bu^t	I	100
H[e]	I	100

[a] Reactions were carried out at 20 °C unless otherwise stated. [b] Determined by NMR spectroscopy. [c] −20 °C. [d] −60 °C. [e] −20 °C.

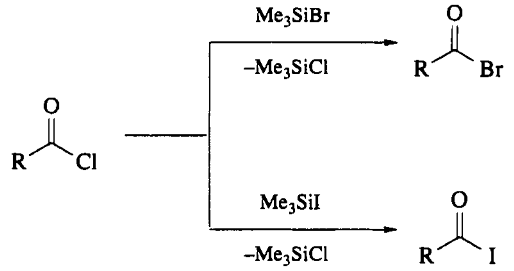
can also be subjected to this reaction. Also thermally unstable acid halides such as formyl chloride or formyl iodide can be made due to the high reactivity of the halogenating agent, which permits the use of temperatures as low as –60 °C.

Some special procedures for the preparation of acid fluorides from carboxylic acids will be added at this point. Several reagents have been suggested recently. Olah proposed the adduct of pyridine and SeF_4.[40] In halogenated solvents at room temperature the acid fluorides are normally isolated in yields greater than 80%. Similar good results were reported for cyanuric fluoride, which is prepared from cyanuric chloride with hydrogen fluoride.[41] The reactions are carried out in acetonitrile in the presence of pyridine. Double bonds, triple bonds and hydroxy groups are tolerated under these conditions. These new methods seem to be superior to sulfur tetrafluoride for the generation of acid fluorides.[42]

2.1.2.2 Acid Halides from Acid Halides by Transformation

As a synthetic approach this reaction is valuable for the generation of acid bromides, acid iodides and acid fluorides. The readily accessible acid chlorides are a convenient starting material. Thus, it is possible to react acid chlorides with hydrogen fluoride, hydrogen bromide or hydrogen iodide to obtain the corresponding acid halides.[43]

More recent approaches which avoid acidic conditions are based on the application of trimethylsilyl bromide or iodide (equation 12).[44] With aliphatic acid halides a high reactivity (often the reaction is exothermic) is observed. The isolation of the products can be effected immediately after the addition of trimethylsilyl halide is complete. With aromatic halides heating is sometimes required. Easy work-up is possible, because only the low boiling trimethylsilyl chloride has to be removed before the product is isolated by distillation. Table 5 gives some examples.

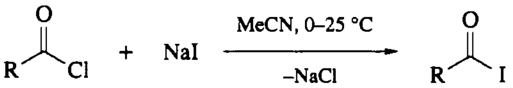


(12)

Table 5 Acid Bromides and Acid Iodides from Acid Chlorides *via* Reaction with Trimethylsilyl bromide or Iodide

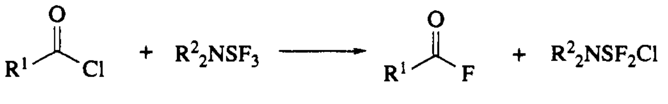
Product	*Yield (%)*	*Product*	*Yield (%)*
EtCOBr	74	MeCOI	46
Pr^nCOBr	89	EtCOI	93
PhCOBr	79	Pr^nCOI	86
$(COBr)_2$	85	PhCOI	83
$(H_2CCOBr)_2$	78		

Another versatile pathway to acid iodides was described by Hoffmann (equation 13).[45] Aliphatic and aromatic acid iodides are prepared in high yields from acid chlorides by reaction with sodium iodide in acetonitrile. A large number of alkanoyl, alkenoyl and aroyl iodides can be prepared in good yields from the corresponding acid chlorides. In the same way it was possible for the first time to obtain diiodides from aliphatic and aromatic dicarboxylic acids.[46] The conversion of acid chlorides to iodides by sodium iodide had been known before;[47,48] the reaction conditions proposed by Hoffmann, however, are milder and the yields are higher.

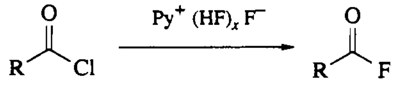


(13)

The transhalogenation reaction has been applied widely to the preparation of acid fluorides.[1] Newer developments include the use of dialkylaminotrifluorosulfonate as reagent (equation 14).[49] This compound not only converts a variety of organic acid chlorides to acid fluorides but is also able to produce thionyl fluoride from thionyl chloride as well as other fluorides of inorganic acids. A mixture of pyridine (30%) and hydrogen fluoride (70%) has been proposed as a replacement for hydrogen fluoride itself, because it is a stabilized, less volatile form of HF (equation 15). This is a versatile reagent which among many other fluorinations can produce acid fluorides in excellent yields.[50]



(14)



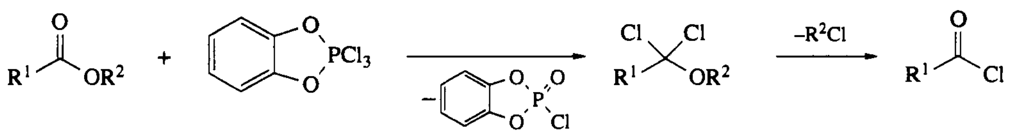
(15)

2.1.2.3 Acid Halides from Acid Anhydrides

Acid anhydrides as activated derivatives of carboxylic acids have found little attention for the preparation of acid halides. Their use can be justified if they are obtained from other sources than from carboxylic acids, *e.g.* phthalic anhydride from the oxidation of naphthalene or *o*-xylene. It is, therefore, no surprise that there exist patents to convert phthalic anhydride to phthalic acid dichloride with carbonyl dichloride in the presence of catalysts.[2,51–53] However, there are some methods available; thus α,α-dichloromethyl methyl ether will convert acid anhydrides to acid chlorides[31] and brenzcatechyl phosphorus tribromide will also achieve this transformation.[36] Fluorides may be prepared similarly with the pyridine/HF mixture of Olah.[50]

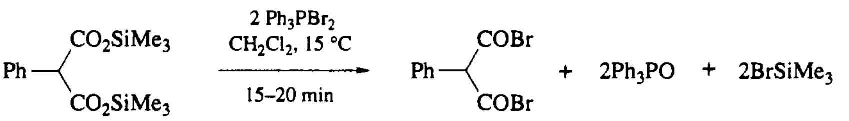
2.1.2.4 Acid Halides from Carboxylic Acid Esters

If carboxylic acid esters are readily available, they provide a convenient basis for the preparation of acid halides. Modified phosphorus halides, like 2,2,2-trichloro-1,3,2-benzodioxaphosphole can be applied successfully.[15] This reagent forms first a 1,1-dichloroalkyl ether, which decomposes to the acid chloride (equation 16). The reaction conditions are rather drastic. For instance *n*-butyl benzoate has to be heated for 4 h at 180 °C in order to get a 90% yield of benzoyl chloride. The only stable and isolable 1,1-dichloro ether is α,α-dichloromethyl methyl ether, which, as described above, is used as a mild reagent for the conversion of carboxylic acids to their chlorides. Similarly severe conditions are required if the chlorine or bromine adduct of triphenylphosphine is selected.[54,55] This reaction may be catalyzed by BF_3. It has been applied successfully to unsaturated esters and to the cleavage of lactones.



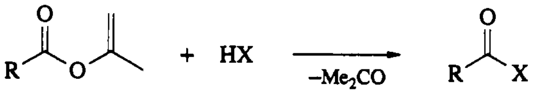
(16)

Neutral conditions are also realized if trimethylsilyl esters are reacted with dibromotriphenylphosphine.[56] This reaction, as shown in equation (17), can also be applied to sterically hindered trialkylsilyl esters.[57]



(17)

A general route to acid fluorides, chlorides, bromides and iodides is provided by the reaction of enol esters, such as isopropenyl esters, with the appropriate hydrogen halide (equation 18).[58,59] Phthalic acid dichloride in the presence of chlorosulfonic acid has been proposed as a reagent for the conversion of carboxylic esters to acid chlorides in high yield, as is shown in equation (19) for the cleavage of the ethyl ester of chlorofluoroacetic acid.[60]



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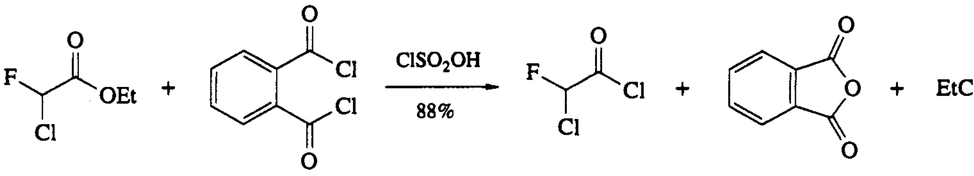
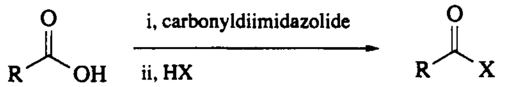


(19)

2.1.2.5 Acid Halides from Acyl Amides and Hydrazides

Staab introduced azolides as versatile reagents in organic synthesis.[61] The reaction of carbonyldiimidazolide with carboxylic acids produces imidazolides under mild conditions which can be converted by the action of hydrogen halides to acid halides in high yield (equation 20). The method does not even require the isolation of the imidazolides, but can be carried out as a one-pot synthesis.[62] The possibility of carrying out this reaction at low temperatures allows the preparation of temperature sensitive compounds. Formyl chloride, which decomposes at –40 °C, has been prepared in this way.



(20)

Other possibilities include the reaction of hydrazides with hydrogen chloride in nitromethane or methylene chloride.[63] Also thionyl chloride or sulfuryl chloride will produce acid chlorides from hydrazides,[64] although these reactions seem to be of limited scope.

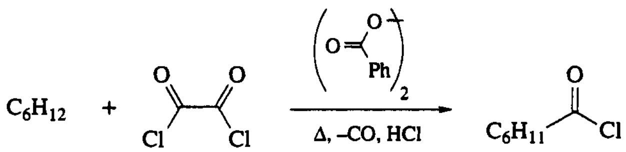
2.1.2.6 Acid Halides from Aldehydes

Aldehydes were among the first compounds to be converted to acid chlorides. Thus, Liebig and Woehler reported the formation of benzoyl chloride from benzaldehyde.[65] A discussion of acid halide syntheses starting from aldehydes is given in ref. 1. Most of these reactions seem to be of free radical character, carried out using reagents like *t*-butyl hypochlorite, *N*-chlorosuccinimide or *N*-bromosuccinimide. In special cases where aldehydes are readily available and where functional groups prevent the application of other methods, these reagents might constitute an alternative for the preparation of acid halides. The use of *N*-bromosuccinimide for the direct oxidation of aldehydes to acid bromides has been taken up recently.[66] Iodobenzene dichloride has also been described as a reagent for producing acid halides directly from aldehydes.[67]

2.1.2.7 Acid Halides by Introduction of a Halocarbonyl Group

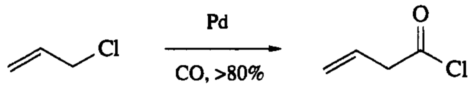
The conversion of an organic compound to an acid halide by introduction of a halocarbonyl group directly is an attractive synthetic possibility. Thus, acid halides can be obtained if hydrocarbons are reacted with oxalyl chloride in the presence of free radical initiators like dibenzoyl peroxide. Obviously, this will not be a very selective procedure and only highly symmetrical compounds with preferentially one type of CH bond will lead to acceptable selectivity and yield. Kharash showed that cyclohexane can give cyclohexanecarboxylic acid chloride in 65% yield according to equation (21).[68] Higher selectivity can be expected if functionalized compounds render one kind of CH bond particularly reactive towards free radical abstraction. Substituted malonic acid dibromides are formed in this way by reaction of acid bromides with oxalyl bromide in yields ranging from 40 to 70%.[69] A radical chain reaction in tetrachloromethane in the presence of carbon monoxide is another alternative.[70,71]

In principle the possibility of introducing a halocarbonyl into aromatic compounds with carbonyl dichloride in the presence of Lewis acids exists. In practice it is difficult to stop the reaction after the first electrophilic substitution, because the reaction products themselves can react further to give ketones.[72] However, there are exceptions. Thiophene reacts with phosgene in the presence of aluminum trichloride to give 2-chlorocarbonylthiophene almost quantitatively.[73]



(21)

An attractive pathway with a lot of potential uses the transition metal mediated reaction of organic halides with carbon monoxide.[74–76] Suitable substrates are organic halides capable of oxidative addition to low-valent transition metal compounds. Insertion of carbon monoxide and reductive elimination of an acid halide will complete the catalytic cycle. In this way it was shown that allyl chloride yields butenoic acid chloride in >80% yield according to equation (22).[77,78] As well as palladium, rhodium and iridium also act catalytically.[2] It is of no surprise that allylic halides, benzylic halides and aryl halides in particular are readily converted to acid halides. Simple aliphatic halides undergo the oxidative addition step more slowly and, if they carry hydrogen atoms on an *sp*^{3} hybridized C atom in the β-position to the halogen atom, may give alkenes *via* β-hydrogen elimination. Alkenes can also be converted to acid halides with carbon monoxide in the presence of transition metal catalysts in solvents such as methylene chloride or tetrachloromethane.[79]



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2.1.2.8 Miscellaneous Methods of Preparation of Acid Halides

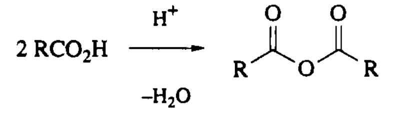
There are a number of specialized methods for the preparation of acid halides which, however, do not seem to have general applicability. For a summary see ref. 1.

2.1.3 ACID ANHYDRIDES AND MIXED ANHYDRIDES

Acid anhydrides play a similar role in organic chemistry to acid halides. The enhanced electrophilic character of the carbonyl groups renders them valuable intermediates in organic syntheses. Several general approaches exist for their preparation and depending on the availability of the starting material or the presence of sensitive functional groups one or the other procedure may be the method of choice for their generation.[80]

2.1.3.1 Acid Anhydrides from Carboxylic Acids by Dehydration

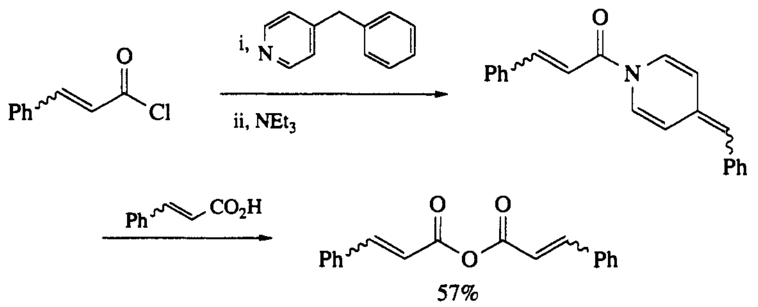
The most general procedure for the preparation of acid anhydrides starts from free carboxylic acids which are activated by suitable reagents in order to make the overall bimolecular dehydration process feasible under moderately mild conditions. Thermal dehydration, in principle the simplest method (equation 23), is only of limited preparative value giving the acid anhydride only in low yield.[81,82] Even in special cases, where dicarboxylic acids may form five- or six-membered rings, anhydride formation requires dehydration agents. In the simplest case concentrated sulfuric acid may be applied.[83] For some examples see ref. 80. The advantage of an intramolecular dehydration, which is favored entropically, is lost in longer chain α,ω-dicarboxylic acids where normally intermolecular reactions with the formation of polymers is the result. In general more specific reagents have to be found to effect the elimination of water from two molecules of carboxylic acid to form an acid anhydride.



(23)

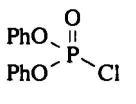
If thionyl chloride is used for activation, it is possible to react the carboxylic acid in the presence of 0.5 equiv. of the reagent. The acid halide formed initially reacts further with free carboxylic acid under elimination of hydrogen chloride. Two modes of operation are possible: either the free acid is boiled under reflux in a solvent in the presence of thionyl chloride[84] or the reaction is carried out in the presence of pyridine as base.[85] Pyridine not only traps the liberated hydrogen chloride but takes part in the mechanism of formation of the acid anhydride, allowing milder conditions than in its absence. Mostly simple aliphatic carboxylic acids have been converted to their anhydrides by this method. The just described processes lead to acid anhydrides *via* the reaction of acid halides formed *in situ* with free carboxylic acid. In some cases, and in particular if mixed anhydrides are desired, it is advantageous to react isolated acid halides with carboxylic acids. This reaction is either carried out in inert solvents in the presence of bases such as pyridine[86] (Schotten–Baumann reaction) or in aqueous medium in the presence of sodium bicarbonate.[87] Acid anhydrides of higher boiling long chain aliphatic acids can be generated by simply heating an approximate 1:1 mixture of acid and acid halide and recrystallizing the product.[88]

An acyl transfer agent which can be used for the synthesis of acid anhydrides is obtained from the reaction of an acid chloride with 4-benzylpyridine (equation 24).[89] In this way benzoic acid anhydride and cinnamic acid anhydride were obtained in 72% and 57% yields, respectively. As the intermediate, 1-acyl-4-benzylidene-1,4-dihydropyridines, can be isolated, this procedure should be well suited for the preparation of mixed anhydrides. Mixed aromatic and aliphatic anhydrides can be prepared with 2-benzoylthio-1-methylpyridinium chloride and salts of carboxylic acids.[90] These reactions are carried out in aqueous solution. They make use of the high reactivity of esters of thiocarboxylic esters towards nucleophiles. The mixed anhydrides of benzoic acid with 3-phenylpropanoic acid, phenoxyacetic acid, isobutyric acid, *p*-toluic acid and cinnamic acid were formed in 82, 79, 61, 91 and 66% yields, respectively.



(24)

Activation of carboxylic acids by phosphorus acid halides in the form of different derivatives (3–7) has been used extensively in more recent years. These methods have been tested not only for saturated aliphatic or aromatic carboxylic acids but also for functionalized derivatives. In Table 6 some examples are collected where (3) and (4) were applied successfully.[91] The reactions are carried out at room temperature in acetone or dichloromethane by treatment of the carboxylic acid with 1 equiv. of triethylamine or *N*-ethylpiperidine and 0.5 equiv. of the reagent (equation 25). The anhydrides are either collected by filtration or recovered by evaporation of the solvent after washing with water.



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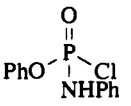

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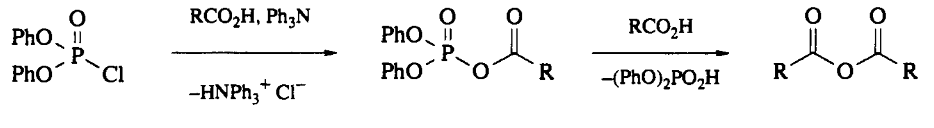
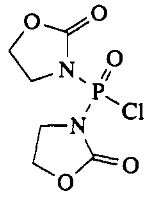


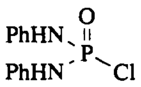
(25)

Table 6 Symmetrical Carboxylic Acid Anhydrides from Carboxylic Acids and Reagents (3) and (4)

RCO$_2$H	*Reagent*	*Yield (%)*
Ph	(3)	98
	(4)	97
3,5-Ph(NO$_2$)$_2$	(3)	54
	(4)	60
4-PhNO$_2$	(3)	91
Bu^t	(3)	90
n-C$_{11}$H$_{23}$	(3)	90
	(4)	91
Ph(CO)$_2$NCH$_2$	(3)	98

A still greater number of acid anhydrides has been prepared with reagent (**5**), which is obtained easily from phosphorus pentachloride.[92] The reactions take place at room temperature in the presence of a tertiary base. Selected examples are given in Table 7. Anhydride formation was also reported with (**6**) and (**7**).[93] Dihalide derivatives of phosphorus oxychloride have been tested as well.[94,95]


(**5**)


(**6**)

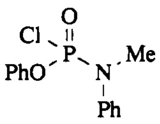
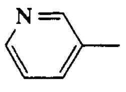
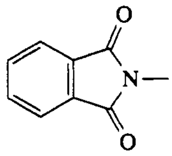
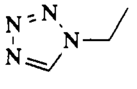
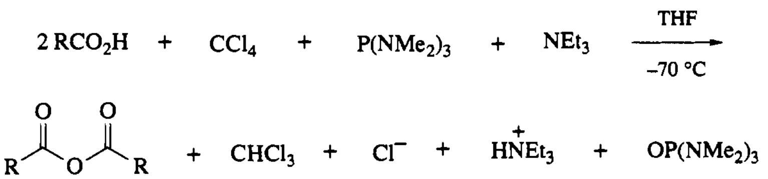

(**7**)

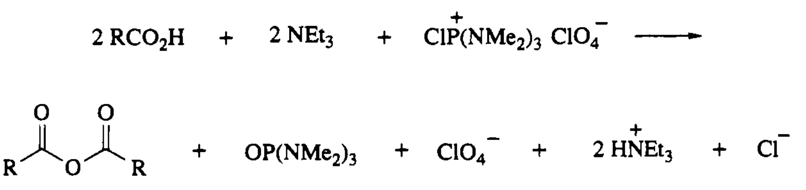
Table 7 Acid Anhydrides from Carboxylic Acids and Reagent (**5**)

RCO_2H	*Yield (%)*	*RCO_2H*	*Yield (%)*
Pr^n	95		82
$BrCH_2$	92		96
Bu^t	90		97
MeHC=CH	100		75
PhCH=CH	97		

A procedure which converts carboxylic acids under very mild conditions to acid anhydrides was discovered in the reaction of 2 equiv. of acid with carbon tetrachloride in the presence of 1 equiv. of hexamethylphosphoramide and 1 equiv. of triethylamine in THF at –70 °C (equation 26). The anhydride of cyclopropanecarboxylic acid is, for example, formed in 76% yield.[96] The reaction can be modified in the sense that preformed chlorotrisdimethylaminophosphonium perchlorate is used as reagent. At room temperature acids are transformed into anhydrides in very good yield according to equation (27).[97] The latter reagent can be applied successfully to the coupling of amino acids to form peptides.

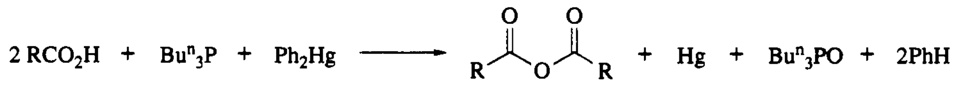


$$2\,RCO_2H + CCl_4 + P(NMe_2)_3 + NEt_3 \xrightarrow[-70\,^{\circ}C]{THF} RC(O)OC(O)R + CHCl_3 + Cl^- + H\overset{+}{N}Et_3 + OP(NMe_2)_3 \quad (26)$$



$$2\,RCO_2H + 2\,NEt_3 + Cl\overset{+}{P}(NMe_2)_3\,ClO_4^- \longrightarrow RC(O)OC(O)R + OP(NMe_2)_3 + ClO_4^- + 2\,H\overset{+}{N}Et_3 + Cl^- \quad (27)$$

On the basis of organomercury compounds Mukaiyama introduced a method for the production of acid anhydrides. Thus the reaction of diphenylmercury with carboxylic acids in the presence of tri-*n*-butylphosphine leads to anhydrides of aliphatic and aromatic carboxylic acids in yields of *ca.* 80% (equation 28).[98] The reaction is regarded as proceeding through initial formation of phenylmercury(II) carboxylates. Oxidation–reduction reactions with tri-*n*-butylphosphine as reducing agent and electron deficient alkenes as oxidizing agents were also proposed as a means of obtaining acid anhydrides from carboxylic acids (equation 29).[99] *trans*-Dibenzoylethylene as electron acceptor in this reaction allows the preparation of aliphatic acid anhydrides in good yield. Quinoidal systems[100] or azodicarboxylates[101] can also assume the role of the electron acceptor.



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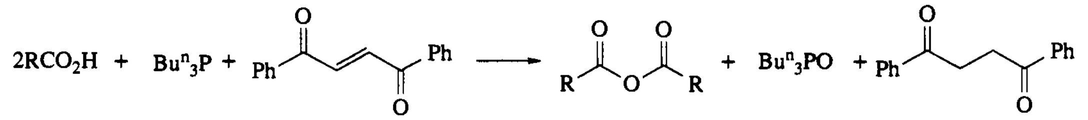
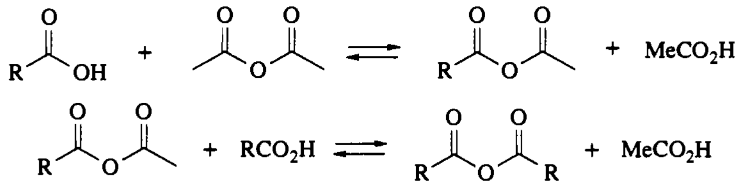


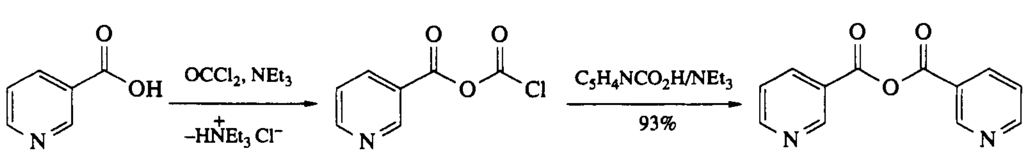
(29)

One of the most widely applied methods of synthesis for acid anhydrides consists of the reaction of a free carboxylic acid with an acid anhydride, in particular with acetic anhydride as dehydrating agent.[102,103] The process (equation 30) involves the intermediate formation of a mixed anhydride and is normally driven to completion by distilling off acetic acid. Acetic anhydride is used as solvent. The method can be used in all those cases where the desired product has a higher boiling point than acetic acid. The yields are good to excellent. Acid halides can be considered as mixed anhydrides of an organic and an inorganic acid. It is therefore obvious that they may be chosen as activated derivatives of carboxylic acids from which acid anhydrides can be formed conveniently. Both aliphatic and aromatic acid anhydrides are accessible by this approach. The reaction is favorably carried out in the presence of pyridine, which forms an acylpyridinium salt with the acid halide. The yields are >80%.[104]



(30)

Carbonyl dichloride can be taken similarly to form acid anhydrides (equation 31). *Via* a mixed anhydride and in the presence of triethylamine, it is possible to prepare symmetrical anhydrides in high yield.[105,106] A variation provides ethyl chloroformate as reagent.[107,108] In a first step the carboxylic acid is ethoxycarbonylated in the presence of triethylamine and then reacted with free carboxylic acid to form the acid anhydride (equation 32). As the intermediate can be isolated, this is a good method of forming mixed anhydrides.[109] In addition it seems to be particularly suitable for functionalized carboxylic acids such as hydroxy acids.[110] Polymer-bound chloroformates may be advantageous in some cases.[111,112]



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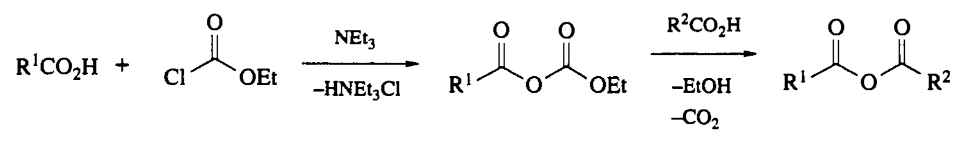
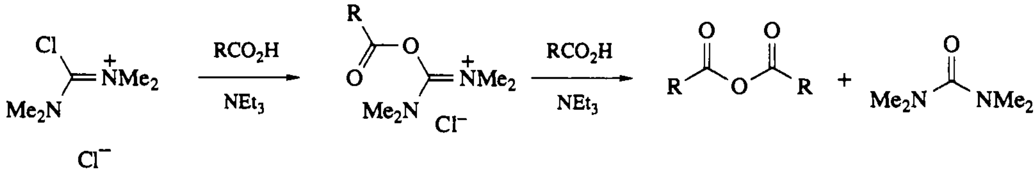


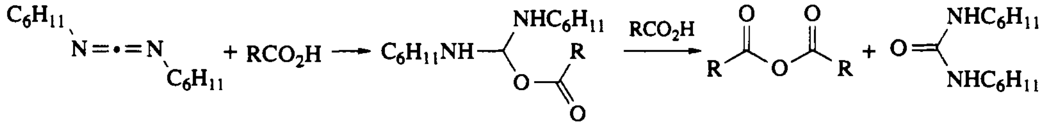
(32)

An analogous methodology can be seen in the proposal to use chloroformamidinium salts as dehydrating agents.[113] *N,N,N′,N′*-Tetramethylchloroformamidinium chloride, used as the condensation agent, is easily available by the reaction of *N,N,N′,N′*-tetramethylurea and oxalyl dichloride. The reaction of carboxylic acids (equation 33) can be achieved at –30 °C in the presence of triethylamine. Thus, for instance, 2-furoic acid, cinnamic acid and crotonic acid yield the anhydrides in 84%, 83% and 83%, respectively.



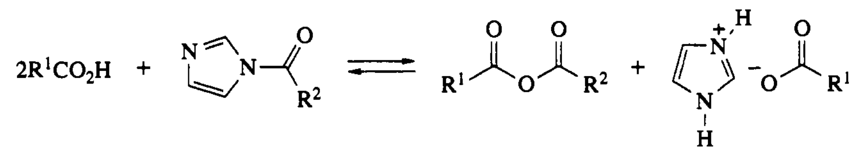
(33)

Carbodiimides, in particular dicyclohexylcarbodiimide, have been applied in many syntheses where dehydration had to be performed under mild conditions. It is therefore no surprise that this reagent was also introduced for the synthesis of acid anhydrides from carboxylic acids.[114,115] In order to avoid *N*-acylation the reactions are carried out at low temperature. First *O*-acylisoureas are formed, which then react further with free acid to the acid anhydride (equation 34). The reaction has been exploited in particular for the preparation of peptides.[116] *N*-alkoxycarbonyl-protected amino acids can be transformed in high yield to the corresponding anhydrides, which themselves are activated acid derivatives and may be converted to peptides. As in many other examples polymer-bound carbodiimides may prove superior sometimes, as the isolation of the products is facilitated. Easy preparation of acid anhydrides is possible in this way.[117]



(34)

The use of imidazolides in organic synthesis has been propagated by Staab and coworkers.[118,119] Acid anhydrides can also be prepared with carbonyldiimidazolide. The reaction of a carboxylic acid with this reagent leads to acid anhydride if the transacylation equilibrium (equation 35) can be shifted to the side of the anhydride. This is possible either if the acid is used in twofold excess and forms an insoluble salt with the liberated imidazole or if trifluoro- or trichloro-acetylimidazolide is taken as the reagent. Symmetrical acid anhydrides can be obtained in a number of cases in good yield according to equation (36).[120]



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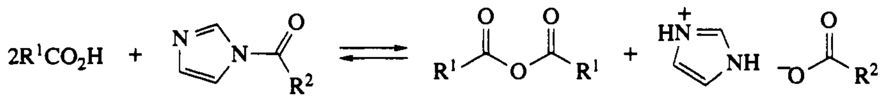
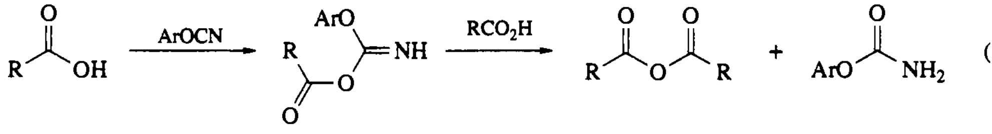


(36)

$R^2 = CCl_3, CF_3$

Another general approach to acid anhydrides from carboxylic acids was developed with esters of cyanuric acid as reagents (equation 37).[121] If the reactions are carried out in solvents like carbon tetrachloride or benzene, the resulting aryl esters of carbaminic acid are insoluble and can be removed by filtration.

Chlorosulfonyl isocyanate was introduced by Olah for the preparation of acid anhydrides. Under very mild conditions it is even possible to obtain formic acid anhydride.[122] This method has been applied successfully to other examples (equation 38).[123]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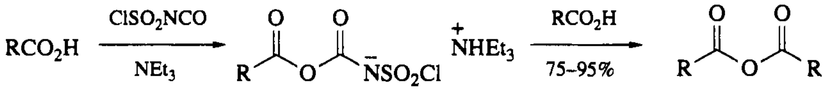

(38)

2.1.3.2 Acid Anhydrides from Carboxylic Acid Salts and Acid Halides

One of the classic procedures for the preparation of acid anhydrides is based on the reaction of metal salts of acids with acid halides. It offers the opportunity to obtain symmetrical and unsymmetrical acid anhydrides. A number of different metal salts have been applied over the years.

For the reaction of sodium salts with acid halides a procedure was developed which allows preparation of acid anhydrides in aqueous solution in the presence of a tertiary base (Table 8).

Table 8 Acid Anhydrides from the Reaction of Sodium Carboxylates with Acyl Chlorides

R^1COCl	*R^2CO_2Na*	*Yield (%)*
Ph	Ph	97
Ph	*o*-ClPh	79
o-ClPh	Ph	96
Ph	*p*-BrPh	75
Ph	*p*-O_2NPh	64
$Me(CH_2)_5$	$Me(CH_2)_5$	94
$Me(CH_2)_{14}$	$Me(CH_2)_{14}$	75

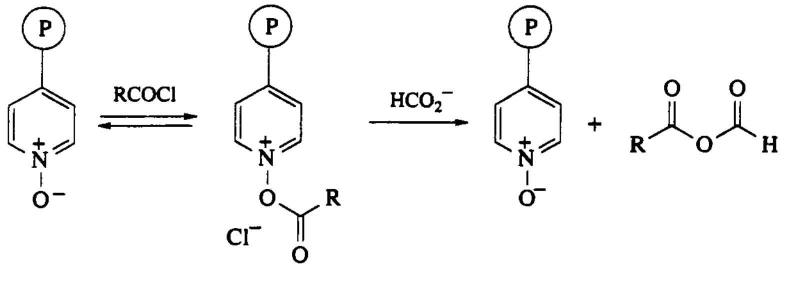
Pyridine is used in catalytic amounts and acylpyridinium salts are assumed to be the reactive acylating agents. The method can be applied to the synthesis of both symmetrical and unsymmetrical acid anhydrides.[124] These can also be obtained in many cases directly from the acid halide and the sodium carboxylate without using a solvent or a catalyst. This approach has been described for a number of mixed acid anhydrides. Thus acetic palmitic anhydride (70%), butyric myristic anhydride (81%) and caproic lauric anhydride (85%) were prepared by heating the components for 2 h at 90 °C.[125] These anhydrides were successfully employed for the *N*-acylation of amino sugars.[126]

Peptides are also acetylated with the mixed anhydride of acetic acid and formic acid. The latter is made by the reaction of acetyl chloride with sodium formate in yields of 80–90%.[127] Mixed formic anhydrides with several carboxylic acids are obtainable with a copolymer of 4-vinylpyridine 1-oxide as catalyst. The reactions are carried out in acetonitrile with equimolar amounts of acid chloride and sodium formate. In most cases the mixed anhydride is the major product (Table 9).[128] The reactions are thought to proceed according to equation (39).

A solid phase copolymer of 4-vinylpyridine is a highly effective catalyst for the synthesis of acid anhydrides from mixtures containing equimolar quantities of carboxylic acids and acid chlorides.[129] The reaction can be simplified even more if a mixture of carboxylic acid and one-half equivalent of thionyl chloride in dichloromethane is treated with the solid state copolymer of 4-vinylpyridine. The conversion is accomplished equally well in batch or column mode.[130] Some examples are given in Table 10.

Table 9 Mixed Formic Anhydrides from the Reaction of Acyl Halides with Sodium Formate

Reactants RCOCl	*Yield (%)*	*Anhydrides (mole ratio)*	
		RCOOOCH	*RCOOOCR*
Me	7	0.00	1.00
Me_3C	48	0.83	0.17
Ph	60	0.85	0.15
p-MeO—Ph	89	0.97	0.03
Ph—CH═CH	72	0.96	0.04



(39)

Table 10 Conversion of Carboxylic Acids to Acid Anhydrides with a Copolymer of 4-Vinylpyridine

Reactant	*Anhydride (%)*	*Production mode*
$MeCO_2H$	89	Batch
$EtCO_2H$	96	Batch
Me_2CHCO_2H	95	Batch
$H_2C{=}CHCO_2H$	52	Batch
$H_2C{=}C(Me)CO_2H$	86	Batch
$MeCO_2H$	89	Column
$EtCO_2H$	95	Column
Bu^tCO_2H	97	Column
$PhCO_2H$	99	Column

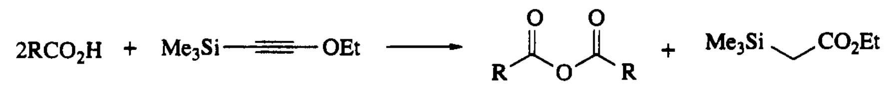
Several other metal salts have been proposed to react with acid halides to give acid anhydrides in good yield. Thus, thallium carboxylates in etheral suspension may be treated with acid halides to lead to acid anhydrides in high yield. The method has the advantage that thallium chloride can be separated by filtration and the product is isolated after evaporation of the solvent.[131] Another synthetic possibility exists in the desulfurization of thioesters with mercury(II) carboxylates.[132] Mercury(II) carboxylates can also be reacted with triethyl phosphite or tri-*n*-butylphosphine to provide acid anhydrides in yields of 60–80%.[133] Another possibility is offered by the reaction of 1 mol of *N*,*N*-dicyclohexylthiourea and 2 mol of silver or mercury(II) carboxylates.[134] Mixed carboxylatocarbamato anhydrides follow from the room temperature reaction of *N*,*N*-dialkylcarbamato metal derivatives with acid chlorides. Either Na, Cu^{II}, Ti^{III} or V^{III} are employed.[135]

2.1.3.3 Acid Anhydrides by Miscellaneous Methods

Mild dehydrating agents are available in yneamines[136] and 1-alkoxyalkynes.[137] They have been applied occasionally to the preparation of acid anhydrides.[136–139] The great advantage of these reagents is that the reaction takes place under neutral conditions and, therefore, acid anhydrides of acid sensitive compounds can be obtained. An extension of this approach was described recently. Trimethylsilylethoxyacetylene, which can be prepared from ethoxyacetylene, serves as a very mild dehydrating agent.[140] By means of this compound various types of acid sensitive carboxylic acid anhydrides can be made quantitatively or almost quantitatively (equation 40). Some examples are collected in Table 11.

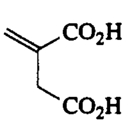
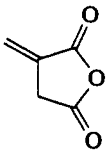
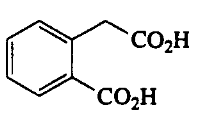
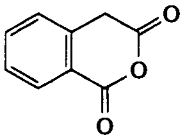
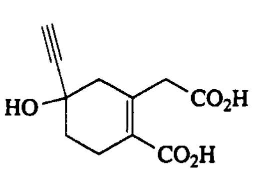
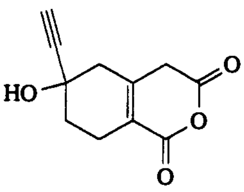
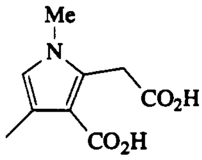
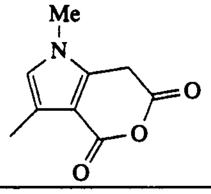
Direct catalytic oxidative carbonylation to form acid anhydrides was achieved with arylmercury acetate.[141] Palladium(II) salts are taken as catalysts. Aromatic compounds such as benzene, toluene, anisole, furan, thiophene and naphthalene can be converted catalytically with palladium(II) acetate and an excess of 1,2-dibromoethane to acid anhydrides in yields of 30–60%.[142]

Of commercial interest is the preparation of acid anhydrides from hydrocarbons by direct oxidation. This methodology has been developed in particular for the synthesis of cyclic anhydrides, which are then introduced for the production of polymers.[143]



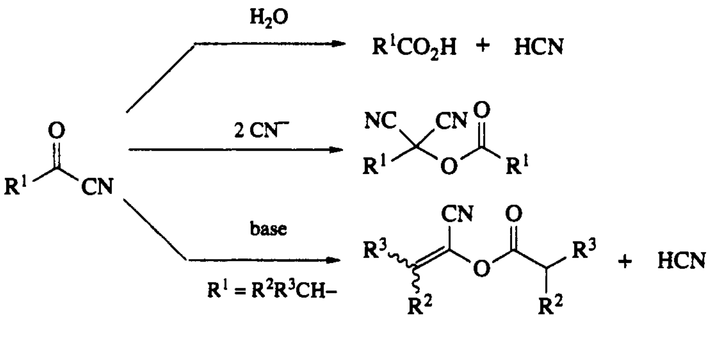
(40)

Table 11 Synthesis of Carboxylic Acid Anhydrides by Reaction with Trimethylsilylethoxyacetylene

Acid	*Product*	*Yield (%)*
		Quantitative
		Quantitative
		99
		90

2.1.4 α-KETONITRILES

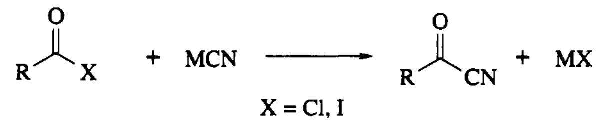
The characteristic feature of α-ketonitriles is the presence of two functional groups, which are capable of adding nucleophiles, next to each other. The electron-withdrawing character of the cyano group leads to enhanced electrophilicity of the carbonyl group, even though the carbonyl activity is less pronounced than in acid halides. Also, the cyano group displays increased reactivity towards nucleophiles as a consequence of the directly attached carbonyl group. These compounds are valuable intermediates for the synthesis of heterocycles. An earlier review[144] has found an actualization more recently.[145] Some information on their preparation can be obtained from Houben–Weyl.[146,147] The synthesis of acyl cyanides starts in general from cyanuric acid or its metal salts and reacts them with acid halides. Most α-ketonitriles are colorless liquids or solids. In the preparation of these compounds it has to be considered that they are mild acylating agents, that they dimerize in the presence of excess cyanide ion and that enolizable derivatives are converted in the presence of base to acylated enols (equation 41).



(41)

2.1.4.1 α-Ketonitriles from Acid Halides

Due to the sensitivity of acyl cyanides towards excess cyanide ions it is in general advisable not to use alkali metal cyanides as reagents unless special conditions are secured. Therefore, in most cases cyanides of heavy metals (low concentration of free cyanide) have been applied. These transformations require rather drastic conditions, which restricts the application mainly to the preparation of aromatic acyl cyanides. The latter can be obtained in good yield if copper(I) cyanide is heated with acid chlorides in aromatic solvents for several hours at temperatures of 160 °C.[148] More recent developments are based on the same strategy, but allow the application of milder conditions. In most cases acid chlorides are converted to acyl cyanides. Some reagents and the reaction conditions for their application according to equation (42) are collected in Table 12.



(42)

Table 12 Preparation of Acyl Cyanides from Acyl Halides

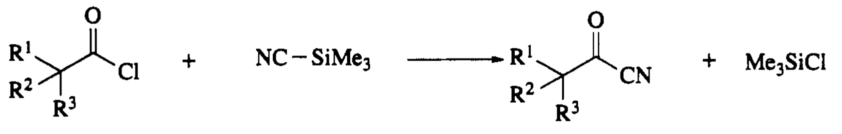
MCN	*Conditions*	*R in RCOX*	*Yield (%)*	*Ref.*
CuCN	MeCN, 40–60 °C, 1 h	Alkyl	50–75	149
CuCN	LiI, Et_2O, 30 °C 2 h or MeCN 80 °C	Alkyl, aryl	50–75	150
TlCN	Et_2O, $MeCO_2R$, 20 °C, 1–3 h	Aryl	45–89	151
NaCN (CuCN)	Organic solvent 50–300 °C	Alkyl, aryl	50–95	152
KCN	18-Crown-6 CH_2Cl_2	RO	62–94	153
Et_4NCN	CH_2Cl_2, –40 to +20 °C	R_2N, PhO	*ca.* 90	154
NaCN	Tetra-*n*-butylammonium bromide, CH_2Cl_2, H_2O	Aryl	20–75	155
$Bu^n{}_3SnCN$	75 °C, 5 min	Aryl	80–95	156

Compared to the older procedures the use of acid iodides in acetonitrile or dichloromethane as solvent constituted a remarkable improvement.[149] Aromatic and aliphatic acyl cyanides are accessible by this route. For example acyl cyanides of cinnamic acid and phenylacetic acid could be obtained in 53% and 49% yields. Copper(I) cyanide in diethyl ether in the presence of lithium iodide gave α-cyano ketones in 50–70%.[150] The reaction can be carried out at room temperature in diethyl ether or slightly above or at 80 °C in acetonitrile. It is not possible to obtain the acyl cyanide from acryloyl chloride, chloroformate or oxalyl chloride by this approach.

Thallium(I) cyanide was introduced by Taylor and McKillop as a reagent.[151] Aromatic and heteroaromatic acyl cyanides are produced in good yield, whereas aliphatic acid halides lead under these conditions mainly to dimerization products. 18-Crown-6 is a good catalyst for the preparation of cyanoformate in methylene chloride with potassium cyanide and chloroformates.[153] Similarly, tetraethylammonium cyanide gives cyanoformates in high yield under very mild conditions.[154] Aroyl cyanides are generated easily by phase transfer catalysis with tetra-*n*-butylammonium bromide.[155] Tri-*n*-butyltin cyanide proved successful only with aromatic acid halides, leading to dimerization products with aliphatic compounds.[156]

A general method for the preparation of α-cyano ketones from acid halides was developed recently (equation 43).[157,158] With trimethylsilyl cyanide as reagent a great number of acyl cyanides can be prepared under mild conditions in high yield. In particular the synthetically useful aliphatic derivatives have become accessible by this reaction. Table 13 lists examples for aliphatic, α,β-unsaturated and benzylic acyl cyanides. The procedure is very simple in that trimethylsilyl cyanide and acid chloride are mixed and kept without solvent. The reaction is followed by IR spectroscopy. As soon as all of the trimethylsilyl cyanide is consumed, the product can be isolated, normally by distillation, or directly used for further reactions.

Sometimes a Lewis acid such as zinc iodide is added in catalytic amounts. Side reactions may sometimes occur if acyl cyanides carry hydrogen atoms in the α-position and are, therefore, enolizable. In those examples trimethylsilyl chloride, which is formed during the reaction, may react to give trimethylsilylated enol ethers (**8**). This methodology can be applied successfully to the synthesis of such com-



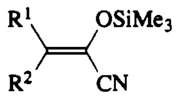
(43)

Table 13 Synthesis of Aliphatic, α,β-Unsaturated and Benzylic Acyl Cyanides

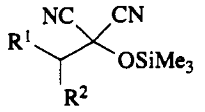
*R*¹, *R*², *R*³	*Yield (%)*[a]	*R*¹, *R*², *R*³	*Yield (%)*[a]
H, H, H	100	$PhCH_2$, Me, H	100
Me, H, H	94	$—(CH_2)_5—$, H	100
Et, H, H	92	Me, Me, Me	91
$—(CH_2)_2—$, H, H	100	Me, Cl, H	90
$CH_2{=}CH—CH_2$, H, H	100	Me, Br, H	81
Me—CH=, H	90	Me, I, H	100
Ph, Ph, H	100	Cl, H, H	53
Ph—CHMe, H, H	100	Br, Et, H	64
$MeO—CH_2$, H, H	80	Br, Pr^i, H	100
Me, Me, H	92	Br, Br, H	69
Ph, Me, H	100	$Cl_2C{=}CCl—CCl{=}$, Cl	46

[a] Yields and purity determined by IR spectroscopy.

pounds.[145] Sometimes excess trimethylsilyl cyanide may add to the carbonyl group of the α-ketonitrile leading to compounds of type (**9**). The latter reaction is predominant for carbonyl chloride, oxalyl chloride and trifluoroacetyl chloride. Compounds of type (**8**) can be taken to generate α-halo substituted acyl cyanides through reaction with halogens.



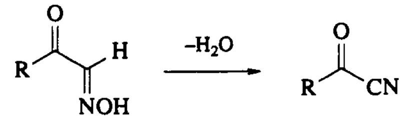
(**8**)



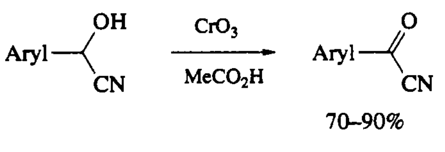
(**9**)

2.1.4.2 α-Ketonitriles by Miscellaneous Methods

α-Cyano ketones have been prepared from derivatives of aldehydes and ketones (equation 44),[159] in particular aromatic derivatives. Oxidation of aromatic cyanohydrins (equation 45) is another possibility.[160] More recently catalytic cyanocarbonylation of aryl iodides has been advanced.[161]



(44)



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2.2
Synthesis of Esters, Activated Esters and Lactones

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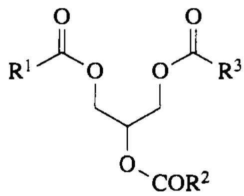
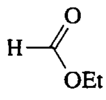
2.2.1 FORMATION OF ESTERS AND ACTIVATED ESTERS

2.2.1.1 General Introduction

The formation and further transformation of esters belongs to the fundamentals of organic chemistry. Moreover, some esters have enormous importance; for example triglycerides (**1**), in the form of fats and oils, are produced in million ton quantities for a number of applications. Other esters, *e.g.* (**2**) and (**3**), are olifactory components; waxes, *e.g.* (**4**), are used commercially to protect metallic surfaces against corrosion. Aspartame (**5**) is an important artificial sweetener, and pyrethrin (**6**) is the prototype of the pyrethroids, an unusually potent class of insecticides.[1] Apart from these more applied considerations, esters are important synthetic intermediates in a number of multistep sequences. Striking examples are chain elongations *via* Horner alkenation or α-alkylations of ester enolates, in particular the ones stereocontrolled by chiral auxiliaries.[2]



(**1**)



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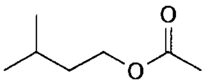

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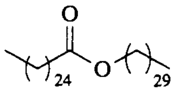

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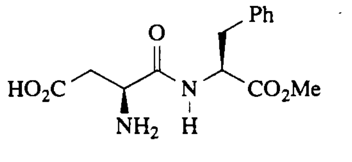
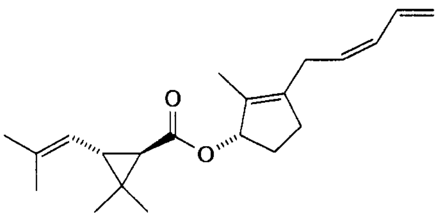


(**5**)

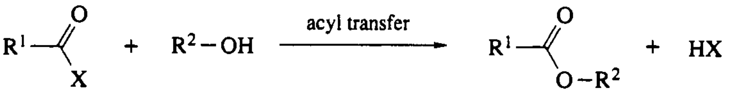


(**6**)

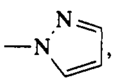
The simplest route to esters is the esterification of carboxylic acids. This subject has been covered in a number of more or less comprehensive reviews.[3] Therefore, the present report can be restricted to the most significant and recent developments.

2.2.1.2 Synthesis of Esters by Acyl Transfer to Alcohols (Carboxy Group Activation, CGA)

This method for the synthesis of esters is the most common method (equation 1). The carboxylic acid or an activated derivative thereof (**7**) is treated with the alcohol (**8**), generally in presence of a base, so that eventually the activating group X is replaced by the OR^2 moiety to form the ester (**9**). In effect this reaction is an S_N process at a trigonal carbon center and may proceed *via* an addition–elimination ('S_N2') or an elimination–addition ('S_N1') sequence. In either case, the configuration with respect to the R^2—O bond is retained and no ^{18}O exchange of this oxygen is observed.[4] X must be a good leaving group on one hand as in the aliphatic S_N reactions and, additionally, its electron donation to the carbonyl function must be minimalized.



(7) (8) (9) (1)

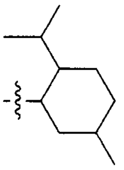
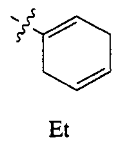
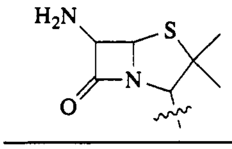
X = $^+OH_2$, ^+OHR, $^+NR_3$, F, Cl, Br, SR^3, , $OPPh_3$, OSO_2R^3, $\overset{\text{O}}{\overset{\|}{\text{OC}}}\text{R}^3$

2.2.1.2.1 *Esters from carboxylic acids and alcohols under acid catalysis: the* $A_{AC}2$ *and* $A_{AC}1$ *mechanism*

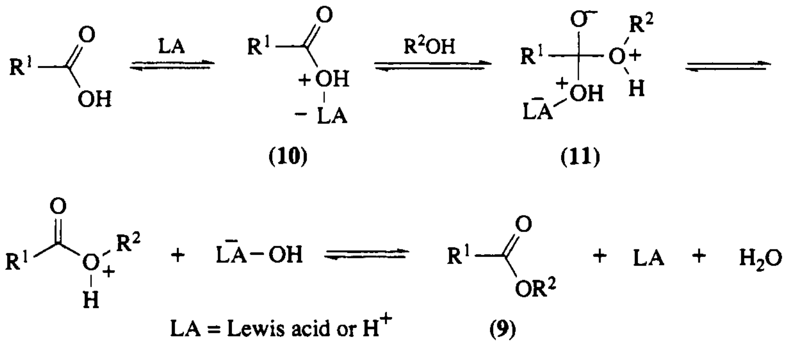
This method is extremely simple and is to be preferred if one of the components is cheap and both the acid and the alcohol do not contain acid sensitive functional groups. As catalysts conc. HCl (Fischer–Spei esterification), anhydrous sulfuric acid or *p*-toluenesulfonic acid or acidic ion exchange resins may be employed. The alcohol generally serves as the solvent, if permitted by its costs, otherwise toluene or xylenes may also be used. A very efficient catalyst is graphite bisulfate in cyclohexane.[5] The reaction generally leads to an equilibrium mixture consisting of about 80% of the ester and 20% of the components. Complete ester formation can be accomplished either by using the alcohol in large excess, *e.g.* as the solvent, or by removing the water from the mixture, for example by means of a Dean–Stark apparatus or a desiccating agent, preferrably 3Å molecular sieve. Volatile esters may be removed from the mixture by distillation. Instead of the proton acids mentioned above, Lewis acids such as boron trifluoride or polymer-supported aluminum chloride and chlorosilanes, may also be used. The advantage of these procedures lies in the high yields and the purity of the esters. Table 1 shows some illustrative examples.

Table 1 Acid-catalyzed Esterifications

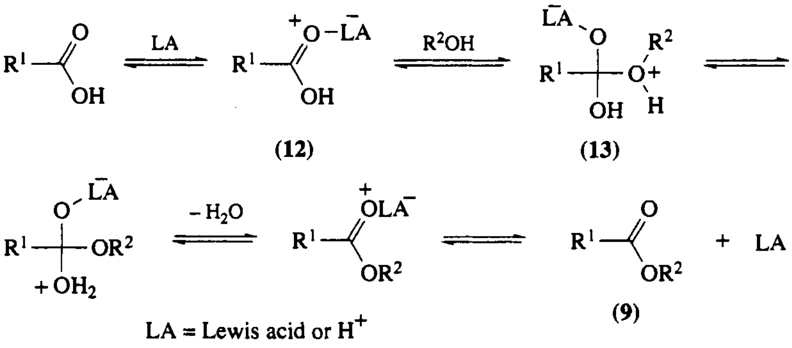
$$R^1CO_2H + R^2OH \longrightarrow R^1CO_2R^2 + H_2O$$

R¹	*R²*	*Catalyst*	*Removal of H₂O*	*Yield (%)*	*Ref.*
Citric acid (triester)	Et	HCl	$CaCl_2$	68	6
Citric acid (triester)	Et	H_2SO_4	Two phase with toluene	80	6
MeCH(OH)	Et	*p*-TsOH	Azeotropic with toluene	90	7
$(EtO)_2CH$	Et	*p*-TsOH		88	8
C_8H_{17}	Me	H_2SO_4	Molecular sieve 3Å	96	9
Me	Ph	H_3BO_3/H_2SO_4	Azeotropic with xylene	86	10
Me	Pr^i	Amberlite IR 20	$CaSO_4$	100	11
PhCO		Graphite–bisulfate	—	50	12
$4\text{-}NH_2C_6H_4SCH_2$	Me	$BF_3{\cdot}OEt_2$	—	78	13
	Et	$BF_3{\cdot}OEt_2$	—	66	14
Et	Bu^n	$AlCl_3$/polystyrene	—	97	15
	Me	Me_3SiCl	—	84	16

The widely accepted mechanism of the acid-catalyzed esterification is designated as the $A_{AC}2$ process (A = acid catalysis, AC = acyl transfer, 2 = bimolecular). As shown in Schemes 1a and 1b the rate-determining step is the reversible attack of the alcohol at the carbonyl function of the activated species (**10**) and (**12**). Two modes of proton (or Lewis acid) activation may be distinguished: either protonation of the OH function (Scheme 1a), leading to (**10**) and (**11**), or protonation of the carbonyl oxygen (Scheme 1b), leading to (**12**) and (**13**). Although the first mechanism is generally formulated in the literature, the second mechanism appears far more plausible regarding the site of the initial protonation,[17] as well as the lesser degree of charge separation in the crucial intermediates (**11**) *versus* (**13**).



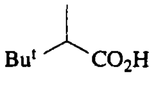
Scheme 1a



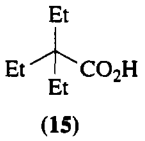
Scheme 1b

(i) Scope and limitation of the AAC2 esterifications

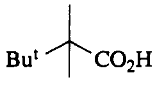
The greatest advantage of the method lies in its simplicity; however, the rather severe conditions (extended heating in presence of a mineral acid) makes it questionable for sensitive substrates. Additionally, α- and β-branching in the carboxylic acid strongly retards the reaction, so that for example, acids (**14**)–(**16**) are too hindered to react. On the other hand, α- and β-branching in the alcohol induces dehydration.



(**14**)



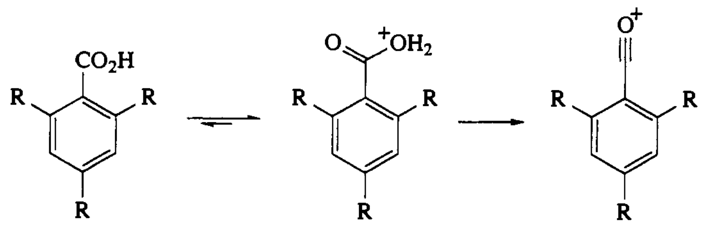
(**15**)



(**16**)

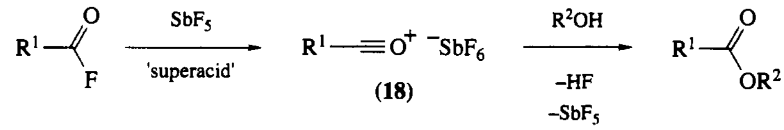
(ii) The AAC1 mechanism

This mechanism (A = acid catalyzed, AC = acyl transfer, 1 = unimolecular) is observed in the esterification of 2,4,6-trisubstituted benzoic acids with R groups of moderate +M effect (*e.g.* methyl).[17] The *A*AC2 mechanism is blocked by the steric interference of the *ortho* substituents. Therefore, the acylium cation (**17**) is generated with anhydrous sulfuric acid and then treated with the alcohol (equation 2).[18] R groups with strong +M effects, like methoxy, are not tolerable, as the aromatic nucleus undergoes sulfonation under the conditions. A variation of the *A*AC1 mechanism for aliphatic acids is achieved by using the fluorides and antimony pentafluoride to generate the acylium ion (**18**),[19] which reacts even with strongly hindered alcohols to form the esters (equation 3).



(**17**)

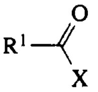
(2)



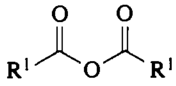
(3)

2.2.1.2.2 Acyl transfer via anhydrides and acid chlorides

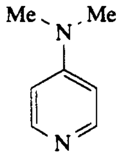
In contrast to the A_{AC} esterifications this method makes use of preformed CGA species (**19**) and (**20**) to which the alcohol is added. The formation of acid chlorides[20] requires strong Lewis acids like thionyl or oxalyl chloride, which may react with acid sensitive functions in the molecule and also cause epimerization of chiral α-centers in the substrate molecule. On the other hand, using anhydrides (**20**) for esterification means to lose 1 mol equiv. of the acid. Thus, both (**19**) and (**20**) should preferentially be used for inexpensive carboxylic acids with a low degree of functionalization. Typical and frequently encountered examples in multistep syntheses are benzoylation and acetylation of primary and secondary alcohols, whereas tertiary alcohols are generally too hindered to react, unless a strong base catalyst (*e.g.* calcium hydride)[21] is added. The acetylations are normally performed in pyridine at 0–25 °C. Acid catalysis is less common. Acid chlorides can be used in pyridine or in dichloromethane with triethylamine as the base. In any case, the anhydride should be preferred, as the reaction mixture remains almost neutral throughout the reaction and the yields are higher, particularly if the acylation is catalyzed with *N,N*-dimethylaminopyridine (DMAP; **21**) or, even better, 4-pyrrolidinopyridine (PPY; **22**).[22] Regular conditions are 0.05–0.2 mol equiv. of the catalyst in aprotic solvents (hexane, dichloromethane, THF, pyridine) at room temperature. Rate enhancements compared to the uncatalyzed reactions are several powers of ten, so that even hindered hydroxy functions (*e.g.* in **23** or **24**) are smoothly acylated.



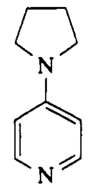
(**19**)



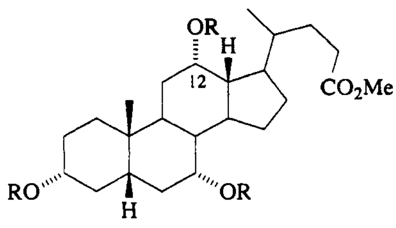
(**20**)



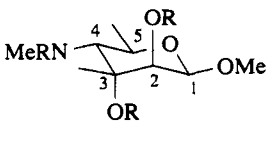
(**21**) DMAP



(**22**) PPY



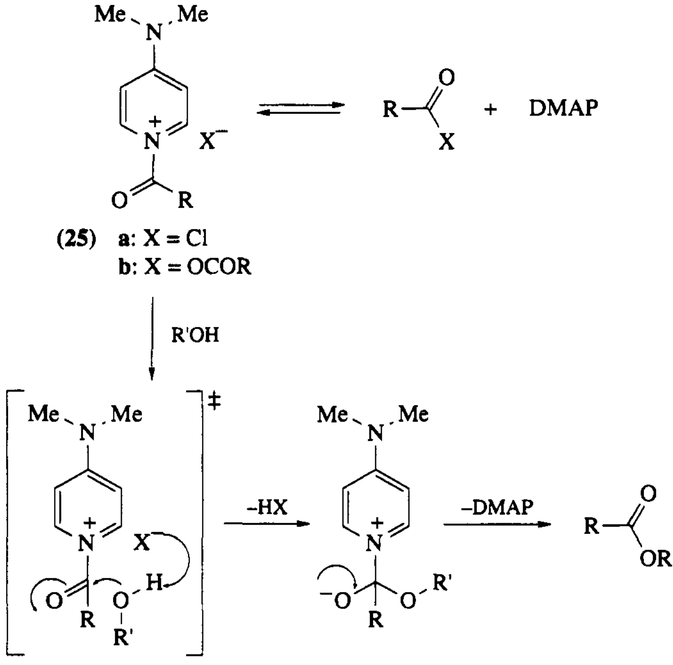
(**23**) a: R = H
b: R = COMe



(**24**) a: R = H
b: R = COMe

(i) Mechanistic aspects

Mechanistically, the alcoholysis of acid chlorides may proceed *via* a one step S_N2-like mechanism or more frequently, *via* the usual tetrahedral intermediate.[23] The reaction is accelerated by electron-withdrawing substituents in the chloride and hardly affected by steric hindrance. On the other hand, benzoyl chlorides with electron-releasing substituents in the aromatic nucleus undoubtedly react *via* an S_N1-like mechanism, especially in protic solvents.[24] Anhydrides prefer the normal addition–elimination pathway, the rate-determining step being the formation of the tetrahedral intermediate. The drastic effect of the catalysts (**21**) and (**22**) may be attributed to the initial formation of the acyl pyridinium salt (**25**), in which X^- serves as the base for the deprotonation of the alcohol during its nucleophilic attack on the carbonyl group (equation 4). This explains why acid chlorides show much smaller rate enhancements with (**21**) and (**22**) than anhydrides, although the equilibrium concentration of (**25a**) is much higher than that of (**25b**). However, chloride is a much weaker base than the carboxylate and cannot remove the proton from the alcohol with similar efficiency. Additionally, X^- must be close to the reaction site, which means that (**25**) is more efficient an acylating agent as a contact than as a solvent-separated ion pair. In fact, the rates are much higher in unpolar than in polar solvents.



(**25**) **a**: X = Cl
b: X = OCOR

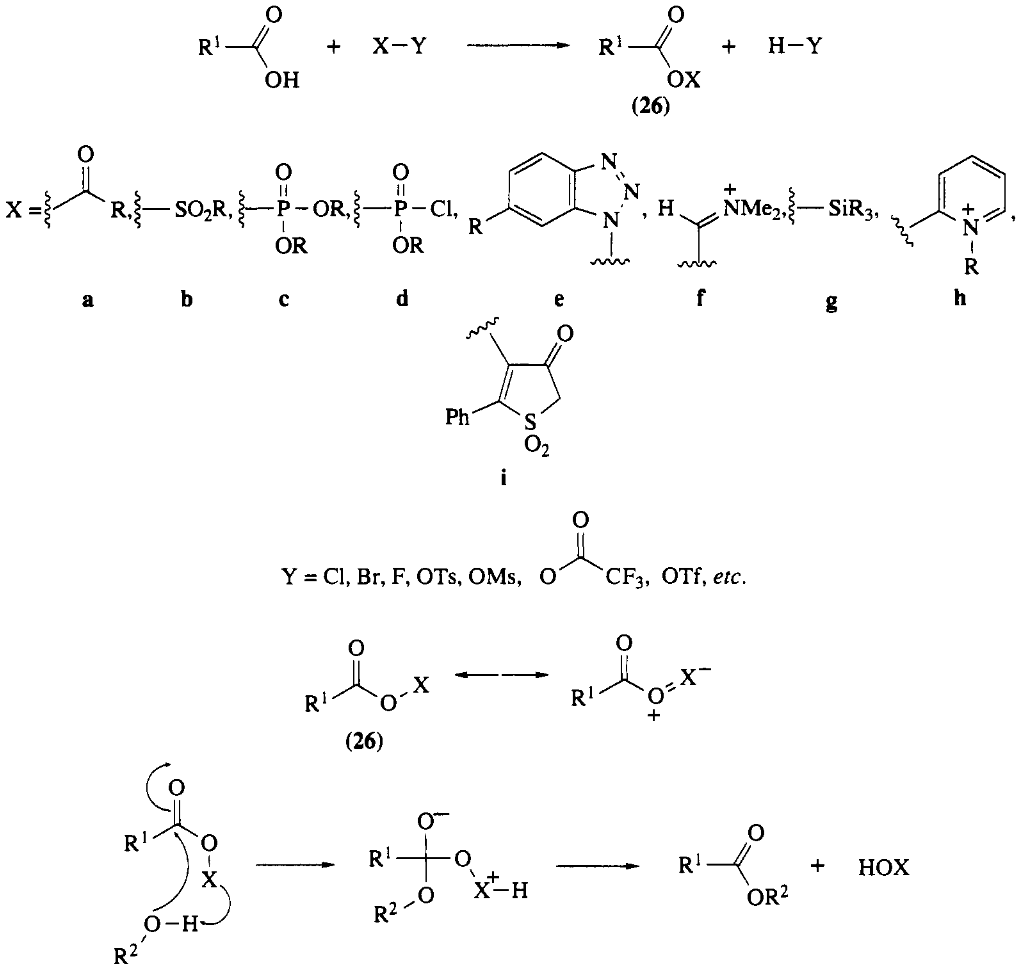
(4)

2.2.1.2.3 Acylation with mixed anhydrides and activated esters

This acylation process is of the utmost importance. In the first step, the carboxylic acid is treated with an activating agent X—Y to form the CGA species (**26**), which acylates the alcohol in the second step. X is a substituent with a strongly electron-withdrawing –I- or –M-effect and Y is a good leaving group. If X contains an acyl function, as in cases a–d, (**26**) is a mixed anhydride; otherwise, for instance in cases e–i, (**26**) is classified as an activated ester. In both types, the activating effect of X is two-fold ('double activation')[25] in facilitating the nucleophilic attack of the alcohol.

As shown in Scheme 2, the electron-withdrawing character of X enhances the electropositive nature of the carbonyl carbon in (**26**). The second, and equally important, effect is the ability of X to accept the proton from the alcohol. In this manner the effective nucleophilicity of the alcohol is drastically increased in the immediate proximity to the reactive center. Thus, (**26**) behaves very similarly to (**25**), with the only difference that (**26**) is neutral and (**25**) is an ion pair. As an additional benefit of the proton transfer, the leaving group quality of the OX fragment is also greatly improved.

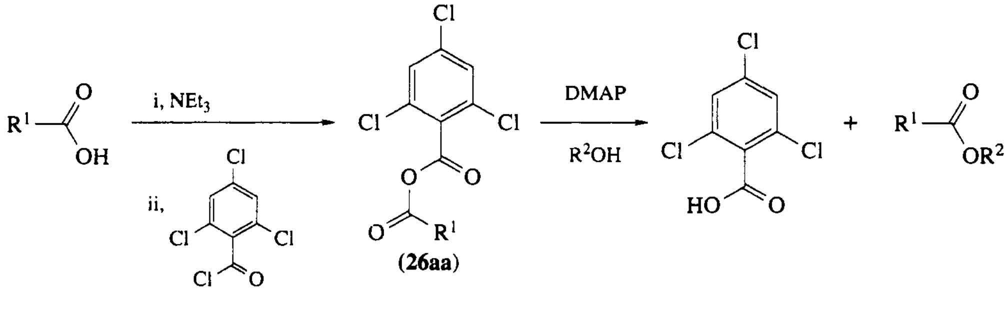
Mixed anhydrides from carboxylic acids (**26a**) have to be so devised that the desired acyl group is transferred. This can be achieved in two ways. The first one is to block the undesired carbonyl position by steric (*e.g.* **26aa**; equation 5) or electronic (*e.g.* **26ab**; equation 6) deactivation. The second one, as illustrated by (**26ac**; equation 7) is to allow the reversible attack of both carbonyl groups; the desired acyl transfer is accomplished by the better leaving group quality of the trifluoroacetate. Specifically, the



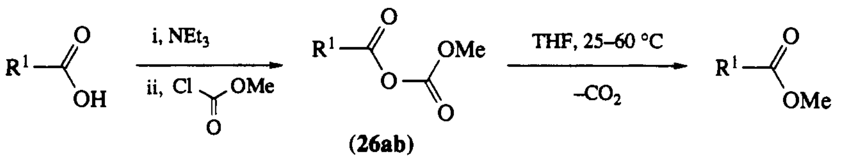
Scheme 2

mixed anhydrides (**26aa**) and (**26ab**) are prepared from the carboxylic acid and 2,4,6-trichlorobenzoyl chloride and methyl(ethyl)chloroformate in an aprotic solvent (THF, dichloromethane, *etc.*) in the presence of triethylamine. In the case of (**26aa**), the solvent is then replaced by benzene and the alcohol and a catalytic amount of DMAP (**21**) are added (equation 5).[26] On the other hand, (**26ab**) is heated to eliminate carbon dioxide under formation of the ester. This reaction, however, requires an R^1 group with electron-withdrawing substituents (equation 6).[27] (**26ac**) is formed from the carboxylic acid and trifluoroacetic anhydride in benzene at about 50 °C, then the alcohol is added without a catalyst (equation 7).[28]

Similarly, the acyl tosylates (**26b**) are prepared from the acid and tosyl chloride in pyridine at 0 °C; then the alcohol is added (equation 8). In view of the basic medium this method is particularly suited for acid sensitive alcohols (tertiary, propargylic, allylic or homoallylic).[29] The acyl phosphate (**26c**) is made

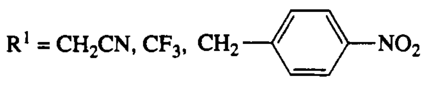


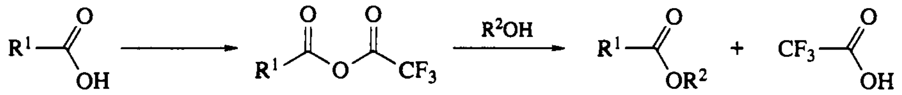
(5)



(26ab)

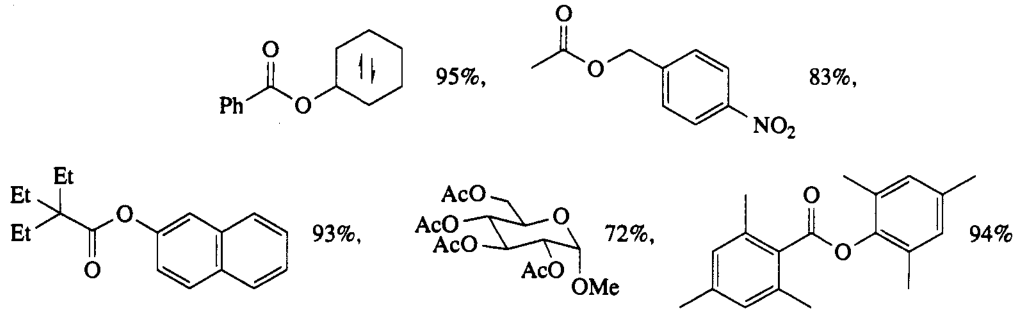
(6)



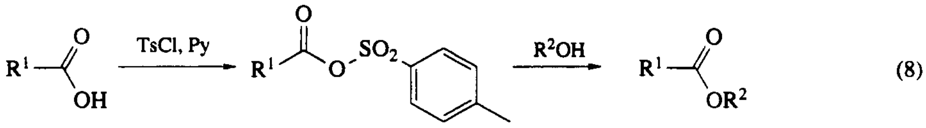


(26ac)

(7)

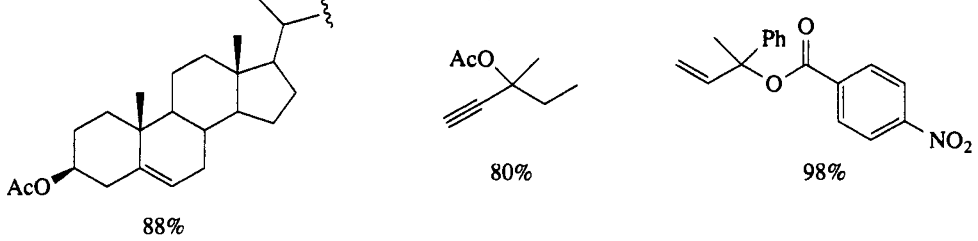


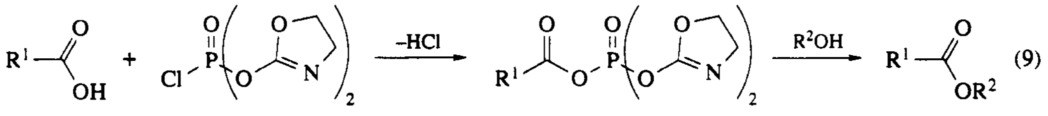
from the carboxylic acid and the chlorophosphate[27] in the presence of triethylamine. The alcohol only reacts with the mixed anhydride (**26c**) and not with the chlorophosphate, which means that it can be added together with the carboxylic acid (equation 9).[30] In a similar way, phosphoric ester dichlorides may be reacted with carboxylic acids to form mixed anhydrides (**26d**) in DMF and after addition of the alcohol component, esters are formed in high yields.[31]



(26b)

(8)



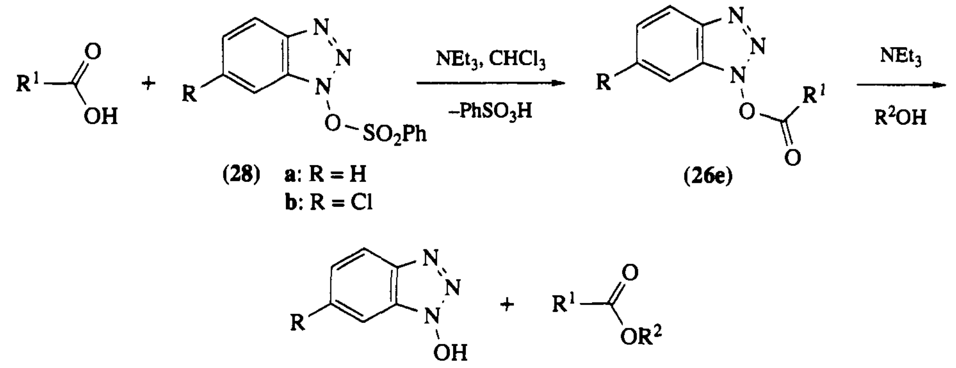


(27) **(26c)**

(9)

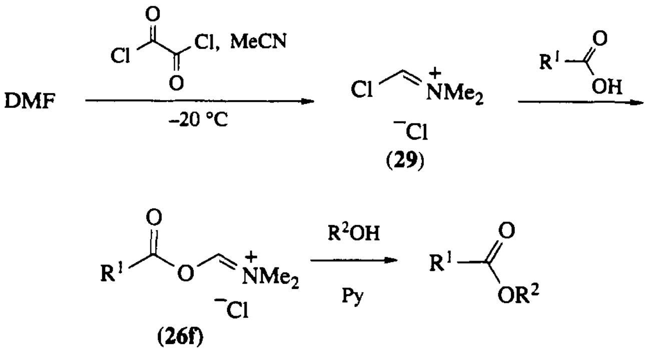
(i) Activated esters

Like the mixed anhydrides, activated esters may also be represented by the general formula (**26**). The only difference between mixed anhydrides and activated esters lies in the fact that HOX corresponds to a carboxylic or inorganic proton acid in the case of the mixed anhydrides and to an (acidified) alcohol in the case of the activated esters. In all other respects the overall procedure is very similar to that used for mixed anhydrides. For example (equation 10), the 1-acyloxy-1,2,3-triazole derivatives (**26e**) are formed from the carboxylic acid and the benzenesulfonates (**28**). Triethylamine is used to neutralize the sulfonic acid and to catalyze reaction of the alcohol with (**26e**).[32] The advantage of this method lies in the high selectivity; primary alcohols are acylated with high preference over secondary ones (see Section 2.2.1.6).

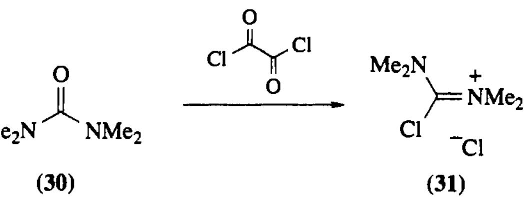


(10)

Chloroformamidinium chlorides (**29**) are generated from DMF and oxalyl chloride in acetonitrile. After addition of the carboxylic acid the activated ester (**26f**) is formed and treated with a solution of the alcohol in pyridine.[33] Phenyl, alkyl and even *t*-butyl esters may be prepared in yields of greater than 80% (equation 11). Reagent (**31**), accessible from (**30**) and oxalyl chloride (equation 12) behaves quite similarly to (**29**).[34] The use of silyl esters (**26g**), which are formed *in situ* in the presence of the alcohol and react then to the esters, has already been mentioned in Section 2.2.1.2.1. An application is described in Table 1.

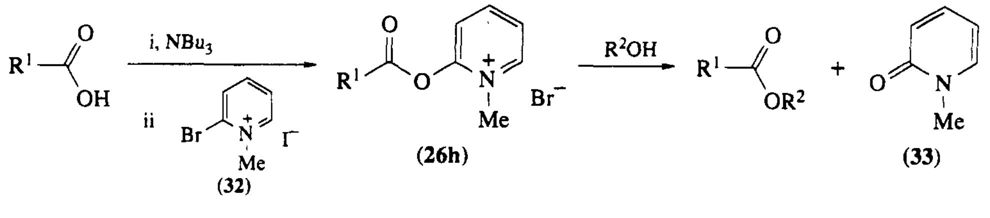


(11)

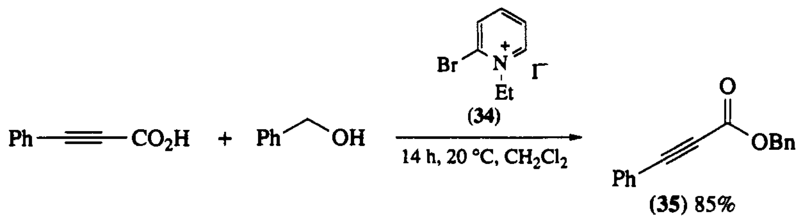


(12)

2-Acyloxypyridinium salts (**26h**) acylate various primary, secondary and tertiary alcohols under very mild conditions. All components (carboxylic acid, **32**, tributylamine and the alcohol) are stirred in dichloromethane at room temperature for several hours[35] to form the desired ester and pyridine (**33**; equation 13). The ester is isolated by chromatography. The synthesis of benzyl phenylpropiolate (**35**) may serve as an example (equation 14).

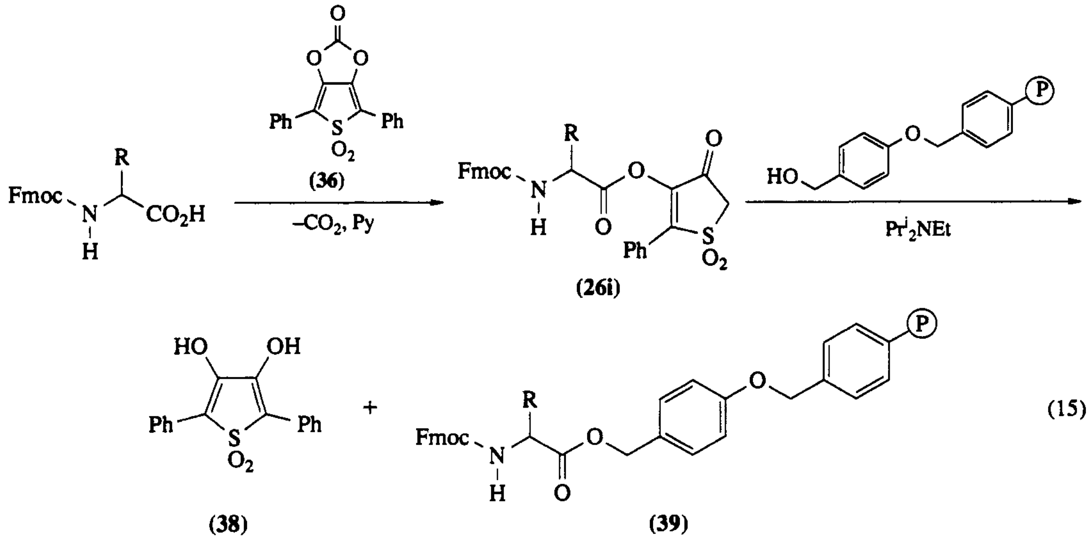


(13)



(14)

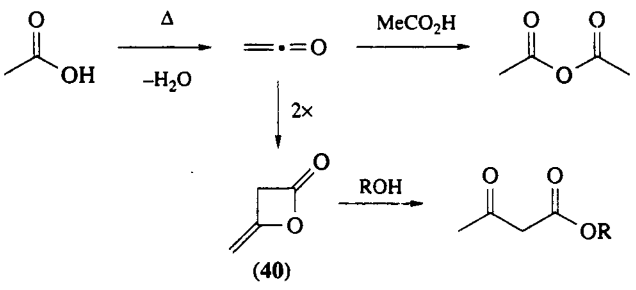
The novel carbonate (**36**) has been developed by Steglich and coworkers[36] to solve a fundamental problem in solid-phase peptide synthesis, *i.e.* the attachment of the terminal *N*-protected amino acid to the Merrifield resin without racemization. To this end, the Fmoc-protected acid is treated with (**36**) to form the activated ester (**26i**), which may be isolated, and is then added together with Hünig's base to the *p*-benzyloxybenzyl alcohol substituted resin. Under elimination of (**38**) the desired immobilized ester (**39**) is formed, from which the Fmoc group is removed with piperidine. The next amino acid can be condensed to the amino group, again using (**36**) as the coupling agent (equation 15).[36]



(15)

2.2.1.2.4 Acylation with ketenes

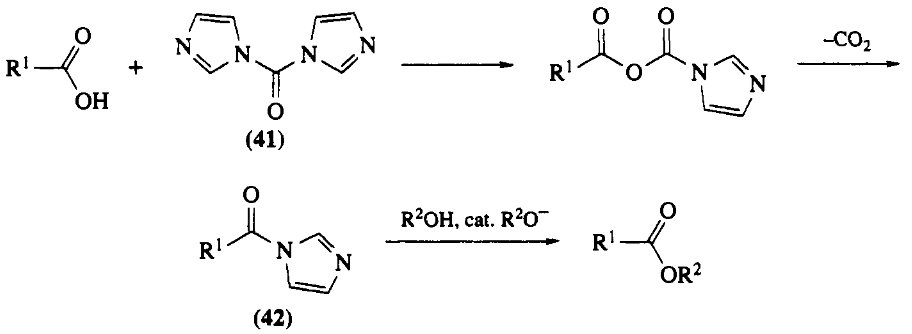
Ketenes are highly reactive acylating agents. However, they have found only limited application, as they are not as readily available as the other acylating agents described so far. The only exception is ketene itself, which is produced on a large scale industrially and is used for the acylation of acetic acid to acetic anhydride (1986, 1.6 millions of tons[37]). A minor amount (1986, 63 000 tons[37]) of ketene is dimerized to diketene (**40**), which is used to acylate alcohols to various esters of acetoacetic acid (equation 16). The corresponding amides are prepared analogously.



(16)

2.2.1.2.5 *Acylation with* N-*acylimidazoles*

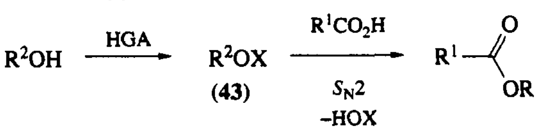
This method was introduced by Staab[38] and is suitable for the acylation of primary, secondary and tertiary alcohols. First the carboxylic acid is converted into the imidazolide (**42**) with carbonyldiimidazole (**41**), and then the alcohol is added together with a catalytic amount of strong base (alkoxide). The ester is formed at room temperature within a few hours (equation 17). If functional groups in the acid or alcohol prevent the use of base, the imidazolide and the alcohol have to be heated to 70 °C for 1–2 h.



(17)

2.2.1.3 Esters from Carboxylic Acids and Alcohols *via* Hydroxy Group Activation (HGA)

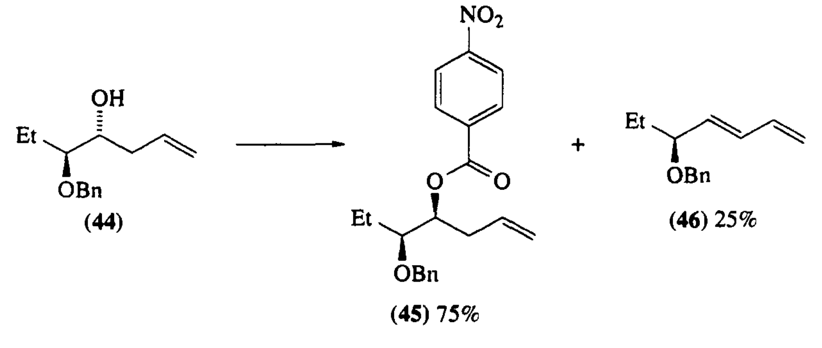
This type is a one-pot reaction with all components present from the beginning. The alcohol is first converted into an S_N-activated (HGA) species (**43**), which undergoes an OX displacement with the carboxylic acid to form the ester (equation 18). Two methods are known to fit into this general scheme: the Mitsunobu reaction[39] and the Vorbrüggen–Eschenmoser reaction.[40]



(18)

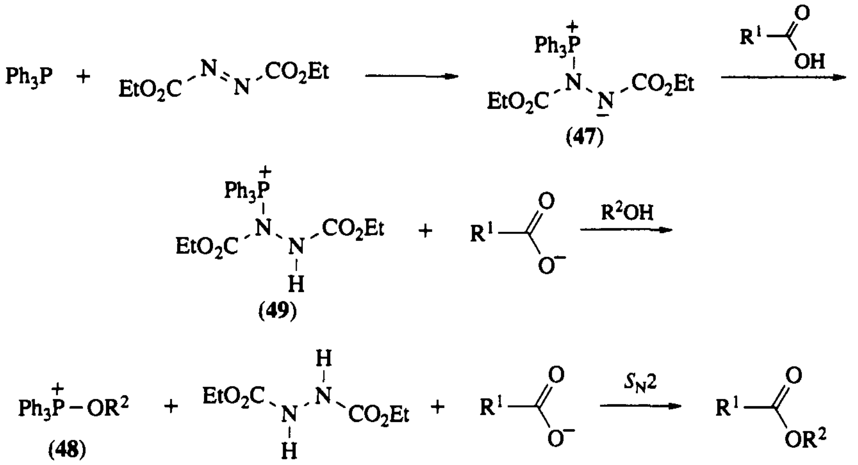
2.2.1.3.1 *Mitsunobu reaction*

This method is unusually mild, using neutral conditions and low temperatures (20 °C and less). It tolerates a number of functional groups in the components (*e.g.* acetals, esters, alkenes, *etc.*). The alcohol, the carboxylic acid and triphenylphosphine are treated dropwise in an inert solvent (dichloromethane, THF, ether) with diethyl azodicarboxylate (DEAD). The ester is formed rapidly. However, tedious chromatography is frequently required to remove the by-products, triphenylphosphane oxide and hydrazo ester. The main value of the reaction lies in the clean inversion of configuration at a secondary carbinol center and in its selectivity towards primary hydroxy groups (*vide infra*). Inversions are usually performed with benzoic or *p*-nitrobenzoic acid. The benzoates are purified and saponified with aqueous base to furnish the inverted alcohols in overall yields of *ca.* 50%. Elimination is the main side reaction. Thus, from (**44**) 75% of the desired S_N2 product (**45**) is formed, along with 25% of the elimination product (**46**) (equation 19).[41] The mechanism of the reaction has been clarified to the point that betaine (**47**) is the pri-



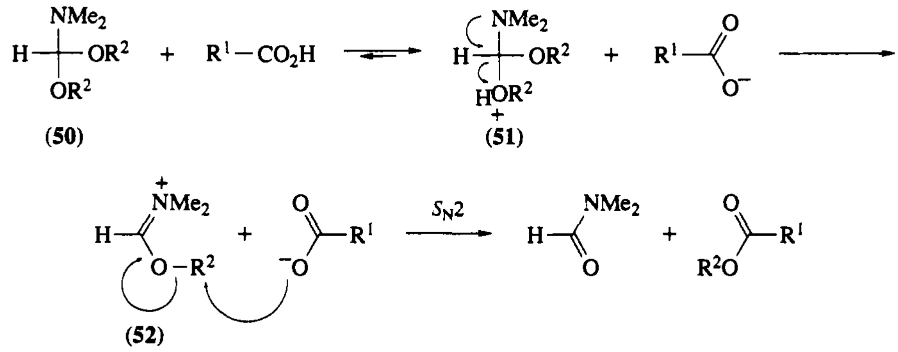
(19)

mary intermediate from which the triphenylphosphonium moiety is transferred to the alcohol from (**49**) to form the HGA species (**48**). The rate-determining step is the final S_N2 reaction with the carboxylate (equation 20).[42]


(20)

2.2.1.3.2 *Eschenmoser–Vorbrüggen reaction*

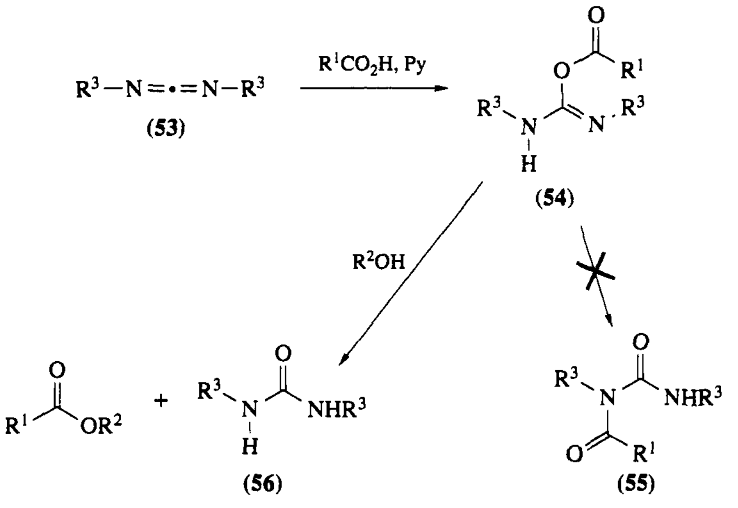
In this reaction the carboxylic acid is heated together with formamidacetals (**50**) in an inert solvent (benzene, *etc.*). The products are the ester, DMF and alcohol R^2OH. Only S_N2 active R^2 groups like methyl, ethyl, benzyl *etc.* can be transferred. Mechanistic studies have shown that the HGA species (**52**) is generated from (**50**) *via* elimination of R^2OH under proton donation from the carboxylic acid. The carboxylate in turn undergoes an S_N2 displacement with (**52**) to form the ester and DMF (equation 21).


(21)

2.2.1.4 CGA and HGA Esterifications at Will: the DCC Method

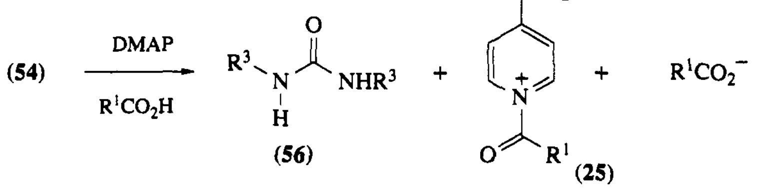
A reagent which allows both CGA and HGA esterifications is DCC (dicyclohexylcarbodiimide; **53**; R^3 = cyclohexyl). CGA esterifications are accomplished by treating a mixture of the carboxylic acid and the alcohol with DCC in hexane or pyridine with a catalytic amount of *p*-TsOH. The *O*-acylisourea (**54**) is postulated as intermediate, which reacts with the alcohol under elimination of the urea (**56**) and formation of the desired ester. The urea is removed by filtration (equation 22).[43] This method is highly recommendable if both the carboxylic acid and the alcohol are valuable and bear sensitive functional groups. Numerous applications in natural product synthesis have been reported.[44]

DMAP catalyzes the reaction most efficiently.[45] From (**54**) and excess carboxylic acid (**56**) the already described ion pair (**25**) is formed, which then acts as the acylating species proper. However, the carboxylate is not wasted in this case, as it reacts immediately with (**53**) and is thus recycled.[46] Thus, the DCC method can also be used for acylations with symmetrical anhydrides; now both acyl moieties are used in the esterification (equation 23).[46] The HGA variant is less common. To this end, the alcohol is first

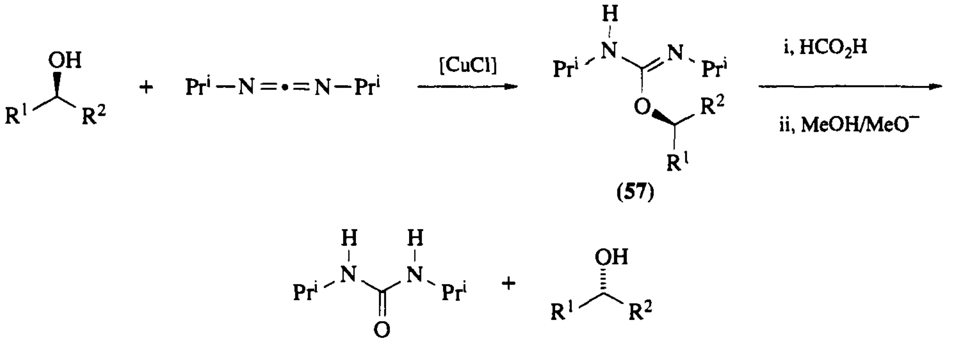


(22)

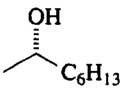
added to DCC under copper(I) catalysis to form the *O*-alkylisourea derivative (**57**), which is isolated and treated with the acid to form the ester *via* S_N2 displacement.[47] In effect, this reaction constitutes an alternative to the Mitsunobu reaction. The carboxylic acid used for the inversion of secondary carbinols is formic acid; the formates are saponified with methoxide (equation 24). The inversion of carbinols (**58**)–(**60**) proceeds with high overall yields.[48]

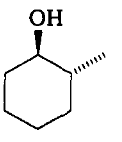


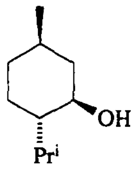
(23)



(24)





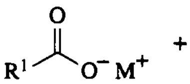


(**58**) (**59**) (**60**)

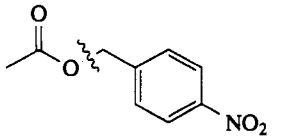
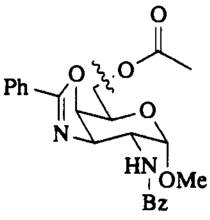
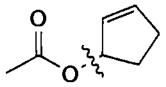
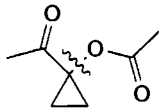
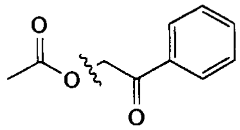
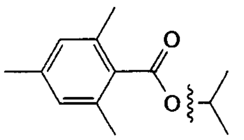
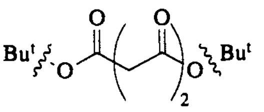
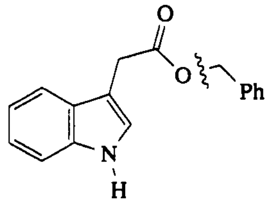
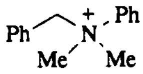
2.2.1.5 Alkylative Esterification

This type of esterification largely resembles the HGA reactions described in Section 2.2.1.3, with the only difference that the alkylating species is now an alkyl halide or tosylate or some quasi-carbenium ion instead of an activated alcohol (**43**). The most straightforward way of achieving alkylative esterification is by the treatment of carboxylate salts with an alkylating agent R^2X (Table 2).

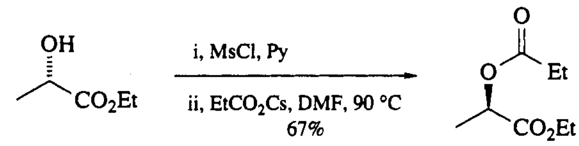
Table 2 Alkylative Esterification



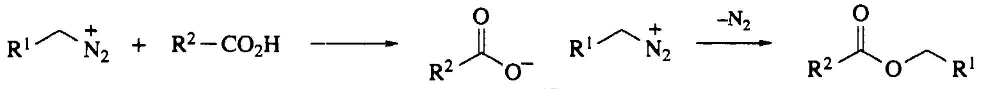
$R^1C(O)O^- M^+$ + R^2X X = OTs, OMs, Cl, Br

Compound	*Ester*	*M*	*X*	*Yield (%)*	*Ref.*
(61a)		Na	Cl	82	49
(61b)		Na	OMs	40	50
(61c)		Na	Cl	80	51
(61d)		Ag	Br	65	52
(61e)		K	Br	Quantitative	53
(61f)		Na	Br	Quantitative	54
(61g)		Ag	I	68	55
(61h)				68	56

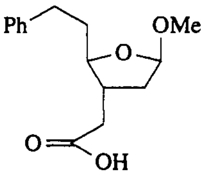
It will be noted from examples (**61a**)–(**61g**) that a wide variety of carboxylates can be used, suitable cations being Na, K or Ag. In particular Ag^+ in combination with an alkyl bromide or iodide permits the S_N reaction even at branched sp^3-centers (**61d**, **61f** and **61g**). Example (**61h**) illustrates the use of quaternary ammonium carboxylates in which on heating the alkyl substituent with the highest S_N2 activity (*e.g.* benzyl > ethyl or methyl) is transferred from N to O. The advantage of the alkylative esterification lies in the neutral conditions under which acid sensitive functional groups can survive (*e.g.* **61b** and **61c**). Like the Mitsunobu reaction and the CuCl-catalyzed DCC activation the alkylative esterification may be used for the inversion of configuration at secondary carbinol centers. For instance, lactic ester (**62**) is mesylated and then heated with cesium propionate in DMF[57] to give (**63**; equation 25). Diazoalkanes (**64**) react with carboxylic acids under proton transfer to give the diazonium carboxylate (**65**),[58] which collapses into the ester and nitrogen (equation 26). This method is the best for methylating sensitive carboxylic acids like (**66**).[59] The extension to diazoalkanes other than diazomethane, however, has been prohibited by their poor availability and the potential danger in handling these compounds. An established procedure for preparing *t*-butyl esters is the treatment of carboxylic acids with isobutene and strong acid in aprotic solvents (equation 27).[60]



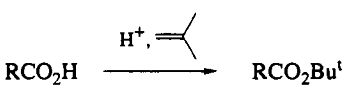
(62) **(63)** (25)



(64) **(65)** (26)



(66)

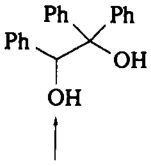


(27)

2.2.1.6 Selective Monoacylation of Polyols

One of the fundamental operations in multistep syntheses is the selective acylation of polyols, mainly for protection purposes, as selectivity in favor of one out of several hydroxy groups in general is far easier to get by acylation than by alkylation. The differentiation between tertiary and secondary or primary OH groups presents no problems, as tertiary groups are acylated only under forced conditions. Standard conditions (*e.g.* acetic anhydride or benzoyl chloride in pyridine) leave tertiary hydroxy groups untouched. Thus, only the secondary OH function in (**67**) is acetylated.[61] Even strongly hindered primary OH functions, *e.g* the one marked in (**68**), are unreactive.[62] A crucial problem, however, is the differentiation of primary and secondary positions, especially in 1,2-diols like (**70**), (**71**), (**75**) or (**76**). A variety of methods have been developed to solve this problem by selective benzoylation of the primary OH group with reagents like benzoyl cyanide, benzoylimidazole and benzoyltetrazole.[63] Recently, 1-benzoyl oxybenzotriazole (**69**) has been reported to furnish product ratios of primary to secondary benzoates of >90:10[64] in a number of cases, *e.g.* (**70**)–(**72**). The reagent even differentiates between secondary OH groups. So the marked positions in (**73**) and (**74**) are benzoylated with >90% selectivity. In favorable cases, primary OH functions in 1,2-diols can be selectively benzoylated simply by using benzoyl chloride in pyridine at –20 °C. (**75**) and (**76**) form the primary monobenzoates under these conditions with no concomitant acylation of the secondary position, but with formation of 5–10% of the dibenzoate.[65] Monobenzoylation of primary OH groups can also be achieved by the Mitsunobu reaction (Table 3).[39]

However, this method fails for 1,2-diols like (**79**) or (**81**), from which the epoxides (**80**) and (**82**) are generated (equations 28 and 29). This involves an S_N2-type cyclization with retention at the secondary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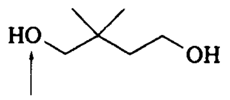
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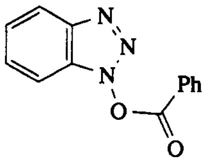
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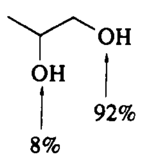

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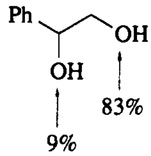

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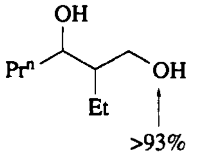
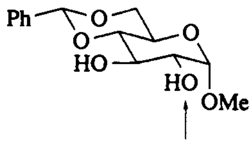


(72)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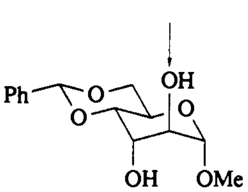
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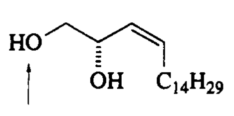

(75)

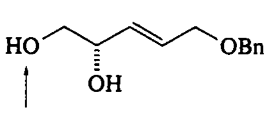
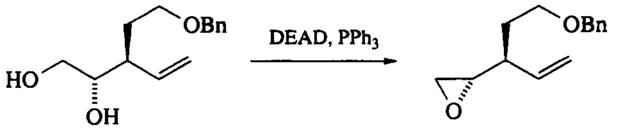

(76)

Table 3 Selective Monobenzoylation under Mitsunobu Conditions[39]


(77) **(78)**

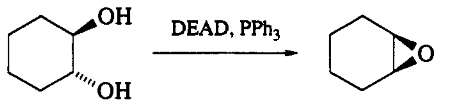
n	*R*^{1}	*R*^{2}	*X*	Yield (%) *X* = *H*	Yield (%) *X* = *Bz*
1	H	H	H or Bz	65	12
2	H	H	H or Bz	66	15
1	Me	H	H or Bz	70	7
1	Me	Me	H or Bz	57	20

center.[66] The comparison between the *cis*- and *trans*-cyclohexane diols (**81**) and (**83**) is quite informative. Only the *trans* isomer gives the epoxide (equation 29), whereas the *cis* compound is monobenzoylated (equation 30). In suitable cases selective acylations with Ac_2O may be achieved by utilizing conformational effects. For instance, in the forskolin precursor (**86**) only the marked OH group is acetylated under standard conditions. Due to the rigid conformation of the molecule this is the only secondary equatorial hydroxy function, whereas the other ones are either tertiary or axial.[67] Sometimes the need arises to get selective acylation of a secondary position in the presence of a primary one. This can be achieved by first peracetylating the compound and removing the more unhindered primary acetate with mild base. In this way, (**85b**) has been prepared from (**85a**) with perfect regiocontrol.[68] Further selective acylations are described in Section 2.2.1.8.



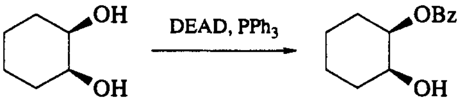
(79) **(80)** 75%

(28)



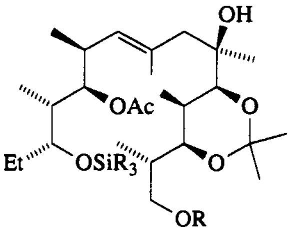
(81) **(82)** 80%

(29)

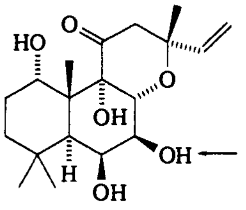


(83) **(84)** 22%

(30)



(85) a: R = Ac
b: R = H

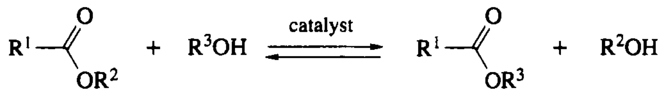


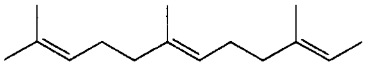
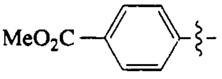
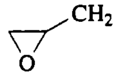
(86)

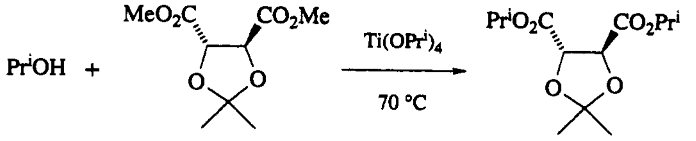
2.2.1.7 Transesterifications

Transesterifications can, in principle, be performed by reaction of esters with alcohols, carboxylic acids and other esters. All three types are reversible, so that the equilibrium has to be shifted to the desired side either by applying an excess of the reagent or by removing a volatile product *via* distillation. In all cases acid or base catalysis is required. In laboratory practice the most common transesterification method is the reaction of valuable esters with an excess of a cheap alcohol under the catalysis of a mild base. Examples are given in Table 4. Recently, $Ti(OPr^i)_4$ has been recommended as an exceptionally mild and efficient transesterification catalyst.[72] Thus, the dimethyl ester (**87**) is cleanly converted into (**88**) without affecting the acetonide ring (equation 31). The alcohol need not necessarily be identical with the OR group in the titanate, as this exchange is slow compared to the transesterification itself. Transesterifications of β-keto esters are most efficiently catalyzed with DMAP, as illustrated by equation 32.[73]

Table 4 Transesterification of Esters and Alcohols

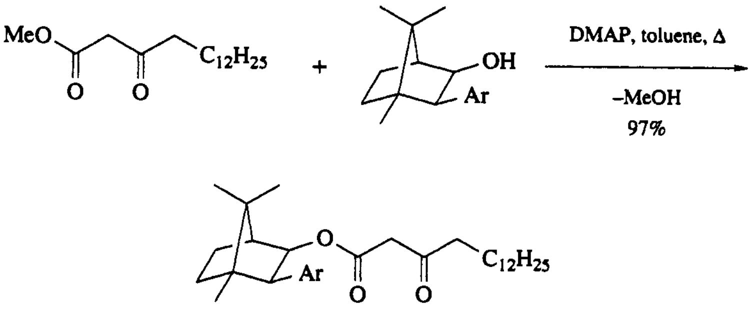


R¹	*R²*	*R³*	*Catalyst*	*Yield (%)*	*Ref.*
	Me	Et	KCN	85	69
C_6H_{13}	Me	Bu^t	Molecular sieves	83	70
	Me		TlCl	94	71



(87) (88) 91%

(31)



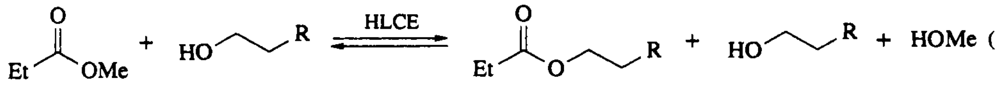
Ar = 1-naphthyl

(32)

2.2.1.8 Enzymatic Acylations and Deacylations

Enzymatic transacylations have received enormous attention in recent years.[74] The enzymes generally employed are lipases from microorganisms like *Candida cylindracea, Rhizopus arrhizus* or *Chromobacterium viscosum*, or from mammalian liver, like porcine pancreatic lipase (PPL). Ester hydrolysis is normally performed in water, sometimes with organic solvents (acetone or acetonitrile) as additives, whereas the acylations are run as transesterifications of the alcohol with esters with the enzyme in organic solvents (ether, benzene, *etc.*). The enzyme may be used as a crude extract or in purified form, sometimes entrapped in sepharose or in chromosorb as a solid support. The great advantage of the enzymatic process lies in its high chemo- and stereo-selectivity. For example selective monoacetylations of the primary OH function in methyl furanosides of D-ribose, D-arabinose, D-xylose and 2-deoxy-D-ribose with crude PPL in THF, using 2,2,2-trifluoroethyl acetate as the acyl donor, have been reported.[75] Optical resolution of racemic mixtures of alcohols can be efficiently achieved by enzymatic acylation or transesterification. In the ideal case, only one enantiomer is reactive, the other remains unchanged. In this way a variety of γ-branched alcohols (**89**) have been resolved with high *ee* values in both the ester and the remaining alcohol (Table 5 and equation 33).[76] α-Branched alcohols have been resolved with similar efficiency (Table 6 and equation 34).[76] The enzymes used were HLCE and yeast lipase on sepharose or chromosorb in water and the acyl-donating ester as solvent.

On the other hand, resolution of racemic α-halo carboxylic acids (**93**) with butanol can be effected with lipase (Table 7 and equation 35).[77] Applications of enzyme-catalyzed acyl transfer reactions, among many others, are the synthesis of the pheromone (*S*)-sulcatol (**95**; equation 36)[78] and of (*R*)-glycidylbu-

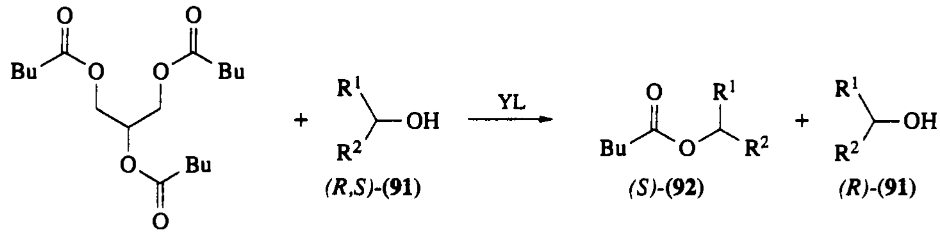


(33)

(*R,S*)-(**89**) (*S*)-(**90**) (*R*)-(**89**)

Table 5 Enzymatic Resolution of Alcohols by Transesterification with Hog Liver Carboxylate Esterase (HLCE) (equation 33)

R	% *ee* (*S*)-(**90**)	% *ee* (*R*)-(**89**)
CH(OMe)Me	98	—
CH(Me)Et	94	94
$CH(Me)(CH_2)_3CHMe_2$	95	97
$CH(Me)CH_2CH_2CH{=}CMe_2$	96	97

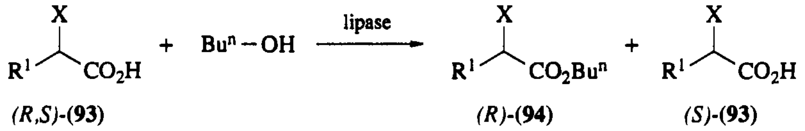


(34)

Table 6 Enzymatic Resolution of Alcohols by Transesterification with Yeast Lipase (YL) (equation 34)

R^1	R^2	(% ee) (S)-(92)	 (R)-(91)
Me	Et	98	97
Me	C_6H_{13}	98	89
H	$CHClCH_2Cl$	93	88

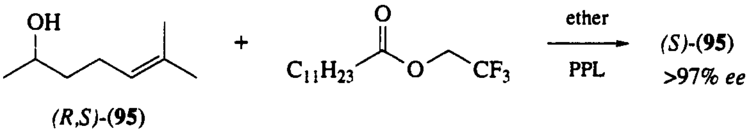
tyrate (**96**), which serves as the starting material for the β-blocker propranolol (**97**). Enzymatic esterification of racemic menthol (**98**) with hexanoic acid leads to optically pure ester (equation 37).[79]



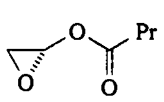
(35)

Table 7 Enzymatic Resolution of α-Halocarboxylic Acids (equation 35)

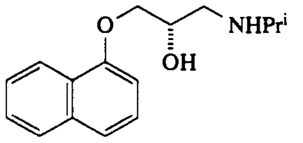
R^1	X	(% ee) (R)-(94)	 (S)-(93)
Me	Br	96	99.6
Me	Cl	95	95
Bu	Br	99	62/73
Ph	Cl	99	—



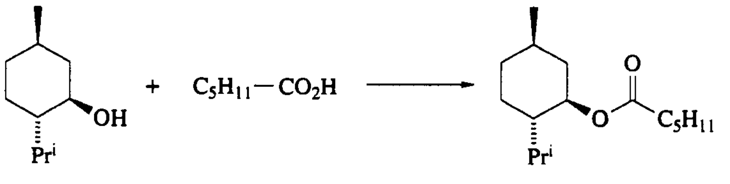
(36)



(96)

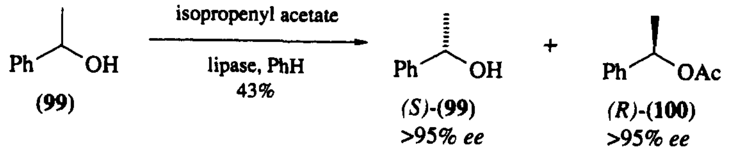


(97)

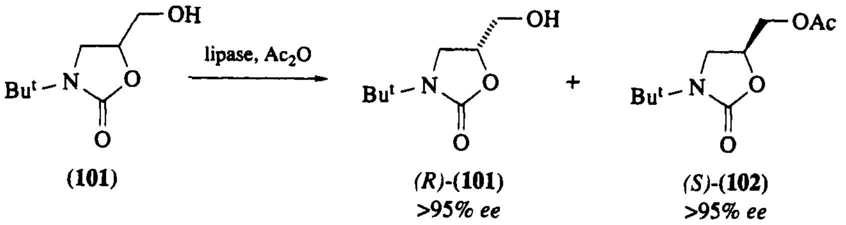


(37)

In contrast to the procedures described so far which all have to use a large excess of one component (ester in equations 33, 34 and 36, alcohol in equation 35 or acid in equation 37) direct enzymatic acylation with isopropenyl acetate or acetic anhydride[80] requires only stoichiometric amounts of the reagents (equations 38 and 39). Both acetate, (**100**) and (**102**), and alcohol, (**99**) and (**101**), are obtained with high enantioselectivity.



(38)



(39)

Enantiotopically selective ester hydrolysis can also be achieved enzymatically (Table 8). Either one ester group in a *meso*-diester (**103**)–(**106**) or one acetate in a *meso*-diacetate (**107**)–(**111**) are saponified with PLE or other lipases. In favorable cases enzymatic acylation and deacylation are stereochemically complementary and may thus be combined to gain access to both enantiomers, as illustrated by the example in Table 9.[89]

2.2.2 SYNTHESIS OF LACTONES

Lactones are intramolecularly formed esters of hydroxy carboxylic acids and may, consequently, be prepared by cycloacylating or cycloalkylating processes. The CGA intermediate (**116**) has to be formed from (**115**) by means of some activating agent, whereas cycloalkylation presupposes the carboxylate (**119**), with some leaving group Y in the ω-position. Y may be an oxygen-leaving group (HGA mechanism) or a halogen. The most significant difference between cycloacylation and cycloalkylation is the retention and inversion of the configurations of the ω-center, respectively. Most lactonizations proceed *via* cycloacylation.

2.2.2.1 Synthesis of α-Lactones

α-Lactones have no significance in synthesis, but in their own right they are interesting, highly strained, and hence, transient species. Classical work has provided evidence that the hydrolysis of α-bromopropionic acid in mild base proceeds *via* (**121**), which is then opened with inversion of configuration, so that the overall result is retention of configuration at the α-center.[90]

α-Lactones of type (**122**) may be generated photolytically in a frozen matrix and polymerize at higher temperature.[91]

2.2.2.2 Synthesis of β-Lactones

β-Lactones are normally stable compounds, which have found ample application as synthetic intermediates,[92] and, quite recently, have been detected as the central structural unit in physiologically active natural products like obaflorin (**123**)[93a] and lipstatin (**124**).[93b] Characteristic applications of β-lactones in synthesis are the stereospecific CO_2 elimination to form di- and tri-substituted alkenes (*e.g.* from **125**; equation 40)[94] or Grignard addition to the carbonyl group (*e.g.* equation 41).[95] Particularly useful is the formation of β-lactone enolates (**126**), which react with a variety of electrophiles (EX) with high stereocontrol (equation 42).[96] Organocuprates may be used in chain elongations to form β-branched carboxylic acids (equation 43).[97]

Table 8 Enzymatic Enantioselective Hydrolysis of *meso*-Diesters or Diacetates

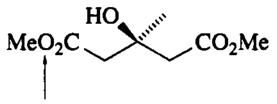
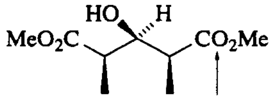
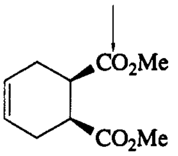
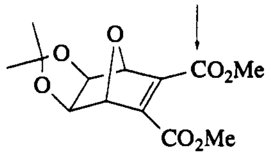
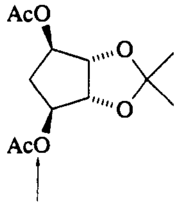
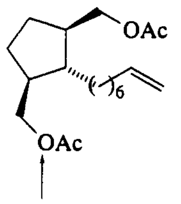
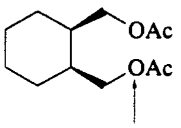
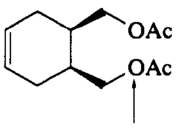
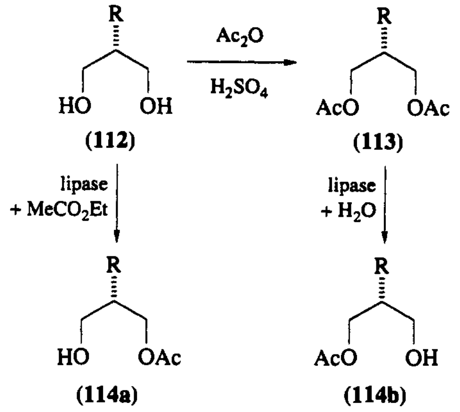
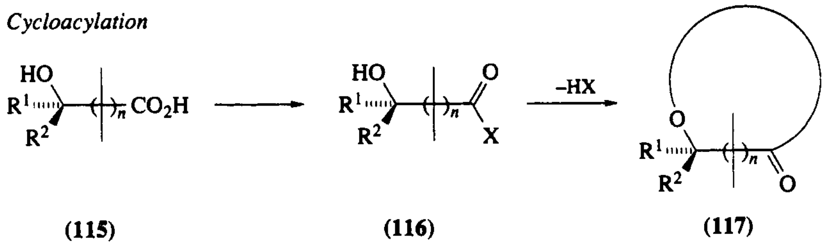
Compound	*Diester or diacetate*	*% ee*	*Ref.*
(103)		99	81
(104)		98	82
(105)		98	83
(106)		77	84
(107)		98	85
(108)		99	86
(109)		93	87
(110)		87	87
(111)		95	88

Table 9 Complementary Enzymatic Acylation and Deacylation

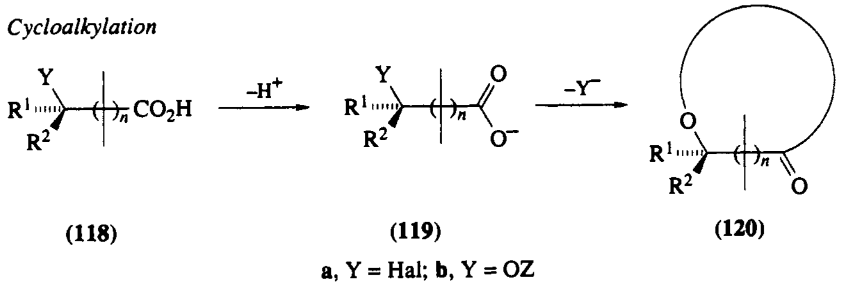


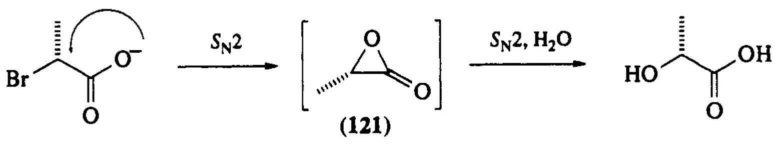
R	*(% ee)*	
	(114a)	*(114b)*
$CH_2CH_2CH{=}CH_2$	90	>95
Ph	92	>95
CH_2Ph	13	61
C_6H_{11}	58	60

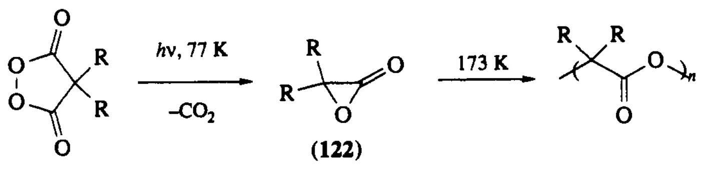
Cycloacylation

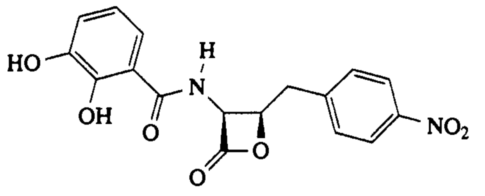


Cycloalkylation

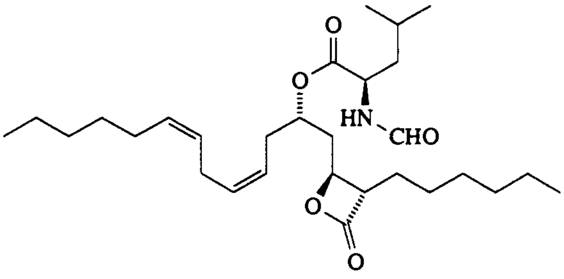




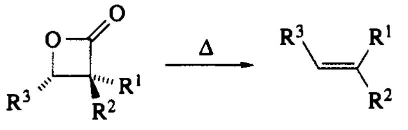




(123)

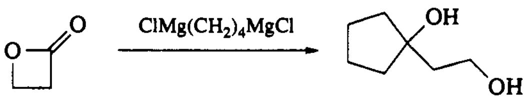


(124)

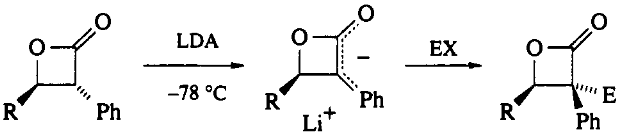


(125)

(40)

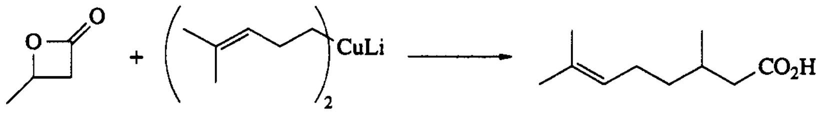


(41)



(126)

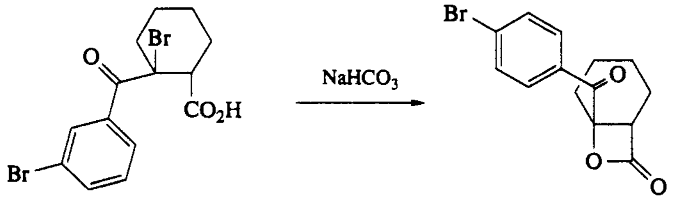
(42)



(43)

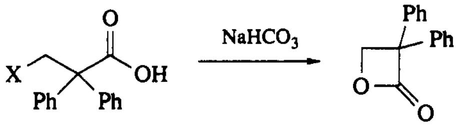
2.2.2.2.1 β-Lactones via cycloalkylation

It has been shown that β-bromocarboxylic acids like (**127**) and (**129**) cyclize with mild base to form β-lactones like (**128**; equation 44)[98] and (**130**; equation 45).[99] The reaction is mostly accompanied by fragmentation to the alkene, as shown by the conversion of (**131**) into (**132**) and (**133**) (equation 46).[100] In this particular example, only *trans*-β-lactone (**132**) was found, inspite of the *threo* configuration of (**131**), which indicates an S_N1- rather than an S_N2-type cyclization.



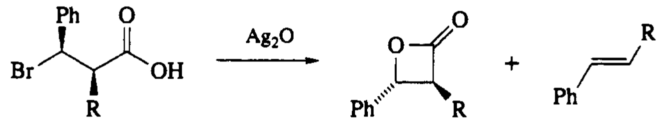
(127) **(128)**

(44)



(129) X = Cl, Br, I **(130)**

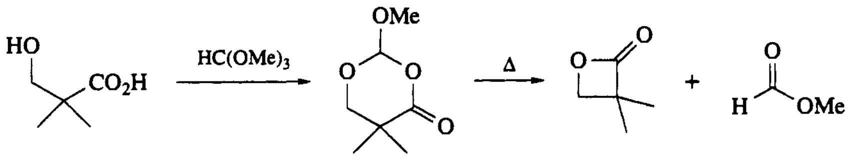
(45)



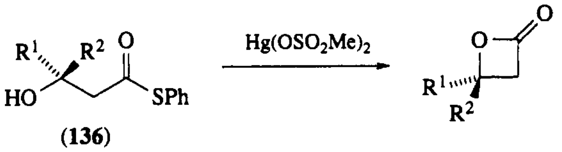
(131) R = Me, Et **(132)** 17% **(133)** 40% (46)

2.2.2.2.2 *β-Lactones* via *cycloacylation*

Cycloacylation of β-hydroxy carboxylic acids can be accomplished with various dehydrating agents. For example **(134)** has been converted into the δ-lactone acetal **(135)** with orthoformate. On heating, **(135)** loses methyl formate under formation of the β-lactone (equation 47).[101] β-Hydroxy thiol esters like **(136)** have been reported to form β-lactones under retention of configuration in high yields (equation 48).[102]

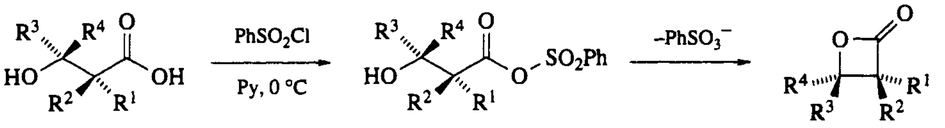


(134) **(135)** (47)



(136) (48)

The method of choice, however, is the reaction of **(137)** with benzenesulfonyl chloride in pyridine at low temperature (equation 49). This conversion proceeds *via* **(138)** with strict retention of configuration and is compatible with a variety of substituents (Table 10).[103] However, it fails for small substituents **(137l** and **137m)** in which case only polyesters are formed. In cyclic systems like **(140)** β-lactone formation cannot occur if the carboxy and the hydroxy functions are *trans* (equation 50) In this case the di-

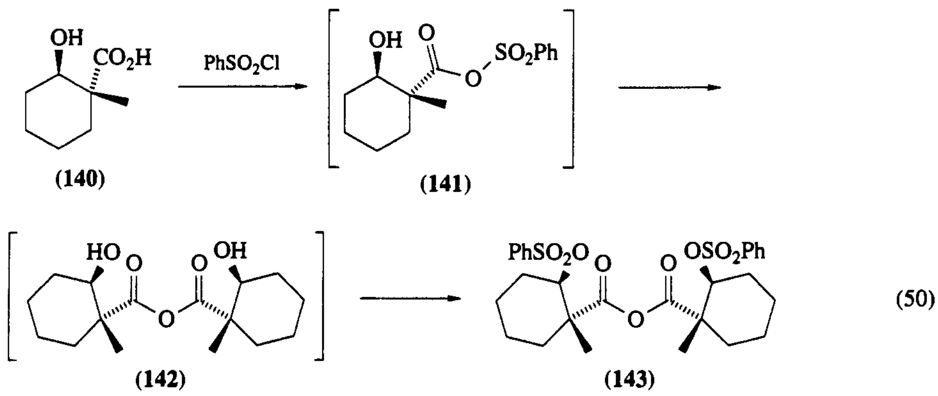


(137) **(138)** **(139)** (49)

Table 10 β-Lactones from **(137)** and Benzenesulfonyl Chloride (equation 49)

Compound	*R*^{1}	*R*^{2}	*R*^{3}	*R*^{4}	*Yield (%)*
(137a)	Me	OMe	Pr^n	Pr^n	77
(137b)	Me	Me	H	Ph	95
(137c)	H	Bu^t	Ph	Ph	100
(137d)	Bu^t	H	H	Ph	88
(137e)	Bu^t	H	Ph	H	73
(137f)	Me	H	H	Ph	81
(137g)	Me	H	Ph	H	15
(137h)	Ph	H	H	Bu^t	92
(137i)	Ph	H	Bu^t	H	85
(137j)	Ph	H	H	Me	15
(137k)	Ph	H	Ph	H	15
(137l)	Me	H	H	Me	—
(137m)	Me	H	H	Et	—
(137n)	Bu^t	H	H	2-Thienyl	83
(137o)	Bu^t	H	2-Thienyl	H	—

sulfonated anhydride (**143**) is formed in *ca.* 40% yield, presumably *via* (**142**) as an intermediate.[104] Alkene formation is the main reaction for systems with strongly electron-donating substituents in the β-position (*e.g.* **137a**). Presumably these β-lactones are unstable and eliminate carbon dioxide very rapidly.[105]

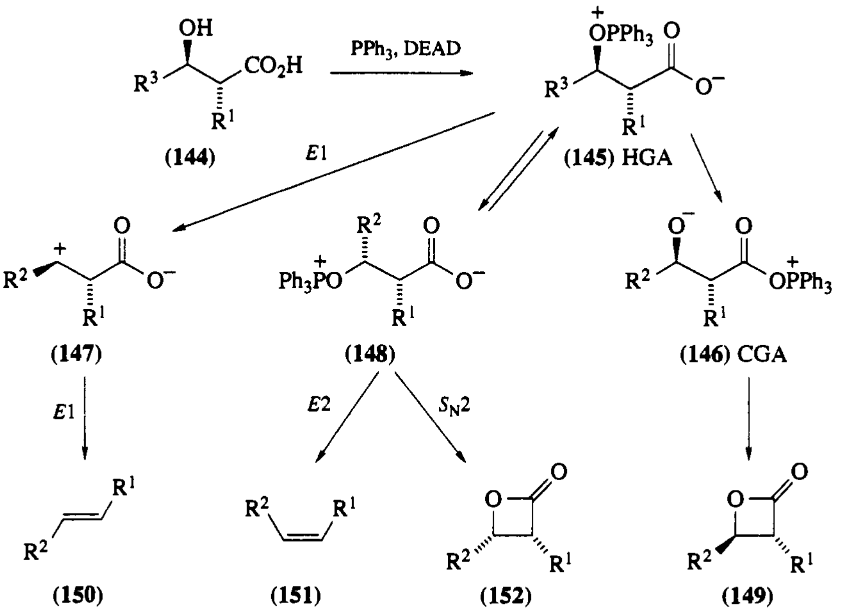


(50)

2.2.2.2.3 *β-Lactones from β-hydroxy carboxylic acids with HGA and CGA reagents*

(i) Mitsunobu conditions

Under Mitsunobu conditions ('*anti*') *threo*-hydroxy carboxylic acids (**144**) form (*Z*)- and (*E*)-alkenes (**150**) and (**151**) and *cis*- and *trans*-β-lactones (**152**) and (**149**) in various ratios, depending on R^1 and R^2 (Table 11). The mechanism (Scheme 3) involves a competition between the HGA and CGA intermediates (**145**) and (**146**). For R^2 with a high +M effect (*e.g.* Ph, 2-thienyl *etc.*), the zwitterion (**147**) also has to be considered. After rotation to (**148**), intermediate (**145**) gives rise to the products (**151**) and (**152**). *Via* (**146**) the lactone (**149**) is generated. It is obvious from Table 11 that only large R^1 and R^2 groups lead to CGA (**144d** and **144i**), whereas the rest prefer the HGA pathway.[106]

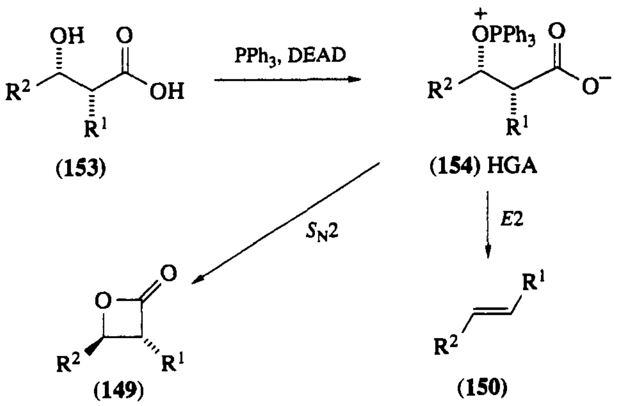


Scheme 3

Table 11 CGA *versus* HGA Reaction of *anti*-Acids (**144**) under Mitsunobi Conditions (Scheme 3)

Compound	R^1	R^2	*Yield (%)* *(150)*	*(151)*	*(152)*	*(149)*	*Total yield (%)*	*Prevailing mechanism*
(**144a**)	Ph	Me	—	88	12	—	85	HGA
(**144b**)	Ph	Et	—	83	17	—	82	HGA
(**144c**)	Ph	Pr^i	—	80	—	20	92	HGA
(**144d**)	Ph	Bu^t	—	—	—	100	92	CGA
(**144e**)	Me	Ph	11	63	36	—	83	HGA
(**144f**)	Et	Ph	17	60	23	—	87	HGA
(**144g**)	Pr^i	Ph	81	12	—	7	81	HGA
(**144h**)	Bu^t	Ph	66	—	—	34	92	HGA
(**144i**)	Bu^t	Bu^t	—	—	—	100	83	CGA

By contrast, ('*syn*') *erythro*-hydroxy carboxylic acids (**153**) react *via* HGA exclusively to form the (*E*)-alkene (**150**), along with minor amounts of *cis*-β-lactone (**149**) *via* (**154**) (Scheme 4 and Table 12).[107]



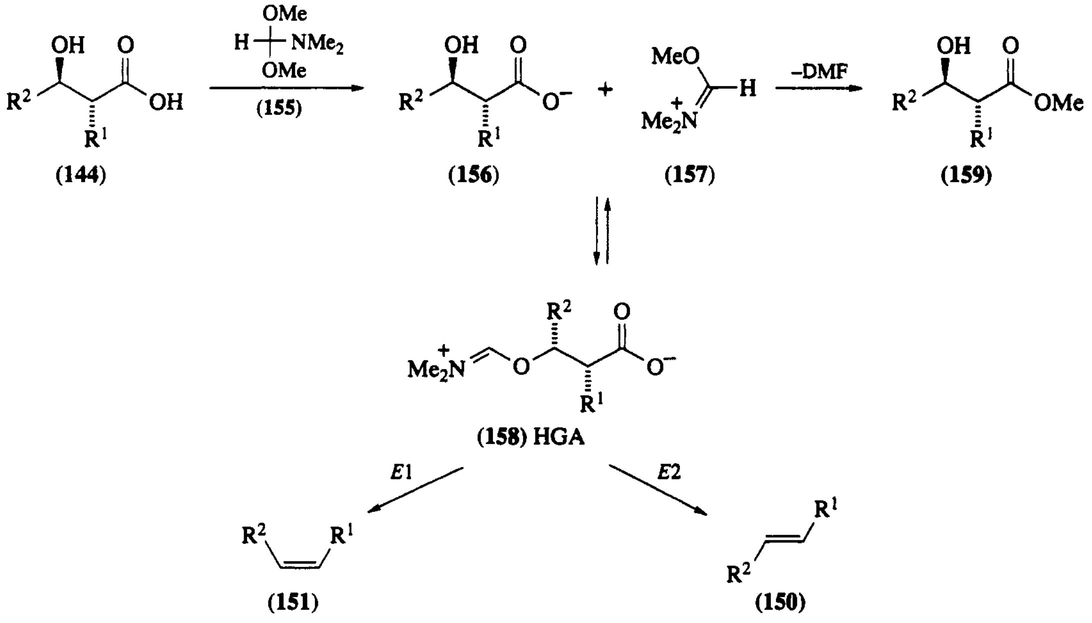
Scheme 4

Table 12 Product Ratios in the Reaction of (**153**) with DEAD/PPh_3 (Scheme 4)

Compound	R^1	R^2	*Yield (%)* *(149)*	*(150)*	*Total yield (%)*
(**153a**)	Ph	Me	8	92	79
(**153b**)	Ph	Et	—	100	82
(**153c**)	Ph	Pr^i	—	100	91
(**153d**)	Ph	Bu^t	—	—	—
(**153e**)	Me	Ph	25	75	87
(**153f**)	Et	Ph	24	76	83
(**153g**)	Pr^i	Ph	21	79	88
(**153h**)	Bu^t	Ph	—	100	90
(**153i**)	Ph	H	100	—	30

(ii) Vorbrüggen–Eschenmoser conditions

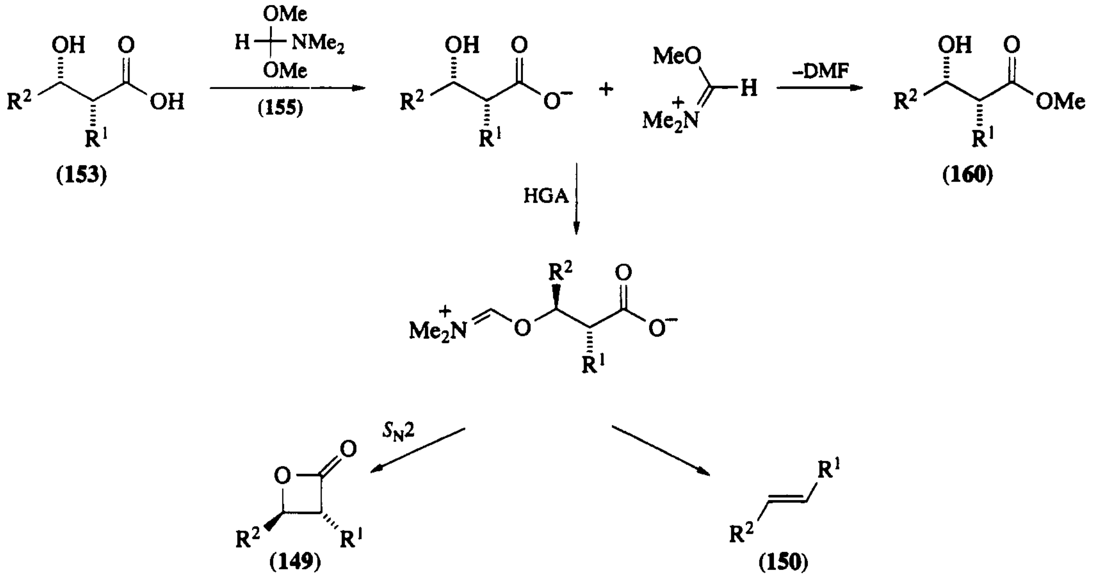
Threo-acids (**144**) react with DMF dimethyl acetal (**155**) at room temperature to give alkenes (**150**) and (**151**) along with the methyl ester (**159**) in varying ratios (Table 13). The mechanism (Scheme 5) suggests the initial formation of an ion pair (**156**) and (**157**), which either collapses to (**159**) (irreversibly) or (**158**) (reversibly). From (**158**) *E*1 and *E*2 fragmentations are possible, generating (**151**) and (**150**), respectively.[108] In general it may be stated that activating, *e.g.* aryl, substituents in the R^2 position are required for alkene formation. No β-lactones are formed from (**144**), quite in contrast to the '*erythro*' analogs (**153**) (Scheme 6 and Table 14), which react to (**149**), (**150**) and (**160**).[108] However, the overall yields of β-lactones (**149**) do not exceed 36% (**153g**).



Scheme 5

Table 13 Product Ratios in the Reaction of (**144**) with DMF Dimethyl Acetal (**155**; Scheme 5)

Compound	*R^1*	*R^2*	*Yield (%)* (**150**)+(**151**)	*Yield (%)* (**159**)	*Total yield (%)*
(**144a**)	Ph	Me	9	91	76
(**144c**)	Ph	Pr^i	<2	>98	75
(**144d**)	Ph	Bu^t	<2	>98	92
(**144e**)	Me	Ph	61	39	81
(**144g**)	Pr^i	Ph	91	9	88
(**144h**)	Bu^t	Ph	95	5	89
(**144j**)	Ph	2-Thienyl	>98	<2	75



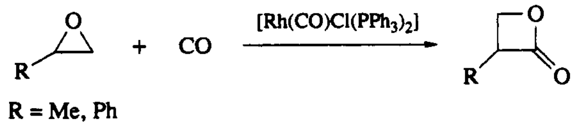
Scheme 6

Table 14 Product Ratios in the Reaction of (**153**) with DMF Dimethyl Acetal (**155**; Scheme 6)

Compound	R^1	R^2	*Yield (%)* (**160**)	*Yield (%)* (**149**)	(**150**)	*Total yield (%)*
(**153a**)	Ph	Me	41	16	43	75
(**153b**)	Ph	Et	35	10	55	72
(**153c**)	Ph	Pr^i	42	22	58	80
(**153d**)	Ph	Bu^t	29	22	71	85
(**153e**)	Me	Ph	<2	7	93	87
(**153f**)	Et	Ph	<2	15	85	82
(**153g**)	Pr^i	Ph	<2	40	60	90
(**153h**)	Bu^t	Ph	<2	<2	98	90

2.2.2.2.4 β-Lactones via *C—C connections*

Although C—C connecting reactions are discussed elsewhere in 'Comprehensive Organic Synthesis',[109] it may be mentioned that epoxides react regioselectively with carbon monoxide under rhodium catalysis (equation 51)[110] and benzyl bromides undergo carbonylation and subsequent lactonization under the influence of a Pd^{II} catalyst (equation 52).[111] The [2 + 2] cycloaddition of ketenes to carbonyl compounds, catalyzed by Lewis acids, is a familiar route to β-lactones (equation 53).[112]



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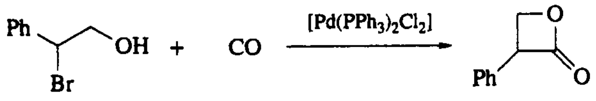

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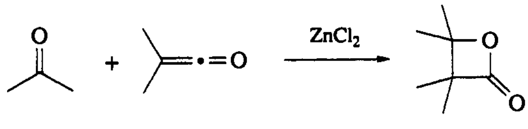


(53)

2.2.2.3 Synthesis of γ-Lactones

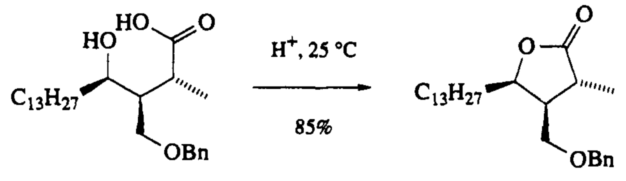
γ-Lactones are among the most abundant substructures in natural products.[113] This fact had kindled enormous activity in the field of γ-lactone synthesis.[114] γ-Lactones have been prepared by direct cycloacylation of γ-hydroxy acids, either as such or generated as transient intermediates, and by cycloalkyl ation, either of γ-halocarboxylates or of β,γ- or γ,δ-unsaturated acids by additions to the double bond.

2.2.2.3.1 γ-Lactones via *direct cycloacylation of γ-hydroxy acids or derivatives*

As indicated in equation (54) γ-lactones may be generated from γ-hydroxy acids, esters or amides, generally under acid catalysis. For esters and amides also base catalysis is appropriate. The rate of cyclization varies with the degree of substitution along the carbon chain. Bulky substituents, particularly if they have to be arranged *cis* to each other during ring formation, retard the reaction. For example (**161**) takes several days at 25 °C (equation 55),[115] whereas **(162)** only requires 14 h to form the lactone (equation 56).[116]

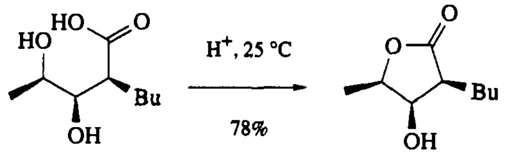
$X = OH, OR, NR_2$

(54)



(161)

(55)

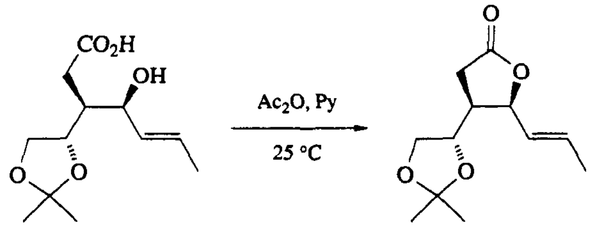


(162)

(56)

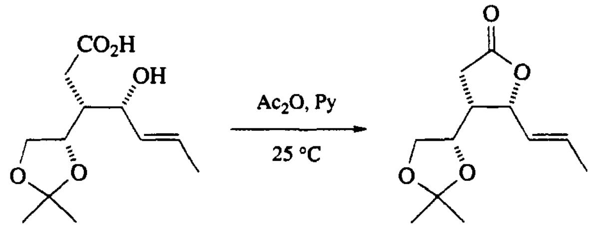
The different rates of cyclization of the four diastereomeric hydroxy acids **(163)**, **(165)**, **(167)** and **(169)** have been utilized for separating **(163)** and **(165)** from **(167)** and **(169)**. On treatment with dilute sulfuric acid in acetonitrile **(167)** and **(169)** spontaneously form the lactones **(168)** and **(170)**, whereas **(163)** and **(165)** remain unchanged and can be cyclized only by treatment with acetic anhydride in pyridine (equations 57–60).[117]

In cyclic systems like **(171)**, **(173)**, **(175)** and **(177)** strain arguments are even more important. All four acids form the lactones only on heating to >130 °C, but the yields reflect the highly different ring strain encountered: the most favorable diequatorial lactone **(172)** is formed quantitatively (equation 61), whereas the strained diastereomers **(174)**, **(176)** and **(178)** form reluctantly (equations 62–64).[118] The ring clo-



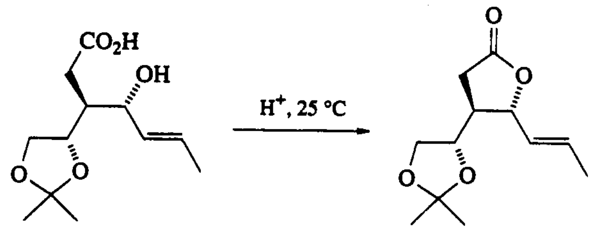
(163) **(164)**

(57)

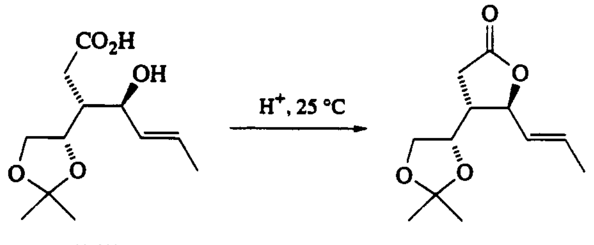


(165) **(166)**

(58)



(167) **(168)** (59)

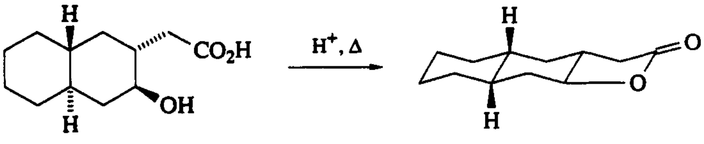


(169) **(170)** (60)

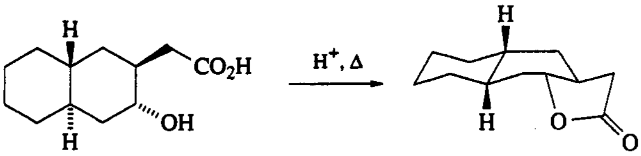
sure of **(179)** to the bridged lactone **(180)** requires prolonged heating with acetic anhydride (equation 65).[119]

Lactonization may sometimes be combined with deketalization, as shown by equation (66).[120] The γ-lactone is formed in preference to the δ-lactone, in analogy to related observations.[121] Transketalization is also shown by **(183)**, which forms the β-anomer of **(184)** with >10:1 selectivity (equation 67).[59]

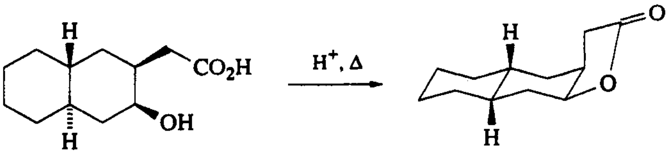
The examples in equations (68–70) demonstrate that unsaturated γ-lactones are also accessible by the usual cyclization. The case of **(185)** shows that again the five-membered lactone is preferred.[122] The (*E*)-



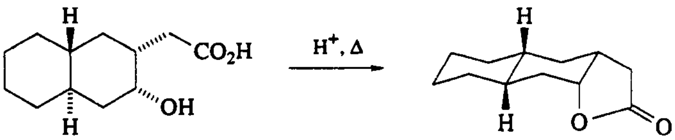
(171) **(172)** 97% (61)



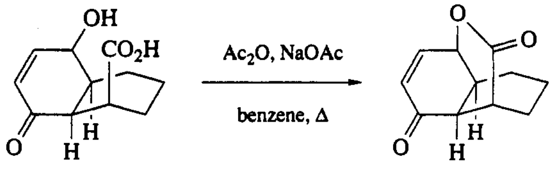
(173) **(174)** 73% (62)



(175) **(176)** 75% (63)

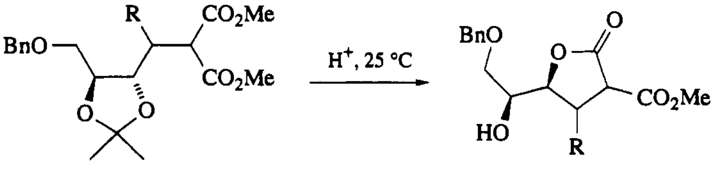


(177) **(178)** 40% (64)



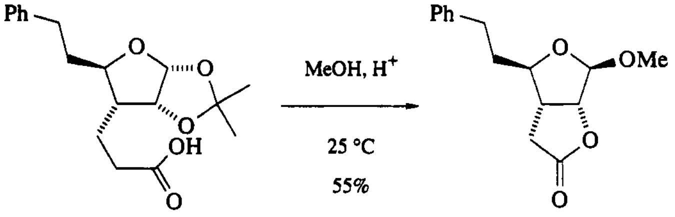
(179) **(180)** 66%

(65)



(181) **(182)**

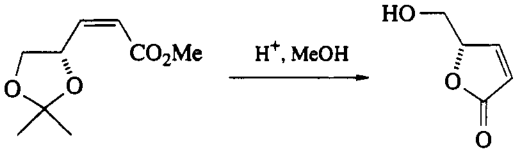
(66)



(183) **(184)**

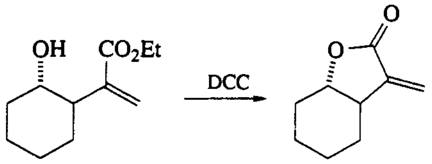
(67)

isomer of (**185**) does not cyclize, but undergoes deketalization to form the diol ester instead.[120] The DCC-mediated cyclization of (**187**) to (**188**) is noteworthy, as it starts from the ester and obviously proceeds under HGA.[123]



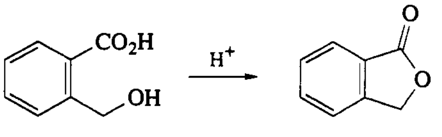
(185) **(186)**

(68)



(187) **(188)**

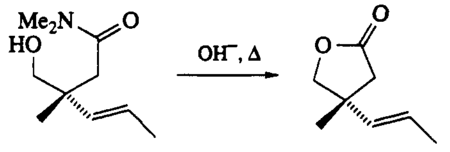
(69)



(189) **(190)**

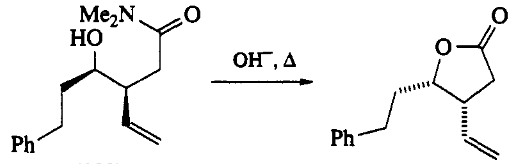
(70)

Equations (71) and (72) illustrate the use of hydroxy amides as γ-lactone presursors. Prolonged heating with strong base and subsequent acidification produces (**192**) and (**194**) in almost quantitative yields.[124]



(191) (192)

(71)

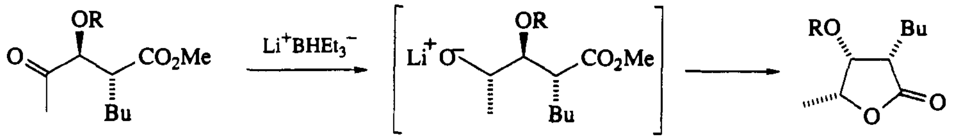


(193) (194)

(72)

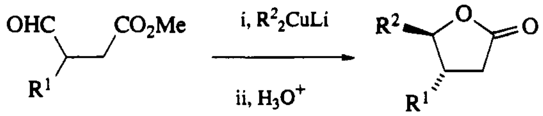
2.2.2.3.2 *γ-Lactones by* in situ *cyclization of γ-hydroxy carboxylic acid intermediates*

In this section sequences are described in the course of which γ-hydroxy carboxylic acid derivatives are formed and immediately cyclized to γ-lactones. For instance, γ-keto ester (**195**) is reduced with 'super hydride' to give the alkoxide ester (**196**) with 7:1 selectivity (equation 73); (**196**) cannot be isolated, due to the rapid formation of lactone (**197**).[125] Similarly, cuprates add to γ-aldehydo esters with high selectivity to form *trans*-4,5-disubstituted γ-lactones after acidification (equation 74).[126]



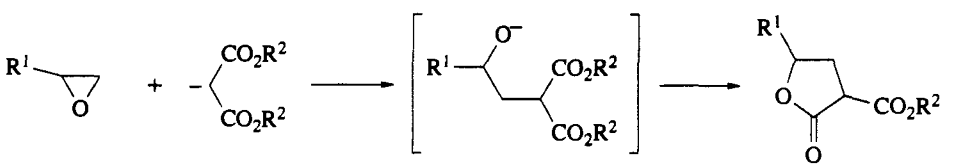
(195) R = COBu^i (196) (197)

(73)



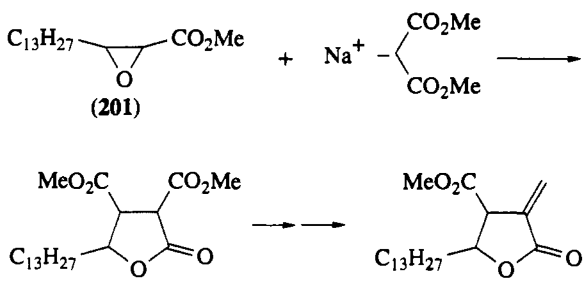
(74)

Another possibility is the addition of malonate anions to epoxides (equation 75), which, *via* the alkoxide ester (**199**), deliver the lactone ester (**200**) immediately.[127] This concept has been used in the non-stereocontrolled synthesis of protolichesterinic acid ester (**203**) from (**201**) *via* (**202**; equation 76).[128]



(198) (199) (200)

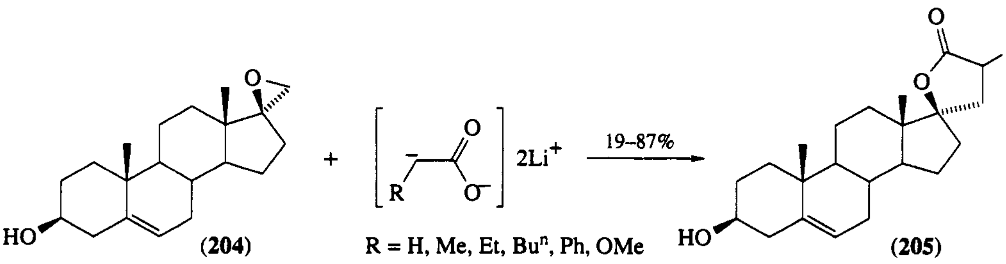
(75)



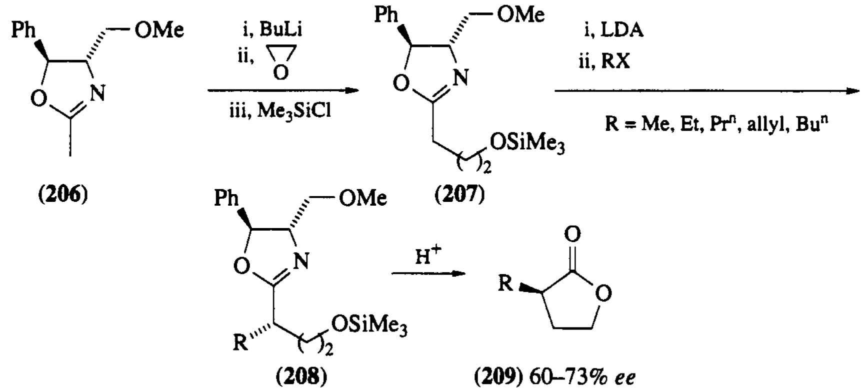
(201) (202) (203)

(76)

Instead of malonic esters the lithium dianions of carboxylic acids may also be used, as shown by equation (77).[129] Enantioselective γ-lactone formation has been achieved by Meyers as a ramification of his well-known oxazoline alkylations. As illustrated by equation (78), (**206**) is deprotonated and alkylated with ethylene oxide to give (**207**), which in a second alkylation step furnishes (**208**) diastereoselectively. The oxazoline ring so far has served as a carboxy synthon. Unmasking with acid immediately generates the α-substituted optically active γ-lactone (**209**).[130]

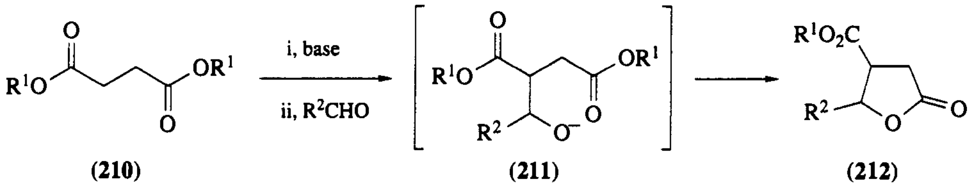


(77)



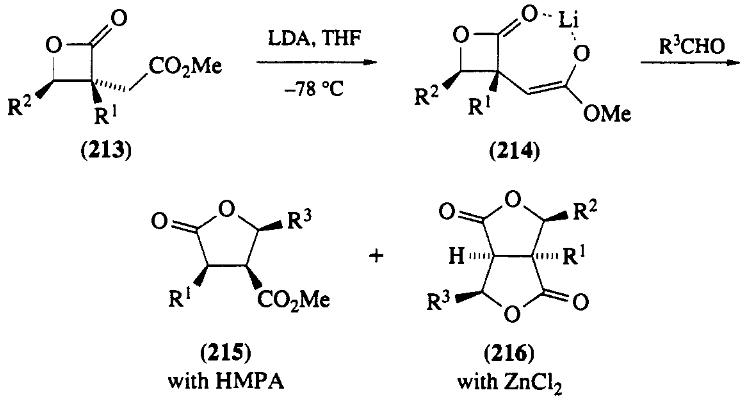
(78)

Instead of epoxides carbonyl compounds may be used as electrophiles to generate the γ-hydroxy carboxylic acid intermediate. In the classical Stobbe reaction (equation 79) succinic esters are deprotonated and treated with aldehydes or ketones to form, *via* the unstable adduct (**211**), the paraconic ester (**212**).[131]



(79)

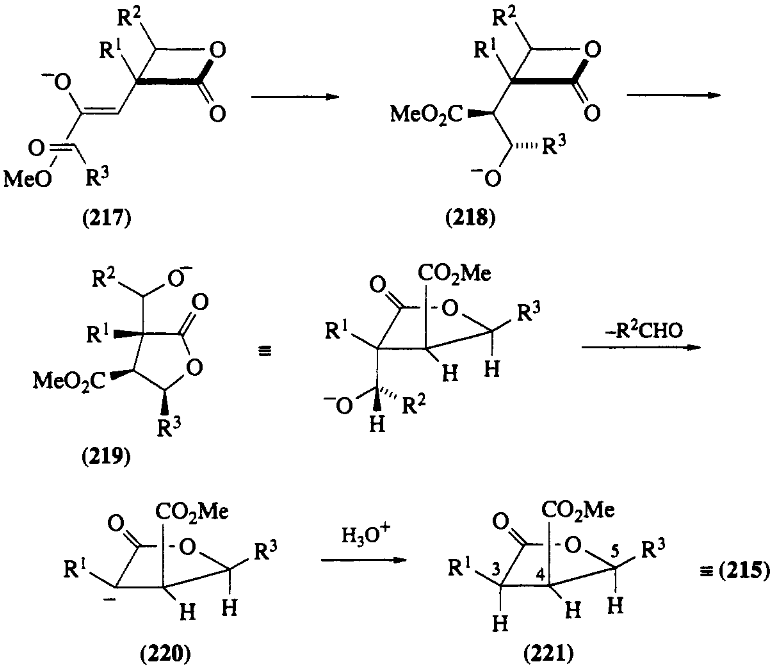
A more recent and stereocontrolled version of the Stobbe reaction is shown in equation (80). β-Lactone ester (**213**) is deprotonated to the enolate (**214**), which adds aldehydes to give either monocyclic



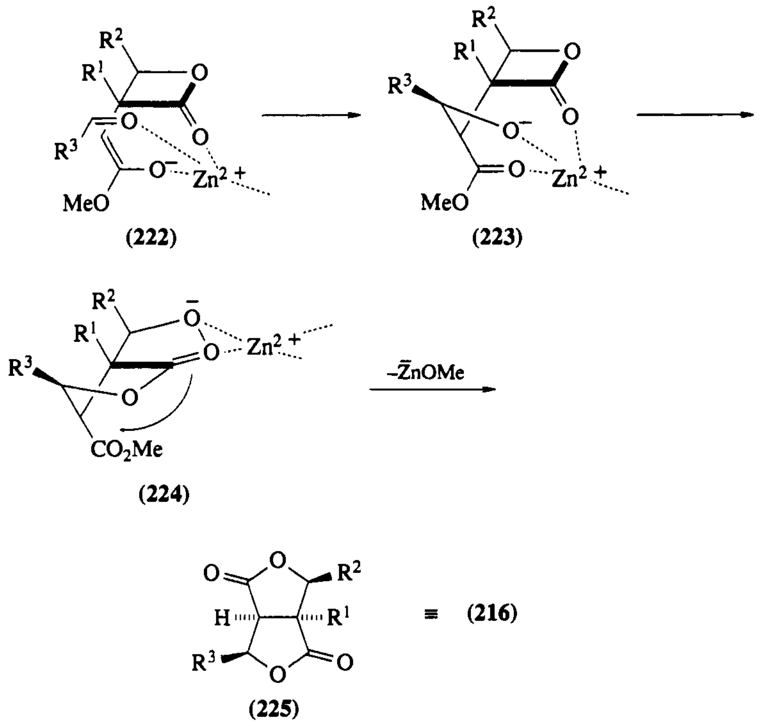
(80)

paraconic esters (**215**) or bicyclic γ-lactones (**216**). In the presence of HMPA (**215**) is formed preferentially, and in the presence of zinc(II) chloride (**216**) is formed (preferentially), in both cases with a high degree of stereocontrol.

A mechanistic rationalization is given in Scheme 7 (HMPA additive) and Scheme 8 ($ZnCl_2$ additive) respectively. In both Schemes analogous adducts (**218**) and (**223**) are formed stereoselectively, which rearrange to the γ-lactone alkoxides (**219**) and (**224**). In the presence of HMPA, retroaldol cleavage to



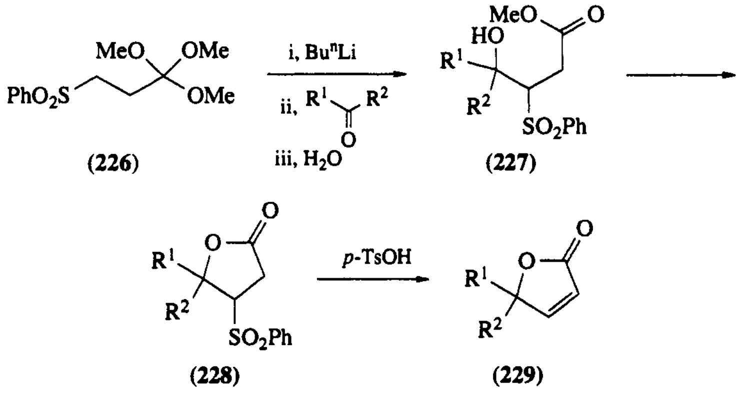
Scheme 7



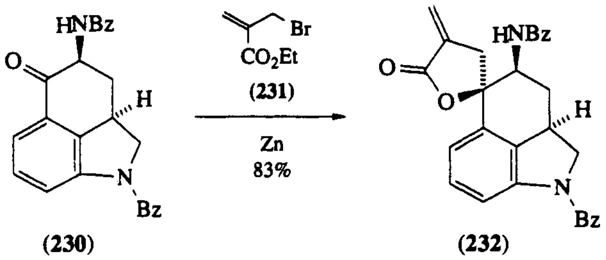
Scheme 8

(**220**) occurs, and after protonation (**221**) is formed. In the presence of the chelating Zn ion, by contrast, a second lactone ring is closed between the ester group and the alkoxide anion, generating (**225**).[125]

Similar condensations can be accomplished with other types of stabilized carbanions, *e.g.* sulfonyl anions, as illustrated by equation (81). The resulting sulfonyl lactone (**228**) eliminates sulfinic acid on treatment with *p*-TsOH to furnish the α,β-unsaturated system (**229**).[132] Spirolactonization is the result of the Reformatsky reaction of ester (**231**) with cyclic ketones.[133] In equation (82), this reaction is applied to the synthesis of the lysergic acid precursor (**232**), which is formed stereoselectively from (**230**).[134]



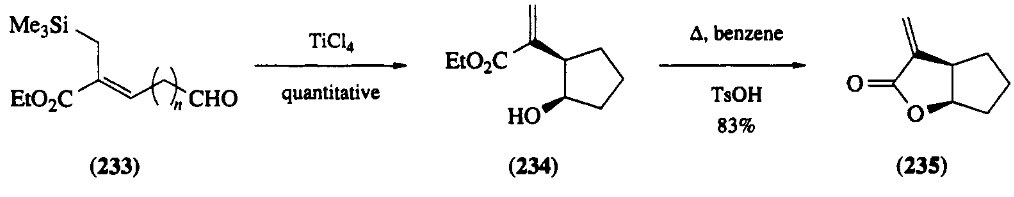
(81)



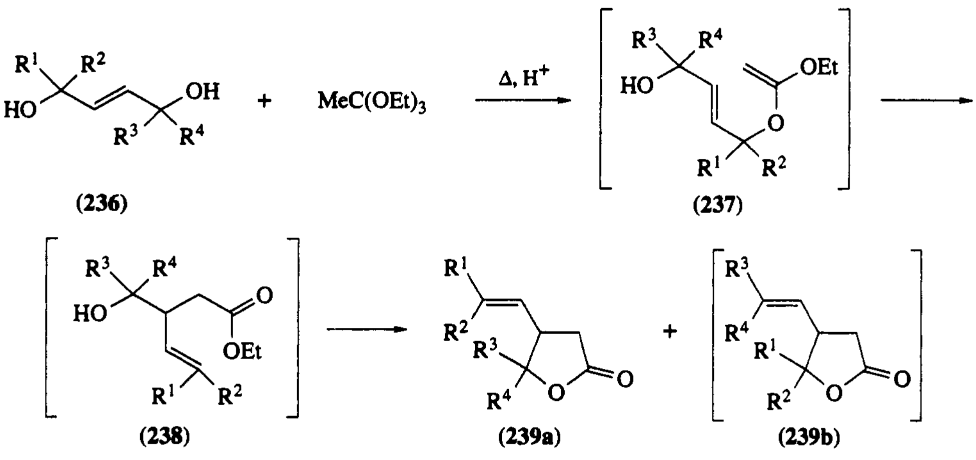
(82)

A carbocyclic ring and a γ-lactone may be created in a concise manner by using the Sakurai cyclization of (**233**) to (**234**) and closing the lactone in the usual manner under acid catalysis (equation 83).[135] The C—C connection required to generate the γ-hydroxy carboxylic acid may be performed by means of a pericyclic arrangement. For instance, the allylic alcohol (**236**) reacts with an orthoester to form, *via* (**237**), the hydroxy ester (**238**), which cyclizes under the conditions to (**239a**). For unsymmetrically substituted alcohols (**236**), the regioisomer (**239b**) is also formed in comparable amounts (equation 84).[136]

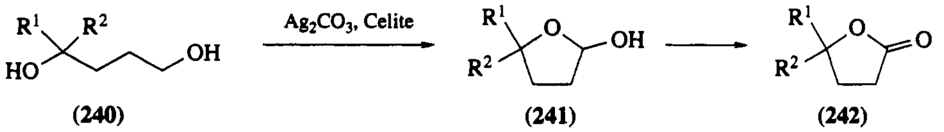
γ-Lactones may be the result of an oxidative cyclization of 1,4-butanediol derivatives (**240**). On treatment with silver carbonate on Celite (Fetizon's reagent) (**242**) is formed, presumably *via* lactol (**241**) (equation 85).[137] A lactol–lactone oxidation is the ultimate step in a rather complex sequence (equation 86). Cyclopropane ester (**243**) may undergo aldol-type additions to give (**244**), which on fluoride treatment opens the cyclopropane ring and gives first the aldehyde (**245**) and then the lactol (**246**). PCC oxidation leads eventually to the paraconic ester (**247**). Although a high degree of substitution is available, the stereocontrol is low.[138]



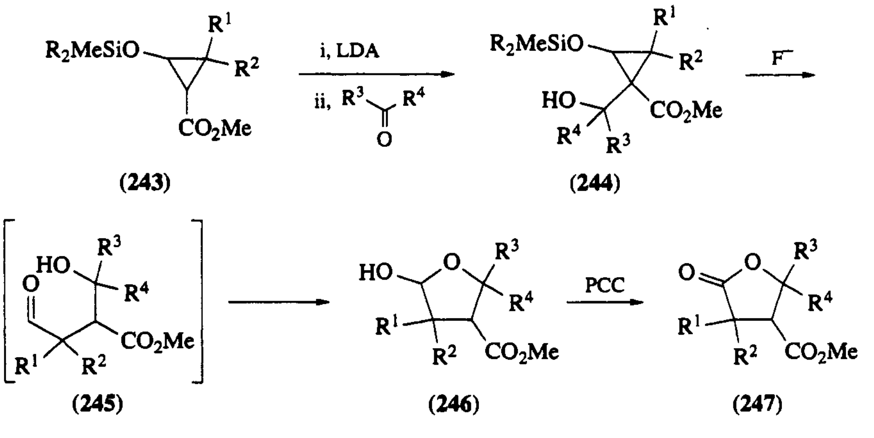
(83)



(84)



(85)



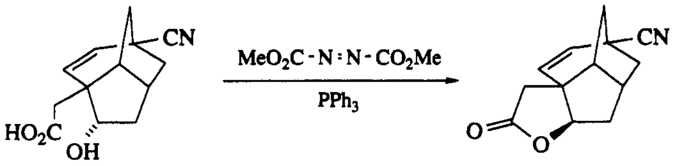
(86)

2.2.2.3.3 γ-Lactones via cycloalkylation

There are numerous variations of cycloalkylating lactone formations. They may be classified into HGA ring closure of γ-hydroxy acids or esters, S_N2 ring closure of γ-bromocarboxylates, lactonizations under participation of alkenic double bonds or γ-lactone formation by carbenium rearrangements.

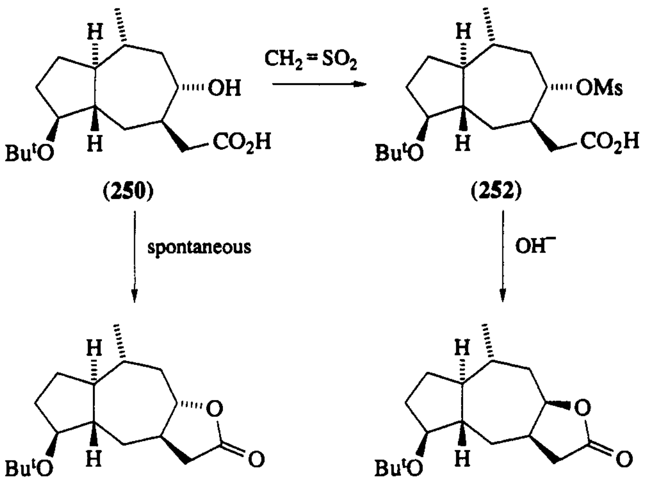
(i) HGA lactonization of γ-hydroxy acids

Such cases are extremely rare, as the normal mode of action involves CGA mechanisms. However, Trost *et al.* have shown (equation 87) that in cases where the normal CGA reaction is prohibited due to ring strain, HGA ring closure under Mitsunobu conditions may be accomplished, *e.g.* from (**248**) to (**249**).[139] In contrast, hydroxy acid (**250**) has been found to undergo CGA ring closure to (**251**) spontaneously, as well as under Mitsunobu treatment. However, HGA reactions can be accomplished (equation 88) by preparing the mesylate (**252**) with sulfene, and by subsequent S_N2 cyclization with base to form (**252**).[140] An acid-catalyzed HGA lactonization has been reported for the hydroxypyrrolidines (**254**) and (**256**), both of which, under acid treatment, form the lactone (**255**), presumably *via* (**257**; equation 89).[141]



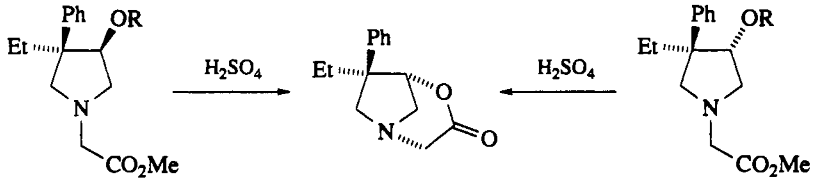
(248) **(249)** 92%

(87)



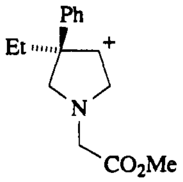
(251) **(253)**

(88)



(254) R = H, Ac **(255)** **(256)**

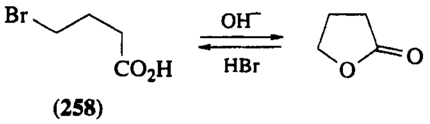
(89)



(257)

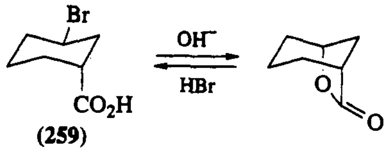
(ii) γ-Bromo carboxylates

γ-Lactones may be obtained from (**258**) with strong base (equation 90). The reaction may be reversed by ring opening with hydrobromic acid, which is by far the more important process. The inversion of configuration on ring closure is demonstrated by means of the cyclic derivative (**259**; equation 91).[142]



(258)

(90)

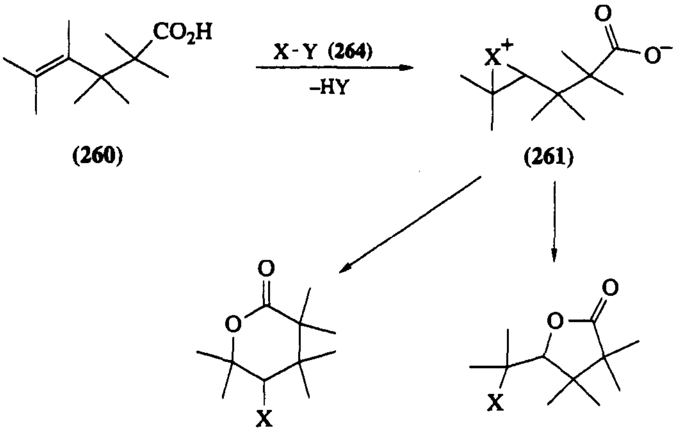


(259)

(91)

(iii) γ-Lactonization of unsaturated carboxylic acids[143]

Usually γ,δ-unsaturated acids (**260**) are employed in these lactonizations. The initial step involves an electrophilic attack at the double bond, either by a proton or a reagent X—Y (**264**). An activated species (**261**) is thus generated, suitable for the nucleophilic addition of the carboxy group, which in principle may close to a six- or five-membered lactone ring (**263** or **262**; equation 92). Normally, (**262**) is preferred on the basis of vector approach analysis.[144]

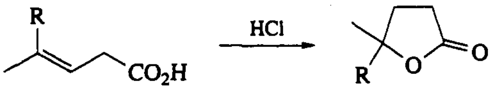


(260) **(261)**

(263) **(262)**

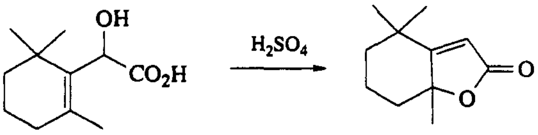
(92)

Equations (93–96) describe proton-catalyzed lactonizations. One can see that even for the β,γ-unsaturated acids (**265**)[145] and (**267**)[146] the γ-lactone prevails; whether this is by kinetic or thermodynamic con-



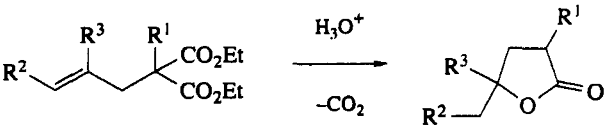
(265) **(266)**

(93)



(267) **(268)**

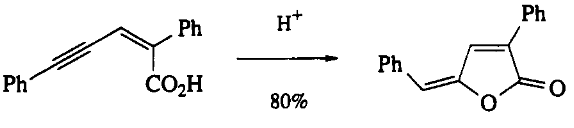
(94)



(269) **(270)**

$R^1 = H, Bu; R^2 = H, Bu, C_5H_{11}; R^3 = H, Me$

(95)

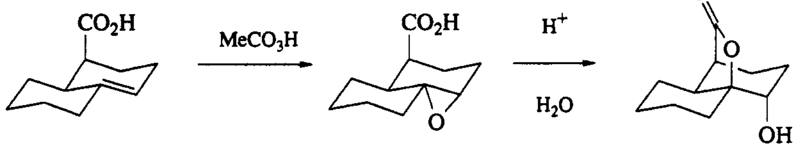


(271) **(272)**

(96)

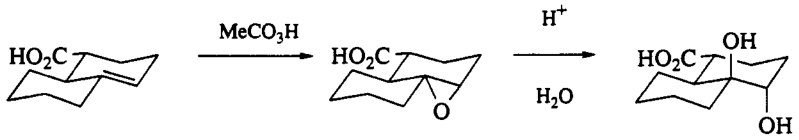
trol remains unclear. The malonic esters (**269**)[147] are decarboxylated after lactonization. The enyne acid (**271**) is lactonized at the triple bond without affecting the alkenic moiety (equation 96).[148]

Hydroxylactonizations (equations 97–99) involve the formation of a stable and, in general, stereochemically defined epoxide intermediate with peroxy acids. In an ensuing step these epoxides are cyclized with acid catalysis under the participation of the carboxylic group. If steric reasons prohibit ring closure, as in equation (98), the diol acid (**278**) is formed instead of the hydroxy lactone (**275**).[149] Equation (99)[150] shows an example for the stereocontrol of the epoxidation step by an axially oriented carboxy group, which is then in an appropriate position to close the lactone ring (**281**).



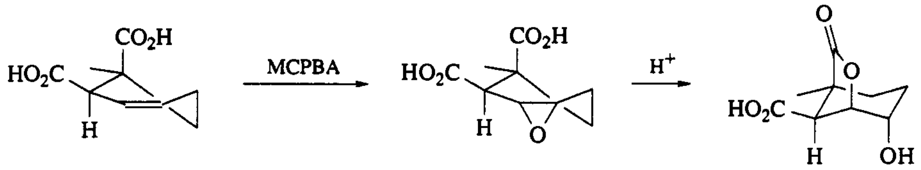
(273) **(274)** **(275)**

(97)



(276) **(277)** **(278)**

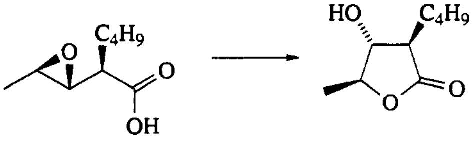
(98)



(279) **(280)** **(281)**

(99)

Equation (100)[116] illustrates the lactonization of a β,γ-epoxy acid. Only the γ-lactone (**283**) is formed, with inversion of configuration.

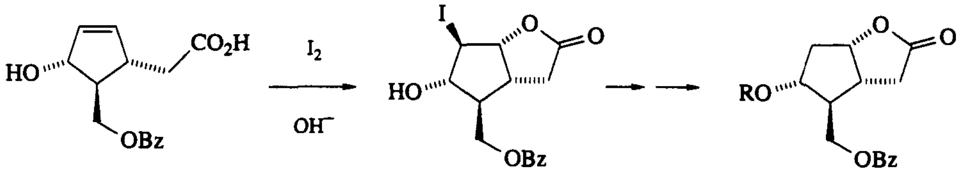


(282) **(283)**

(100)

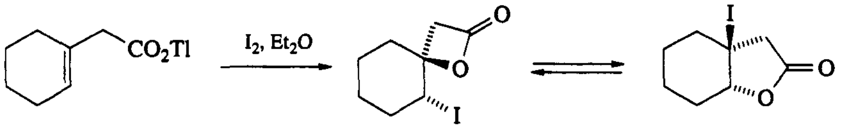
Halolactonizations have been used extensively for achieving high degrees of functionalization in a regio- and stereo-controlled manner.[151] The conversion of (**284**) into (**285**; equation 101)[152] is a key step in Corey's prostaglandin synthesis to prepare the central intermediate (**286**). For β,γ-unsaturated acids like (**287**) the β-lactone (**288**) is formed under kinetic control, which then equilibrates to the γ-lactone isomer (**289**; equation 102).[153]

In acyclic systems like (**290**) the facial selectivity of the double bond addition may be directed by a free OH function (Scheme 9).[154] It can also be shown that the regiocontrol depends on the reagent. Mercurilactonizations (equation 103)[155] are related to halolactonizations. The C—Hg bond may be cleaved reductively by a radical process.



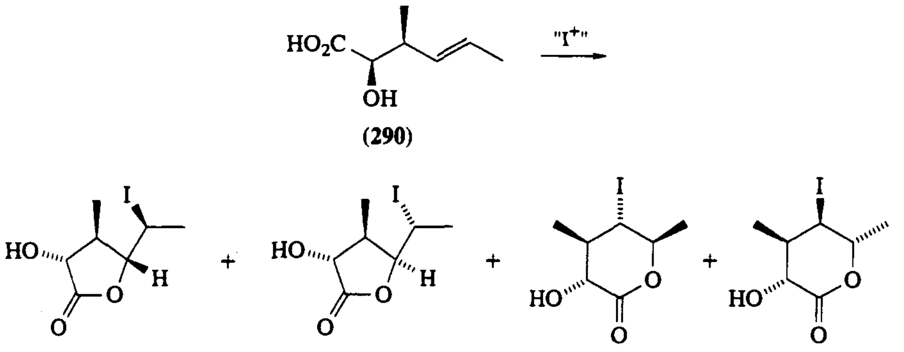
(284) **(285)** **(286)**

(101)



(287) **(288)** **(289)**

(102)

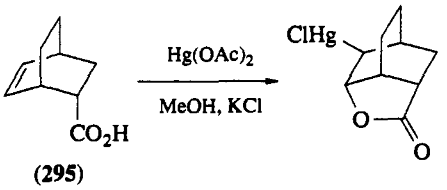


(290)

(291) **(292)** **(293)** **(294)**

I^+	*(291)*	:	*(292)*	:	*(293)*	:	*(294)*
NIS, $CHCl_3$	2	:	2	:	3	:	1
I_2, $CHCl_3$	>20	:	1	:	0	:	0

Scheme 9

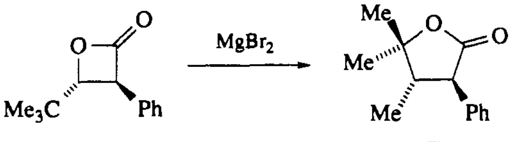


(295)

(103)

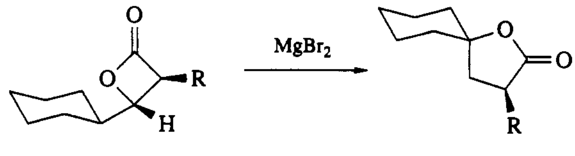
(iv) γ-Lactones via *rearrangements*

Under $MgBr_2$ catalysis β-lactones like (**296**) rearrange to γ-lactones (**297**) under dyotropic migration of an alkyl or hydrogen substituent (equation 104).[156] The stereochemistry as shown in the stereoformulae (**302**) and (**303**) requires an antiperiplanar arrangement of the migrating groups. In cyclic systems spiroannulation and angular annulation may be achieved, depending on the ring sizes (equations 105 and 106).[157]



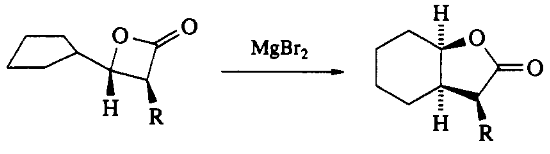
(296) **(297)**

(104)



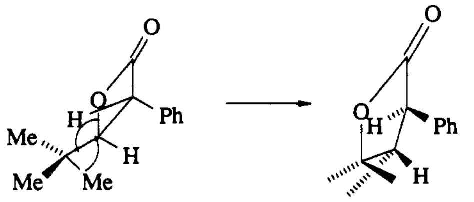
(298) **(299)**

(105)



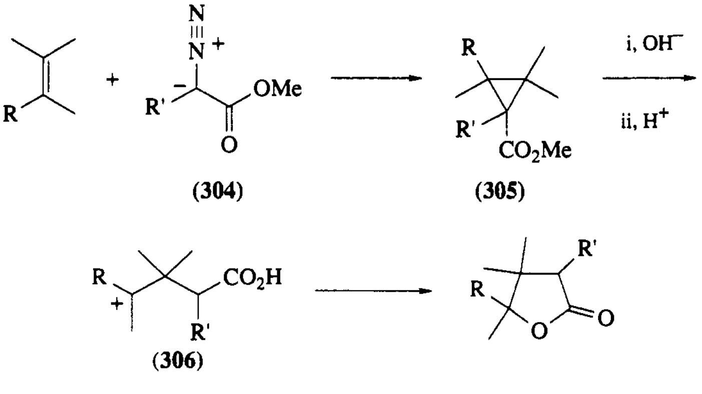
(300) R = Ph, SPh, OPh **(301)**

(106)



(302) **(303)**

An interesting and potentially useful sequence is shown in equation (107). Cyclopropane esters (**305**) may be prepared by the addition of diazo esters (**304**) to double bonds under elimination of nitrogen. After saponification the acid is *O*-protonated to open the cyclopropane ring, and the resulting carbenium ion (**306**) is trapped by lactonization. In effect a γ-lactone has been annulated to a double bond in a regiodefined manner.[158-160] Examples are given in Scheme 10. A related reaction involves the conversion of the cyclopropane ester (**307**) into the lactone (**308**; equation 108).[161]



(304) **(305)**

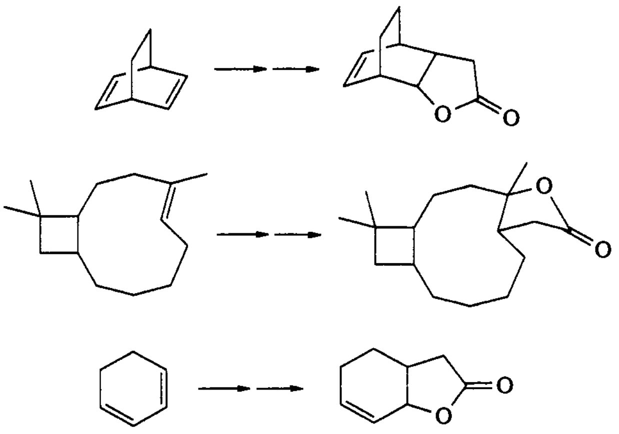
(306)

(107)

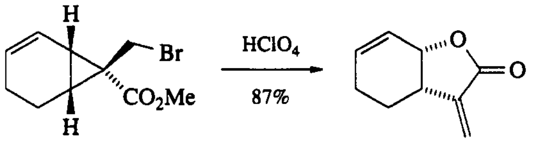
2.2.2.3.4 γ-*Lactones* via *carbonylation of homoallylic alcohols*

It has been shown recently[162] that homoallylic alcohols (**309**) undergo regiocontrolled carbonylation–lactonization to form (**310**) or (**311**) in good yield (equation 109). In the reaction of *cis*-3-hexenol, (**315**) is formed as a side product to (**313**), presumably *via* the isomerization of intermediate (**312**) to (**314**) (Scheme 11).

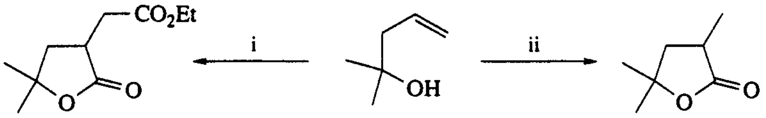
A direct way to α,β-unsaturated γ-lactones involves the Pd-catalyzed carbonylation of *cis*-vinyl iodides (**316**; equation 110).[163] In a similar way *exo*-methylene lactones[319] may be prepared from the alkynols (**318**; equation 111).[164]



Scheme 10

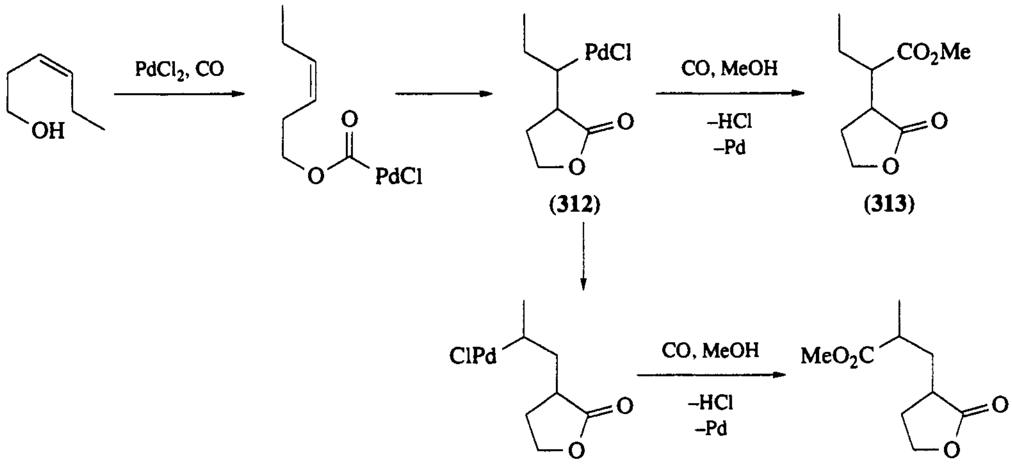


(307) (308) (108)



(310) (309) (311) (109)

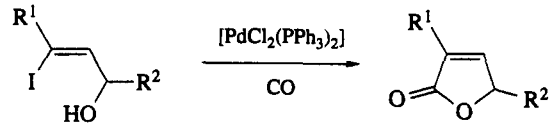
i, $PdCl_2$, $CuCl_2$, CO, $MeC(OEt)_3$, MeOH, propylene oxide; ii, $PdCl_2$, $CuCl_2$, CO, HCl



(312) (313)

(314) (315)

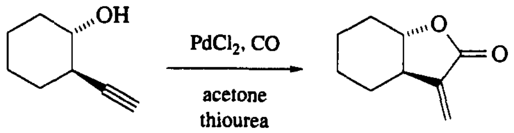
Scheme 11



(316) (317)

R^1 = H, Me, Ph; R^2 = H, Me, Ph; 46–100%

(110)

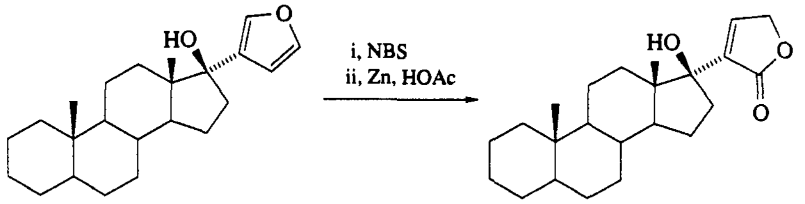


(318) (319)

(111)

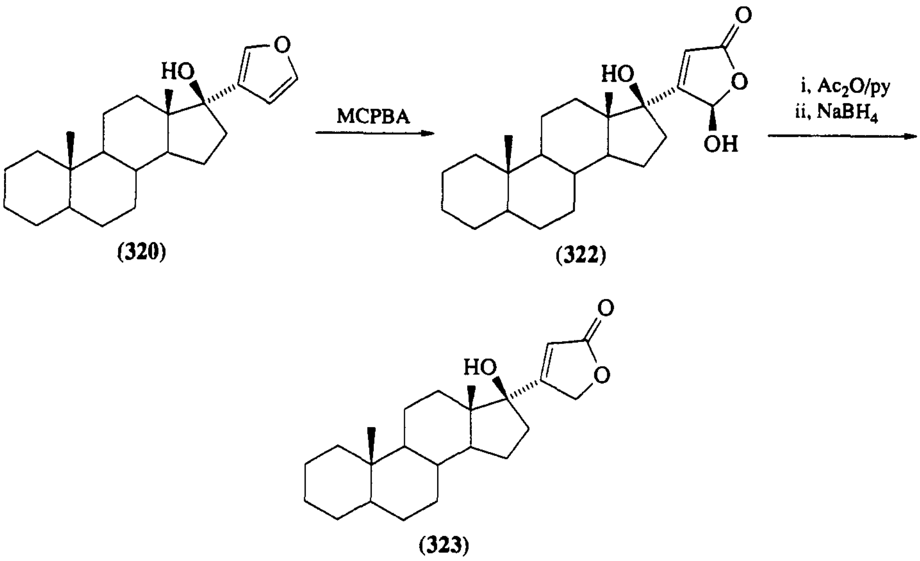
2.2.2.3.5 *γ-Lactones from furans*

A fundamentally different route to unsaturated lactones involves the oxidation of furanes (*e.g.* **320**) with NBS and subsequent debromination with Zn to give the butenolide (**321**; equation 112). The alternative regioisomer (**323**) may be prepared by using MCPBA as the oxidant to furnish the hydroxy lactone (**322**), which is then reduced to (**323**; equation 113).[165]



(320) (321)

(112)



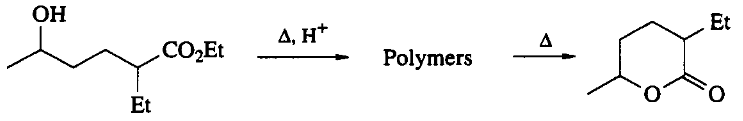
(320) (322)

(323)

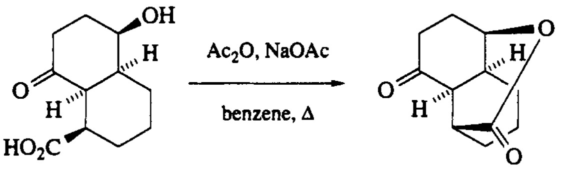
(113)

2.2.2.4 Synthesis of δ-Lactones

The methods applied for the synthesis of δ-lactones are very similar to those described for γ-lactones. In general, the tendency to form a six-membered ring is slightly lower than that for γ-lactonization. This is illustrated by equation (114); δ-hydroxy esters polymerize on acid treatment. Depolymerization takes place on heating, and the δ-lactone is formed.[166] Strained δ-lactones may be closed using acetic anhydride activation (**324**; equation 115),[119] whereas transannulations to decalin systems readily occur on heating (equation 116).[118] δ-Lactones can be efficiently prepared by glycol cleavage of 1,2,6-triols (**326**; equation 117). The lactol (**327**) is oxidized to (**328**) with PCC.[167]

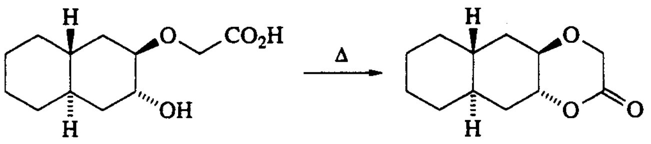


(114)



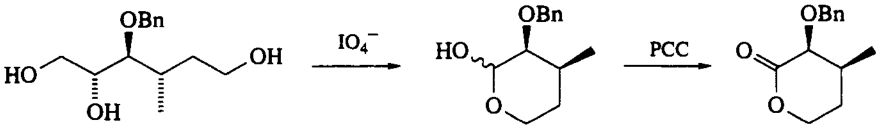
(115)

(324)



(116)

(325)

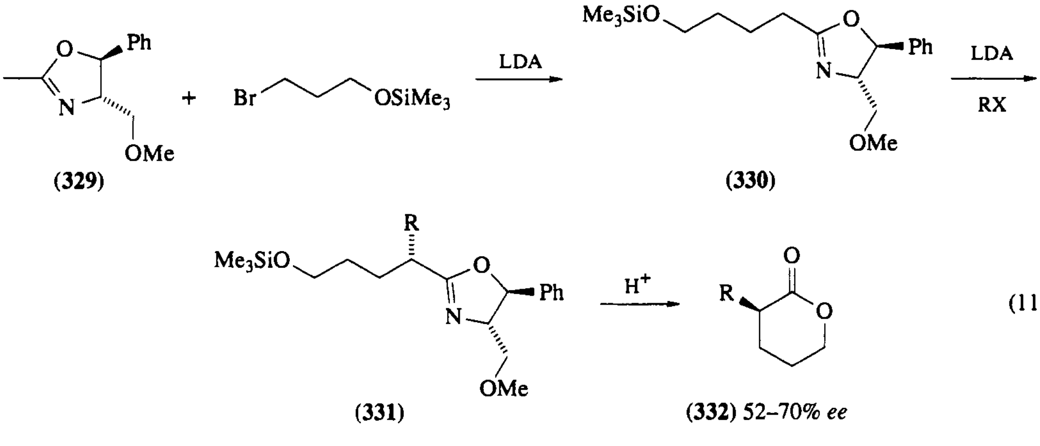


(117)

(326) **(327)** **(328)**

Meyers' approach to α-chiral lactones may be expanded to the δ-lactone series with *ee* values comparable to those achieved for lactones (equation 118).[168] Mercuri- and similarly halo-lactonizations of δ,ε-unsaturated carboxylic acid derivatives are an efficient way to achieve stereocontrolled heteroatom–carbon ring closure, *e.g.* of (**333**) to (**334**; equation 119).[143]

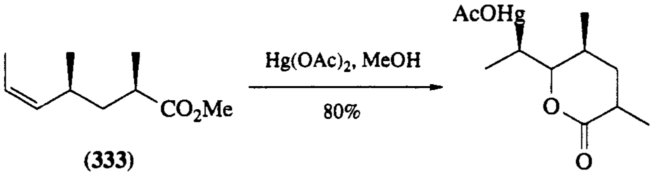
An interesting case of a δ-lactonization under inversion of configuration has been reported by Prasit and Rockach (equation 120).[169] Triol ester, (**335**), with a good leaving group in the terminal position undergoes a Payne rearrangement to (**336**) and (**337**) with aqueous base, and (**337**) cyclizes to form (**338**). As in the γ-lactone series, lactonization may be preceded by a C—C connecting process. For instance, as shown in equation (121), enamine alkylation generates a δ-keto ester, which after saponification, reduction and acidification delivers the δ-lactone.[170]



(329) **(330)**

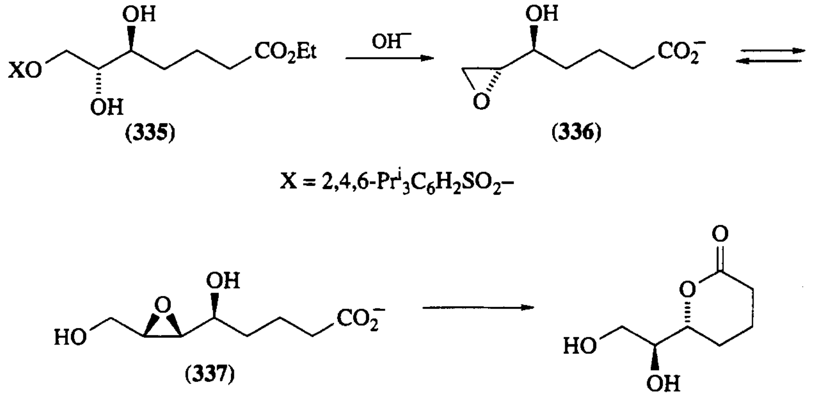
(331) **(332)** 52–70% *ee*

(118)



(333) **(334)**

(119)

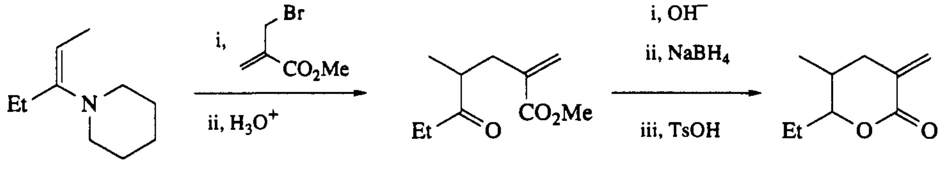


(335) **(336)**

X = 2,4,6-Pr$^i_3$C$_6$H$_2$SO$_2$–

(337) **(338)** >98% *ee*

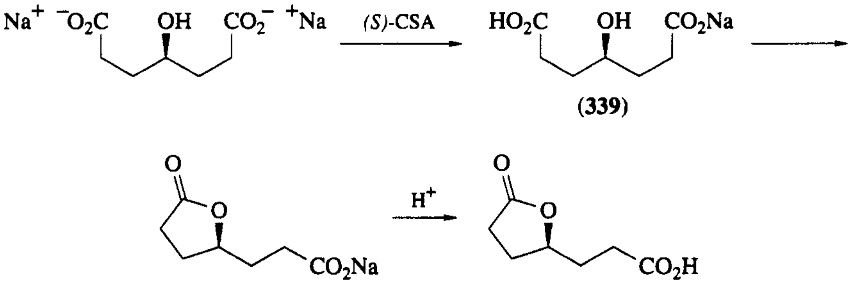
(120)



(121)

2.2.2.5 Enantioselective Lactonization

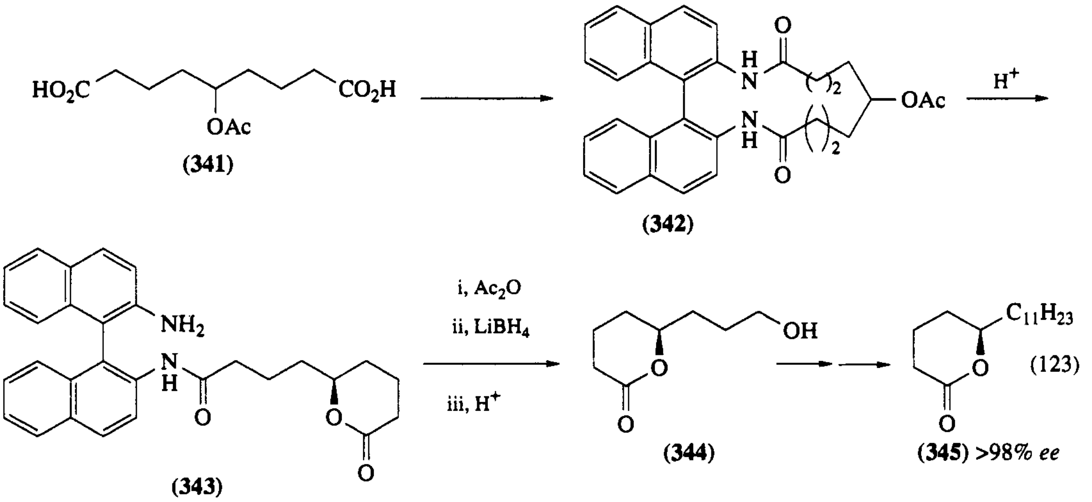
Much attention has been devoted to asymmetric lactonization of *meso*-hydroxy acids. In the case of 4-hydroxypimelate (*S*)-camphorsulfonic acid [(*S*)-CSA] has been found to deliver a proton enantioselectively to the *pro-R* appendage. In this way lactone (**340**) is generated with 94% *ee* (equation 122).[171] A different approach has been used in the case of (**341**). An axially chiral binaphthylamine is used as an auxiliary for forming the dimamide (**342**), which is hydrolyzed enantioselectively to the mono amide (**343**). In this way an optically active lactone is created, which is removed from the auxiliary by acylation of the free amino group, and reduction of the amide to form (**344**). To secure the configuration and the optical purity, (**344**) was converted into the known derivative (**345**; equation 123).[172]



(339)

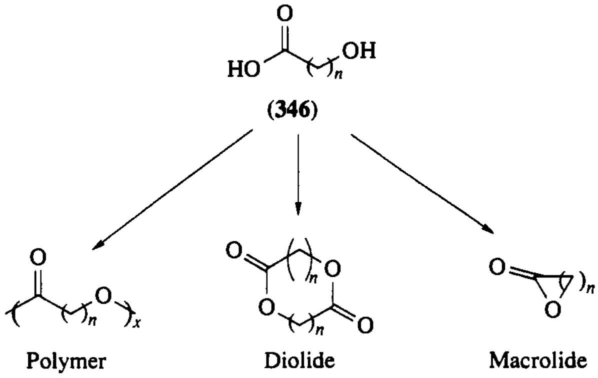
(340) 94% *ee*

(122)



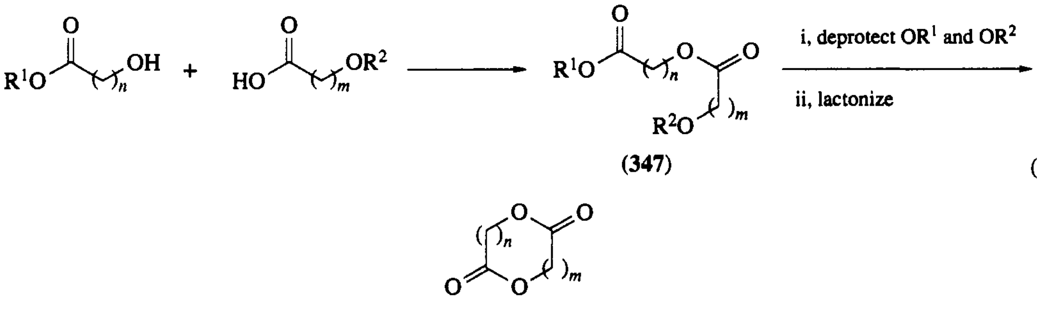
2.2.2.6 Macrolactonization

The synthesis of lactones with ring sizes of more than nine (macrolides) has been one of the central objectives in the past 10 years.[173] In most cases these syntheses involve the construction of an acyclic ω-hydroxy carboxylic acid ('seco-acid') by a number of C—C connecting steps, which eventually is submitted to the lactonization process proper. After the lactonization, some deprotecting steps have to follow to establish the desired functionality. For the lactonization essentially the same methods are used as those described in Section 2.2.1 for esterifications. The crucial problem, however, in lactonizing a seco-acid (**346**) is to avoid polymerization and to direct the reaction either to a monomeric (macrolide) or a dimeric ('diolide') lactone. Polymerization in general can be overcome, to a certain degree, by employing high dilution conditions. The dichotomy of macrolide *versus* diolide can be influenced by the proper choice of the reagent; for instance, Mitsunobu conditions preferentially lead to diolides, whereas most other reagents induce macrolide formation (Scheme 12).



Scheme 12

A controlled way to achieve diolide formation is the application of protecting groups for the hydroxy function of one hydroxy acid moiety and the carboxy group of the other and thus to prepare a seco-acid (**347**) by esterification (equation 124). After deprotection, (**347**) may be lactonized to the diolide. In macrolactonization one encounters frequently the situation that the seco-acid has more than one hydroxy group suitable for ring formation. To avoid lactones of undesired ring sizes, protective groups have to be attached to the unwanted positions in course of the synthesis of the seco-acid which are stable under the lactonization conditions, and can be removed without destroying the lactone ring. In the following discussion the subdivisions follow the reagents employed for lactonization rather than the target structures envisaged. As for the esterifications one may distinguish macrolactonizations with retention of configuration (cycloacylations) or inversion of configuration (cycloalkylation). It will be noted that for one and the same seco-acid type, different lactonizing agents have been used, which suggests that the choice of these reagents has been made according to the personal taste and experience of the individual author, and not following a deeper rationale.



(347)

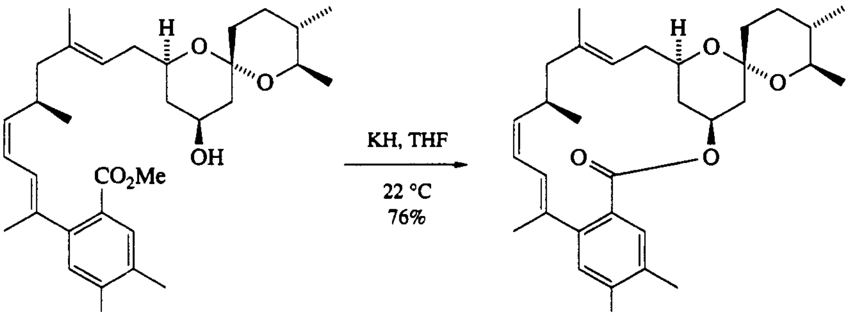
(124)

(348) Diolide

2.2.2.6.1 *Cycloacylating macrolactonization*

(i) Macrolactonization of hydroxy esters under base catalysis

The simplest way of macrolactonization is the use of acid or base catalysis so that after the ring closure no tedious separation of the lactone from auxiliary by-products is required. However, there are only very few such examples. The 16-membered macrolide ring of milbemycin β_3 is closed very efficiently by simply treating the hydroxy ester (**349**) with potassium hydride. OH deprotonation induces ring formation with retention of configuration to (**350**; equation 125).[174]



(349)

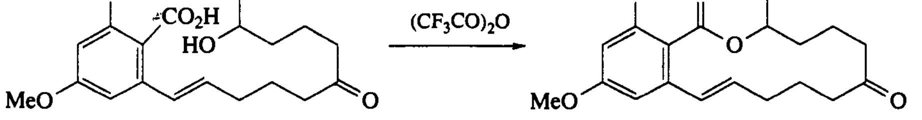
(350)

(→ Milbemycin β_3)

(125)

(ii) Macrolactonization with mixed anhydrides

The formation of mixed anhydrides, which in some cases may be isolated, is an established method. For instance, racemic zearalenone (**352**) has been obtained by treating the seco-acid (**351**) with trifluoroacetic anhydride (equation 126).[175] Similarly, antimycin A_3 has been prepared.[176] A more modern procedure makes use of Yamaguchi's 2,4,6-benzoyl chloride esterification.[26] For example, a synthesis of methynolide is based on the lactonization of the alkynic seco-acid (**353**) to (**354**; equation 127).[177]

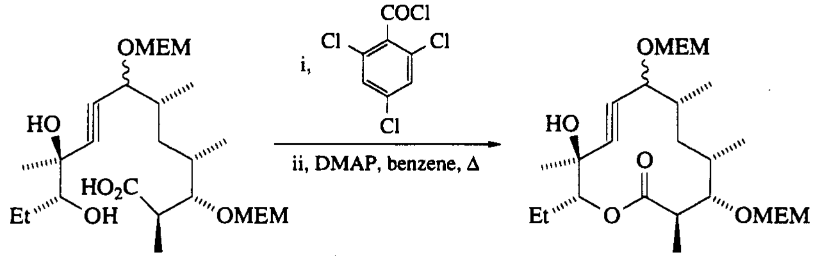


(351)

(352)

(→ Zearalenone)

(126)

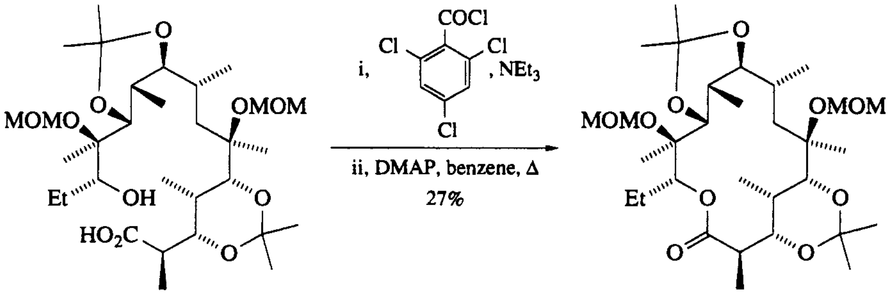


(127)

(353) **(354)**

(→ Methynolide)

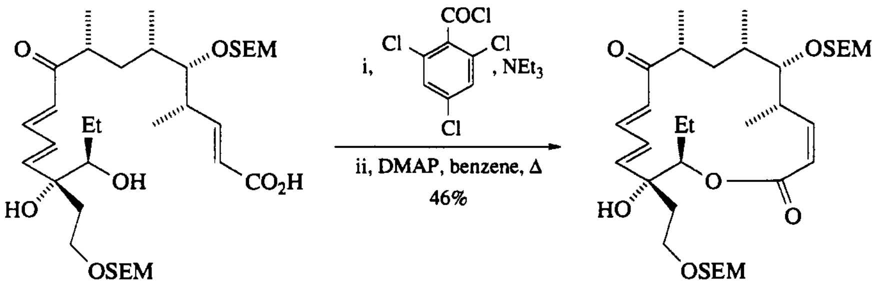
A more complex hydroxy acid is lactonized in a synthesis of (9*S*)-9-dihydroerythronolide A, albeit in low yield (equation 128).[178] By acid treatment (**356**) is deprotected to give the desired target molecule. The presence of sp^2-centers in the seco-acid obviously facilitates lactonization, as shown by the preparation of the mycinolide V precursor (**357**; equation 129).[179] A mixed carbonate is used in the synthesis of the tylonolide precursor (**358**; equation 130).[180] In general, DMAP catalysis is helpful in the ring closing step in most cases.



(128)

(355) **(356)**

(→ (9*S*)-9-Dihydroerthronolide)



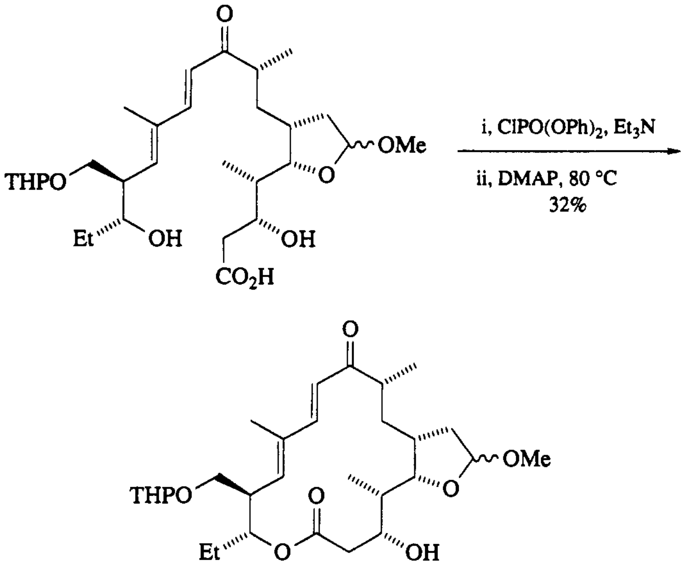
(129)

(357)

(→ Mycinolide V)

(iii) Thiol ester mediated macrolactonization

Although thiol esters are not common for normal esterifications they have found ample application in macrolactonization. Thus, the Corey–Nicolaou procedure which uses Mukaiyama's preparation of 2-thiopyridyl esters *via* a redox condensation[181] is one of the most general and efficient macrolactonization methods described so far. By forming a chelate hydrogen bridge double activation is achieved to facilitate the conversion of the activated ester (**359**) into the tetrahedral intermediate (**360**), which eliminates thiopyridone to form the lactone (equation 131).[182] The method has been applied to the syntheses of zearalenone (*via* **361**),[182] brefeldin A (*via* **362**),[183] tylonolide (*via* **363**),[184] and (+)-18-deoxynargenicin A_1 (*via* **364**) (note that no protective groups are necessary for the OH on ring c).[185]



i, $ClPO(OPh)_2$, Et_3N

ii, DMAP, 80 °C

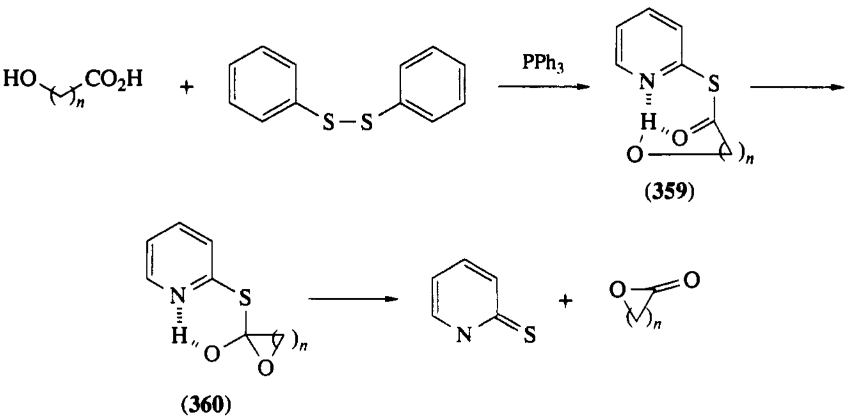
32%

(358)

(→ Tylonolide)

(130)

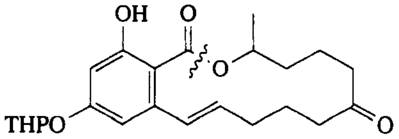
In all cases, the indicated *O*-acyl bond is closed following Corey's original procedure.[182] In the case of the vermiculine precursor (**365**) diolide formation to (**366**) is observed (equation 132).[186] To meet the special requirements of his erythronolide A and B syntheses Corey developed a diimidazolyl disulfide (**367**) by which (**368**) is obtained from the seco-acid in acceptable yields.[187] The same reagent has been used in a recent synthesis of erythronolide B (*via* **369**).[188a] Gerlach has found that silver(I) ions drastically enhance the rate of the lactonization,[188b] presumably by forming a silver–thiol bond in the activating complex. Masamune also has resorted to thiol ester activation in his macrolide syntheses. In contrast to Corey he used the *t*-butyl thiol esters (*e.g.* **370**), which are lactonized under treatment with copper(I) triflate to remove the thiol, and Hünig's base to abstract the OH proton. In this way a respectable yield of



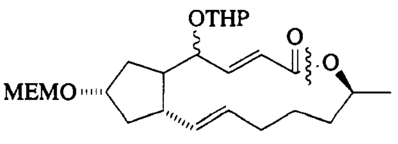
(359)

(360)

(131)



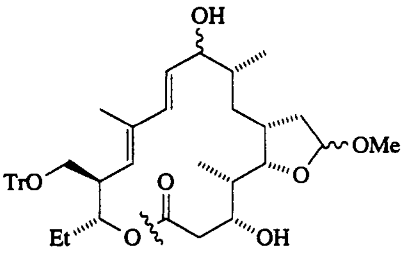
(361)



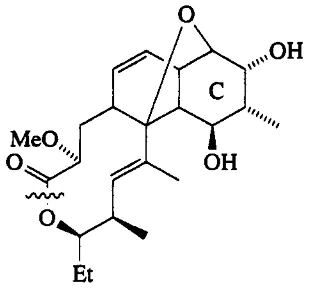
(362) 44%

i, dipyridyl disulfide, PPh_3; ii, xylene, Δ

(→ Brefeldin A)

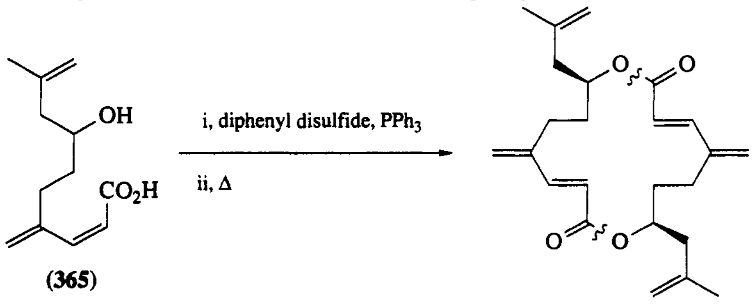


(363)
i, dipyridyl disulfide, PPh_3; ii, toluene, Δ
(→ Tylonolide)



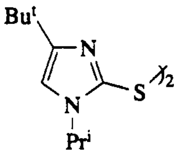
(364) 20%
i, dipyridyl disulfide, PPh_3; ii, xylene, Δ
(→ (+)-18-Deoxynargenicin A_1)

the 6-deoxyerythronolide B precursor (**371**) is obtained (equation 133).[189] In the first synthesis of methymycin (*via* **372**), mercury(II) methanesulfonate was used in a phosphate buffer.[190]

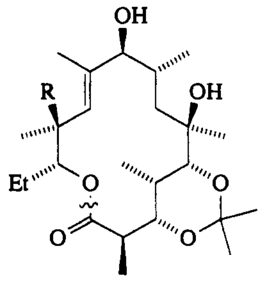


(365) (132)

(366)
(→ Vermiculine)

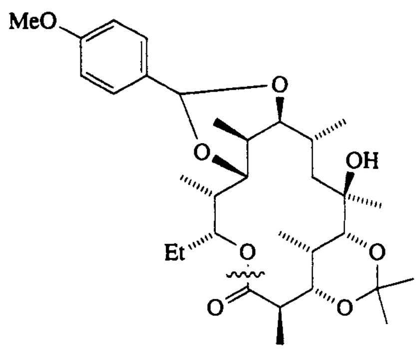


(367)

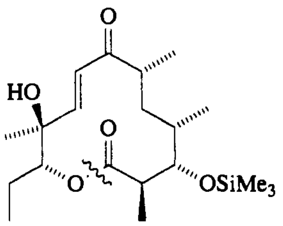


(368)

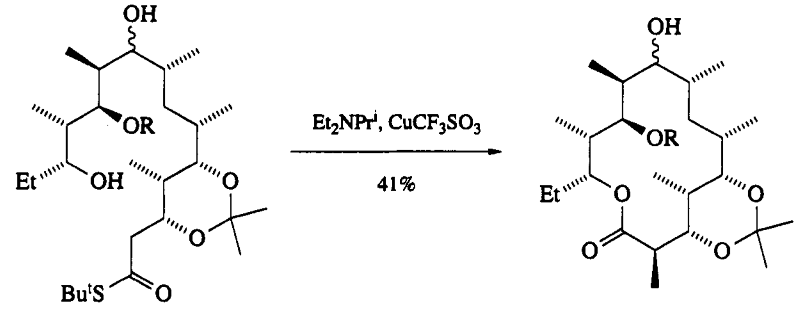
i, (**367**), PPh_3; ii, toluene, Δ
R = H, 50%; R = OMTM, 30%
(→ Erythronolides A and B)



(369) 72%
(→ Erythronolide B)



(372) 30%
(→ Methymycin)



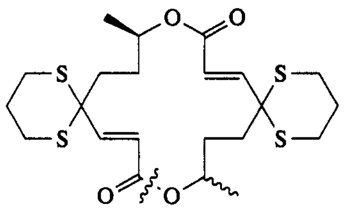
(370) **(371)**

(→ 6-Deoxyerythronolide B)

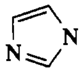
(133)

(iv) Macrolactonization via *activated amides*

Staab's *N*,*N*-carbonyldiimidazolide method has been applied in a synthesis of pyrenophorine (*via* **373**), in which the indicated bond has been closed.[191] More recently, the usual activated amide (**374**) has been used to obtain the *N*-protected antimycin A3 derivative (**374**) under acid catalysis (equation 134).[192]

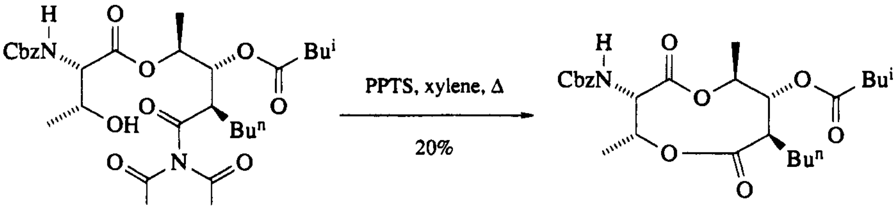


(373)



$(\text{Im})_2$ C=O. DBN

(→ Pyrenophorin)



(374) **(375)**

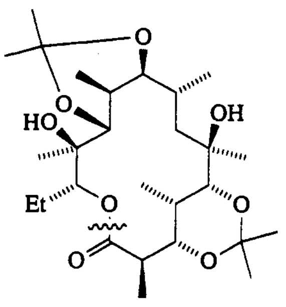
(→ Antimycin A$_3$)

(134)

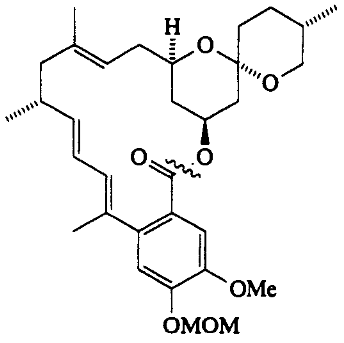
(v) Macrolactonization via *activated esters*

DCC coupling serves in Stork's erythronolide A synthesis for closing the lactone (**376**) at the indicated C—O bond.[193] A modified DCC-type reagent (**378**) was successful in the preparation of the milbemycin β3 precursor (**377**).[194] The resulting urea derivative is water soluble and can thus be easily separated from (**377**) during work-up. An interesting enol ester type activation has been devised by Gais *et al.* to prepare the brefeldin A precursor (**383**; equation 135).[195] The hydroxy acid (**379**) adds the carboxy oxygen to the triple bond of the ynamine ketone (**380**) to form the enol ester (**381**), which spontaneously forms (**382**) *via* a 1,5-acyl migration in 96% yield. Under acid catalysis (**382**) lactonizes to (**383**).

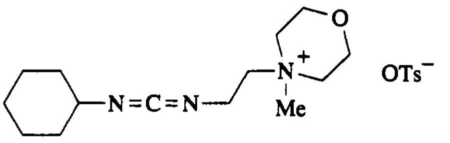
Mukaiyama's 2-halopyridinium activation has also been applied to macrolactonization, to prepare, for instance, the brefeldin A intermediates (**384**)[196] and (**385**).[197] In a very elegant synthesis of (+)-aspicilin the macrolactonization has been performed with the aid of a hydroxy ketene intermediate (**387**), which had been generated *in situ* by the photolytic ring opening of (**386**). The primary macrolide (**388**) is then converted into (**389**) by elimination of sulfinate and acetyl azide (equation 136).[198] A cyclic alkoxy stannylene carboxylate (**391**) has been employed in a number of model macrolactonizations leading to nodusmycin, ingramycin and others (equation 137).[199] Compound (**391**) is readily formed from the hydroxy acid (**390**) and Bu2SnO. As in Corey's method, intramolecular hydrogen bridging is postulated to effect double activation.



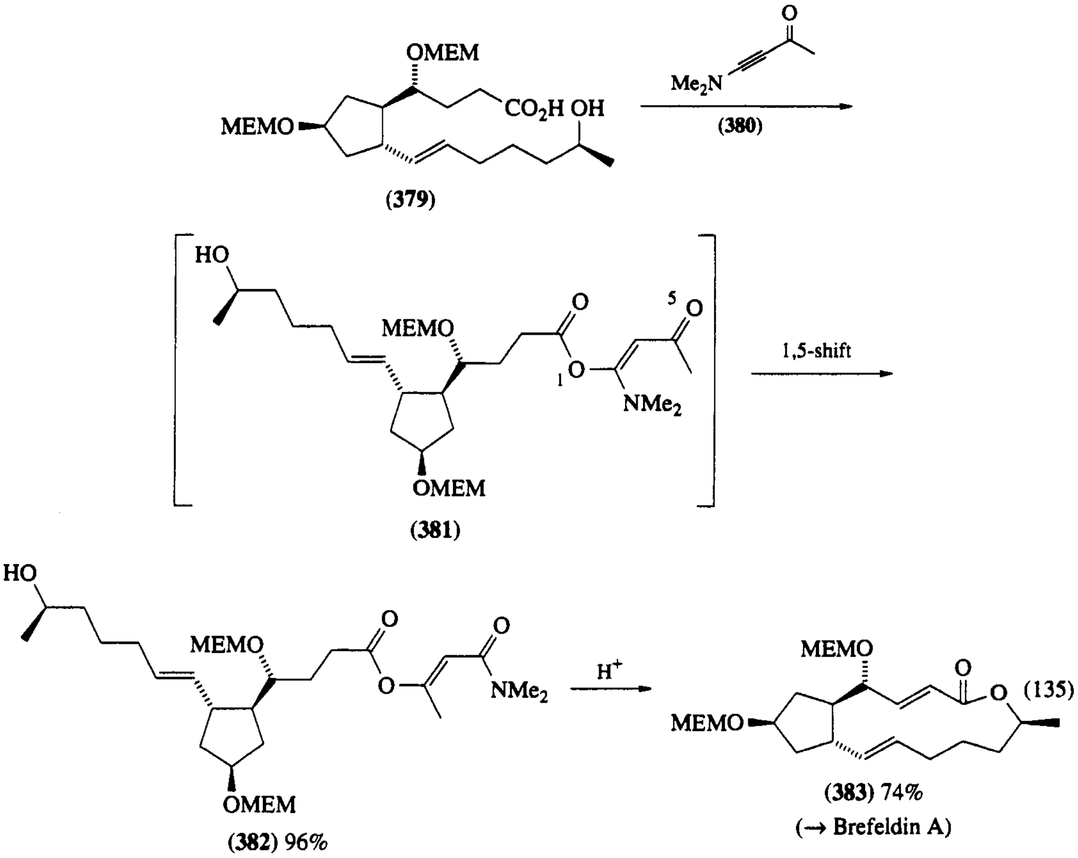
(**376**) 65%
DCC, DMAP, TFA, Δ in $CHCl_3$
(→ Erythronolide A)



(**377**)
(→ Milbemycin β_3)



(**378**)

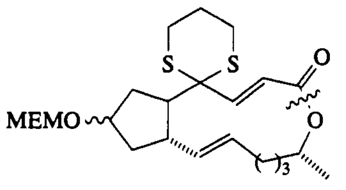


(**379**)

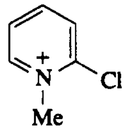
(**381**)

(**382**) 96%

(**383**) 74%
(→ Brefeldin A)

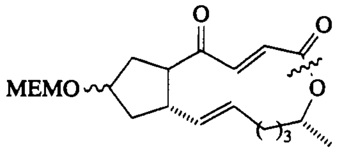


(384) 57%

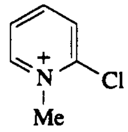


I^-, Et_3N, MeCN

(→ Brefeldin A)

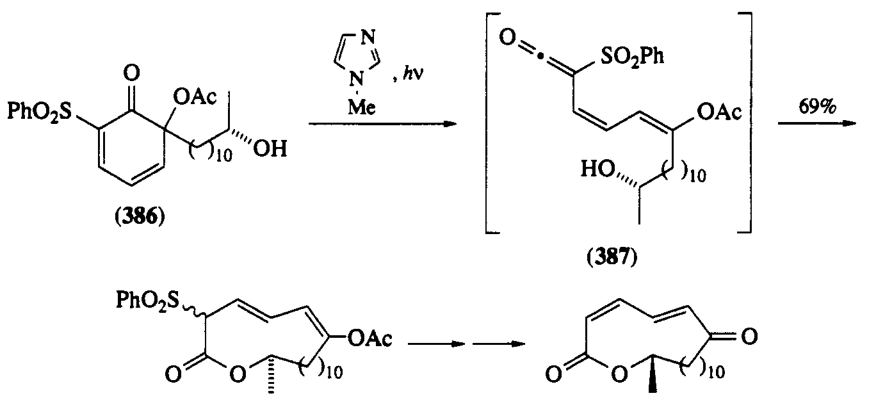


(385) 37%



BF_4^-, Et_3N, CH_2Cl_2

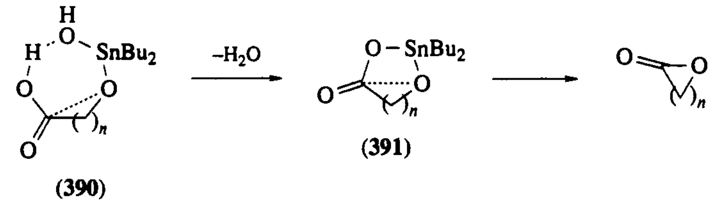
(→ Brefeldin A)



(386) **(387)** **(388)** **(389)**

(→ (+)-Aspicilin)

(136)



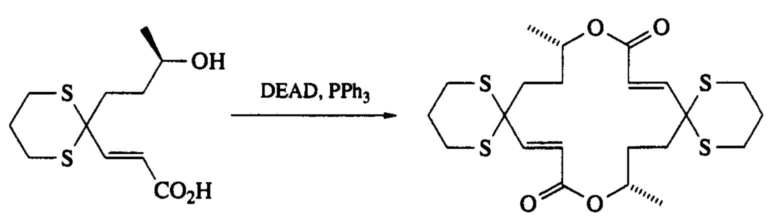
(390) **(391)**

applied to nodusmycin, ingramycin, *etc.*

(137)

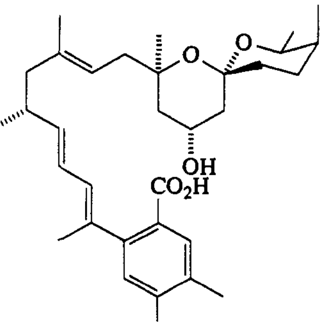
2.2.2.6.2 Cycloalkylating macrolactonization

The Mitsunobu procedure has found considerable application, so it has been used for diolide formation in pyrenophorin (equation 138)[200] and colletodiol[201] syntheses. Yamaguchi's method[26] is much inferior.[202] As expected, the ring closure in equation (138) proceeds with inversion of configuration. In a



(→ Pyrenophorin)

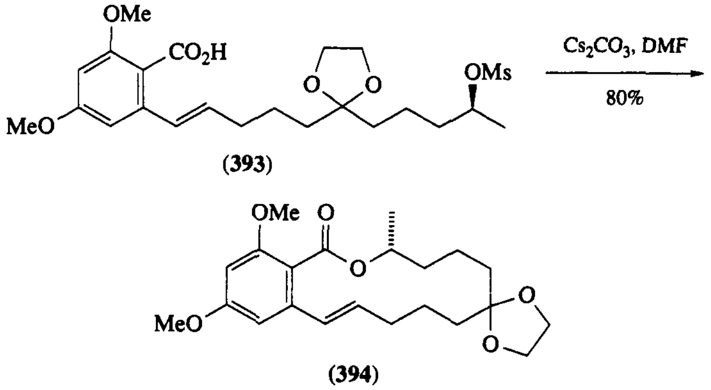
(138)



(392) 77%

(→ (+)-Milbemycin β_3)

recent synthesis of milbemycin β_3 Mitsunobu's reagent was used for achieving the required inversion of the carbinol center during lactonization of the seco-acid (**392**).[203] Classical S_N2 lactonizations have been rarely performed. Kellogg has applied his alkylative esterification in the lactonization of (**393**) to the zearalenone precursor (**394**; equation 139).[204]



(**393**)

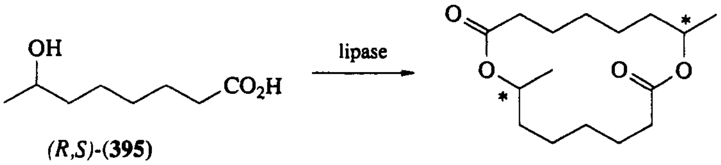
(**394**)

(→ Zearalenone)

(139)

2.2.2.6.3 *Enzymatic macrolactonization*

So far, enzymatic macrolactonizations are on a model stage yet. Sih has tested the enantio- and diastereo-selectivity in the diolide formation from racemic (**395**). With lipase, high enantiomer selection in favor of the (*R,R*)-(**396**) has been observed, whereas the diastereoselection is disappointingly low (equation 140).[205]



(*R,S*)-(**395**)

(**396**)

ee (*R,R*):(*S,S*) = 96:4

de (*R,R*) + (*S,S*):(*R,S*) = 12:5

(140)

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2.3

Synthesis of Amides and Related Compounds

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2.3.1 AMIDES

The chemistry of amides has a long history, and since the end of the last century a plethora of synthetic methods has been developed.

The occurrence of the amide group in important technical polymers (*e.g.* polyacrylamides, nylon polyamide), in drugs (*e.g.* β-lactam antibiotics), in peptides and proteins has stimulated research leading to safe, simple, and in the case of α-asymmetric carboxylic acids nearly racemization-free, condensation methods.

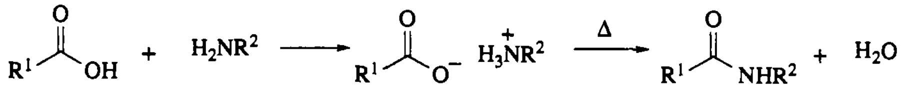
The synthesis of amides was recently reviewed by several authors. Short contributions came from Smith,[1] and Millar and Springall.[2] Especially due to practical aspects, those by Beckwith,[3] Challis and Challis,[4] Sandler and Karo,[5] and Döpp and Döpp[6] are more detailed.

With respect to peptide chemistry, Wünsch[7] discussed the scope and limitations of nearly all known procedures, and Merrifield and Barany[8] reviewed the application of several methods to solid phase peptide chemistry.

2.3.1.1 Carboxylic Acids and Amines

2.3.1.1.1 Dehydration of ammonium salts

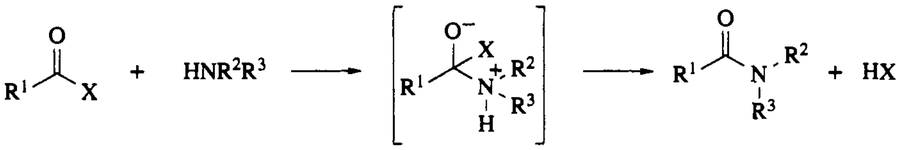
With simple carboxylic acids and amines, direct conversion to amides takes place at elevated temperatures (equation 1).[9] Generally, this reaction may be catalyzed by acid[10] or by cation exchange resin.[11] Addition of ammonium carbonate or urea[12] as a source of ammonia reduces reaction temperatures and improves yields.



(1)

2.3.1.1.2 Activation of the carboxy group (acylation of amines)

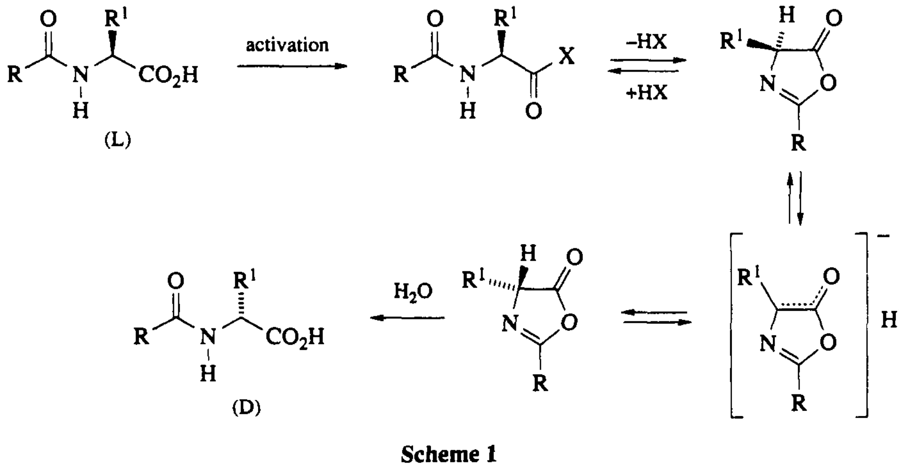
This is the most useful method of amide formation (equation 2). An activated carboxylic acid acylates ammonia, primary or secondary amines by a formal S_N2 substitution of leaving group X. The reactivity of the acylating reagent depends on the acidity of HX, and therefore the order of reactivity is RCOHal > $(RCO)_2O \approx RCON_3 > RCO_2R > RCONH_2 > RCOR$. Moreover, the reaction rate increases with higher nucleophilicity of the amine as well as base or acid catalysis.



(2)

In the case of peptide synthesis one always has to take the double functionality of α-amino acids into account. Therefore, protection of one of these groups is necessary to direct peptide bond formation to a defined product. Moreover, the protection group has to be stable against the peptide bond-forming reaction and should be easily cleaved to generate an appropriate functional group for the next coupling.

With the exception of glycine, all proteinogenic α-amino acids are chiral. The prevention of racemization in the case of the most commonly used α-protected amino acids is a prerequisite of successful peptide synthesis. *N*-acylamino acids might lose their stereochemistry according to the mechanism shown in Scheme 1. The proper choice of the protection group (*e.g.* urethane-derived), activation method and additives has to be made carefully.

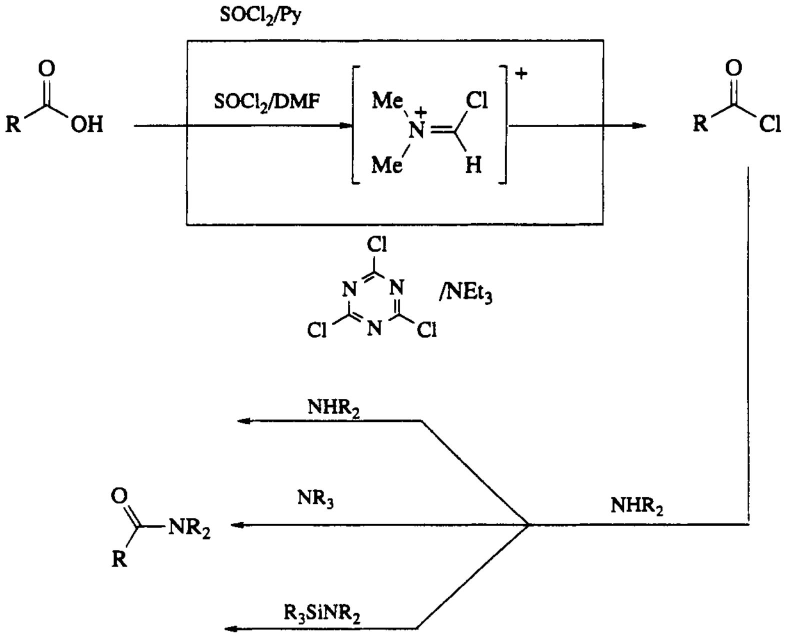


Scheme 1

Though the amide (peptide) forming reaction may be carried out by the use of hundreds of reagents and procedures, it is advisable to concentrate first on the most often applied reagents and conditions published in the literature. A further advantage is that these reagents are mostly commercially available.

(i) Carboxylic acid halides

Activation of the carboxylic acid can easily be accomplished by the classical thionyl chloride method.[13,14] To generate acid chlorides under mild conditions without the evolution of gaseous HCl the reaction is carried out in $SOCl_2$/DMF[15] or started with the dicyclohexylammonium salt of the carboxylic acid.[16] Addition of DMF accelerates the reaction.[17] An imide chloride is considered to be the reactive species (Scheme 2). Other methods include activation with cyanuric chloride[18] or triphenylphosphine/tetrachloromethane.[19,20]



Scheme 2

Conversion to the corresponding amides with ammonia, primary or secondary amines proceeds by adding two equivalents of amine (to trap excess hydrogen chloride),[21] refluxing with one equivalent of amine in aromatic solvents,[22] or reacting with dialkylaminotrimethylsilane[23] under formation of the volatile trimethylchlorosilane. The latter method has advantages especially in the preparation of sterically hindered amides like acetic acid *t*-butylamide.[24]

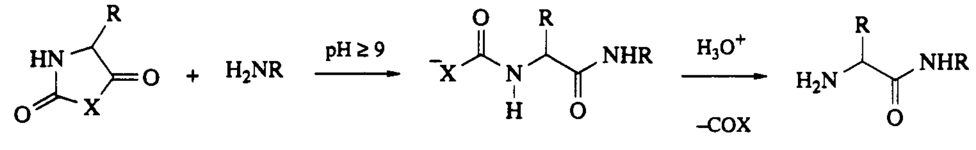
For peptide chemistry, protected amino acid chlorides are too highly activated and therefore not used due to their racemization tendency, reactions with amino acid side chains (*e.g.* asparagin), loss of selectivity against nucleophiles and the formation of internal Leuchs' anhydrides.[25]

Carboxylic acid fluorides are more stable to water and other nucleophiles. They are readily prepared by the use of cyanuric fluoride and converted to amides by silylated amines.[26] In contrast to the chlorides, protected amino acid fluorides exert virtually no racemization in peptide coupling.[27]

(ii) Carboxylic acid anhydrides

(a) Intramolecular.

The preparation and use of α-amino-*N*-carboxylic anhydrides (NCA) and α-amino-*N*-thiocarboxylic anhydrides (NTA) for peptide synthesis was recently reviewed.[28] The main advantage of this coupling method lies in its simplicity. Protection of the nitrogen and activation of the carboxy group are achieved in one step (equation 3). NCAs (X = O) are prepared by the method of Leuchs, starting with *N*-substituted oxycarbonyl amino acid halides[29,30] and subsequent cyclization, or by the method of Fuchs–Farthing,[31,32] condensing the parent amino acid with phosgene. An alternative procedure that avoids gaseous phosgene uses trichloromethylchloroformate (TCF)[33] at elevated temperatures with a drastic reduction of reaction times. The preferred method of preparing NTAs (X = S) starts with *N*-alkoxythiocarbonyl amino acids and cyclization with PBr_3 at low temperature.[34-36] Alternatives starting with amino acid thiocarbamates or α-amino thioacids are more tedious and necessitate additional steps resulting in lower yields. Both NCAs and NTAs can be obtained in moderate to good yield with an optical purity exceeding 98% *ee*.



(3)

X = O (NCA); X = S (NTA)

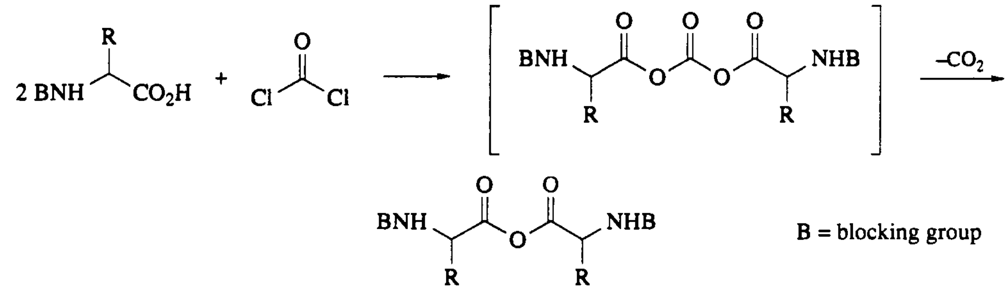
For peptide coupling, only lysine and cysteine have to be protected in their side chains. In NCA couplings, reaction parameters have to be carefully controlled:[37] rapid mixing, temperature (*ca.* 0 °C) and pH (optimum pH 10.2). Under these conditions racemization is virtually absent. In the case of NTAs, the coupling pH is lower (pH ≈ 9) and the overall yield is somewhat higher. Due to their generally higher racemization tendency, only the use of glycine-, alanine- and histidine-NTA is recommended in comparison to the NCAs.

The NCA/NTA technology has found application in the synthesis of fragments of ribonuclease A,[38] as well as in the large scale synthesis of ACE inhibitor precursors of enalapril[39,40] and the artificial sweetener aspartam.[35]

(b) Intermolecular symmetric.

Symmetrical anhydrides are prepared according to reactions reviewed in Chapter 2.1 of this volume. Advantageously, in contrast to unsymmetric anhydrides nucleophilic attack on both possible carbonyls gives the correct product. The disadvantage is the waste of one equivalent of carboxylic acid (which will be recovered in the case of expensive protected amino acids). The most widely used is acetic anhydride,[6] which acetylates amines under mild conditions.

In peptide chemistry two methods are used frequently. The reaction of phosgene with protected amino acids leads to symmetric anhydrides (equation 4), after disproportionation and release of carbon dioxide, which can be readily used to build up a growing peptide chain.[41,42] More recently, symmetrical amino acid anhydrides have been generated by carbodiimides like DCC,[43,44] water soluble carbodiimide[45] and diisopropylcarbodiimides[46] *in situ*. They are extensively applied to automated solid phase peptide synthesis. Attention has to be paid to the proper solvent system, as aprotic dipolar solvents tend to slow down reactions and increase formation of side products.[43]



B = blocking group (4)

(c) Intermolecular mixed from C-*acids.*

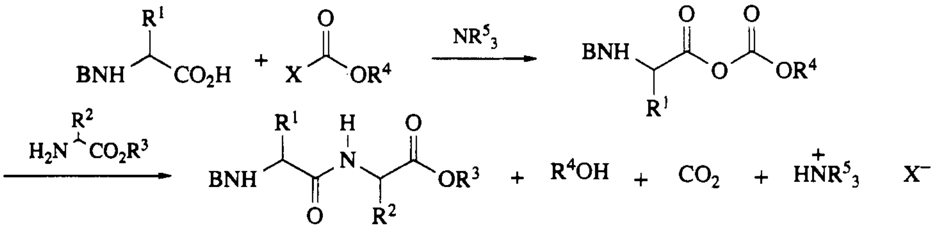
In mixed anhydrides, the difference between the two carbonyl groups with respect to their electrophilic character should be pronounced.

Formylation of amines is performed with formic acid/acetic acid anhydride.[47] The application of other mixed anhydrides with acetic acid as well as benzoic acid[48] is less favorable, because both possible amides will form in varying amounts.

An improvement resulting in a decreased amount of the second acylation product is the introduction of mixed anhydrides with α-branched carboxylic acids like isovaleric[49] and pivalic acid,[50] due to deactivating electronic and steric effects.

In peptide chemistry, activation with pivalic acid mixed anhydrides allows condensation with α-alkyl-α-amino acids (*e.g.* Aib),[51] *N*-methyl-α-amino acids[52] (resulting in the total synthesis of cyclosporin A) and Boc-Asn.[53]

Mixed anhydrides of carbonic acid half esters contain an activating carbonyl group with reduced electrophilic character (due to lone pairs of electrons on the vicinal oxygen atom) and are rapidly amidated by amines. The anhydride is formed at low temperature in the presence of tertiary amines (equation 5).

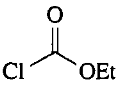
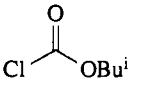
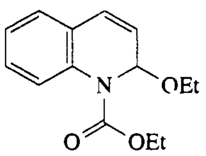
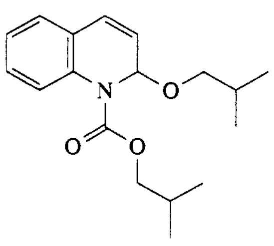
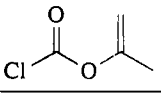


X = halogen

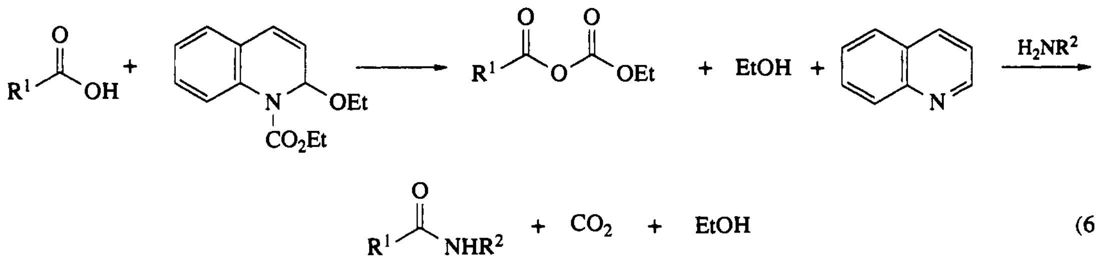
(5)

Isobutyl chloroformate is most frequently applied in peptide chemistry,[54–56] followed by ethyl chloroformate (see Table 1).[57] The advantage of this method is that the mixed anhydride does not have to be isolated, and during work-up only carbonic acid half esters are formed, which decompose to an alcohol and carbon dioxide. Only in the case of sterically hindered amino acids does the opening of the anhydride at the undesired carbonyl occur in considerable amounts. Furthermore, short activation times (30 s) at low temperatures lead to peptides with minimal racemization.[55] With isopropenyl chloroformate[58] the mixed anhydride is prepared at room temperature, and during reaction only acetone and carbon dioxide are formed.

Table 1 Amides *via* Mixed Anhydrides: Use of *C*-acids

Reagent	*Structure*	*Ref.*
Ethyl chloroformate		57
Isobutyl chloroformate		54, 55
2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ)		59
2-Isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (IIDQ)		60, 61
2-Propenyl chloroformate		58

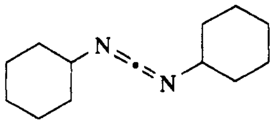
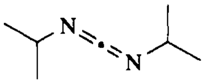
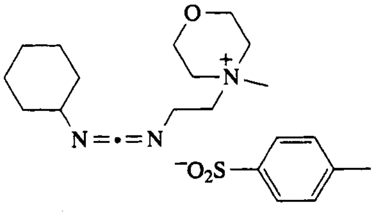
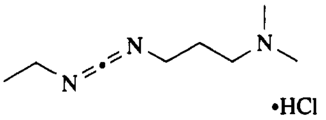
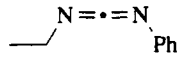
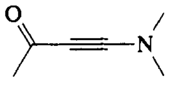
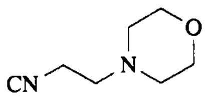
The coupling reagents EEDQ[59] and IIDQ[60,61] permit the formation of amides from carboxylic acids and amines in one pot, at ambient temperatures, without the need for a tertiary base (equation 6).



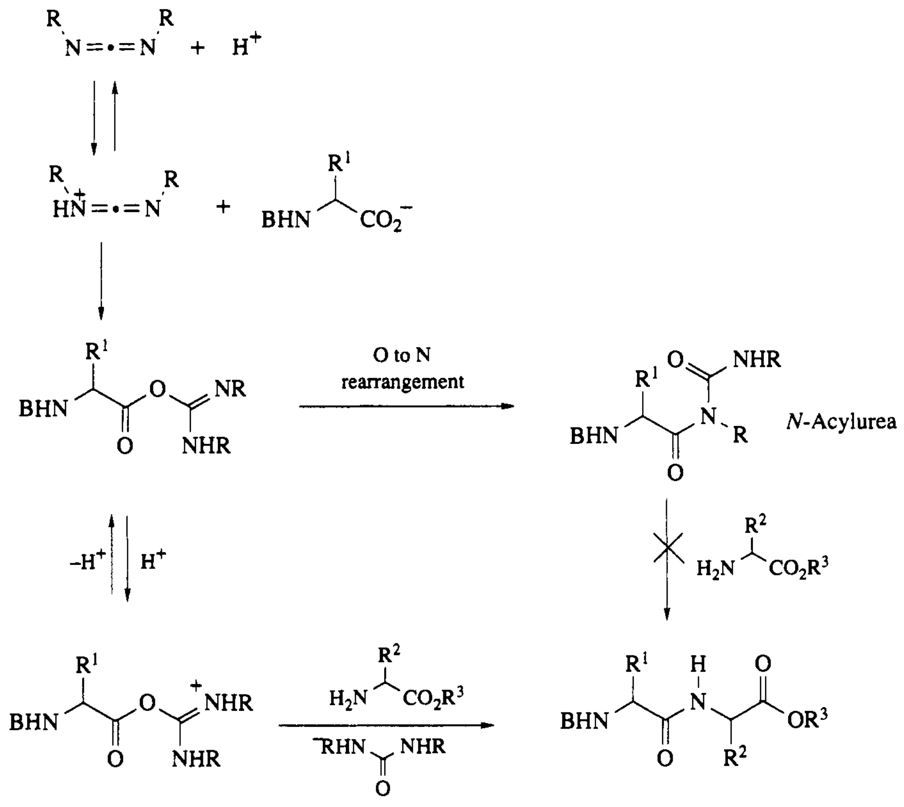
(6)

Carbodiimides are the major coupling reagents in peptide chemistry and are frequently used in solution as well as in solid phase synthesis (Table 2).

Table 2 Amides *via* Mixed Anhydrides: Use of *C*-acids

Reagent	*Structure*	*Ref.*
Dicyclohexylcarbodiimide (DCC)		62
Diisopropylcarbodiimide (DIC)		66, 67
1-Cyclohexyl-3-(2-*N*-methylmorpholiniumylethyl)-carbodiimide-*p*-toluenesulfonate		63
1-Ethyl-3-(3-dimethylamino)propylcarbodiimide (EDC)		64
Ethylphenylcarbodiimide		68
Ethoxyethyne	≡—OEt	75
4-Dimethylamino-3-butyn-2-one		76
1-(4-Chlorophenyl)-3-(4-methylpiperazinyl)-2-propyn-1-one		77
Trimethylsilylethoxyethyne	EtO—≡—SiMe$_3$	74
2-Morpholinylethyl isocyanide		73
t-Butyl isocyanide	Bu^{t}NC	71, 72

The reaction proceeds *via* a 1,2-addition of carboxylic acids to the carbodiimides to give acyllactims (Scheme 3), and leads to the peptide after nucleophilic attack of an amine. The by-product of this reaction, *N,N'*-dicyclohexylurea in DCC-mediated couplings,[62] is easily removed by filtration from the reaction mixture. Because it is not completely insoluble in most organic solvents, contamination of the products occur. The introduction of water soluble carbodiimides[63–65] facilitates the work-up procedure by extracting the urea with water. Diisopropylcarbodiimide[66,67] is frequently used in solid phase synthesis,[46] because its corresponding urea is soluble in a variety of organic solvents and readily removed by filtration.



B = blocking group

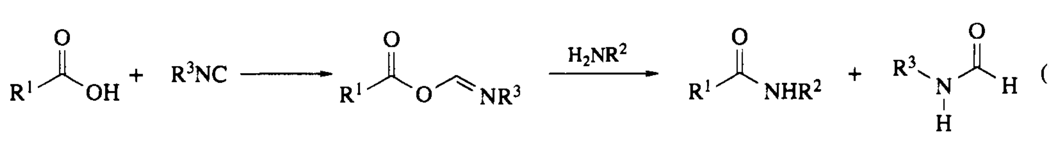
Scheme 3

Two side reactions, the O to N acyl shift and racemization, limit the application to some extent. Lower reaction temperatures, shorter reaction times or the use of unsymmetric carbodiimides[68] suppress these reactions. The addition of reactive nucleophiles will be discussed in a later section (active esters).

Dicyclohexylcarbodiimide has been used in the acylation of all common amino acids and is the most familiar condensation reagent in peptide chemistry, in spite of its skin-irritating and allergic properties. Outside peptide chemistry, dicyclohexylcarbodiimide has been used only infrequently for the condensation of carboxylic acids and amines, probably due to its high costs.

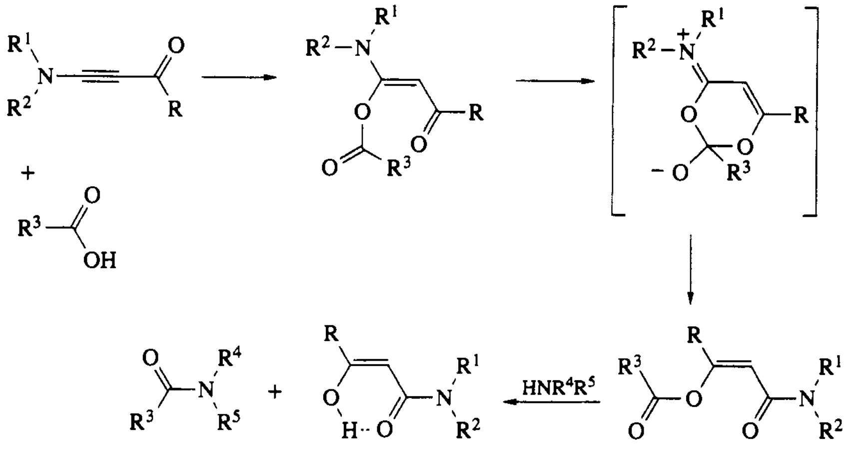
α,β-Unsaturated carboxylic acids[69] and α-oxocarboxylic acids[70] give low yields of amides. The condensation of carboxylic acids with isocyanides is related to that of carbodiimides (equation 7).[71–73] The mild reaction conditions tolerate unprotected hydroxy groups of amino acids even with long reaction times. Generation of side products like acylureas is not possible and racemization is lower than with DCC.

2-Morpholinylethyl isocyanide[73] gives good results in fragment condensations and the by-product is simply removed by acid washing.



(7)

Activation by addition of a carboxylic acid to a triple bond occurs with ethyl ethynyl ether,[74,75] which forms amides *via* reactive enol esters. The reaction is catalyzed by mercury(II) oxide under almost neutral conditions. Push–pull alkynes exert higher reactivity.[76,77] The intermediate enol esters (Scheme 4) rearrange and react with the amino function of a second amino acid. Hydroxy, thiol and imidazole functional groups do not have to be protected. The degree of racemization is low, and yields are good in the case of small peptides.



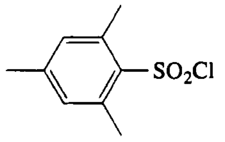
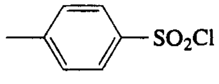
Scheme 4

(d) Intermolecular mixed from S*-acids.*

Activation of aliphatic and aromatic carboxylic acids with sulfuric acid derivatives yields amides (Table 3). Sulfuryl chloride fluoride and primary amines[78] or chlorosulfonyl isocyanate and secondary amines[79] are used as reaction partners.

Activation with sulfonic acid chlorides[80,81] is more general, rendering amides with the possible participation of symmetric anhydrides after disproportionation.[82] This method has also found use in the synthesis of modern β-lactam antibiotics.[83] However, in peptide chemistry this activation method leads to unwanted side reactions, like formation of nitriles in the cases of glutamine and asparagine,[84] and racemization.[85] In a convenient one-pot procedure, the carboxylic acids are activated by sulfonyl chlorides under solid–liquid phase transfer conditions using solid potassium carbonate as base and a lipophilic ammonium salt as catalyst.[86]

Table 3 Amides *via* Mixed Anhydrides: Use of *S*-acids

Reagent	*Structure*	*Ref.*
Sulfuryl chloride fluoride	SO_2ClF	78
Chlorosulfonyl isocyanate	$ClO_2S{-}N{=}{\bullet}{=}O$	79
Methanesulfonyl chloride	$MeSO_2Cl$	80
Methanesulfonyl chloride	$MeSO_2Cl$ (Phase transfer conditions)	86
2-Mesitylenesulfonyl chloride		81
p-Toluenesulfonyl chloride		

(e) Intermolecular mixed from P-*acids.*

In recent years organophosphorus reagents have received much attention (Table 4). Their mixed carboxylic–phosphorous acid anhydrides are very reactive intermediates and are opened chemoselectively by nitrogen nucleophiles to give amides. The by-products in these coupling reactions are mostly water soluble, oxygen-containing phosphorus compounds. Therefore, medium scale technical syntheses of amides and peptides are also feasible.[87,88] The tendency for disproportionation to the symmetrical anhydrides is small.[89,90] Most of these reagents activate urethane-blocked amino acids without racemization,[91] while others are rapidly converted to their corresponding azides (DPPA)[92] or active esters[93–96] (BNPP,[97,98] BOP[99,100] and NPTP[101]; *cf.* Section 2.3.1.1.2.iii.a).

Advantages have been claimed for DPPCl[89] and BOP-Cl[102–104] in the condensation of *N*-methylamino acids, namely high yields and low racemization rates. For cyclization to cyclopeptides both DPPA[92,105] and (5-nitropyridyl)diphenylphosphinate,[96] to β-lactams NPTP[101] and DMPC,[106] have been applied.

DPPA, the Bates reagent and BOP are toxic, the latter due to the formation of HMPA. A substitute for the widely used BOP is TBTU [174], which releases tetramethylurea as a harmless side product.

The redox coupling found by Mukaiyama makes use of the facile oxidation of phosphines and the strength of the P—O bond (Table 5). In each case the reaction proceeds *via* an acyloxyphosphonium intermediate (equation 8). The oxidation is carried out by disulfides[108–110] and related compounds,[111,112] DEAD,[113] and halogens.[114–117] Although this method has been applied to the solid phase synthesis of peptides, it has not found broad application.

(f) Intermolecular mixed from N-*acids.*

Carboxylic acid azides give rise to three different reactions under different conditions. Azide coupling (equation 9) was the earliest method[131] in peptide synthesis and is still one of the most important in fragment condensation[132] and preparation of cyclic peptides due to its almost complete lack of racemization. At elevated temperatures a frequent side reaction is the Curtius rearrangement. Trapping of the intermediate isocyanate with amines (equation 10) gives urea derivatives and with carboxylic acids rearranged amides are obtained (equation 11).[133]

Carboxylic acid azides are prepared from carboxylic acid halides or from amino acid/peptide esters *via* hydrazides, followed by nitrosylation with nitrous acid in water[134] or with alkyl nitrites in organic solvents.[135] Also, the aforementioned diphenylphosphorazidate (*cf.* Section 2.3.1.1.2.2.ii.e) is often used in this preparation method starting from carboxylic acids.

Activation of carboxylic acids with carbonyldiimidazole (equation 12) and subsequent reaction with amines gives amides and peptides in good yield.[136–138] Through the same intermediate, the activation also occurs with the more stable *N,N'*-oxalyldiimidazole[139] and the mixture of triphenyl phosphite and imidazole.[140]

Imidazolides are powerful acylating agents. Therefore moisture has to be excluded and the acids have to be preactivated before addition of the amine. The tendency toward racemization is low, especially in DMF. The by-products of the reaction, imidazole and carbon dioxide, are easily removable. Other activating reagents (Table 6) can be applied. The advantage of COMODD[141] and *N,N'*-carbonyldi-2-thione-1,3-thiazolidine[142] is that the activated carboxylic acids are stable and isolable.

(iii) Carboxylic acid esters

The direct aminolysis of unactivated esters and lactones is particularly difficult with secondary amines, since even primary amines require temperatures higher than 200 °C.[143] Application of high pressure (8 kbar, 1 bar = 100 kPa) at lower temperatures (room temperature to 45 °C) makes this reaction possible.[144] Sodium cyanide catalyzes this reaction at atmospheric pressure and it proceeds without racemization of amino acid esters.[145]

Alternative methods include deprotonation of the amine, to enhance its nucleophilicity, by one equivalent of sodium methoxide,[146] sodium amide, metallic sodium,[147] *n*-butyllithium,[148] sodium hydride in dimethyl sulfoxide[149] or Grignard reagent.[150] Under less drastic basic conditions 2-hydroxypyridine catalyzes the reaction at elevated temperatures (130–170 °C).[151]

Treatment of the parent ester with Lewis acids like boron tribromide and subsequent addition of amine results in amides in good yields.[152]

Table 4 Amides *via* Mixed Anhydrides: Use of *P*-acids

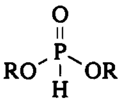
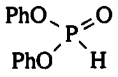
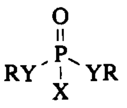
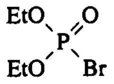
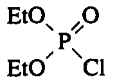
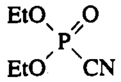
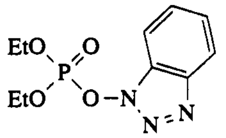
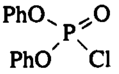
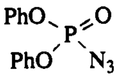
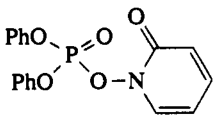
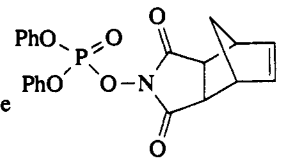
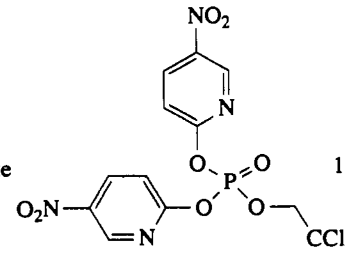
Class	*Reagent*	*Structure*	*Ref.*
 Phosphorous acids	Diphenyl phosphite		118
 Phosphoric acids	Diethyl phosphorobromidate		91
Y = O, NR	Diethyl phosphorochloridate		119
	Diethylphosphoryl cyanide (DEPC)		120
	Diethyl-1-(benzo-1,2,3-triazolyl)phosphonate		93
	Diphenyl chlorophosphate		121
	Diphenylphosphoryl azide (DPPA)		92, 105
	2-Pyridone diphenyl phosphate		94
	Norborn-5-ene-2,3-dicarboximidoyl diphenyl phosphate (NDPP)		95
	Bis(5'-nitro-2'-pyridyl) 2,2,2-trichloroethyl phosphate (NPTP)		101

Table 4 *(continued)*

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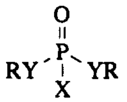
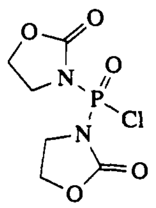
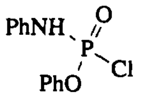
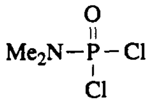
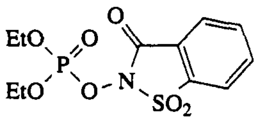
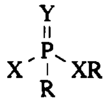
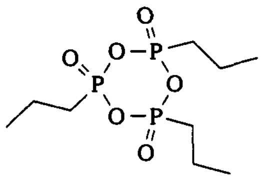
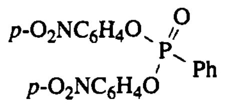
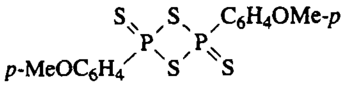
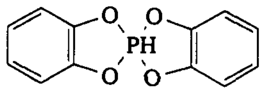
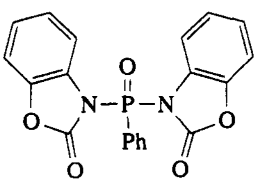
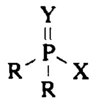
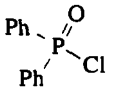
 Phosphoric acids $Y = O, NR$	Bisoxazolidonylphosphoroxy chloride		102
	Phenyl *N*-phenylphosphoramidochloridate		122
	N,*N*-Dimethylphosphoramidic dichloride (DMPC)		106
	Diethyl 2-(3-oxo-2,3-dihydro-1,2-benzisosulfonazolyl) phosphonate		123
 Phosphonic acids $X = O, NR, S$ $Y = O, S$	*n*-Propylphosphonic anhydride (n-PPA)		124
	Bis(*o*-nitrophenyl) phenylphosphonate (BNPP)		97, 98
	Lawesson reagent		125
	1,4,6,9-Dioxa-5-phosphaspiro[4.4]dibenzononane		126
	3,3'-(Phenylphosphinylidene)bis(2(3*H*)-benzoxazolone		127
 Phosphinic acids $Y = O, S$	Diphenylphosphine chloride (DPPCl)		89, 90

Table 4 *(continued)*

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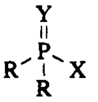
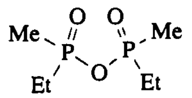
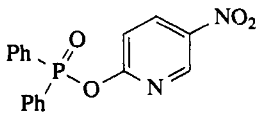
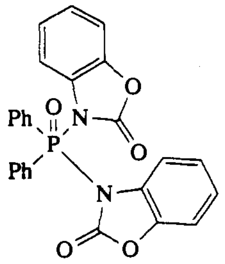
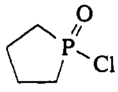
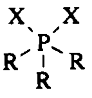
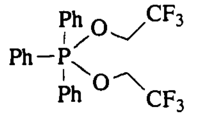
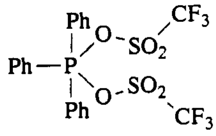
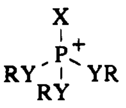
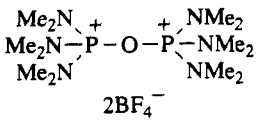
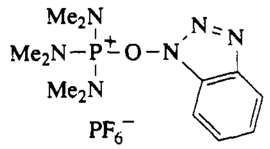
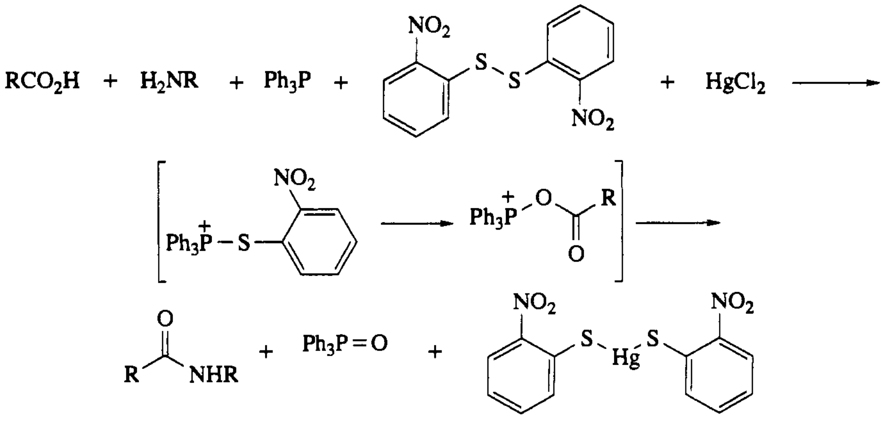
 Phosphinic acids Y = O, S	Ethylmethylphosphinic anhydride (EMPA)		87
	2-(5-Nitropyridyl) diphenylphosphinate		96
	3,3'-(Phenylphosphinylidene)bis(2(3*H*)benzoxazole)		85
	1-Oxo-1-chlorophospholane		88
	Bis(2,2,2-trifluoroethoxy)triphenylphosphorane		128
	Bis(trifluorosulfonyl)triphenylphosphane		129
	Tris(dimethylamino)phosphonium anhydride bis(tetrafluoroborate) (Bate's reagent)		107
	Benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP)		99, 100

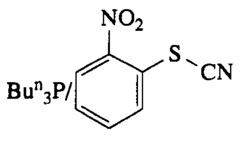
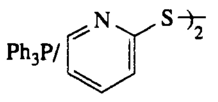
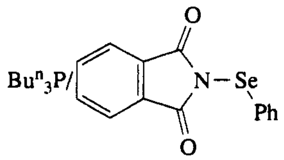
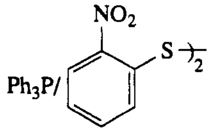
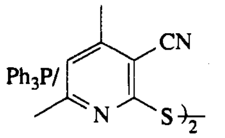
A mild and general method involves pretreatment of amines with one equivalent of trimethylaluminum followed by addition of the ester or lactone.[153] Similarly $RhCl_3$ catalyzes amide bond formation leading to diketopiperazines.[154]

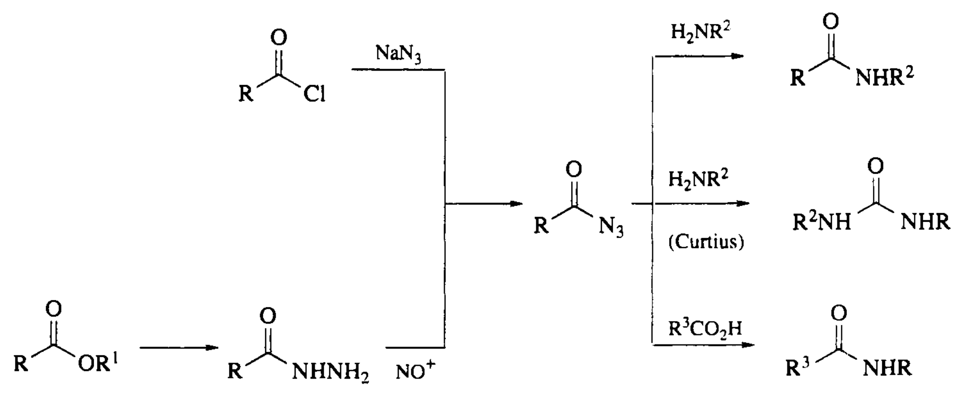
Some simple examples exploit the electrochemical amidation of esters with amines in the cathodic compartment.[155]



(8)

Table 5 Amides *via* Mixed Anhydrides: Use of *P*-acids (Oxidation–Reduction)

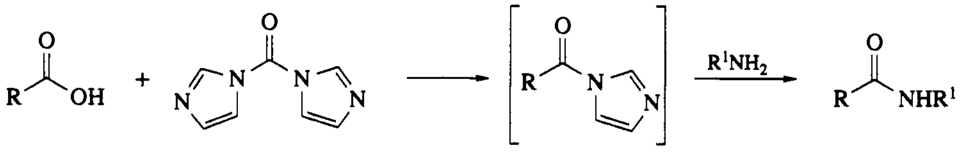
Structure	*Ref.*	*Structure*	*Ref.*
Ph_3P/CCl_4	114	Ph_3P/DEAD	113
Ph_3P/NBS	115		111
	108, 109		112
	110	$(Me_2N)_3P/Cl_2$ or C_2Cl_6	116, 117
	130		



(9)

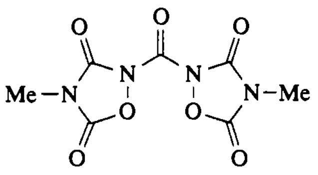
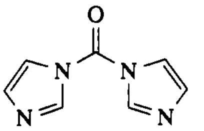
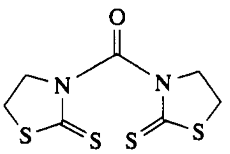
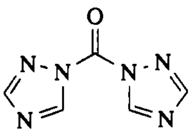
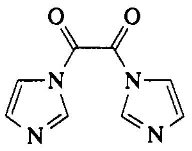
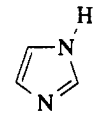
(10)

(11)



(12)

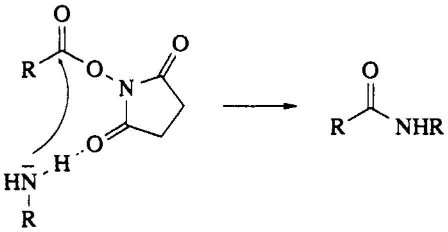
Table 6 Amides *via* Mixed Anhydrides: Use of *N*-acids

Reagent	*Structure*	*Ref.*
2,2'-Carbonylbis(3,5-dioxo-4-methyl-1,2,4-oxadiazolidine) (COMODD)		141
1,1'-Carbonyldiimidazole		136
N,N'-Carbonyldiimido-2-thiono-1,3-thiazolidine		142
N,N'-Carbonyldiimidotriazole		143
N,N'-Oxalyldiimidazole		139
Azide	N_3	131
Triphenyl phosphite, imidazole	$(PhO)_3P$, 	140

(a) Intermolecular from active esters.

To facilitate the amidation of esters, phenols substituted with strongly electron-withdrawing groups have been applied to this reaction. The nucleophile, a primary or secondary amine, only attacks the ester bond at the electrophilic carbonyl group. This reaction has found broad acceptance in peptide chemistry, also due to the fact that many active esters are available as crystalline compounds. Table 7 shows the most important groups. Aromatic alcohols like *p*-nitrophenols[156] or pentafluorophenols[157] are often used to prepare active esters, the latter compounds being used in combination with the *N*-amino protecting group FMOC in solid phase synthesis. These aminolyses can further be catalyzed by the addition of hydroxybenzotriazole.[158]

O-Acyl derivatives of substituted hydroxylamines react readily with amines and amino acids with almost no racemization due to an anchimeric assistance (equation 13) in the transition state. The active esters are prepared either by the activation reagents shown in Table 7 or by activation with DCC and trapping by the hydroxylamine. TBTU[174] reacts fast and has found increasing interest in solid phase synthesis. Following a similar mechanism, oxime esters[159,160] are also used for activation.


(13)

C-Terminal amino acid oxime esters on a polymeric phase have been applied to solid phase peptide synthesis;[161] the protected peptide is cleaved by amino acid esters and other nucleophiles.

Enol ester intermediates are formed from cyclic carbonates,[162,163] a color change indicating the progress of the reaction.

(b) Intermolecular from active thioesters.

In analogy to the active esters, thioesters are prepared by condensation of thiols with carboxylic acids/DCC[178] or carboxylic acid chlorides.[179–181] Aryl thioesters react readily with nucleophiles like amines to give amides. Peptides are prepared without racemization. In the case of *t*-butyl thioesters activation is accomplished by treatment with AgO_2CCF_3.

2,2′-Pyridine disulfide reacts with triphenylphosphine and carboxylic acids to yield active thioesters, which can be amidated with secondary amines.

Due to their obnoxious smell and catalyst-poisoning properties, active thioesters have only encountered limited use.

(c) Miscellaneous.

Lewis acids like tetrachlorosilane in pyridine[182,183] or titanium tetrachloride[184] are reported to give simple amides in moderate yields. Boron trifluoride etherate in the presence of a strong base amidates carboxylic acids in an excess of primary amine.[185] These reactions have not found broad application.

(d) Enzyme-catalyzed peptide bond formation.

The fact that hundreds of coupling reagents have been developed for peptide chemistry demonstrates that there is still a need for general methods with high reaction rates employing equimolar amounts of carboxy and amino components without racemization.[186,187]

Hydrolyzing enzymes, especially proteases, constitute an alternative to chemical synthesis. The principal advantages are the use of unprotected side chain amino acids (except cysteine), racemization-free couplings (especially in fragment couplings) and the specificity of the involved enzyme. As a consequence, the number of synthetic steps is drastically reduced and the procedures are environmentally safe.

The peptide-forming reaction can be carried out under thermodynamic or kinetic control (equation 14). The equilibrium between substrates and product is unfavorable for the peptide (endergonic process due to a loss in entropy). Shifting the equilibrium to the right (increasing K_{syn}) is achieved by optimizing the reaction conditions through increasing K_{ion} by proper choice of pH, use of water miscible organic solvents and use of biphasic systems. The reversal of hydrolysis by formation of insoluble products or extraction of products increases the yield.

For these thermodynamically controlled syntheses a variety of enzymes may be used, *e.g.* serine proteases like chymotrypsin[188] and trypsin,[189] cysteine proteases (thiol proteases) like papain,[190,191] aspartate proteases like pepsin[192] and metalloproteases like thermolysin.[193]

Kinetically controlled syntheses, which are more often studied, can only be carried out by enzymes forming a reactive acyl–enzyme intermediate (serine or cysteine protease, Scheme 5). The reaction starts with weakly activated amino acids (*e.g.* esters), and the rapidly formed reactive intermediate RCOE is attacked by nucleophiles like amines and water. If $k_4 >> k_3$ and $k_4[H_2NR'] > k_3[H_2O]$, the desired peptide accumulates. Short reaction times, low enzyme concentrations and the danger of secondary hydrolysis of the peptide product are characteristics of these reactions. The optimal pH usually lies above pH 8.

Immobilized enzymes which have the same efficiency as soluble enzymes can easily be recovered and reused and exert no proteolytic activities on synthesized peptides.[194]

Table 7 Amides *via* Active Esters

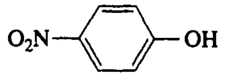
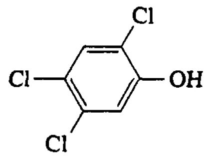
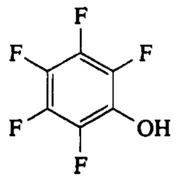
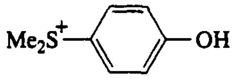
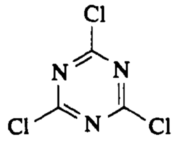
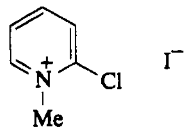
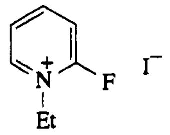
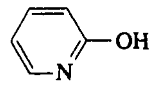
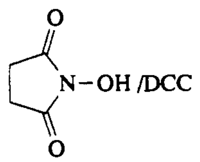
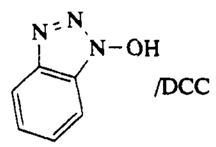
Class	*Reagent*	*Structure*	*Ref.*
Aromatic compounds	*p*-Nitrophenol		156
	2,4,5-Trichlorophenol		164
	Pentafluorophenol		157
	(*p*-Hydroxyphenyl)dimethylsulfonium methyl sulfate (HODMSP *x* $MeSO_4$)		165
	2-Chloro-4,6-disubstituted-1,3,5-triazines		166
	2-Chloro-1-methylpyridinium iodide (CMPI)		167
	2-Fluoro-1-ethylpyridinium iodide		168
	2-Pyridone		169
Hydroxylamines	*N*-Hydroxysuccinimide		158
	1-Hydroxybenzotriazole		158

Table 7 *(continued)*

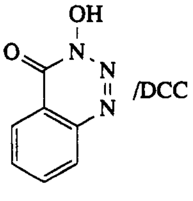
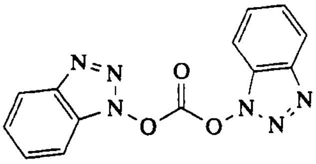
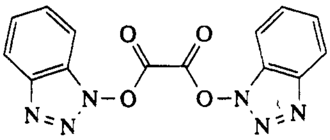
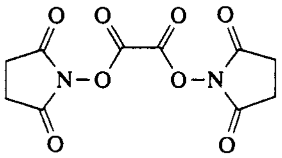
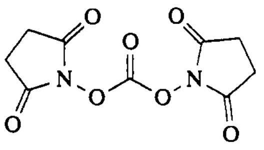
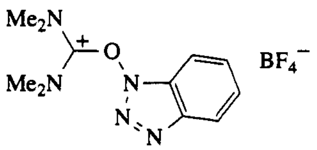
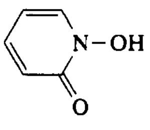
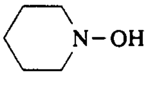
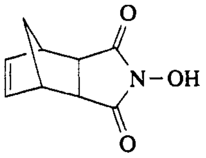
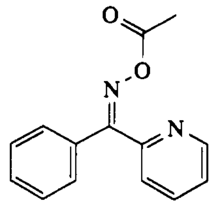
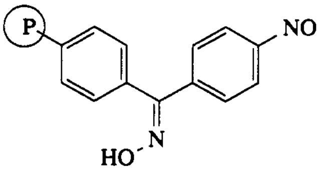
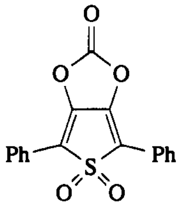
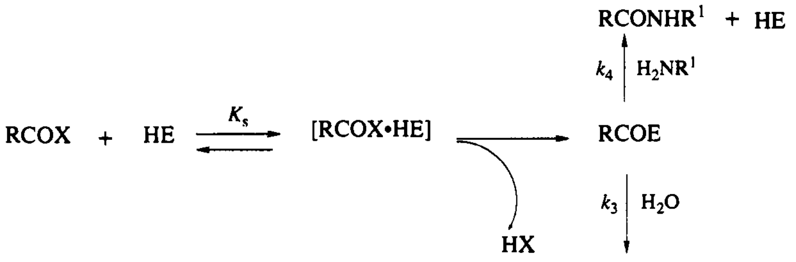
Class	*Reagent*	*Structure*	*Ref.*
Hydroxylamines	3-Hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine		170
	Bis(1-benzotriazolyl) carbonate		171
	Bis(1-benzotriazolyl) oxalate		172
	Bis(*N*-succinimidyl) oxalate		172
	Bis(*N*-succinimidyl) carbonate		173
	2-(1*H*-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate		174
	N-Hydroxypyridone		175
	N-Hydroxypiperidine		176
	N-Hydroxy-5-norbornene-2,3-dicarboxamide		177

Table 7 *(continued)*

Class	*Reagent*	*Structure*	*Ref.*
Oximes	*syn*-Phenylpyridyl *O*-acetyloxime		159
		 /DCC	160
Enol esters	Steglich's reagent		162, 163

$$\mathrm{RCO_2^-} + \mathrm{H_3\overset{+}{N}R'} \xrightleftharpoons{K_{\mathrm{ion}}} \mathrm{RCO_2H} + \mathrm{H_2NR'} \xrightleftharpoons{K_{\mathrm{inv}}} \mathrm{RCONHR'} + \mathrm{H_2O} \qquad (14)$$

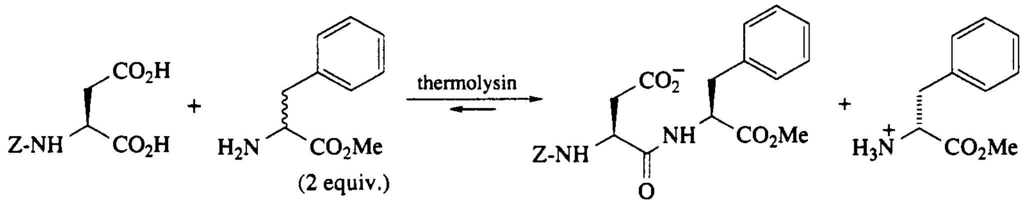
$$K_{\mathrm{syn}} = K_{\mathrm{ion}} + K_{\mathrm{inv}}$$



E = enzyme

Scheme 5

Enzymatic methods were applied to the synthesis of aspartame (equation 15),[195] an artificial sweetener.

 (15)

In the case of thermolysin, a thermodynamically controlled reaction takes place. Only L-Phe reacts with the side chain unprotected L-Asp. The reaction proceeds to the product side by the formation of an insoluble salt with the remaining D-Phe.

Enkephalins, hormones with morphine-like activities, have been synthesized with chymotrypsin and papain[196] as well as carboxypeptidase Y[197] under kinetically controlled conditions.[190]

Further commercial interest was found by the transpeptidation reaction of porcine insulin to human insulin, the latter only differing in the last amino acid of the B-chain (Ala-B30 to Thr-B30). This reaction proceeds under kinetic control with trypsin,[198,199] carboxypeptidase Y[200] or *achromobacter lyticus* protease I.[201]

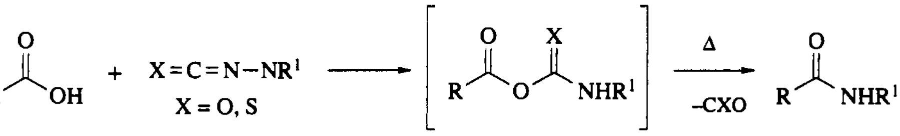
The enzymatic method was extended using chemically modified serine proteases like thiolsubtilisin[202] for the synthesis of the ribonuclease T$_1$ (12–23) fragment.

Recent progress was made in the incorporation of D-amino acids in peptides *via* subtilisin-mediated syntheses in organic solvents[203] or in the application of the nonproteolytic lipases[204] in anhydrous organic solvents.

In general, the enzymatic methods cannot be used universally and have to be optimized for each peptide synthesis. High specificity of an enzyme drastically reduces its wide application; broad specificity has the advantage of universal use, but suffers from early proteolytic cleavage of products.

2.3.1.1.3 *Activation of the amino group*

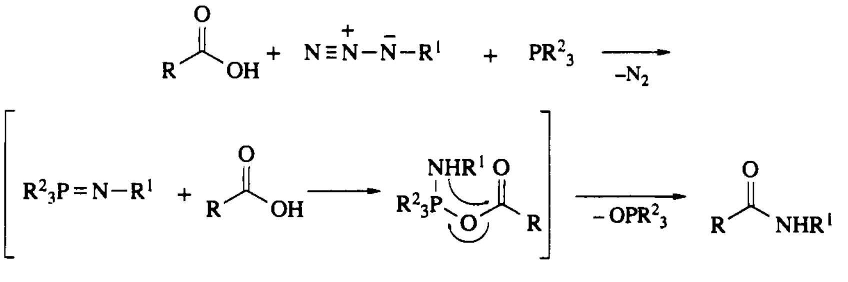
A conceptual alternative way to the activation of the carboxylic acid function is the reaction of carboxylic acids with amino groups activated as isocyanates[205,206] and isothiocyanates (equation 16).[207] Preparation of these derivatives is racemization free. The reaction proceeds *via* mixed acid anhydrides in aromatic hydrocarbon solvents at elevated temperatures, and decarboxylation leads to the *N*-substituted amide. Pyridine as solvent enhances the conversion rate but increases also the amount of the urea side product *via* disproportionation.[205] Application to peptide chemistry is limited, because peptide ester fragments tend to form hydantoins.[205]



(16)

Reaction with *N*-urea-protected amino acids is racemization free, whereas the fragment condensation shows considerable racemization.[208] The analogous condensation with isothiocyanates[207] runs at higher temperatures.

Activation of organic azides with trivalent phosphines under mild conditions followed by reaction with carboxylic acids leads to amides *via* iminophosphoranes in moderate to good yields (equation 17).[209] The driving force of this method lies in the intramolecularity of the acyl transfer and the expulsion of a thermodynamically stable end product.



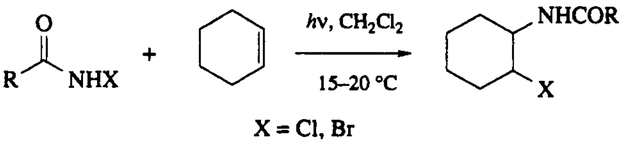
(17)

2.3.1.2 Alkylation and Arylation of Amides

The preparation of *N,N*-disubstituted amides is easily performed with sodium salts of *N*-monosubstituted amides and alkyl bromides or iodides.[210]

Under phase transfer conditions (boiling benzene, 50% aquous sodium hydroxide solution and tetra-*n*-butylammonium hydrogenphosphate) benzamides are monoalkylated.[211] In the solid–liquid PTC system potassium hydride, tetrahydrofuran and 18-crown-6, acidic trifluoroacetamides are rapidly deprotonated and alkylated with lower alkyl, allyl and benzyl halogenides in high yield.[212] Methylation of trifluoroacetamides is carried out under less basic conditions in KOH/acetone.[213] A similar reaction in KOH/DMSO generally allows the efficient reaction of benzamide and acetanilide with primary alkyl halides; with secondary halides only moderate yields are accomplished, whereas tertiary halogenides are not alkylated due to dehydrohalogenation.[214]

The photochemical 1,2-addition of *N*-halogen amides to alkenes results in a mixture of diastereomers (equation 18).[215]

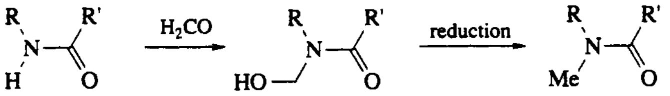


(18)

N-Arylation of benzamide or acetamide is possible under drastic reaction conditions in aryl halides as solvent and at high temperatures,[216] with copper powder as catalyst. A simplified procedure, using tris(3,6-dioxaheptyl)amine (TDA-1) and copper(I) chloride as PTC system, performs this reaction with quasi-stoichiometric quantities of bromobenzene under relatively mild conditions.[217]

The addition of mercury(II) nitrate activated alkenes to amides follows the rule of Markovnikov. Subsequent $NaBH_4$ demercuriation leads to more highly substituted amides in moderate to good yields.[218]

An efficient two-step procedure for the *N*-methylation of amides (equation 19) involves the preparation of intermediate methylols with subsequent reduction using triethylsilane, hydrogen/Pd–C[219] or cyanoborohydride.[220,221]



(19)

2.3.1.3 Nitriles

2.3.1.3.1 Hydration

Under neutral conditions and at high temperatures (*ca.* 180 °C) nitriles react with water to give amides (equation 20). ZnO and CdO are efficient catalysts.[222] To accelerate the reaction rate, acid treatment under a variety of conditions can be carried out: hydrochloric acid,[223] hydrogen chloride or bromide in formic acid,[224] alcoholic hydrogen chloride solutions,[225-227] polyphosphoric acid[228,229] and boron trifluoride in aqueous acetic acid[228] are all effective.

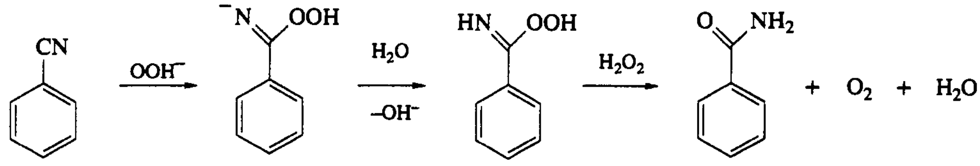
(20)

Alternatively, applying basic reaction conditions, partial hydrolysis with hydroxide-loaded anion exchangers in boiling water leads to aromatic amides in good yield.[230-232]

Hydrolysis with powdered potassium hydroxide or potassium fluoride on alumina[233] in *t*-butyl alcohol converts nitriles to amides without further hydrolysis to carboxlic acids.[234] Under similar conditions, addition of alkyl halides gives *N*-alkylcarboxyamides.[235] Less drastic acidic or basic hydrolysis conditions involve disproportionation of alkaline hydrogen peroxide with concomitant hydration of the nitrile (equation 21).[236,237]

Aromatic nitriles generally afford amides in yields of 80–90%, but in the aliphatic series only 50–60% yields are achieved.

A modification of this method using phase transfer catalysis leads to improved yields in shorter reaction times.[238]



(21)

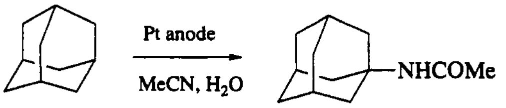
With the help of metal catalysis amidation takes place at room temperature under apparently neutral conditions. Manganese dioxide in large quantities,[239] or, even better, manganese dioxide on silica gel,[240] is well suited to this conversion. Even compounds with functional groups labile to manganese dioxide, for example benzylic groups, are suited for the hydration. With pentacarbonylmanganese bromide, nitrile hydration takes place under PTC conditions.[241]

Copper(0) catalyzes the hydration of sensitive nitriles like 2-acrylamide.[242]

Other processes involving metal catalysts like nickel(II), zinc(II), palladium(II) and ruthenium(I) have not found broad application, but a related amidation of nitriles uses the ruthenium catalyst [$RuH_2(PPh_3)_4$].[243]

2.3.1.3.2 Ritter-type reactions

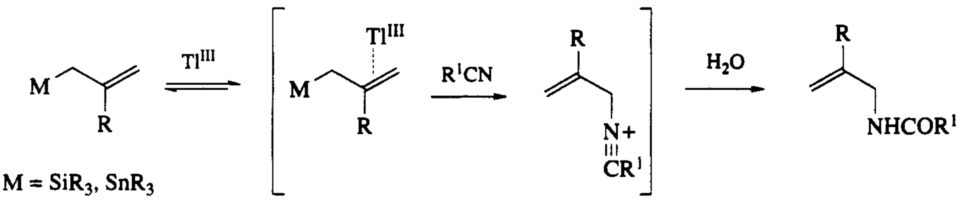
In general, treatment of carbonium ions with nitriles under a variety of conditions yields *N*-substituted amines.[244] Anodic oxidation in acetonitrile converts selected aliphatic compounds to acetamides, *e.g.* adamantane to adamantylacetamide (equation 22).[245]



(22)

Alkenes and alcohols condense with nitriles under drastic acidic conditions. In most cases sulfuric acid is used either neat or with solvents such as acetic acid.[244,246] In liquid hydrogen fluoride containing defined amounts of water, nitriles react with linear or branched alkenes to form amides in good yields.[247]

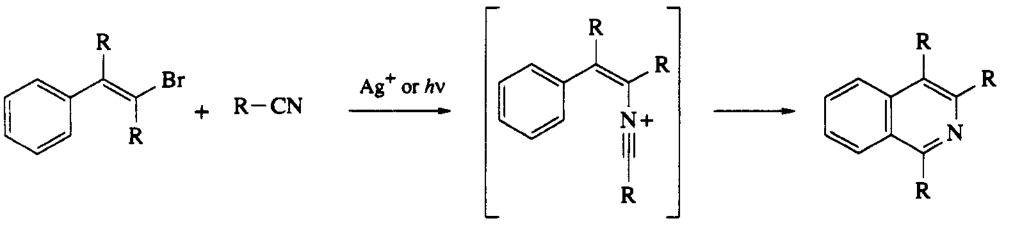
Treatment of allylsilanes and allylstannanes with thallium(III) salts in acetonitrile activates the alkene for nucleophilic attack of the nitrile group. The generated nitrilium cation (equation 23) is hydrolyzed to the corresponding *N*-allylamide.[248]



(23)

Allyl halides react with acetonitriles after anodic oxidation[245,249] under acidic conditions[244,250] or in the presence of nitrosonium hexafluorophosphate[251] to give the corresponding amides.

Vinyl cations, generated from β-arylvinyl bromides by silver(I)-assisted solvolysis or by photolysis, are trapped by nitriles to yield isoquinolines (equation 24).[252]

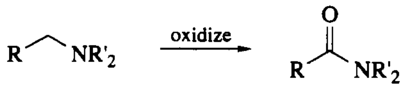


(24)

The reaction of nitriles with carbon monoxide, carbonyl compounds, carboxylates, ketenes, 1-aminoalkynes and carbenes has been reviewed recently.[250]

2.3.1.4 Oxidation

Oxidation of amines containing α-hydrogen atoms is of variable difficulty (equation 25). Permanganate oxidation of 1-aryl-5-(tertiary)amino-*v*-triazoles leads to the corresponding amides.[253] Benzyl(triethyl)ammonium permanganate[254] oxidizes a variety of simple, substituted amines. Tertiary amines give good yields of amides, but secondary and primary amines give moderate yields due to the formation of imines.



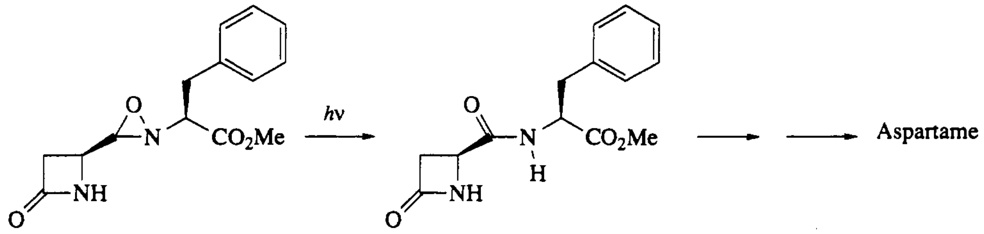
(25)

A similar selective oxidation of *N*-methyl groups has been accomplished with osmium tetroxide in the alkaloids delphinine and mesaconitine.[255]

Lactams are formed by bromination (bromine, *N*-bromosuccinimide) of cyclic tertiary amines, resulting in an intermediate iminium salt that can be isolated.[256] Oxidation by metal oxides,[257] autoxidation,[258] photochemical oxidation[259] and electrooxidation[260] are alternatives with limited scope.

The oxidation of aldehydes in the presence of amines occurs at low temperatures with nickel peroxide.[261] Similarly, the oxidation of aromatic aldehydes with manganese dioxide[262] or ruthenium chloride[263] in the presence of sodium cyanide and an amine leads to the corresponding amides.

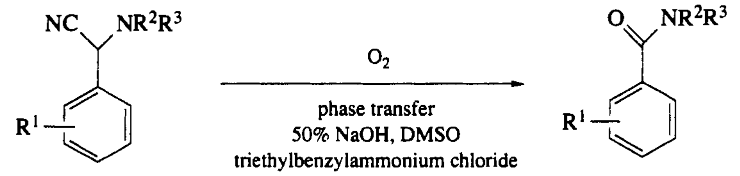
The dipeptide sweetener aspartame has been synthesized *via* an oxaziridine, which was rearranged by irradiation with UV light (equation 26).[264]



(26)

Aldehyde bisulfite adducts are oxidized by dimethyl sulfoxide/acetic anhydride and converted to simple amides in good yield.[265]

In the oxidative decyanation of dialkylaminophenylacetonitriles under phase transfer conditions the generated α-carbanion is oxidized by a stream of oxygen (equation 27).[266] Catalytically, a direct conversion occurs with the system consisting of $Pd(OAc)_2$, benzyl bromide and potassium carbonate.[267]



(27)

Oxidations of hydroxamic acids[268] by periodate (assumed to involve a nitrosylacyl intermediate) and of hydrazides[269] by potassium ferrocyanide, followed by quenching with amines, are of limited preparative value.

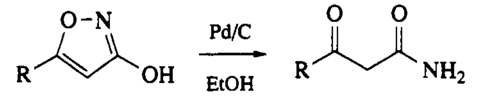
2.3.1.5 Reduction

Under mild conditions, titanium trichloride reduces hydroxamic acids to the corresponding amides and lactams (including β-lactams) in good yield (equation 28).[270]

(28)

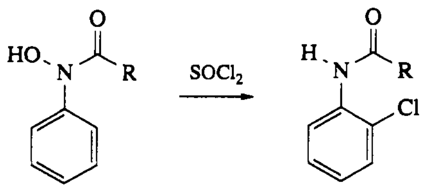
Brief heating of hydroxamic acids in phosphorus tribromide/benzene,[271] as well as treatment with Raney-Ni,[272] results in the formation of lactams.

Isoxazole derivatives, considered as cyclic β-ketohydroxamic acids, are opened by hydrogenation over palladium or platinum[273] to give the corresponding β-ketoamides in excellent yields (equation 29).



(29)

Thionyl chloride reacts with *N*-arylhydroxamic acids to form the corresponding amides *via* ortho-halogenation (equation 30).[274]



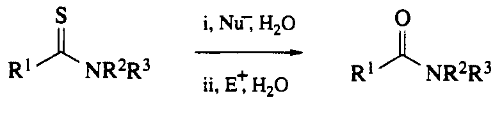
(30)

Hydrazides are hydrogenated by a substantial excess of Raney nickel.[275] Phenylhydrazides are reductively cleaved over palladium/charcoal as catalyst, and the corresponding amides are obtained in good yields.[276]

The reductive cleavage of benzoyl azide runs at low temperature with tetracarbonylhydridoferrate, $[HFe(CO)_4]^-$,[277] and with diphosphorus tetraiodide in benzene under reflux.[278] Curtius rearrangement side products are not observed.

2.3.1.6 Thioamides

Due to the ease of preparation of thioamides (*cf.* Chapter 2.4. of this volume) there is considerable interest in the desulfurization of these to the corresponding amides (equation 31).

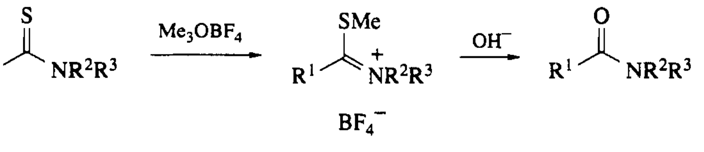


(31)

With the exception of a few examples of nucleophilic attack on the thiocarbonyl group, including a more recently published method using sodium hydroxide under phase transfer conditions,[279,280] most conversions are carried out with oxidative reagents. Sodium peroxide,[281] dimethyl sulfoxide with acid[282] or iodine,[283] selenium-derived reagents[284,285] and bis(*p*-methoxyphenyl)telluroxide[286] have been used.

Catalytic amounts of halogen accelerate the conversion, especially with strong base under phase transfer conditions.[280,287] *m*-Chloroperbenzoic acid reacts with thiolactams and thioamides and gives good yields of amides with precipitation of sulfur.[288]

Alkylation of thioamides with Meerwein's reagent (trialkoxonium fluoroborate)[289] proceeds *via* a thioiminoester and subsequent base hydrolysis with sodium carbonate (equation 32). For the synthesis of 2-pyridones from 2-thiopyridones, chloroacetic acid has been used.[290] Mild reaction conditions are provided by nitrosyl species which are derived from a variety of reagents: excess $NaNO_2/HCl$[291] in aqueous medium, nitrosonium tetrafluoroborate[292] in dichloromethane, dinitrogen tetroxide[293] in acetonitrile at low temperature and *t*-butyl thionitrate.[294]

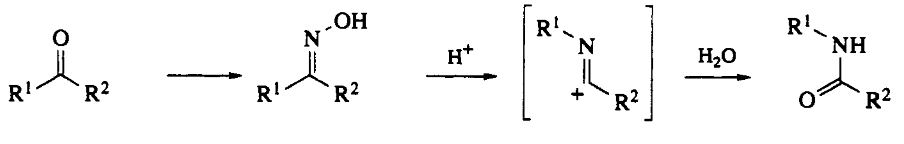


(32)

2.3.1.7 Rearrangements

2.3.1.7.1 Beckmann, Schmidt

The Beckmann rearrangement converts oximes to amides or lactams and was reviewed recently (equation 33).[295]


(33)

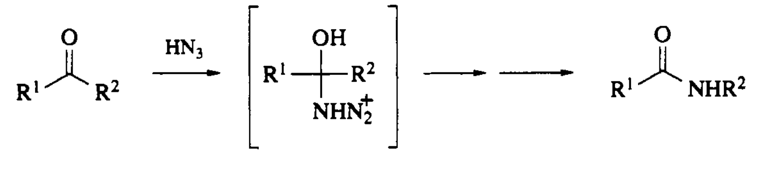
In general, this rearrangement is stereospecific, involving the migration of the residue *anti* to the leaving group on nitrogen. The reaction usually occurs under acidic conditions. PCl_5 in ether,[296] thionyl chloride in dioxane,[297] boric acid[298] and more frequently polyphosporic acid[299] are used at elevated temperatures. Due to its viscosity and low dissolving ability resulting in large reaction volumes, polyphosphoric acid can be effectively replaced by trimethylsilylpolyphosphate[300] (readily prepared from phosphorus pentoxide and hexamethyldisiloxane) or the two phase system polyphosphoric acid/xylene.[301] The mildly basic hexamethylphosphoramide causes rearrangement at higher temperatures.

Activation of the oxime with benzenesulfonyl chloride or *p*-toluenesulfonyl chloride leads to sulfonate esters which undergo the Beckmann reaction with or without isolation.[302,303] The sulfonate esters also rearrange under mild reaction conditions on silica gel.[304] Under neutral conditions, *N,N*-carbonyldiimidazole activates oximes in the presence of allyl bromide, followed by spontaneous Beckmann rearrangement.[305]

Dependent on the stereochemistry of the oxime sulfonate and the different groups R^1, R^2, in many cases only one preferred stereoisomer rearranges. In hydrochloric acid/acetic acid, isomerization gives rise to only one final product.[306]

Hydroxylamine sulfonic acid,[307] hydroxylamine and catalytic amounts of trifluoromethanesulfonic acid,[308] or *O*-mesitylenesulfonylhydroxylamine[309] converts ketones directly to the lactams under mild conditions (reflux in formic acid).

The Schmidt reaction is closely related to the Beckmann reaction (equation 34). Acyclic and cyclic ketones are transformed to amides and lactams by treatment with hydrogen azide.[310,311] With bridged bicyclic ketones, the regioselectivity of the migration is opposite to the direction of the Beckmann reaction.[311,312] The Schmidt reaction has been applied to asymmetric synthesis starting from optically active α,α-dialkylated β-keto esters. High chemical and optical yields have been obtained (equation 35).[313]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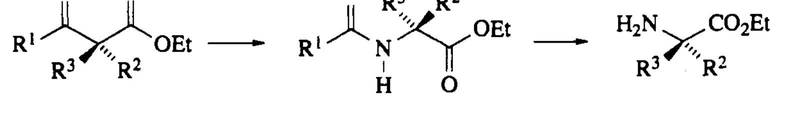
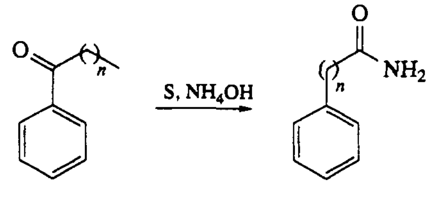

(35)

2.3.1.7.2 Willgerodt

In the Willgerodt reaction, aryl alkyl ketones react with sulfur and ammonium hydroxide to give amides with the same number of carbon atoms (equation 36).[314] In an extension, aliphatic ketones,[315] aldehydes[316] and unsaturated hydrocarbons[317] also can be used as starting materials.

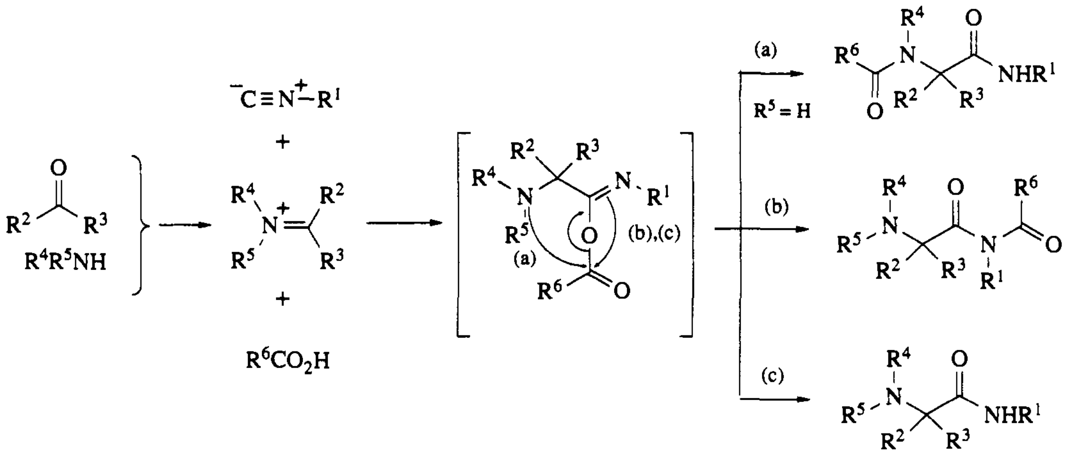


(36)

The Kindler modification of the Willgerodt reaction uses sulfur and dry amines, ammonia, primary amines or secondary amines, which leads to the formation of thioamides (conversion of thioamides to amides *cf.* Section 2.3.1.7).[318] This reaction can also be extended to aldehydes,[319] hydrocarbons[320] and heterocyclic ketones.[321] Due to the usually low to moderate yields this reaction has not found general application.

2.3.1.7.3 Ugi four component reaction

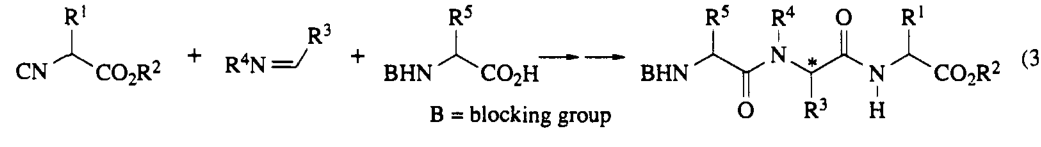
The four component condensation (Ugi reaction)[322–324] converts a mixture of substituted amine, isonitrile, aldehyde (or ketone) and carboxylic acid (Scheme 6) to α-acylaminocarboxylic acid amides (pathway a), to diacylamines (pathway b) and to α-aminocarboxylic acid amides (pathway c).[325]



Scheme 6

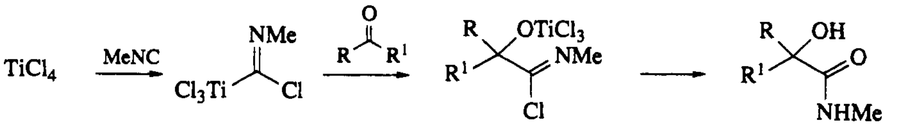
Also, β-lactams are obtained in high yield by the reaction of β-aminocarboxylic acids with aldehydes and isocyanides.[324,326]

Tripeptides can be obtained in good yields by reacting primary amines with aldehydes leading to the intermediate Schiff base. Applying pathway (b; Scheme 6) with isocyanide amino acid esters and *N*-protected amino acids, the Ugi reaction occurs[322,323] with good yields (equation 37). Asymmetric induction on the new stereogenic centre (*) is low, but can be enhanced by the use of chiral amines.



(37)

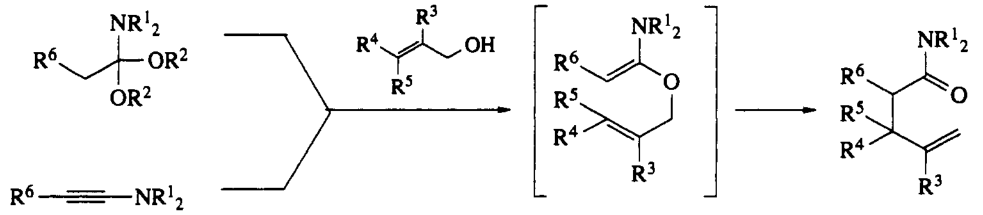
A stereochemical control of the Ugi reaction can be effected with carbohydrates as chiral templates (*e.g.* tetrakis(*O*-pivaloyl)galactosylamine), which gives rise to easily separable amides. From these a variety of non-natural amino acids can be derived after acidic hydrolysis.[327] The Passerini reaction,[328] related to the Ugi rearrangement, gives α-hydroxyamides. A modification of this reaction using titanium tetrachloride gives α-branched amides in high yields *via* *C*-metalated imidoyl chlorides[329] (equation 38).



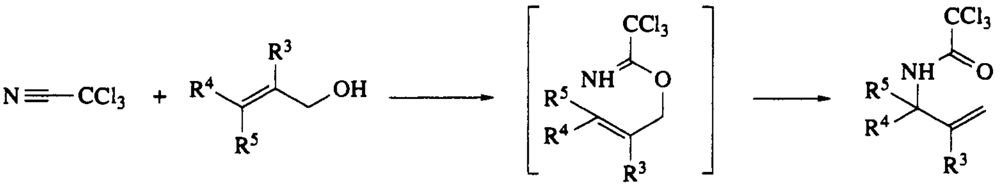
(38)

2.3.1.7.4 Miscellaneous

The amide acetal Claisen rearrangement[330] and the ynamine Claisen rearrangement[331,332] proceed *via* a common [3,3] sigmatropic shift of *N*,*O*-ketene acetals (equation 39) and lead to γ,δ-unsaturated amides under mild conditions. Modification of this procedure involves the use of 3-(trimethylsilyl)allyl alcohols for the preparation of β,γ-unsaturated amides,[333] or conversion of propargyl alcohols to β-allenic amides, which may be rearranged to 2,4-dienamides.[334] Similarly, allylic and propargylic imidic esters[335] undergo stereospecific [3,3] sigmatropic rearrangement to allylic acetamides.



(39)

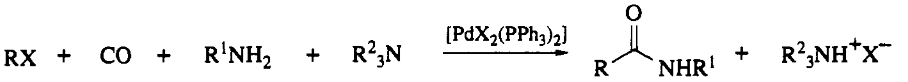


(40)

With trichloroacetimidates, 1,3-conversion of allylic alcohols to allylic amines proceeds smoothly (equation 40).

2.3.1.8 Construction of the Carbon Frame

In the Heck reaction, aryl, heterocyclic and vinyl halides[336,337] or aryl triflates[338] react with excess carbon monoxide and primary or secondary amines to give substituted amides, in the presence of a palladium(II) catalyst (equation 41). *Cis*- and *trans*-vinyl halides react stereoselectively.

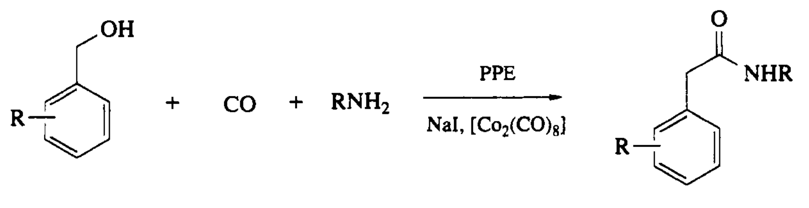


$$RX + CO + R^1NH_2 + R^2{}_3N \xrightarrow{[PdX_2(PPh_3)_2]} RC(O)NHR^1 + R^2{}_3NH^+X^- \quad (41)$$

Intramolecularly, insertion of carbon monoxide into vinyl halides bearing a secondary amino group yields α-methylene five-, six- and seven-membered ring lactams.[339]

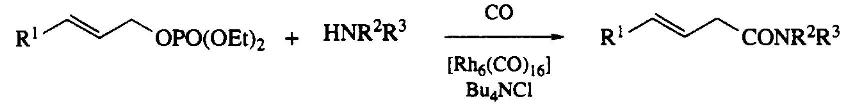
Catalytic double carbonylation of organohalogen compounds[340,341] or simple alkenes[342] needs higher CO pressures (10 atm at room temperature), and mainly provides α-ketoamides.

Substituted benzyl alcohols can be converted with cobalt carbonyl to the homologous amides under mild conditions, even using sterically hindered secondary amines (equation 42).



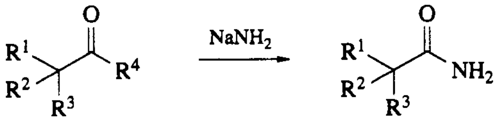
(42)

Vinyl bromides are directly aminocarbonylated by nickel carbonyl and amines.[343] Very similarly, $Rh_6(CO)_{16}$ and Bu_4NCl as catalyst convert allylphosphates to β,γ-unsaturated amides *via* π-allylrhodium complexes (equation 43).[344] Although palladium(0) complexes are more reactive than rhodium(I) complexes, palladium(0) complexes undergo side reactions, like reductive elimination in the presence of carbon monoxide, and direct nucleophilic attack by amines.



(43)

The Haller–Bauer reaction is applied to nonenolizable ketones which react with fresh sodium amide to form amides (equation 44).[345] Cleavage of aliphatic or alicyclic phenyl ketones to produce tertiary carboxamides is the most useful. With equivalent amounts of 1,4-diazabicyclo[2.2.2]octane (DABCO) the reaction proceeds under milder conditions.[346]



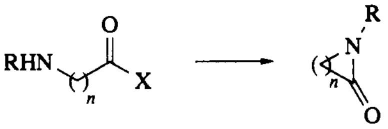
(44)

2.3.2 LACTAMS

2.3.2.1 Intramolecular Acylation of Amino Acid Derivatives

Generally, the formation of lactams follows the same activation procedures as those discussed in Section 2.3.1.1.

To minimize dimerization products, intramolecular condensations have to be carried out under carefully controlled conditions and in high dilution. The formation of small rings obeys the Baldwin rules (equation 45).[347]



(45)

$n \geq 2$; X = OR, OH

Simple five-, six- and seven-membered lactams are obtained under cyclodehydration conditions by boiling ω-amino acids and alumina or silica gel in excess toluene.[348]

Metal compounds like organostannyl oxides[349] and titanium(IV) alkoxides[350] have been used in the synthesis of macrocyclic lactams.

Reduced copper–titanium catalysts convert ε-aminocapronitrile to ε-caprolactam.[351]

Intramolecular opening of *N*-(haloalkyl)azetidin-2-ones *via trans* amidation affords medium and unstrained ring azalactams.[352]

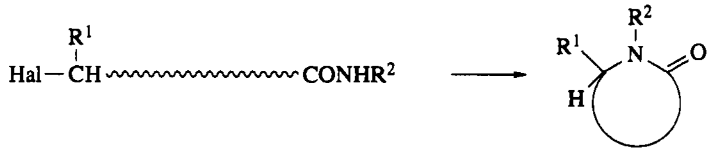
For the preparation of cyclic peptides, standard procedures are still the azide and the active ester method. In a variety of bicyclic analogs of somatostatin, azide coupling is applied twice and yields can be improved by catalysis with *N*-hydroxybenzotriazole.[353]

Cyclopeptide alkaloids are prepared in good yield by catalytic hydrogenation of pentafluorophenyl esters of ω-(*Z*)-aminocarbocyxlic acids. The slow release of the amino function under these conditions minimizes dimerization.[354]

Other masked forms of the ω-amino function include the azido function, which can be readily reduced by triphenylphosphine[355] and the nitro function, which can be reduced by standard hydrogenating procedures including an electrochemical process.[356]

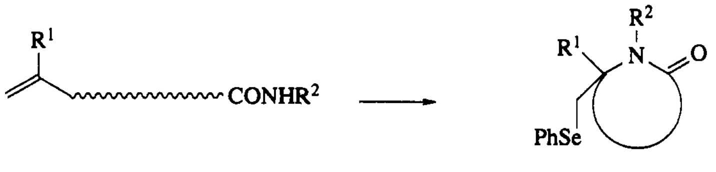
2.3.2.2 Intramolecular Alkylation of Amide Derivatives

Cyclization of ω-halocarboxamides (equation 46) requires the use of metallic amides and hydrides under anhydrous conditions. Phase transfer catalysis with strongly basic ion exchange resins in 50% sodium hydroxide solution give four- to seven-membered lactams in good to excellent yield.[357]



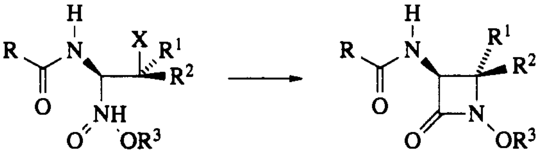
(46)

Reaction of *N*-alkylalkenamides with organoselenium compounds activates the double bond and gives rise to lactams (equation 47).[358]



(47)

In total syntheses of β-lactam antibiotics, the formation of 2-azetidinones is crucial. In a biomimetic synthesis, the N—C4 bond is best closed by the open chain hydroxamate (equation 48),[359] because, depending on the different pK_a values of the three potentially ionizable positions, only the ring-forming amide is ionized. β-halohydroxamates are cyclized by base treatment, whereas β-hydroxyhydroxamates cyclize *via* the Mitsunobu reaction (diethyl azodicarboxylate, Ph_3P).[360] More highly substituted precursors yield isomeric β-lactams after rearrangement.[361]

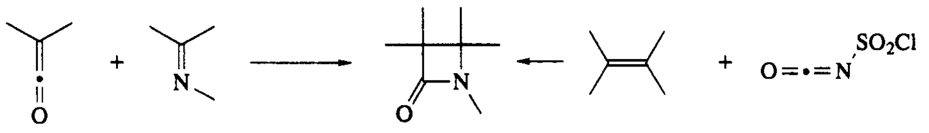


(48)

Under oxidative (iodosobenzene diacetate, I_2) and photolytic conditions some nonactivated amides from the alkaloid and steroid series form lactams *via* radical mechanisms.[362]

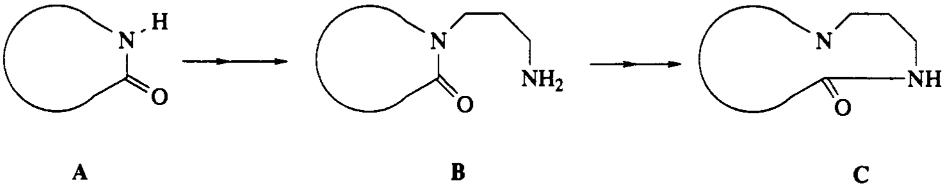
2.3.2.3 Construction of the Carbon Frame

The main principles of lactam, especially β-lactam, formation by cycloaddition, exemplified by equation (49),[363] are described in Volume 5, Part 2 of this series.



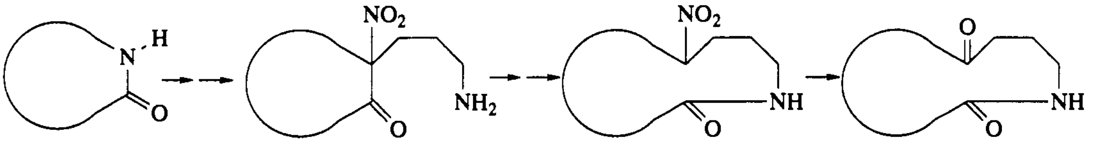
(49)

Chain elongation leading to ring enlargement of lactams takes place in the ZIP reaction (equation 50),[364] where derivatives of trimethylenediamines isomerize to lactams containing a secondary amine and a monosubstituted amide. The reaction sequence can be repeated several times to gain access to larger ring systems.



(50)

In a modified reaction sequence starting with cyclic α-nitro ketones the same reaction leads to nitrolactams, which can be converted to ketolactams in moderate yields (equation 51).[365] The same class of compounds is obtained when α-alkylamino-β-diketo derivatives are treated with base.[366]

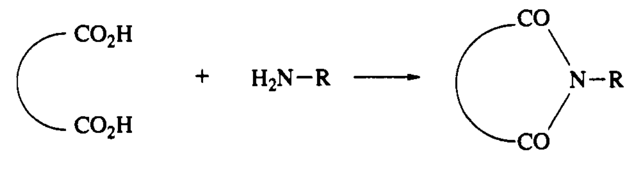


(51)

2.3.3 IMIDES

Imides are monoacyl derivatives of amides or lactams and are used as valuable intermediates in organic synthesis as well as in biologically active compounds like drugs, fungicides and herbicides.

The preparation of imides was reviewed recently and many methods are recommended.[3-6,367] Under somewhat drastic conditions (≈ 200 °C) dicarboxylic acids react with ammonia, or compounds which are able to produce ammonia like urea, thiourea, formamide, sulfamic acid, ammonium carbonate and others to form cyclic imides (equation 52).[367] Monoammonium salts of dicarboxylic acids give imides under pyrolytic conditions when distilled under reduced pressure.[368]



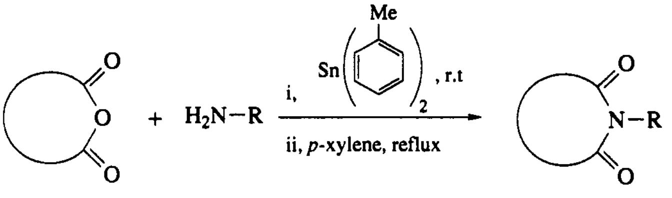
(52)

Ammonia and amines react with partially or fully activated carboxylic acid derivatives (acylating reagents) like acid anhydrides, acid halides, ammonium salts of monoesters, monoamides with heating, diesters under basic conditions and dinitriles after partial hydrolysis.[367]

Intramolecular cyclization occurs with carboxylic acid nitriles, amide nitriles, and ester amides under strongly basic and anhydrous conditions.

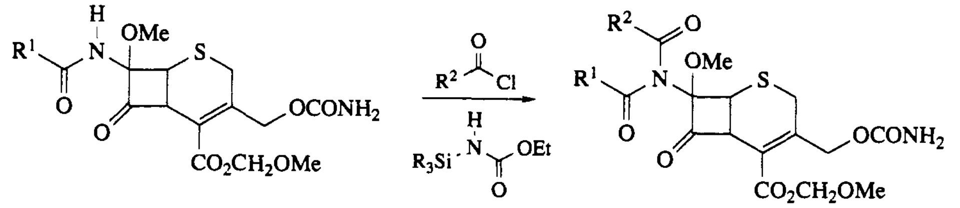
To avoid gaseous ammonia dicarboxylic anhydrides are heated with a slight excess of urea, until the cessation of gas evolution indicates completion of the reaction.[368]

Under milder, neutral conditions, organometallics like 1,1-dimethylstannocene (equation 53) react as Lewis acid and dehydrating reagents at room temperature with cyclic anhydrides and amines.[369]



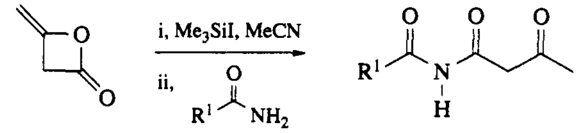
(53)

Acylation of amide bonds in peptides can be accomplished by silylation with trimethylsilyl chloride followed by treatment with acid chlorides.[370] A modified procedure has been applied to acylation of the sensitive β-lactam antibiotic cephamycin, where silylamides like trimethylsilylurethane trap generated HCl (equation 54).[371]



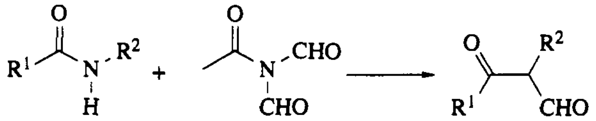
(54)

Diketenes react with carboxamides in the presence of trimethylsilyl iodide to yield *N*-acetoacetylcarboxamides (equation 55).[372]

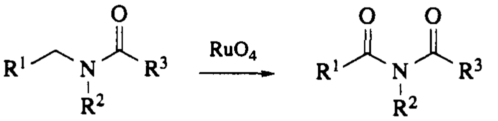


(55)

With the powerful formylation reagent *N*,*N*-diformylacetamide imides are obtained from amides or lactams in good yield (equation 56).[373] Oxidation reactions also have found some application in the synthesis of imides. For example, catalytic amounts of ruthenium tetroxide and 10% aqueous $NaIO_4$ as cooxidant in an optimized reaction medium (ethyl acetate–water) oxidize acyclic amides to imides.[374] The reaction rate is inversely related to the electron-withdrawing power of the acyl group, *i.e.* the electron density at the nitrogen atom (equation 57).



(56)



(57)

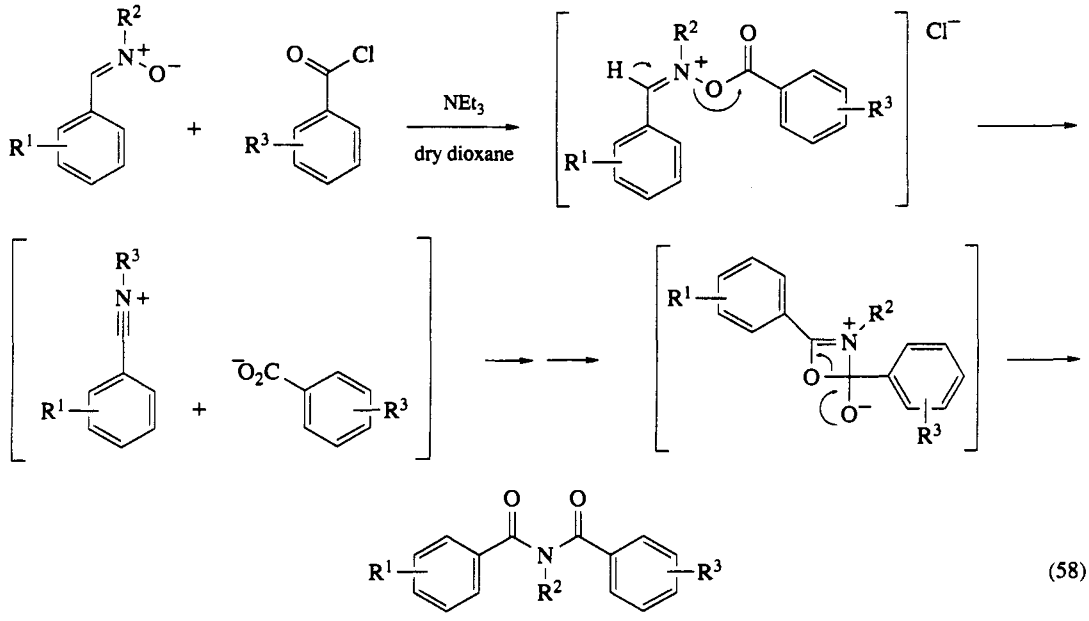
According to the same procedure, *N*-alkyllactams are converted to cyclic imides, where the position of the new carbonyl group depends on the ring size of the lactam.[375] Racemization of chiral *N*-acyl-pyrrolidines or -piperidines can be ruled out.[376,377]

Electrochemical anodic oxidation of amides and *N*-alkyllactams can be carried out with *N*-hydroxyphthalimide as mediator.[378] Oxidation takes place predominantly at the endocyclic carbon α to the nitrogen. The susceptibility of five-membered rings to oxidation is much higher than that of six-membered rings.

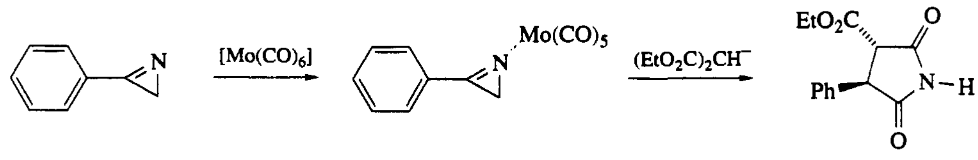
A photocatalytic oxidation takes place in a suspension of titanium(IV) oxide and five-membered or six-membered ring lactams.[379]

Reaction of nitrones with aroyl chlorides in the presence of triethylamine yields *N*,*N*-diacylamines (equation 58).[380] The reaction can be rationalized by formation of an aroyloxy(benzylidene)ammonium chloride, with elimination of the carboxylic acid and readdition of carboxylate to the nitrilium ion followed by 1,3-acyl shift to give the *N*,*N*-diacylamine.

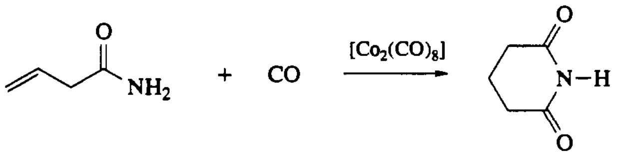
Transition metal complexes are used as catalysts and as reagents in the synthesis of imides. Molybdenum hexacarbonyl activates strained aziridines and allows the nucleophilic attack of carbanions. Intramolecular rearrangement and a final oxidation yields imides completely stereospecifically (equation 59).[381] Dicobalt octacarbonyl catalyzes the conversion of β,γ-unsaturated amides to imides in the presence of carbon monoxide (equation 60).[382]



(58)



(59)



(60)

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2.4
Synthesis of Thioamides and Thiolactams

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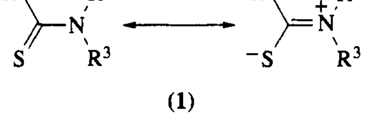
2.4.1 INTRODUCTION

The size difference between carbon and sulfur atoms leads to relatively inefficient overlap of π-orbitals in the C=S bond. Consequently, thiocarbonyl compounds are in general highly reactive and have a tendency to di-, oligo- or poly-merize. This is particularly true for thioaldehydes, thioketones,[1] and thioketenes.[2] In contrast, thioamides (**1**) are usually perfectly stable and can be handled without problems. This stability can be understood in terms of a pronounced resonance interaction between the C=S π-bond and the nonbonding electron pair on nitrogen. The analogous electron delocalization prevails in thiolactams.[3]



(**1**)

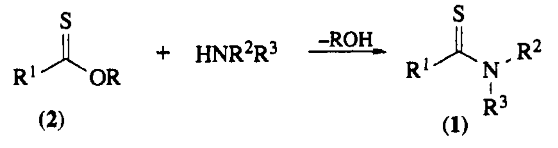
A large body of work has been directed toward synthesis and applications of thioamides.[4–7] The most important uses are as synthetic intermediates[5,8–10] and in heterocyclic synthesis.[5,11,12] Among the wealth of synthetic methods that lead to thioamides, thioacylation routes are certainly of prime importance.

Alternatively, for *N*-monosubstituted thioamides, methods based on nucleophilic addition of hydride, carbanions, or cyanide to isothiocyanates are available,[4,5,7] and, quite often, thionation of the corresponding amides provides a convenient route to thioamides (*cf.* Volume 6, Chapters 4.1 and 4.3).[13]

2.4.2 THIOACYLATION OF AMINES

2.4.2.1 Thioacylation with *O*-Alkyl Thiocarboxylates

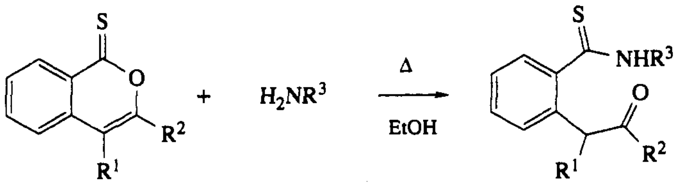
Nucleophilic attack of ammonia or of a primary or secondary amine on an *O*-alkyl thiocarboxylate (**2**) provides a formally straightforward approach to thioamides and a number of examples have been reported (equation 1).[14,15] However, some limitations should be noted. Thus, there is a tendency of esters (**2**) to rearrange to their *S*-alkyl isomers on heating (*cf.* Volume 6, Chapter 2.5)[15] and these yield amides with amines rather than thioamides. Besides, excess primary amine will lead to amidine formation, or the tetrahedral intermediate of the substitution reaction may break down to an imidate rather than a thioamide (*cf.* Volume 6, Chapter 2.7). These unwanted side reactions are favoured in polar, protic solvents such as ethanol. In contrast, THF has proven to be particularly useful in the synthesis of tertiary thioamides according to equation (1).[14] For improved reactivity in the preparation of *N*-aryl derivatives and milder reaction conditions, it is advantageous to employ the amine in the form of its Mg salt.[14]



(**2**) (**1**) (1)

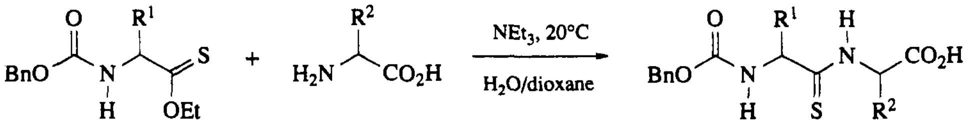
No activation is required in the synthesis of thioformamides using HCSOEt; this particularly reactive thioester allows one to work at 0 °C and offers the best route to the unsubstituted thioformamide (**1**; $R^1 = R^2 = R^3 = H$; 90%)[16] or *N*-alkylthioformamides.[16,17] This reagent has also been successfully employed in the thioformylation of hydroxylamines to give thioformohydroxamic acids (**1**; $R^1 = H$, $R^2 = OR^4$)[18] and, in a basic medium, also of hydrazines to give thioformohydrazides (**1**; $R^1 = H$, $R^2 = NR^4R^5$).[19]

Using primary aliphatic amines, ring opening of isocoumarin-derived thiolactones (**3**) according to equation (2) offers a convenient access to *o*-(2-oxoalkyl)thiobenzamides (**4**) with yields in the 80% range; aromatic amines give side reactions.[20]



(**3**) (**4**) (2)

O-Methyl thiocarboxylates are very suitable for the *N*-thioacylation of *N*-unprotected amino acids. Thus, shaking a heterogenous mixture of PhCSOMe in ether and the amino acid in aq. NaOH gives good yields of *N*-thiobenzoylated material.[21] Using *O*-alkyl thiocarboxylates of amino acids (**2**; $R^1 = R^2NHCHR^3$), the approach has been extended to synthesize endothiopeptides such as (**5**);[22–24] formation of imidates may interfere with the desired process.[23] The reaction has been carried out in water/THF using Na_2CO_3[24] or as shown in equation (3).[22]

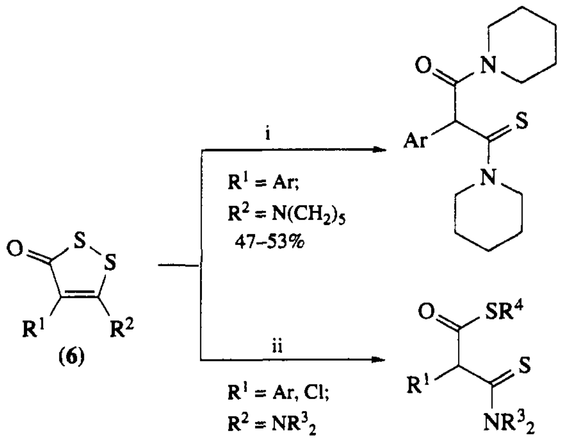


(**5**) (3)

$R^1 = R^2 = Me$, 45%; $R^1 = Bn$, $R^2 = Me$, 57%

2.4.2.2 Thioacylation with 3*H*-1,2-Dithiol-3-ones

Cleavage of the S—S bond in 3*H*-1,2-dithiol-3-ones (**6**) by nucleophiles liberates the latent thioamide group. Piperidine in DMF or DMSO[25] and Grignard reagents[26,27] have been employed and allow synthesis of malonic acid monothioamides (Scheme 1).

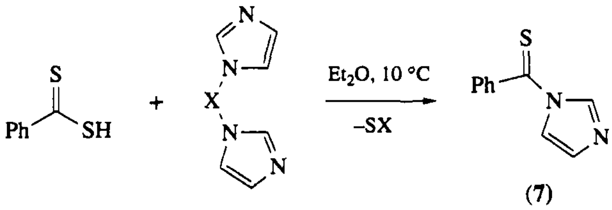


i, $HN(CH_2)_5$; ii, R^4MgBr in THF, then quench with H_2O

Scheme 1

2.4.2.3 Thioacylation with Dithiocarboxylic Acids

Contrary to carboxylic acids which, under normal conditions, only give salts with amines, dithiocarboxylic acids, RCS_2H, are quite reactive in nucleophilic displacement reactions. However, the compounds are unpleasant to handle and, due to their limited stability, often give only low yields of thioamides in the reaction with amines.[1,28,29] The approach was successfully employed in the synthesis of thiobenzoyl azolides, *e. g.* in the formation of (**7**) according to equation (4).[30]



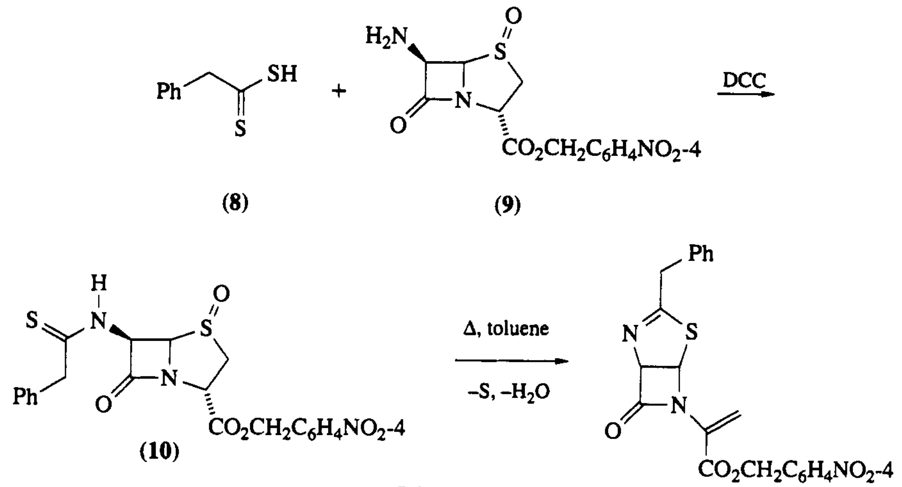
(**7**) (4)

X = CO, 78%; X = CS, 77%; X = SO, 64%

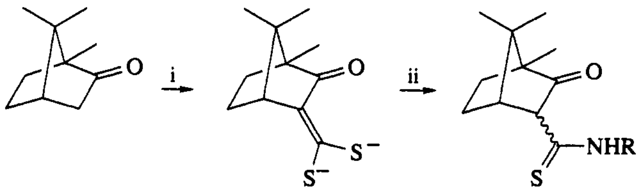
Phenyldithioacetic acid (**8**) allows thioacylation of the 7-amino group in penicillanate (**9**); the resulting highly nucleophilic thioamide (**10**) gives intramolecular trapping of the sulfenic acid, RSOH, which is in thermal equilibrium with the thiazolidine *S*-oxide moiety in (**10**; Scheme 2).[31]

Thioacylation reactions with dithiocarboxylic acids are not limited to amines, but, employing the Mg salt, can also be carried out with hydroxylamine to give thiohydroxamic acids[18] or with hydrazine and some substituted hydrazines to provide thiohydrazides.[19]

The reaction of CH acidic compounds with CS_2 in the presence of excess base yields dianions of dithiocarboxylic acids.[32] Starting from camphor, neutralization with HCl and addition of primary amines yields 3-oxonorbornanethiocarboxamides (**11**) with undefined stereochemistry (Scheme 3).[33]



Scheme 2



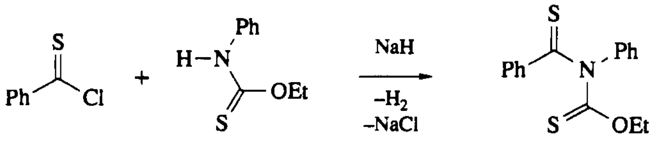
(11)

i, $NaNH_2$, CS_2; ii, HCl, then RNH_2 or $ArNH_2$ in Et_2O or PhH

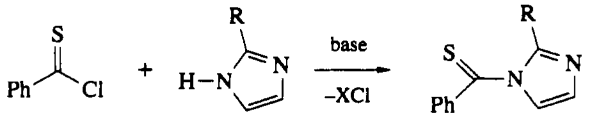
Scheme 3

2.4.2.4 Thioacylation with Thioacyl Chlorides

Thioacyl chlorides, RCSCl, are powerful thioacylating agents as is obvious from the quantitative thiobenzoylation of the only moderately nucleophilic nitrogen in thiocarbamate (**13**; equation 5).[34] However, severe limitations are the difficult accessibility of thioacyl chlorides and their thermal lability.[35] Even if they are prepared from dithiocarboxylic acids using an improved procedure,[36] only thioaroyl chlorides, particularly PhCSCl (**12**), can be handled sufficiently easily to be used in synthetic work. Thus, various azoles react with (**12**) to furnish *N*-thiobenzoyl azolides (**14**) in the presence of excess azole or NEt_3 (equation 6); a particularly clean and fast reaction is achieved if *N*-silylated azoles are employed.[30] However, considering the fact that the chloride has to be prepared from the dithiocarboxylic acid, the approach of equation (4) presents a shortcut to the products.



(12) (13) (5)

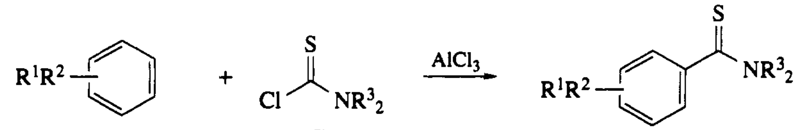


(12) (14) (6)

R = H, 87%; R = Me, 47%

In contrast to thioacyl chlorides, thiophosgene, $CSCl_2$, is readily accessible and conveniently handled making it an important reagent in the synthesis of thiocarbamoyl chlorides (**15**; $ClCSNR_2$),[37] *O*-alkyl thiourethanes ($ROCSNR'_2$),[38] and thioureas (R_2NCSNR_2) (*cf.* Volume 6, Chapter 2.8).[39,40]

On the other hand, thiocarbamoyl chlorides (**15**) may be used in thioamide synthesis, though *via* carbon–carbon bond formation in Friedel–Crafts-type reactions (*cf.* Volume 2, Chapter 3.1). The approach is limited to fairly electron-rich aromatics such as alkylbenzenes, anisole, and furan, but fails for benzene; equation (7) gives some details.[41,42] Phenol does not require a Lewis acid catalyst in the reaction with H_2NCSCl, but gives a mixture of 2-/4-hydroxythiobenzamides along with *O*-phenyl thiocarbamate.[43]



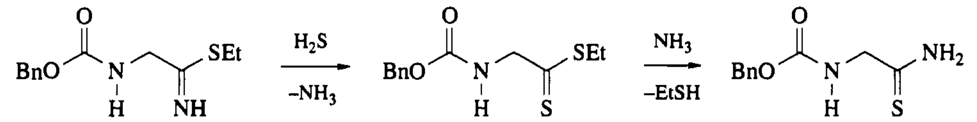
(15) (7)

$R^1 = R^3 = Me, R^2 = H$, 53% (ref. 41); $R^1 = R^2 = Me, R^3 = H$, 61% (ref. 42);
$R^1 = OMe, R^2 = H, R^3 = Me$, 77% (ref. 41); $R^1 = R^2 = OMe, R^3 = Me$, 56% (ref. 41)

Another application of thiocarbamoyl chlorides (**15**) and related activated thiocarbonic acid derivatives in thioamide synthesis is found in their reaction with carbanions of highly CH acidic compounds EWG_2CH_2 to give thioamides $EWG_2CHCSNR_2$.[7,44]

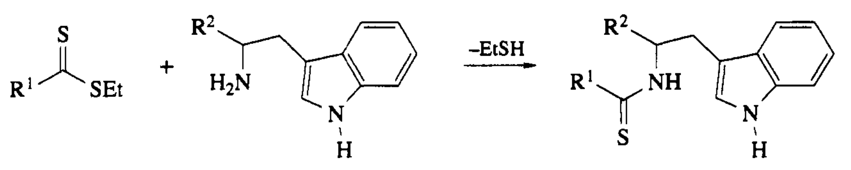
2.4.2.5 Thioacylation with Dithiocarboxylates

Dithiocarboxylates, R^1CSSR^2, give a faster reaction with amines than *O*-alkyl thiocarboxylates (**2**; *cf.* Section 2.4.2.1).[45] As shown in equation (8), this pronounced reactivity may lead to an undesired *in situ* reaction with the liberated ammonia to give a primary thioamide, when the ester is generated by thiolysis of a thioimidate.[23]



(8)

On the other hand, dithiocarboxylates allow the chemoselective thioacylation of the amine moiety in tryptamine or tryptophane (**16**; equation 9).[46]



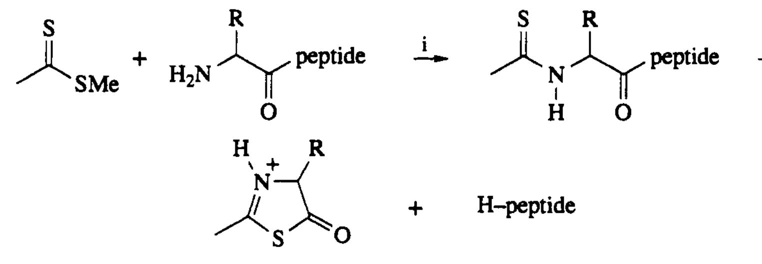
(16) (9)

$R^1 = Me, Br, Ph; R^2 = H, CO_2Me$

Dithiocarboxylates are particularly useful reagents in the thioacylation of the terminal amino group in peptides. Combination with a subsequent cleavage by anhydrous TFA results in a modified Edman degradation[47] and a protocol has been worked out with conditions that are compatible with the ones required for an automatic sequential analysis (Scheme 4).[48]

By analogy with the reaction of equation (3) *N*-protected dithiocarboxylates of amino acids react with amino acids or peptides with a free NH_2 group to give endothiopeptides.[23,49] A systematic study of thio analogs of enkephalin revealed that attempted removal of benzyloxycarbonyl protective groups with HBr/HOAc results in decomposition, but that the t-BOC group can be cleanly cleaved from the product using liquid HF/anisole.[23] Therefore, dithiocarboxylates, t-BOCNHCHR^{1}CSSR^2, appear to be the reagents of choice in endothiopeptide synthesis.

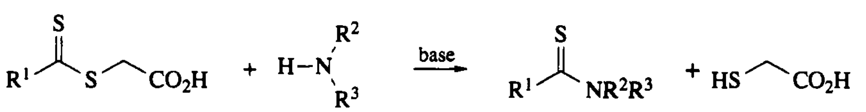
Thioamide synthesis from dithiocarboxylates and amines under basic conditions gives thiols as rather unpleasant parallel products. This problem is avoided by using *S*-thioacylated thioglycolic acids (**17**), as



i, $\mathrm{NEt_3}$ or $\mathrm{H\overset{+}{N}Et_3OAc^-}$ in DMF; ii, anhydrous TFA

Scheme 4

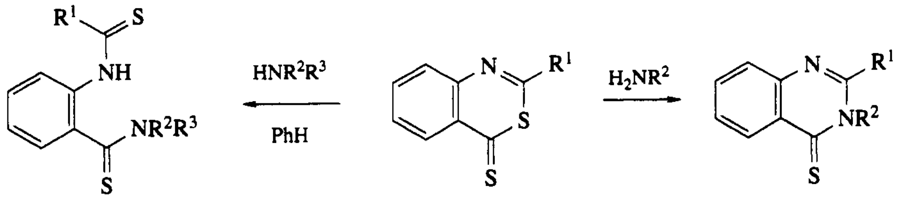
was first suggested by Holmberg.[50] As shown in equation (10) these esters display the usual reactivity of dithiocarboxylates,[28,51,52] but displacement reactions yield the thiol (**18**), which is soluble in aqueous base and so readily disposed of. However, esters (**17**) may fail to thioacylate sterically hindered amines and the derivative with $R^1 = H$ is too labile to be used in thioformylations.



(**17**) (**1**) (**18**) (10)

Several uses of the reaction in equation (10) for the *N*-thioacylation of amino acids, their esters, or amides have been reported.[21,53,54] It is noteworthy that these reactions occur without racemization allowing a CD study of *N*-thioacyl amino acids.[55] Moreover, the reaction of equation (10) is not limited to amines or amino groups, but has also been employed to thioacylate hydrazines and hydroxylamines to give thiohydrazides[19,56] and thiohydroxamic acids,[18] respectively.

In a heterocyclic environment, the dithiocarboxylate functionality may give a more complex reaction pattern, as shown by dithiolactones (**19**). Here, secondary aliphatic amines lead to ring cleavage providing 2-(thioacylamino)thiobenzamides (**20**),[57] whereas primary aliphatic or aromatic amines give thiolactams (**21**; Scheme 5).[58]



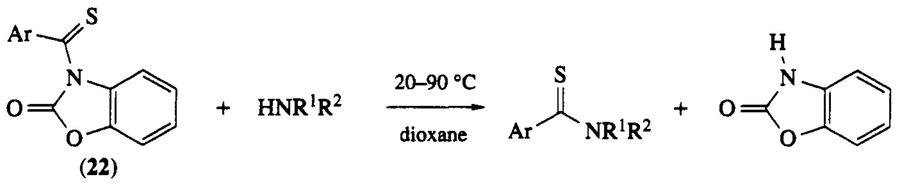
(**20**) (**19**) (**21**)

Scheme 5

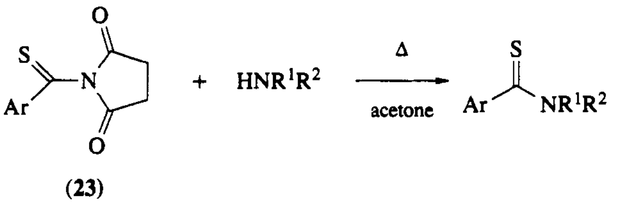
In accord with the special reactivity of a dithiocarboxylate moiety, *O*,*S*-dialkyl dithiocarbonates, ROCSSR′, yield *O*-alkyl thiourethanes, $\mathrm{ROCSNR'_2}$, on addition of amines.[38] Similarly, trithiocarbonates, $\mathrm{(RS)_2CS}$, yield thioureas.[39,40,59]

2.4.2.6 Thioacylation with Thioamides

Whether transamidation of a thioamide by addition of an amine is feasible depends on the interplay of the nucleophilicity of the incoming amine and the leaving-group ability of the amine to be replaced. The reaction is of particular importance in using some *N*-thioacylated heterocycles such as the benzoxazole derivative (**22**),[60] the succinimide (**23**),[61] and azoles (**24**) (equations 11–13).[30] The last mentioned approach appears to be the most general and proceeds under particularly mild conditions; in contrast to the reaction of equation (10), the method allows the thiobenzoylation of *N*-methylaniline, PhNHMe, using the imidazole derivative (**24**; $R^3 = Me$). The reactivity of the reagent can be further increased by employing azoles with more ring nitrogens and could be extended to the synthesis of thiohydrazides.[30]



(11)



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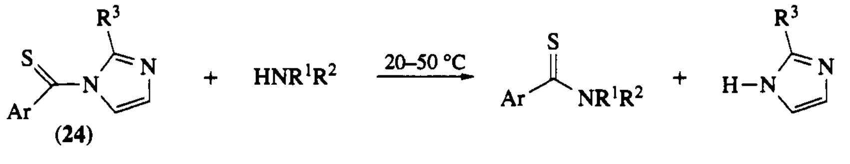
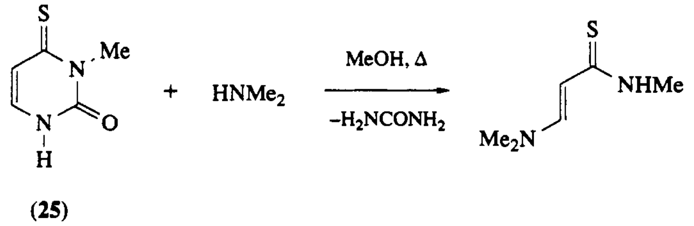


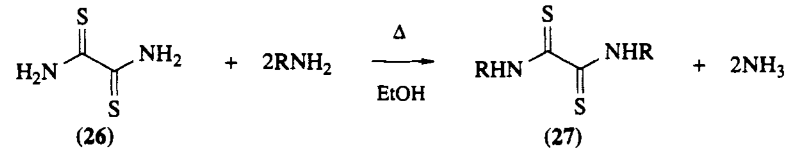
(13)

Cleavage of the *N*-acyl thioamide moiety in the 4-thiouracil (**25**) gives an example for the conversion of a thiolactam into a thioamide (yield 25%; equation 14).[62]



(14)

Heating of dithiooxamide (**26**) with primary amines yields the corresponding *N*-alkyl derivatives (**27**);[63] the reaction is catalyzed by acid with even CO_2 being effective (equation 15).[5,64]

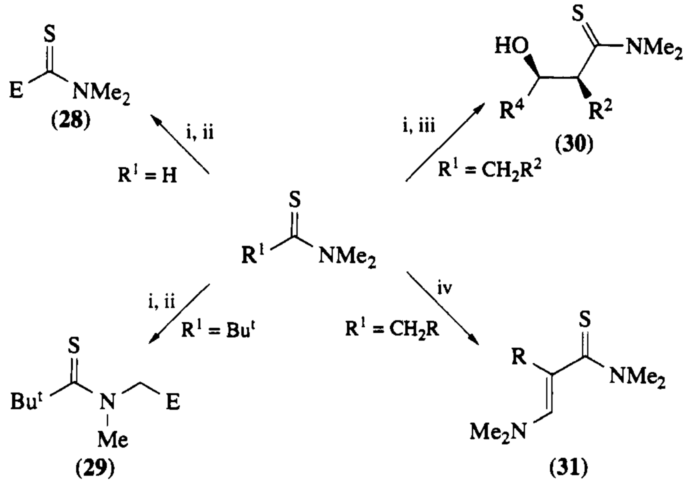


(15)

In a number of reactions thioamides are converted into other thioamides by C—C bond formation (Scheme 6). Examples from Seebach's umpolung chemistry include *C*-lithiation of $HCSNMe_2$ and subsequent reaction with electrophiles to give (**28**)[8] and deprotonation of one of the *N*-methyl groups in Bu^tCSNMe_2 and again electrophilic addition to yield products (**29**).[9]

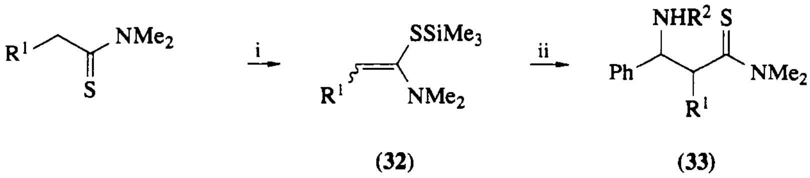
Another possibility to obtain thioamides from thioamides is *via* electrophilic attack in the α-position (Scheme 6). Thus, aldol-type reactions are feasible and proceed with high *erythro* selectivity providing (**30**),[65] or even allowing optically active products (*cf.* Volume 2, Chapter 1.6).[66] Heating with a formamide *O*,*N*-acetal gives an α,β-unsaturated thioamide (**31**) in a sequence of electrophilic attack and elimination.[67,68]

Finally, thioamides can be modified *via* their *S*-silylated derivatives (**32**). With Lewis acid catalysis, addition of a Schiff base yields β-aminothioamides (**33**) as a mixture of diastereomers (Scheme 7).[69]



i, LDA; ii, E^+; iii, R^4CHO; iv, $(Me_2N)CHOBu^t$

Scheme 6



i, LDA, then Me_3SiCl; ii, $PhCH{=}NR^2$, $ZnBr_2$ or $SnCl_4$, then H^+

Scheme 7

2.4.2.7 Thioacylation with Thioketenes or Thioketene Equivalents

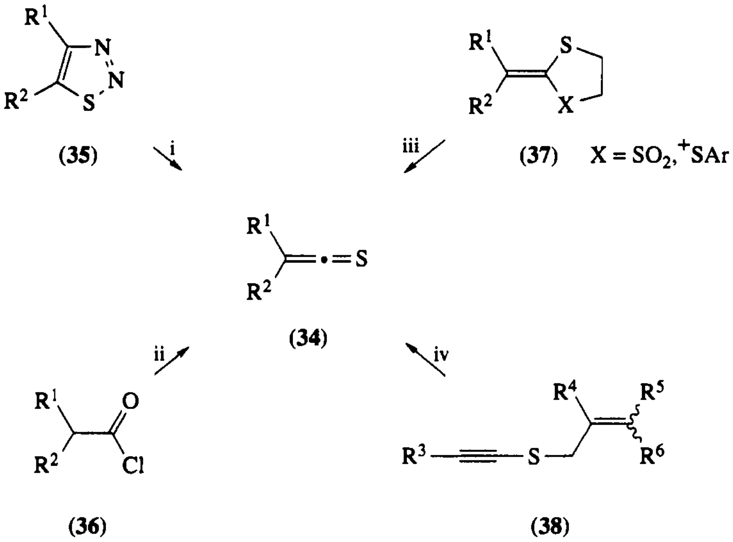
Thioketenes (**34**) have a nonstabilized C=S group and consequently, except for sterically hindered examples,[70,71] exhibit a high tendency to oligo- or poly-merize.[2] Their application in synthesis depends on the availability of convenient routes to generate these species and, at least for the more elusive examples, trap them *in situ*. Recently, a number of routes to thioketenes have been developed, allowing them now to be considered as useful reagents.[2] The most handy methods to obtain thioketenes are based on: the flash-vacuum pyrolysis of 1,2,3-thiadiazoles (**35**);[72,73] the thionation of sterically hindered acyl chlorides (**36**);[70,71] the [3 + 2] cycloreversion of modified 2-alkylidene-1,3-dithiolanes (**37**);[74] and the 3,3-sigmatropic rearrangement of alkynyl allyl sulfides (**38**; Scheme 8).[75]

Thioketenes (**34**) are highly electrophilic and give a smooth reaction with ammonia or amines. In fact, addition of a secondary amine offers the best way to scavenge a suspected thioketene.[2] But the approach also deserves interest from the point of view of thioamide synthesis as it allows very mild and nonreducing conditions, tolerating the presence of sensitive additional functional groups such as cyano, nitro, or sulfonyl residues (equation 16).[74]

In the reaction of alkynyl thiolates (**39**) with excess diethylamine, the amine provides the proton to generate an aldothioketene (**40**) and, at the same time, serves as the trapping reagent (Scheme 9).[76]

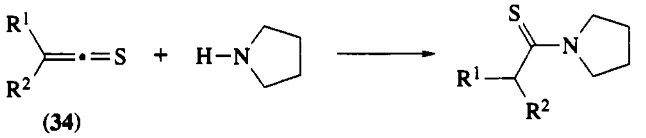
Bis(trimethylsilyl)thioketene (**41**) gives a smooth reaction with amines, but one silyl group is always displaced in the process yielding thioamides (**42**; equation 17).[77]

Alknyl silyl sulfides, $R^1C{\equiv}CSSiR^2_3$, which are readily obtained by silylation of anions (**39**), react as thioketene equivalents. Thus, β-thiolactams are formed in the reaction with C=N systems (*cf.* Volume 5, Chapter 2.2)[3] and thioamides on addition of amines;[78,79] equation (18) shows a typical example.[79] This approach has great promise for the thioacylation of very sensitive natural products.



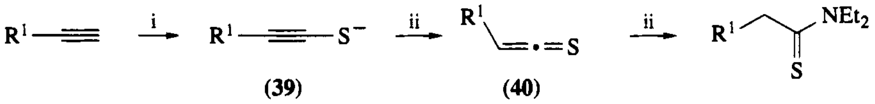
i, 530 °C, 10^{-4} Torr; ii, P_2S_5, Py; iii, base; iv, heat

Scheme 8



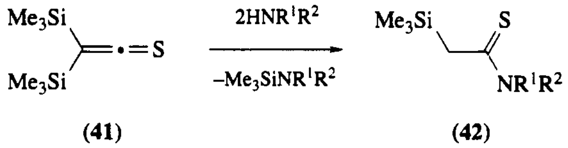
(16)

$R^1 = NO_2$, $R^2 = H$, 53%; $R^1 = PhSO_2$, $R^2 = H$, 38%; $R^1 = NC$, $R^2 = Ph$, 82%



i, $LiNEt_2$, then S_8; ii, $HNEt_2$

Scheme 9



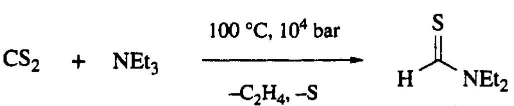
(17)

45%

(18)

2.4.2.8 Thioacylation with Carbon Disulfide

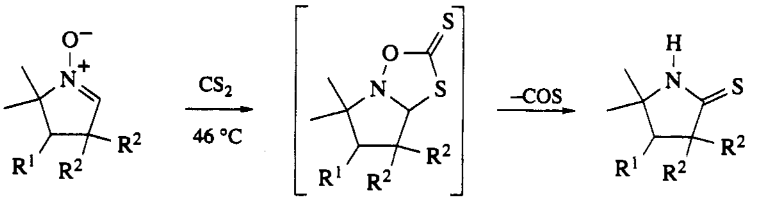
At elevated temperatures and under pressure, carbon disulfide converts triethylamine into thioformamide (**43**) in 49% yield (equation 19); similarly, the reagent yields thioformamides (23–36%) from the corresponding amides.[80]



(43)

(19)

Thiolactams (**46**) are isolated on addition of carbon disulfide to cyclic nitrones (**44**); the products are formed in a sequence of [3 + 2] cycloaddition giving (**45**) and cycloreversion (equation 20).[81]



(44) **(45)** **(46)**

$R^1 = R^2 = H$, 45%; $R^1 = H$, $R^2 = Me$, 62%; $R^1 = Ph$, $R^2 = H$, 62%

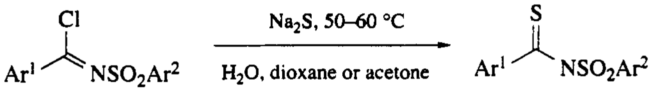
(20)

Use of carbon disulfide has particular significance for the synthesis of dithiocarbamates[82] and thioureas in thioacylation reactions.[39,40,82]

2.4.3 THIOLYSIS OF IMIDOCARBOXYLIC ACID DERIVATIVES

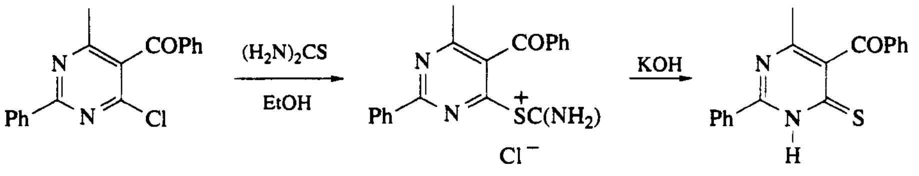
2.4.3.1 Thiolysis of Imidoyl Chlorides

Thiolysis of imidoyl chlorides offers a straightforward route to thioamides. The formation of *N*-sulfonyl thioamides (**47**) in equation (21) gives an example,[83] but the method works particularly well for the synthesis of *N*,*N*-disubstituted thioamides including thiolactams from the corresponding imidium chlorides, $R^1C(=NR^2)Cl$.[84] Quite often, the chlorides are generated *in situ* from the corresponding amides by the action of $COCl_2$ so that the overall process represents an alternative to the thionation of amides.[13] In a useful modification, $HS(S)P(OEt)_2$ is used to achieve the thiolysis and allows very high yields of thiobenzamides and of dithiooxamides; nitro-substituted derivatives are not reduced under the reaction conditions.[85] Thiourea has been employed to convert α-chlorine-substituted azines (**48**) into thiolactams (**50**); as shown in equation (22), thiuronium salts (**49**) are supposed to be intermediates in this transformation.[86]



(47)

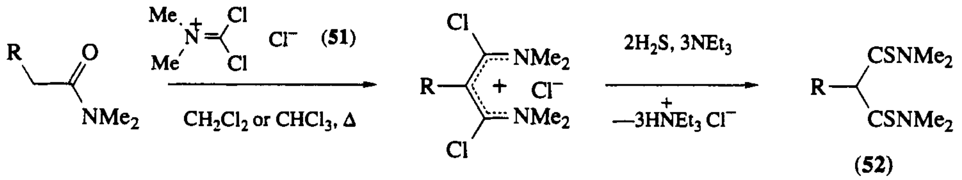
(21)



(48) **(49)** **(50)**

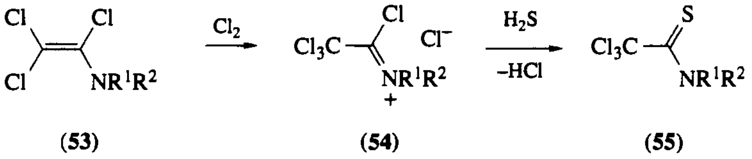
(22)

The reaction of tertiary amides with phosgene immonium chloride (**51**) allows this approach to be extended to the synthesis of thiomalonamides (**52**; equation 23).[87]

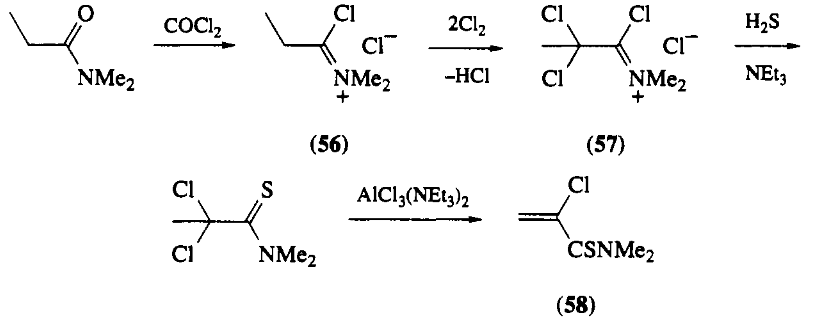


R = H, 70%; R = Et, 83%; R = Ph, 55% (23)

The thiolysis of imidoyl chlorides has proven to be particularly useful in the synthesis of α-chlorothioamides. Thus, chlorine can be added to trichlorovinylamines (**53**) and the resulting imidium salt (**54**) thiolyzed to give trichlorothioacetamides (**55**; equation 24).[88] Similarly, addition of HCl and H_2S to di- or tri-chlorovinylamines (**53**) yields tertiary mono- and di-chlorothioacetamides, respectively.[88] In a recent modification, α,α-dichlorination of propionimidium salt (**56**) giving (**57**) is achieved and, subsequently, thiolysis and dehydrohalogenation using $AlCl_3$-modified triethylamine to obtain α-chlorothioacrylamides (**58**; equation 25).[89]

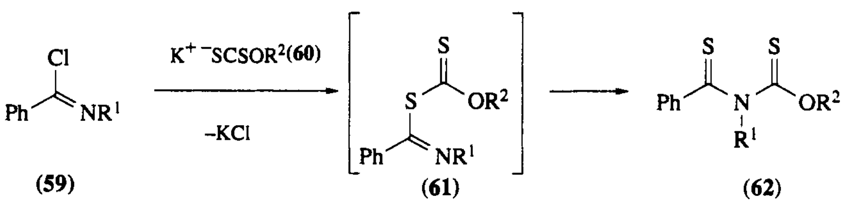


(24)



(25)

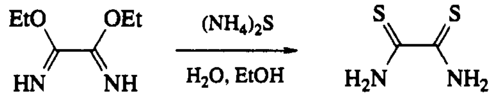
The reaction of benzimidium chlorides (**59**) with dithiocarbamate (**60**) yields a thioimidate (**61**) as primary product which rearranges in a Chapman-type interchange of heteroatoms to give the thioacylated thiobenzamide (**62**) in almost quantitative yield (equation 26).[34]



(26)

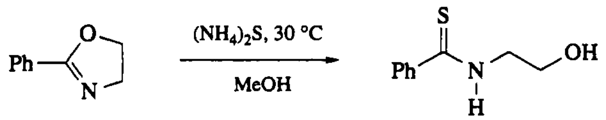
2.4.3.2 Thiolysis of Imidates

The most common source of imidates is nitriles (*cf.* Volume 6, Chapter 2.7) and, as these can be directly transformed into thioamides (*cf.* Section 2.4.3.4), this one-step approach is usually preferred. Moreover, depending on the reaction conditions and the substitution pattern, thiolysis of imidates may give thioesters rather than thioamides (*cf.* Volume 6, Chapter 2.5).[21] However, some high-yield applications of imidates in thioamide synthesis have been reported and are detailed in equations (27)[90] and (28).[91]



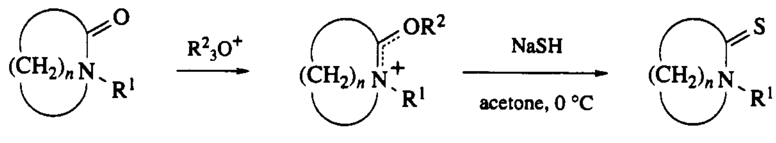
(26)

(27)



(28)

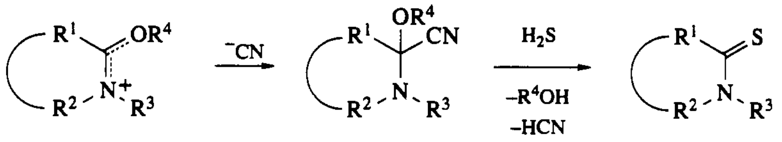
N-Substituted thiolactams (**65**) are obtained from lactams (**63**) in 55–100% yield by alkylation with Meerwein reagent and subsequent thiolysis of the resulting imidium salt (**64**; equation 29).[92] The approach has been extended to other thiolactams and acyclic examples employing a cyanohydrin derivative (**66**; equation 30).[93] Similarly, *N*,*N*-acetals of formyl cyanide, $(R_2N)_2CHC{\equiv}N$, yield thioformamides on treatment with H_2S.[94]



(**63**) (**64**) (**65**)

R^1 = Me, $(CH_2)_3F$; $R^1 \neq$ H; n = 3, 4

(29)

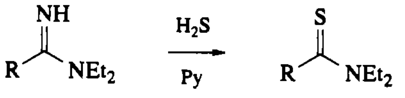


(**66**)

(30)

2.4.3.3 Thiolysis of Amidines

Thiolysis of *N*-monosubstituted amidines, $R^1C({=}NH)HNR^2$, proceeds unselectively giving a mixture of thioamides $R^1C(S)NH_2$ and $R^1C(S)NHR^2$.[95] However, *N*,*N*-disubstituted examples (**67**) can be cleanly transformed into tertiary thioamides (**68**; equation 31).[95]



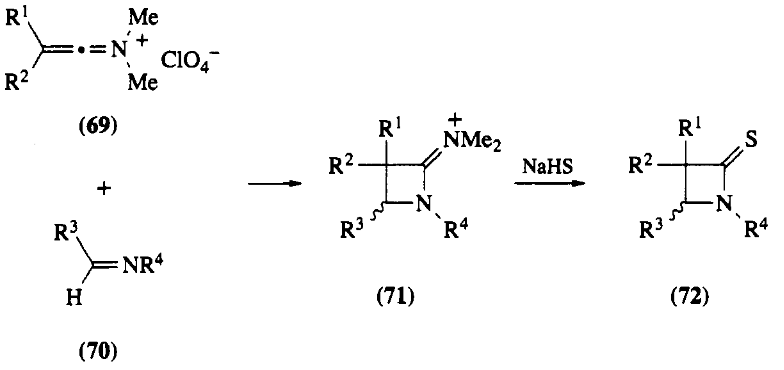
(**67**) (**68**)

(31)

Cyclic amidinium salts (**71**) are obtained by [2 + 2] cycloaddition of ketenimmonium compounds (**69**) to Schiff bases (**70**; R^3 = H, Ph, MeO_2C) or thioimidates (**70**; R^3 = SBn); their thiolysis provides an elegant access to β-thiolactams (**72**; equation 32).[96]

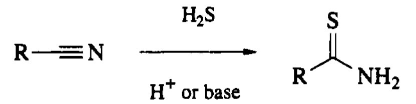
2.4.3.4 Thiolysis of Nitriles

Addition of H_2S to nitriles (**73**) represents an important method for the synthesis of primary thioamides (**74**; equation 33). The reaction is carried out under base or acid catalysis. The base-catalyzed process is particularly useful in the preparation of aromatic thioamides, *i.e.* for R = aryl, hetaryl in (**73**); triethylamine in molar proportion or pyridine, which at the same time also serves as solvent, are employed most commonly.[97] The approach tolerates the presence of various other functionalities such as an amide,[98] hydrazone,[99] enamine,[68] α-oxo,[100] α-acetoxy[101] or α-amino group.[102] Moreover, the reaction has been applied to the synthesis of thioasparagine as such[103] or incorporated into a dipeptide, as shown

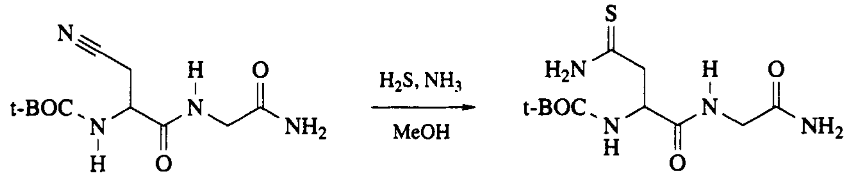


(69) (70) (71) (72) (32)

in equation (34).[104] Alternatively, a basic ion-exchange resin in methanol has been suggested to catalyze the transformation of nitriles (**73**) into thioamides (**74**).[105]

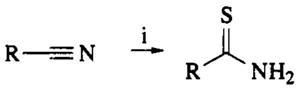


(73) (74) (33)



(34)

Without special measures, aliphatic nitriles (**73**; R = alkyl) often give low yields in the base-catalyzed thiolysis.[106] It has proven advantageous to work in the presence of diethylamine, a tetraalkylammonium hydroxide, or a guanidine derivative in DMF, DMSO or sulfolane; these conditions allow one to work at atmospheric pressure and provide aliphatic thioamides in medium to good yields.[107] However, as detailed in Scheme 10, pressure is required in the phase transfer modification of the reaction which gives excellent yields for aromatic (R = Ph, 3-pyridyl) and moderate to good yields starting from aliphatic substrates (R = Bn, Pr).[108] Similarly, 13–17 atm of H_2S are a prerequisite in the synthesis of thioformamide, $HCSNH_2$, from HCN with addition of triethylamine[109] or of a basic ion-exchange resin.[110] In the presence of the $Cu(NH_3)_4^{2+}$ cation, NaCN reacts with H_2S to yield 77% dithiooxamide (**26**).[111]

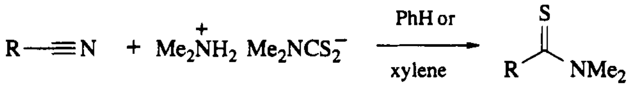


(73) (74)

i, Na_2S, H_2S (2 atm), R'_4NCl or dibenzo-18-crown-6 in H_2O, PhH

Scheme 10

According to equation (35), heating of nitriles (**73**) with dithiocarbamate (**75**) gives up to 80% of *N*,*N*-dimethylthioamides (**76**).[112] In a related reaction, *N*-mono- and *N*,*N*-di-substituted thioformamides are isolated on heating HCN and H_2S in the presence of an amine.[94,109,113]



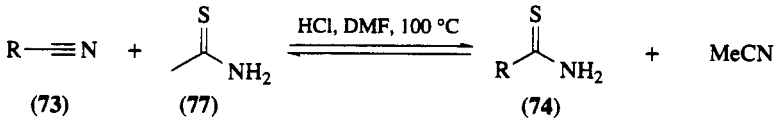
$$R{-}{\equiv}N + Me_2\overset{+}{N}H_2\ Me_2NCS_2^- \xrightarrow[\text{xylene}]{\text{PhH or}} RC(S)NMe_2$$

(73) (75) (76) (35)

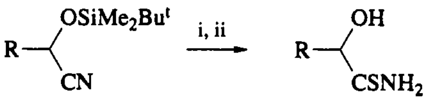
The thiolysis of nitrile groups can also be applied to cyanamides giving thioureas.[39,40,114]

In the acid-catalyzed thiolysis of nitriles (**73**) H_2S is commonly replaced by appropriate precursors or equivalents. Thus, thioacids, RCOSH, have been used together with HCl[115] or $SnCl_4$.[116] Thioacetamide (**77**) is a very convenient source of H_2S; as shown in equation (36), an equilibrium is established which is shifted to the right, if the liberated MeCN is removed by distillation.[117] Alternative sources of H_2S are dithiophosphoric, $HSP({=}S)(OR)_2$ with R = Et[118] or Pr^i,[119] or phosphinodithioic acid derivatives, $HSPPh_2({=}S)$.[120] The last mentioned approach allows the elegant synthesis of α-hydroxythioamides (**78**) in Scheme 11.[121]

Heating of P_4S_{10} with nitriles (**73**) yields adducts incorporating a P_4 tetrahedron; hydrolytic cleavage furnishes thioamides.[122]



(36)



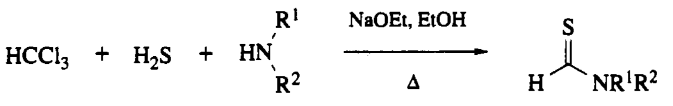
(**78**)

i, $Ph_2P(S)SH$, 60 °C, Pr^iOH; ii, TBAF

Scheme 11

2.4.4 THIOLYSIS OF 1,1,1-TRIHALIDES

In a process reminiscent of isonitrile hydrolysis, dichlorocarbene as generated from $CHCl_3$ reacts with H_2S in the presence of primary or secondary amines to yield thioformamides (**79**; equation 37).[123] If pressure is employed, CCl_4 or Cl_3CCCl_3 can also be used with the latter giving dithiooxamides (**27**), *e.g.* with $BuNH_2$, 65% of BuNHCSCSNHBu.[124]



(**79**)

(37)

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2.5

Synthesis of Thioesters and Thiolactones

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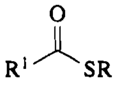
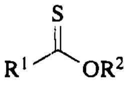
2.5.1 INTRODUCTION

Three different types of thiocarboxylic esters (and also thiolactones) exist: the thiol, thioxo- and dithioesters which, according to the IUPAC rules, are named *S*-alkyl (*S*-aryl) carbothioates (**1**), *O*-alkyl (*O*-aryl) carbothioates (**2**) or alkyl (aryl) carbodithioates (**3**). Acylation-type reactions were used for the first preparations of thiol carboxylic esters (**1**) by Tjuttschew (1863),[1] Saytzeff and Lukaschewicz (1868)[2] and Michler (1875).[3] Thioxocarboxylic esters (**2**) were first obtained *via* an acylation route by Matsui (1908).[4] On the other hand, alkyl dithiobenzoates (**3**; R^1 = Ph), which were first mentioned in a patent by Bloch and Höhn (1908),[5a] and alkyl alkanedithioates (**3**; R^1 = Me, Et, $PhCH_2$), first described by Houben and Schultze (1910),[5b] were prepared by alkylation of the corresponding metal carbodithioates.


(1)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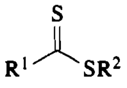
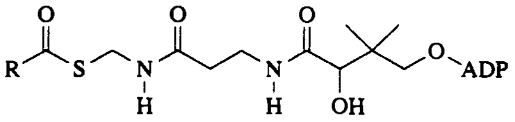

(3)

Some structural characteristics and significant spectroscopic properties of thiocarboxylic esters are compiled in Table 1. These data might be helpful for preparative work. The IR frequencies of the CX—SR group are especially indicative of a thioester even if strong vibrational coupling occurs, as in the case of (**2**) and (**3**). The best and unequivocal spectroscopic feature is the ^{13}C NMR signal of the CX carbon atom. The CS groups of thioxo- (**2**) and dithio-esters (**3**) can be distinguished in most cases since the chemical shifts are clearly different. It should be mentioned, however, that the intensity of the signals is sometimes extremely low and the lines can thus be detected only at high signal-to-noise ratios.

Table 1 Physical and Spectroscopic Data of Thiocarboxylic Esters

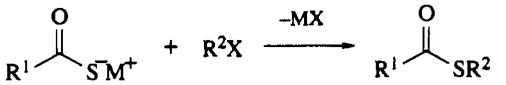
R^1—CX—YR^2	*(1)* $X = O, Y = S$	*(2)* $X = S, Y = O$	*(3)* $X = Y = S$	*Refs.*
d (C—X) (pm)	119–121	161–163	160–167	6–13
d (C—Y) (pm)	174–178	132–137	168–175	6–13
μ (D)	1.3–1.7	2.1–2.6	1.7–1.9	6,14
λ_{max} (nm)	232	400–440	450–530	6,14
[log ε]	[3.7]	[1.2–2.0]	[1.2–2.1]	
		250–290	300–330	
		[4.0–4.3]	[3.8–4.3]	
ν_{cx} (cm^{-1})	1660–1715	1000–1050	980–1030	6,14–18
		1200–1230	1180–1250	
δ_{cx} ^{13}C (p.p.m.)	190–200	210–230	225–245	6,14,19–22

Thiocarboxylic esters do not play a major role in biochemistry, with the one exception of acetyl-CoA (**4**; R = Me), the prototype of acyl-CoAs (**4**), which represent important energy rich intermediates in amino acid, lipid and glucose metabolism.[23] In fact the thiol esters (**4**) fit in with the scope of this chapter. They are often formed by acylation reactions and themselves react as acylating agents.

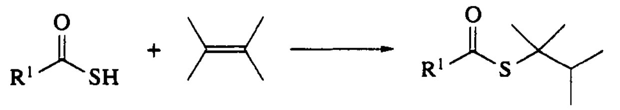


(**4**)

Although acylation reactions rank among the best-known methods for the synthesis of thiocarboxylic *S*-esters (**1**), there exist other important and convenient routes,[6,24] *e.g.* the alkylation of thiocarboxylate anions (equation 1) or radical addition of thiocarboxylic acids to carbon–carbon double bonds (equation 2). These methods are not dealt with here (*cf.* Volume 4, Chapter 1.5).

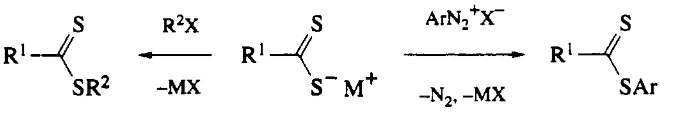


(1)



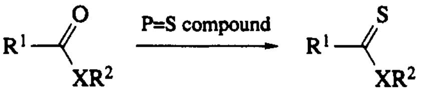
(2)

Alternatives to the acylation-type reaction are even more important in the thioxo- and dithio-carboxylic ester series[6,14,15,24–29] since dithiocarboxylate salts are most conveniently obtained from a variety of precursors and can be not only alkylated but also arylated by arenediazonium hydrogen sulfates (equation 3).[14,30] An advantage of the latter method is that no thiophenols are needed, which are necessary, but sometimes not easily obtained, educts in most other *S*-aryl thiocarboxylate preparations (*cf.* Chapter 1.5).



(3)

In the last decade the methods of converting carbonyl to the corresponding thiocarbonyl compounds have been substantially improved.[6,15,25–28] Therefore, thioxo- as well as dithio-carboxylic esters are accessible from esters, thiol esters and even carboxylic acids by reacting them with phosphorus pentasulfide or 1,3,2,4-dithiadiphosphetane 2,4-disulfides such as Lawesson's[19] or Davy's[31] reagent (equation 4; *cf.* Chapter 4.1, this volume).



(4)

X = O, S

Finally, sigmatropic processes (*cf.* Volume 5, Part 7) are useful procedures for the preparation of certain thioxo- and dithio-carboxylic esters.

2.5.2 THIOL ESTERS AND THIOL LACTONES

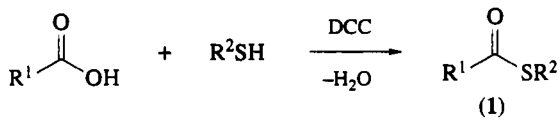
Thiol carboxylic esters (**1**) are the most common compounds among the three types of thioester. They are activated derivatives of carboxylic acids and exhibit acylating properties similar to those of carboxylic acid anhydrides. They have therefore found widespread application in synthetic chemistry and have been used for preparing esters, amides and peptides, especially macrocyclic ketones and lactones. Several review articles concerning the chemistry of thiol carboxylic esters[6,24,32,33] and thiol lactones[34] have appeared.

2.5.2.1 Acylation of Thiols with Carboxylic Acids

Unlike carboxylic esters, open-chained *S*-alkyl thiocarboxylates cannot be obtained by direct proton-catalyzed esterification. Whereas thiocarboxylic acids react with alcohols to form esters as expected, thiol esters are formed on reaction of carboxylic acids with thiols, but the equilibrium is shifted towards the educts and the reaction is not useful for synthetic purposes. Therefore, activation is necessary and several methods have been developed to meet this requirement.

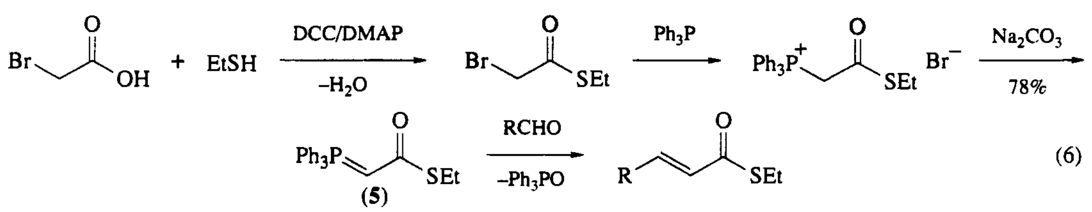
Condensing agents that are well known for peptide synthesis are also very suitable for the preparation of thiol carboxylic esters.

DCC can be used to prepare *S*-alkyl and *S*-aryl thiocarboxylates (**1**) from carboxylic acids and thiols according to equation (5).[35] This method has been successfully applied to the synthesis of thiol esters with sensitive substituents, *e.g.* *S*-methyl thioacrylate, a natural product.[36] In particular, *N*-protected amino acid and peptide *S*-phenyl esters, which are useful building blocks in peptide synthesis, are obtained in excellent yields without racemization.[37] *N*-Hydroxyphthalimide[38] and DMAP[39] have been used as cocatalysts to facilitate the reaction. The preparation of the Wittig reagent (**5**) by this route[39] is shown in equation (6).



(**1**)

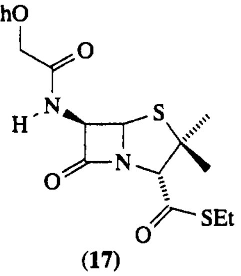
(5)



(**5**)

(6)

Activation of the carboxyl group is also achieved by various phosphorus compounds (**6**–**16**; *cf.* Table 2). Obviously, mixed anhydrides are the reactive intermediates, but these need not be isolated. The yields are generally high. *S*-Alkyl monothiomalonates and *S*,*S*′-dialkyl dithiomalonates are obtained by means of (**15**). *N*-Protected amino or hydroxy as well as 6-acylaminothiopenicillanic acids (**17**) can be converted to the corresponding thiol esters without racemization if (**11**), (**12**) or (**13**) are used as activators. Steric hindrance by bulky groups R^1 or R^2 during the formation of the carbon–sulfur bond in (**1**) is overcome by using (**8**), (**9**) or (**13**) as catalysts. This is important since the *t*-butylthiocarbonyl group is a good protecting group during the synthesis of macrocyclic lactones.[42,51,52] Antibiotics of the macrolide type have also been prepared *via* thiol esters, which were obtained by selective activation of the corresponding ω-hydroxycarboxylic acids with carbonyldiimidazole or similar reagents.[53–56]



(**17**)

Table 2 Phosphorus Compounds $R^1R^2P(O)X$ used as Activators for the Preparation of Thiol Carboxylic Esters (**1**)

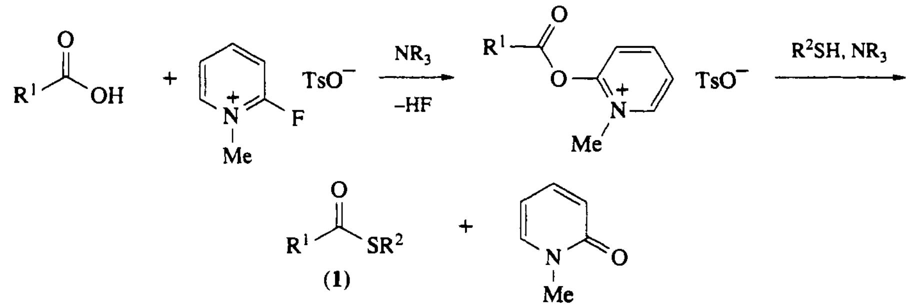
Compound	R^1	R^2	X	*Refs.*
(**6**)	Cl	Cl	Cl	40
(**7**)	Ph	Ph	Cl	38,41
(**8**)	OEt	OEt	Cl	42
(**9**)	OPh	Cl	Cl	43
(**10**)	NMe_2	Cl	Cl	44
(**11**)	OEt	OEt	CN	45,46
(**12**)	OPh	OPh	N_3	45,46
(**13**)	OPh	OPh	ODO[a]	47
(**14**)[b]	SPh	SPh	SPh	48
(**15**)	Ethyl polyphosphate			49
(**16**)	Hexachlorocyclotri(phosphazene)			50

[a] 2-Oxo-2,3-dihydro-1,3-oxazolyl; [b] $(PhS)_3PS$/imidazole.

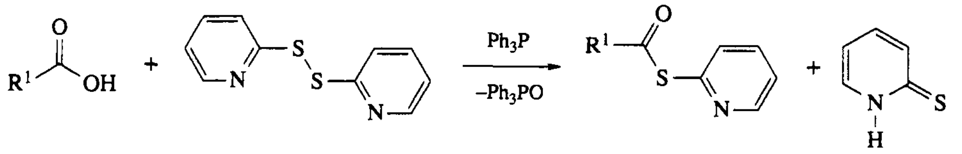
2-Halo-pyridinium or -benzothiazolium salts[56,57] have been applied in the preparation of *S*-alkyl or *S*-aryl carbothioates from carboxylic acids *via* acyloxypyridinium salts (*cf.* equation 7).

Another efficient method seems to be Mukaiyama's[58] redox condensation, which has found widespread application in total syntheses of natural products. Originally *S*-(2-pyridyl)carbothioates (**18**), obtained from carboxylic acids, 2,2′-dipyridyl disulfide and triphenylphosphine (equation 8), were used in follow-up reactions.[59] The use of (**18**) has been reviewed in the literature.[51,52,60–63]

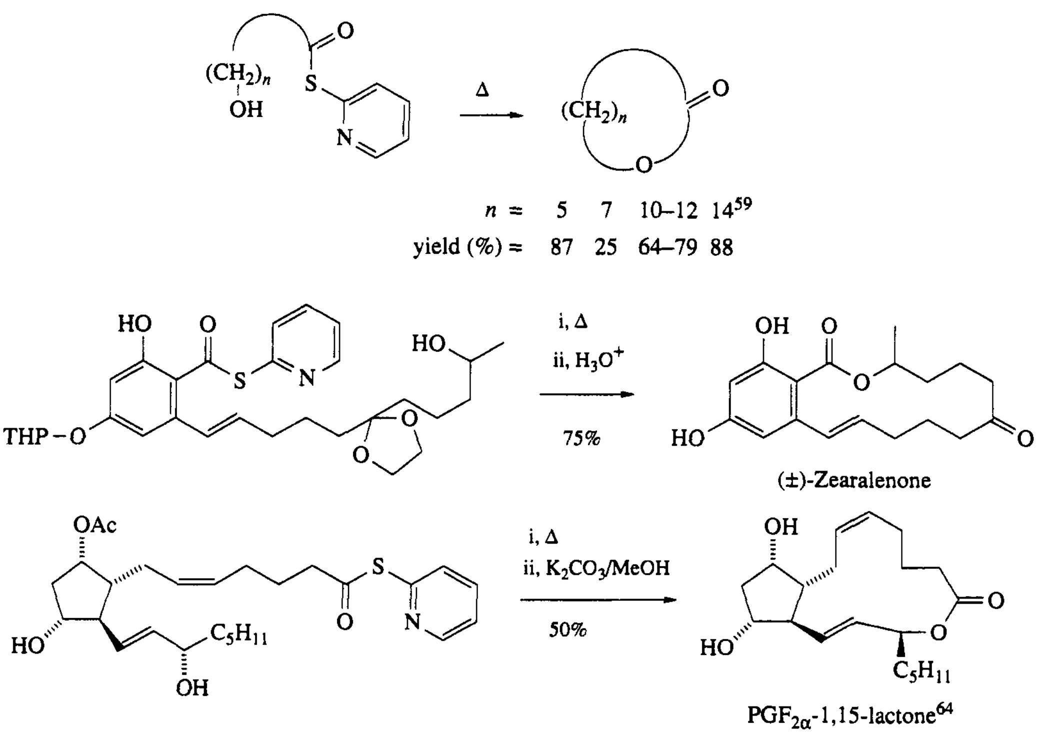
Carboxylic esters, especially lactones, are conveniently obtained *via* the pyridyl thioesters (**18**). Some examples are given in Scheme 1.[64] The 2-pyridyl thiol ester method can be further improved if silver ions ($AgClO_4$) are used as activators.[65] Corey and Brunelle[66] have also introduced other heterocyclic disulfides, and (**19**) was found to be superior to other reagents tested for the formation of lactones from ω-hydroxyalkanoic acids.



(7)


(8)

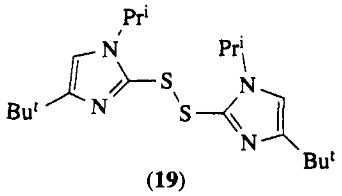
(18)


n = 5 7 10–12 14[59]
yield (%) = 87 25 64–79 88

(±)-Zearalenone

$PGF_{2\alpha}$-1,15-lactone[64]

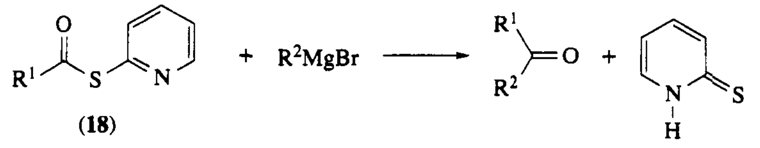
Scheme 1


(19)

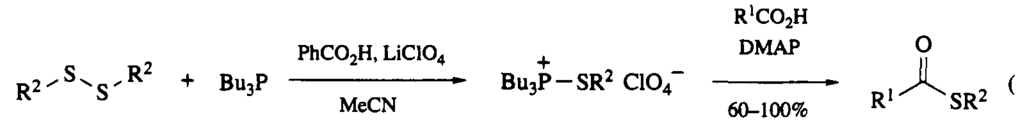
Grignard reaction of (**18**) yields open-chained as well as cyclic ketones, including natural products such as jasmone, in a selective way since formation of carbinols or Claisen-type condensation products is completely inhibited (equation 9).[58,67]

The use of diphenyl disulfide in the presence of triphenylphosphine to prepare thiol carboxylic esters has been described in the recent literature[68] and even *S*-alkyl alkanethioates can be obtained in good yields if DMAP is used as the base in the second step (*cf.* equation 10).[69]

S-Methyl[70] and *S*-aryl[71] thiocarboxylic esters can also be prepared directly from carboxylic acids if thiocyanates or chlorothioformates[72] are used instead of thiols (equations 11 and 12).


(18)

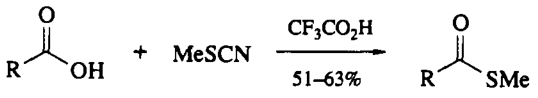
(9)



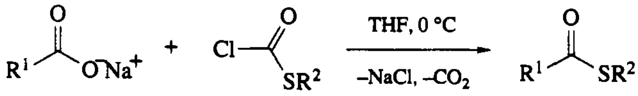
(10)

R^2 = Me, Et, Bu, $PhCH_2$, Ph

(1) $R^1 = C_6H_{13}$, Ph



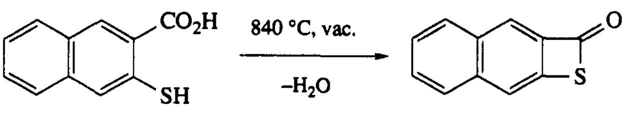
(11)



(1)

(12)

Finally, it should be mentioned that γ- and δ-thiol lactones are in many cases formed simply by heating the corresponding mercaptocarboxylic acids[34] or by treating them with phosphorus pentoxide.[73] The β-thiolactone (**20**) has also been obtained by flash pyrolysis of 3-mercapto-2-naphthoic acid (equation 13).[74]



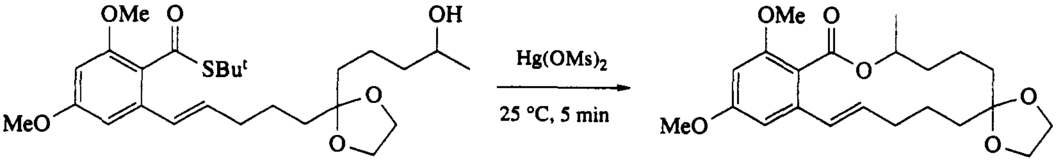
(20) 25%

(13)

2.5.2.2 Acylation of Thiols with Acyl Halides

Reaction of thiols or thiolates with acyl halides, chlorides in particular, represents the standard method for preparing thiol carboxylic esters (*cf.* ref. 33 and the literature cited therein). Since thiols are strong nucleophiles, the acylation even takes place in the absence of base. However, to obtain excellent yields under mild conditions, tertiary amines are added or metal (Si, Sn, Tl^I Cu^I) derivatives of the thiols are used. The following examples demonstrate the scope of the method.

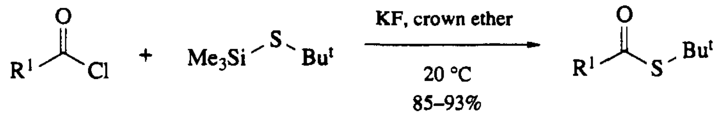
Thallium(I) thiolates have been introduced by Masamune *et al.*[75,76] Their use is especially advantageous if *S*-*t*-butyl thiocarboxylic esters are to be prepared which can serve as educts for macrolide synthesis. Zearalenone dimethyl ether ethylene acetal (**22**; *cf.* also Scheme 1) was obtained from the corresponding acid chloride and thallium(I) α-methylpropanethiolate *via* the *S*-*t*-butyl benzenecarbothioate (**21**; equation 14)



(21) **(22)** 90%

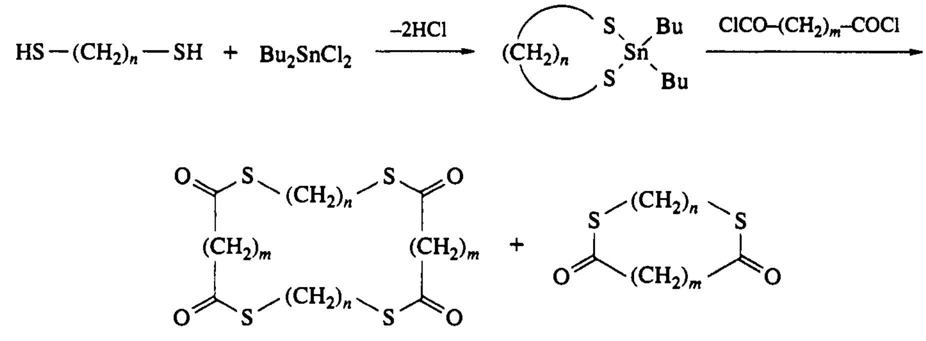
(14)

S-*t*-Butyl thiocarboxylic esters are also accessible from acyl chlorides and *t*-butylthiotrimethylsilane in the presence of potassium fluoride and dicyclohexyl-18-crown-6 (equation 15).[33,77]



(15)

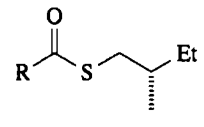
Stannyl thiolates[33,78] were recently shown to be applicable to the formation of the macrocyclic polythiolactones (**23**) and (**24**), according to equation (16).[79]



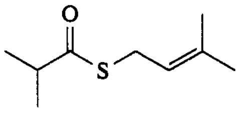
(16)

(**23**) (**24**)

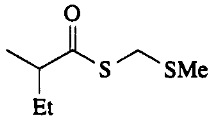
Several optically active *S*-(2-methylbutyl) alkanethioates (**25**)[80] and the naturally occurring thiocarboxylic esters (**26**)[81] and (**27**)[82] were synthesized from the corresponding acid chlorides and thiols, as well as *S*-phenyl arenecarbothioates and thiocinnamates, which are applicable for the preparation of radio-labeled CoA derivatives (**14**; equation 17),[83] and the acyl sulfenates (**28**) occurring in the cultural media of *Pseudomonas* species (equation 18).[84]



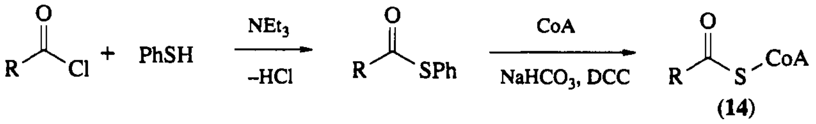
(S)-(**25**)



(**26**)

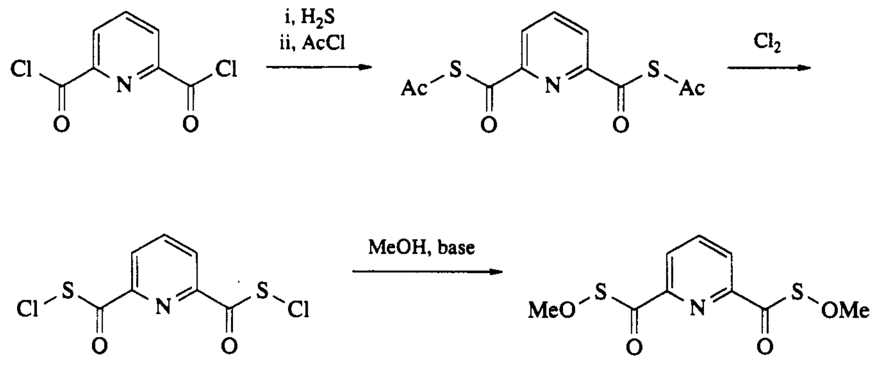


(**27**)



(14)

(17)

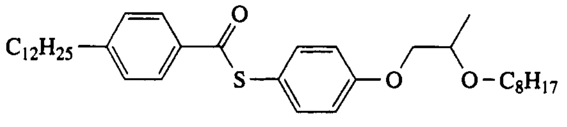


(18)

(**28**)

Special thiol carboxylic esters (**29**) were prepared from aroyl halides and arene thiolates.[85] These 4,4′-disubstituted *S*-aryl arenecarbothioates might gain importance from a practical point of view, since they exhibit liquid crystal properties and could be useful as components of a display cell. Another thiocarboxylic ester (**30**), which was obtained from a zinc thiochelate and benzoyl chloride (equation 19),[86] might be potentially useful as a precursor for organic conductors.

Thiol carboxylic esters of an unusual type are formed if thioamides react with acyl chlorides. 2-Acylthiopyridine *N*-oxides, which are yellow crystalline compounds, are the primary reaction products



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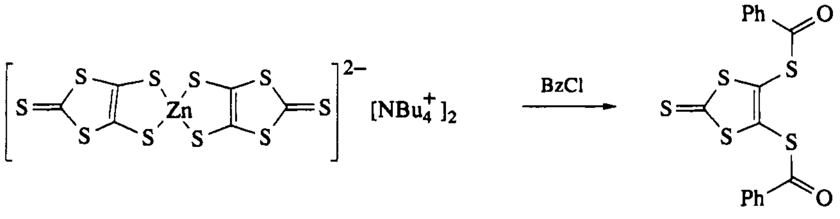
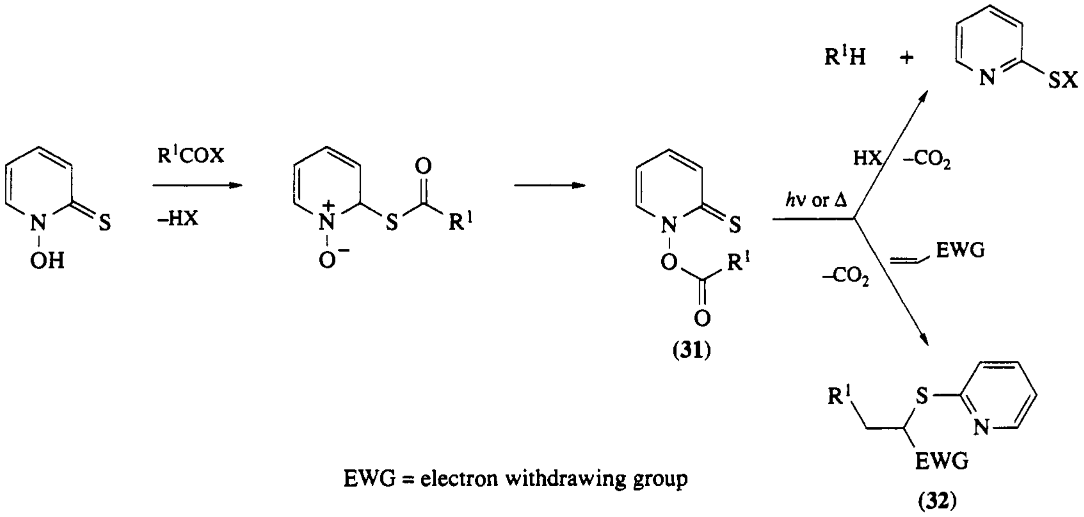


(30)

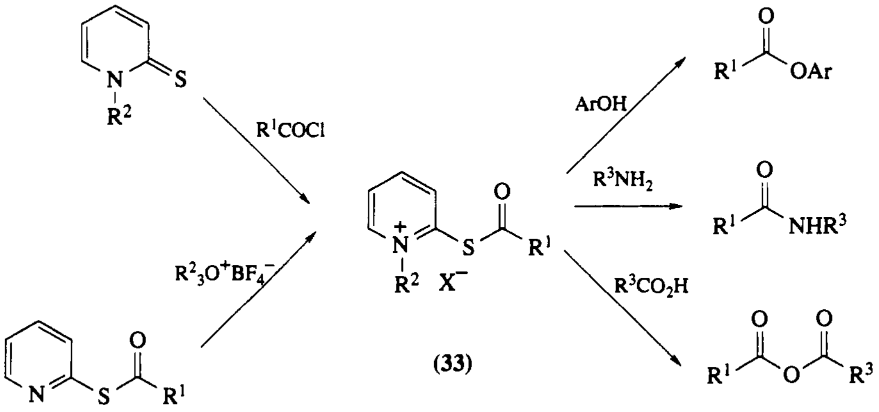
(19)

of *N*-hydroxy-α-thiopyridone and acyl chlorides. They undergo spontaneous rearrangement to yield the *N*-acyloxy-α-thiopyridones (**31**), which are new and versatile sources of alkyl radicals for use in organic synthesis. Reductive decarboxylation of (**31**) takes place on photolysis or thermolysis in the presence of a suitable hydrogen donor HX (*e.g.* Bu^tSH) and alkanes R^1H are formed in high yields (Scheme 2).[87] Addition of electron poor alkenes leads to products (**32**) in which a carbon–carbon and a carbon–sulfur bond have been formed (Scheme 2).[87] The related 2-acylthio-*N*-alkylpyridinium salts (**33**) can serve as water soluble acylating agents for phenols, amines or carboxylic acids according to equation (20).[88]



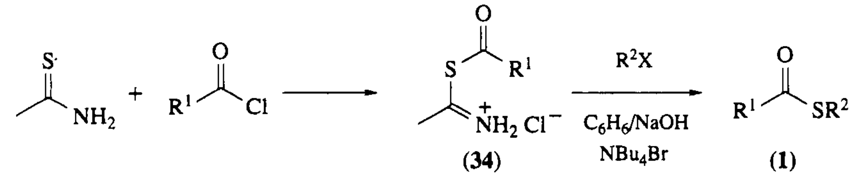
EWG = electron withdrawing group

Scheme 2



(20)

The open-chained thioacetamide, on the other hand, yields iminium salts (**34**) on acylation. Reaction of (**34**) with alkyl halides and subsequent hydrolysis results in the formation of thiocarboxylic esters (**1**).[89] This reaction is actually performed in one step under phase transfer catalysis (equation 21). No unpleasant smelling thiols or thiocarboxylic acids are required as educts, the yields are high and a large variety of substituents R^1 and R^2 are possible.[89]



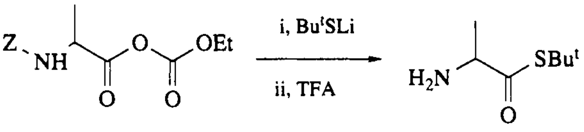
(21)

R^1 = *n*-alkyl, Bu^t, Ar, PhCH=CH; R^2 = *n*-alkyl, $PhCH_2$, $MeCH=CH{-}CH_2$

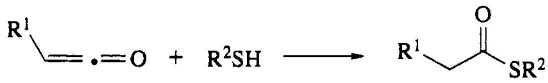
2.5.2.3 Acylation of Thiols with Anhydrides, Ketenes and Esters

Acid anhydrides in the presence of basic catalysts can be used instead of acyl chlorides in acylation reactions of thiols.[33] Mixed anhydrides of *N*-protected amino acids and ethyl carbonate yield the corresponding *S*-*t*-butyl thiocarboxylic esters, which are useful reagents for peptide syntheses (equation 22).[90]

Acylation of thiols with ketenes (equation 23) is a method of long standing.[33] In many cases the yields are nearly quantitative. Functionalities such as acetamino groups or carbon–carbon double bonds in the thiol are not attacked under the mild reaction conditions and optically active thiol esters are obtained without racemization.[33,78]



(22)



(23)

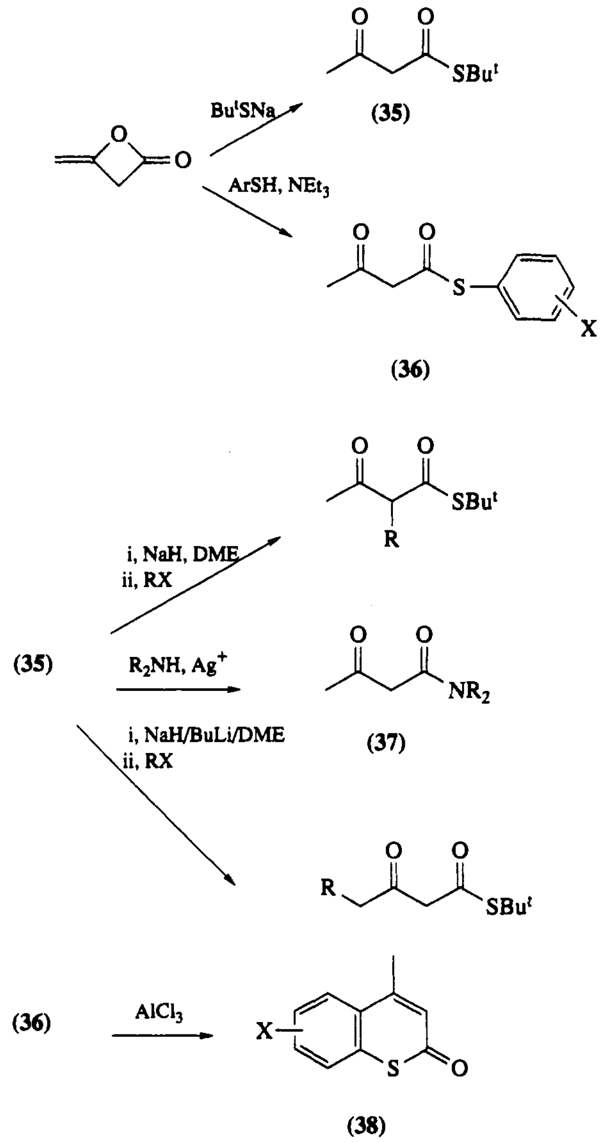
Metal thiolates or benzenethiols in the presence of triethylamine also react very smoothly with diketene to yield *S*-alkyl (**35**)[91] or *S*-aryl acetothioacetates (**36**).[92] The β-keto thioesters (**35**) can be used in exceptionally mild preparations of β-keto amides (**37**),[93] whereas (**36**) can be cyclized by Lewis acids to form thiocumarins (**38**).[92] The *S*-*t*-butyl thiol ester (**35**) is also a suitable substrate for *C*-alkylation in the β-position or, after double deprotonation, in the δ-position (Scheme 3).[91]

Acylation of a simple thiol with an alkyl carboxylate is not a very suitable method for preparation of *S*-alkyl thiocarboxylates. Transesterification is, however, possible if either the thiol or the carboxylic ester is activated. The enhanced reactivity of boron, aluminum and silicon thiolates has been utilized for the synthesis of a large variety of thiocarboxylic *S*-esters, including hydroxy derivatives (from lactones).[33] α,β-Unsaturated thiol esters, *e.g.* cinnamoyl or 2-butenoyl derivatives, are also accessible. Michael addition, an undesirable side reaction of thiols, is completely avoided if alkyl trimethylsilyl sulfides or tris(arylthio)boranes are applied.[33]

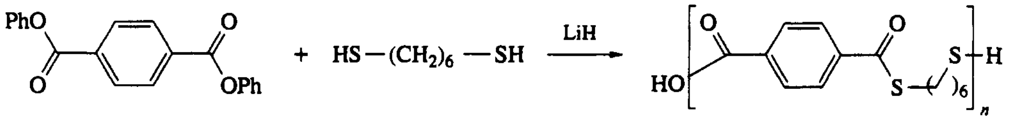
Phenyl carboxylates are reactive enough to form thiocarboxylic esters directly with thiols or thiolate anions.[33] This reaction was applied for the preparation of polyhexamethylene thioterephthalates (equation 24).[94]

The highly activated 4-acyloxypyridines react with thiols under particularly mild conditions (room temperature, no acids or bases) to form *S*-alkyl or *S*-phenyl carbothioates in excellent yields (equation 25).[33,95]

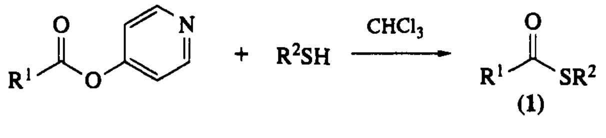
As expected, formation of five- and six-membered thiolactones is a favored process. It occurs easily therefore, even with unactivated esters,[34] as for instance in the case of thiocumarins (**38**) and dihydrothiocumarins (**39**; Scheme 4).[96]



Scheme 3



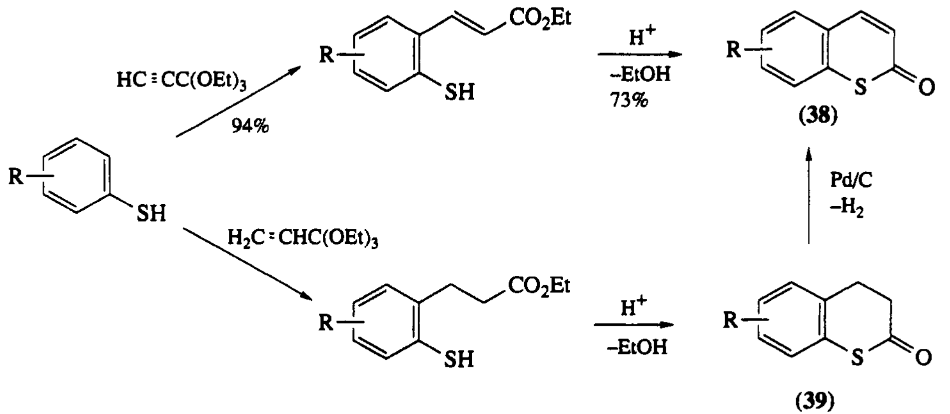
(24)



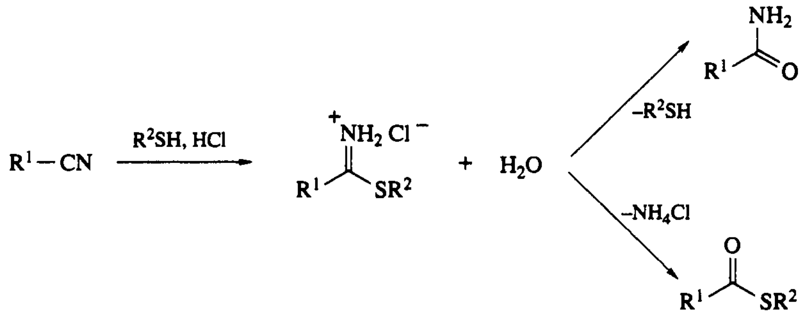
(25)

2.5.2.4 Acylation of Water (Hydrolysis) with Imidothioates, Thioorthoesters and Ketene *S,S*-Acetals

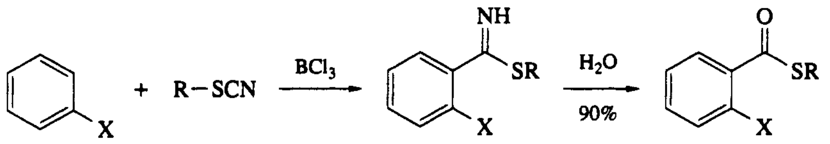
Imidothioates are easily accessible from nitriles (equation 26)[6] or, in special cases, from alkyl thiocyanates (equation 27).[97] Their hydrolysis represents a route to thiol carboxylic esters.[6,33,97] However, the alternative, formation of amides, is not easy to avoid and the yields are therefore often low.[33,98]



Scheme 4



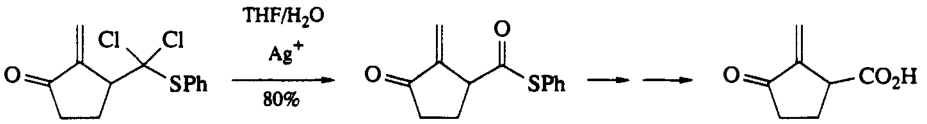
(26)



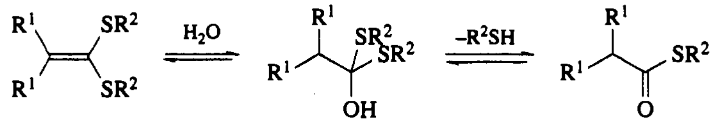
(27)

Thioorthoesters[6] as well as α,α-dihalo sulfides and related compounds may be partially hydrolyzed to yield thiol carboxylic esters.[99] This reaction has been utilized in a sarcomycin synthesis (equation 28).[99]

Ketene *S*,*S*-acetals are also hydrolyzed with aqueous acid *via* dithioorthoesters as has been shown recently,[100] and thiol carboxylic esters are obtained in good yields (equation 29).[6]



(28)

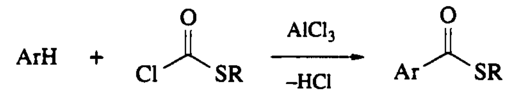


(29)

2.5.2.5 Acylation of Arenes and Carbanions under Formation of Carbon–Carbon Bonds

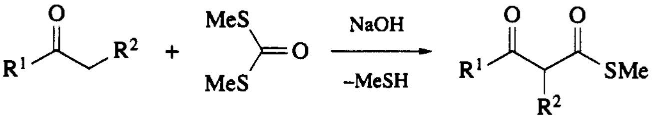
Although reactions of this type are dealt with in other volumes or chapters of this book, a short overview should be given here because in some cases they represent interesting and useful methods for the synthesis of thiol carboxylic esters.

Friedel–Crafts acylation of arenes (*cf.* Volume 2, Chapter 3.1) can be achieved with *S*-aryl or *S*-*n*-alkyl chlorothioformates in good to moderate yields (equation 30).[33]



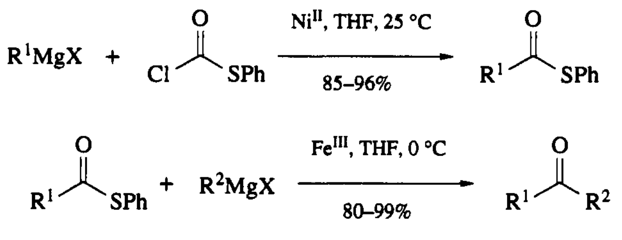
(30)

S,S-Dimethyl dithiocarbonate also reacts with carbonyl-stabilized carbanions (equation 31).[33]



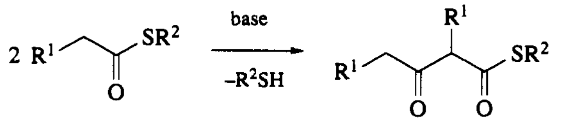
(31)

The Grignard reaction (*cf.* Volume 1, Chapter 1.16) was recently used in a highly efficient route to ketones through sequential coupling of *S*-phenyl chlorothioformate in the presence of transition metal catalysts (equation 32).[101]

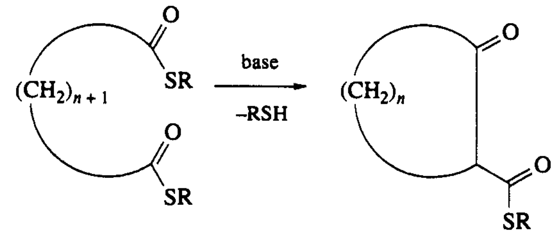


(32)

Claisen (*cf.* Volume 2, Chapter 3.4) and Dieckmann (*cf.* Volume 2, Chapter 3.5) condensation reactions work well with thiocarboxylic esters (equations 33 and 34).[33]



(33)



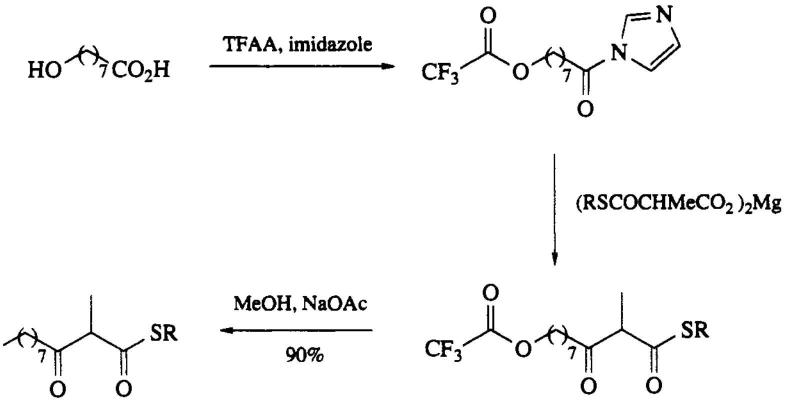
(34)

Magnesium or lithium enolates of thiol carboxylic esters can be acylated with suitable reagents (*cf.* Volume 2, Part 1).[33] Highly functionalized new derivatives are obtained. The example shown in equation (35)[33,102] is closely related to the *C*-acylation of malonyl-CoA with acetyl-CoA, which plays an important role in the biosynthesis of polypeptides and fatty acids. (*S*)-4-Hydroxy-5-methyl-3-oxo-hexanoyl-L-leucine esters (**41**), 2-demethyl analogs of the Hip-Leu moiety of didemnin antibiotics, can be prepared *via* the β-keto thiol carboxylic esters (**40**; equation 36).[103]

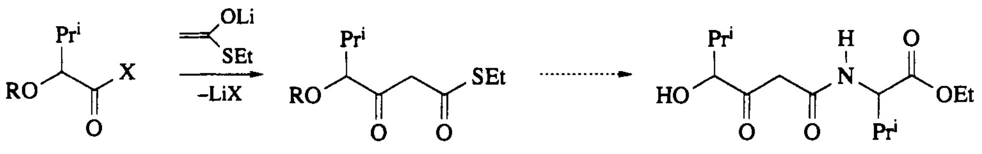
S-Alkyl arenecarbothioates (**42**), on the other hand, undergo deprotonation at the *S*-alkyl group. The resulting dipole-stabilized carbanions may be acylated by the starting compound (**42**) to form *S*-(2-oxoalkyl) arenethioates (equation 37).[33]

2.5.3 THIOXOESTERS AND THIOXOLACTONES

Thioxocarboxylic esters are the least conveniently available type of thioester because of their decreased stability. Oxidation or hydrolysis to form the corresponding esters occurs very easily and thiol esters are formed by rearrangement. On the other hand, the pronounced reactivity makes them promising candidates for synthetic utilization. This valuable chemical property of thioxocarboxylic esters has only

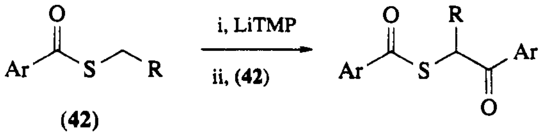


(35)



(40) **(41)**

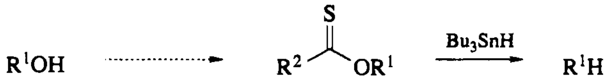
(36)



(42)

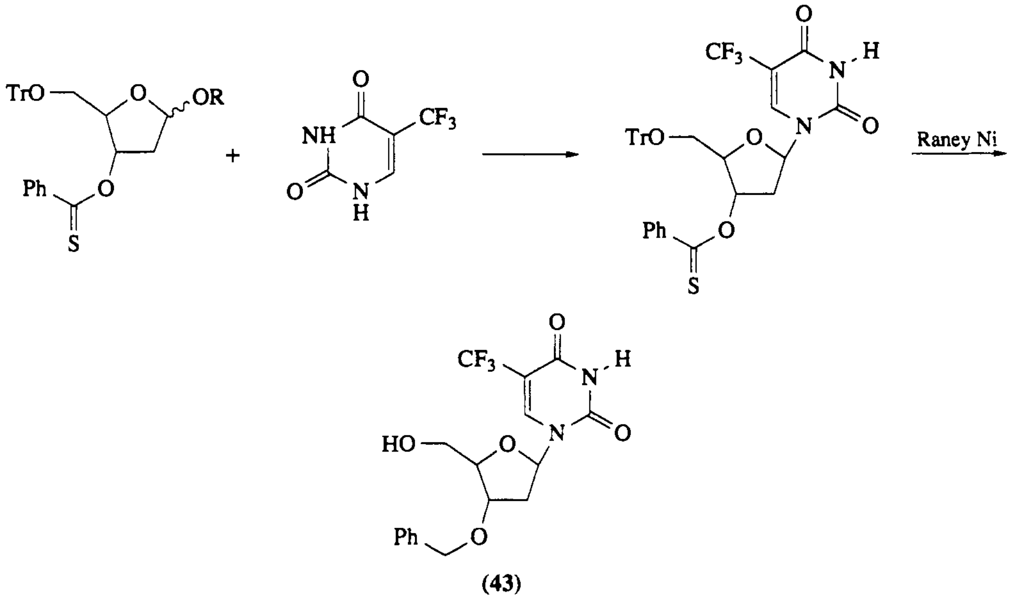
(37)

recently attracted attention. Primary, secondary and tertiary alcohols are, for instance, reducible to the corresponding hydrocarbons *via* thioxoesters (equation 38).[28,104]



(38)

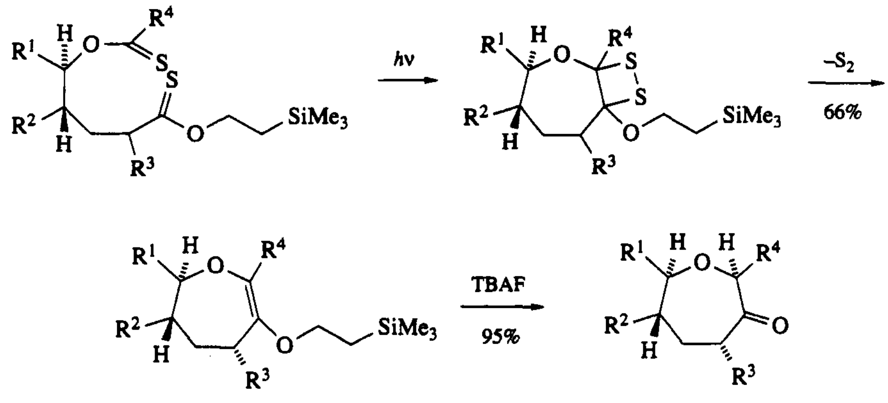
Reductive desulfurization of the thiocarbonyl group with Raney nickel results in good yields of ethers.[28] 3′-*O*-Benzyl-2′-deoxy-5-trifluoromethyl-β-uridine (**43**), claimed as a possible antitumor agent, has been prepared in this way (equation 39).[105]



(43)

(39)

Nicolaou and coworkers have not only used thioxocarboxylic esters as precursors of the first stable 1,2-dithietane,[106] but also as a photochemical approach to the oxepane system (equation 40),[106–109] which could be useful in a total synthesis of brevetoxin B.[109]

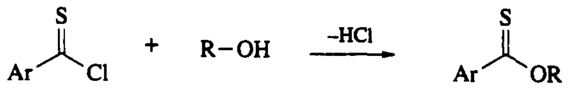


(40)

On account of the increased attention the class of thioxocarboxylic esters has recently gained, new and successful efforts have led to a considerable improvement in the methods that are available for the preparation of these compounds. The advances in this field are clearly described in several review articles and monographs which have appeared in the last decade.[6,14,15,25,28]

2.5.3.1 Thioacylation of Alcohols and Phenols with Thioacyl Halides

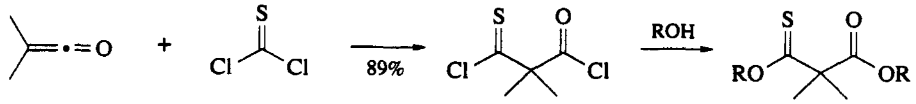
Thioacyl halides are not easily accessible. Aliphatic derivatives, in particular, can only be isolated in rare cases. Thioacylations of alcohols are therefore less important as synthetic methods than acylation of thiols with acyl halides. Nevertheless, a variety of *O*-alkyl and *O*-aryl arenecarbothioates (**2**) have been obtained according to equation (41).[6,14,25,28]



(41)

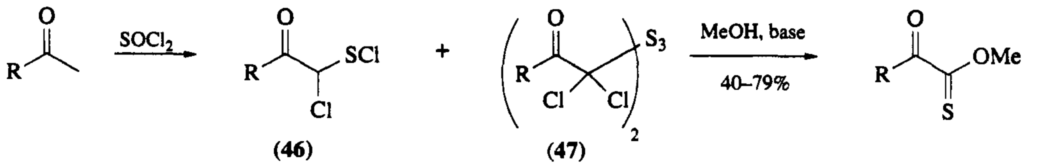
(2)

A stable aliphatic thioacyl chloride (**44**) was obtained according to equation (42) and used in alcoholysis reactions to prepare thioxo malonates (**45**).[110] A mixture of sulfenyl chloride (**46**) and trisulfide (**47**), which does not however contain an α-oxothioacyl chloride,[111] also yields thioxoesters on base-catalyzed reaction with methanol (equation 43).[111]



(42)

(44) **(45)** R = Me, Ph

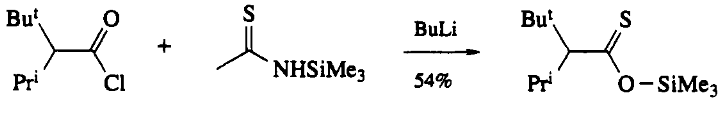


(43)

(46) **(47)**

Interestingly, *O*-trimethylsilyl carbothioates are formed if acyl chlorides react with trimethylsilyl sulfides (equation 44)[14,25] or *N*-trimethylsilylthioacetamide (equation 45).[112] This is obviously due to the strong silicon–oxygen bond present in the products. *O*-Alkyl perfluoroalkanethioates, *e.g.* **(48)** and **(49)**, were also obtained by alcoholysis of perfluoroalkane thiocarbonyl chlorides.[6,14,25,28]

(44)



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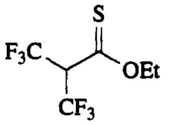

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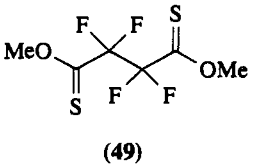
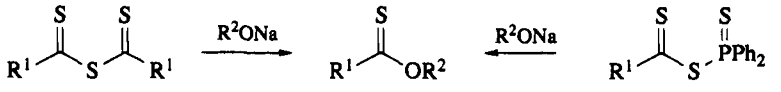


(49)

2.5.3.2 Thioacylation of Alcohols and Phenols with Anhydrides, Thioketenes, Thioesters and Dithioesters

The utility of various thioxo- and dithio-carboxylic anhydrides was recently reviewed by Martin and Barnikow,[113] who pointed out that bisthioacylthioanhydrides and the mixed anhydrides of dithiocarboxylic and diphenyldithiophosphinic acids are effective thioacylating agents for alcohols (equation 46), whereas carboxylic dithiocarboxylic anhydrides transfer an acyl group to a nucleophile.

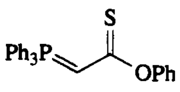


(46)

Thioketenes are stable isolable compounds only if the heterocumulene system is protected against dimerization by bulky substituents or perfluoroalkyl groups.[114] In these cases they are suitable educts for addition of hydroxylic compounds.[6,14,25,28,114,115] This reaction is also possible for the ylid **(50)**. The resulting thioxoester **(51)** does not however react with *p*-nitrobenzaldehyde in a Wittig reaction.[115]

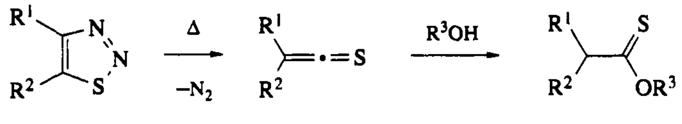
$Ph_3P{=}\bullet{=}\bullet{=}S$

(50)



(51)

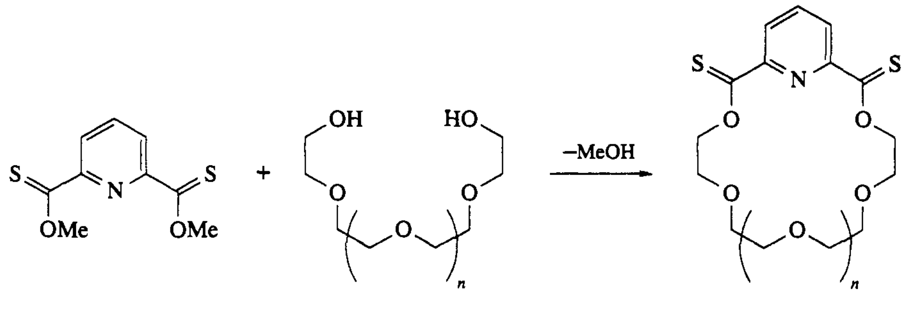
Furthermore, transient thioketenes with a wide variety of substituents R^1 and R^2, including hydrogen, can be generated by flash vacuum thermolysis of 1,2,3-thiadiazoles.[114] By *in situ* reactions thioxoesters are formed with alcohols (equation 47).



(47)

Interconversion of a thioxocarboxylic ester with an alcohol can be achieved in the presence of a base.[25,28] The reaction takes place with high yields if amino alcohols or diols are used. A series of macrocyclic polyether thioxoesters has been prepared by treating *O,O'*-diethyl dithiooxalate and *O,O'*-dimethyl 2,6-pyridinedicarbothioate with glycols. Methanol or ethanol were removed from the equilibrium mixture by distillation or adsorption in molecular sieves (equation 48).[28,116]

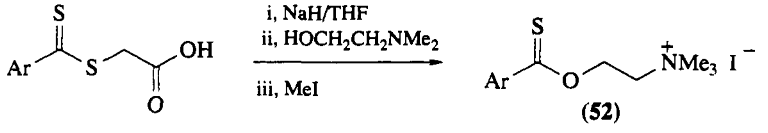
Transesterification of dithiocarboxylic esters with alcohols or alcoholates occurs in the presence of bases. In particular, the highly reactive sodium salts of methoxycarbonyl carbodithioates are used, which can be applied conveniently in aqueous solution or, if hydrolysis has to be avoided, in dry



(48)

$n =$ 2 3 4 5
yield = 71 39 26 10 %

THF.[14,25,28,117,118] For instance, the thioxobenzoylcholine (**52**), which is a powerful *N*-thiobenzoylating agent itself and can be advantageously used in peptide sequence analysis, was prepared according to equation (49).[118]

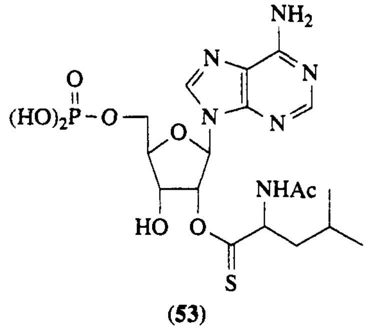


(49)

The above-mentioned *O*-deoxyribosyl thiobenzoate (*cf.* equation 39) was obtained from 1,5-protected deoxyribose and phenyl dithiobenzoate.[105] Also vinyl arenecarbodithioates were shown to be applicable for the synthesis of thioxoesters.[119]

The interesting *O*-alkyl ferrocenecarbothioates are available from *S*-methyl ferrocenecarbodithioate.[120]

Instead of thioxo- or dithio-carboxylic esters thioacylimidazoles were successfully applied in certain cases,[6] for instance in preparing 2′- (**53**) or 3′-*O*-(*N*-acetylthioleucyl)adenosine 5′-phosphate.[121]



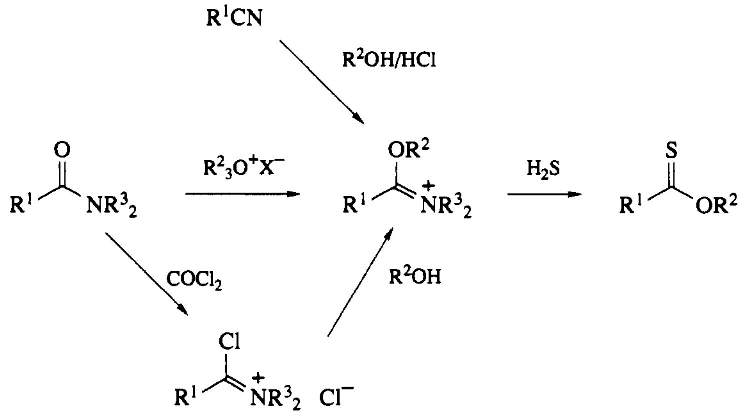
(53)

2.5.3.3 Acylation of Hydrogen Sulfide (Sulfhydrolysis) with Imidates and Orthoesters

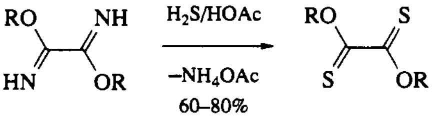
Sulfhydrolysis of imidates is one of the most powerful tools in the field of thioxoester synthesis.[6,14,15,25,28] Advantageously, hydrochlorides or acetates are used as substrates instead of the free bases. Nitriles are useful precursors, but in some cases amides or imidochlorides are preferred as the starting material, according to Scheme 5.[6,14,15,25,28]

This method can be applied with almost every substituent R^1 and R^2. Thioxoesters of dicarboxylic acids can also be prepared *via* the imidates. Fully characterized authentic compounds of this type were, however, not obtained until the 1970s. Synthetic problems arise especially if the thioxoester groups are close enough to each other to permit formation of heterocycles during their synthesis.

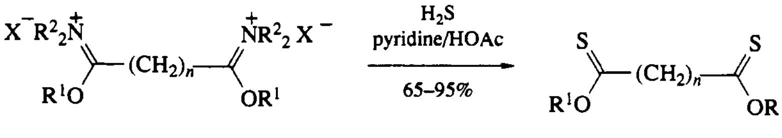
Dialkyl bisthioxooxalates are obtained if the sulfhydrolysis is performed in the presence of acetic acid (equation 50).[122,123] The method also works successfully in the case of the homologous dicarboxylic acids (equation 51),[21,124] including the unsaturated fumaric acid.[20] The preparation and further reaction of the appropriate imidates is not always straightforward. As Hartke and coworkers[20,21,124] have shown, special substituents R^2 at the nitrogen atoms and carefully chosen reaction conditions are required in order to get high yields and pure products.



Scheme 5



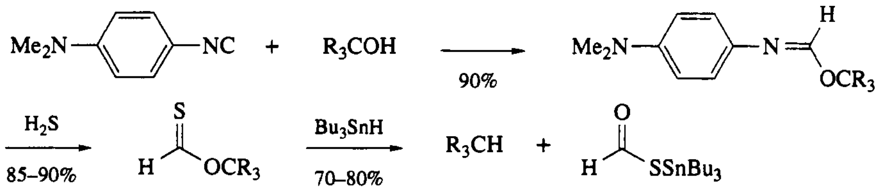
(50)



(51)

$2R^2 = 2H, 2Me, -(CH_2)_5-$ $\qquad$ $n = 1–5; R^1 = Me, Et$

Sulfhydrolysis of imidates is also the method of choice for preparing *O-t*-alkyl thioformates (equation 52),[104] *O*-methyl 2-hydroxy-, 2-mesyloxy- and 2-acetoxy-thiocarboxylic esters (**54**),[125] and especially the thioxoesters of amino acids and peptides. The first examples of the latter class of compound were described by Ried and von der Emden (1960).[126] More recently the preparation as well as the biochemical behavior, the thioacylating properties in particular (*cf.* Section 2.4, this volume), have been intensely studied[126–130] and thioxoesters of amino acids with different protecting groups (**55**) have been explored. Attempts to improve the leaving properties of the alkoxy groups by introduction of a 2-nitro substituent resulted in poorer yields of thioxoesters.[127]



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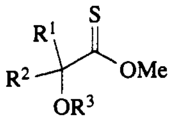
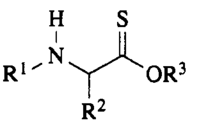
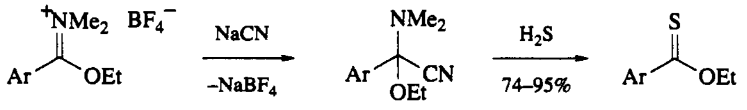


(54) $R^1 = H, R^2 = Ph$
$R^1 = R^2 = Me$
$R^3 = H, Ms, Ts$



(55)
R^1 = Ac,[128] Bz,[128, 129] Z,[126, 127, 129]
t-BOC,[130] Ts,[126] Phth,[126] Fmoc[127]

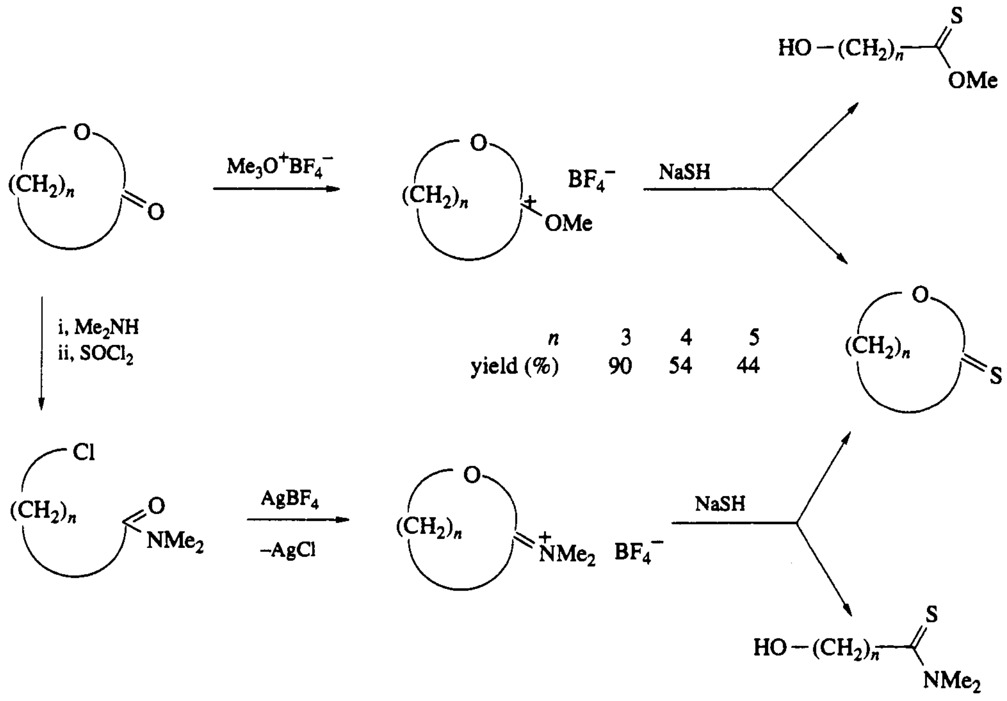
A special route from imidates to *O*-ethyl arenecarbothioates *via O,N*-acetals of α-keto nitriles as intermediates is also suitable for the preparation of nitro derivatives which are difficult to obtain in good yields by other methods (equation 53).[131]



(53)

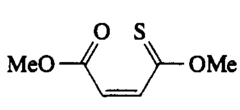
Orthoesters undergo sulfhydrolysis in the presence of proton or Lewis acids ($ZnCl_2$, $FeCl_3$).[25] This method is still the best for the preparation of *O*-ethyl thioformate.[25,132]

In a similar way to the formation of open-chain thioxocarboxylic esters, thioxolactones are obtained from cyclic imidates.[28] Kaloustian *et al.*[133] have studied this reaction and its mechanism in detail. It is closely related to the sulfhydrolysis of dialkoxycarbenium ions, which also results in the formation of thioxoesters or thioxolactones (Scheme 6).[134]

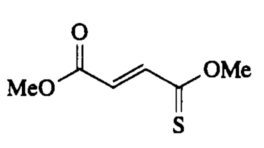


Scheme 6

O,O-Dimethyl monothiomaleate (**56**) and monothiofumarate (**57**) are formed in a complicated reaction from 2,5-dimethoxythiophene *via* an intermediate of the orthoester type.[135] *O*-Trimethylsilyl ketene-*O,O*-acetals are readily formed from carboxylic esters and can be transformed to thioxoesters, without being isolated, by reaction with hydrogen sulfide, according to equation (54).[136] Methyl thioxoarachidonate (**58**) was prepared by this route.[136]



(56)



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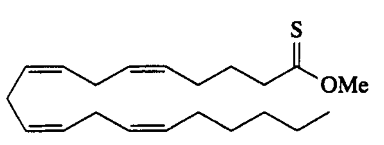
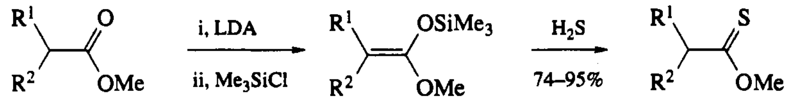


(58)

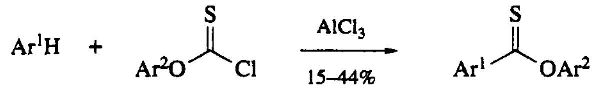


(54)

2.5.3.4 Thioacylation of Arenes and Carbanions under Formation of Carbon–Carbon Bonds

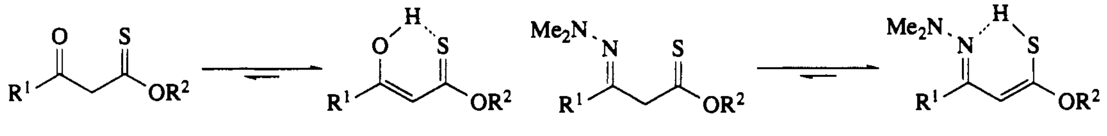
As with the thiol ester series (Section 2.5.2.5) acylation reactions of this type are treated in other parts of this work. However, the most important synthetic reactions should be mentioned here.

Friedel–Crafts thioacylation (*cf.* Volume 2, Chapter 3.1) can be performed with *O*-aryl chlorothioformates (equation 55). The yields are only moderate and no *O*-alkyl derivatives are available.[25]

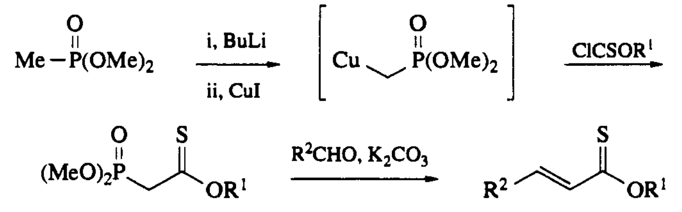


(55)

Carbanions (*cf.* Chapter 2, Chapter 3.4) derived from ketones, hydrazones or phosphonates react with *O*-alkyl chlorothioformates or thiocarbonates, resulting in *O*-alkyl β-oxo- (**59**),[137] β-hydrazono- (**60**)[138] or α,β-unsaturated-carbothioates (equation 56).[139]



(59) **(60)**



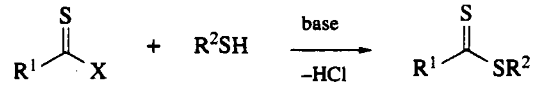
(56)

2.5.4 DITHIOCARBOXYLIC ESTERS AND DITHIOLACTONES

Although, presumably, dithiocarboxylic esters are prepared by alkylation of the strongly nucleophilic dithiocarboxylate salts in most cases (Section 2.5.1), thioacylation procedures provide a valuable alternative.[6,14,15,26,27,29,140,141] In particular, the sulfhydrolysis of imidothioates (Section 2.5.4.3) has retained its importance due to the convenient availability of the starting material, a nitrile or thioamide.

2.5.4.1 Thioacylation of Thiols with Thioacyl Halides, Thioacyl Anhydrides and Thioketenes

Thioacyl halides react with thiols in the presence of base and high yields of alkyl or aryl dithiocarboxylates (**3**) are obtained according to equation (57).[26]



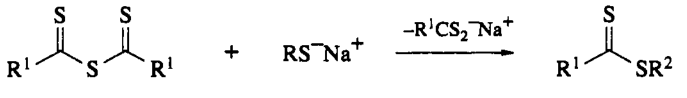
(57)

(3)

Thiols can also be thioacylated, in the same way as alcohols (Section 2.5.3.2),[113] by reaction with bisthioacyl thioanhydrides (equation 58). The preparation of aromatic as well as aliphatic thioanhydrides is possible according to novel procedures described by Kato *et al.*,[142–144] *e.g.* from the corresponding dithiocarboxylic acids and DCC[142] or 2-chloro-*N*-methylpyridinium iodide.[143] Even sterically hindered dithioesters are obtained (equation 58).[144]

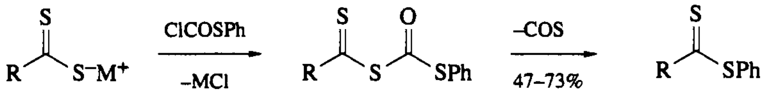
Phenyl carbodithioates are obtained in acceptable yields by an intramolecular thioacylation according to equation (59).[145] The intermediate mixed thiocarboxylic thiocarbonic acid anhydride is not isolated but spontaneously eliminates carbon oxysulfide.

Thioacyl diphenylthiophosphinyl sulfides are useful thioacylating reagents too, which give dithioesters in good yields under mild reaction conditions (equation 60).[146]

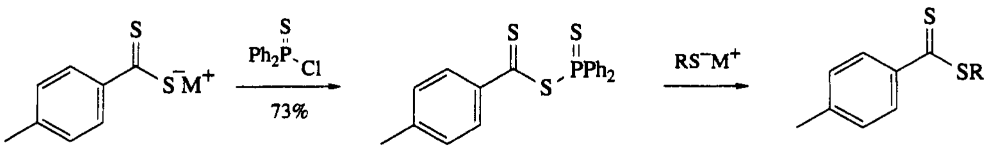


(58)

(3) $R^1 = Pr^i$, $R^2 = Bu^t$; 20%



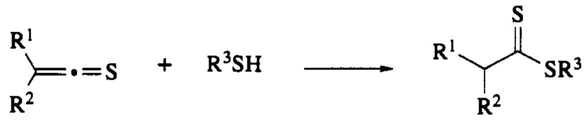
(59)



(60)

R = Et, M = Li; 74%
R = Ph, M = Na; 90%

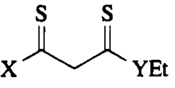
Stable, as well as transient, thioketenes give dithiocarboxylic esters on reaction with thiols (equation 61).[114]



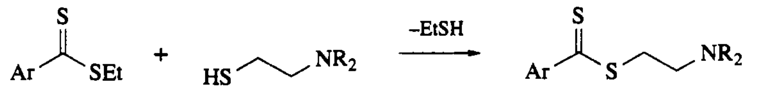
(61)

2.5.4.2 Transesterification of Thiols

The interchange reaction between a thioxoester and a thiol does not, in general, represent a meaningful synthetic procedure since dithioesters are more readily available than thioxoesters in most cases. However, *O*,*S*-diethyl trithiomalonate (**61b**) and diethyl tetrathiomalonate (**61c**) were prepared from *O*,*O*-diethyl dithiomalonate (**61a**).[21] On the other hand, the transformation of one dithiocarboxylic ester into another can be a useful and practicable reaction. For instance, ethyl arenecarbodithioates are interconverted to 2-dialkylaminoethyl arenecarbodithioates,[14] according to equation (62).

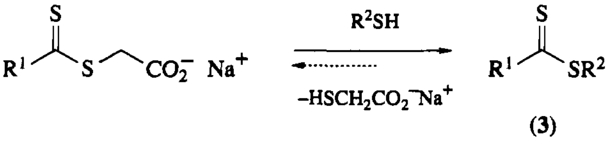


(**61a**) X = Y = O
(**61b**) X = O, Y = S
(**61c**) X = Y = S



(62)

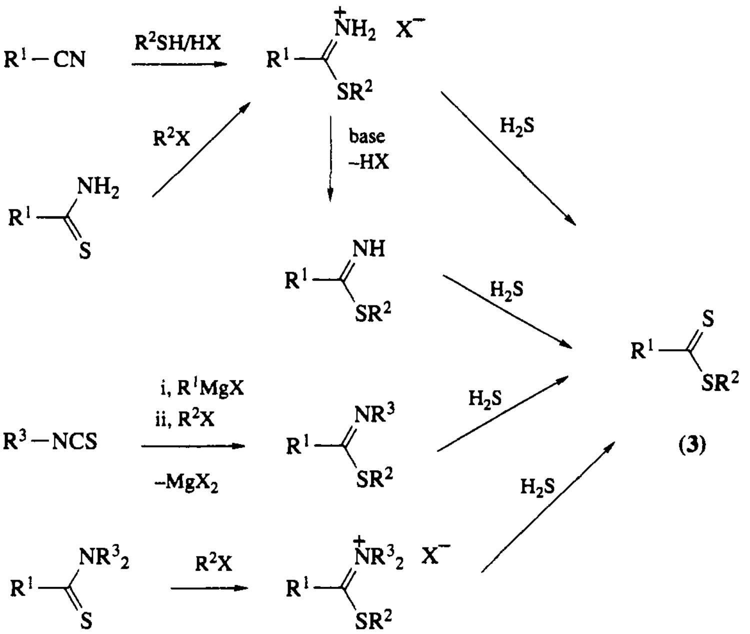
The highly activated sodium salts of carboxymethyl carbodithioates, which can be easily obtained by alkylation of sodium carbodithioates with bromoacetic acid,[14,147,148] have especially found application for the thioacylation of thiols.[6,14] Since the products are insoluble in water, the equilibrium reaction (equation 63) is shifted to the product side. Also vinyl arenecarbodithioates are reactive enough to be interconverted with potassium alkanethiolates.[119]


(63)

The unnatural coenzyme A dithioesters were synthesized by transesterification and their reactions with enzymes (acetyl transferase) studied.[149]

2.5.4.3 Acylation of Hydrogen Sulfide (Sulfhydrolysis) with Imidothioates and Related Compounds

Imidothioates in the neutral or ionic form are the most generally applied educts for the preparation of dithiocarboxylic esters. They are themselves prepared from nitriles, thioamides or isothiocyanates, and react with hydrogen sulfide under appropriate conditions to yield the dithioesters (Scheme 7).[6,14,26,27,29,141] Interesting examples (**62**)–(**73**) were described in the recent literature.

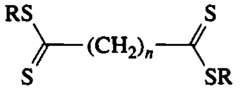


Scheme 7

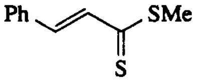
Nitriles can be used as starting material for the bisdithioesters (**62**; *n* = 4, 5, 10),[124,150] whereas the derivatives with shorter chain lengths (**62**; *n* = 1–3),[21,124] as well as methyl dithiocinnamate (**63**),[20] are accessible from *N,N*-disubstituted thioamides *via* the corresponding imidothioate iodides. Methyl dithioacrylate (**65**), the simplest unsaturated dithioester, was prepared by flash vacuum thermolysis of a precursor dithioester (**64**), which had been obtained from the corresponding nitrile (equation 64).[151] It can be isolated as a red monomeric compound at 77 K but dimerizes rapidly at room temperature. The β,γ-unsaturated isoprene derivative (**66**)[152] and the methyl 2-arylpropanedithioates (**67**)[141] were prepared from phenyl isothiocyanate and used as educts for syntheses of lavandulal and *ar*-curcumene. Also ethyl furane-3-carbodithioate (**68**), as prepared from the nitrile, has found application in syntheses of the natural products egona ketone and *ar*-turmerone.[141]

Markedly branched alkyl 3,3,3-trialkylpropanedithioates (**69**) can be prepared by 1,4-addition of organometallics to α,β-unsaturated imidothioates and subsequent sulfhydrolysis of the ketene *S,N*-acetals according to equation (65).[141,153]

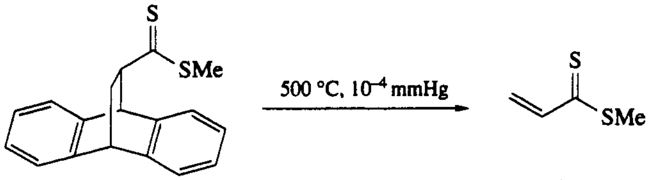
Dithioesters of various amino acids with different *N*-protecting groups have been prepared. The corresponding nitriles are suitable educts in many cases (**70**).[154,155] Using ^{13}C sodium cyanide or ^{15}N ammonium chloride as starting material, Storer *et al.*[154] were able to prepare the respective isotopically labeled



(62) n = 1–5, 10

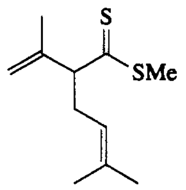


(63)



(64) **(65)**

(64)



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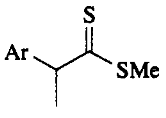

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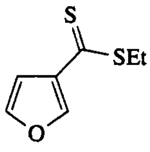
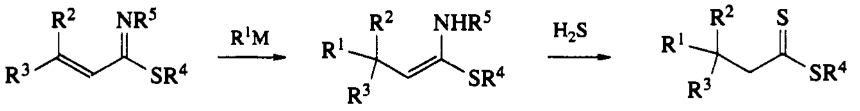


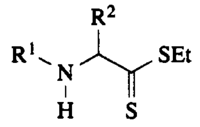
(68)



(69)

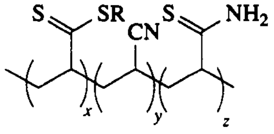
(65)

amino acid dithioesters, model compounds for studies on enzyme–substrate complexes. However, *N*-*t*-butyloxycarbonyl derivatives (**71**)[130] cannot be obtained in this way, since obviously deprotection occurs under the strongly acidic conditions of the first step. Instead, amino acid thiopiperidides have been successfully used.[130] Levesques *et al.* have prepared polydithioesters of type (**72**) from polyacrylonitrile[156] and (**73**) from polyethylene oxide *via* the polythioamide.[157]

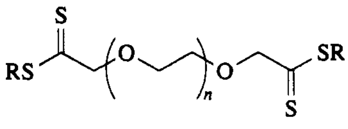


(70) R^1 = Ac, Bz, PhCH$_2$CO, Z

(71) R^1 = t-BOC



(72)

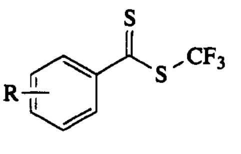


(73)

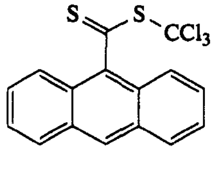
2.5.4.4 Dithiocarboxylation of Arenes and Carbanions under Formation of Carbon–Carbon Bonds

As in previous sections of this chapter, only short comments will be made on this type of thioacylation. Reaction of benzene and activated arenes with alkyl or aryl chlorodithioformates under Friedel–Crafts conditions or with (alkylthio)thiocarbonyl hexafluoroantimonates, $(RSC{=}S)^+$ SbF_6^-,[158] results in formation of the corresponding arenecarbodithioates.[6,14,26,27,156] Three interesting new examples, (**74**),[159] (**75**)[160] and (**76**),[156] may illustrate the scope of the reaction.

Methyl chlorodithioformate has also been used to prepare the methyl cyclopropanecarbodithioate (**77**; equation 66),[161] whereas dimethyl trithiocarbonate was reacted with the carbanions of ketones[162] and



(74) R = H, F, CF_3, OMe



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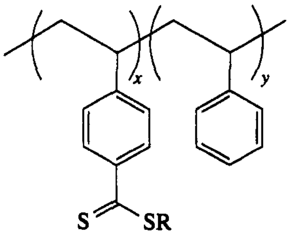
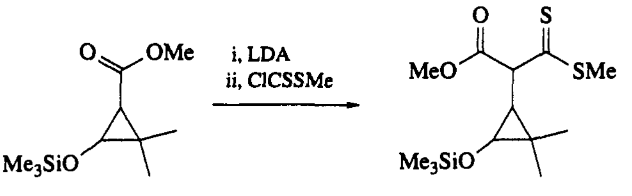


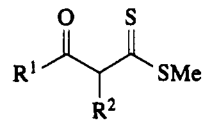
(76)

other compounds with activated methyl or methylene groups[163] to yield, for example, the methyl carbodithioates (**78**)[162] and (**79**).[163]



(66)

(77)



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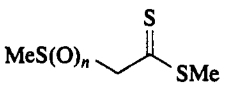

(79) $n = 1, 2$

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2.6

Selenoesters of All Oxidation States

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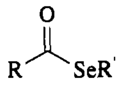
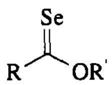
2.6.1 INTRODUCTION

As well as thiol esters, selenol esters (**1**) frequently exhibit a high and selective reactivity toward nucleophiles, which is enhanced even further by activation with heavy ions or oxidizing agents. These properties make selenol esters valuable acyl transfer agents. This review deals with general methods for the synthesis of selenol esters and their reactivity as acyl transfer agents. Furthermore, selenoesters (**2**), isomeric compounds of selenol esters, and their derivatives selenoamides (**3**) are also described. These compounds show the characteristic reactivity based on the carbon–selenium double bond.

Hitherto known reviews for the chemistry of selenol esters and their derivatives are shown in refs. 1–5.



(1)



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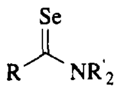


(3)

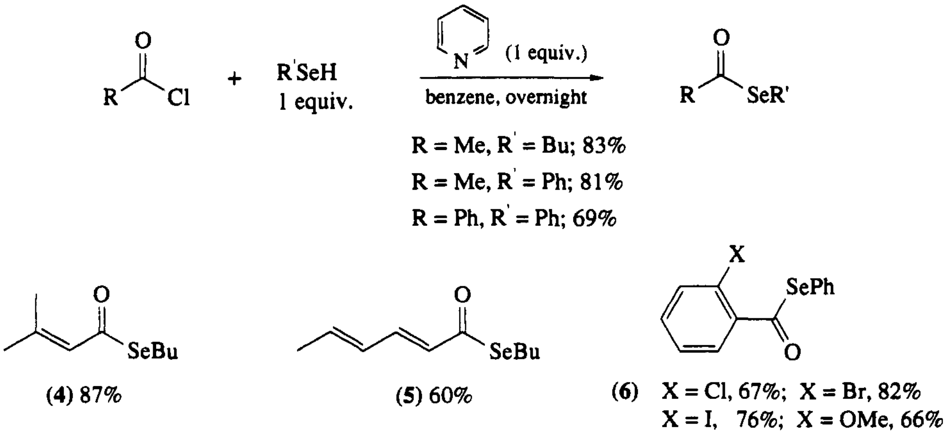
2.6.2 SELENOL ESTERS

2.6.2.1 Preparation

Many methods for the preparation of selenol esters have been developed. These can be classified into the following five general methods according to the types of reaction.

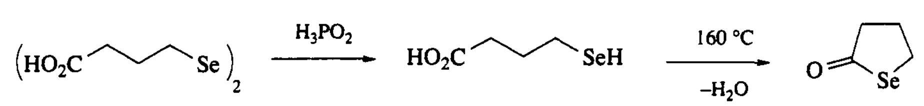
2.6.2.1.1 *Acylation of selenols and their metal salts*

In 1962 Renson *et al.* reported that a variety of selenol esters can be synthesized by the reaction of the appropriate acyl chlorides with selenols in the presence of pyridine.[6,7] Selenols can easily be prepared from elemental selenium and the corresponding Grignard reagents. In addition to simple selenol esters, α,β-unsaturated selenol esters (**4**) and (**5**) and *o*-substituted aromatic selenol esters (**6**) have been obtained by this method, as shown in Scheme 1. Butyl selenol esters are generally colorless or light yellow liquids, whereas the phenyl or substituted phenyl selenol esters are white solids, which are easily purified by recrystallization. More recently other groups have used Renson's method to synthesize similar selenol esters.[8–10]



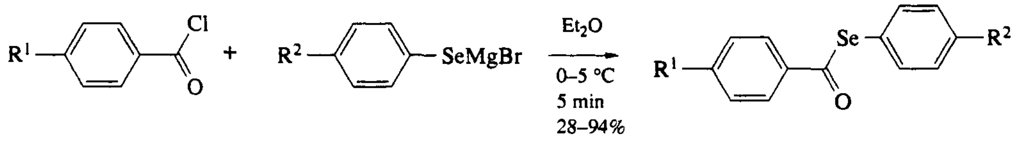
Scheme 1

It has been reported that some selenols are directly acylated by carboxylic acids to give selenol esters.[11–14] For example, heating of 4-hydroselenobutyric acid at about 160 °C resulted in ring closure to give the corresponding γ-lactone (equation 1).[11]



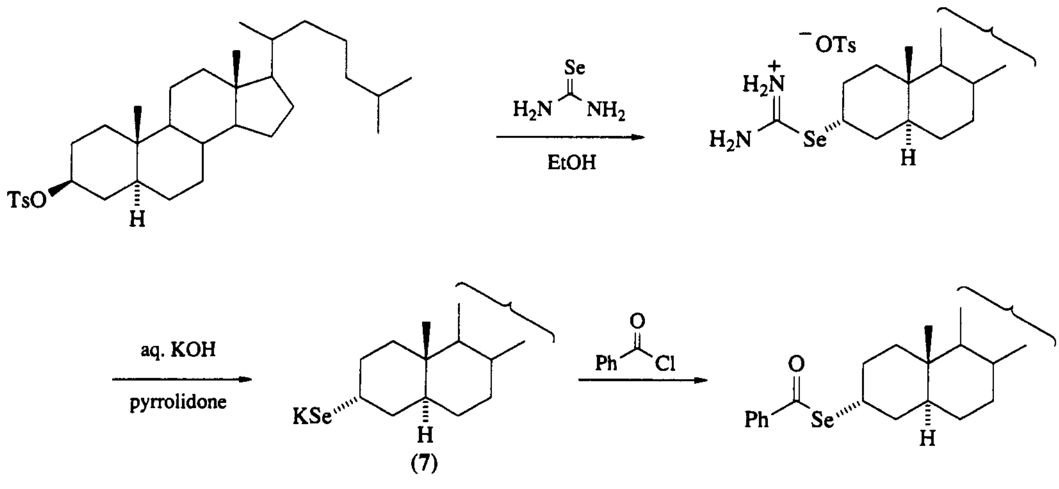
(1)

Areneselenyl magnesium bromide has been reported to react with *p*-substituted benzoyl halides, giving aromatic selenol esters[15–17] as the first examples exhibiting liquid crystal properties (equation 2).[15]



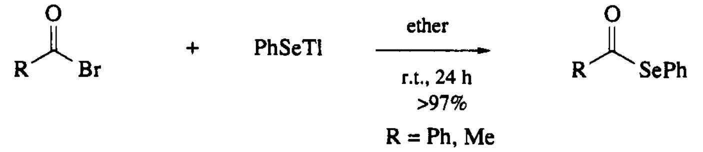
(2)

Alkali metal salts of selenol can also be used in the synthesis of selenol esters.[17–22] Axial and equatorial selenol esters of cholestane and androstanone have been prepared from the potassium salt (**7**) and benzoyl chloride (Scheme 2 illustrates the axial isomer).[18]



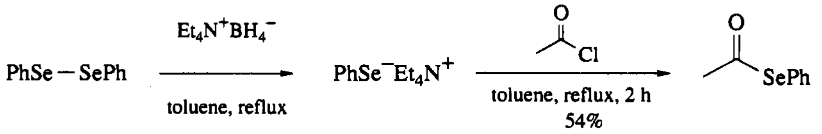
Scheme 2

Reaction of acyl or aroyl halides with thallium(I) phenyl selenide, prepared by the reaction of either thallium(I) ethoxide or thallium(I) phenoxide with benzeneselenol, gave the corresponding phenyl selenol esters in yields over 97% (equation 3).[23]



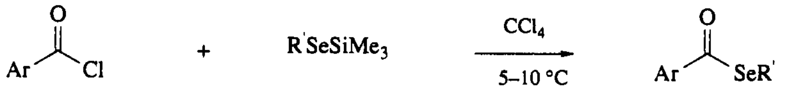
$$\mathrm{RC(O)Br} + \mathrm{PhSeTl} \xrightarrow[\substack{\text{r.t., 24 h}\\ >97\%\\ \mathrm{R = Ph, Me}}]{\text{ether}} \mathrm{RC(O)SePh} \tag{3}$$

Tetraethylammonium borohydride reduces diphenyl diselenide to phenylselenolate anion. When an acyl halide is added to the toluene solution of phenylselenolate anion, the corresponding acylation product is isolated in good yield (equation 4).[24] Resin-supported phenyl selenide anion underwent acylation with acetyl chloride under mild reaction conditions.[25]



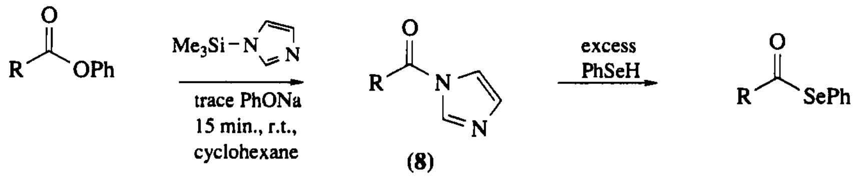
$$\mathrm{PhSe{-}SePh} \xrightarrow[\text{toluene, reflux}]{\mathrm{Et_4N^+BH_4^-}} \mathrm{PhSe^-Et_4N^+} \xrightarrow[\substack{\text{toluene, reflux, 2 h}\\ 54\%}]{\mathrm{CH_3C(O)Cl}} \mathrm{CH_3C(O)SePh} \tag{4}$$

Selenol esters have also been prepared from trimethylsilyl selenides and acyl halides, as shown in equation (5).[26]

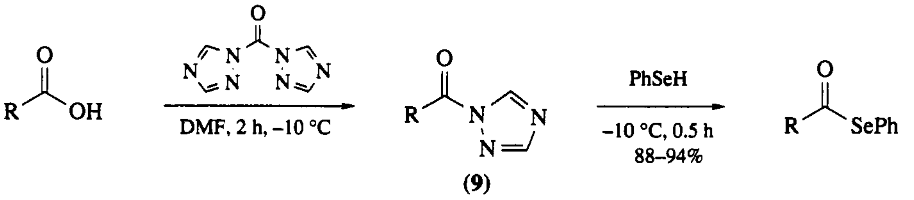


$$\mathrm{ArC(O)Cl} + \mathrm{R'SeSiMe_3} \xrightarrow[5\text{–}10\,^\circ\mathrm{C}]{\mathrm{CCl_4}} \mathrm{ArC(O)SeR'} \tag{5}$$

A mild and convenient method has been attained by using the imidazolide (**8**; equation 6) or triazolide (**9**; equation 7) of carboxylic acids as a key intermediate. Treatment of an imidazolide of carboxylic acid with 1.2 equiv. of benzeneselenol and 0.02 equiv. of sodium phenoxide provided the selenol ester in a quantitative yield.[27] In the case of the triazolide of carboxylic acids, the reaction proceeded in the absence of base.[28]

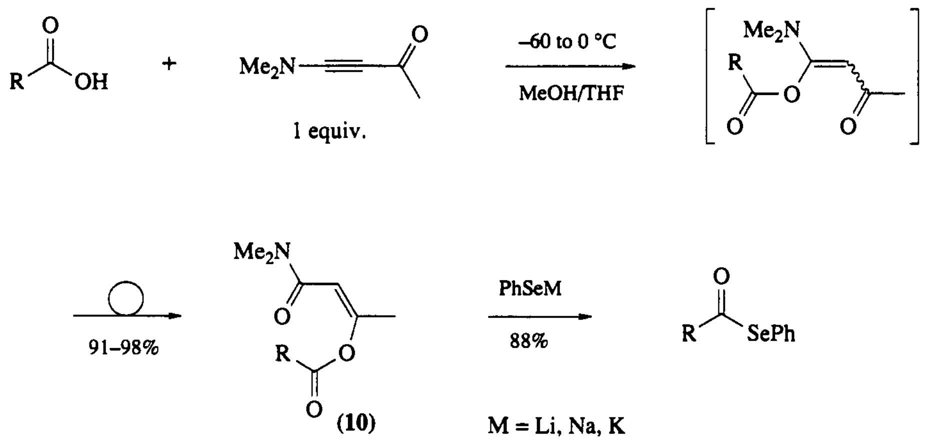


(6)



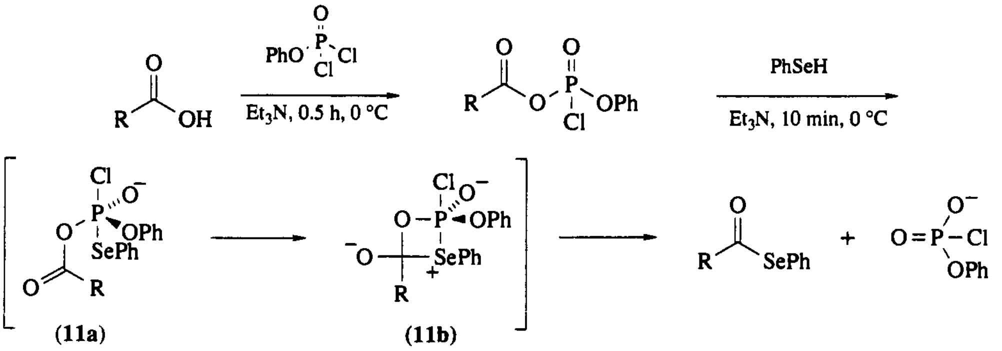
(7)

Reaction of some vinyl esters (**10**; Scheme 3) of carboxylic acids with selenolate gave the corresponding selenol esters in high yields because of the good leaving ability of enolate.[29]



Scheme 3

Reaction of carboxylic acids with phenyl dichlorophosphate, followed by the addition of benzeneselenol to the mixture afforded selenol esters (Scheme 4).[30] The reaction is assumed to proceed *via* the pentacovalent oxyphosphorane intermediates (**11a**) and (**11b**).

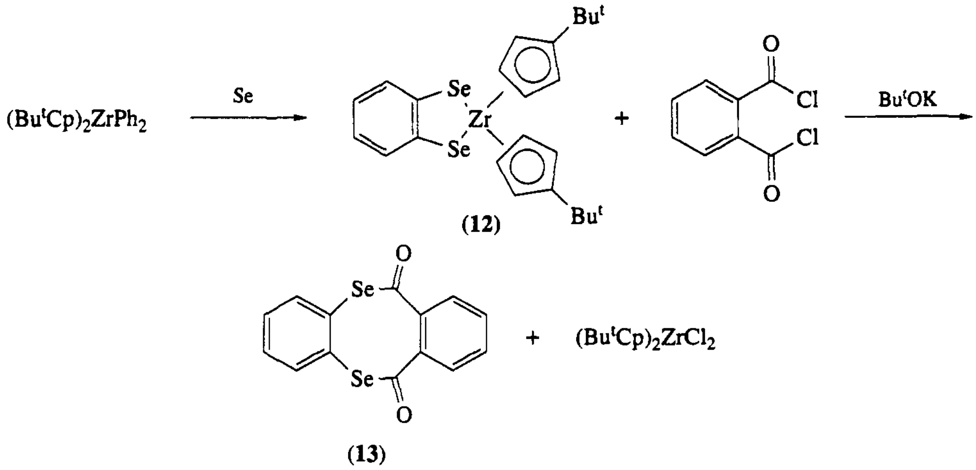


Scheme 4

It has recently been disclosed that the electrophilic cleavage of zirconocene complex (**12**; Scheme 5) leads easily to new *Se,Se′*-disubstituted derivatives of benzene-1,2-diselenol (**13**) in good yields, with quantitative recovery of the organometallic moiety of the reagent.[31,32]

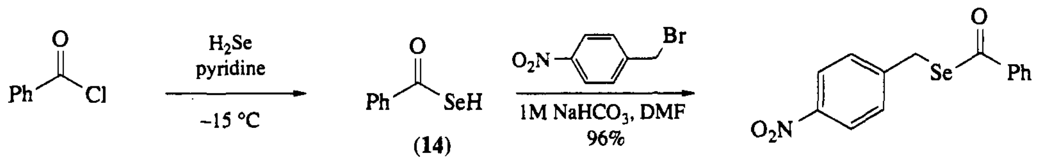
2.6.2.1.2 Alkylation of selenocarboxylates

As well as acylation of selenols, alkylation of selenocarboxylates with alkyl halides is one of the most straightforward methods for synthesis of selenol esters. However, known examples of selenol esters synthesized using this strategy have been limited to a few cases,[33–37] due to the difficulty of the preparation of selenocarboxylates.



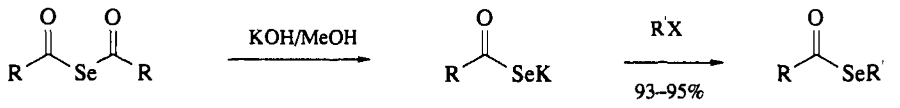
Scheme 5

Jensen *et al.* reported that selenobenzoic *Se*-acid (**14**; equation 8) is formed as the primary product of the reaction of benzoyl chloride with hydrogen selenide in pyridine, but (**14**) is a very unstable liquid that reversibly loses hydrogen selenide to give dibenzoyl selenide. On rapid treatment with *p*-nitrobenzyl bromide, the selenobenzoic *Se*-acid formed *in situ* produced (*p*-nitrobenzyl)selenobenzoate in high yield.[33]



(8)

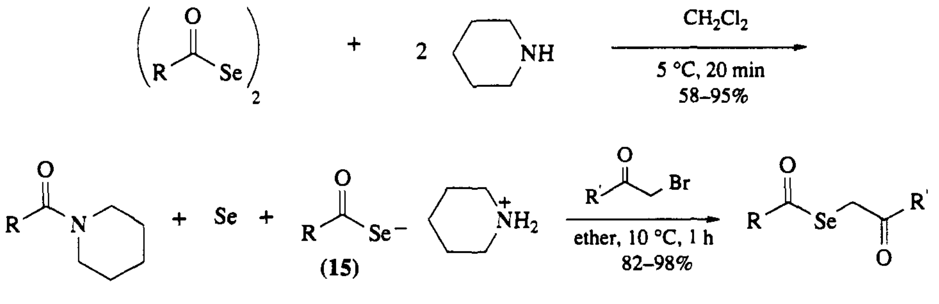
Potassium selenocarboxylates, which are useful starting materials for the preparation of selenol esters,[34,35] can be prepared by the reaction of diacyl selenides with methanolic potassium hydroxide (equation 9).



(9)

R = Ph, p-Cl-C_6H_4, n-$C_{17}H_{35}$; R' = Me, $PhCOCH_2$

Piperidinium selenocarboxylates (**15**; equation 10) have been isolated in high yields from the reaction between diacyl diselenides and piperidine. The salts (**15**) dissolved in common protic and aprotic solvents and readily reacted with alkylating agents such as phenacyl bromide to give the corresponding esters in almost quantitative yields.[36,37]

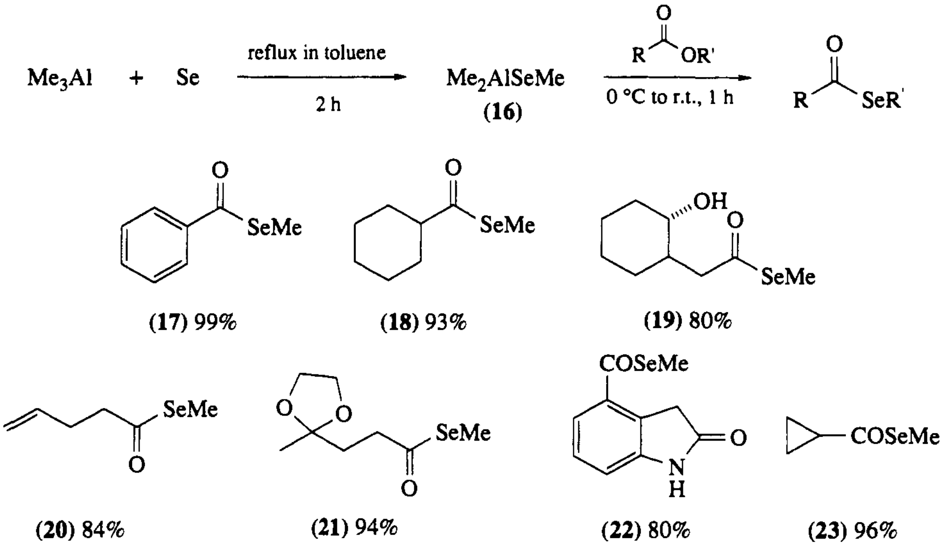


(10)

2.6.2.1.3 Reaction of esters with aluminum selenolate

One of the most general methods for synthesis of selenol esters uses dimethylaluminum methylselenolate (**16**), which has been found to be a remarkably efficient and versatile reagent for the conversion of *O*-alkyl esters to their corresponding methylselenol esters under mild conditions.[38,39] The reagent (**16**) is conveniently prepared by heating a toluene solution of trimethylaluminum with powdered selenium for 2 h under reflux. The transformation of various esters to selenol esters can be completed within 1 h. Representative results are shown in Scheme 6 (**17–23**). This method can also be applied to cyclic esters (**19**) and esters (**20**)–(**23**) containing other functional groups.

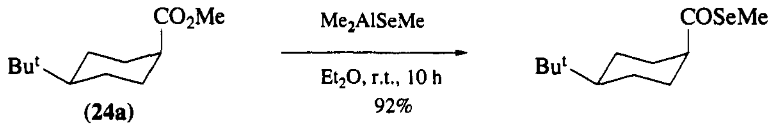
Reaction of methyl *trans*-4-*t*-butylcyclohexanecarboxylate (**24b**; equation 12) with (**16**) proceeded much faster than the reaction of the *cis* isomer (**24a**; equation 11), a result suggesting that this method is highly sensitive to steric factors.[40–42]



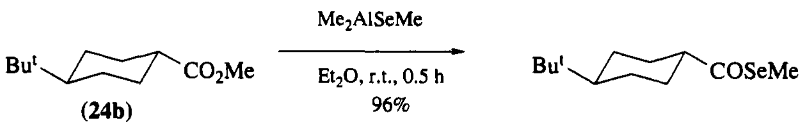
(**17**) 99% (**18**) 93% (**19**) 80%

(**20**) 84% (**21**) 94% (**22**) 80% (**23**) 96%

Scheme 6



(**24a**) (11)



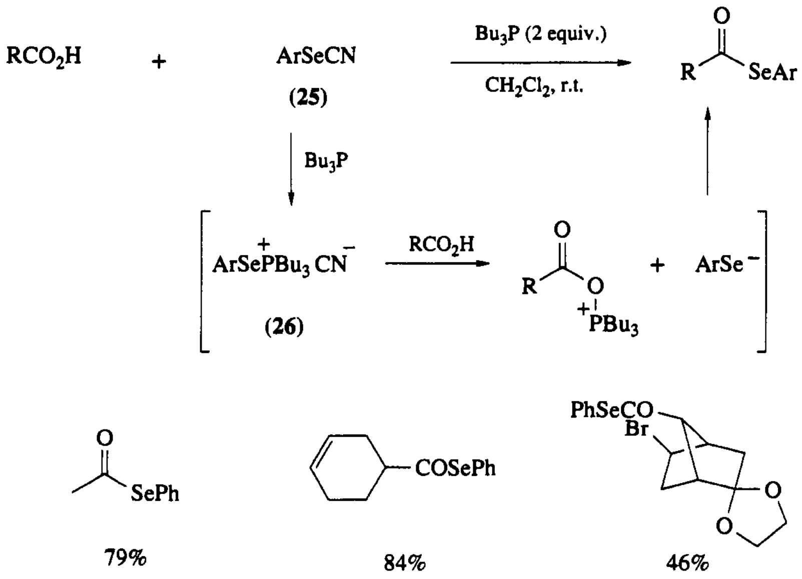
(**24b**) (12)

2.6.2.1.4 Reaction of carboxylic acids with selenocyanates or N-PSP in the presence of trialkylphosphine

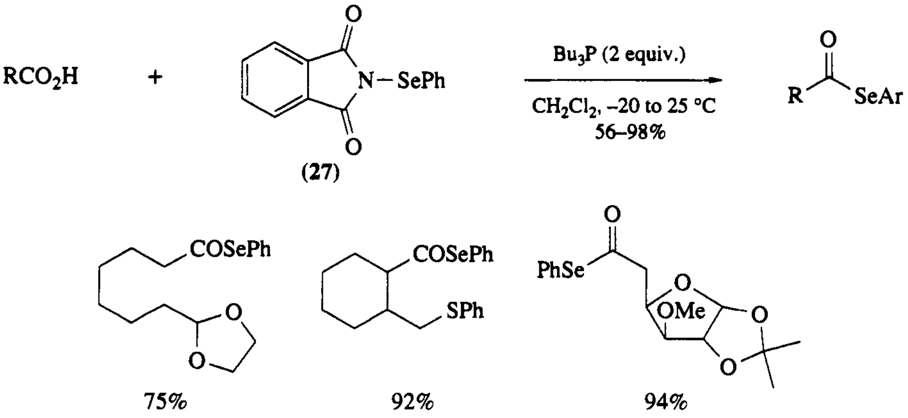
It has been reported that aryl selenocyanate (**25**; Scheme 7) reacts with carboxylic acids in the presence of tributylphosphine under mild conditions, giving rise to selenol esters in good yields.[43] The process may involve the reaction of carboxylic acids with selenophosphonium salt (**26**), which is the key intermediate.

Since phenyl selenocyanate (**25**; Ar = Ph) is a sensitive liquid, which slowly decomposes on storage during a few days, an improved method using *N*-phenylselenophthalimide (*N*-PSP; **27**), a stable crystalline compound, has been developed.[44,45] In general, the yields of selenol esters prepared from *N*-PSP/Bu_3P are higher than those obtained employing ArSeCN/Bu_3P.

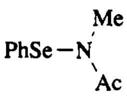
N-Acetylselenenamide (**28**) can also be used in place of (**25**) or (**27**).[46]



Scheme 7



Scheme 8



$PhSe{-}N(Me)(Ac)$

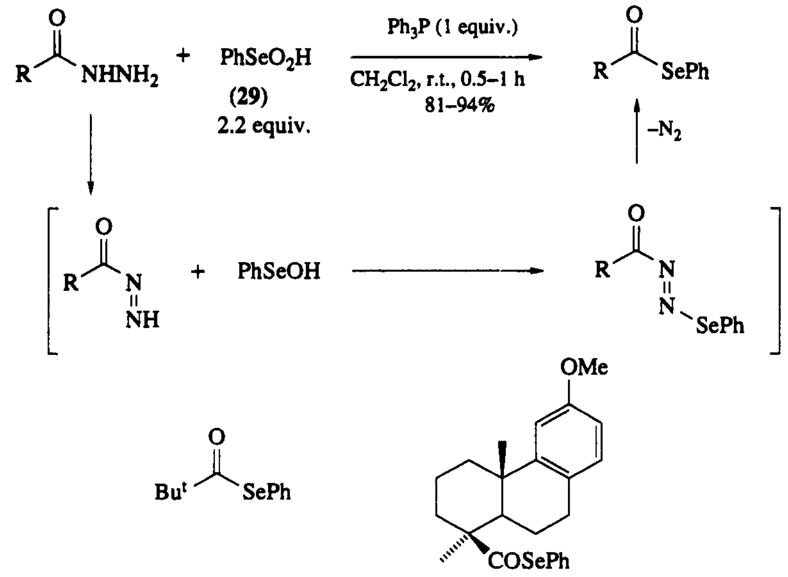
(28)

2.6.2.1.5 Miscellaneous

The reaction of *N*-acylhydrazines with benzeneseleninic acid (**29**; Scheme 9) in the presence of triphenylphosphine afforded high yields of diverse selenol esters.[47–49] Alkyl, cycloalkyl and aryl selenol esters were prepared, even in the case of the highly hindered compounds (**30**) and (**31**).

The removal of sulfur and selenium atoms from compounds (**32**) and (**33**) using triphenylphosphine easily furnished the corresponding selenol esters (equation 13).[50,51]

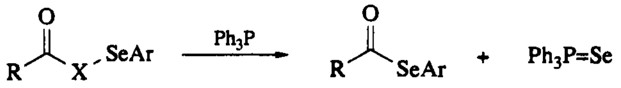
Diaryl diselenides reacted with carbon monoxide (5–100 atm) at 100–200 °C, in the presence of $Co_2(CO)_8$ as a catalyst, to give the corresponding selenol esters of aromatic carboxylic acids in 21–96% yields (equation 14).[52]



(30) 83%

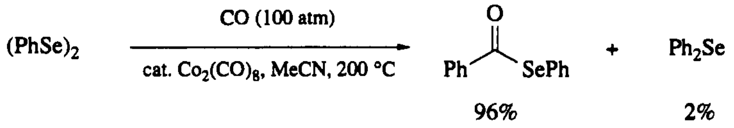
(31) 84%

Scheme 9



(32) X = S
(33) X = Se

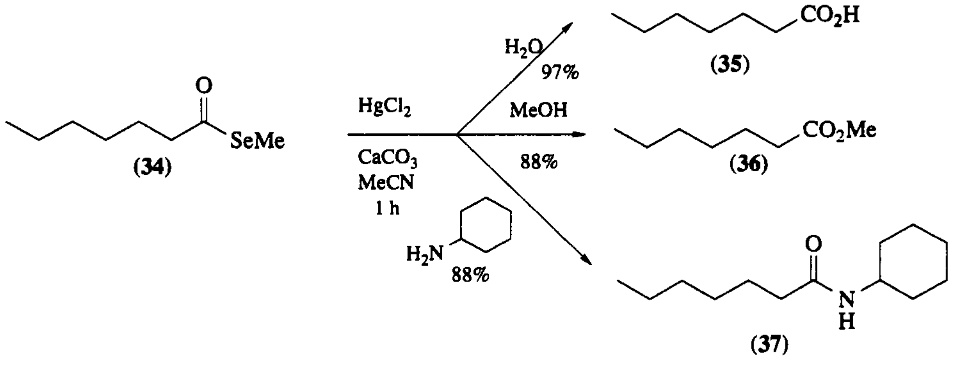
(13)



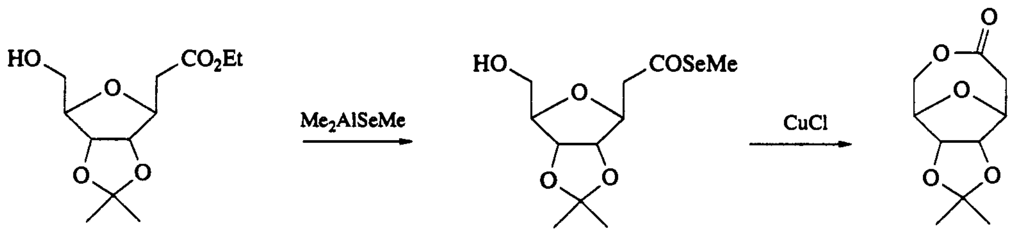
(14)

2.6.2.2 Reactions

Selenol esters are expected to be a more reactive species than the corresponding thiol esters or oxo esters due to the comparatively weak bonding between carbon and selenium. The ability of the selenol esters to serve as active acyl transfer agents has been readily demonstrated by the easy conversion of the selenol ester (**34**; equation 15) to its corresponding acid (**35**), ester (**36**) or amide (**37**).[38,53] This acyl-selenium bond cleavage has also been promoted by Cu^{I} and Cu^{II} salts.[38,39] The isopropylidene derivative (**38**; equation 16) of ribofuranosylacetate has been converted to a lactone (**40**) in good yield *via* the selenol ester (**39**).

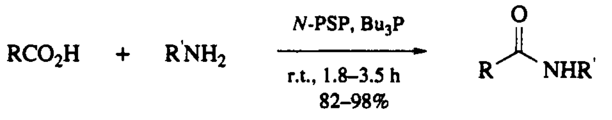


(15)



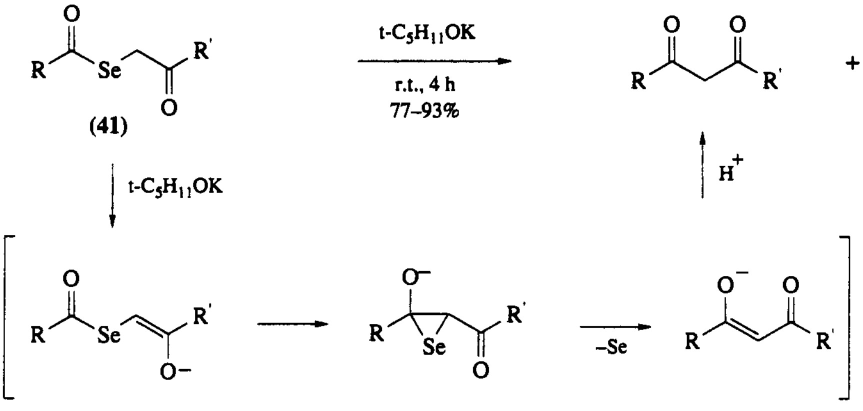
(38) **(39)** **(40)** (16)

Single-step conversion of carboxylic acids to amides has been achieved using the *N*-PSP/Bu_3P reaction system in the presence of amines (equation 17).[44,45]



$$RCO_2H + R'NH_2 \xrightarrow[\text{r.t., 1.8–3.5 h; 82–98\%}]{N\text{-PSP, }Bu_3P} RC(O)NHR' \qquad (17)$$

Some examples of carbon–carbon bond formation by the reaction of selenol esters with carbon nucleophiles have been reported. *Se*-Acylmethyl selenocarboxylates (**41**) readily extruded selenium by treatment with potassium *t*-pentoxide to form 1,3-diketones in good yields.[35] A proposed pathway is outlined in Scheme 10.

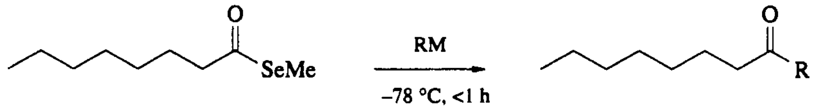


(41)

Scheme 10

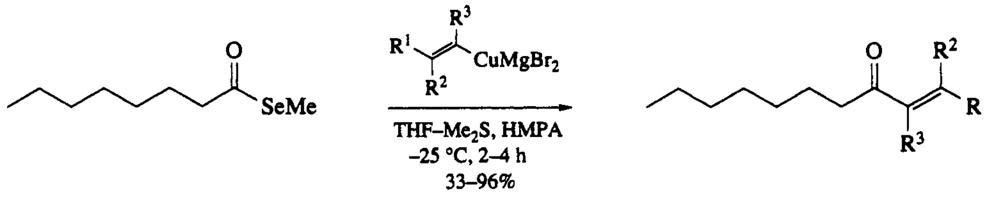
A mild and efficient transformation of esters into ketones *via* selenol esters has been developed. Selenol esters smoothly reacted with organocuprates to produce ketones in excellent yields (equation 18).[40] Reaction with a vinylcopper(I) reagent gave α,β-unsaturated ketones (equation 19).[54] Butylmanganese chloride also transformed selenol esters into ketones, although 3 equiv. of the reagent are required to complete the reaction. Me_2Cd and PhHgBr were not effective for this transformation.

The copper or copper(I) iodide-catalyzed insertion of diazomethane into the acyl–selenium linkage of selenol esters was reported to afford the corresponding ketones as the chief products.[55,56] A nonconcerted mechanism involving a tetrahedral intermediate (**42**; Scheme 11) has been suggested.

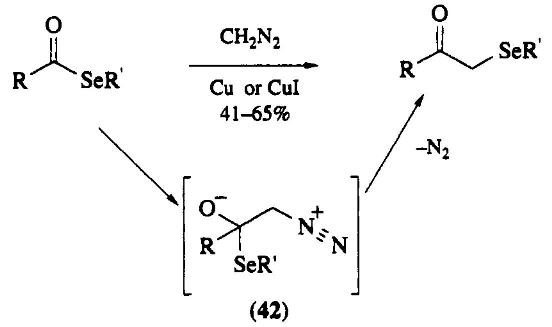


(18)

RM = Me_2CuLi; Bu_2CuLi; $Bu^tCuSPhLi$ R = Me, 98%; R = Bu, 96%; R = Bu^t, 98%

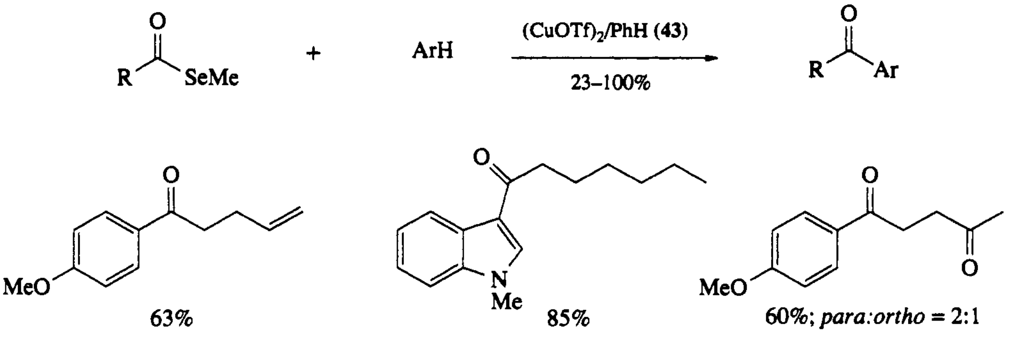


(19)

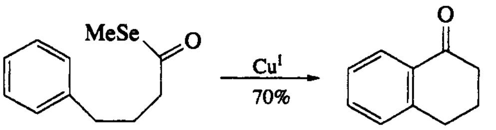


Scheme 11

Moreover, the selenol esters can acylate reactive arenes and heteroaromatic compounds when copper(I) triflate is employed as the selenophilic metal cation.[39,57] The acylation of aromatics by use of the benzene complex of copper(I) triflate (**43**; Scheme 12) was complete within an hour at room temperature, with benzene as solvent, and the acylation products were obtained in high yields. Intramolecular acylation was examined successfully, as shown in equation (20).



Scheme 12

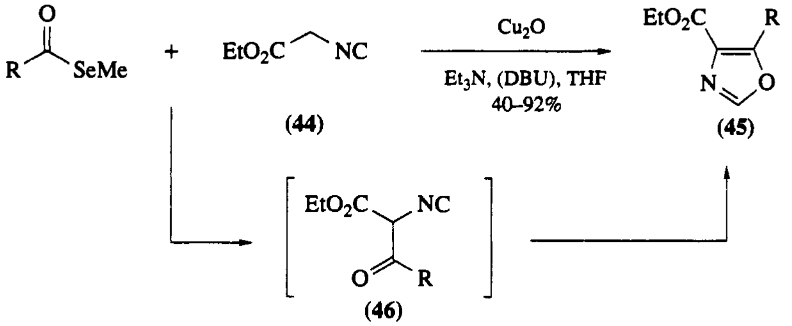


(20)

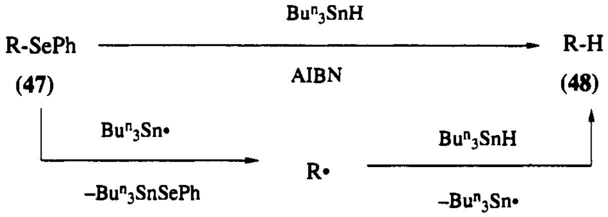
Selenol esters also reacted with isonitrile (**44**; Scheme 13) at room temperature for 6–20 h in the presence of 1.5 equiv. of copper(I) oxide and triethylamine (or DBU) to give oxazole (**45**).[39,57] The reaction presumably proceeds through an intermediate β-ketoisonitrile (**46**), and copper(I) oxide functions as a reagent for complexation to the selenium moiety.

Recently it has become apparent that phenyl selenides (**47**; Scheme 14) are efficiently reduced to alkanes (**48**) with tin hydride by a free radical process.[58]

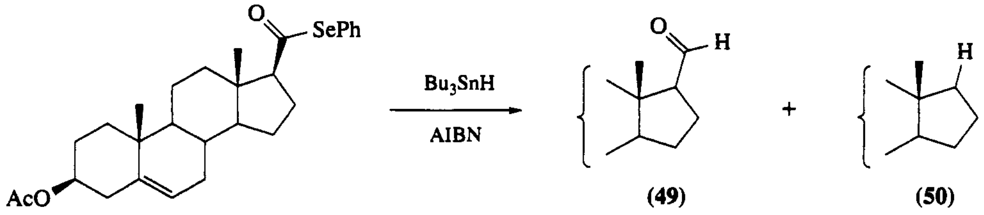
The reaction of selenol esters with tributyltin hydride resulted in the formation of the corresponding aldehydes (**49**) and alkanes (**50**).[59,60] The formation ratio of aldehydes to alkanes depends on the reaction temperature, as exemplified in Scheme 15. When the reaction was carried out with UV irradiation at ambient temperature, the aldehyde was formed predominantly, in high yields.



Scheme 13



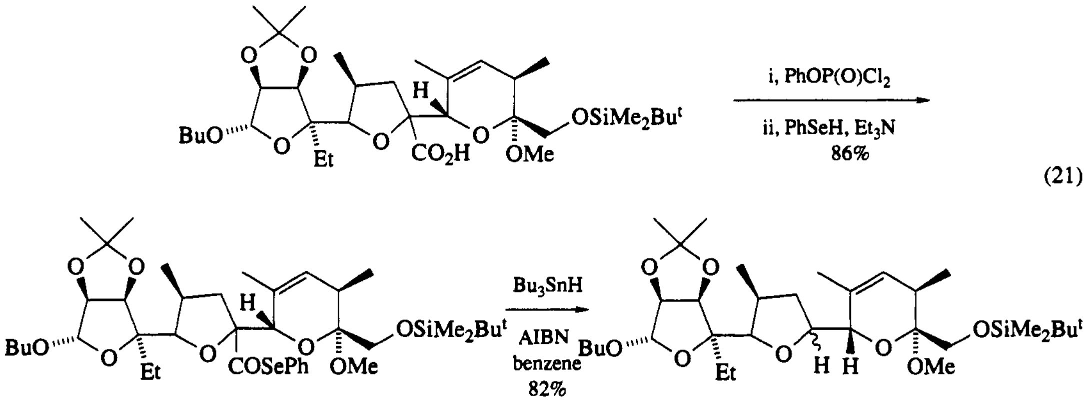
Scheme 14



	(49)	(50)
benzene, 80 °C	82%	17%
mesitylene, 164 °C	18%	80%

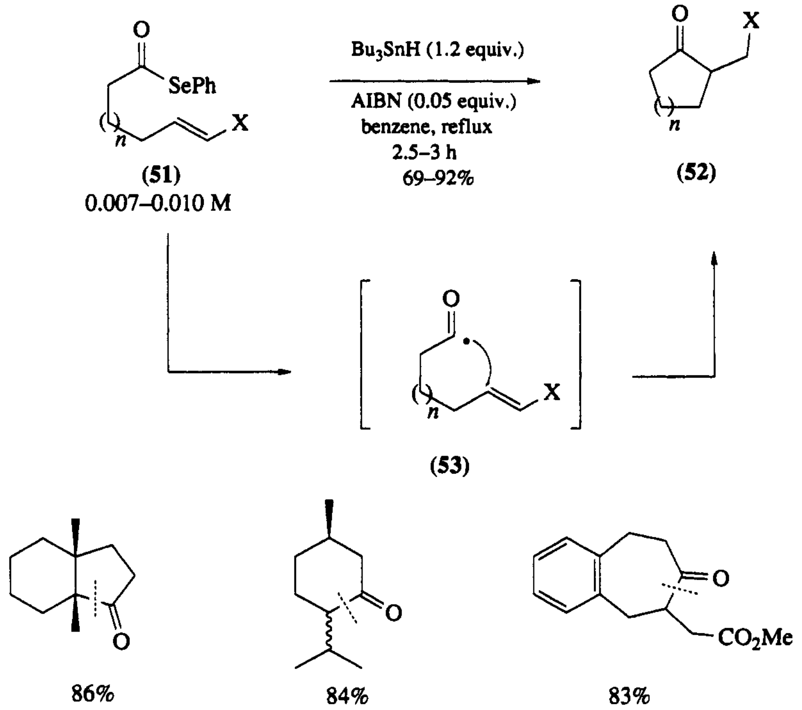
Scheme 15

A new method for the transformation of —CO_2H to —H has been attained by formation of the selenol ester from carboxylic acid, followed by its reduction.[59–64] Owing to high chemoselectivity and mild reaction conditions, this method is often utilized for the synthesis of natural products (equation 21).[30]



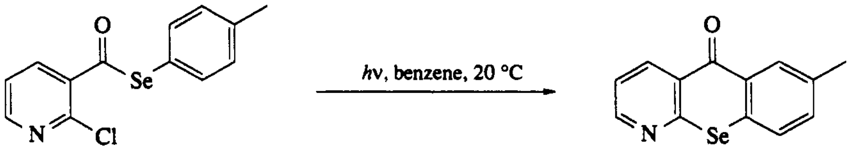
(21)

Intramolecular capture of the acyl radical formed *in situ* from a selenol ester and tin hydride has been examined successfully.[65] Phenyl selenol esters (**51**), with an unsaturated functional group (C═C *etc.*) at the appropriate position of the molecule, reacted with 1.2 equiv. of tin hydride in the presence of 0.05 equiv. of AIBN in benzene under reflux to yield ketones (**52**) through radical cyclization of the acyl radical (**53**; Scheme 16).[65,66]



Scheme 16

It was reported that UV irradiation of *o*-substituted aromatic selenol esters (**54**) led to the 5*H*-[1]benzoselenino[2,3-*b*]pyridine (**55**) ring system *via* a selenol ester–seleninone transformation.[67,68]

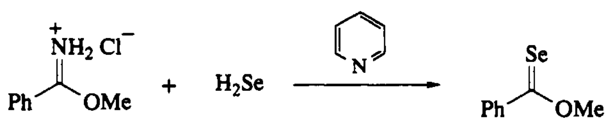


(**54**) (**55**) (22)

2.6.3 SELENOESTERS

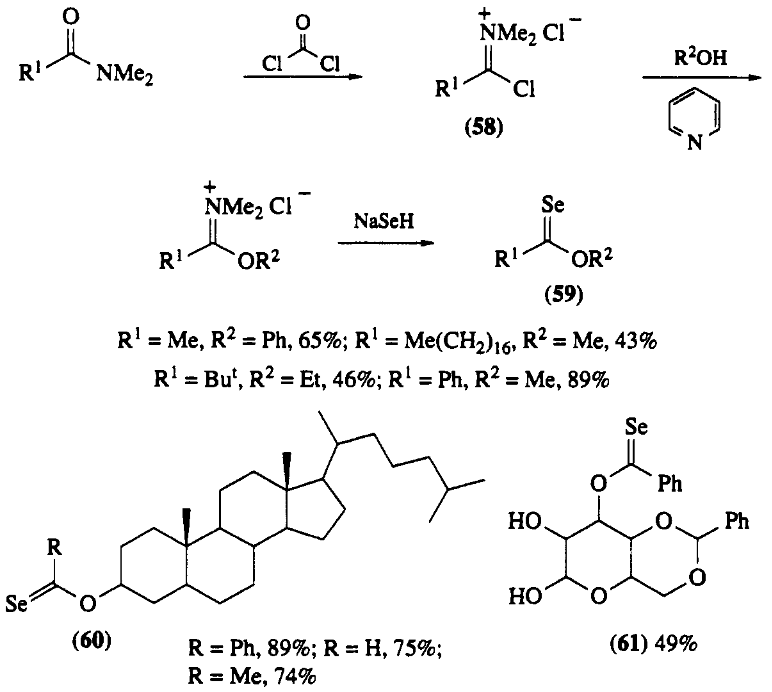
2.6.3.1 Preparation

In an earlier investigation, aryl selenoesters have been prepared by the reaction of hydrogen selenide with imido esters (**56**; equation 24), but the yields were very low (**56**; R = Ph, 5.6%; **56**; R = *p*-tol 3%).[69,70] The yield was somewhat improved by employing methyl benzimidate hydrochloride (**57**; equation 23) as the starting material.[71]



(**57**) 36% (23)

A practically useful method for synthesis of selenoesters has been developed by Barton *et al.* A wide range of aliphatic and aromatic selenoesters have been synthesized from the appropriate *N,N*-disubstituted imidoyl chlorides (**58**) using sodium hydrogen selenide to introduce selenium.[72,73] Imidoyl chlorides (**58**) can be obtained by the reaction of amides with phosgene. Representative results are shown in Scheme 17 (formulae **59**–**61**).

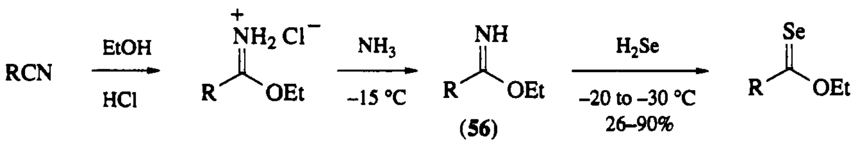


R^1 = Me, R^2 = Ph, 65%; R^1 = $Me(CH_2)_{16}$, R^2 = Me, 43%
R^1 = Bu^t, R^2 = Et, 46%; R^1 = Ph, R^2 = Me, 89%

R = Ph, 89%; R = H, 75%;
R = Me, 74%

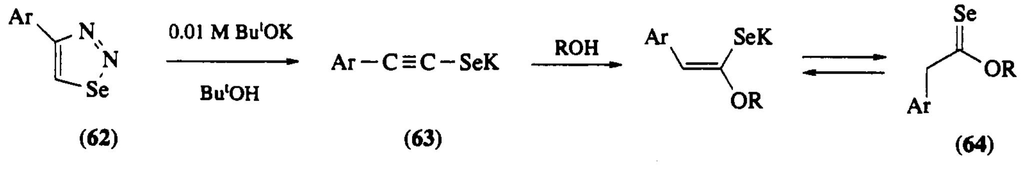
Scheme 17

Cohen investigated in detail the addition of hydrogen selenide to imido esters (**56**), and found that selenoesters can be prepared by the reaction at −20 to −30 °C in the presence of pyridine–triethylamine.[74]



(24)

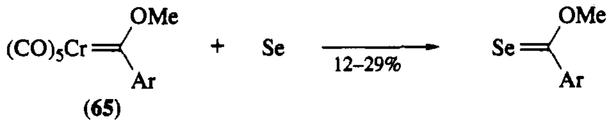
α-Substituted selenoesters (**64**) have been synthesized by the reaction of alcohols with arylethynylselenolate salts (**63**), prepared from 4-aryl-1,2,3-selenadiazoles (**62**).[75]



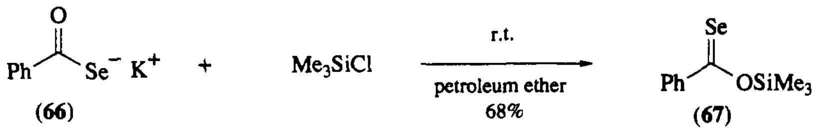
Scheme 18

The transition metal complex pentacarbonyl(methoxyarylcarbene)chromium(0) (**65**), gave selenoesters on treatment with elemental selenium.[76]

Although alkylation of potassium selenobenzoate with alkyl halides led to the formation of selenol esters *via Se*-alkylation, as described in Section 2.6.2.1.1 (equation 9), the reaction of (**66**; equation 26) with trimethylsilyl chloride proceeded through *O*-silylation to give trimethylsilyl selenobenzoate (**67**) in 68% yield.[77] The driving force of the reaction may be due to the strong affinity of silicon for oxygen.



(25)

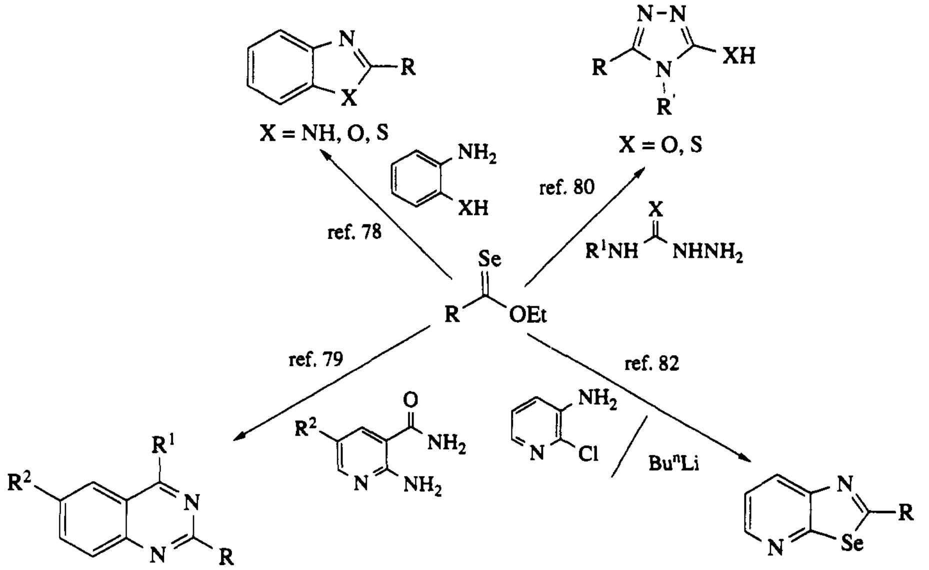


(26)

The aliphatic selenoesters are generally yellow liquids, while the aromatic esters are deep red oils, the latter being more stable. However, after 2–3 days, these begin to decompose slowly, accompanied by the deposition of elemental selenium, although they can be stored in a refrigerator for a few months without any such precipitation.[74]

2.6.3.2 Reactions

Owing to the high polarizability of the carbon–selenium double bond, selenoesters can easily be attacked by nucleophiles. This property makes a selenoester a useful reagent for the synthesis of heterocycles.[78–83] Condensation of selenoesters with bifunctional aromatic or aliphatic amines has yielded a variety of nitrogen-containing heterocyclic compounds (Scheme 19).

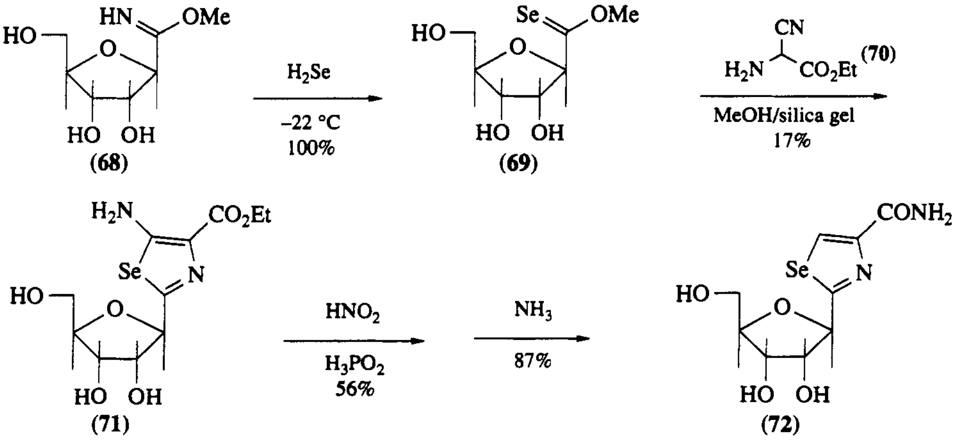


Scheme 19

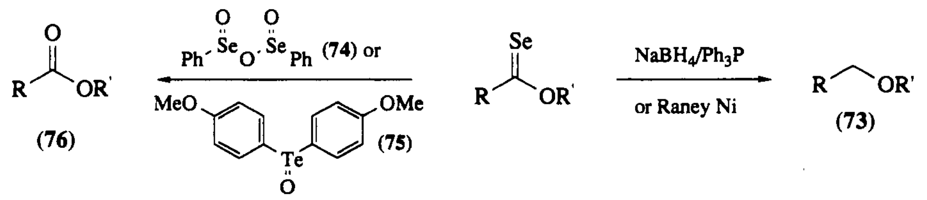
Selenazofurin (**72**), a promising antitumor agent, has been synthesized from methyl 2,5-anhydroallonimidate (**68**), as illustrated in Scheme 20. The key step of the synthesis is the formation of the selenazole (**71**) by the condensation of the selenoester (**69**) with ethyl 2-amino-2-cyanoacetate (**70**).[83]

In order to clarify the fundamental chemical reactivity of selenoesters, Barton *et al.* investigated their reaction behavior towards a number of common reagents.[72] The reduction of selenoesters was examined using sodium borohydride–triphenylphosphine or Raney nickel (W-2). In both cases, the corresponding ether (**73**) was obtained in high yield. On the other hand, selenoesters were converted into their parent oxocarbonyl derivatives (**76**) in high yield on treatment with oxidizing agents such as benzeneseleninic anhydride (**74**)[84,85] and bis(*p*-methoxyphenyl) telluroxide (**75**; Scheme 21).[86]

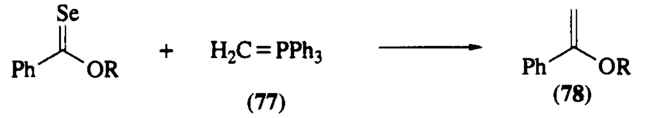
The reaction of a selenoester with the methylene Wittig reagent (**77**) readily produces the vinyl ether (**78**; equation 27).[72]



Scheme 20



Scheme 21



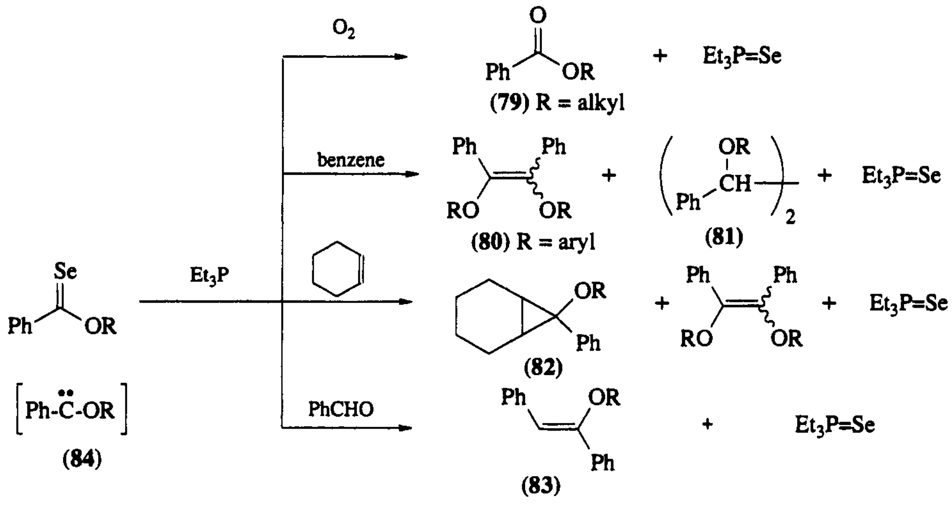
(27)

During these investigations, it was observed that the selenoester reacts with triphenylphosphine in the presence of atmospheric oxygen to give the parent ester.[72] Hansen investigated in detail the reactions between triethylphosphine and a number of aliphatic and aromatic selenoesters.[87] Under oxygen-free conditions, the reaction of aliphatic selenoesters with triethylphosphine gave a purple intermediate, which was quenched with atmospheric oxygen to give the corresponding esters (**79**). In the case of aromatic selenoesters, the same reaction under oxygen-free conditions led to deselenative coupling to afford α-dialkoxy-stilbenes (**80**) and -dibenzyls (**81**). When the reaction was carried out in cyclohexene, 7-alkoxy-7-phenylbicyclo[4.1.0]heptanes (**82**) were formed. These results suggest the formation of α-alkoxycarbene (**84**). The presence of benzaldehyde in the reaction mixture led to α-alkoxystilbenes (**83**; Scheme 22).

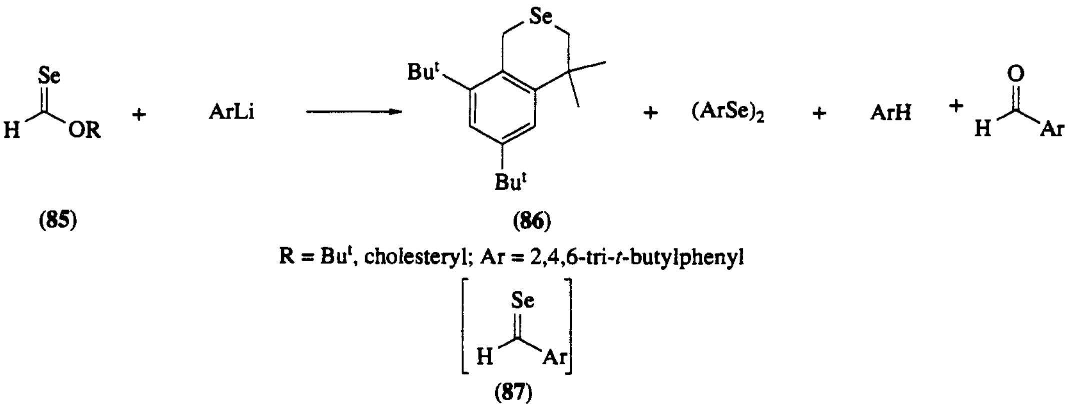
Recently, the synthesis of selenoaldehyde was examined by the reaction of *O*-alkyl selenoformates (**85**) with aryllithium.[88–90] 2,4,6-Tri-*t*-butylphenyllithium reacted with selenoformates (**85**) at three different sites, *i.e.* the selenoformyl carbon, the selenoformyl hydrogen and the selenium, to give several reaction products including 6,8-di-*t*-butyl-3,4-dihydro-4,4-dimethyl-1*H*-2-benzoselenin (**86**). The formation of (**86**) is explained in terms of the intermediacy of 2,4,6-tri-*t*-butylselenobenzaldehyde (**87**; Scheme 23).

Selenoesters have easily undergone exchange reactions with sulfur to give the corresponding thioesters (**88**), on heating with elemental sulfur (equation 28).[91,92]

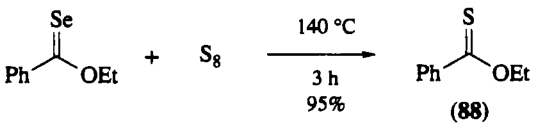
Some other reactions concerning selenoesters are shown in refs. 93 and 94.



Scheme 22



Scheme 23



(28)

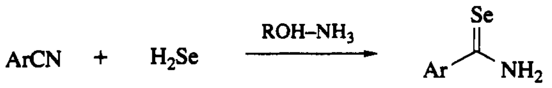
2.6.4 SELENOAMIDES

2.6.4.1 Preparation

2.6.4.1.1 *N-Unsubstituted selenoamides*

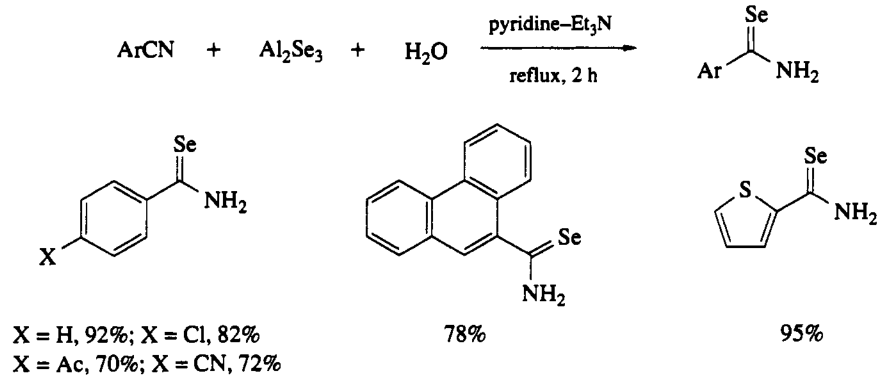
In general, *N*-unsubstituted selenoamides have been prepared by the addition of hydrogen selenide to the corresponding nitriles in the presence of base.

In an earlier investigation of the synthesis of aromatic selenoamides, gaseous hydrogen selenide was directly introduced into the reaction vessel. The first report[95] described the synthesis of benzeneselenoamide by the reaction of benzonitrile with hydrogen selenide in ethanolic ammonia (equation 29), while its 4-methyl derivative was synthesized under similar conditions.[96]

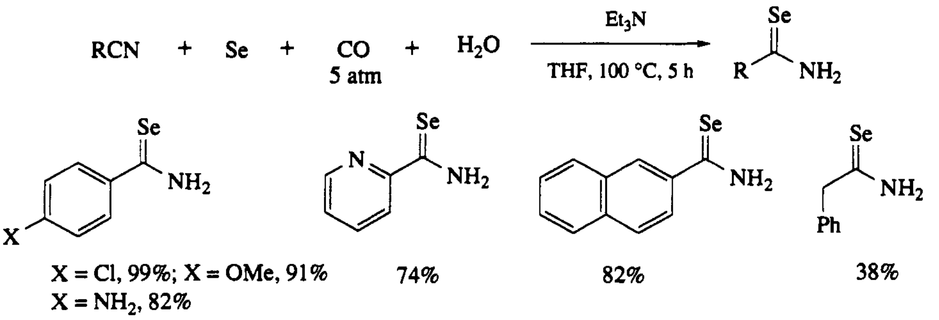


(29)

In order to avoid the handling of poisonous hydrogen selenide, two other useful syntheses have been devised. One method[97] uses the reaction of aromatic nitriles with aluminum selenide in the presence of pyridine, triethylamine and water (Scheme 24), while the other[98] is performed by the reaction of nitriles with selenium, carbon monoxide and water in the presence of triethylamine (Scheme 25). These methods are exceedingly convenient in terms of manipulation without the isolation of hydrogen selenide for the preparation of selenoamides. Using these methods, a variety of aromatic and heterocyclic selenoamides can be obtained from the corresponding nitriles in high yields.

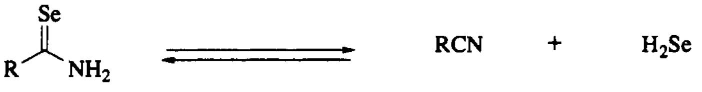


Scheme 24



Scheme 25

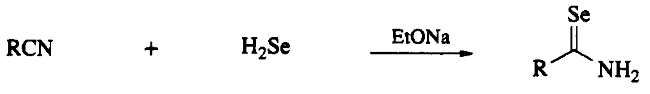
The aromatic selenoamides are generally yellow solids and are stable enough under nitrogen at ordinary temperature to be kept for several weeks in high purity. On exposure to air, they gradually decompose into the starting nitriles, elemental selenium and water, at room temperature or below. These observations suggest that the selenoamides are in equilibrium with the corresponding nitriles and hydrogen selenide (equation 30).[98]



(30)

In contrast to aromatic selenoamides, little is known about the isolation of *N*-unsubstituted aliphatic selenoamides, which lack the stabilizing conjugation between the aromatic ring and the selenocarbonyl group. Hitherto known procedures are Kindler's method,[99–101] using the reaction of nitriles with hydrogen selenide in the presence of sodium ethoxide (equation 31), and the method using nitriles and Se–CO–H_2O (Scheme 25).

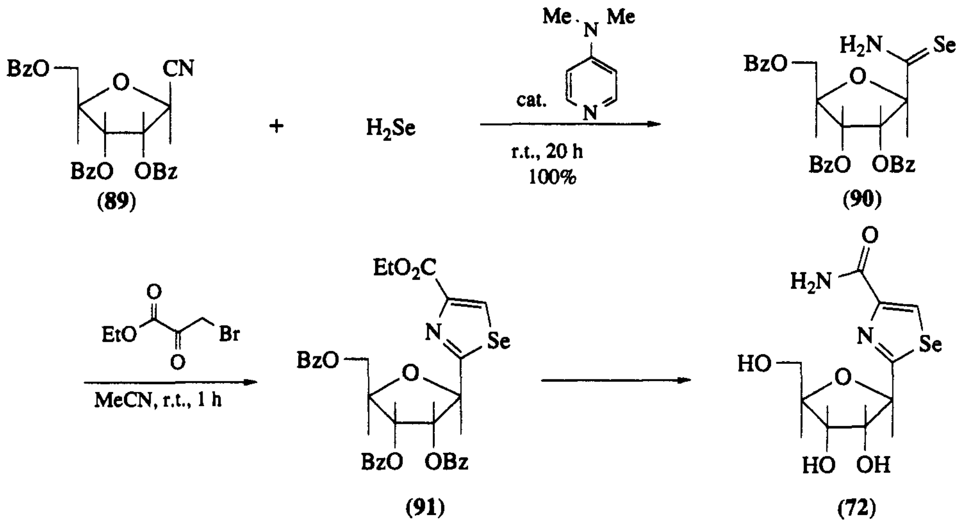
Treatment of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl-1-carbonitrile (**89**) with liquid hydrogen selenide, with 4-(dimethylamino)pyridine as the catalyst, provided 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonselenoamide (**90**). Compound (**90**) was treated with ethyl bromopyruvate to provide ethyl 2-(2,3,5-tri-*O*-ben-



$$\mathrm{RCN} + \mathrm{H_2Se} \xrightarrow{\mathrm{EtONa}} \mathrm{RC(=Se)NH_2} \qquad (31)$$

R = Me, 77%; R = $PhCH_2$, ~100%;
R = $H_2NC(=Se)CH_2$, 36%

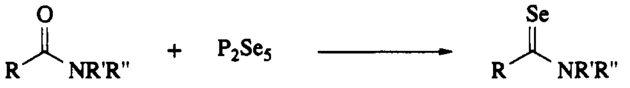
zoyl-D-ribofuranosyl)selenazole-4-carboxylate (**91**), followed by ammonolysis to give 2-β-D-ribofuranosylselenazole-4-carboxamide (**72**) as a promising antitumor agent.[102]



Scheme 26

2.6.4.1.2 N-*Substituted selenoamides*

N-substituted aliphatic selenoamides have been obtained on treatment of the corresponding amides with phosphorus pentaselenide in refluxing benzene,[101,103] but the yields were generally low (equation 32). Aromatic selenoamides can be obtained in moderate to high yields by the same method.[104] Improved yields of unhindered aliphatic selenoamides were obtained by heating the analogous amides with phosphorus pentaselenide in the presence of barium carbonate in boiling xylene.[105] Synthesis of selenolactams (*n* = 3–5, 7 and 11) was accomplished by heating a mixture of the lactam with red phosphorus and gray selenium in refluxing xylene for 24 h.[106]

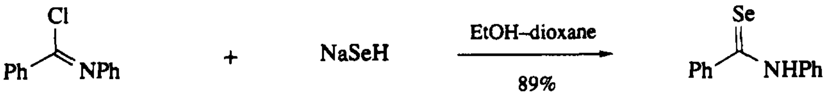


$$\mathrm{RC(=O)NR'R''} + \mathrm{P_2Se_5} \longrightarrow \mathrm{RC(=Se)NR'R''} \qquad (32)$$

R' = alkyl; R'' = alkyl or H

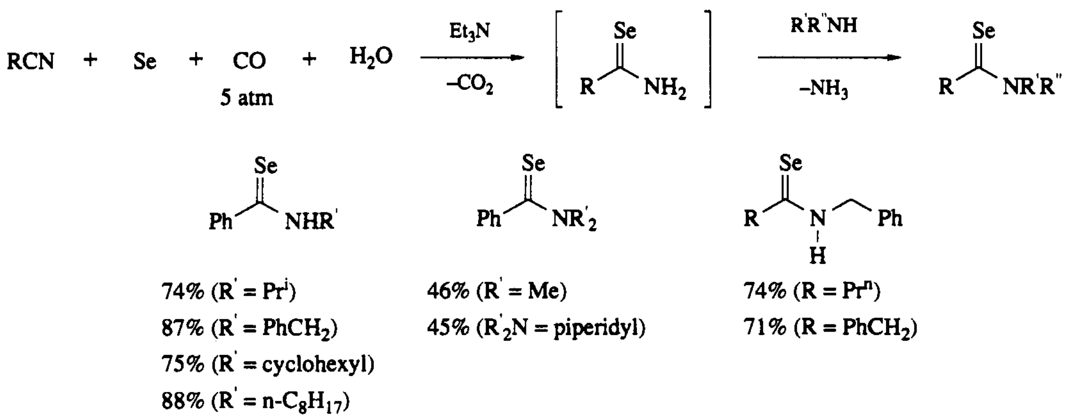
Ref.	*R*	*Condition*	*Additive*	*Yield*
101, 103	Alkyl	Benzene reflux	None	<23%
104	Aryl	Pyridine reflux	None	52–82%
105	Alkyl	Xylene reflux	$BaCO_3$	<61%

The reaction of an imidoyl chloride with sodium hydrogen selenide gave high yield of the selenoamide (equation 33).[107]



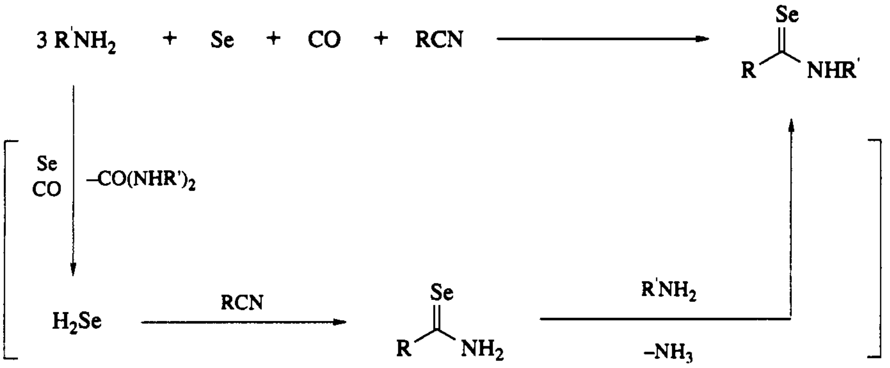
$$\mathrm{PhC(Cl)=NPh} + \mathrm{NaSeH} \xrightarrow[89\%]{\text{EtOH–dioxane}} \mathrm{PhC(=Se)NHPh} \qquad (33)$$

Convenient one-pot syntheses of *N*-substituted selenoamides from nitriles, metallic selenium, carbon monoxide, water and amines have been developed on the basis of an amino group exchange reaction between the *N*-unsubstituted selenoamides formed *in situ* and the primary or secondary amines.[108] Aromatic or aliphatic, and *N*-mono- or *N,N*-di-substituted selenoamides can be obtained in good yields by this method (Scheme 27).



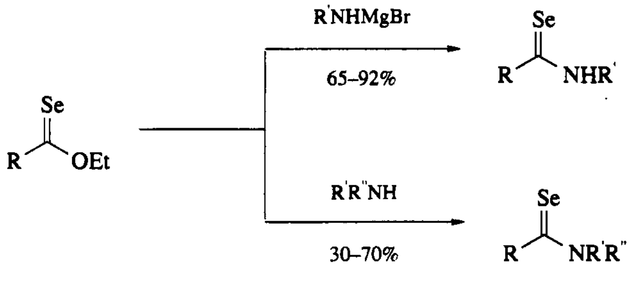
Scheme 27

In the cases of primary amines, the corresponding selenoamides have also been obtained from nitriles, selenium, carbon monoxide and excess primary amines by a single step mixing at the beginning of the reaction (Scheme 28).[108]



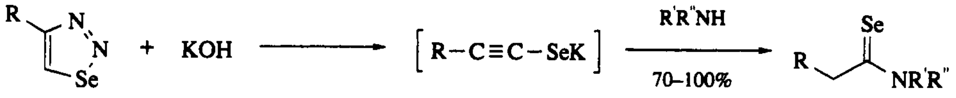
Scheme 28

A method for synthesis using the reaction of selenoesters with amines or their magnesium salts has been reported.[74] The reaction of aliphatic selenoesters with various primary alkylamide magnesium bromides in diethyl ether gave *N*-monosubstituted selenoamides, whereas direct addition of secondary amines to selenoesters afforded *N,N*-disubstituted selenoamides (Scheme 29).



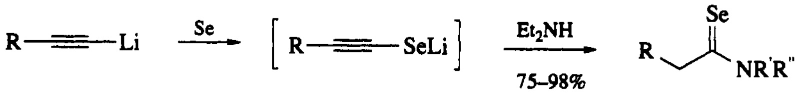
Scheme 29

Based on the observation that 1,2,3-selenadiazoles can be converted to selenoesters (Scheme 18), Yalpani *et al.* have found that reacting 5-unsubstituted 1,2,3-selenadiazoles with various amines gave, in most cases, quantitative yields of the selenoamides (equation 34).[109,110]



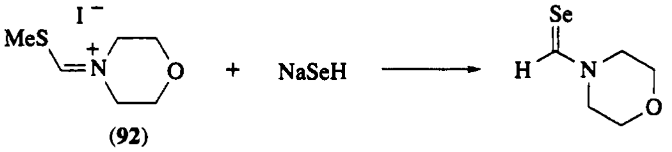
(34)

Selenoamides have been prepared in good yields by adding selenium powder to a solution of lithium acetylides in an excess of diethylamine (equation 35).[111]



(35)

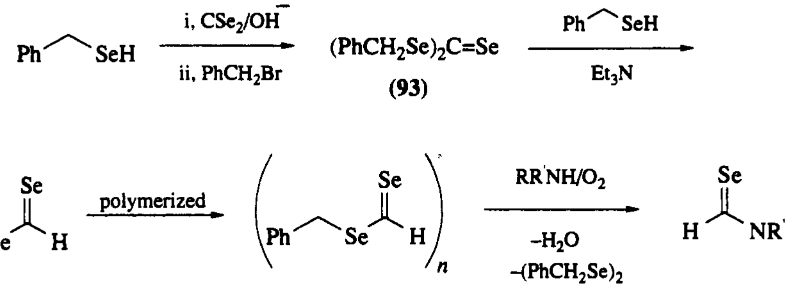
A few methods for the synthesis of selenoformamides have been reported. (Mercaptomethylene)imminium salt (**92**) reacted with NaSeH to give the corresponding selenoformamide (equation 36).[112]



(**92**)

(36)

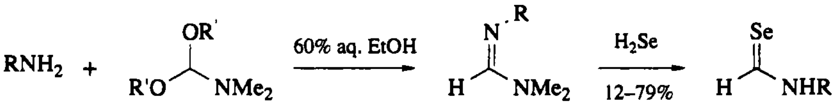
An alternative synthetic route to selenoformamides has been developed by the reaction of carbon diselenide with phenylmethaneselenol to produce triselenocarbonate (**93**), which reacts with primary or secondary amines to give the selenoformamide (Scheme 30).[113]



(**93**)

Scheme 30

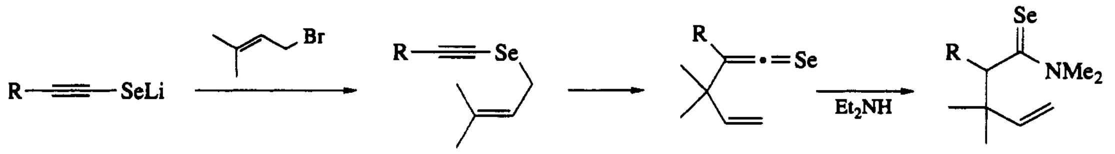
The *N*,*N*-dimethylaminomethylenamino compounds (**95**), obtained from amines and dimethylformamide diacetal (**94**), react smoothly with hydrogen selenide to give the desired selenoformamides (equation 37).[114]



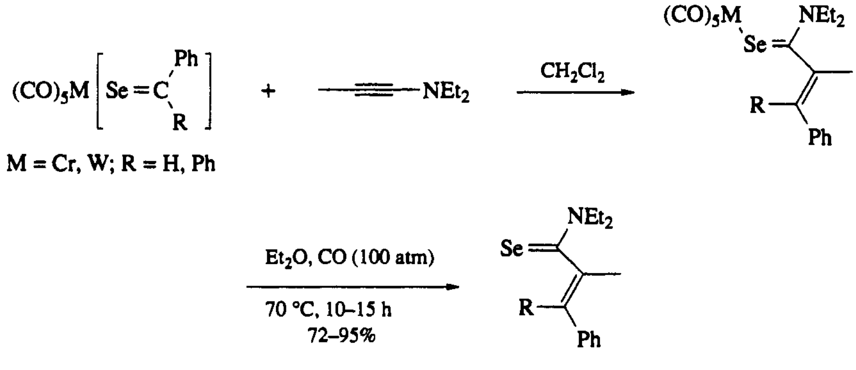
(**94**) (**95**)

(37)

Some other methods for the synthesis of selenoamides are shown in Schemes 31[115] and 32.[116]



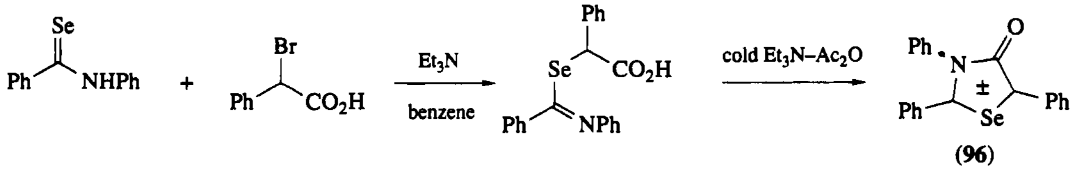
Scheme 31



Scheme 32

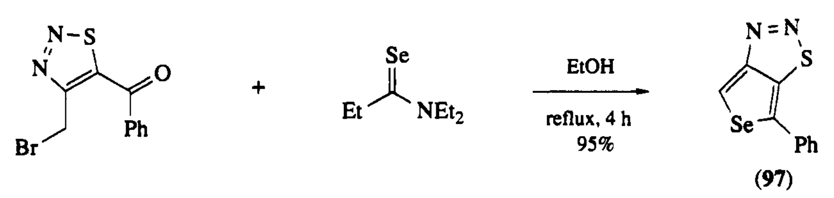
2.6.4.2 Reactions

As with selenoesters, selenoamides are excellent reagents for the synthesis of selenium-containing heterocycles.[117–122] Anhydro-2,3,5-triphenyl-4-hydroxyselenazolium hydroxide (**96**), as the first mesoionic selenium heterocycle,[107] selenophene derivatives (**97**)[118–121] and 1,3-selenazoles (**98**)[122] have been synthesized as shown in Scheme 33 and equations (38) and (39).



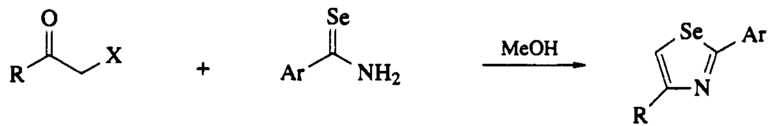
(96)

Scheme 33



(97)

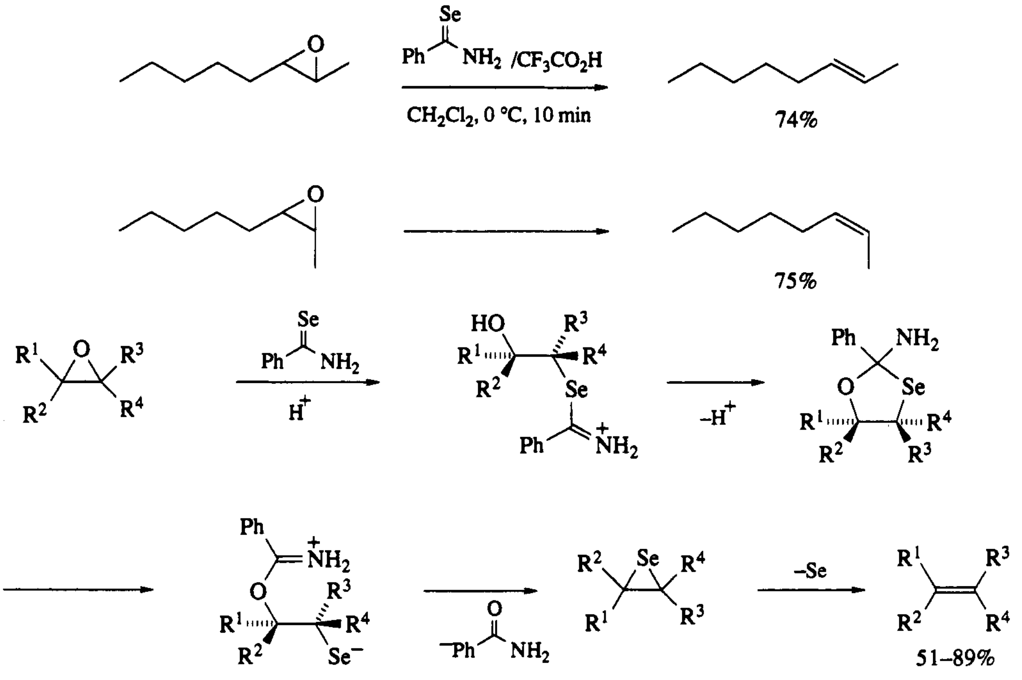
(38)



(98)

(39)

It has recently been reported that selenoamide is a useful reagent for the stereospecific deoxygenation of epoxides under mild conditions.[123] This deoxygenation can be applied to various epoxides, *i.e.* mono-, di- and tri-substituted epoxides and cyclic epoxides. A suggested reaction path is illustrated in Scheme 34.



Scheme 34

Some other reactions are shown in refs. 91, 124 and 125.

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2.7

Synthesis of Iminium Salts, Orthoesters and Related Compounds

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2.7.1 INTRODUCTION AND SCOPE

This chapter deals with 'activated amides', *i.e.* salt-like compounds, imino derivatives of carboxylic acids as well as compounds which formally arise by complete esterification or amidation of carboxylic orthoacids.

Well known compounds of this type are Vilsmeier–Haack adducts, imino esters, amidines, carboxylic orthoesters, orthoamides *etc*., which have proven their synthetic utility in thousands of reactions. As a consequence of the synthetic importance of these compounds, more or less extensive reviews are available for all of them.

There exists a series of compounds which can also be regarded as activated amides, *e.g.* α-haloenamines, ketene *O,N*-acetals, ketene aminals or ynamines, which are not dealt with in this chapter. To show the scope of the contribution, the formulae of all the types of compounds which are treated in the text, together with references of the relevant reviews are listed in Table 1.

2.7.2 SALT-LIKE COMPOUNDS (IMINIUM SALTS)

2.7.2.1 Adducts from Amides (Thioamides) and Acylating Reagents

2.7.2.1.1 Phosphorus oxychloride and phosphorsulfur trichloride

In preparative organic chemistry adducts from *N*-formylamines, *e.g. N*-methylformanilide and *N,N*-dimethylformamide, and $POCl_3$, which are used to formylate activated aromatic compounds and alkenes, are very important.[4] For these purposes it is not necessary to isolate the amide/$POCl_3$ adducts; usually they are prepared *in situ*. As a consequence of this only a few acid amide/$POCl_3$ adducts have been prepared in the pure state; examples are the adducts of $POCl_3$ with *N*-methylformanilide and *N,N*-dimethylformamide.[5] Elemental analysis revealed that adduct formation takes place in a 1:1 ratio. There has been much confusion on the constitution of these compounds.[1–5,7] There is no doubt that in solution adduct formation proceeds *via* attack at the carbonyl oxygen of the amide. This primary product (**1**) reacts further to give a salt (**2**) consisting of a chloromethyleneiminium ion with dichlorophosphate as the counterion (equation 1).

In formylation reactions both types of iminium compounds may act as electrophilic reagents. It has been demonstrated that the DMF–$POCl_3$ adduct is more reactive in formylation reactions than *N,N*-dimethylchloromethyleniminium chloride, which has the same cation. This indicates that the more reactive primary adduct from DMF and $POCl_3$ is the formylation species. But this conclusion is not fully convincing, because ion pair formation may take place in different amounts, meaning that in iminium chlorides there are more ion pairs than in the corresponding dichlorophosphates. Many reactions are known in which $POCl_3$ is used as a condensating agent, which indicates that there are adducts formed which act as reactive intermediates. From such experiments one may conclude that nearly all types of amides form adducts with $POCl_3$. Some examples of amides used in such reactions are: formamide, *N*-monosubstituted formamides,[5] *N,N*-disubstituted formamides,[4,5,7]. *N*-monosubstituted acetamides,[39,40] *N,N*-disubstituted acetamides,[41–44] mono- and di-substituted propionamides,[39,45] chloroacetamides,[39,46] phenylacetamides,[45] monosubstituted[40] and disubstituted[41] isobutyramides, malono ester amides,[47–54] cyanoacetamides,[45,55,56] *N*-monosubstituted[40,46,57] and disubstituted[41,46,58–60] benzamides, secondary aromatic[61] and higher aliphatic amides[61] as well as secondary[46] and tertiary[46,60] heterocyclic carboxamides, acylhydrazides[62–66] and lactams.[4,5,67–76]

Table 1

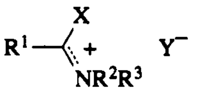
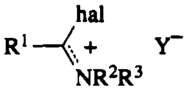
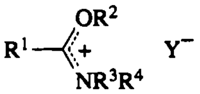
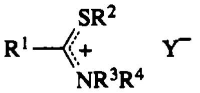
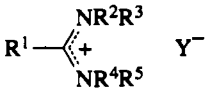
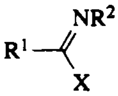
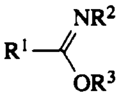
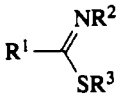
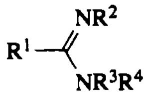
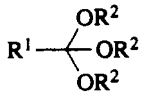
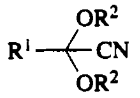
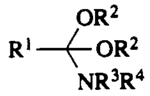
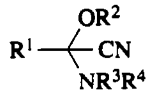
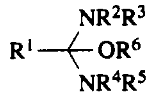
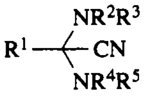
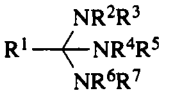
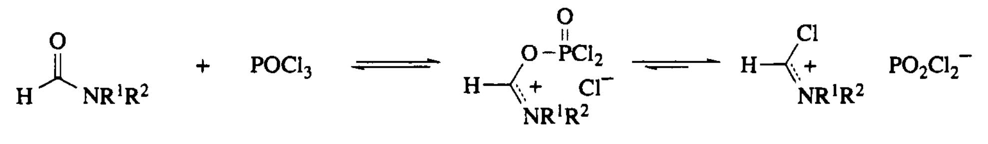
Formula		*Type of compound*	*Ref.*
 $[\mathrm{R^1C(X)NR^2R^3}]^+\ \mathrm{Y^-}$	(X ≠ halogen)	Adducts from amides and acylating reagents	1–7
 $[\mathrm{R^1C(hal)NR^2R^3}]^+\ \mathrm{Y^-}$		Halomethyleneiminium salts	1–9
 $[\mathrm{R^1C(OR^2)NR^3R^4}]^+\ \mathrm{Y^-}$		Alkoxymethyleneiminium salts	6, 7, 10
 $[\mathrm{R^1C(SR^2)NR^3R^4}]^+\ \mathrm{Y^-}$		Alkylmercaptomethyleneiminium salts	7, 11–13
 $[\mathrm{R^1C(NR^2R^3)NR^4R^5}]^+\ \mathrm{Y^-}$		Amidinium salts	7, 14
 $\mathrm{R^1C(X){=}NR^2}$	X = halogen	Imidoyl halides	1–3, 7
 $\mathrm{R^1C(OR^3){=}NR^2}$		Imidic acid esters (imidates, imino esters)	7, 15, 16
		Lactimidic acid esters	17
		Cyclic imidates	12, 19
 $\mathrm{R^1C(SR^3){=}NR^2}$		Imidic acid thioesters (thioimidates, imino thioesters)	7, 12
 $\mathrm{R^1C(NR^3R^4){=}NR^2}$		Amidines	7, 20, 21
 $\mathrm{R^1C(OR^2)_3}$		Carboxylic orthoacid esters	7
 $\mathrm{R^1C(OR^2)_2CN}$		2,2-Bis(alkoxy)carbonitriles	28, 29
 $\mathrm{R^1C(OR^2)_2NR^3R^4}$		Amide acetals	6, 7, 24, 28, 30–35
		Lactam acetals	7, 24, 28, 34, 35
		Bicyclic amide acetals	24, 36
 $\mathrm{R^1C(OR^2)(CN)NR^3R^4}$		2-Alkoxy-2-dialkylaminocarbonitriles	7, 28, 29, 35
 $\mathrm{R^1C(NR^2R^3)(OR^6)NR^4R^5}$		Bis(dialkylamino)alkoxyalkanes (aminal esters)	6, 7, 24, 28, 32, 35

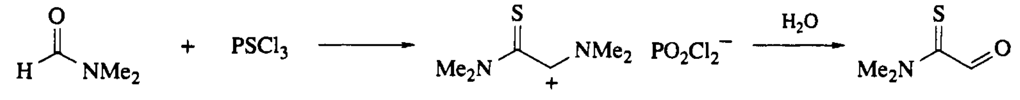
Table 1 *(continued)*

Formula	*Type of compound*	*Ref.*
 $R^1C(NR^2R^3)(NR^4R^5)CN$	2,2-Bis(dialkylamino)carbonitriles	7, 28, 29, 35
 $R^1C(NR^2R^3)(NR^4R^5)NR^6R^7$	Tris(dialkylamino)alkanes	6, 7, 24, 28, 32, 35



(1) (2) (1)

The adducts have been used for preparation of heterocyclic compounds,[4,5,37,46–48,52–54,56,59,63] in Beckmann rearrangement,[43] for cyclizations,[4,5,38,40,44,45,57,62,64,66,68] (a review covering cyclizations under Vilsmeier–Haack conditions is available[77]), for preparation of amidines,[5,7,39,41,42,55,76] in von Braun degradation,[61] in rearrangements,[68] in condensation reactions,[69] in substitution of aromatic compounds,[4,6,7,71,74] in reduction of amides,[72] in amide dimerization[73] and for preparation of isonitriles.[5] The adduct from DMF and $POBr_3$ was used for similar purposes.[4,5,7,78–81] The adduct formation either from thioamides and $POCl_3$ or amides and $PSCl_3$ has been studied.[82] The adduct of *N*,*N*-dimethylthioformamide with $POCl_3$ is said to be more reactive than the oxygen analog adduct.[4,5,7] It has been demonstrated that DMF undergoes selfcondensation with $PSCl_3$ to give *N*,*N*-dimethylglyoxylicthioamide (**3**) on hydrolysis (equation 2).[5]

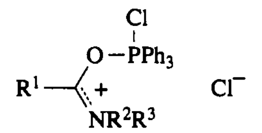


(2)

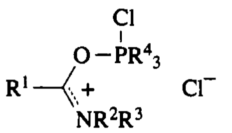
(**3**)

For preparative purposes it should be kept in mind that the use of these adducts, *e.g.* for C—C bond forming reactions,[1–4,6,83] can be restricted by several side reactions,[84] depending on the structure of the adducts. *N*,*N*-Unsubstituted adducts can decompose to nitriles by loss of HCl and $HOPOCl_2$ (this procedure was often used to prepare nitriles from amides[5,85–87]). *N*-Monosubstituted amides can split off HO-$POCl_2$ giving imidoyl chlorides (a reaction which is a standard procedure in heterocyclic chemistry, whenever a CONH unit is to be converted into a CCl=N unit); the imide chlorides thus formed on heating can lose alkyl chlorides—a process which is well known as von Braun degradation.[1–3,5,61] Adducts of *N*-monosubstituted formamides, especially in the presence of bases, furnish isonitriles by elimination of HCl and $HOPOCl_2$. This reaction is a very important method for the preparation of isonitriles.[1,5,88–97] Finally adducts derived from tertiary carboxamides, with CH_2—, or at least CH—, groups in the α-position to the amide function, can undergo selfcondensation, yielding products which can be regarded as adducts of $POCl_3$ with 2,3-disubstituted 3-chloroacrylic acid amides, which after hydrolysis afford β-keto acid amides.[1–5,7] In other cases heterocycles have been prepared by this type of condensation.[4,98]

Acid amide–triphenylphosphine dihalide adducts (**4**) have found wide application in organic synthesis.[5,7] Synthetic equivalents are adducts (**5**) from acid amides and triphenylphosphine/CCl_4, which are prepared *in situ* from the educts.[5,7] With these reagents the following transformations have been performed: dehydration of amides or aldoximes to nitriles, preparation of isonitriles from secondary formamides, preparation of imidoyl halides from amides or acylhydrazines and preparation of ketene imines from amides. Using polymer-supported triphenylphosphine the work-up procedure is much easier to achieve.[99] Triphenylphosphine can be replaced by tris(dialkylamino)phosphines.[5,7] Instead of CCl_4 hexachloroethane, hexabromoethane or 1,1,2,2-tetrabromo-1,2-dichloroethane can be used;[100] the adducts thus formed are assumed to be more effective than those from the triphenylphosphine/CCl_4 system.

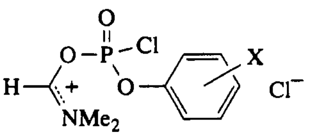


(4)

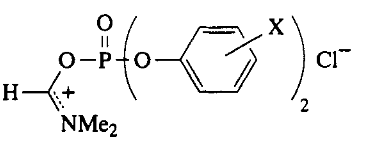


(5)

Adducts (**6**) and (**7**) from amides and chlorophosphoric acid aryl esters or dichlorophosphoric acid aryl esters respectively are well known.[5,7] The adducts are formed in a 1:1 ratio. They have been applied to the synthesis of mixed anhydrides from diarylphosphoric acids and carboxylic acids, as well as mixed substituted esters of pyrophosphoric acid. The adduct formation between primary or secondary carboxamides and dichlorophosphates has been used to prepare nitriles and isonitriles respectively.[5] The adduct from DMF and phenyldichlorophosphate is a useful reagent for the preparation of: carboxylic acid esters from the corresponding acids and alcohols,[101] β-lactams from imines and carboxylic acids,[102] carboxylic acid anhydrides,[103] carboxylic acid esters and thiol esters.[103] Adducts of amides with ester amides or diamides of chlorophosphoric acid have been studied.[103,104]

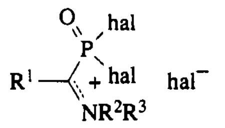


(6)



(7)

A still unresolved problem is the structure of the often used adducts from phosphorus trihalides and carboxylic acid amides, which might be described by the formulae (**8**) or (**9**). With the aid of *in situ* generated adducts of acid amides and PX_3 amidines,[5,7] isonitriles,[5] quinazolinones,[105] alkyl chlorides,[5] aminomethylenediphosphonic acids,[5,106] carbamoyl halides,[5] triformylaminomethane,[5,7] 1,3,4-oxadiazoles,[107] sulfides (from sulfoxides),[108,109] nitriles (from primary nitro compounds)[110] and bromoquinolines (from methoxyquinolines)[111] have been prepared.



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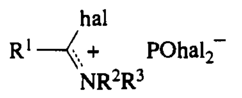

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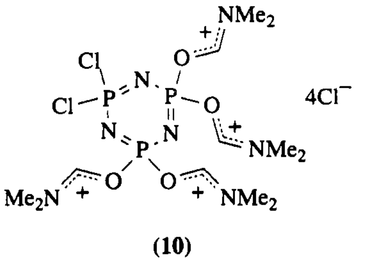


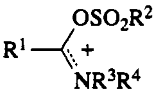
(10)

The adduct of DMF and dichlorophenylphosphine has been used to convert primary aromatic amides to nitriles by dehydration,[112] as well as to synthesize 2,5-diaryl-1,3,4-oxadiazoles from *N*,*N*′-diacylhydrazides.[113]

Phosphorus nitrile chloride forms adduct (**10**) with DMF in the ratio 1:4, which is useful for the preparation of formamidines and azavinylogous formamidinium salts.[5] It is supposed that the dehydration of primary amides to nitriles with $(PNCl_2)_3$ as well as the formation of 2-alkylbenzothiazoles from 2-(methylthio)anilides and $(PNCl_2)_3$ in the presence of triethylamine proceed *via* similar adducts.[114]

2.7.2.1.2 Adducts from acid amides and sulfur compounds

Sulfonyl halides (*e.g.* benzenesulfonyl chloride) form adducts (**11**) with acid amides in an equilibrium reaction.[5] From these adducts or *via* adducts of this type *O*-sulfonated lactim ethers, isonitriles, adenine, nitriles, amidines, amidinium salts and formic acid esters were prepared.[5] The adducts from DMF and chlorosulfonamides (**12**) can be used to prepare amidines or amidrazones.[5] *N*-Chlorosulfonylcarboxylic acid amides yield nitriles on treatment with DMF or other tertiary amides, presumably *via* an acid amide sulfonyl chloride complex (**13**; equation 3).[5]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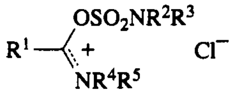
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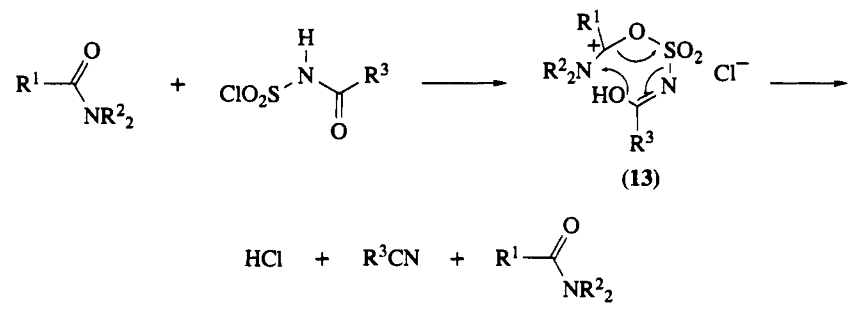
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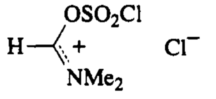
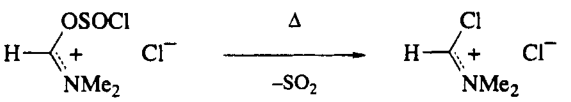
(3)

In contrast to these adducts the DMF–sulfuryl chloride adduct (**14**) has been prepared in a pure state.[5,7] It thermally decomposes to *N,N*-dimethylcarbamoyl chloride.[5] Secondary formamides form similar adducts, which on heating afford isocyanates.[5] Aromatic compounds such as anisole are not formylated by the DMF–SO_2Cl_2 adduct but chlorosulfonated.[5] This reaction was also performed with thiophenes; 2-thiophenecarbaldehydes are formed as byproducts.[115] The formation of triformaminomethane from formamide and SO_2Cl_2 has been reported.[5]


(14)

Thionyl chloride forms a fairly stable primary adduct (**15**) with DMF, which has been isolated.[5,7] On heating it decomposes to SO_2 and *N,N*-dimethylformamide chloride (equation 4).[5] Treatment of the adduct (**15**) with carboxylic acids affords iminium salts (**16**; equation 5) in which the carboxylic acid function is strongly activated, *e.g.* for amide formation.[116] With imines β-lactams are formed, sodium azide is converted to acyl azides.[117]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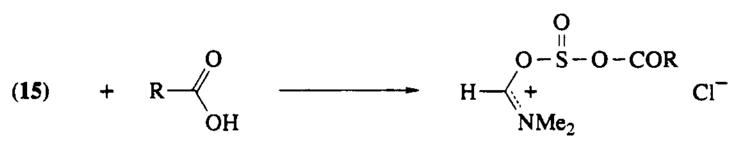
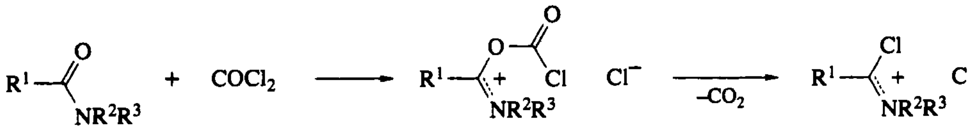

(16)

(5)

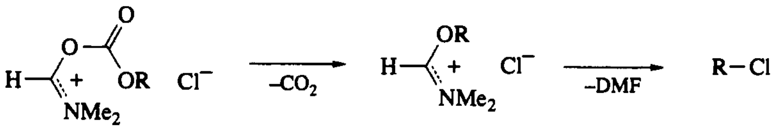
2.7.2.1.3 Adducts from amides and carbonic acid derivatives

Phosgene and tertiary carboxylic acid amides form very labile adducts (**17**; equation 6; not yet isolated or used for preparative purposes as such), which decompose with loss of CO_2 very rapidly to give amide chlorides (see Section 2.7.2.2.1.i). Decomposition with evolution of CO_2 is a common fate of primary adducts of carbonic acid chloride derivatives. Primary adducts from DMF and chloroformic acid esters (**18**), for example, decompose immediately to give alkoxymethyleneiminium chlorides, which react to give alkyl chlorides and DMF (equation 7).[5,118] Adducts (**19**) from secondary and tertiary carboxamides and *N,N*-dialkylcarbamoyl chlorides are formed at elevated temperatures (about 120 °C). However, under these conditions the adducts thus formed decompose to yield amidinium salts (equation 8).[5]



(17)

(6)



(18)

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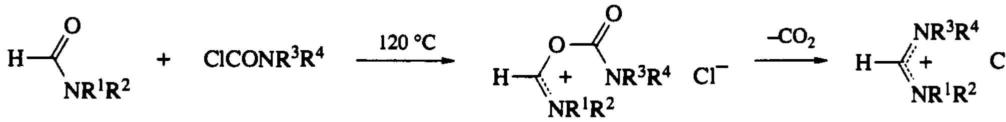
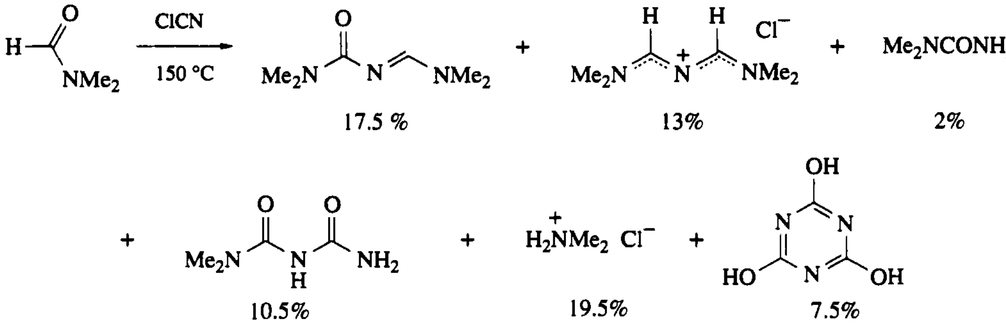


(19)

(8)

Adduct formation between cyanogen chloride and DMF was proposed to explain the complex product mixture, which was obtained by reaction of these educts at 150 °C (equation 9).[5] More important are adducts (**20**) from cyanuric acid chloride and tertiary formamides. These compounds are formed in a 1:2 ratio and they are isolable when DMF or *N*-formylpyrrolidine is used.[5,121] The adducts have been used to formylate ketones at the α-CH_2 groups,[122] sterically hindered phenols can be formylated at the oxygen,[123] amides are dehydrated to nitriles[124] and secondary formamides are transformed to isonitriles.[5] Using these adducts, amidines,[5] *N*-acylamidines,[123] alkyl halides[5] and amidinium salts[5] have been synthesized. In the preparation of these adducts an excess of amide must be avoided, because the 2:1 adducts (**20**) react with further tertiary formamide to give a labile, not isolable 1:3 adduct (**21**; equation 11), which, in the presence of excess amide, decomposes with great ease with evolution of CO_2 to give azavinylogous formamidinium salts.[5] The mechanism of this complex reaction has been established.[125]



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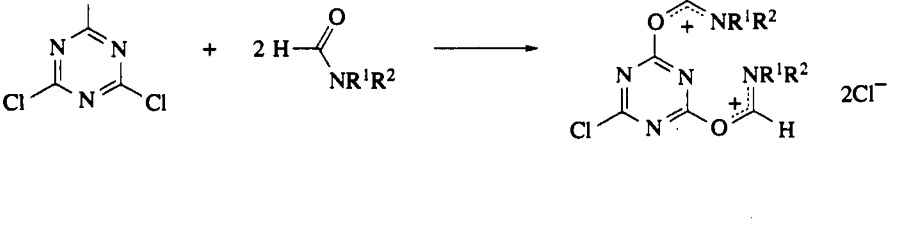

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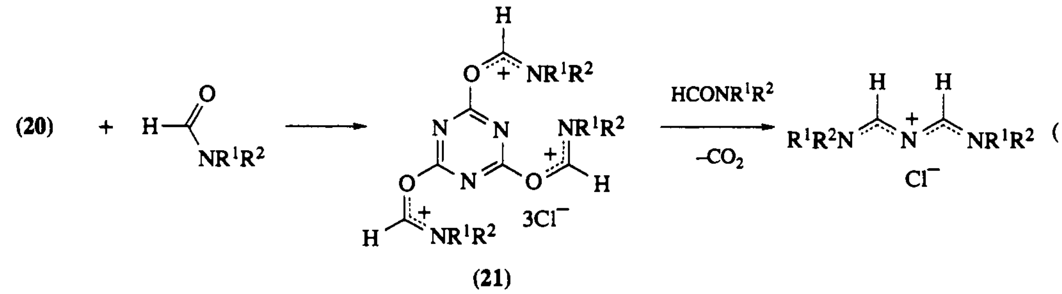
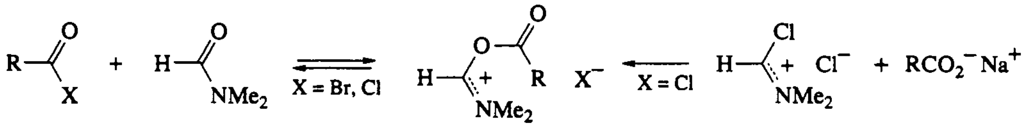


(21)

(11)

2.7.2.1.4 *Adducts from acid amides and carboxylic acid derivatives*

Conductivity measurements have revealed that DMF and carboxylic acid chlorides form salt-like adducts (**22**) in an equilibrium reaction (equation 12).[5,7] Such adducts can be prepared either from DMF and acid halides (chlorides and bromides)[5] or from chloromethyleneiminium salts and salts of carboxylic acids.[5,126] Acyloxyiminium salts (**23**) can be prepared in the pure state by reacting acid amides with carboxylic acid chlorides in the presence of silver trifluoromethanesulfonate (equation 13).[127] Salts of type (**24**; equation 14) are regarded as being intermediates in the synthesis of ketones from carboxylic acids and Grignard reagents in the presence of α-chloroenamines[128] as well as in the preparation of acyl halides (F, Cl, Br, I) by action of α-haloenamines on carboxylic acids.[129]



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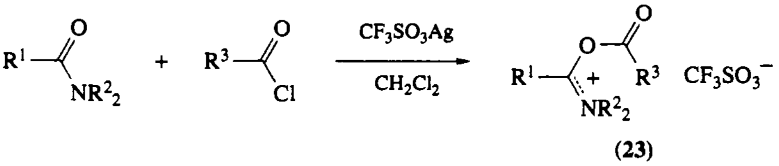

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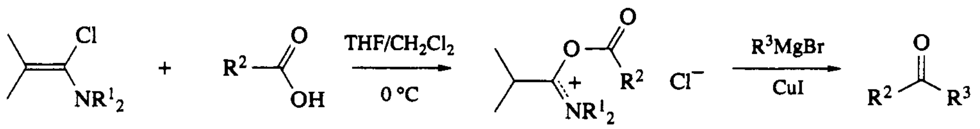


(24)

(14)

Acid amide–acid halide adducts have been used in synthetic organic chemistry to prepare various types of compounds (see Table 2).

Crystalline adducts from thioamides and aromatic acid chlorides are well known.[5] A very convenient synthesis of diacyl sulfides[139] and thiocarboxylic acids[139,140] proceeds *via* adducts of thio-DMF with acid chlorides.

From formylation reactions of CH-acidic compounds, which take place if mixtures of carboxylic acid amides and anhydrides are used as formylating agents, it was concluded that the latter compounds form similar adducts to those from amides and acid halides.[5]

Table 2 Preparative Applications of Acid Amide–Acid Chloride Adducts

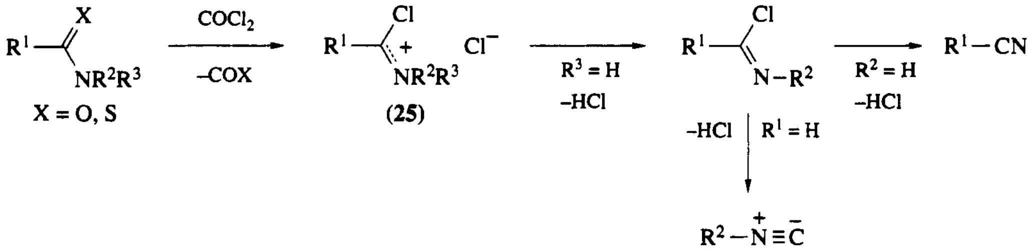
Starting amides	*Ref.*	*Products*	*Ref.*	*Products*	*Ref.*
Formamide	5, 130	Formimino ester hydrochlorides	5	Tris(1-methyl-3-indolyl)methane	132
Vinylogous formamides	5	Orthoesters	130	Vinylogous amidinium salts	5
		Amidines	5	Formylindoles	131, 134
DMF	5, 131–135	Amidinium salts	133	Formates	135
		Carbonates	5	Aldehydes	137, 138
		Trisformamidomethane	5	*N*-Substituted hydroxamic acids	126
		Acid anhydrides	5, 136		
		Acyl azides	5		

2.7.2.2 Halomethyleneiminium Salts (Amide Halides)

2.7.2.2.1 From halogenating reagents and acid amides

(i) Phosgene, diphosgene, carbonyl dibromide, carbonyl difluoride, oxalyl dihalides

Phosgene, as well as the easier to handle 'diphosgene' (chloroformic acid trichloromethyl ester)[141] or 'triphosgene' (carbonic acid bis(trichloromethyl) ester) transform primary, secondary and tertiary amides and thioamides to chloromethyleneiminium chlorides (**25**; equation 15),[1,7–9] whereby the reaction with thioamides is of broader scope and proceeds with fewer side reactions. The amide chlorides derived from primary and secondary amides can lose HCl, giving nitriles or imidoyl halides, respectively.[9] *N*-Substituted formamides can be converted to isonitriles *via* amide halides.[9]

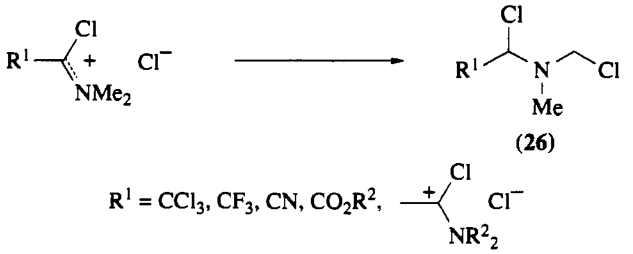


(15)

It should be noted that amide chlorides bearing strong electron acceptors (*e.g.* CCl_3, CF_3, CN, CO_2R, $ClCNMe_2$ groups) in the α-position readily undergo rearrangement to α,α′-dichloroamines (**26**; equation 16).[142–144] Oxalyl chloride has been used to prepare amide chlorides (*e.g.* **27**; equation 17) from tertiary amides; side reactions are known if α-halogenated amides or thioamides containing α-CH_2 groups are used in this reaction.[5] From carbonyl dibromide and tertiary carboxamides the corresponding bromomethyleneiminium salts (**28**; Scheme 1) were synthesized, which often possess Br_3^- as a counterion from which Br_2 can be split off by treatment with cyclohexene.[7,9] The action of carbonyl difluoride on tertiary amides gives rise to formation of α,α-difluoroamines (**29**),[7,9,145] which seem to be dissociated only to a very small extent.[7,9,146,147]

(ii) Phosphorus compounds

Wallach was the first (1874) to report on the transformation of carboxylic acid amides to amide chlorides by treatment with PCl_5;[7–9] various types of amides were converted by this reagent to chloromethyleneiminium chlorides (**30**; equation 18).[7–9,148,149] Side reactions can include the α-chlorination of the amide chloride.[8,9] If excess PCl_5 is used, the formation of iminium salts with complex ions (**31**) has been reported.[150] The very labile bromomethyleneiminium bromides (**32**; equation 19) can be obtained by action of PBr_5 on tertiary amides.[7,9] The iodomethyleneiminium salt (**33**) was prepared from DMF and diphosphorus tetraiodide in CS_2.[151]



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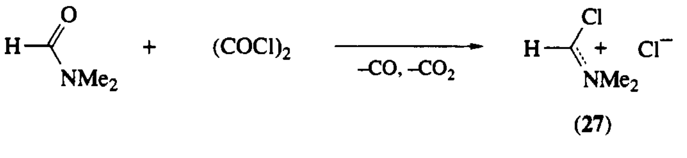

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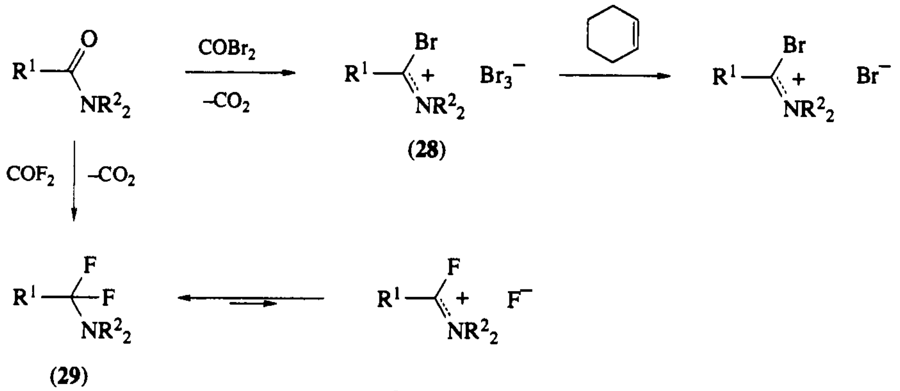
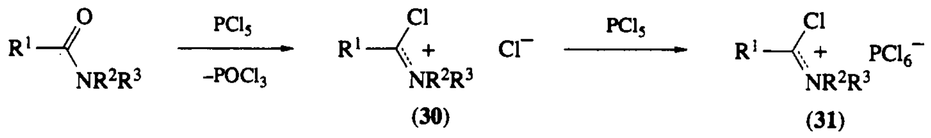


Scheme 1



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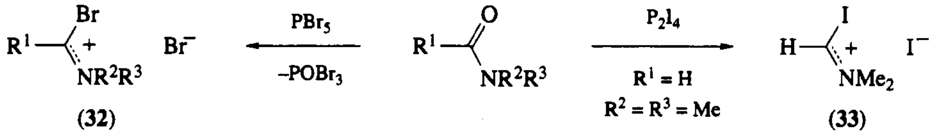
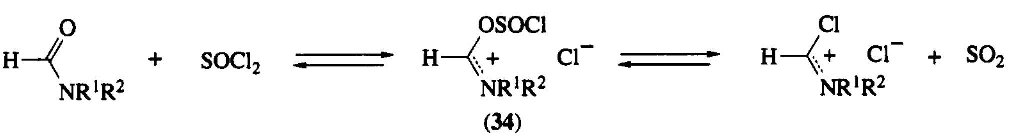


(19)

(iii) Sulfur compounds

Thionyl chloride was often used to synthesize amide chlorides from amides. The mechanism of this reaction has been thoroughly studied.[9] According to these investigations a primary adduct is formed (**34**; equation 20), which loses SO_2 in a reversible reaction to give the amide chloride (compare Section 2.7.2.1.2).[9] Mixtures of $SOCl_2$ with PCl_5 have also been used to convert amides to amide chlorides.[152] Amide fluorides (α,α-difluoroamines) (**35**; equation 21) can be obtained by the action of sulfur tetrafluoride on amides[7,9,153] or thioamides.[9,154] In the presence of KF tertiary formamides react with SF_4 to give α,α,α-trifluorodialkylamines.[155]



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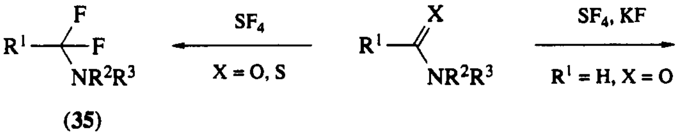
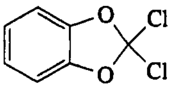


(21)

(iv) Miscellaneous reagents

A very efficient preparation of amide chlorides comprises the action of elemental chlorine on thioamides in CH_2Cl_2 or CCl_4; even amide chlorides which possess electron-attracting substituents in the α-position have been prepared in this way.[7,9,143,156]

DMF was converted to the corresponding iminium salt (**27**) by the following reagents:[5] perfluorobutyryl chloride, 2,2-dichlorobenzodioxole (**36**) and 2,2,2-trichlorobenzodioxaphosphole (**37**).



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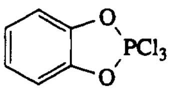
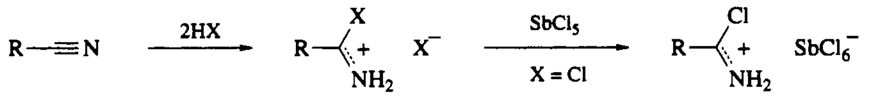


(37)

2.7.2.2.2 By addition reactions

(i) Hydrogen halides to nitriles or imidoyl halides

The formation of amide chlorides from nitriles and hydrogen halides under anhydrous conditions is a well-known reaction of wide scope.[7,9] There has been some confusion on the nature of the reaction products, but it has turned out that the isolable species are amide chlorides. The thermal stability of the addition products strongly depends on the acidity of the hydrogen halide used. Iodides are more stable than bromides, which in turn are more stable than the chlorides. As a consequence, thermally stable HCl adducts (**38**; equation 22) can be prepared if Lewis acids are present, which incorporate the chlorine anion to give a less basic anion (**39**).



X = I, Br, Cl

(38) **(39)**

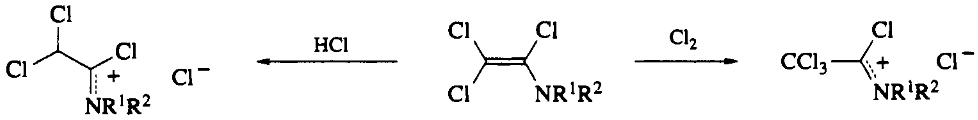
The reaction of fluorinating reagents such as F_2,[157] HgF_2,[158] CoF_3[159] and AgF_2,[159] in the presence of halogens[158] or interhalogen compounds,[157] with nitriles produces *N*-halogenated amide fluorides (*e.g.* **40** and **41**; equation 23). *N*-Alkylated imidoyl halides add HCl or HBr to give the corresponding iminium salts (**42**; equation 24).[7,9]

$$\underset{\textbf{(40)}}{RCF_2NClF} \xleftarrow{F_2,\ ClF} R{-}{\equiv}N \xrightarrow{Cl_2,\ HgF_2} \underset{\textbf{(41)}}{RCF_2NCl_2} \qquad (23)$$

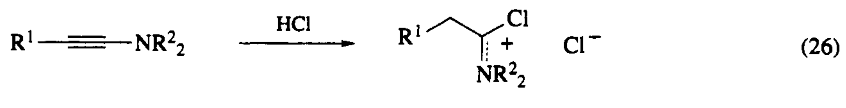
(42)

(ii) Hydrogen halides or halogens to α-chloroenamines or ynamines

Hydrogen halides (*e.g.* HCl) or halogens (*e.g.* Cl_2) add to chloroenamines to give amide chlorides (**43** and **44**; equation 25). The HCl addition seems to proceed reversibly.[9] By addition of HCl or Cl_2 to ynamines the iminium salts (**45**; equation 26) and (**46**; equation 27) were synthesized.[9,143]



(43) **(44)**



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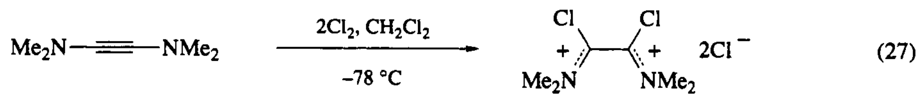
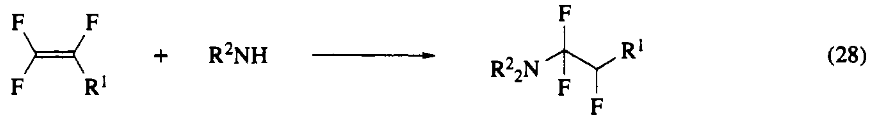


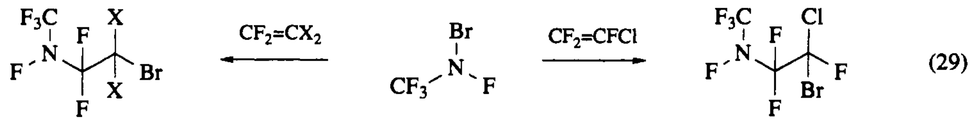
(46)

(iii) Amines to 1,1-dihalogenated alkenes

Perfluoroalkenes[9,160] and perfluorinated chloroalkenes[161] add secondary amines to give α,α-difluoroamines (**47**; equation 28). The *N*-halogenated amine (**48**) reacts with perhalogenated alkenes in a similar fashion. (equation 29).[162]



R^1 = F, CF_3 **(47)**

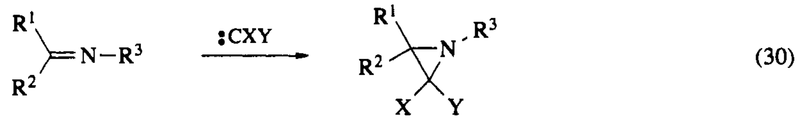


X = F, Cl, Br

(48)

(iv) Dihalocarbenes to C=N group containing compounds

Dihalocarbenes generated from haloforms and strong bases (*e.g.* alkoxides) or from haloforms and alkali metal hydroxides under phase transfer conditions[9,163–165] or organomercurytrihalomethanes,[9] add to azomethines to yield 2,2-dihaloaziridines (**49**; equation 30). The following carbenes have been used for such purposes: dichlorocarbene,[1,9,163–168] dibromocarbene,[165–167] difluorocarbene,[169,170] bromochlorocarbene[167] and bromofluorocarbene.[167] The addition of dihalocarbenes to azoxybenzene[9,171] or azobenzene affords dihaloaziridines (*e.g.* **50**; equation 31) among other products.



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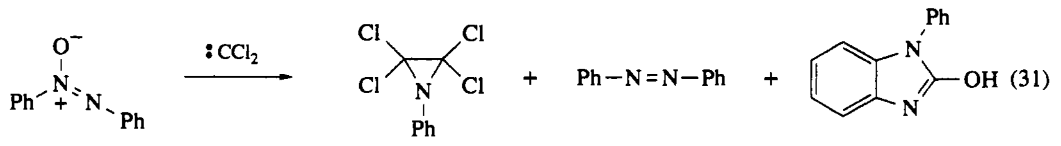
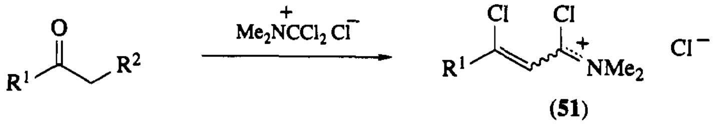


(50)

2.7.2.2.3 From dihalomethyleneiminium salts (phosgene iminium salts, PI salts)

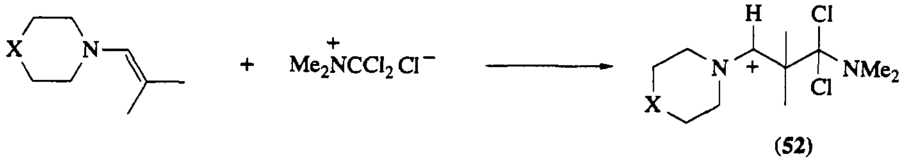
Dihalomethyleneiminium salts undergo condensation reactions with CH-acidic compounds such as ketones, carboxylic acid chlorides, nitriles and amides, to give amide halides, *e.g.* (**51**; equation

32).[7,9,172–174] Amide chlorides were obtained by the same method from enamines,[9,172] fulvenes,[175] barbituric acid derivatives[176] or pyridopyrimidines[177] and PI salts (*e.g.* **52**; equation 33).



(51)

(32)



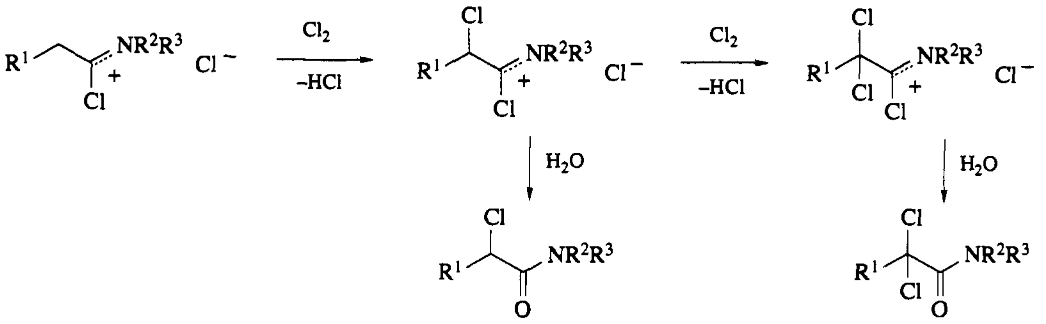
(52)

(33)

2.7.2.2.4 *From halomethyleneiminium salts*

(i) By halogenation

Amide chlorides which contain an α-CH or α-CH_2 group readily undergo chlorination in these positions. The amide chlorides thus formed were not isolated but their hydrolysis products, α-chlorinated amides (**53**) and (**54**; Scheme 2)[8,9,144] were formed.[8,9,144]

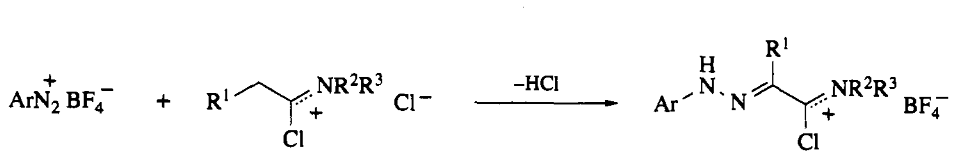


(53) **(54)**

Scheme 2

(ii) By diazocoupling

In a few examples it was demonstrated that diazonium salts are capable of coupling with amide chlorides in the α-position yielding hydrazones of α-keto acid amide chlorides (**55**; equation 34).[8,9]

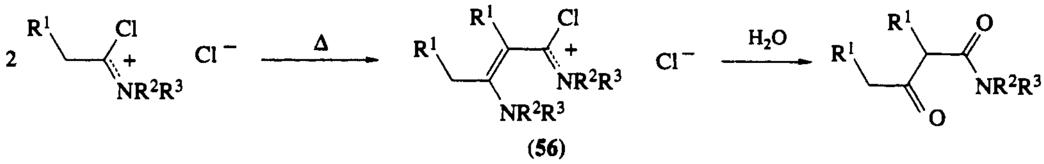


(55)

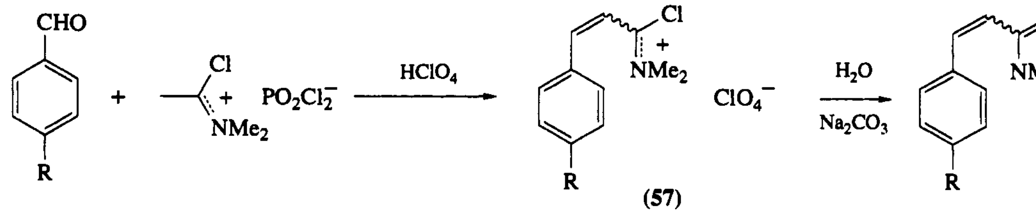
(34)

(iii) By condensation with carbonyl compounds or by selfcondensation

Although the selfcondensation of amide chlorides proceeds well to give amide chlorides derived from β-keto acids (**56**; equation 35) this reaction has only been used to synthesize β-keto acid amides, which result after hydrolysis of the condensation products (**56**), and not to prepare the salts (**56**) in the pure state. The condensation reaction of aromatic aldehydes with the *N,N*-dimethylacetamide–$POCl_3$ adduct in the presence of $HClO_4$ affords iminium salts (**57**; equation 36), which are hydrolyzed to cinnamic acid amides.[178]



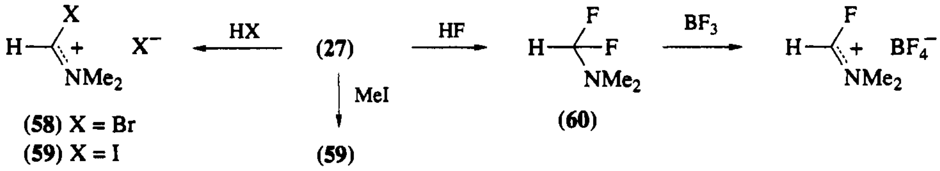
(35)



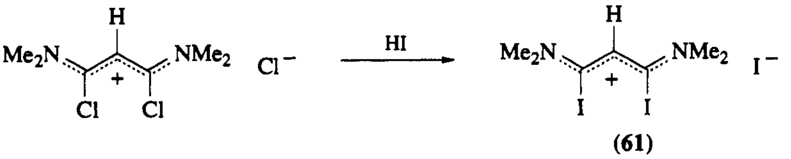
(36)

(iv) By halogen exchange or anion exchange reactions

Both chlorines in the iminium chloride (**27**) can be replaced by fluorine, bromine or iodine, giving compounds (**58**)–(**60**) (Scheme 3) if the salt is treated with the corresponding hydrogen halide under anhydrous conditions.[7,9] By chloro–iodo exchange with HI from the 3-chloroacrylamide chloride the corresponding amide iodide (**61**; equation 37) was prepared.[179] Dimethylformamide chloride (**27**) is converted by methyl iodide to dimethylformamide iodide (**59**).[180] Remarkably the difluoro compound (**60**) is a nonionic, distillable liquid which can be ionized by addition of boron trifluoride.[9]



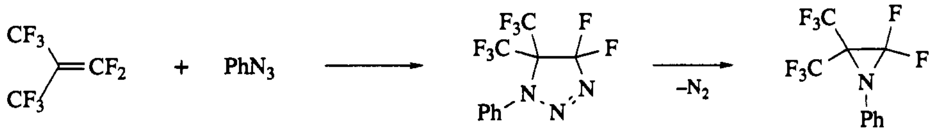
Scheme 3



(37)

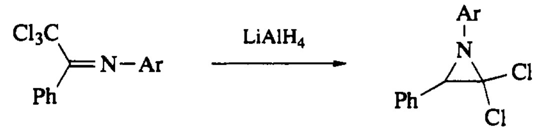
(v) Miscellaneous methods

Octafluoroisobutene reacts with phenyl azides, presumably *via* a triazole which loses nitrogen to give the difluoroaziridine (**62**; equation 38).[170] *N*-Aryltrichloroethylamines are cyclized to dichloroaziridines (**63**; equation 39) on treatment with potassium *t*-butoxide.[181] A related procedure is the reduction of trichloroacetophenone imines by $LiAlH_4$, which can be stopped at the stage of the dichloroaziridines (**64**; equation 40).[182] Triethylamine splits off hydrogen iodide from the iminium salt (**61**) to give the 2-propinylium iodide (**65**; equation 41).[179] With fluorosulfonic acid methyl ester the imidoyl chloride (**66**) was methylated to yield the iminium salt (**67**, equation 42).[183]

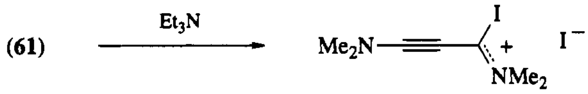


(62) (38)

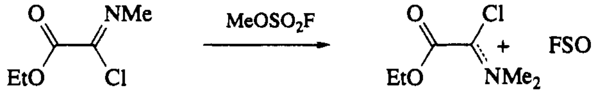
(63) R = OMe, OEt, Me (39)



(64) (40)



(65) (41)



(66) (67) (42)

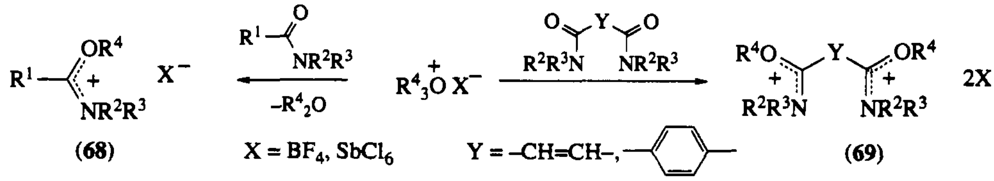
2.7.2.3 Alkoxymethyleneiminium Salts

2.7.2.3.1 From amides and alkylating reagents

Fifty years ago Meerwein demonstrated that tertiary oxonium salts alkylate amides at the oxygen of the carbonyl group.[7,10] Since then a lot of amides have been converted by these reagents to the corresponding iminium salts (**68**; Scheme 4). The results show that there is little restriction in the use of this procedure. Only strongly electron-attracting groups eventually, in connection with high steric efficiency, are able to prevent the alkylation of the oxygen of the amide function. Thus *N*,*N*-dimethyltrichloroacetamide or *N*,*N*-dimethylcarbamoyl chloride do not react with triethyloxonium tetrafluoroborate.[10] If other functional groups are present in the amide molecule which are sensitive to strong alkylating reagents, *e.g.* orthoester structures,[10] thiadiazoline compounds,[184] amino groups *etc.*, they may also be attacked or degraded; however, there are known alkylations of 4-amino-5-aminocarbonylimidazolyl nucleosides at the oxygen of the amide function.[185] Steric effects alone seem not to be able to block the reaction as can be seen from the alkylation of isobutyramides[186] or pivalic acid dimethylamide.[10] No restrictions of the alkylation procedure are known either in the series of aromatic acid amides[7,10,187–189] or in the case of *N*,*N*-diaryl-substituted carboxylic acid amides. Triple bonds[10,190,191] and double bonds[10,192] can be present in the amide molecule.

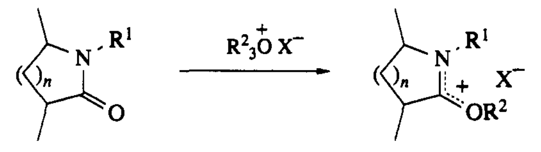
Oxonium salts alkylate diamides of dicarboxylic acids twice, provided the amide groups are separated by at least two carbon atoms,[10,193,194] thus the bis(dimethylamides) of maleic acid or terephthalic acid have been converted to dications (**69**; Scheme 4) by means of oxonium salts.[10]

N-Acylimino compounds are converted by oxonium salts to iminium salts, which can be regarded as azaallenium salts.[195–198] A lot of lactams have been alkylated by oxonium salts at the carbonyl oxygen to give salts of type (**70**; equation 43).[7,10,199–207]



R^1 = H, alkyl, RC_6H_4, CH_2Cl, $CHCl_2$, $CH(OR)_2$, RC≡C, RCH=CH;
R^2, R^3 = H, alkyl, aryl, $=CR^5R^6$ (R^6 = alkyl, aryl, OR)

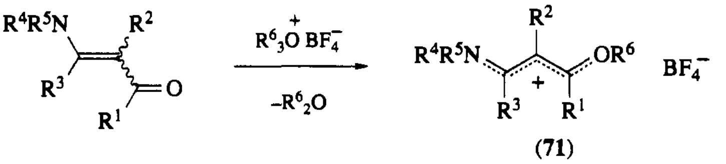
Scheme 4

 (43)

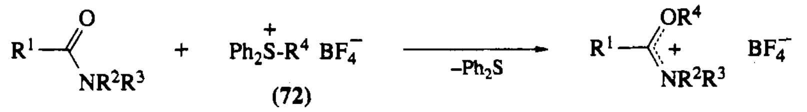
(70) R^3 = Me, Et; X = BF_4

The action of oxonium salts on vinylogous amides affords iminium salts (**71**; equation 44), which are useful for synthetic purposes in heterocyclic chemistry.[10,208–211,214] Alkyldiphenylsulfonium tetrafluoroborates (**72**; equation 45) were recommended as reagents which alkylate amides and lactams under smooth conditions.[212] With the aid of fluorosulfonic acid esters[7,10,186,213] as well as with trifluoromethanesulfonic acid esters,[7,10,214,215] which have alkylation power comparable to oxonium salts, iminium salts, *e.g.* (**73**) and (**74**; Scheme 5), could be synthesized from amides,[186,214] vinylogous amides[213] and lactams.[215] Trimethylsilyloxymethyleneiminium salts (**75**; equation 46) are accessible by reacting trimethylsilyltrifluoromethanesulfonate with amides.[216,217]

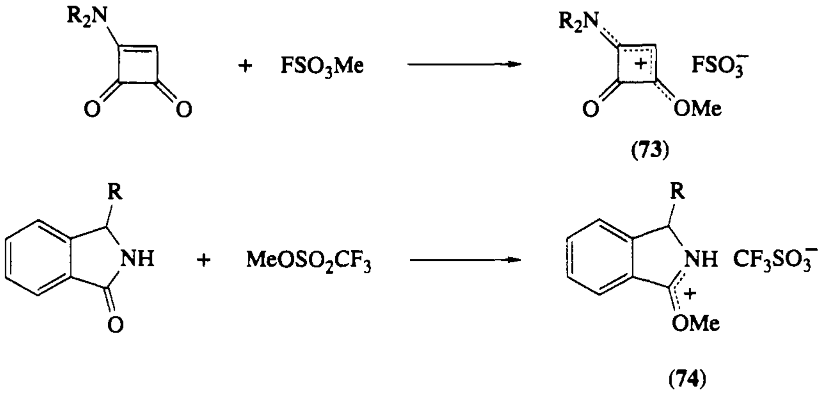
Although carboxonium salts (**76**; equation 47) are easily available and of high alkylation power, they have found little application for alkylation of amide groups.[10]

 (44)

(71)

 (45)

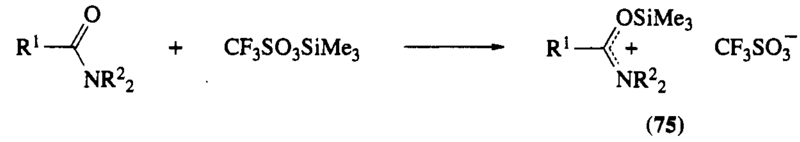
(72)

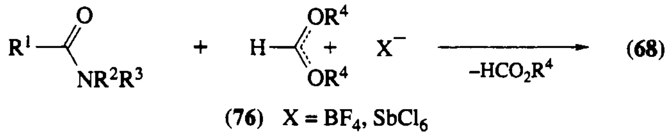


(73)

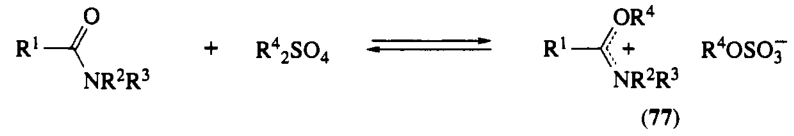
(74)

Scheme 5

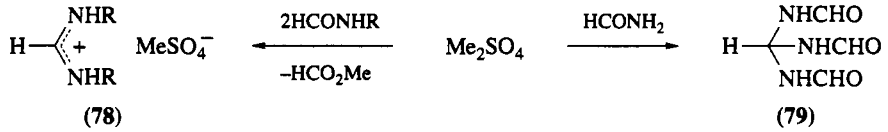

(46)


(47)

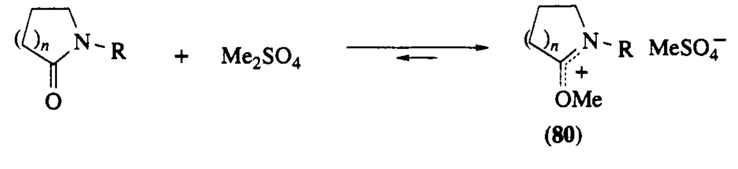
Dialkyl sulfates alkylate acid amides in an equilibrium reaction at the carbonyl oxygen to give iminium salts (**77**; equation 48).[7,10] The position of the equilibrium depends on the nature of the substituents: bulky and electron-attracting groups shift it to the starting compounds. Fortunately in the case of the most important iminium salts, derived from *N*,*N*-dialkylated formamides or acetamides, the position of the equilibrium is situated far on the side of the iminium compounds, so that this reaction is by far the most convenient way to produce salts derived from formamides and acetamides. The alkylation is slow at room temperature, it can be accelerated by heating the components up to 80 °C. Higher temperatures should not be applied in order to avoid side reactions. *N*-Monosubstituted formamides react with dimethyl sulfate in a molar ratio of 2:1, yielding *N*,*N'*-disubstituted formamidinium salts (**78**; equation 49); formamide itself reacts in a more complicated way to give tris(formylamino)methane (**79**).[10]


(48)

R^1 = H, alkyl (C_1–C_5), Ph, $PhCH_2$, CH_2CONR_2


(49)

In the alkylation of lactams the equilibrium position also lies at the side of the iminium compounds (**80**; equation 50), so it is not surprising that 4- to 12-membered ring lactams have been methylated by dimethyl sulfate to produce the corresponding cyclic iminium salts.[10]

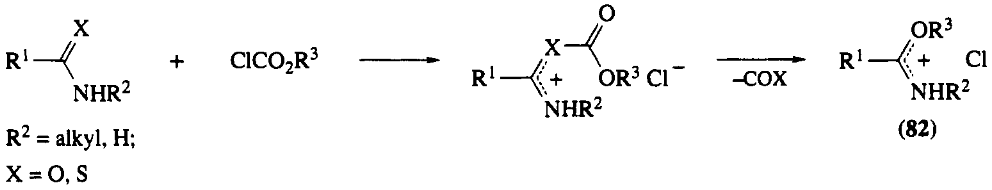

(50)

The alkylation of amides by alkyl halides or simple sulfonic acid esters is usually of little importance because the alkylation equilibrium is placed on the side of the starting compounds. This is not the case, however, in either the alkylation of vinylogous amides (which has been achieved even with alkyl iodides[218]) or if intramolecular alkylation is possible, *e.g.* in *N*-(2-haloethyl)amides. In the latter case cyclic iminium compounds (**81**; equation 51) are readily available by replacing the more nucleophilic halide by less nucleophilic complex anions, which can be achieved by addition of Lewis acids or $AgBF_4$.[10,219]

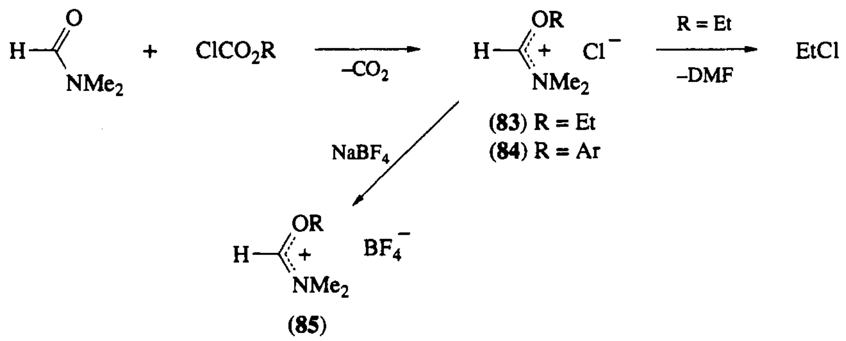
(81) (51)

2.7.2.3.2 From carboxylic acid amides and acylating reagents

Primary and secondary amides and thioamides react with alkyl chloroformates with loss of CO_2 or COS, forming iminium chlorides (**82**; equation 52). In some cases this method is complementary to the Pinner imido ester hydrochloride synthesis.[7,10] The iminium salt (**83**; Scheme 6) formed by action of ethyl chloroformate on DMF is labile and decomposes rapidly to ethyl chloride. If the reaction is performed in the presence of $NaBF_4$, the iminium salt (**85**) is isolable. Aryl chloroformates react in the same fashion with DMF or DMA, but in these cases the aryloxymethyleneiminium compounds are fairly stable, so this reaction is an important method for the preparation of compounds of this type.[7,10] Succinic acid monoamides, phthalic acid monoamides and related compounds are cyclized to iminium salts (**86**; equation 53) by treatment with acetic anhydride and $HClO_4$.[220] With the aid of trifluoromethanesulfonic anhydride lactams and amides can be converted to dication ether salts (**87**) and (**88**; Scheme 7).[221,222]

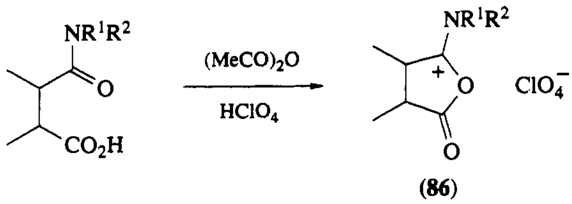


(82) (52)



(83) R = Et
(84) R = Ar
(85)

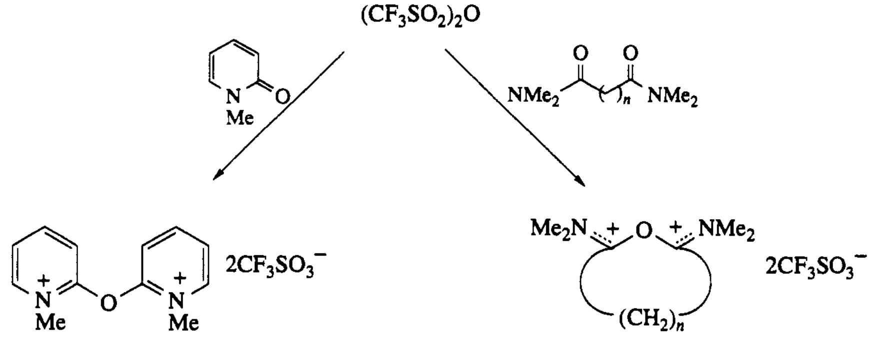
Scheme 6



(86) (53)

2.7.2.3.3 By alkylation or acylation of imino esters

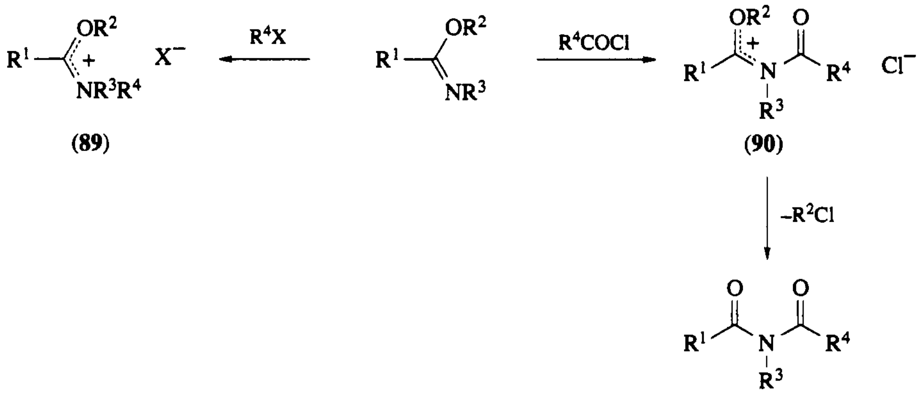
Alkylation and acylation of imino esters proceeds at the nitrogen of the imino ester function. In many cases it is not advisable to use alkyl halides or acyl halides for such reactions because the iminium salts (**89**) or (**90**; Scheme 8) are readily dealkylated by the halide anions. This can be prevented by the use of stronger alkylating reagents, *e.g.* tertiary oxonium salts, dialkyl sulfates or alkyl triflates, which produce in the course of the alkylation only anions with low nucleophilicity.[10,223,224] Heterocycles containing



(87) **(88)**

Scheme 7

imino ester structures, *e.g.* 1,3-oxazolines or lactim ethers, can be transformed easily by alkylation to the corresponding heterocyclic iminium compounds.[10]

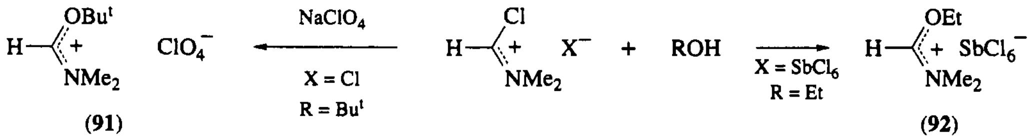


(89) **(90)**

Scheme 8

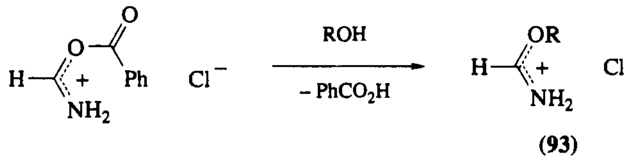
2.7.2.3.4 *From halomethyleneiminium salts and related compounds*

The reaction of amide chlorides with alcohols to yield alkoxymethyleneiminium salts, *e.g.* (**91**) and (**92**; Scheme 9), is important for the preparation of cations with bulky alkoxy groups, *e.g.* *t*-butoxy. These alcoholysis reactions demand the presence of salts with less nucleophilic anions in order to avoid dealkylation of the cations. This difficulty does not arise if the iminium hexachloroantimonates, which are obtained from the chlorides by addition of $SbCl_5$, are used for alcoholysis.[7,10] A convenient route to *N*-unsubstituted salts (**93**; equation 54) is the alcoholysis of the formamide–benzoyl chloride adduct.[7,10] The reaction of phenols with dimethylformamide chloride (**27**) affords aryloxymethyleneiminium salts (**94**; equation 55) which are hard to prepare by other methods. By addition of alkynols to the α-haloenamine (**95**) alkoxymethyleneiminium salts have been obtained (equation 56).[225]

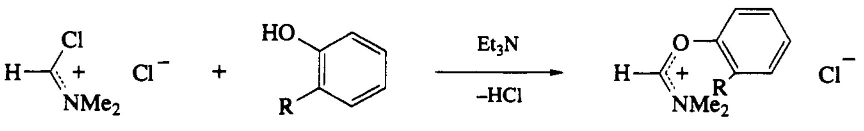


(91) **(92)**

Scheme 9



(93) (54)



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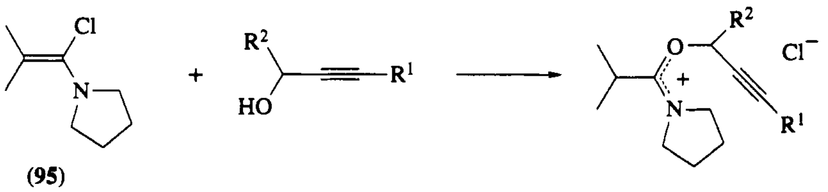
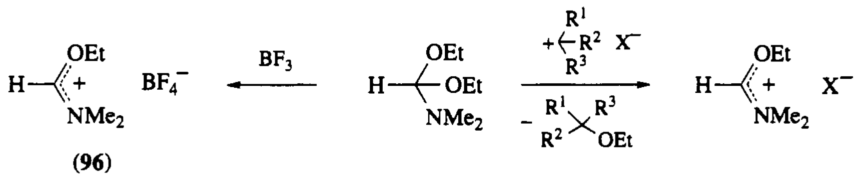


(56)

2.7.2.3.5 *From orthoamide derivatives and related compounds*

Strong Lewis acids abstract alkoxide groups from amide acetals or lactam acetals to give the corresponding iminium salts, *e.g.* (**96**; Scheme 10). Alkoxide transfer from amide acetals to less stable carbenium ions is also a route from amide acetals to iminium compounds (**97**).



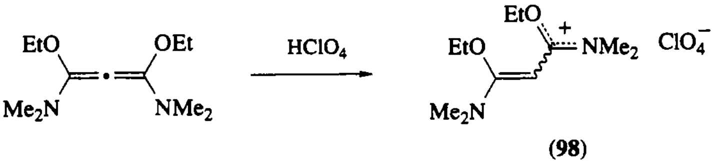
$R^1 = H, R^2 = R^3 = OEt; X = BF_4$ (**96**)

or $X = SbCl_6$ (**97**)

$R^1 = R^2 = R^3 = Ph; X = BF_4$

Scheme 10

Protonation of ketene *O,N*-acetals with strong acids gives rise to the formation of iminium compounds, *e.g.* (**98**; equation 57). Ketene *O,N*-acetals are transformed by alkyl halides or acyl halides to α-substituted amides *via* unstable iminium salts (**99**; equation 58).[10] Iminium compounds of this type are isolable if they are immediately precipitated, *e.g.* as perchlorate salts (**100**; equation 59).[227] Heterocumulenes such as isocyanates,[10] isothiocyanates[10] or SO_2[226] form 1,4-dipoles with ketene *O,N*-acetals, which can be stabilized by protonation with perchloric acid to give salts, *e.g.* (**101**; equation 60).



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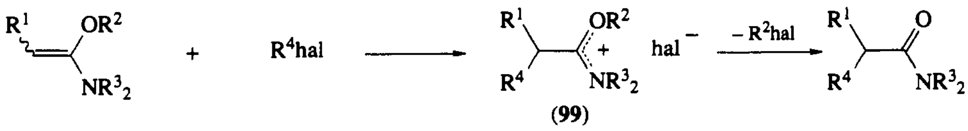

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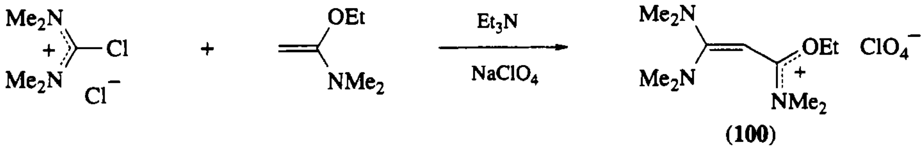

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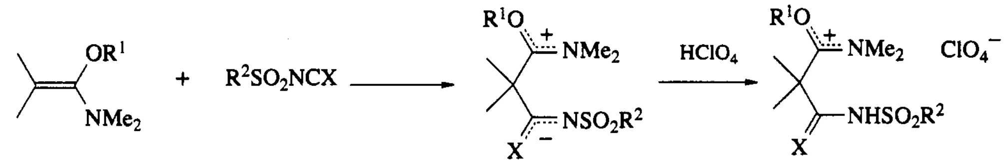
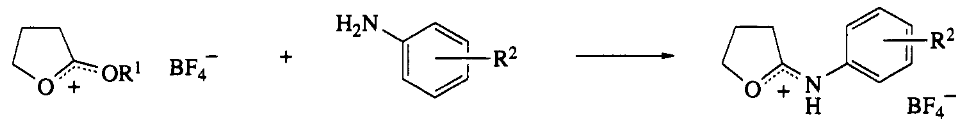


(101)

(60)

2.7.2.3.6 *From carboxonium salts*

Dialkylcarboxonium ions possess a very high alkylation power. If they are reacted with amines or amine derivatives, the substitution of the alkoxy group by the amino compound competes with the dealkylation of the carboxonium ion. Therefore only a few examples for the preparation of iminium salts are known, *e.g.* (**102**; equation 61), from carboxonium salts.[10,228,229]



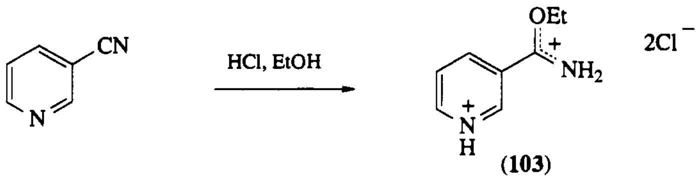
R^2 = 4-Me, 4-Cl, 2-CO_2Et

(102)

(61)

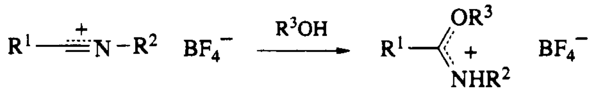
2.7.2.3.7 *From nitriles or nitrilium salts*

The addition of water-free alcohols to the nitrile group in the presence of HCl or HBr in a temperature range of 0–5 °C is a versatile synthesis for *N*-unsubstituted alkoxymethyleneiminium salts. Detailed reviews on these reactions have been published.[16,230,231] More recently it has been demonstrated that 'imido ester hydrochlorides' can be prepared, *e.g.* (**103**; equation 62), from heterocyclic nitriles[232,233] even if they have strong basic character.[232–234] The transformations of α-aryloxynitriles,[237] adamantanedicarbonitriles,[237] glycosidic-bound oxynitriles[238] and benzonitriles[239,240] with highly reactive functional groups, *e.g.* enol ether structures, to the corresponding imido ester hydrohalides have been described. Nitrilium salts add alcohols and phenols to give *N*-monosubstituted alkoxymethyleneiminium salts (**104**; equation 63).[7,10,241,242]



(103)

(62)

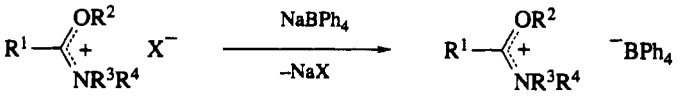


(104)

(63)

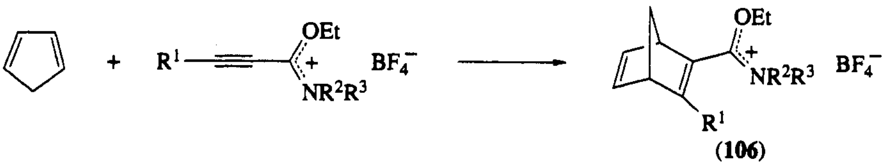
2.7.2.3.8 *Miscellaneous methods*

In alkoxymethyleneiminium salts the anions are exchangeable (Cl^- *versus* ClO_4^- or $SbCl_6^-$ *etc.*). This procedure can be used to purify the iminium compounds for analytical purposes. Tetraphenylborates (**105**), which are easy to obtain from the iminium salt and sodium tetraphenylborate in dry acetonitrile (equation 64), and which crystallize easily, are suitable reagents. The carbon skeleton of α,β-unsaturated alkoxymethyleneiminium compounds can be altered by cycloadditions, *e.g.* Diels–Alder reactions, to give compounds of type (**106**; equation 65).[7,10]



(105)

(64)



(106)

(65)

2.7.2.4 Alkylmercaptomethyleneiminium Salts

2.7.2.4.1 From thioamides and alkylating reagents

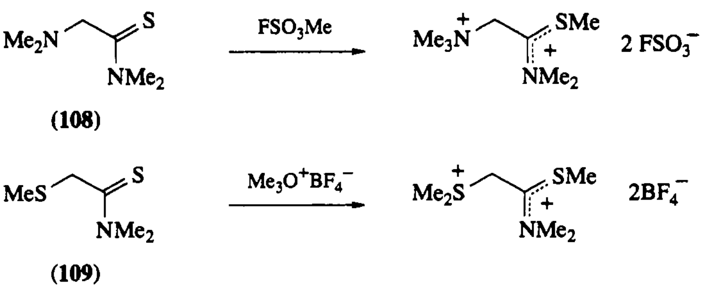
The high nucleophilicity of sulfur facilitates the alkylation of thioamides. The alkylation of thioamides and thiolactams is a long-known synthesis of alkylmercaptomethyleneiminium compounds (**107**; equation 66), which has been reviewed several times.[7,11-13,243] Nearly all types of alkylating reagents and amides were used for these reactions (see Table 3).

(107)

(66)

R^1 = alkyl, Bu^t, $Ar(CH_2)_n$, Ar;
R^1, R^3 = H, alkyl, aryl;
R^4 = alkyl, $ArCH_2$, $RCOCH_2$

If the substrate molecule contains further nucleophilic centers, these can be attacked first. With powerful alkylating reagents both functions are alkylated,[13,279] *e.g.* in (**108**) and (**109**; Scheme 11). Tertiary alkyl halides, *e.g.* trityl chloride, under basic conditions can alkylate primary thioamides at the nitrogen of the thioamide group.[13] From thio-DMF and 2,4-dinitrochlorobenzene the corresponding *S*-arylmethyleneiminium compound was prepared.[285]



(108)

(109)

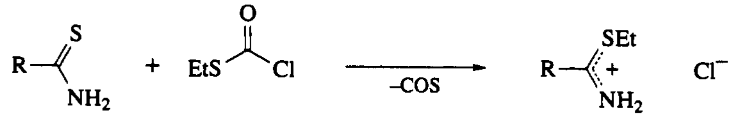
Scheme 11

2.7.2.4.2 From thioamides and acylating reagents

A simple and efficient route to alkylmercaptomethyleneiminium salts (**110**; equation 67) is the action of alkyl thiochloroformates on thioamides.[7,13,286] β-Chlorovinyl ketones react with thioamides to form iminium compounds (**111**; equation 68),[13,287,288] which can serve as precursors for 1,3-thiazinium salts.[288] Bromine forms labile *S*-bromoiminium salts (**112**) with thioamides,[289,290] which react with enamines to give *S*-vinyl-substituted salts (**113**; equation 69).[290]

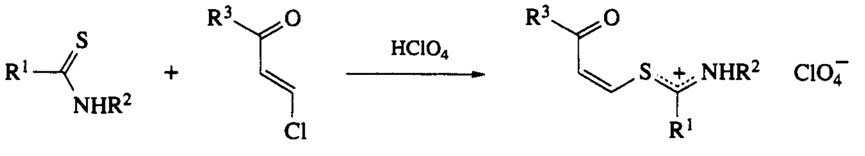
Table 3 Alkylating Reagents and Thioamides Suited as Starting Compounds for Alkylmercaptomethyleneiminium Compounds

Alkylating reagents	*Ref.*	*Thioamides*	*Ref.*	*Thioamides*	*Ref.*
Alkyl iodides	244–261	Simple saturated aliphatic thioamides	263, 265, 275, 279, 281	Ester thioamides of aliphatic dicarboxylic acids	253
Alkyl bromides	252, 254, 262–266				
Alkyl chlorides	254, 263, 266–268	Arylalkythiocarbonamides	244, 246, 250, 257, 258	Dithioamides of dicarboxylic acids	284
				Four-membered thiolactams	277
				Five-membered thiolactams	254, 255, 261, 266, 270, 272, 276, 280, 283
α-Halocarboxylic acid esters	263, 269–272	Long-chain aliphatic thioamides	248		
α-Halo ketones	273–276				
Dialkyl sulfates	12	Aromatic thioamides	249, 251, 253, 259, 260, 269, 271		
Alkyl fluorosulfonates	277–279			Six-membered thiolactams	253, 261, 273, 274
				Seven-membered thiolactams	256
Trifluoromethanesulfonic acid esters	280	Vinylogous thioamides	245, 247, 252, 253, 282		
Oxonium salts	279, 281–284				
		Unsaturated thioamides	268		
		Chain-branched aliphatic thioamides	250, 278		
		Malonanilidedimethylthioamide	268		



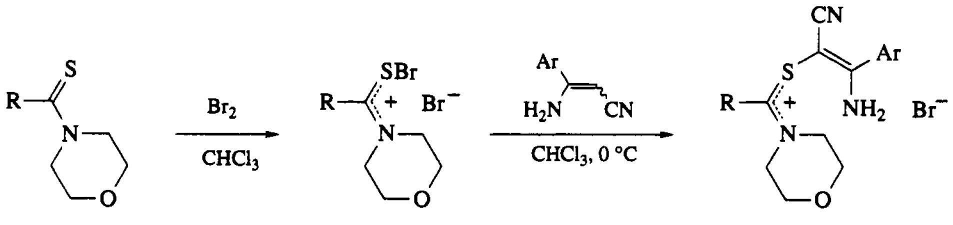
(110)

(67)



(111)

(68)

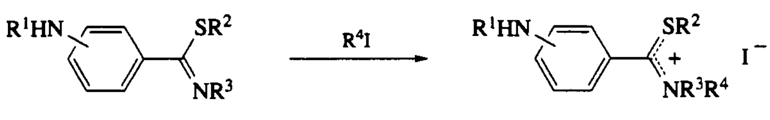


(112) (113)

(69)

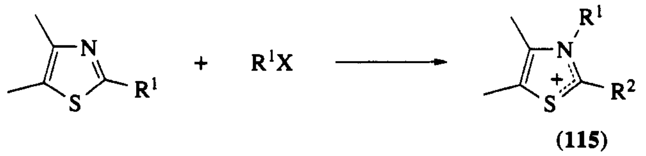
2.7.2.4.3 *From thioimido esters by alkylation or acylation*

Alkylation of thioimino esters affords salts of type (**107**). This procedure was not often applied as the thioimido esters needed are usually prepared *via* alkylmercaptomethyleneiminium compounds. Provided there is an acceptable way to synthesize the imino ester, the method is of particular use if strong nucleophilic groups are present in a thioamide molecule so that a direct route to the iminium compound *via* alkylation of the amide is not possible. The nucleophilicity of the thioimido ester function exceeds even that of amino groups, as can be seen by the reaction of the thioimino ester (**114**; equation 70) with alkyl iodides.[13] Heterocycles containing the thioimino ester structure are easy to alkylate at the nitrogen. In this way a great number of 1,3-thiazolium salts, *e.g.* (**115**; equation 71), have been prepared. Alkylating reagents used in such processes were: alkyl iodides,[291-295] alkyl bromides,[293,296] toluenesulfonic acid methyl ester,[297] dimethyl sulfate[298] and triethyloxonium tetrafluoroborate.[299]



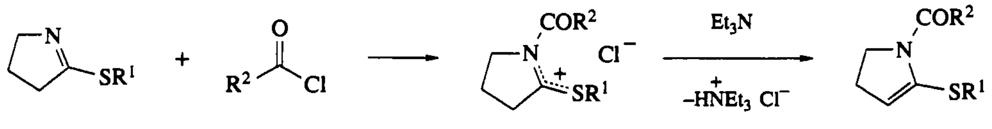
(o,p) (**114**)

(70)


(**115**)

(71)

Generally the acylation of thioimino esters takes place at the nitrogen, the salts (**116**; equation 72) thus formed were not usually isolated but reacted further, *e.g.* deprotonated.

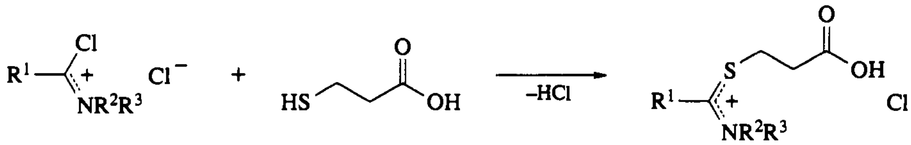


(116)

(72)

2.7.2.4.4 From other methyleneiminium salts

It is well known that the action of mercapto group containing compounds on chloromethyleneiminium salts affords alkylmercaptomethyleneiminium salts, *e.g.* (**117**; equation 73); this type of reaction has only rarely found application.[13]

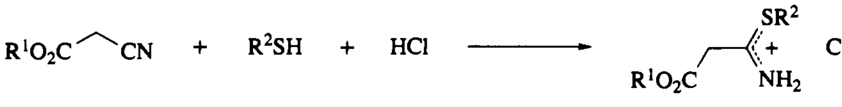


(117)

(73)

2.7.2.4.5 By addition of SH group containing compounds to nitriles

Thiols and benzenethiols add to nitriles in the presence of hydrogen halides to give *N*-unsubstituted iminium salts, *e.g.* (**118**, equation 74).[13,300] The reaction seems to have no advantage over other known preparative procedures.

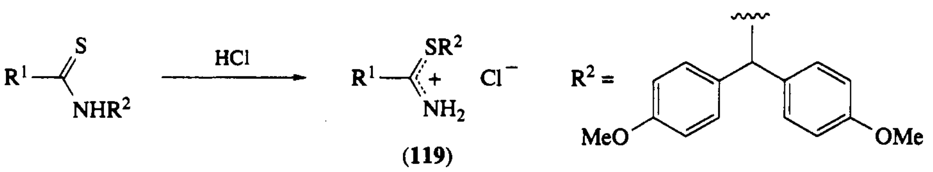


(118)

(74)

2.7.2.4.6 By rearrangement of thioamides

Thioamides with bulky substituents bound to the nitrogen can be rearranged to iminium compounds (**119**; equation 75) by treatment with HCl, provided the bulky groups can form stable carbenium ions.[7,13]

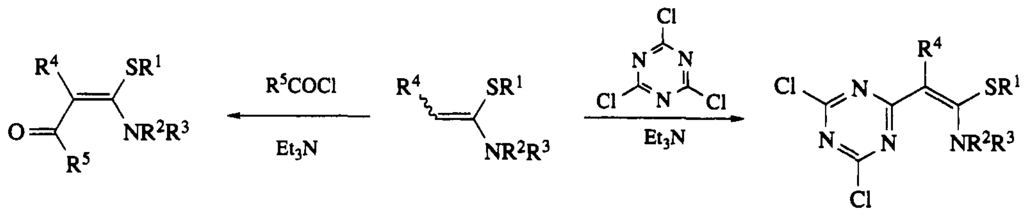


(119)

(75)

2.7.2.4.7 From orthoamide derivatives and related compounds

Ketene *S,N*-acetals are usually attacked by electrophilic reagents at the β-carbon, yielding iminium salts, thus ketene *S,N*-acetals have been alkylated and acylated. Similar reactions are described with chloroformic acid esters, cyanuric chloride, *m*-nitrophenylsulfenyl chloride, 2,4-dinitrochlorobenzene, 3-chloro-2-cyanoacrylonitriles and 2-chlorovinyl phenyl ketone. Usually it is not the initially formed iminium compounds but the substituted ketene *S,N*-acetals which are isolated, *e.g.* (**120**) and (**121**; Scheme 12).[13]

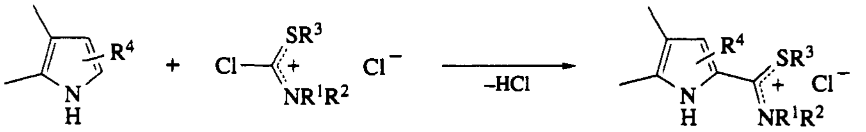


(120) **(121)**

Scheme 12

2.7.2.4.8 *From orthocarbonic acid derivatives*

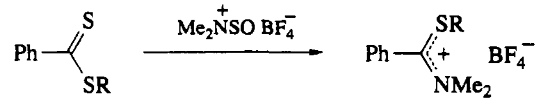
It was demonstrated that indole and substituted pyrroles undergo electrophilic substitution with alkylmercaptochloromethyleneiminium chlorides giving heterocyclic iminium chlorides (**122**; equation 76).[7,12] Probably this reaction type is of more general applicability.



(122) (76)

2.7.2.4.9 *Miscellaneous methods*

N-Sulfinyldimethylammonium tetrafluoroborate transforms methyl dithiobenzoate to the corresponding iminium salt (**123**; equation 77).[301]



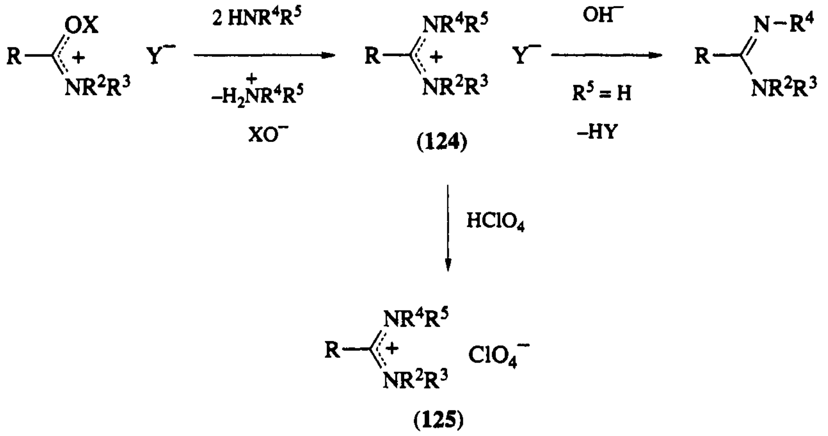
(123) (77)

2.7.2.5 Amidinium Salts (Aminomethyleneiminium Salts)

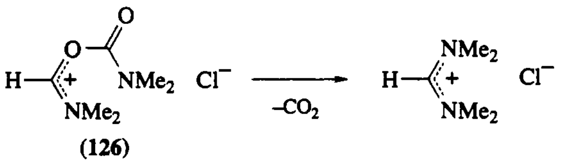
2.7.2.5.1 *From amide–acylating reagent adducts and amines or amine derivatives*

The adducts from secondary or tertiary carboxylic acid amides and $POCl_3$, PCl_3, $(PNCl_2)_3$, RSO_2Cl and $R^1R^2NSO_2Cl$ (see Section 2.7.2.1) react with compounds containing primary or secondary amino groups to give amidinium salts (**124**; Scheme 13), but these are usually hard to isolate from the mixtures of amidinium and ammonium salts formed. Therefore in general the reaction mixture is made alkaline and the released amidine is extracted with organic solvents;[7,14] so this reaction is best suited to the preparation of *N*,*N*′-disubstituted or *N*,*N*′,*N*′-trisubstituted amidines rather than the synthesis of the corresponding salts. Under certain circumstances the amidinium salts (**125**) are isolable by addition of NaI, $NaClO_4$ or $HClO_4$ *etc.* using the fact that amidinium ions with iodine or ClO_4 anions form only slightly soluble salts.

A versatile method for the preparation of *N*,*N*,*N*′,*N*′-tetrasubstituted formamidinium salts[7,14,302,303] and *N*,*N*,*N*′-trisubstituted carbonamidinium salts[119,120] is the thermal decomposition of the *in situ* formed adducts, *e.g.* (**126**; equation 78), from secondary or tertiary formamides or higher secondary carboxylic acid amides with *N*,*N*-dialkylcarbamoyl chlorides. By the same procedure vinylogous amides have been converted to vinylogous salts (**127**; equation 79).[304] Similarly the adducts (**128**; equation 80) formed from phenylisocyanide dichloride with tertiary formamides decompose on heating to give formamidinium salts (**129**).[7,14] The 2:1 DMF–cyanuric acid adduct (**20**) has been used to prepare *N*,*N*,*N*′-trisubstituted formamidinium salts (**130**; equation 81).[14] The *in situ* formed adducts of DMF with trimethylhalosilanes react with arylamines to yield *N*,*N*′-diarylformamidinium salts (**131**; equation 82).[305]



Scheme 13



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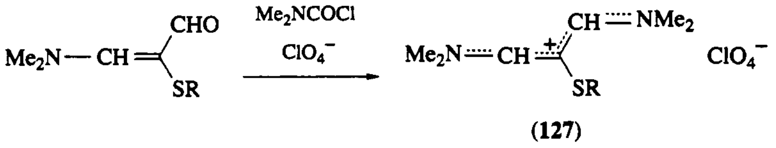

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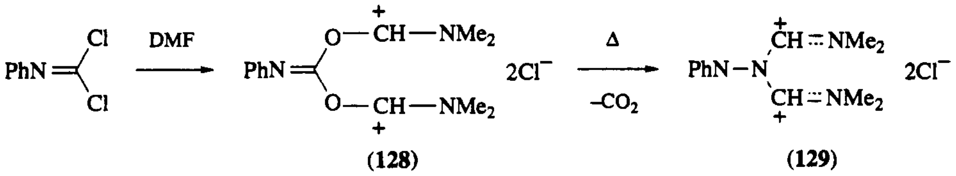

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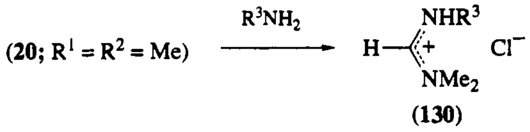

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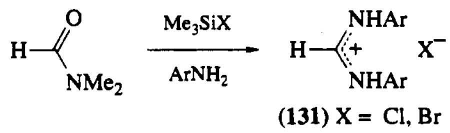
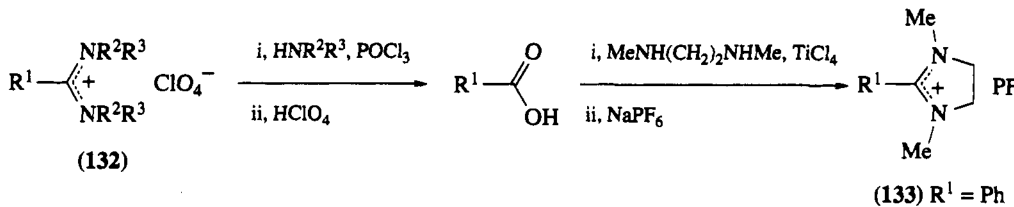


(82)

2.7.2.5.2 From carboxylic acids, amines and various condensing agents

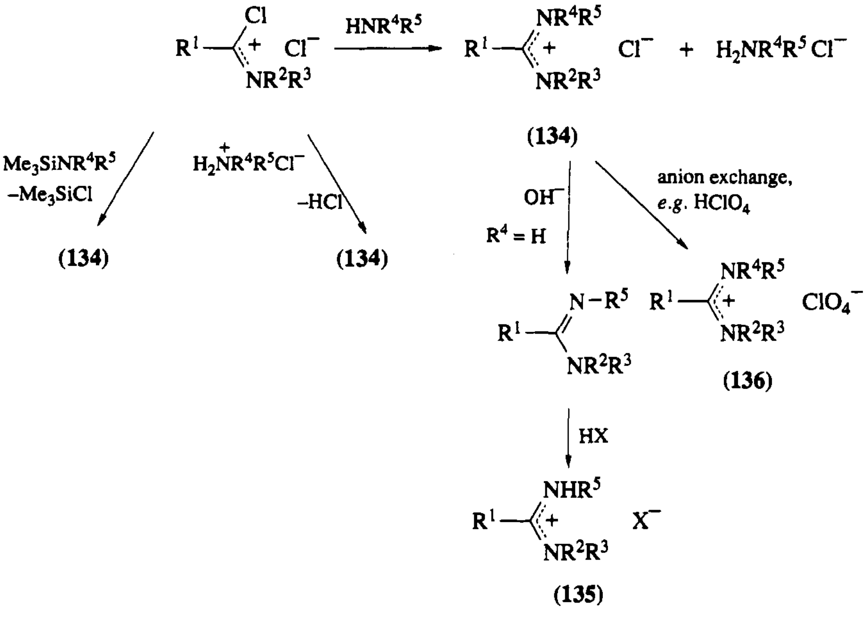
A very simple procedure for the preparation of amidinium salts is the condensation of carboxylic acids with excess amine in the presence of $POCl_3$.[7,14] Using this method, the selfcondensation reaction of amide–$POCl_3$ adducts is suppressed. The salts are usually isolated as perchlorates (**132**; Scheme 14). In a related reaction benzoic acid is transformed by means of *N*,*N*′-dimethylethylenediamine and $TiCl_4$ to the imidazolium chloride, which was separated as the PF_6^- salt (**133**).[14]



Scheme 14

2.7.2.5.3 *From iminium salts*

The reaction of amide chlorides with primary and secondary amines or amine derivatives yields amidinium salts (**134**; Scheme 15).[7,14,306] In the course of the reactions HCl is produced, which converts the amino compound to its hydrochloride. The salt mixtures thus formed are difficult to separate. Provided the amidinium compound in the mixture is at most an *N*,*N*′,*N*′-trisubstituted one, separation can be achieved *via* the free amidine, which, after separation, is easily converted to the desired amidinium salt (**135**) by acidification with water-free acids. From salt mixtures containing *N*,*N*,*N*′,*N*′-tetrasubstituted amidinium salts, the pure amidinium compound, *e.g.* (**136**) can sometimes be isolated *via* anion exchange by addition of $HClO_4$, $NaClO_4$[156] or NaI (in acetone/acetonitrile).

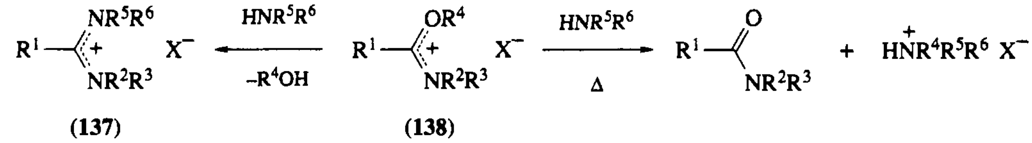


Scheme 15

Some ideas exist on circumventing the problem. Amine hydrochlorides at higher temperatures are in equilibrium with HCl and the amine. Provided the amide chloride is thermally stable (no von Braun degradation, no selfcondensation), which is true for a lot of aromatic amide chlorides or formamide chlorides, the amine hydrochloride can be reacted at elevated temperatures (150–170 °C) for strongly basic aliphatic amines, whereas weakly basic aromatic amides react under more gentle conditions. In another approach, instead of the amine the *N*,*N*-dialkylsilylamine is used, hence trimethylsilyl chloride is formed as a byproduct, which can be removed by distillation.

The reaction of amide chlorides with *N*-unsubstituted carbaminic acid esters or *N*,*N*,*N*′-trisubstituted ureas or thioureas affords the corresponding amidinium salts in good yields.[14,307]

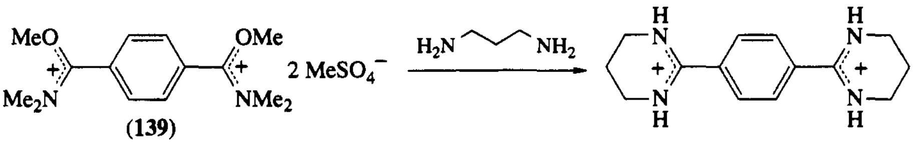
By treatment of alkoxymethyleneiminium salts or alkylmercaptomethyleneiminium salts with primary or secondary amines the alkoxy group or the alkylmercapto group, respectively, is replaced by the amino group forming amidinium salts (**137**; Scheme 16). The byproducts, alcohols or thiols, are easy to remove by distillation *in vacuo*. Especially in the case of alkoxymethyleneiminium salts it is necessary for the reaction temperature to be as low as possible to suppress the competing dealkylation of the salt (**138**) by the amine giving rise to ammonium salt formation.



Scheme 16

Since alkoxymethyleneiminium salts with nearly any substitution pattern are easy to prepare, this amidine synthesis has attained widespread application. Thus *N*-unsubstituted,[235–240] *N*-monosubstituted[7,14] and *N*,*N*-disubstituted alkoxymethyleneiminium salts (**138**)[7,14] have been transformed to amidinium salts (**137**) by treatment with ammonia,[235–240] primary and secondary amines and amine derivatives.[7,10,14]

It has been noted in some exchange reactions, performed under neutral conditions, that the amino group and not the alkoxy group is replaced.[10] 1,2-Diamines[308] and 1,3-diamines[7,10,14] react with iminium salts, *e.g.* (**139**) by substitution of both the alkoxy and the amino group.[7,10,14] In lactim ester salts (**140**; equation 84) the alkoxy groups can be replaced in the same fashion.[7,10,14]



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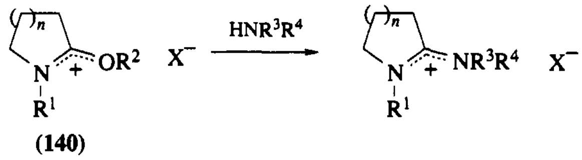
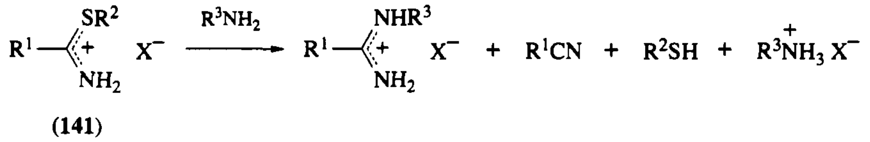


(84)

From alkylmercaptomethyleneiminium salts various types of amidinium salts have been synthesized. Ammonia,[309] primary and secondary amines,[7,13,14] hydrazines[7,13,14,309] and *N*-unsubstituted[310,312] and *N*-monosubstituted hydrazones[311–313] were the reaction partners. Side reactions can include the dealkylation of the iminium salt by the amine. If *N*,*N*-unsubstituted salts (**141**; equation 85) are treated with amines, the desired exchange reaction can be accompanied by nitrile formation.



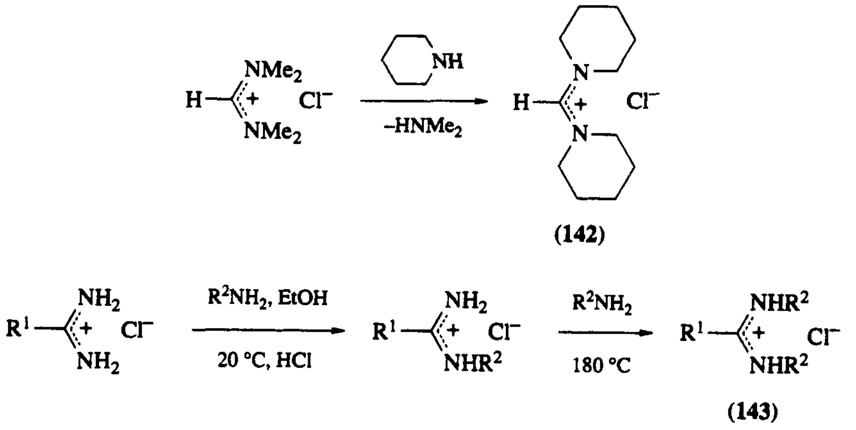
$$R^1C(SR^2)(NH_2)^+\ X^- \xrightarrow{R^3NH_2} R^1C(NHR^3)(NH_2)^+\ X^- + R^1CN + R^2SH + R^3\overset{+}{N}H_3\,X^- \quad (85)$$

Amidinium salts can also serve as starting materials for transamination reactions, *e.g.* Scheme 17.[7,14,314] The condensation of orthoamides with amidinium salts containing α-CH$_2$ groups affords α,β-unsaturated amidinium salts, *e.g.* (**144**; equation 86).[315]

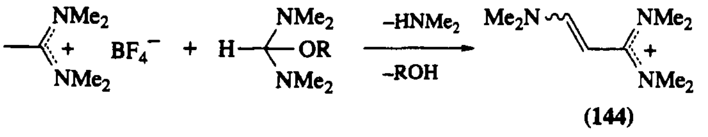
2.7.2.5.4 From imidoyl compounds

Imidoyl halides react with NH- and NH$_2$-containing compounds to give amidinium salts,[1–3] which were sometimes isolated,[14,316] but the free amidine bases were usually prepared from them. Since amidines are converted by water-free acids to the corresponding amidinium salts, amidinium salts with nearly every desired anion are accessible by this procedure. The alkylation of *N*,*N*,*N*′-trisubstituted amidines,[317] as well as those of symmetrically *N*,*N*′-disubstituted, *N*-monosubstituted and *N*-unsubstituted amidines are unambigous reactions. By this method a lot of amidinium salts, *e.g.* (**145**), (**146**) and (**147**) (equation 87), have been prepared. The alkylation of *N*-monosubstituted and *N*,*N*′-unsymmetrically substituted amidines can give rise to product mixtures of amidinium salts.[14]

1,1,2-Trimethyl-4-phenylbenzamidrazone reacts with methyl iodide uniformly to give (**148**; Scheme 18), whereas 1,1,4-trisubstituted amidrazones (**149**) yielded product mixtures by attack of the alkylating



Scheme 17



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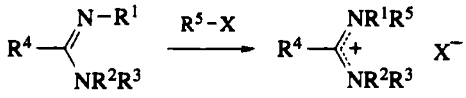
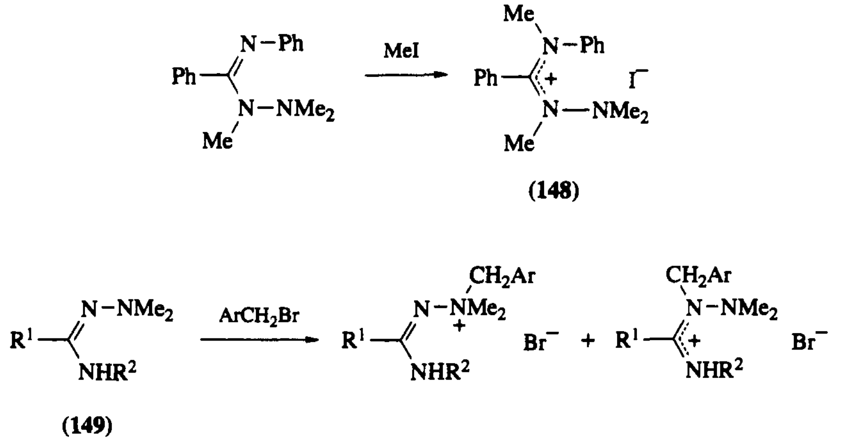


(87)

(145) $R^1 = R^2 = R^3 = H$
(146) $R^1 = R^2 =$ alkyl, aryl, $R^3 = H$
(147) $R^1, R^2, R^3 =$ alkyl

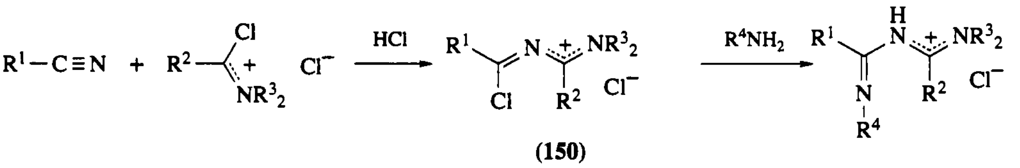
reagent on both nitrogens of the hydrazino group.[318] By alkylation of 2-acylimidazoles[319] or acylation of 1-methylimidazole[320] as well as by methylation of imidazolines[321] imidazolium salts are accessible.



Scheme 18

2.7.2.5.5 From nitriles or nitrilium salts

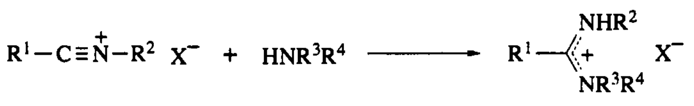
Simple ammonium salts, as well as those derived from primary and secondary amines add to nitriles on heating. The yields can often be increased by application of pressure. By this method *N*-monosubstituted and *N*,*N*-disubstituted amidinium salts can be prepared.[14,20] The action of chloromethyleneiminium salts on nitriles gives rise to formation of 3-chloro-2-azapropenium salts (**150**; equation 88), the reaction has to be catalyzed by HCl in the case of aromatic nitriles. The salts (**150**) can be transformed to other amidinium salts by treatment with various nucleophiles (*e.g.* H_2O, H_2S, $ArNH_2$). Recently a review covering these reactions has appeared.[322]



(150)

(88)

Nitrilium salts add amines and amine derivatives readily to give amidinium salts (**151**; equation 89). Alkaline work-up procedures often give the free amidines rather than the amidinium salts as the products. In these studies primary and secondary amines[7,14,323-325] and amino acids[14] have been used.

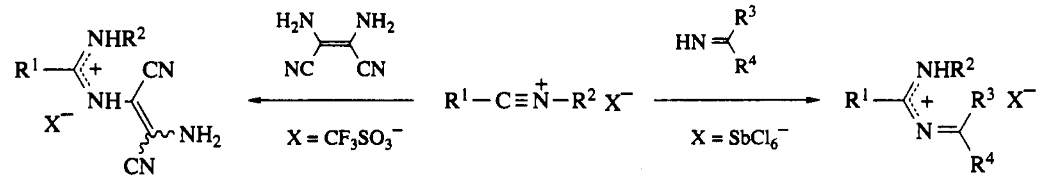


$X = BF_4, FeCl_4, SbCl_6, CF_3SO_3$

(151)

(89)

1,2-Diaminomaleic acid dinitrile[326] as well as imines[327] were added to give the amidinium salts (**152**) and (**153**; Scheme 19), respectively. The amidinium salts (**152**) are useful for the synthesis of imidazoles.



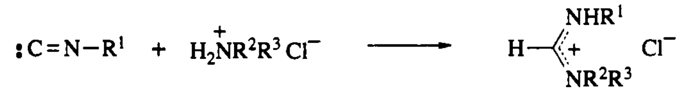
(152) $R^1 = R^2 = Me$

(153) $R^2 = Pr^i, R^3 = Bu^t$

Scheme 19

2.7.2.5.6 *From isonitriles*

Amine hydrochlorides as well as hydroxylamine hydrochlorides add to isonitriles to produce formamidinium salts (**154**; equation 90).[14]

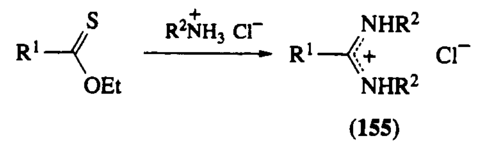


(154) $R^2 = H, R^3 = Ar; R^2 = alkyl, R^3 = OH$

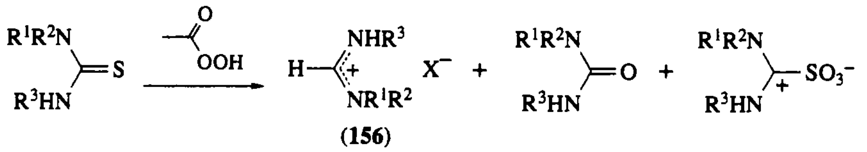
(90)

2.7.2.5.7 *From thioamides, thioxo esters, thioureas, amides and various reagents*

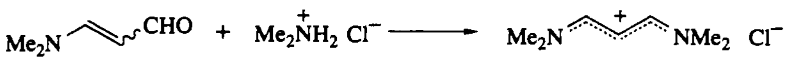
The reaction of amine hydrochlorides with thioxoesters affords amidinium salts (**155**; equation 91).[14] Formamidinium salts (**156**; equation 92) with bulky substituents at the nitrogens can be obtained by oxidation of *N*,*N*,*N*′-trisubstituted or *N*,*N*′-disubstituted thioureas with peracetic acid.[7,14] Byproducts in this reaction can be ureas and thiourea trioxides. β-Dimethylaminoacrolein reacts with dimethylamine hydrochloride to give (**157**; equation 93), the parent compound of the vinylogous amidinium salt series.[328,329] From *N*,*N*-dimethylthiobenzamide and *N*-sulfinyldimethylammonium tetrafluoroborate the benzamidinium salt (**158**; equation 94) was prepared.[301]


(155)

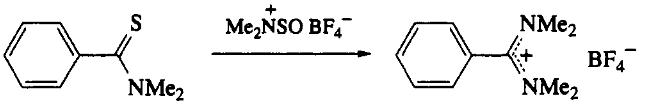
(91)


(156)

(92)


(157)

(93)

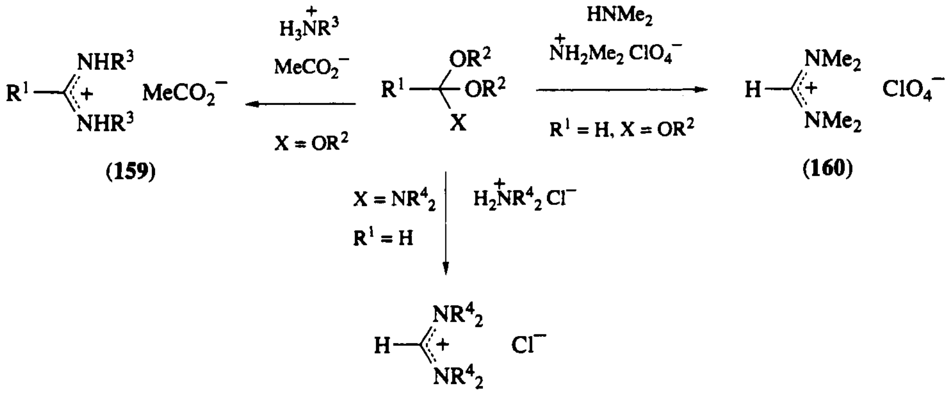

(158)

(94)

2.7.2.5.8 From orthoesters, orthoamide derivatives and related compounds

N,N′-Disubstituted amidinium salts (**159**; Scheme 20) and *N,N,N*′,*N*′-tetramethylformamidinium perchlorate (**160**) have been prepared by action of orthoesters on the appropriate ammonium salts.[7,14] Formamidinium salts (**161**) can be synthesized in a similar fashion from amide acetals and salts of secondary amines.[7,330] Generally the amidine salt formation by treatment of aminal esters or tris(dialkylamino)alkanes with hydrogen halides is of little synthetic interest since *N,N,N*′,*N*′-tetraalkylcarbonamidinium salts thus formed are usually the starting compounds for the synthesis of the corresponding orthoamide derivatives.[7,14] Only in cases where the orthoamides are readily available by other methods is this route acceptable; examples are the synthesis of *N,N*′-dialkyl-*N,N*′-diarylformamidinium salts (**162**; equation 95) or *N,N*′-diacylamidinium salts (**163**). Instead of hydrogen halides or mineral acids, acid halides or Lewis acids can be used for such purposes. From tris(dialkylamino)methanes and CS_2 formamidinium *N,N*-dialkyldithiocarbaminates were obtained;[7,330] in a similar reaction an amidinium salt has been prepared from tris(dimethylamino)methane and iron pentacarbonyl.[331]

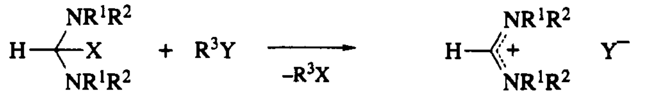
Ketene aminals can be transformed by various electrophilic reagents to amidinium salts, thus mineral acids, alkyl halides, *N,N*-dialkyliminium salts, alkoxymethyleneiminium salts, formamidinium salts,[14] acyl halides,[14] diazonium salts, vinylogous amidinium salts,[332,333] sulfonyl halides, ketene dichlorides[334]


(159)

(160)

(161)

Scheme 20

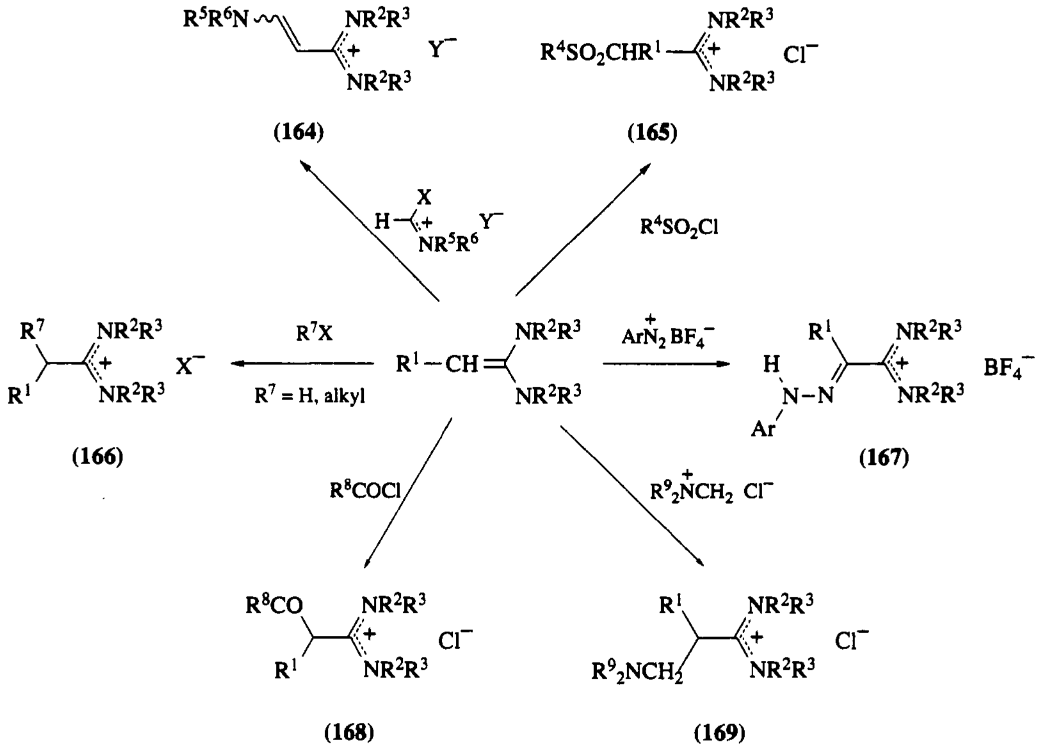


(95)

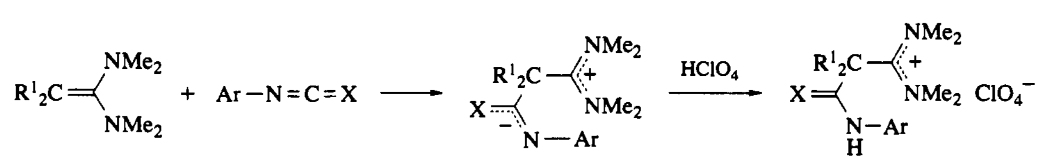
$X = OR, NR^1R^2$; $R^3 = H$, $Y = hal, HSO_4$;
$R^3 = RCO$, $Y = hal$

(162) R^1 = alkyl, R^2 = aryl
(163) $R^1 = H$, $R^2 = COR, CO_2R$

and dithiolium salts[335] have been reacted with ketene aminals to give amidinium salts, *e.g.* (**164**)–(**169**) (Scheme 21). Heterocumulenes react with ketene aminals to form dipoles, which, with strong acids, yield amidinium salts, *e.g.* (**170**; equation 96).[14]



Scheme 21

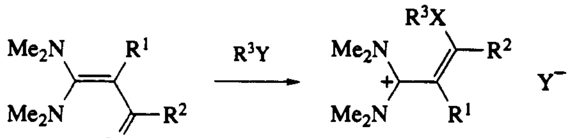


(96)

(170)

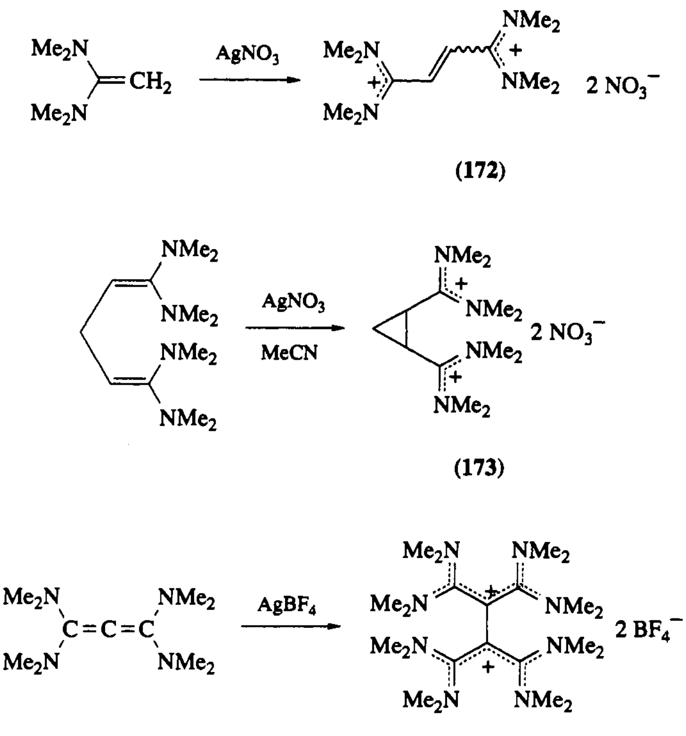
β-Ketoketene aminals[333,336] as well as β-(methylmercaptothiocarbonyl) ketene aminals[335] can be alkylated at the oxygen or sulfur, respectively, to afford the corresponding amidinium salts (**171**; equation 97). Ketene aminals, being electron rich compounds, are easily oxidized to yield amidinium salts. In the course of such investigations interesting results were obtained, for example dimerizations or cyclizations can occur[7,14,337–339] as well as formation of simple amidinium salts. By oxidation amidinium salts can be synthesized which are accessible only with difficulty by other methods, *e.g.* (**172**), (**173**) and (**174**) (Scheme 22).

The oxidation of triaminoethylenes (*e.g.* with Br_2) and tetraaminoethylenes (with N_2O_4, Cu^+, Ag^+, Br_2, CCl_4, C_2Cl_6) occurs with extreme ease to give bisamidinium salts, *e.g.* (**175**; equation 98) and (**176**; equation 99).[7,14] Even on reaction with malonodinitrile the oxamidinium system (**175**) is formed.



(171) X = O, S

(97)

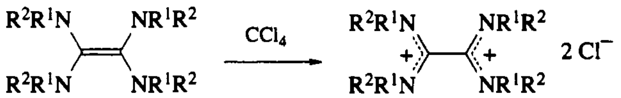


(172)

(173)

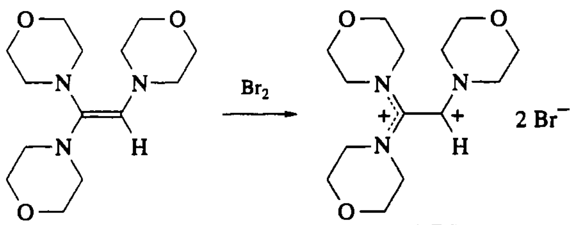
(174)

Scheme 22



(175)

(98)

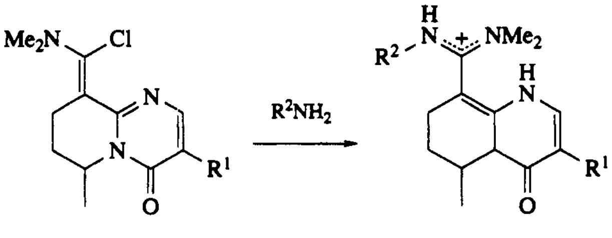


(176)

(99)

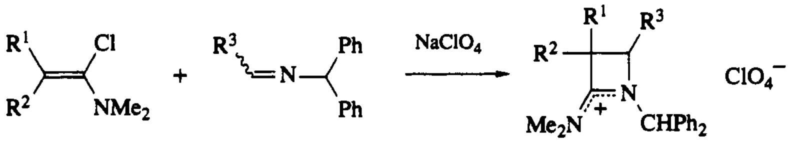
The reaction of α-chloroenamines with primary or secondary amines affords amidinium salts, *e.g.* (**177**; equation 100).[340] In most cases not the amidinium salts but their deprotonation products (ketene animals or amidines) have been isolated; these reactions have been reviewed.[341] Imino compounds undergo cycloadditions with α-haloenamines in which α-azetidylideneammonium salts (**178**; equation 101) are formed.[341-343] Ynamines are converted to amidinium salts, *e.g.* (**179**), (**180**) and (**181**) (Scheme

23), by halogenation, alkylation and *via* cycloaddition with methyleneiminium salts. These reactions have been thoroughly reviewed.[344]



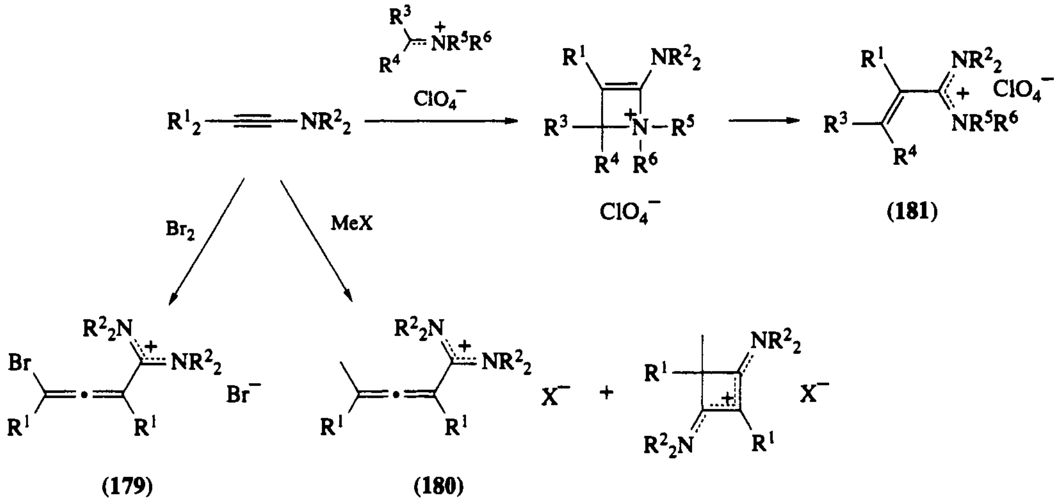
(177)

(100)



(178)

(101)



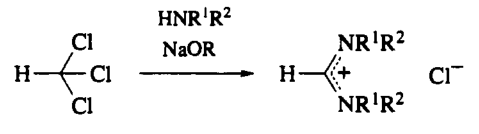
(181)

(179) (180)

Scheme 23

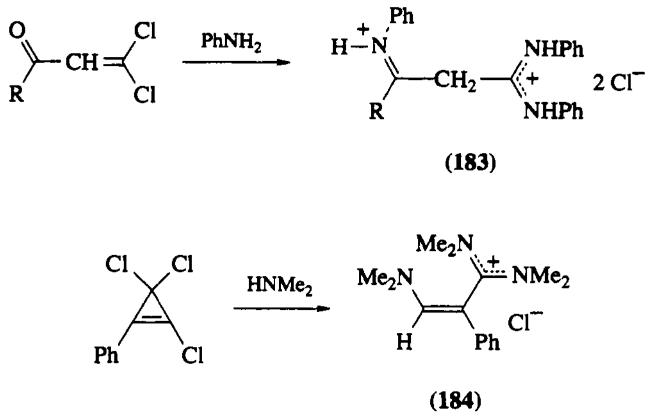
2.7.2.5.9 From halogen compounds

By action of excess secondary amine on chloroform in the presence of sodium alkoxide some formamidinium salts (**182**; equation 102) have been prepared.[14] The aminolysis of β,β-dichlorovinyl ketones or trihalocyclopropenes gives rise to the amidinium salts (**183**) and (**184**) (Scheme 24), respectively.[14]



(102)

(**182**) R^1–R^2 = $(CH_2)_n$, n = 4, 5; R^1 = R^2 = Et



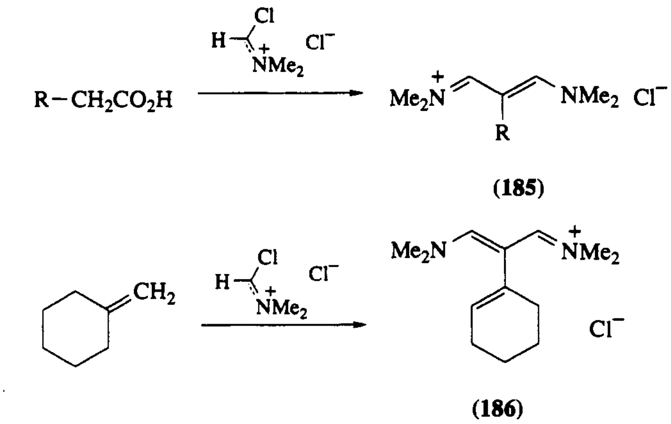
(183)

(184)

Scheme 24

2.7.2.5.10 Vinylogous and azavinylogous amidinium salts

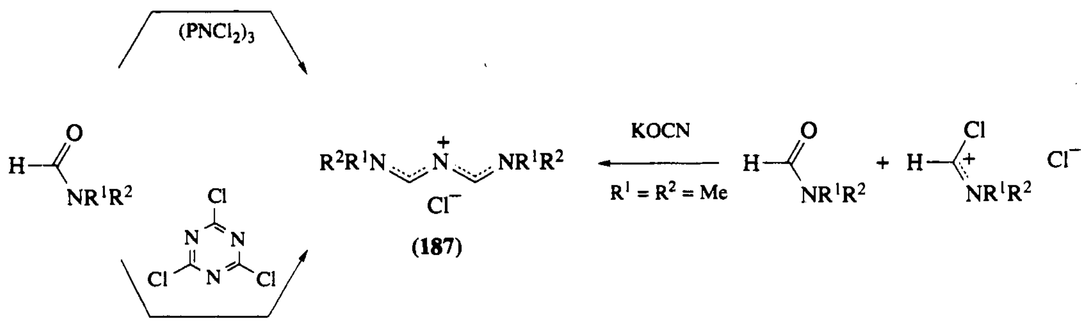
Many vinylogous amidinium salts, *e.g.* (**185**) and (**186**) (Scheme 25), are readily available by double formylation of CH_2-acidic or alkenic compounds.[4] Reviews on the chemistry of vinylogous amidinium salts are available.[345] The first azavinylogous formamidinium salt (**187**; Scheme 26) was prepared in 1960 by reaction of DMF with cyanuric chloride.[14] The mechanism of this reaction has been established.[125,346] Based on these findings new methods for the synthesis of these compounds were developed, *e.g.* the reaction of isocyanatomethyleneiminium salts with tertiary formamides affords salts (**187**).[125,346] In the synthesis of the salts (**187**) cyanuric chloride can be replaced by phosphorus nitride chloride $(PNCl_2)_3$.[314]



(185)

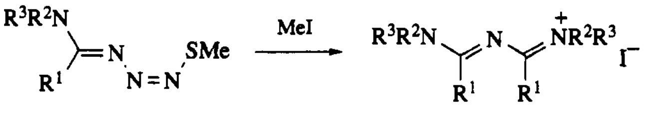
(186)

Scheme 25



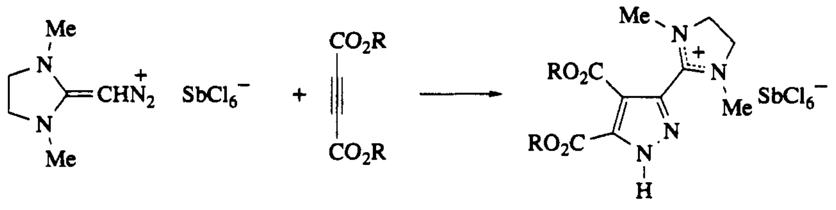
(187)

Scheme 26



(188)

(103)



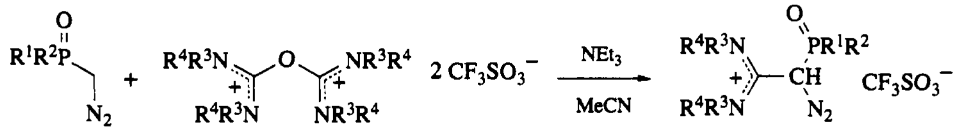
(189) **(190)**

(104)

2.7.2.5.11 Miscellaneous methods

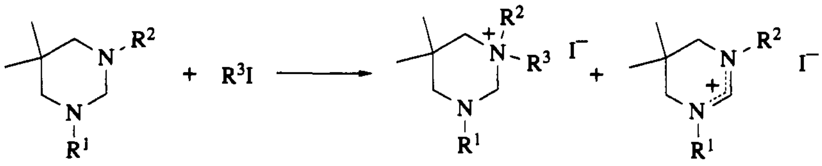
Azavinylogous amidinium salts (**188**; equation 103) were obtained by treatment of triazenes with methyl iodide.[347] Acetylenedicarboxylic acid ester reacts with the diazonium salt (**189**; equation 104) *via* cycloaddition to give the imidazolium salt (**190**).[348]

In diazophosphoryl compounds (**191**) electrophilic substitution occurs on treatment with bis(formamidinium) ether salts (**192**) to afford the diazoamidinium salts (**193**; equation 105).[349] In the alkylation of 1,3-dialkyl-5,5-dimethylhexahydropyrimidines with alkyl iodides mixtures of ammonium salts and iminium compounds (**194**; equation 106) result, which can be the sole products if R^1, R^2 and R^3 are bulky groups.[350]



(191) **(192)** **(193)**

(105)



(194)

(106)

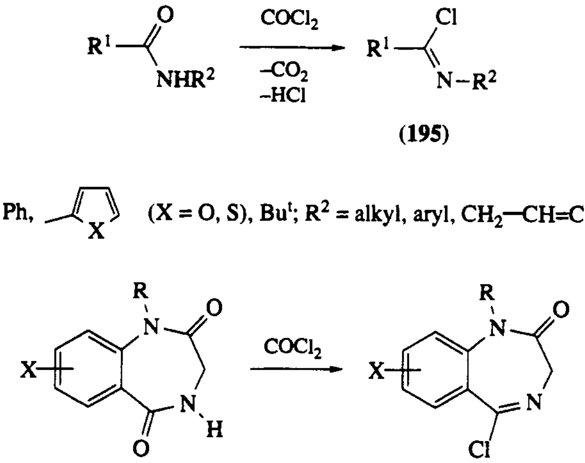
2.7.3 IMIDOYL COMPOUNDS

2.7.3.1 Imidoyl Halides

2.7.3.1.1 From amides, thioamides and halogenating reagents

(i) Phosgene, diphosgene, carbonyl difluoride, oxalyl dichloride

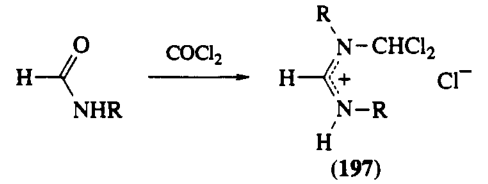
Phosgene is a suitable reagent for converting secondary amides[1-3,351,352] and *N*-unsubstituted lactams[353] to imide chlorides, *e.g.* (**195**) and (**196**) (Scheme 27). The substituents at nitrogen might be saturated aliphatic or aromatic groups, but even unsaturated groups seem to be possible.[352] The reaction, which can be catalyzed with pyridine,[351] has been performed with aliphatic,[1–3,351] aromatic[1–3,352] and heterocyclic[352] amides. Phosgene can be replaced by the easier to handle 'diphosgene' (chloroformic acid trichloromethyl ester)[354] or triphosgene [bis(trichloromethyl)carbonate]. These methods have the advantage that only gaseous byproducts are formed, which facilitates product isolation. *N*-Monoalkylated formamides react with phosgene *via* the imidoyl chloride to *N*-dichloromethylformamidinium chlorides (**197**; equation 107).[1,3,9] Carbonyl difluoride is not suited to such reactions,[1–3,9] *e.g.* *N*-methylformamide is attacked at nitrogen and not at oxygen. Oxalyl chloride, is not very effective either for the preparation of imidoyl chlorides,[355] at elevated temperatures it reacts at the amide nitrogen.[5,356]



(195)

(196)

Scheme 27



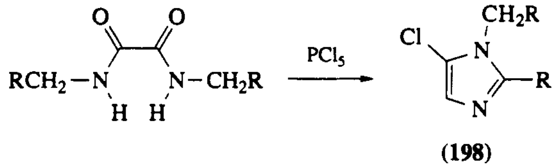
(197)

(107)

(ii) Phosphorus pentahalides, phosphorus trihalides, triarylphosphorane dihalides, tetraarylphosphorane halides, triphenylphosphine/carbon tetrahalides

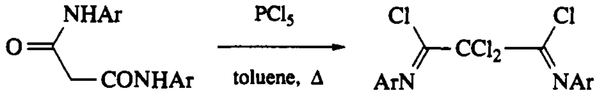
Wallach[1,3,7,9] in 1874 introduced PCl_5 as a reagent for the preparation of amide and imide chlorides from amides. Since that time this procedure has been developed to a standard procedure and several reviews deal with this topic.[1–3,357] Amides of aliphatic,[355,358–362] aromatic[355,363–367] and heterocyclic[368,369] acids bearing aliphatic,[358,362,364,365,368] aromatic[359,360,369] or heterocyclic[361,363,367] substituents or acyl groups[366] at nitrogen, as well as lactams[370,371] and dibenzamidoalkenes[372] have been transformed by this method to the corresponding imidoyl chlorides. *N*,*N*′-Dialkyloxamides react with PCl_5 *via* unstable imidoyl chlorides to give 4-chloroimidazoles (**198**; equation 108),[1,3] whereas imide chlorides of *N*,*N*′-diaryl oxamides can be prepared in the pure state.[3] *N*,*N*′-diarylmalondiamides react with PCl_5 to give the α,α-dichlorinated bisimide chlorides (**199**; equation 109).[373,374]

In general in the preparation of imide chlorides excess PCl_5 should not be used if α-chlorination is undesired. In contrast to triple bonds, double bonds conjugated with the amide carbonyl group do not add the HCl set free in the course of imidoyl chloride formation.[1] In the case of α,α,α-trihalogenated amides



(198)

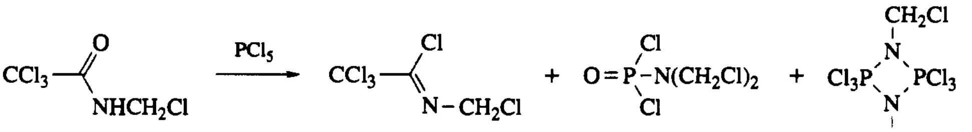
(108)



(109)

(199)

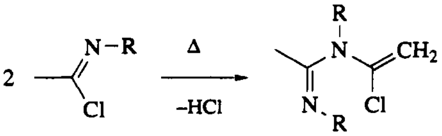
side reactions are known, which arise from the attack of the PCl_5 molecule at the amide nitrogen, *e.g.* formation of compounds (**200**) and (**201**) (equation 110).[1,3,355]



(110)

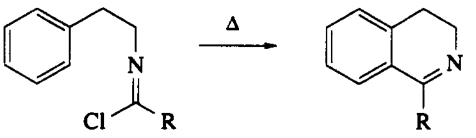
(200) **(201)**

If α-CH bonds are present in the imide chloride molecule selfcondensation can occur at elevated temperatures to yield compounds (**202**; equation 111),[355] a fact which should be kept in mind when choosing the reaction conditions. Starting with *N*-arylethylcarbonamides the imidoyl chlorides can cyclize to give heterocyclic compounds[376–378] (Bischler–Napieralksi reaction[375]), *e.g.* (**203**; equation 112). For such cyclizations $POCl_3$ has also been used as the condensing agent.[379–382] Treatment of ketoximes with PCl_5 affords imidoyl chlorides (**204**; equation 113), which readily cyclize to yield isoquinoline derivatives.[382–384]



(111)

(202)



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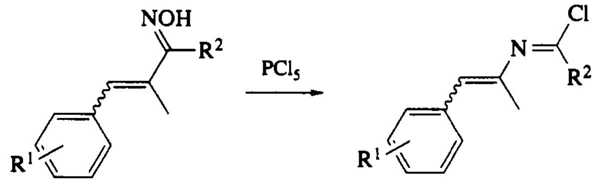
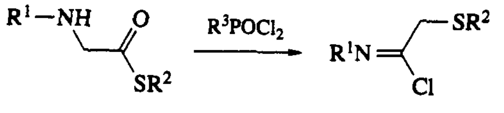
(203)



(113)

(204)

Other phosphorus compounds, *e.g.* PBr_5,[1,3] mixtures of PBr_3 and Br_2[3] or PCl_3/Cl_2[3] and phenyltetrachlorophosphorane ($PhPCl_4$)[3] have been used to convert amides to imidoyl halides. The formation of imidoyl halides proceeds under mild conditions by action of triphenylphosphine/CCl_4 or triphenylphosphine dihalides on secondary amides[385,386] or ketoximes.[387] The work-up procedure can be facilitated by use of polymer-supported triphenylphosphine/CCl_4.[99] By the action of $POCl_3$, phenyl- or methyl-phosphonic acid dichloride on aminocarboxylic acid thiol esters in the presence of triethylamine the imidoyl chlorides (**205**; equation 114) are formed in moderate to good yields.[388] The mechanism of this reaction has not been established. The methylene dialkylchlorophosphorane (**206**; equation 115) allows the conversion of secondary aromatic amides to imidoyl chlorides under very mild conditions.[389]



(114)

(205)

$R^1 = Bu^n, R^2 = Bu^i$

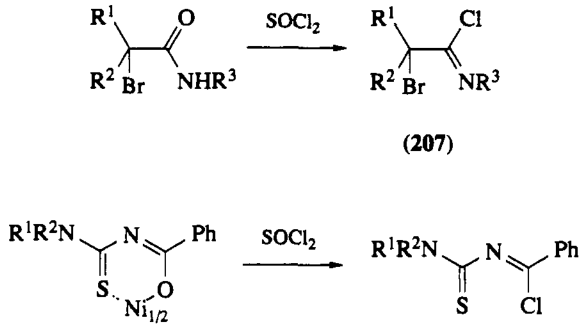
$R^3 = Cl$, 50%; $R^3 = Me$, 90%; $R^3 = Ph$, 96%

(115)

(206)

(iii) Thionyl halides, nitrosyl chloride

Thionyl chloride is a versatile reagent for transforming secondary amides[9,357,390,391] and lactams [392] to imidoyl chlorides, *e.g.* (**207**; Scheme 28) because only gaseous byproducts are formed. Thionyl chloride can be used in excess. Even from the Ni complexes of *N*-benzoylthioureas and $SOCl_2$ imide chlorides (**208**) could be prepared.[393]

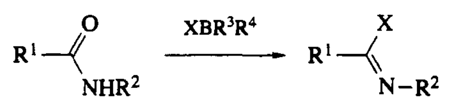


(**207**)

(**208**)

Scheme 28

The action of nitrosyl chloride on thioamides affords imidoyl chlorides with moderate yields.[3] α-Halogenated secondary amides react with boron trihalides or alkylhaloboranes to give imidoyl halides (**209**; equation 116) in low to moderate yields.[394]



(116)

(**209**)

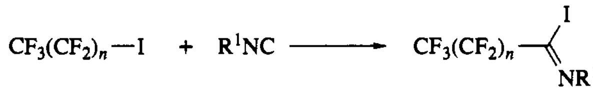
$R^1 = CF_3, CHCl_2, CCl_3$; $X = Cl, Br$; $R^3, R^4 = Ph, Me, Cl, Br$

2.7.3.1.2 From isonitriles, nitriles and ketene imines

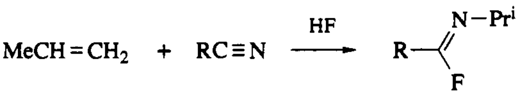
Isonitriles add carboxylic acid chlorides to yield α-oxoimidoyl chlorides (**210**; equation 117).[1,3,5,395,396] With copper catalysis, from perfluorinated alkyl iodides and isonitriles imidoyl iodides (**211**; equation 118) can be obtained.[397,398] Alkenes react with nitriles in the presence of HF[399] or Cl_2[400,401] to afford the corresponding imidoyl derivatives (**212**; equation 119). By addition of chlorine[3] or arenesulfenyl chlorides[402–404] to ketene imines the α-substituted imidoyl chlorides (**213**) and (**214**) can be prepared (Scheme 29).


(117)

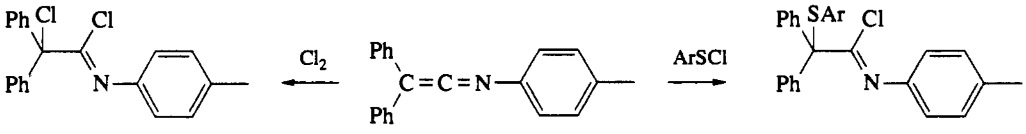
(210)


(118)

R^1 = alkyl, aryl **(211)**


(119)

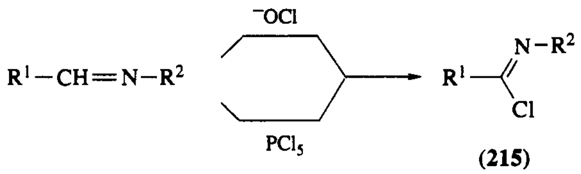
(212) R = H, alkyl


(213) **(214)**

Scheme 29

2.7.3.1.3 From imines by oxidation

High temperature chlorination of imines makes a few special (perhalogenated) imidoyl chlorides accessible.[357] From the preparative point of view the oxidation of aldimines with *t*-butyl hypochlorite or alkali metal hypochlorite[1,405] is more convenient and of broader scope for the synthesis of imidoyl chlorides (**215**; Scheme 30). Aldimines are converted to imidoyl chlorides (**215**) by heating with PCl_5 in xylene.[406]


(215)

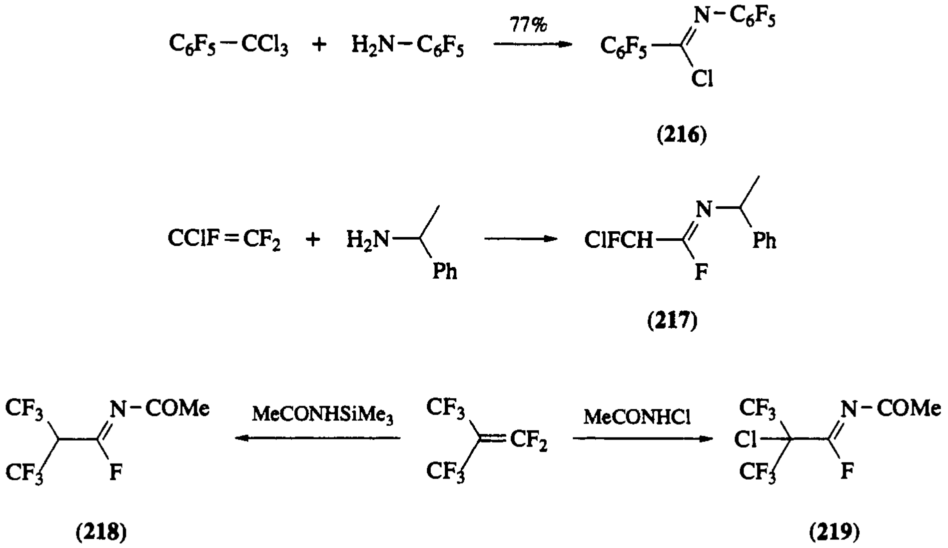
Scheme 30

2.7.3.1.4 From amines and haloalkanes or haloalkenes

At temperatures of about 500 °C pentafluorophenyltrichloromethane reacts with perfluorinated aromatic or heterocyclic amines to give imidoyl chlorides (yields 23–77%), *e.g.* (**216**; Scheme 31).[407] Chlorotrifluoroethylene reacts with 1-phenylethylamine to give the imidoyl chloride (**217**) in high yields.[408] The action of perfluoroisobutene on trimethylsilylacetamide or *N*-chloroacetamide gives rise to formation of the *N*-acetylimidoyl fluorides (**218**) and (**219**).[409]

2.7.3.1.5 From imidoyl halides

Imidoyl chlorides are transformed to the fluorides (**220**; equation 120) by reaction with CsF (at elevated temperatures)[386] or with KF and crown ethers.[410] On heating with triethylamine the *N*-benzyltrifluo-



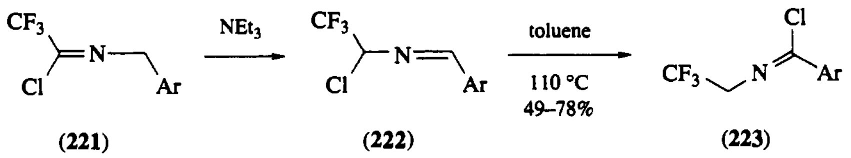
Scheme 31

roacetimidoyl chlorides (**221**; equation 121) isomerize *via* the isolable imines (**222**) to yield the *N*-trifluoroethylbenzimidoyl chlorides (**223**).[411,412]

$$R^1-C(=N-R^2)Cl \xrightarrow{MF} R^1-C(=N-R^2)F \qquad (120)$$

(220)

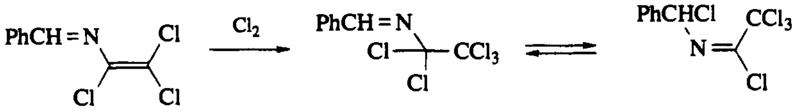
R^1 = Me, CCl_3, Ph; R^2 = C_6H_{11}, Me, CH_2Cl



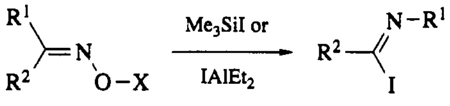
(121)

2.7.3.1.6 Miscellaneous methods

Chlorine adds to *N*-trichlorovinylbenzaldehydeimine to give the *N*-benzylideneamide chloride (**224**) which is in equilibrium with the imidoyl chloride (**225**; equation 122).[413] The action of trimethylsilyl iodide or diethylaluminum iodide on *O*-acylketoximes affords imidoyl iodides (**226**; equation 123) with excellent yields.[414]



(122)



(123)

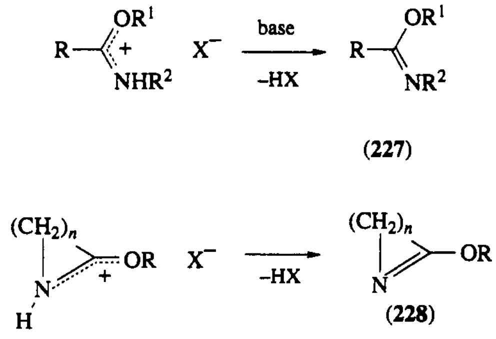
(226)

X = SO_2Me, CO_2Et, COMe, COPh; $R^1 = R^2$ = Me, Et; R^1–R^2 = $(CH_2)_n$, n = 5, 11; R^1 = Ph, R^2 = Me

2.7.3.2 Imidates (Imidic Acid Esters, Imido Esters, Imidoates)

2.7.3.2.1 From alkoxymethyleneiminium salts or nitrilium salts

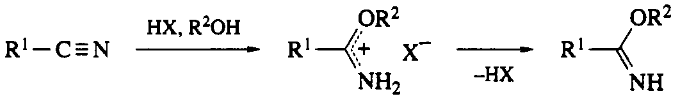
N-Unsubstituted and *N*-monosubstituted alkoxymethyleneiminium salts are readily deprotonated by bases like tertiary amines, carbonates, alkoxides *etc.* to give the corresponding imidates (**227**; Scheme 32). By the same procedure cyclic imidates (lactim esters) (**228**) can be prepared. The iminium salts needed are readily available (see Section 2.7.2.3); often they were synthesized and transformed to the imidates without further purification. The Pinner synthesis, which produces the *N*-unsubstituted salts, is widely applicable and has been reviewed several times[7,15–17,22] (for some more recent examples see Section 2.7.2.3.7). To demonstrate the range of the reaction, a selection of nitriles, which have been transformed *via* Pinner synthesis to the corresponding imidates (**229**; equation 124) is compiled in Table 4.



(227)

(228)

Scheme 32



(124)

(229)

Not only the Pinner synthesis provides alkoxymethyleneiminium salts; the action of chloroformic acid esters on primary or secondary amides or thioamides[7,10,16] as well as on lactams[424] is a versatile method to get these salts and from them the imino esters, *e.g.* (**230**; equation 125). Primary and secondary amides have been alkylated by several reagents and the iminium salts thus formed were converted to imino esters with the aid of bases. A collection of imino esters prepared by this method can be found in a review;[10] the more recent results listed in Table 5 demonstrate the scope of this procedure.

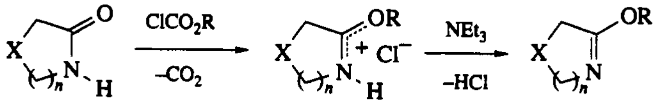
The addition of alcohols to nitrilium salts gives rise to formation of alkoxymethyleneiminium salts, which react with bases to yield imido esters (**231**; Scheme 33).[241,242] By deprotonation of carboxylic acid amides ambident anions are formed, which can be alkylated in the presence of silver ions to give imido esters, *e.g.* (**232**).[463–466] Secondary amides react with trifluoroacetic acid anhydride or trifluorosulfonic acid anhydride to give mixed anhydrides of imidic acids (**233**).[467]

Table 4 Nitriles which are Suited for Pinner Synthesis

Nitrile	*Ref.*	*Nitrile*	*Ref.*
Cyanocytidine	415	5-Cyano-3-pyridinecarbonic acid ester	419
o-Azidobenzonitrile	416		
2,6-Dimethoxybenzoyl cyanide	417	3-Chloro-4-pyridinecarbonitrile	420
3,5-Di(*t*-butyl)-4-hydroxybenzonitrile	418	5-(3,3-Dimethyl-1-triazeno)imidazole-4-carbonitrile	421
Substituted phenylacetonitriles and 3-phenylpropionitrile	418	Long-chain (C_{11}–C_{18}) nitriles	422
Alkylmercaptoacetonitriles and alkylmercaptopropionitriles	418	Cyanoacetic acid ester	423

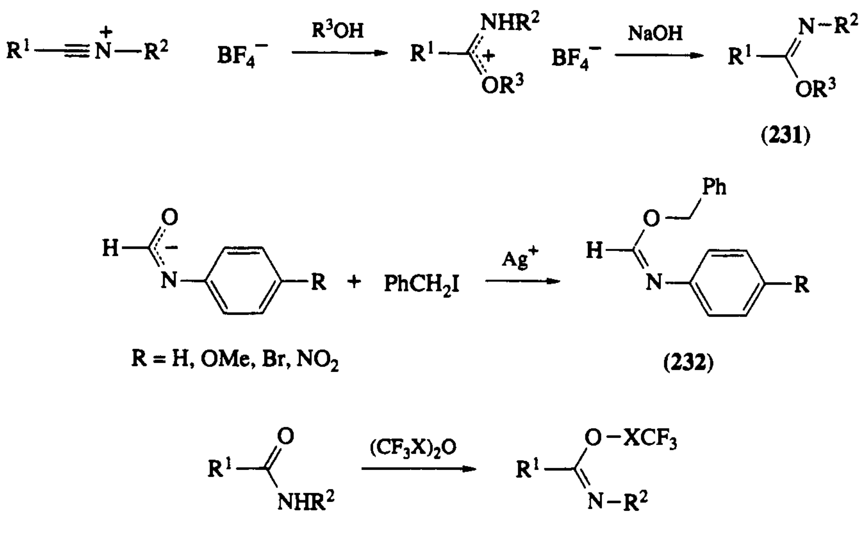
Table 5 Alkylating Reagents and Carboxylic Acid Amides as Starting Materials for Imidates

Alkylating reagent	*Ref.*	*Amides*	*Ref.*
Dimethyl sulfate	425–429	5-Amino-4-imidazolecarbonamides	185
Trimethyloxonium tetrafluoroborate	430–443	(Optically active) acetamides	448, 462
Triethyloxonium tetrafluoroborate	203, 425, 426, 429, 444–461	Propionamides	448
		Benzamide	462
Methyl trifluoromethanesulfonate	215, 462	Dihydroxypyrmidones	429
		Acrylamide	445
		Crotonamide	445
		Cinnamic acid amide	445
		Five-membered lactams	203, 215, 425, 430, 444, 449
		Six-membered lactams	425, 451–453, 462
		Seven-membered lactams	425, 438, 445, 446, 456, 461
		Eight-membered lactams	427, 428, 457, 458
		Nine-membered lactams	439, 440
		13-membered lactams	441, 442
		Bicyclic [2.2.2] lactams	437
		Bicyclic [3.2.1] lactams	426
		2,5-Diketopiperazines (→ monoethers)	454
		1-Aza[14]annulen-2-one	459, 460
		1-Aza[16]annulen-2-one	459, 460
		1-Aza[18]annulen-2-one	459, 460



(125)

(230)



(231)

R = H, OMe, Br, NO_2

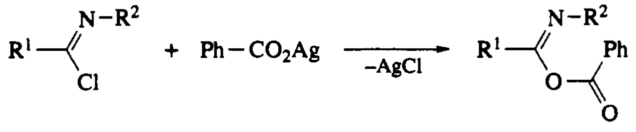
(232)

(233) X = CO, SO_2

Scheme 33

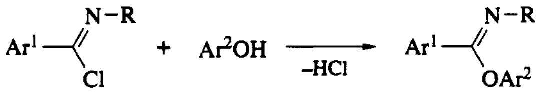
2.7.3.2.2 From imidoyl halides and related compounds

Mixed anhydrides (**234**; equation 126) are formed in the reaction of silver benzoate with imidoyl chlorides.[16] Imidoyl chlorides react with alcohols or phenols in the presence of base (alkoxide, tertiary amine) to give imidates, *e.g.* (**235**; equation 127).[3,364,370,468–474] This method is especially useful for the preparation of arylimidates; the reaction can be performed under phase transfer catalysis.[470] In the Lewis acid catalyzed reaction of polyoxymethylene with the benzimide chloride (**236**; equation 128) the chloromethylbenzimidate (**237**) is formed.[355]



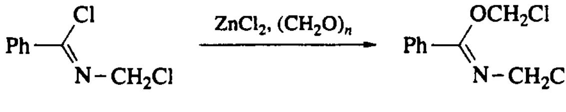
(126)

(234)



(127)

(235)

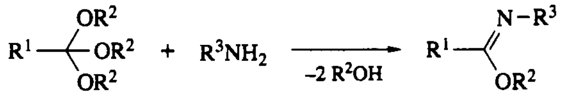


(128)

(236) **(237)**

2.7.3.2.3 *From carboxylic orthoesters, carboxylic orthoamide derivatives and related compounds*

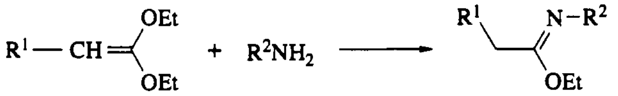
Orthoesters react with primary amines to give imino esters (**238**; equation 129). The condensation proceeds usually at temperatures above 100 °C and can be catalyzed by mineral acids, sulfonic acids, Lewis acids and carboxylic acid anhydrides.



(129)

(**238**)

This reaction was often used to transform primary heterocyclic amines to imino esters. The following selection of more recent examples will demonstrate the range of the method. Orthoesters of formic acid,[16,369,475–489] acetic acid[484,485,489–491] and propionic acid[484] have been reacted with substituted anilines,[475,484,485,488–490] naphthylamines,[16,369,481,485,489] aminouracil,[486] aminoimidazoles,[476,482] aminoquinolines,[369] aminothiophenes,[479] aminopyrans,[480] aminopyrimidines,[369] aminomalonodinitrile,[477,478] aminomalono esters[483,487] and amino acid esters[491] to give imidates. According to this scheme the following compounds can be converted to imino esters: cyanamide, *O*-protected hydroxylamines, hydrazines and hydrazine derivatives, phosphorus amides, sulfonamides *etc.* Such reactions have been reviewed.[7,15,16] Ketene acetals react with primary amines to give imino esters, *e.g.* (**239**; equation 130).[492,493]

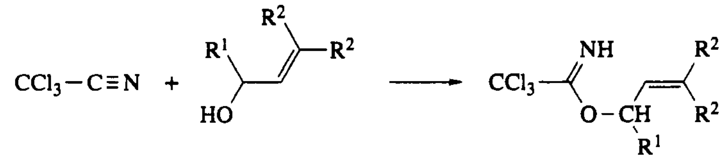


(130)

(**239**)

2.7.3.2.4 *From nitriles and isonitriles*

The base-catalyzed addition of alcohols to nitriles to give imidates proceeds well, if there are electron-attracting groups in the α-position. In such cases the Pinner synthesis is less effective, because nitrile basicity is less. This shows that both methods are complementary.[16] Recently attention has been paid to the long-known addition of alcohols to trichloroacetonitrile,[16] since it was found that imidates prepared from protected saccharides, amino alcohols *etc.* and trichloroacetonitrile are useful reagents for the synthesis of nucleosides,[494] disaccharides and other natural products.[495] The trichloroacetimidic acid esters (**240**; equation 131) of fluorinated,[16] unsaturated aliphatic alcohols[496–500] and benzyl alcohol[500] have been prepared for synthetic purposes.

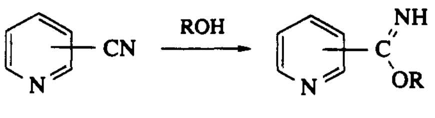


(131)

(**240**)

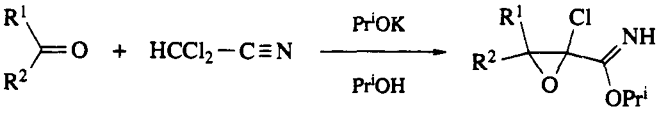
Addition of alcohols to nitriles was preferably used for the synthesis of aromatic or heterocyclic carboxylic acid imide esters, *e.g.* (**241**; equation 132),[501–504] as well as for α-arylamino- or α-arylmercaptocarboxylic acid imide esters[505] and for bicyclobutanimidic acid esters.[506] By condensation of dichloroacetonitrile with ketones in the presence of alkoxide oxiranylimido esters (**242**; equation 133) are accessible.[507] Formimido esters (**243**; equation 134) can be prepared by copper compound catalyzed addition of alcohols to isonitriles.[16,508,509] From alkylaminomethoxycarbene–gold complexes formimino esters have been obtained.[510] Isonitriles react with aldehyde *O,N*-acetals to give α-aminoacetimidates (**244**; Scheme 34).[511] Under diethylaluminum chloride catalysis the addition of α,β-unsaturated ketones to isonitriles is possible, affording imino esters (**245**).[512]

Various acids (nitrobenzoic acids, picric acid, toluenesulfonic and phosphonic acids) have been reacted with isonitriles to give mixed anhydrides (**246**; equation 135).[513,514]



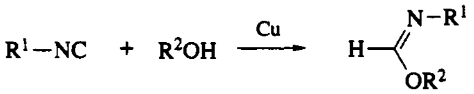
(132)

(241)



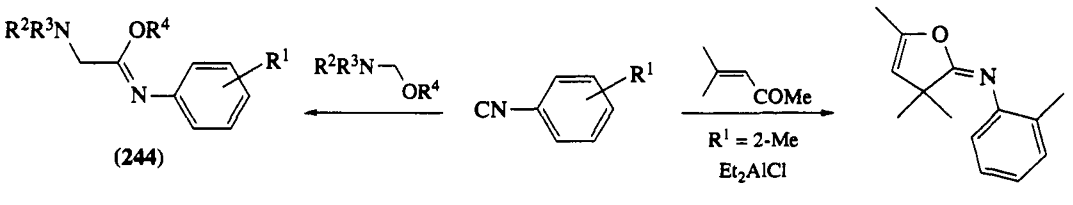
(133)

(242)



(134)

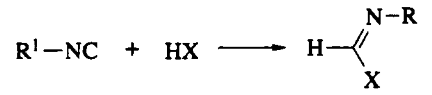
(243) R^2 = alkyl, aryl



(244)

(245)

Scheme 34

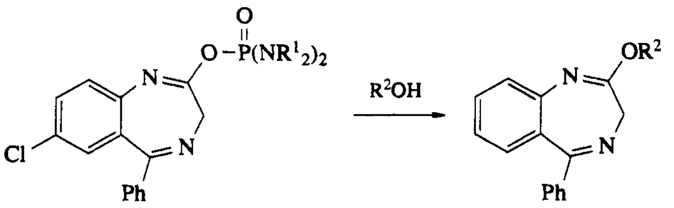


(135)

(246) X = $ArCO_2$, $ArSO_3$, ArO, $ArPO_3H$

2.7.3.2.5 From imidates

Transesterification of imidates is a well-known reaction, which is catalyzed preferably by alkoxides.[16] In *O*-phosphorylated compounds (**247**; equation 136) such an exchange occurs with ease.[515] From imidates and 1,2- and 1,3-amino alcohols 1,3-oxazolines[16,516–518] and 1,3-oxazines,[519] respectively, were synthesized.

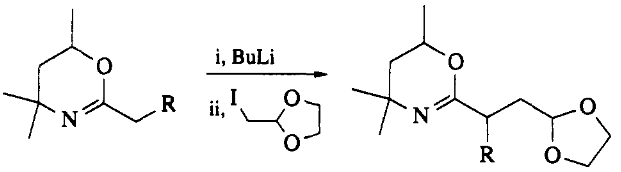


(136)

(247)

2-Alkyloxazolines and 2-alkyloxazines are weakly CH-acidic compounds. The carbanions derived from them have been reacted with a variety of electrophiles to give substituted 'cyclic imidates', *e.g.* (**248**; equation 137). Reviews on such synthetic procedures are available.[520–522]

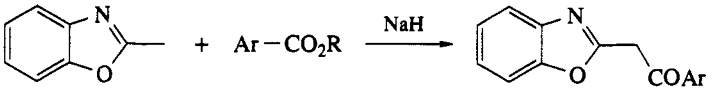
2-Alkylbenzoxazoles were condensed with esters of aromatic acid esters to give 2-phenacylbenzoxazoles (**249**; equation 138).[523] 2-Alkyloxazoles are acylated by electrophiles, *e.g.* anhydrides, catalyzed



(137)

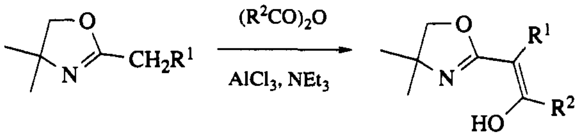
(248)

by Lewis acids,[524] to produce the enols (**250**; equation 139). *N*-Unsubstituted imidates have been transformed to *N*-carboxylated and acylated imidates (**251**)–(**253**) (Scheme 35) by reaction with isocyanates,[525] isothiocyanates,[526] chloroformic acid esters[527] or acid chlorides.[447,528–530] In the course of such reactions cyclizations can occur to give heterocycles, *e.g.* (**254**; Scheme 36);[531] a very useful synthesis for amino acid derivatives, *e.g.* (**255**), is based on the anions derived from 2,5-dialkoxy-3,6-dihydropyrazines. These applications have been reviewed.[532,533] *N*-Unsubstituted imino esters are phosphorylated at nitrogen, to give compounds (**256**; equation 140) by treatment with dialkyl phosphites in the presence of CCl_4/triethylamine.[534]



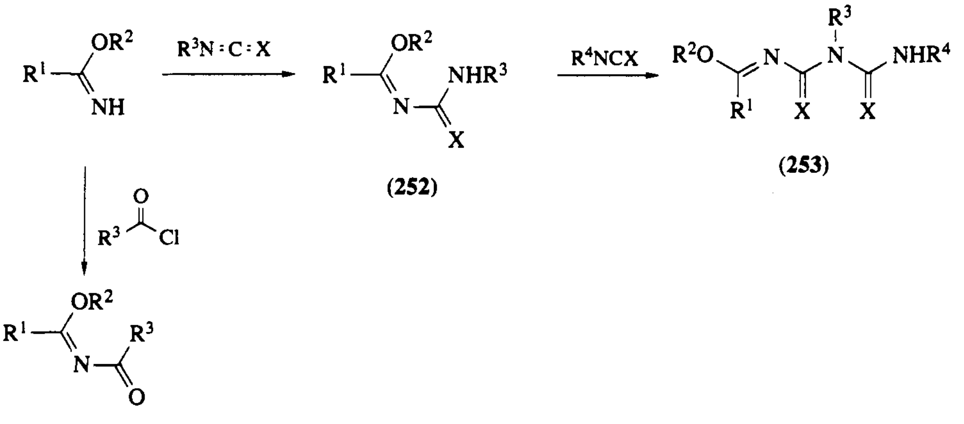
(138)

(249)



(139)

(250)



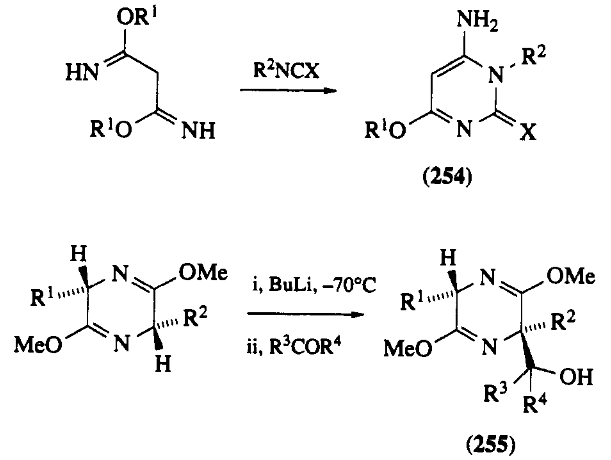
(252) **(253)** **(251)**

Scheme 35

2.7.3.2.6 Miscellaneous methods

Under the influence of bases *N*-acylaminosulfonium salts are rearranged to imino esters (**257**; equation 141).[535,536] Photolysis of aromatic or heterocyclic azides in the presence of alkoxides affords imino esters, *e.g.* (**258**; equation 142).[537–541]

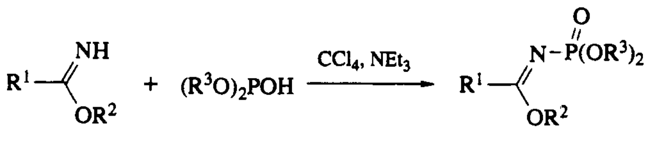
1-Azirines can be transformed to imino esters (**259**) and (**260**) (Scheme 37) by addition of alcohols[542] or 'alkoxy carbenes'[543] respectively. By sodium methoxide catalyzed addition of methanol to the ketene imine (**261**; Scheme 38) the imino ester (**262**) is obtainable.[544] Keteneimines undergo photoinduced addi-



(254)

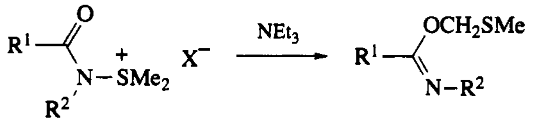
(255)

Scheme 36



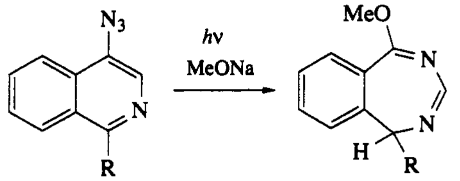
(256)

(140)



(257)

(141)



(258)

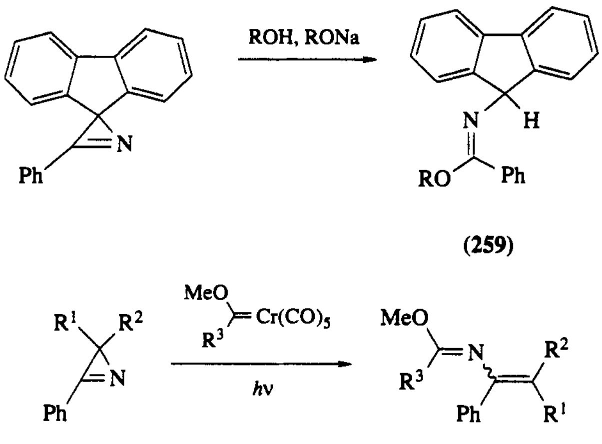
(142)

tion to quinones to yield imidates (**263**).[545] Oxidative dimerization of oxazolines allows the preparation of 2,2′-bisoxazolines (**264**; equation 143).[546] On heating oxime carbonates are transformed to arylimidates (**265**; equation 144); the reaction seems to be related to the Beckmann rearrangement.[547]

2.7.3.3 Thioimidates

2.7.3.3.1 From alkylmercaptomethyleneiminium salts

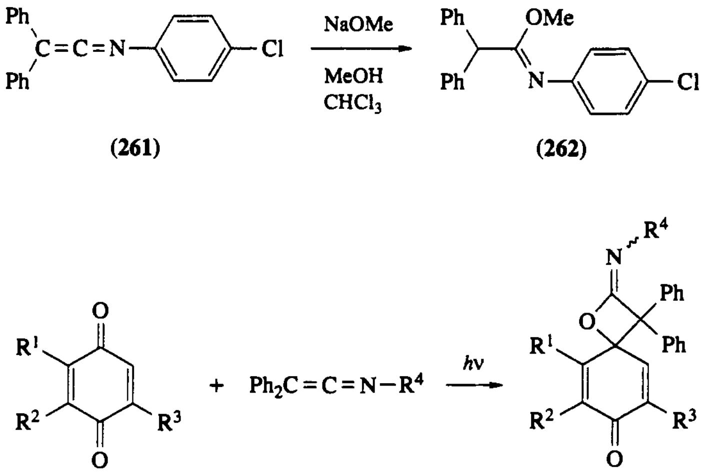
Due to the high nucleophilicity of sulfur it is easy to alkylate primary and secondary thioamides as well as thiolactams, even with reagents of low alkylating ability (compare Section 2.7.2.4.1). Deprotonation of these salts, often without previous isolation or purification, affords thioimidates (**266**; equation 145).[16,548] A selection of compounds accessible by this procedure can be found in ref. 13. Some more recent results are briefly summarized in Table 6.



(259)

(260)

Scheme 37

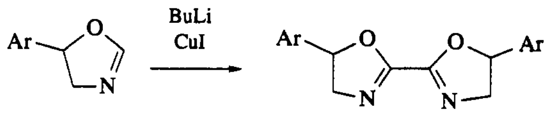


(261)

(262)

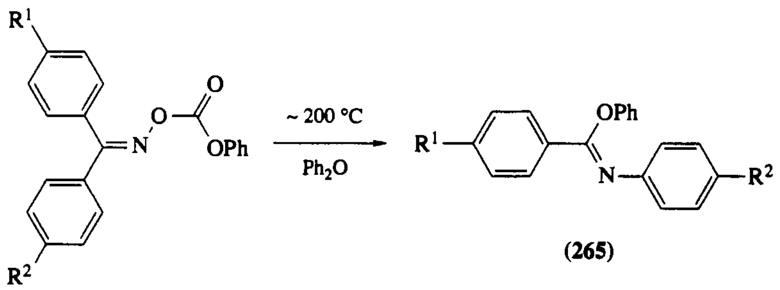
(263)

Scheme 38



(264)

(143)



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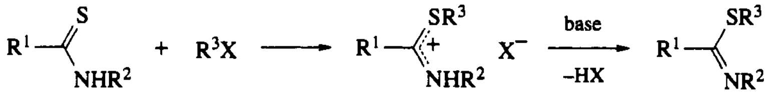
(144)

Alkylmercaptomethyleneiminium salts (**267**; Scheme 39), which are accessible either by addition of thiols to the nitrile function in the presence of hydrogen halides[16] or by reaction of chloroformic acid thioethyl ester with thioamides,[286,576] can also be transformed to the corresponding thioimidates (**268**).

Table 6 Starting Compounds for the Synthesis of Thioimidates by Alkylation of Thioamides

Alkylating reagent	*Ref.*	*Thioamide*	*Ref.*
Alkyl halides	535–563	*N*-Thioformylaminoisobutyric acid ester	553
Benzyl halides	556, 564, 565		
Benzylammonium salts	556	Secondary thioformamides	556, 572
Allyl halides	567	Thioacetamide	564
Dialkyl sulfates	445	*N*-Toluenesulfonyloxymethylthioacetamide	549
α-Halo ketones	554		
α-Halo esters	556, 562, 568–570	Secondary thioacetamides	567, 572
α-Halonitriles	562, 570	4-Substituted thiobenzamides	561, 563, 565
Oxonium salts	571–575	*N*-Phosphorylated thiobenzamides	570
		N-Toluenesulfonyloxymethylenethiobenzamide	549
		N-Benzoylthiobenzamide	559
		N,*N'*-Bis(thiobenzoyl)alkylenediamines	550
		Five-membered thiolactams	540, 560, 568, 569, 571
		Six-membered thiolactams	552, 560
		Seven-membered thiolactams	445, 552, 573
		Eight-membered thiolactams	557
		Imidazolethiocarbonamides	551, 555
		2-Thiono-1-azapenam derivatives	562
		Thioamide *S*-oxides (alkylation at oxygen)	574, 575



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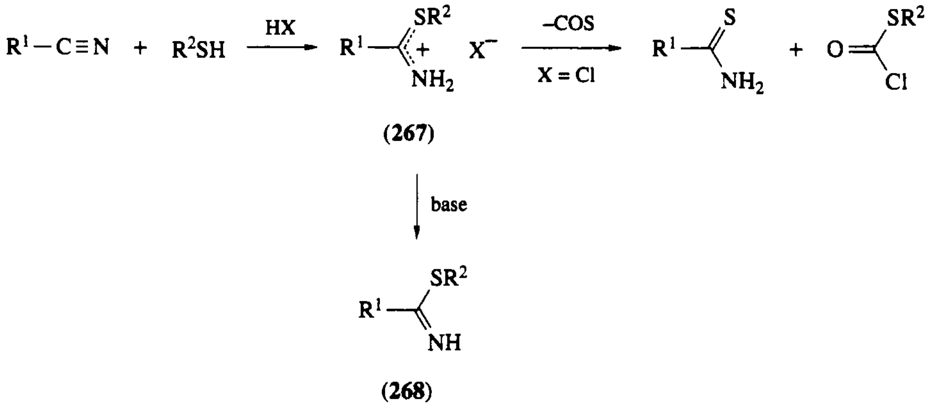
(145)



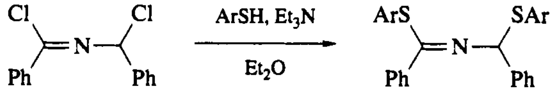
(267)

(268)

Scheme 39

2.7.3.3.2 *From imidoyl halides*

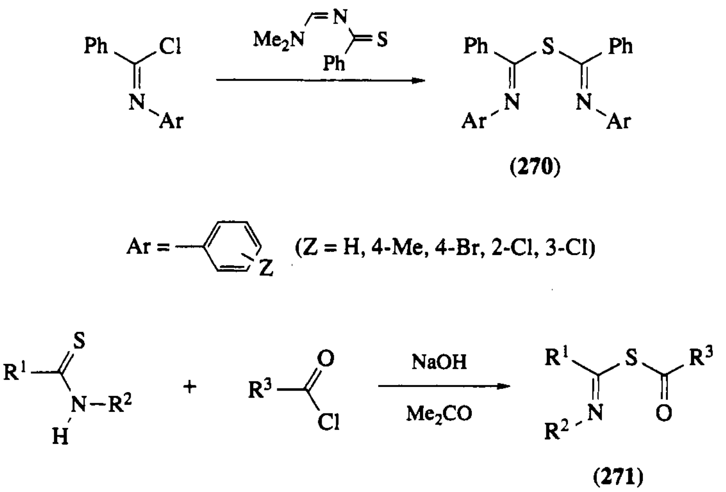
Although long known, the reaction of imidoyl halides with thiolates to give thioimidates is of less importance.[1,470,577] In special cases, such as the synthesis of multifunctional thioimidates, *e.g.* (**269**; equation 146), this method can be of interest.[577]



(146)

$Ar = 4\text{-}ClC_6H_4, 4\text{-}MeC_6H_4$ (**269**)

Benzimidoyl chlorides and *N*,*N*-dimethyl-*N*′-thiobenzoylformamidine react to afford thioimidic acid anhydrides (**270**; Scheme 40).[578] Spirocyclic thioimino esters have been prepared from benzimidoyl chlorides and thiazolin-5-thiones.[579] Carboxylic acid imidothio acid anhydrides (**271**) can be synthesized from carboxylic acid chlorides and secondary thioamides.[580]



(270)

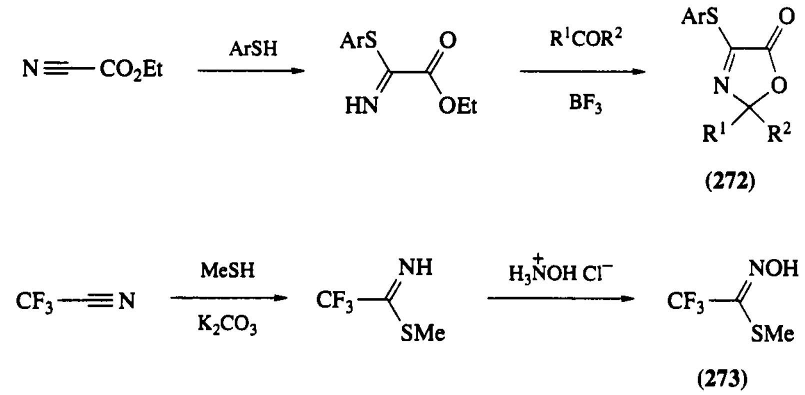
(Z = H, 4-Me, 4-Br, 2-Cl, 3-Cl)

(271)

Scheme 40

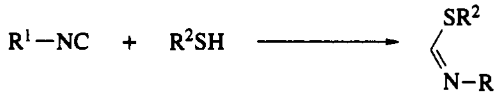
2.7.3.3.3 *From nitriles and isonitriles*

Catalyzed by bases, thiols add to the nitrile function to give thioimidates. The reaction is facilitated if electron-attracting groups are present in the α-position to the nitrile group. Very often the thioimidates thus formed were not isolated but reacted further to other products, *e.g.* (**272**) and (**273**; Scheme 41).[581–583]



Scheme 41

By addition of thiols to isonitriles thioformimidates (**274**; equation 147) are accessible.[509] 2-Methylpropaneisonitrile inserts into the thietane system to give triiminothiolanes (**275**; Scheme 42).[584] A related insertion of isonitriles into a C—S bond was observed in the reaction of alkylmercaptocyanoacetic acid esters, labile thioimidates (**276**) are the products.[585,586] The addition of thiocarboxylic acids to isonitriles, giving mixed anhydrides of thioformimidic acids and carboxylic acids has been studied.[587]



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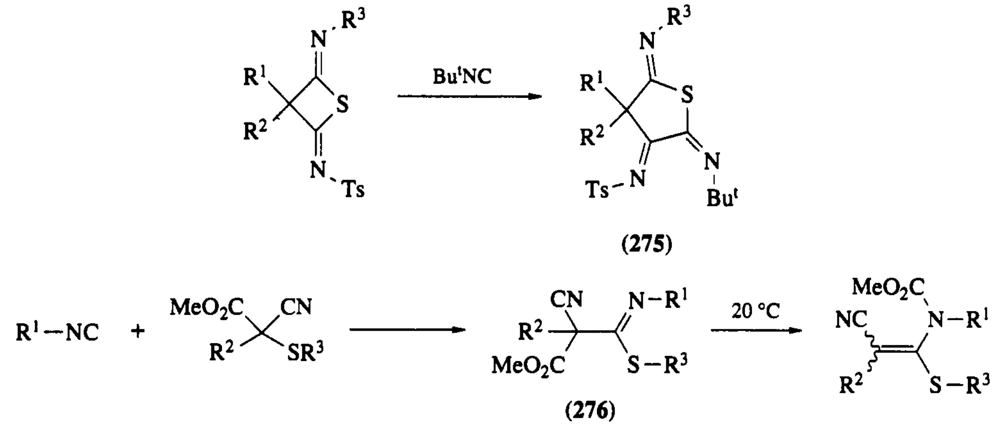
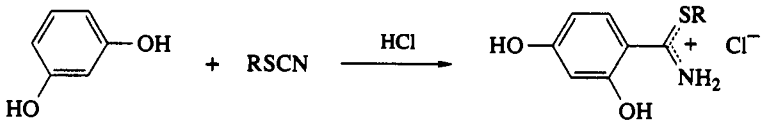


Scheme 42

2.7.3.3.4 *From activated aromatic compounds, alkenes, carbanions and carbenes*

The alkylmercaptomethyleneiminium salts (**277**; equation 148) can be synthesized by the action of alkyl isothiocyanates on resorcinol in the presence of HCl or $ZnCl_2$.[588] Isothiocyanates react with the ketene *O,N*-acetal (**278**; equation 149) to give primary products (**279**), which are stabilized by transalkylation to the thioimidates (**280**).[589] Similar transalkylation reactions were observed in the reactions of dimethylformamide acetals with aryl isothiocyanates giving thioimidates (**281**; equation 150).[590,591]



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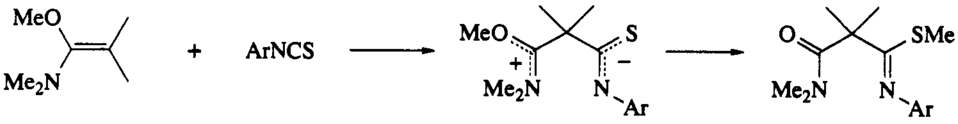
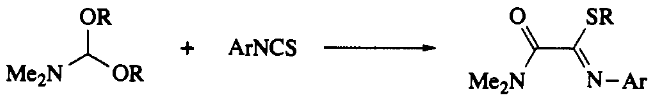
(148)



(278) **(279)** **(280)**

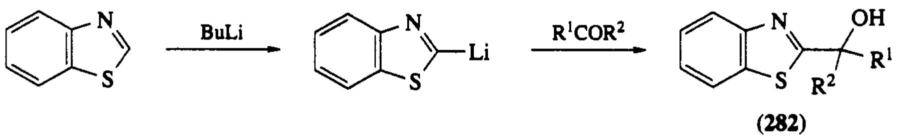
(149)



(281)

(150)

Benzothiazole can be metallated by treatment with butyllithium; the compound thus formed reacts with various electrophiles to furnish 2-substituted benzothiazoles, *e.g.* (**282**; equation 151).[592]

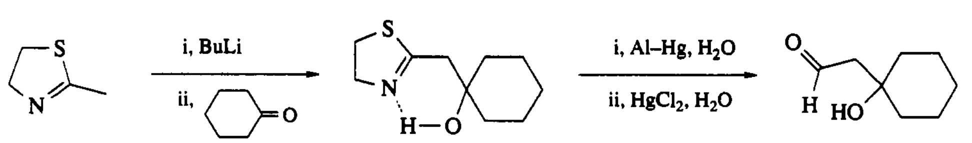


(282)

(151)

2.7.3.3.5 *From thioimidates*

In 2-methyl-1,3-thiazolines the α-CH bonds are acidic enough to be metallated. These carbanions have been alkylated, acylated, *etc.* to give 2-substituted-1,3-thiazolines, *e.g.* (**283**; equation 152). The thiazoline ring system is quite easy to reduce, the thiadiazolidines thus formed suffer hydrolytic ring opening to give aldehydes.[593,594] The whole sequence is a versatile aldehyde synthesis, which has been reviewed.[595] Isocyanates carboxylate the five-membered thiolactim ether (**284**; Scheme 43) at C-3 of the ring system to give the thiolactim ether (**285**), whereas six- and seven-membered lactim ethers are attacked at the ring-nitrogen to afford ketene *S,N*-acetals (**286**).[596] By acylation of thioimidates the new thioimidates (**287**; equation 153) were obtained, which are in equilibrium with ketene *S,N*-acetals.[597]



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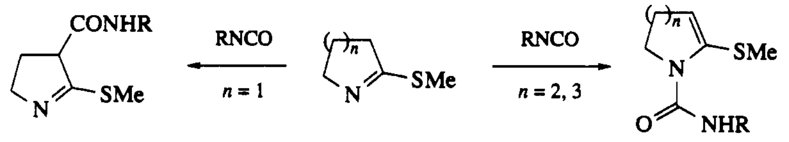
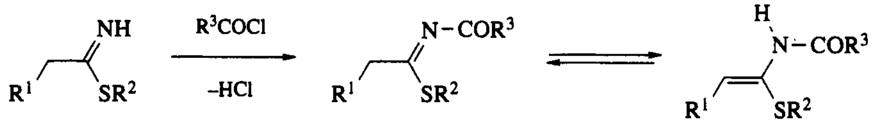
(152)



(285) **(284)** $n = 1$ **(286)**

Scheme 43

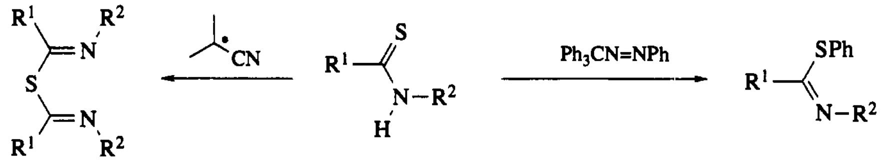


(287)

(153)

2.7.3.3.6 Miscellaneous methods

Secondary thioamides react with dimethylcyanomethyl radicals to give thioimidic acid anhydrides (**288**; Scheme 44), in poor yields,[598] whereas with phenyl radicals phenylthioimidates (**289**) are obtained in fairly good yields.[599] Thiolactim ethers (**290**; equation 154) (ring size 6–9) have been prepared by rearrangement of 1-azido-1-methylmercaptocycloalkanes.[600]



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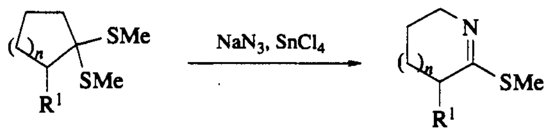
(289)

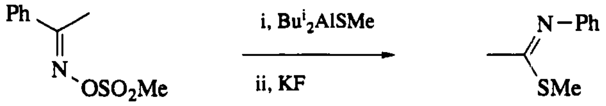
Scheme 44



(290)

(154)

Oxime sulfonates were rearranged in the presence of diisobutylaluminum methyl sulfide to produce methylthioimidates, *e.g.* (**291**; equation 155), and methylthiolactim ethers in good yields.[601] The adducts formed in the reaction of Grignard reagents with trimethylsilylmethyl isothiocyanate can be alkylated to furnish the *N*-trimethylsilylmethylthioimidates (**292**; equation 156).[602,603]



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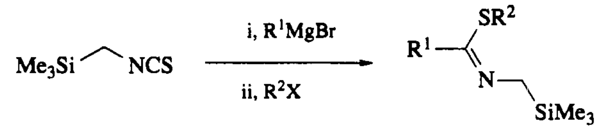
(155)



(292)

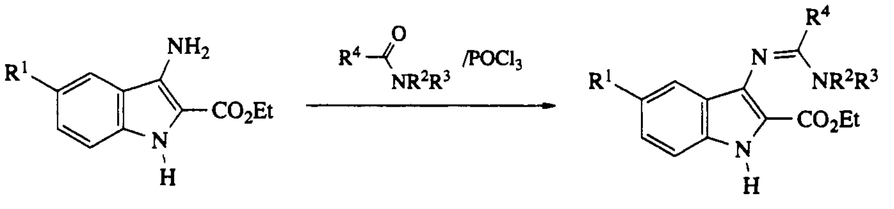
(156)

2.7.3.4 Amidines

2.7.3.4.1 From iminium salts

(i) Adducts from amides with acylating reagents

Adducts from tertiary amides (mostly DMF) or lactams with $POCl_3$ or PCl_3 were reacted with different kinds of primary amines and amine derivatives to give amidinium salts which were deprotonated to produce the free amidine, *e.g.* (**293**; equation 157). This amidine synthesis is a standard procedure. A collection of examples demonstrating the scope of the method is available.[5,14] The following selection of more recent examples will underline the importance of this synthetic procedure.

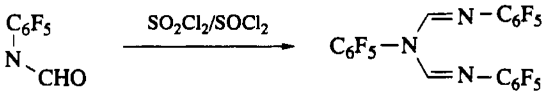


(157)

(**293**)

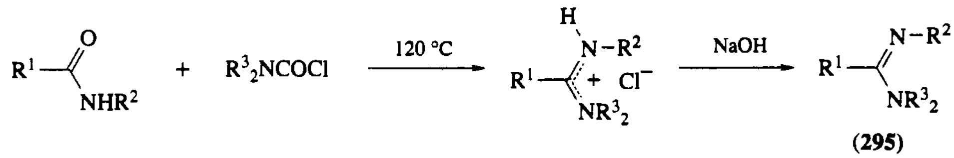
Adducts from $POCl_3$ and formamides,[604–617] acetamides,[39,42,615] malono ester amides,[47,48] cyanoacetamides[55,56] or lactams[618] have been transformed to amidines by reaction with the following amino compounds: 2-acylaminothiophenes,[607] 2-aminoisoxazole,[604] 4-aminotriazole,[605] 3-aminoimidazole,[610] aminoindoles,[608,611,615] 2-acylaminoanthraquinones,[606] 2,6-diaminoanthraquinone,[42,56] 6-aminouracil,[609] *N*-arylacetamides,[612] *N*,*N*-disubstituted thioureas,[613] *N*-arylchloroacetamides,[612] anilines,[55,614,618] *o*-phenylenediamines,[47,48] anthranilic acid amide[617] and acylaminobenzothiophene.[613]

Some of these transformations were accompanied by additional reactions, *e.g.* formylation of the aromatic[39] or heteroaromatic[607,608,615] nucleus or CH-acidic methyl groups;[609] further dehydration of amides to nitriles was observed.[617] Adducts from amides and PCl_3,[612] sulfonyl halides[42] or $SO_2Cl_2/SOCl_2$[619] from which amidines can be obtained by reaction with amine derivatives (compare Section 2.7.2.5 and refs. 5 and 14) have not found wide application for this purpose. An interesting reaction is the preparation of the amidine (**294**; equation 158) from *N*-pentafluorophenylformamide.[619] By thermal decomposition of the adducts from secondary amides and *N*,*N*-dialkylcarbamoyl chlorides amidinium salts were synthesized from which the amidines (**295**; equation 159) were set free by treatment with bases.[119,120]



(158)

(**294**)



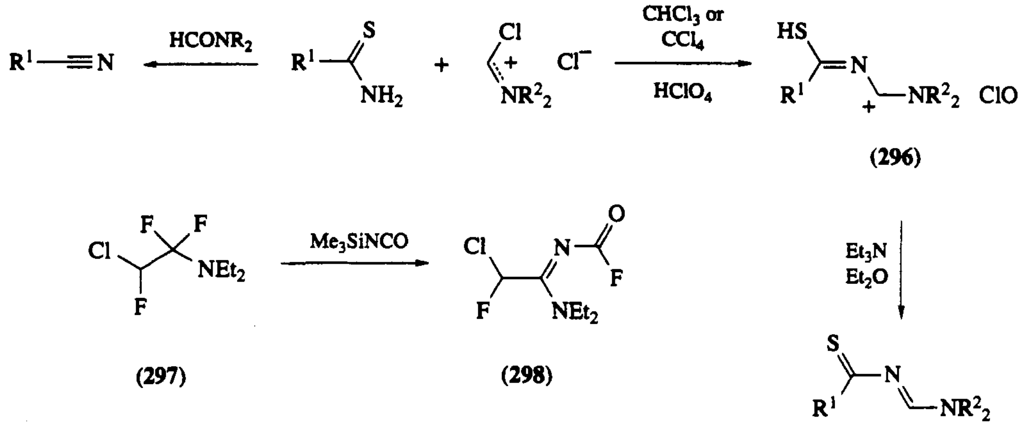
(159)

(**295**)

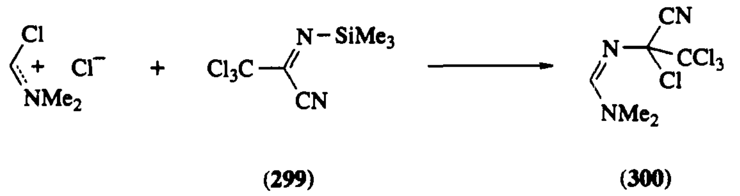
(ii) From halomethyleneiminium compounds or nitrilium salts

It is well known that halomethyleneiminium salts, often prepared *in situ* (see Section 2.7.2.2) react with ammonium salts, primary amines, secondary amides, urea and *N*-substituted ureas to afford amidinium salts, from which the free amidines can be obtained by addition of bases.[8,14] Some recent results are given below. Dimethylformamide chloride[306,612,620] and other *N*,*N*-disubstituted formamide chlorides[620,621] were reacted with acetanilides,[612] chloroacetanilides,[612] 6-aminopenam derivatives,[621] 2-aminopyrimidine,[306] 4-aminouracil,[306] 2-amino-4-chloropyridazine,[306] 2-aminothiazole,[306] 2-aminobenzothiazole[306] and thiobenzamides[620] to give the amidines *via* the amidinium salts. In the reaction of *N*,*N*-disubstituted formamide chlorides with thiobenzamides the solvent seems to be decisive for the course of the reaction. In tertiary formamides the thiobenzamides are desulfurized to nitriles, whereas in $CHCl_3$ or CCl_4 amidinium salts (**296**; Scheme 45) are formed.[620] From trimethylsilyl isocyanate and the fluorinated amine (**297**) the *N*-fluorocarbonylamidine (**298**) is accessible.[622]

In the reaction of dimethylformamide chloride with the imidoyl cyanide (**299**; equation 160) the amidine (**300**) is formed.[623] Isoxazolines, prepared from amide chlorides and hydroxylamine, rearrange on heating or irradiation to give 2-aminoazirine (**301**; Scheme 46).[624] Azirines (**302**) can also be prepared by treating chloroenamines with base and sodium azide.[341,625]



Scheme 45



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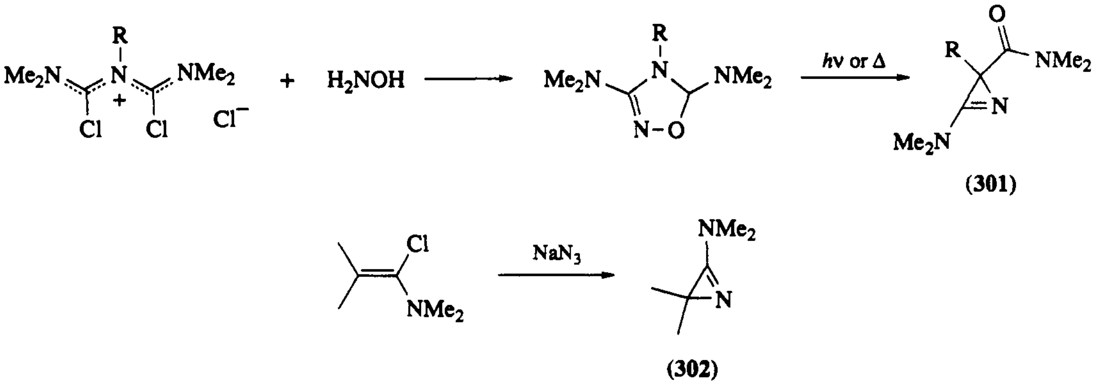
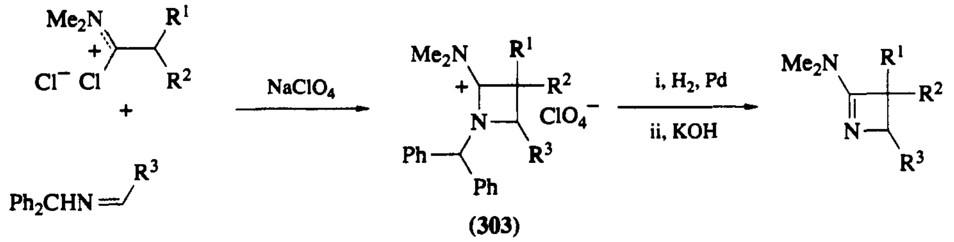


Scheme 46

Dehydrohalogenation of amide chlorides affords α-chloroenamines, which undergo cycloaddition with *N*-diphenylmethylaldimines to furnish azetidinium salts (**303**; equation 161). From these salts the diphenylmethyl group can be removed by hydrogenation, subsequent deprotonation yields 2-amino-1-azetines.[342,626] The addition of primary or secondary amines to nitrilium salts gives rise to formation of amidinium salts[5,323–325,627] and amidines respectively, *e.g.* (**304**; equation 162). In a similar reaction from copper(I) imidazolide, *t*-butyl bromide and nitriles amidines (**305**; equation 163) were prepared.[628]



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(304)

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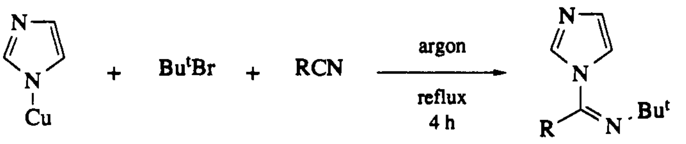
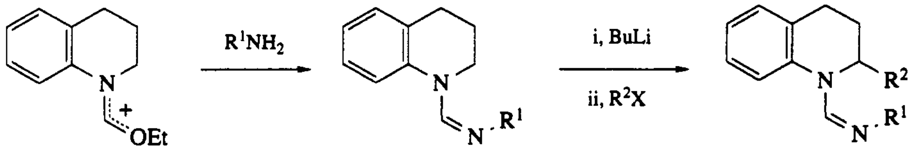


(305)

(163)

(iii) From alkoxymethyleneiminium salts or alkylmercaptomethyleneiminium salts

The action of ammonia, primary and secondary amines on alkoxymethyleneiminium salts or alkylmercaptomethyleneiminium salts affords amidinium salts. Provided the educts are chosen in such a manner that the substitution pattern of the resulting amidinium salts does not exceed that of *N,N,N'*-trisubstituted salts, the amidines can be released from the salts by addition of bases[9–15] (see also Section 2.7.2.5.3). Very often the alkoxymethyleneiminium salts were prepared *in situ* and reacted without further purification with the amino compound to give the desired amidine. This amidine synthesis is of special synthetic interest, since it was stated that formamidines, derived from alicyclic amines, *e.g.* (**306**; equation 164), which are simple to obtain by this method, are readily transformed to reactive carbanions.[629–631] Heterocycles, *e.g.* (**307**; equation 165), containing amidine structures, are accessible by reaction of appropriate difunctional compounds with iminium salts.[632]



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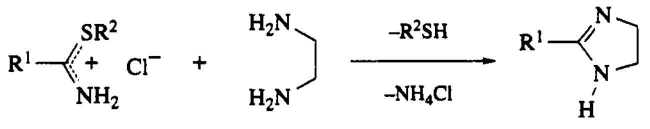


(307)

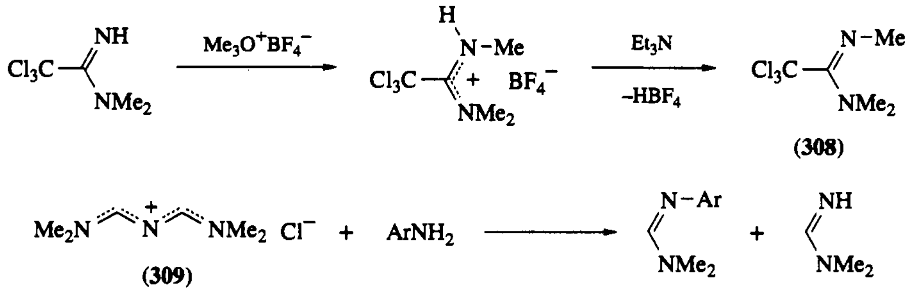
(165)

(iv) From amidinium salts

Amidinium salts (obtainable by various methods, compare Section 2.7.2.5) which are not peralkylated at nitrogen are converted to amidines by treatment with strong bases, *e.g.* aqueous alkali metal hydroxides, alcoholic alkoxides,[633] tertiary amines *etc.* As already mentioned it is not difficult to alkylate amidines (see Section 2.7.2.5.4), thus by subsequent alkylation and deprotonation reactions amidines can be synthesized carrying the desired substituents at nitrogen, *e.g.* (**308**; Scheme 47).[14,634] A series of *N,N,N'*-trisubstituted formamidines have been prepared by reaction of anilines with the azavinylogous formamidinium salt (**309**).[635]

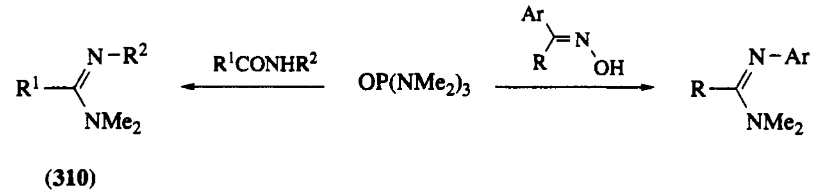
2.7.3.4.2 From carboxylic acids or carboxylic acid amides and amines in the presence of condensing agents

Heating of secondary carboxylic acid amides with HMPA gives rise to formation of *N*-substituted *N',N'*-dimethylamidines (**310**; Scheme 48).[636,637] In this procedure the secondary amide can be replaced by a ketoxime in which at least one substituent has to be an aromatic one.[638] Similar methods were de-

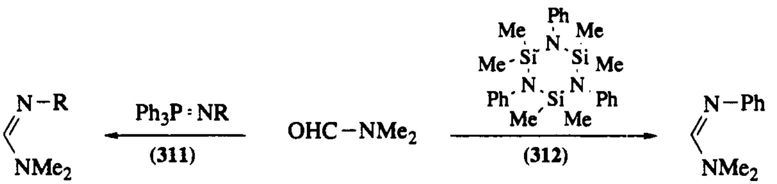


Scheme 47

veloped and thus formamidines were prepared by heating P_4O_{10} with mixtures of *N*,*N*-dialkylformamides with secondary carboxylic acid amides,[639] or by reacting secondary amides with mixtures of P_4O_{10} and secondary amines.[640] Even carboxylic acids can be transformed to amidines by reaction with anilines and polyphosphorus acid trimethylsilyl ester,[641,642] or with mixtures of P_4O_{10}, alkylammonium chlorides and *N*,*N*-dimethylcyclohexylamine.[643] Iminophosphoranes (**311**; Scheme 49)[644] or cyclotrisilazanes (**312**)[645] react with DMF to yield formamidines.



Scheme 48



Scheme 49

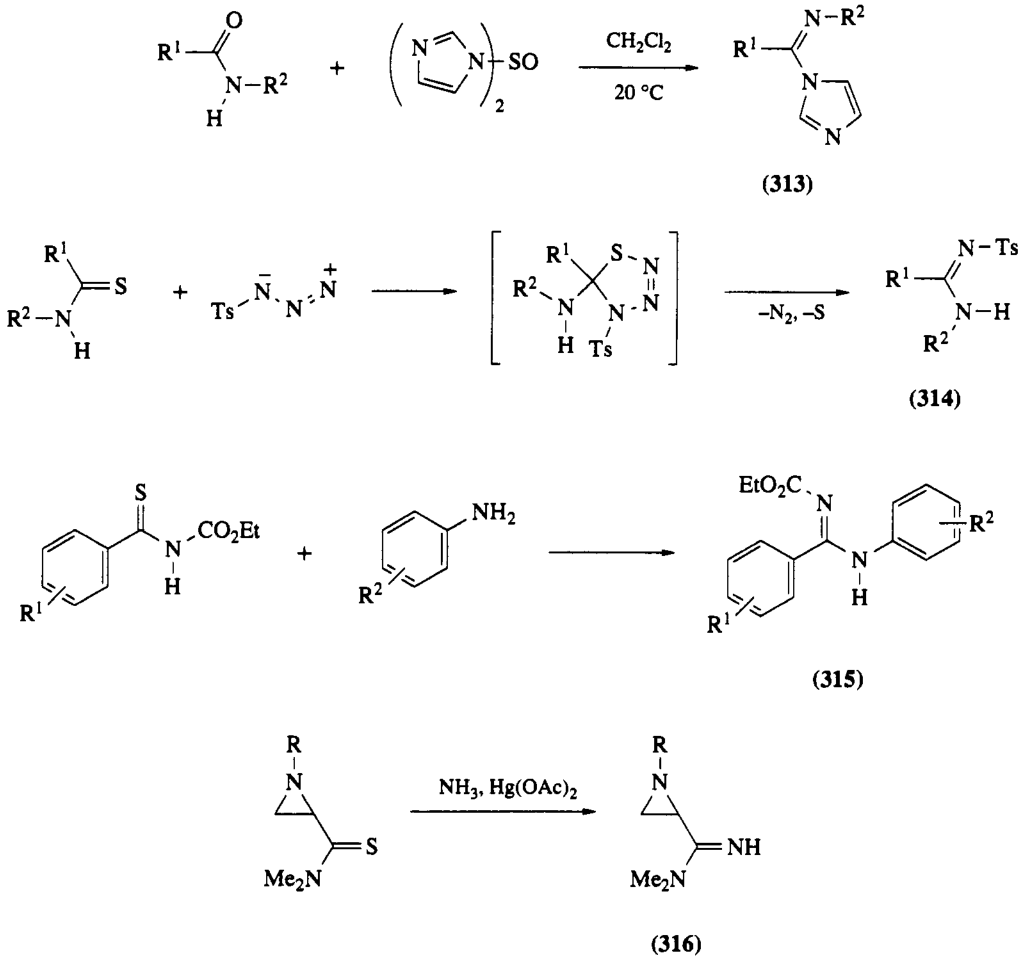
Tetrakis(dimethylamino)titanium is a useful reagent for preparing amidines from secondary amides.[646] From *N*,*N*′-thionyldiimidazole and secondary amides of both aromatic and aliphatic carboxylic acids amidines (**313**; Scheme 50) are formed under mild conditions in moderate to good yields.[647] *N*-Tosylamidines (**314**) can be obtained by reacting secondary thioamides (aliphatic and aromatic) with tosyl azide.[648] Thiobenzamides have been condensed with anilines to afford amidines (**315**).[648] Thioamides can be converted to amidines, *e.g.* (**316**), by treatment with ammonia in the presence of mercury acetate.[317]

2.7.3.4.3 *From nitriles, isonitriles, ketene imines, carbodiimides and cyanamides*

The addition of ammonia, primary and secondary amines to the nitrile group proceeds well if electron-attracting groups are present in the α-position to the nitrile function. Thus it is well known that amines add rapidly to trihaloacetonitriles[634,649,650] or cyanogen[651] to give amidines (**317**) and (**318**) respectively (Scheme 51). Recently it was reported that the addition of aliphatic amines and diamines to aliphatic or aromatic nitriles, respectively, proceeds with good yields if lanthanide triflates are present as catalysts.[652]

Metal amides can be added to ordinary nitriles (*e.g.* lithium, sodium or magnesium amides), thus forming amide imide salts, which on addition of water or alcohol afford amidines.[20,21] Some recent results demonstrate the wide applicability of the method, *e.g.* from metal amides and trialkoxyacetonitriles, trialkoxyacetamidines (**319**; Scheme 52)[653] were prepared and from lithium imides and nitriles *N*-alkylideneamidines (**320**)[654] could be synthesized.

The addition of amines to isonitriles, catalyzed by copper compounds, furnishes formamidines.[509] The method has found further application, *e.g.* piperidine was added to benzeneisonitrile[655] or to trimethylsilylmethaneisonitrile[656] to give the amidine (**321**; Scheme 53). *N*-Sulfonylformamidines (**322**) were the



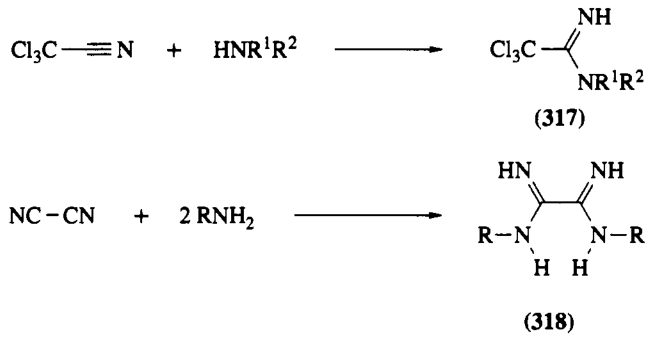
(313)

(314)

(315)

(316)

Scheme 50



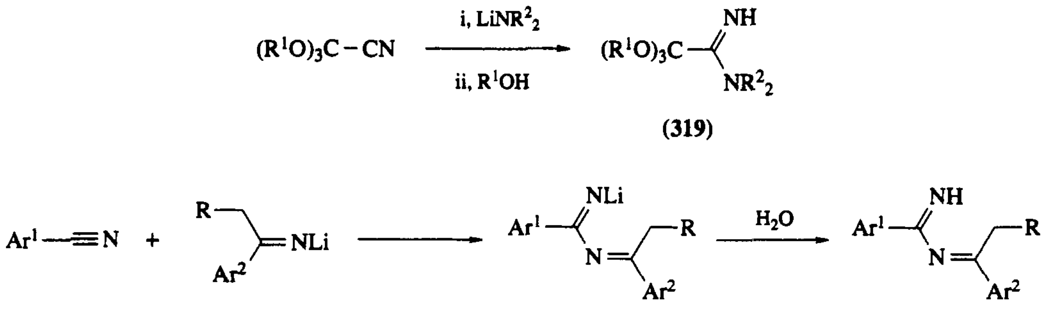
(317)

(318)

Scheme 51

products when sulfonamides were reacted with isonitriles.[657] It has turned out that silver chloride catalyzes the addition of aziridine to isonitriles to produce formamidines (**323**).[658]

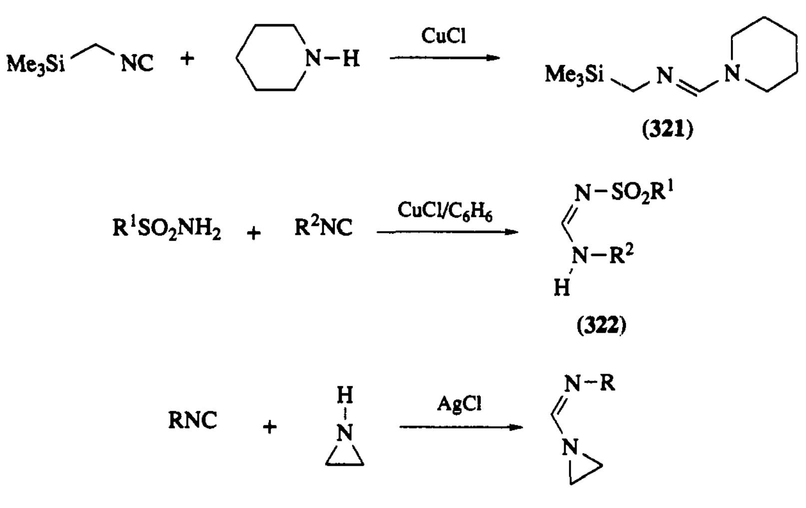
N-Vinylformamidines (**324**; equation 166) are accessible from the reaction of aldehydes with isocyanoacetic acid esters and amines.[659,660] Isonitriles can insert into the C—N bond of aminals with formation of α-aminoacetamidines (**325**) and (**326**) (equation 167).[661,662] From ketene imines and primary[663,664] or secondary[664,665] amines amidines (**327**; Scheme 54) have been prepared; the ketene imines needed can be generated *in situ* from isoxazoles.[666] In the presence of triethylamine from the ketene imine (**328**) and the urethane (**329**), the iminoaziridine (**330**) is obtainable.[667] Ketene imines with *N*-sulfinyldimethylammonium tetrafluoroborate form adducts (**331**), which are decomposed by aqueous alkali to yield amidines in good yields.[668]



(319)

(320)

Scheme 52



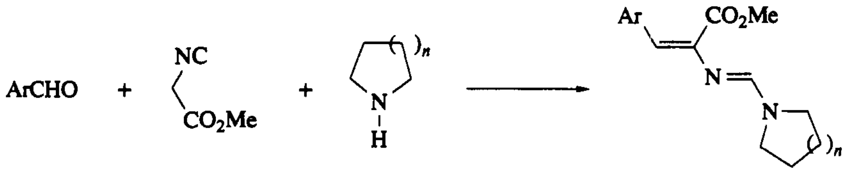
(321)

(322)

(323)

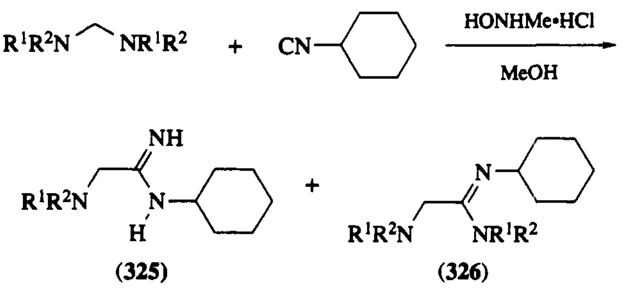
Scheme 53

Carbodiimides (332; Scheme 55) form amidines on treatment with: NaBH$_4$ in alcohols,[669] Grignard reagents,[20] sodium phenylacetylide,[20] carbon monoxide in the presence of *s*-butyl- or t-butyl-lithium[670] and nitrones catalyzed by HBF$_4$.[671] In the reaction of stannylated or silylated ynamines with carbodiimides



(324)

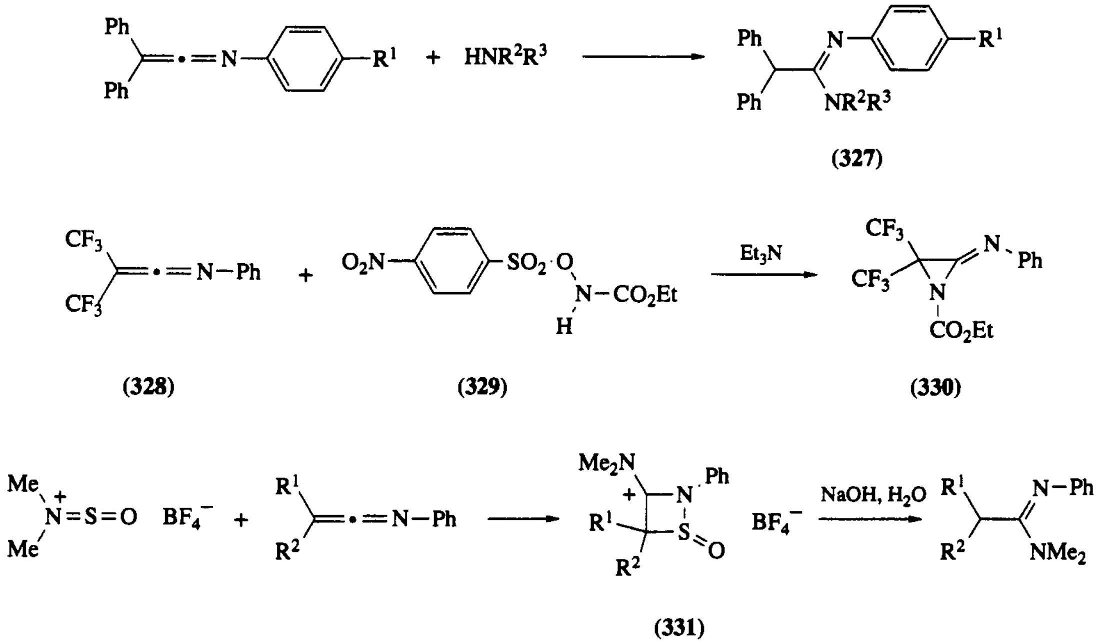
(166)



(325)

(326)

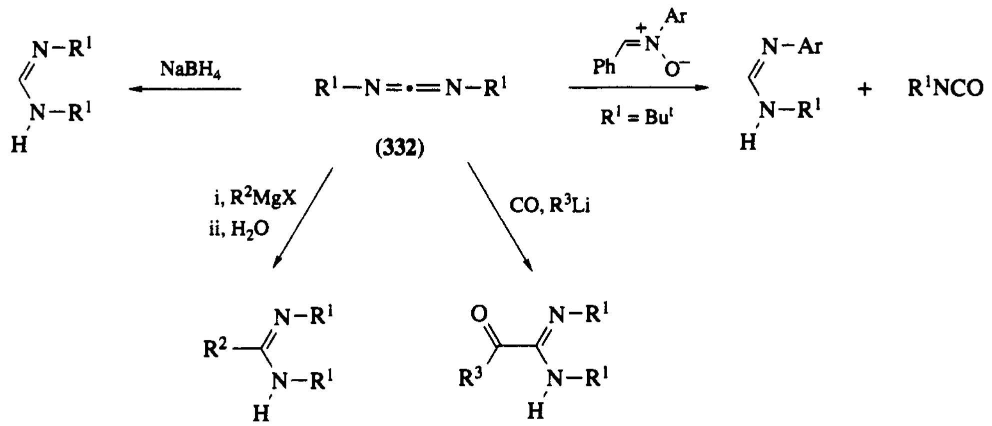
(167)



(327) (328) (329) (330) (331)

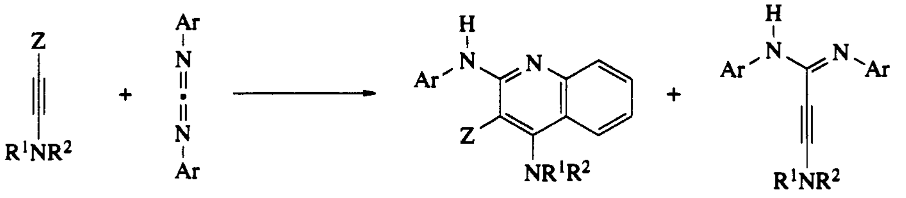
Scheme 54

propiolamidines (**333**; equation 168) are byproducts.[672] *N*,*N*-Disubstituted cyanamides react with Grignard reagents to yield amidines (**334**; equation 169).[20]

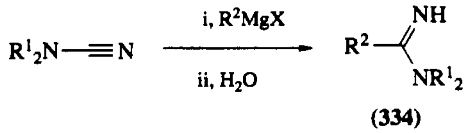


(332)

Scheme 55



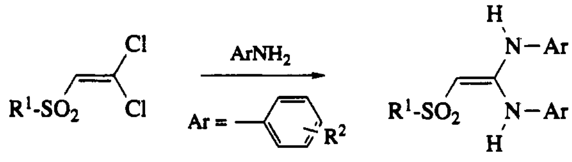
(333) (168)



(334) (169)

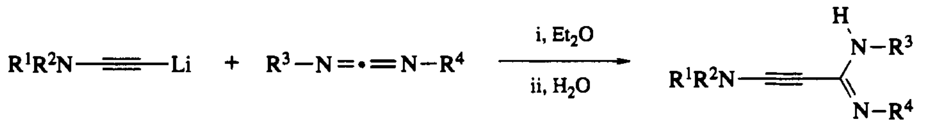
2.7.3.4.4 From 1,1-dihaloalkenes or ynamines

In β,β-dichlorovinyl sulfones aromatic amines replace both chlorine atoms to furnish β-sulfonylacetamidines (**335**; equation 170).[673,674] 3-Aminopropiolamidines (**336**; equation 171) are accessible from lithio ynamines and carbodiimides after hydrolysis of the initially formed adduct.[675] From ynamines and *N*-sulfinyltosylamide the amidines (**337**; Scheme 56) are formed *via* cycloaddition and cycloreversion steps.[676] In a similar way from ynamines and *N*-sulfonylimines or *N*-phenylsulfonylthioimidates amidines (**338**) and (**339**), respectively, can be prepared.[677]



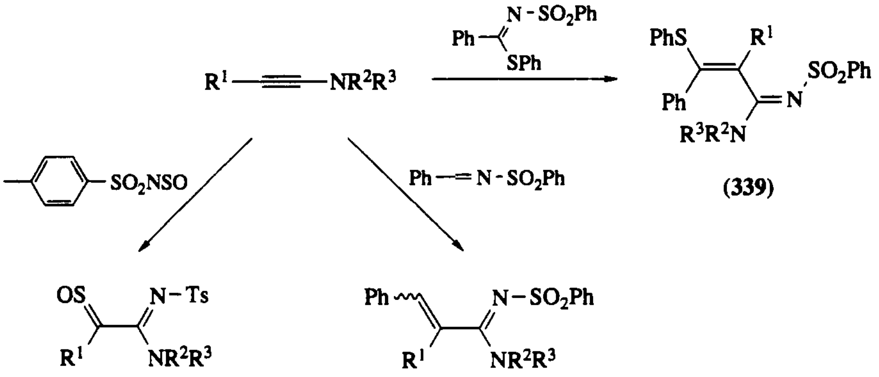
(335)

(170)



(336)

(171)



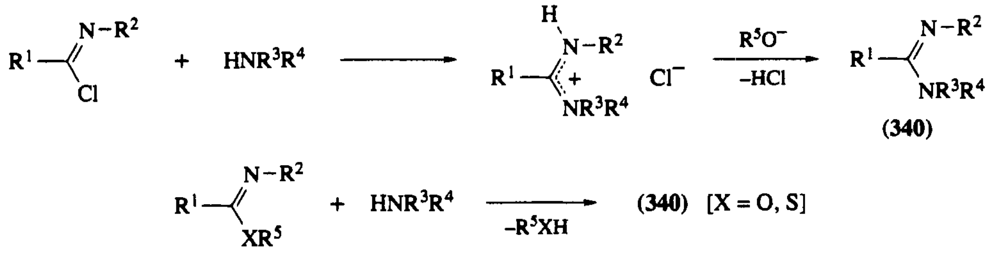
(339)

(337) **(338)**

Scheme 56

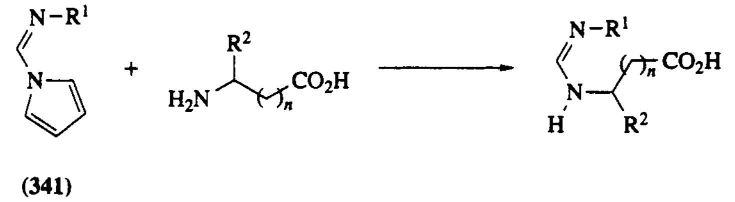
2.7.3.4.5 From imidoyl compounds

As already mentioned the action of ammonia, primary and secondary amines on imidoyl halides affords amidinium salts, from which the amidines (**340**; Scheme 57) can be set free by treatment with bases (see Section 2.7.2.5.3 and 2.7.2.5.4). In imidates[42,421,479–482,488,490,678,679] and thioimidates[500,552,563] the alkoxy groups and alkylmercapto groups respectively are readily replaced by amino groups giving amidines (**340**).

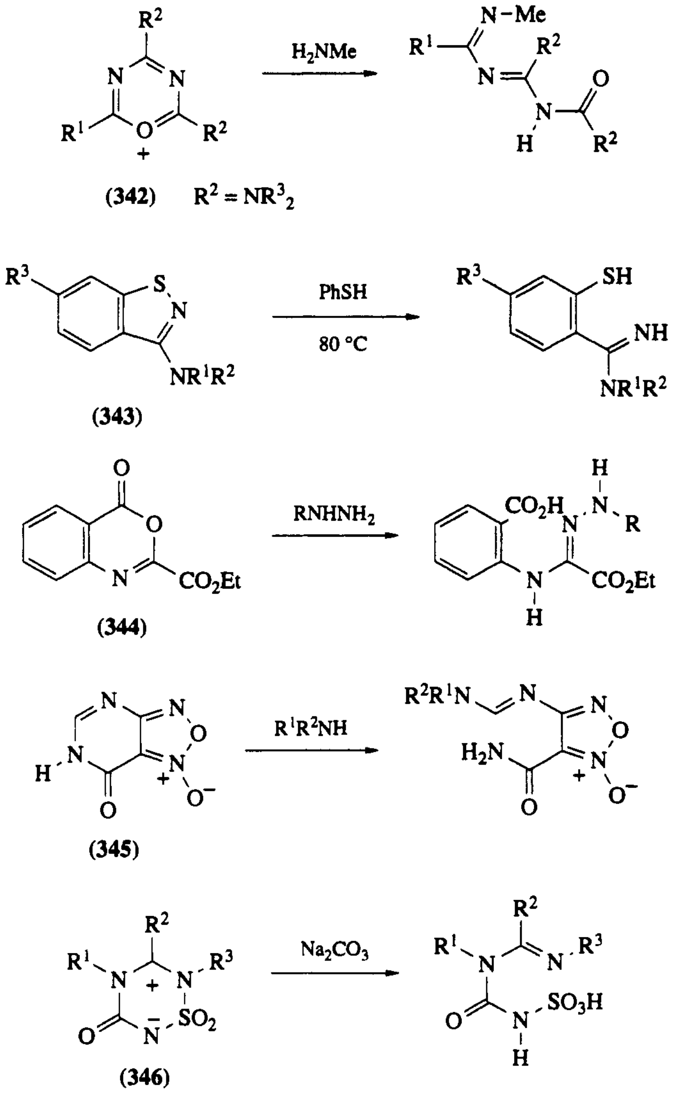


Scheme 57

In amidines transamination is possible,[680–683] especially useful for such purposes are imidoylimidazolides, *e.g.* (**341**; equation 172).[680] In some cases it is useful to prepare amidines by ring opening of suitable heterocycles, which can be achieved by treatment with amines or other nucleophilic (basic) compounds. Examples are the synthesis of amidines from 1,3,5-oxadiazinium salts (**342**),[684,685] 3-amino-1,2-benzisothiazoles (**343**),[686] 2-ethoxycarbonyl-3,1-benzoxazin-4(4*H*)-one (**344**),[687] 1,2,5-oxadiazolo[3,4]pyrimidine 1-oxides (pyrimidofuroxans; **345**)[688] and 1,2,4,6-thiatriazenium-5-olate 1,1-dioxides (**346**)[689] as shown in Scheme 58.



(341) (172)



(342) $R^2 = NR^3_2$

(343)

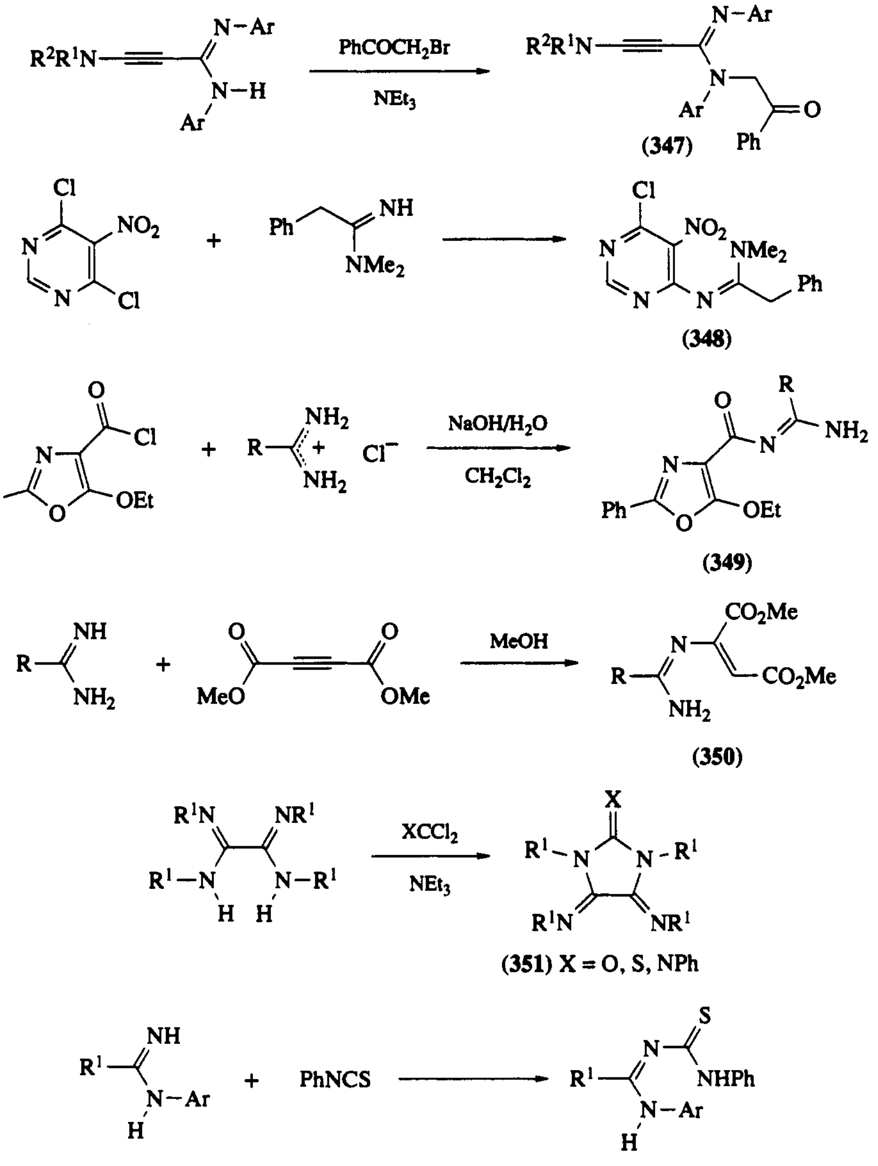
(344)

(345)

(346)

Scheme 58

Amidines with a more complicated substitution pattern have been prepared from amidines by alkylation—either at nitrogen[690–692] or at nitrogen substituents.[693,694] Variations at these positions have been achieved by heteroarylation,[695] acylation,[675,696,697] vinylation[698] or carboxylation with phosgene,[699] thiophosgene,[699] isocyanide dichlorides[699] or isothiocyanates.[700] Some interesting amidines, *e.g.* (347)–(352) (Scheme 59), have been prepared in this manner. The amidine skeleton can also be varied by halogenation,[325,667] hydrolysis,[622] isomerization[658] or catalytic hydrogenation[655] or other addition reactions if there are C=C double bonds present as in (353; equation 173) for example.[701]



(347)

(348)

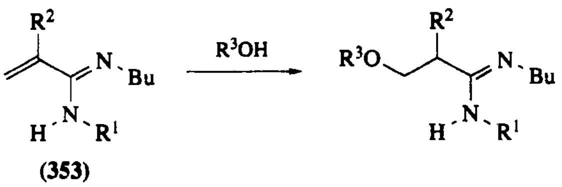
(349)

(350)

(351) X = O, S, NPh

(352)

Scheme 59

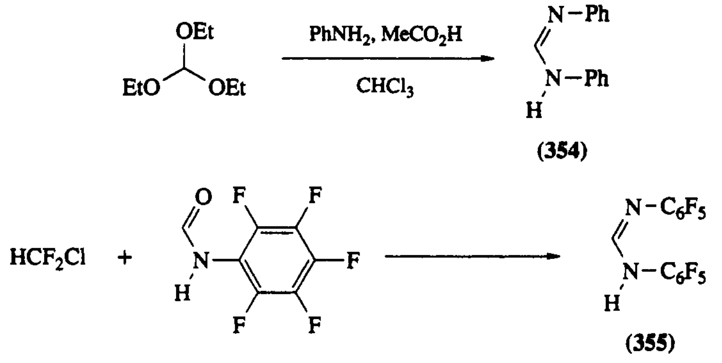


(353)

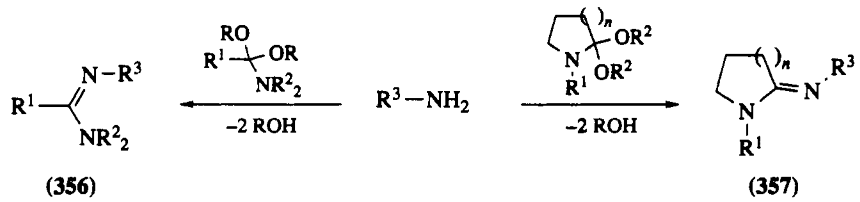
(173)

2.7.3.4.6 From orthoesters, orthoamides and related compounds

Orthoesters react with excess amines, catalyzed by acids, to afford amidines;[702–704] imino esters are isolable intermediates (see Section 2.7.3.2.3). A lot of *N*-naphthylformamidines,[702] *N*-pyridylformamidines[703] and *N,N'*-diphenylformamidines (**354**; Scheme 60)[704] were prepared by this method. In a similar reaction from dichlorofluoromethane and pentafluoroformanilide the formamidine (**355**) was prepared.[705] The condensation of NH-acidic compounds with orthoamide derivatives affords amidines (**356**) and (**357**) (Scheme 61). This is one of the most general and easy to perform syntheses of amidines, which has found wide application in the last 15 years. In Tables 7a and 7b are compiled orthoamide derivatives and amino compounds which have been reacted to give amidines.

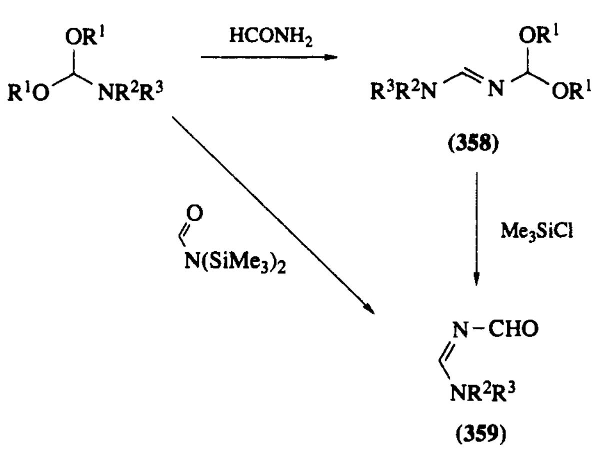


Scheme 60



Scheme 61

In addition to the construction of the amidine structure *N*-alkylation reactions can occur;[722,723] ring opening in the case of heterocyclic amines[728] and formylation of acidic methylene or methyl groups.[760,761,795] The reaction of formamide with excess *N,N*-dialkylformamide acetals deviates from this reaction pattern, here azavinylogous formamide acetals (**358**; Scheme 62) are formed.[796] *N,N*-Dialkyl-*N'*-formylformamidines (**359**) can be prepared either by action of *N,N*-dialkylformamide acetals on bis(trimethylsilyl)formamide[797] or by treatment of azavinylogous amide acetals (**358**) with trimethylchlorosilane.[798]



Scheme 62

Table 7a Amidines from Orthoamide Derivatives and Amino Compounds

Orthoamide derivatives	*Ref.*
N,N-Dimethylformamide acetals	42, 706–782
N-Formylpyrrolidine acetals	760, 783
N-Formylpiperidine acetals	754
N-Formylmorpholine acetals	754, 760
N,N-Dimethylacetamide acetals	724, 729, 741, 747, 756–758, 765, 775, 779–781, 784–787
N-Acetylpiperidine acetal	788
N-Acetyl-*N'*-(2-pyridyl)piperazine acetal	788
N,N-Dimethylbenzamide acetals	772, 775
N-Alkylpyrrolidone acetals	729, 731, 763, 765, 780, 784, 785, 787, 789–794
N-Methylpiperidone acetals	729, 763, 765, 784, 785,789–792

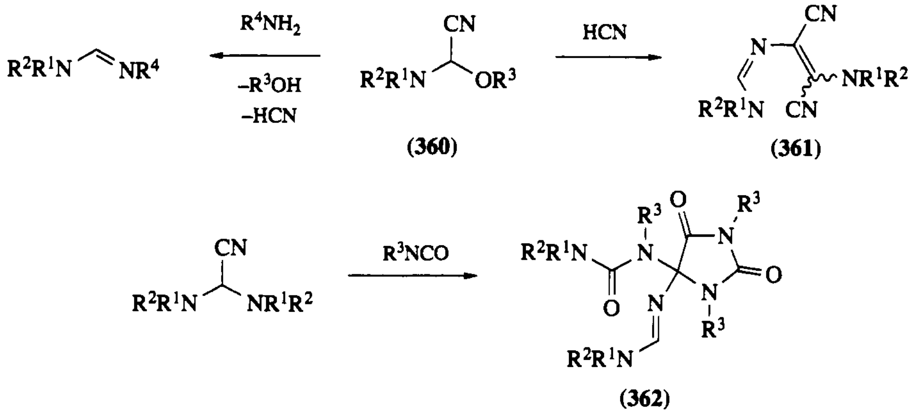
Table 7b Amidines from Orthoamide Derivatives and Amino Compounds

Amino compounds	*Ref.*
Aminoanthraquinones	42, 787, 794
Anilines	715, 719, 720, 731, 759
Aminocoumarins	736
Aminoindazoles	712
Aminopurines	721, 730
Aminopyridines	713, 715, 716, 726, 741, 782, 785
Aminopyrimidines	715, 718, 743, 744, 747, 784
Aminouracils	706–708, 795
Aminopyrazines	714, 717, 746, 747
Aminopyridazines	739,747
Aminoquinazolines	710
Amino-1,2,4-triazines	715, 747
Amino-1,2,4-triazoles	715
Aminopteridines	709, 714
Aminobenzimidazole	715
Aminopyrimidopyrimidines	716
Aminobenzotriazines	724
Cytosines	722, 723
Pyrazinethionhydroxamic acid amide	725
Aminothiazoles	727
Aminothiophenes	727, 788
Aminopyrazoles	728, 729, 733, 738, 745
Aminoisoxazoles	728
Pyrroloazepinones	729
Aminotriazolopyrimidines	732
Aminotetrahydronaphthyridines	734
Aminopyrazolopyridines	735
Aminopyridazinones	739
Aminopyridopyrimidines	740
Amino-1,3,4-thiadiazoles	742
Aminoimidazoles	742
Sulfonamides	748
Amino sugars	749
N-Arylbenzamidines	750
Thioamides	751–754, 756, 760, 781
Benzylamines	755
Aromatic acid amides	757, 758

Formamidines are accessible from 2-dialkylamino-2-alkoxyacetonitriles (**360**; Scheme 63) and primary amines.[799] The action of HCN on the nitriles (**360**) gives rise to formation of *N*-vinylamidines (**361**).[800] Formamidines (**362**) are formed from bis(dialkylamino)acetonitriles and isocyanates in excellent yields.[801,802] This reaction is interesting from the mechanistic point of view.

2.7.3.4.7 Miscellaneous methods

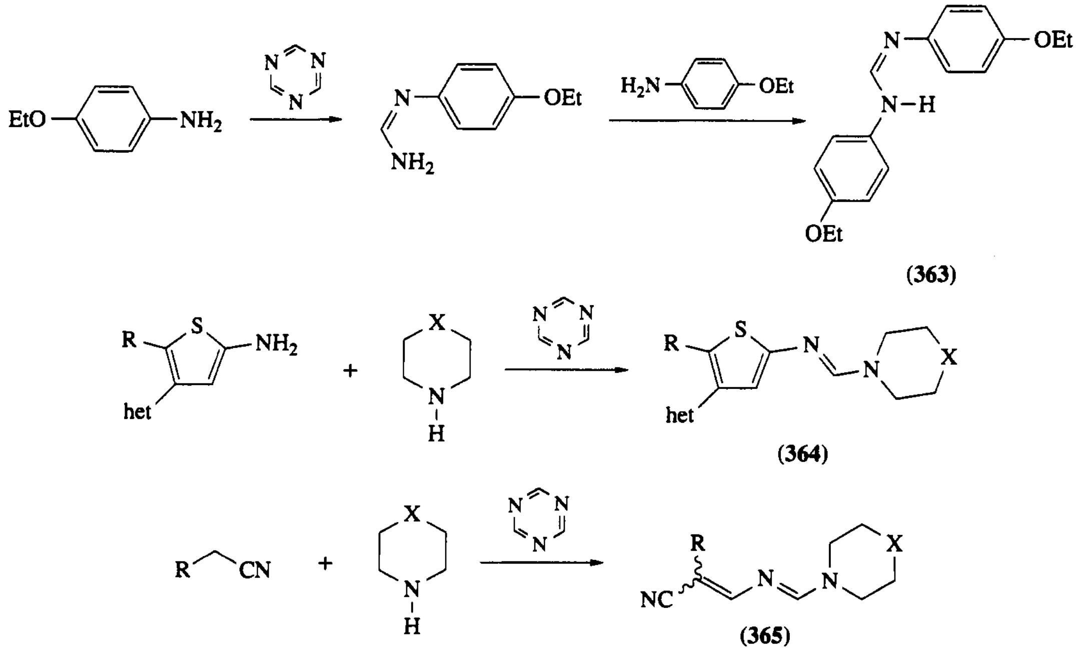
Anilines[803,804] and heterocyclic amines[805,806] react with 1,3,5-triazine to furnish formamidines, *e.g.* (**363**) and (**364**) (Scheme 64). CH_2-acidic compounds, *e.g.* nitriles, can be formylated by heating with 1,3,5-triazine. In the course of such reactions the enamines thus obtained can be converted to formamid-



(360) **(361)** **(362)**

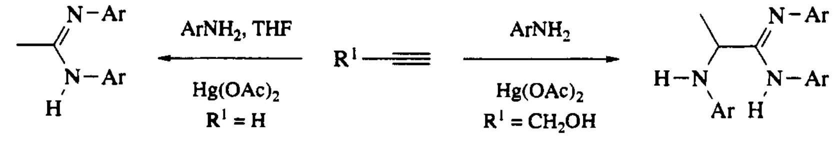
Scheme 63

ines (**365**) if secondary amines are present.[807,808] From hydrocyanic acid and primary amines *N,N'*-disubstituted formamidines were prepared.[809] The mercury acetate catalyzed addition of aromatic amines to acetylene affords acetamidines (**366**; Scheme 65);[810] in a similar procedure α-arylaminopropionamidines (**367**) from propargyl alcohol and arylamines have been prepared.[811,812] 1,2-Diaminoethylenes react with aryl azides or tosyl azide to give α-aminoamidines (**368**; equation 174).[813,814] Amidines (**369**) and (**370**) (Scheme 66) are accessible from thioureas by desulfurization with Raney nickel[815] or by sulfide contraction.[816] In an unexpected reaction sequence α-ketoamidines (**371**; equation 175) are produced from enamines and nitrosobenzene in moderate yields.[817]



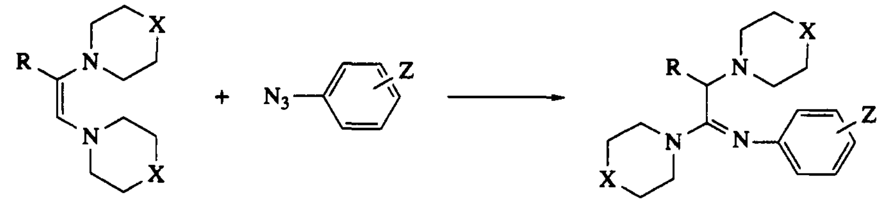
(363) **(364)** **(365)**

Scheme 64



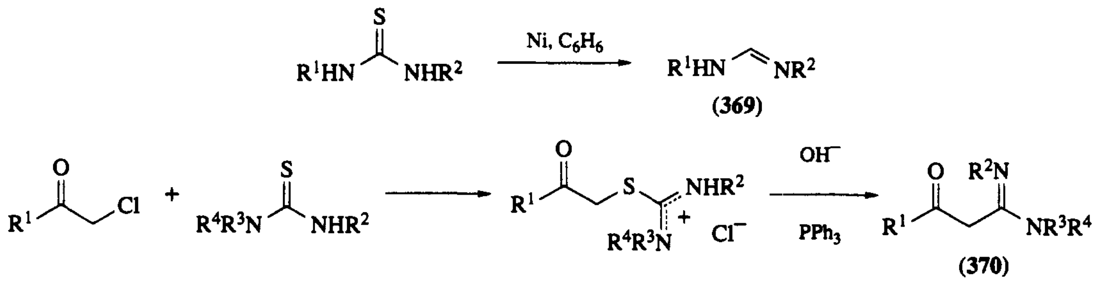
(366) **(367)**

Scheme 65



(174)

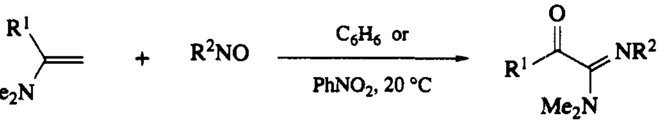
(368)



(369)

(370)

Scheme 66



(175)

(371)

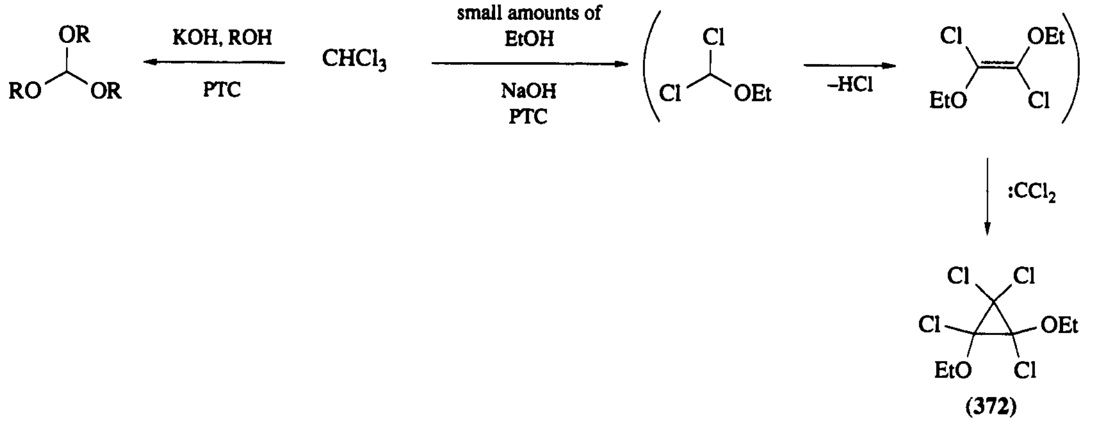
2.7.4 CARBOXYLIC ORTHOACID DERIVATIVES

2.7.4.1 Carboxylic Orthoesters

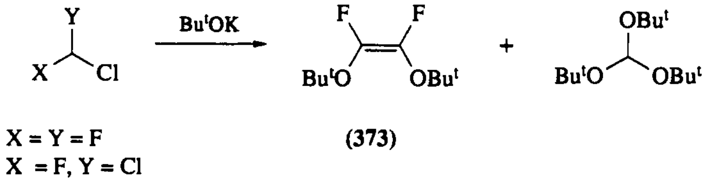
2.7.4.1.1 From 1,1,1-trihaloalkanes, α,α-dihalo ethers, haloalkenes, ketene acetals and alkoxyalkynes

The preparation of orthoformic acid esters from chloroform and alkali metal alkoxides is a long known procedure,[7,22-27] which can be performed under phase transfer catalysis.[818] If small amounts of alcohol are present in the phase-catalyzed process, cyclopropanes (**372**; Scheme 67) can be produced by addition of dichlorocarbene to 1,2-dialkoxy-1,2-dichloroethylenes, which are thought to be intermediates.[819] Alkenes of this kind, *e.g.* (**373**; equation 176), have been observed as byproducts in the synthesis of tri-*t*-butylorthoformate from chlorodifluoromethane or dichlorofluoromethane and potassium *t*-butoxide.[820] Trimethoxyacetonitrile was prepared from trichloroacetonitrile and sodium methoxide.[821]

In the reaction of geminal trihaloalkanes with alkoxides elimination (alkene formation) is preferred over substitution (orthoester formation). There are a few known exeptions, *e.g.* the preparation of β-keto orthoesters (**374**; equation 177) from fluorinated ketones,[822] or the synthesis of trimethoxymethylalkyne from 1,4-dichloro-2,3-dibromo-2-butene.[823] Triaryl orthoesters can be prepared from perhalogenated alkenes,[824] dichloronitroalkenes (**375**; Scheme 68),[825,826] dihalomethylenefuranone[827] or, very favorably, from dichloromethyl aryl ethers (**376**)[828] and phenoxides. In general the action of alkoxides on α,α-dichloro ethers is a reliable method for the preparation of substituted orthoesters like 2,2,2-trialkoxyacetic acid esters[829,830] or pentaalkoxyethanes.[831] Aromatic and heteroaromatic orthoesters, *e.g.* orthobenzoic acid esters[7,22,24] or the bisorthoesters (**377**)[832] and (**378**)[833] can be synthesized from the corresponding trihalomethyl compounds.



Scheme 67



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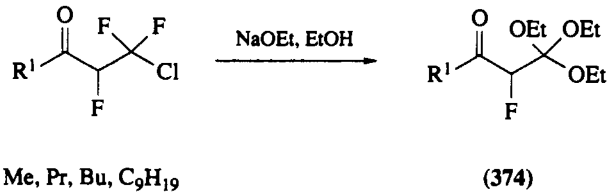

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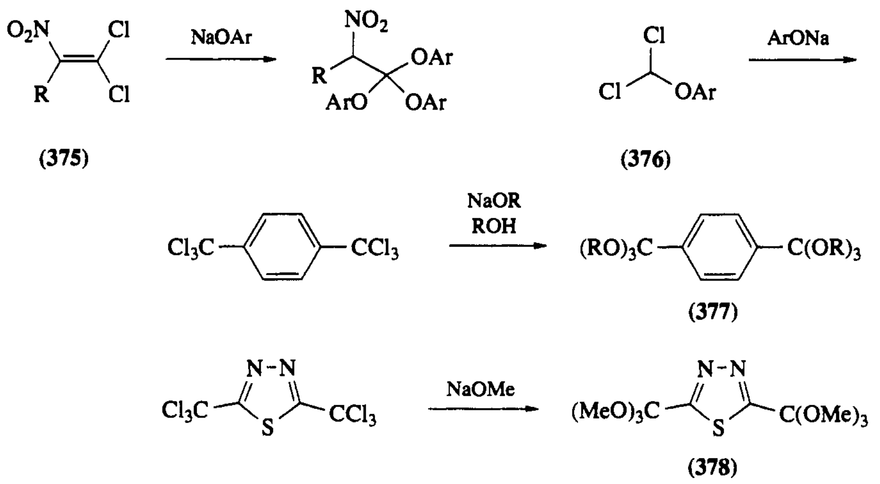
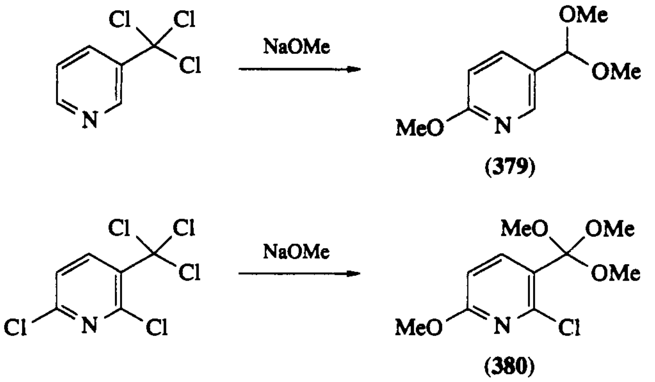


Scheme 68

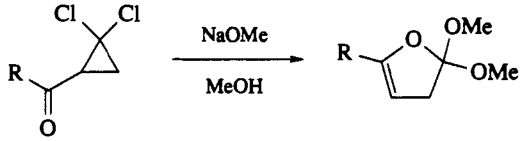
In the reaction of sodium methoxide with 3-trichloromethylpyridine the nicotinecarbaldehyde acetal (**379**; Scheme 69) is formed, whereas by action of methoxide on 2,6-dichloro-3-trichloromethylpyridine the orthoester (**380**) is accessible.[834] The 1,1-dichloro-2-acylcyclopropanes on treatment with sodium methoxide undergo ring enlargement to yield the cyclic orthoester (**381**; equation 178).[835,836] A mixture of isomeric cyclopentadiene carboxylic orthoacid esters results when the bis(methylthio)fulvene (**382**; equation 179) is reacted with excess alkoxide.[837]



(379)

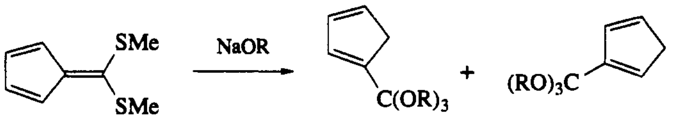
(380)

Scheme 69



(178)

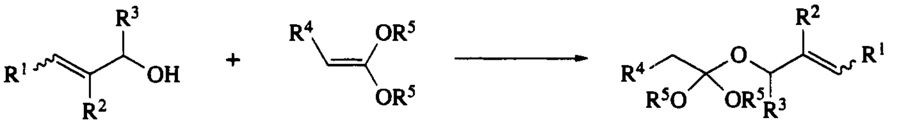
(381)



(382)

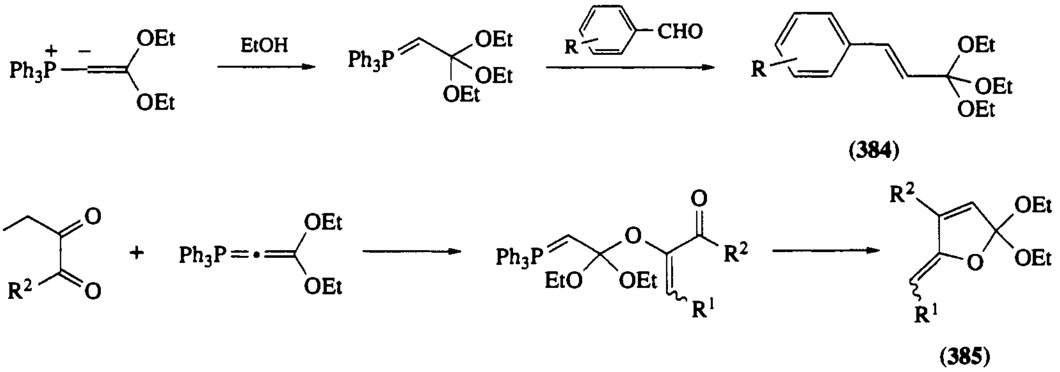
(179)

Mixed substituted orthoesters, *e.g.* (**383**; equation 180), can be obtained by addition of alcohols to ketene *O,O*-acetals.[838] With the aid of phosphoranes containing a ketene *O,O*-acetal structure, various orthoesters, *e.g.* (**384**) and (**385**) (Scheme 70) were prepared.[839–844] Cyclic orthoesters (**386**)–(**390**) (Scheme 71) are formed in cycloaddition reactions of ketene *O,O*-acetals with aldehydes,[845–848] ketones,[847,848] acyl cyanides,[849] oxiranes,[850] α-keto esters,[851] α-diketones[852] or ketones[853] (with irradiation), α,β-unsaturated aldehydes and ketones[854–856] (under pressure or catalyzed by $ZnCl_2$), diazoacetophenone,[857,858] diazoacetone[858] and azodicarboxylate.[859]



(180)

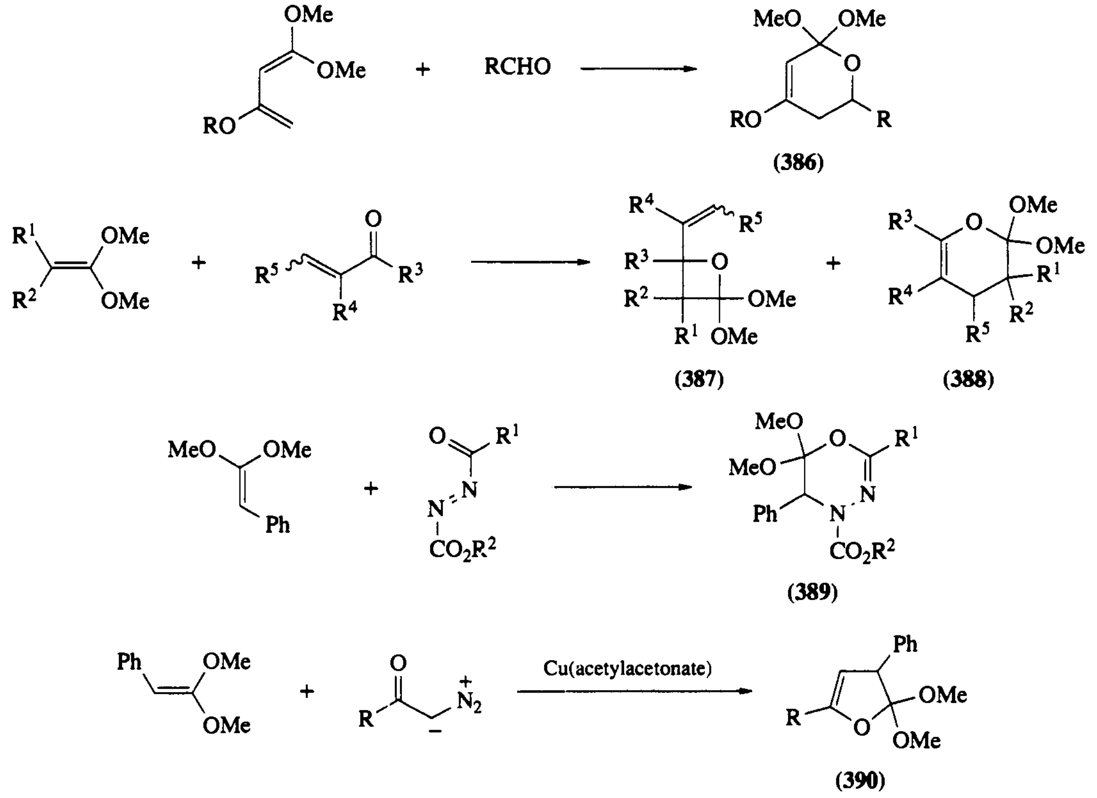
(383)



(384)

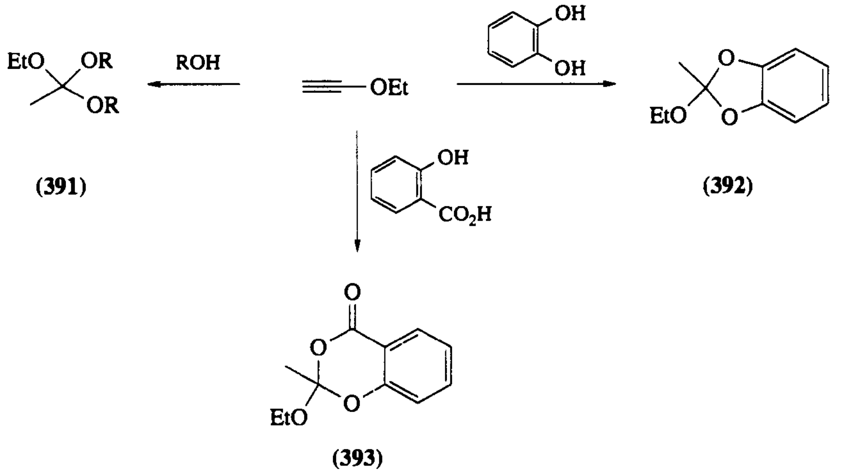
(385)

Scheme 70

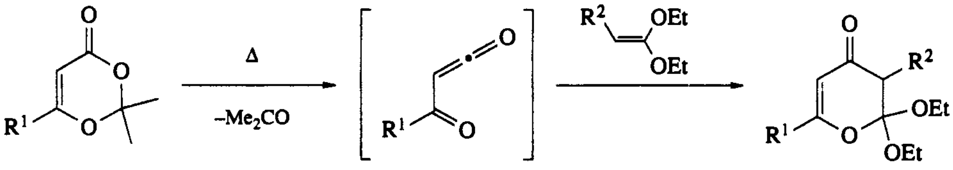


Scheme 71

Ethoxyacetylene adds, catalyzed by mercury acetate and $ZnCl_2$, aliphatic or aromatic alcohols to produce mixed substituted orthoesters, *e.g.* (**391**)–(**393**) (Scheme 72).[860] Acyl ketenes are formed on thermolysis of 1,3-dioxin-4-ones, which can be trapped with ketene acetals to give orthoesters (**394**; equation 181).[861–863] 2,2-Dialkoxydihydrofurans (**395**; equation 182) are accessible by addition of ketones to cyclopropenone acetals.[864] Treatment of 2-chloro-2,3-dimethoxy-1,4-dioxane with sodium methoxide affords the 2,2,3-trimethoxy-1,4-dioxane (**396**; equation 183).[865]

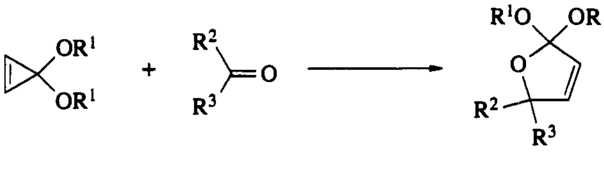


Scheme 72



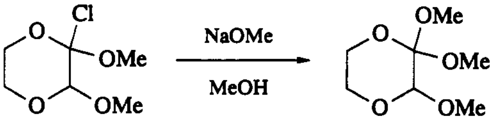
(394)

(181)



(395)

(182)

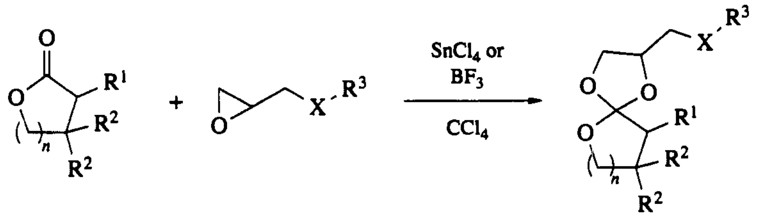


(396)

(183)

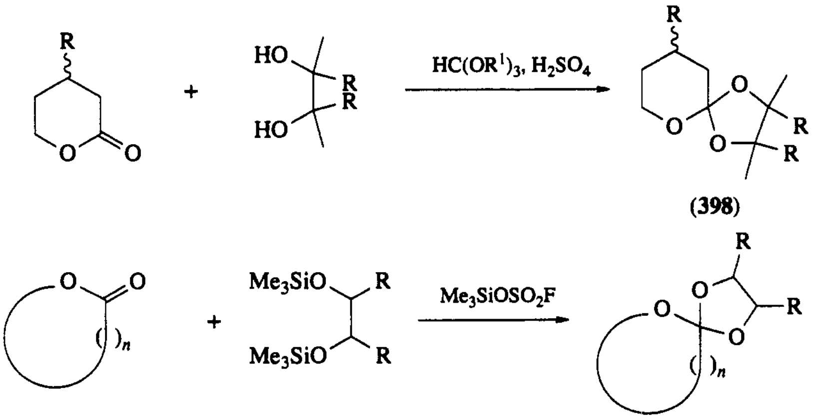
2.7.4.1.2 *From esters and diols or epoxides*

Spirocyclic orthoesters, *e.g.* (**397**; equation 184), have been synthesized by Lewis acid catalyzed addition of epoxides to lactones.[866,867] Lactones can be transformed to spirocyclic orthoesters, *e.g.* (**398**) and (**399**) (Scheme 73), by treatment with mixtures of either diols and orthoformates[868] or 1,2-bis(trimethylsiloxy)alkanes and trimethylsilyl triflate.[869,870]



(397)

(184)



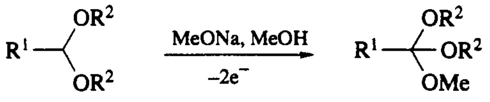
(398)

(399)

Scheme 73

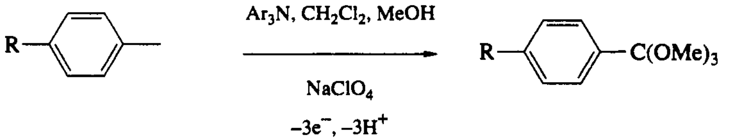
2.7.4.1.3 By oxidation of carbonyl compounds and derivatives

By electrochemical oxidation in alcoholic solution, *e.g.* in the presence of alkoxides, of aldehyde acetals or 1,3-dioxolanes derived from aldehydes orthoesters, *e.g.* (**400**; equation 185), can be obtained.[871–873] Orthobenzoates (**401**; equation 186) are accessible by electrolysis of substituted toluenes in the presence of triarylamines in solvents such as methanol/methylene chloride.[874] Decarboxylation and subsequent electrochemical oxidation of the dicarbonic acid (**402**; equation 187) in methanol affords cyclic orthoesters (**403**).[875]



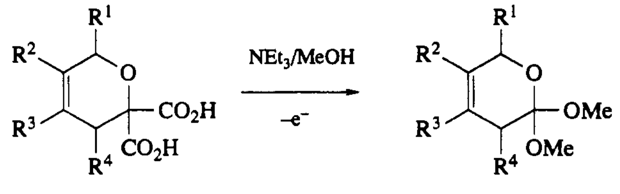
(**400**)

(185)



(**401**)

(186)

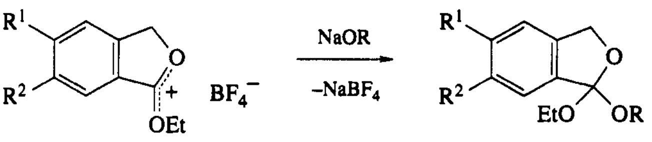


(**402**) (**403**)

(187)

2.7.4.1.4 From carboxonium salts, alkoxymethyleneiminium salts and related compounds (including amide acetals)

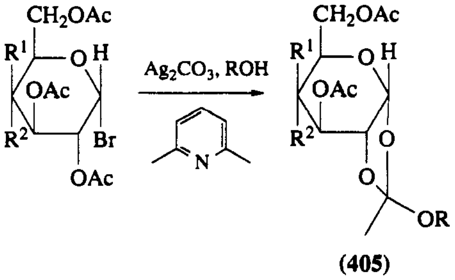
The reaction of lactones with trialkyloxonium salts furnishes lactonium salts, *e.g.* (**404**; equation 188), which react with alkoxides to give cyclic orthoesters.[22,24,27,876–878]



(**404**)

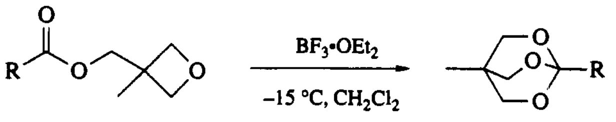
(188)

By means of silver salts, alcohols and 2,6-dimethylpyridine 'sugar orthoesters' (**405**; equation 189) have been prepared from *O*-acetylated glycosyl halides.[879] Bicyclic orthoesters (**407**; equation 190) are accessible by rearrangement of the esters (**406**).[880] Excess oxalyl chloride reacts with tetrahydrocarbazole to give the acid chloride (**408**; equation 191) which is converted by alcohols to orthoesters (**409**).[881,882]



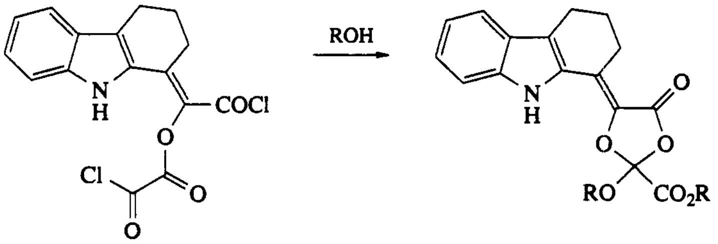
(**405**)

(189)



(406) **(407)**

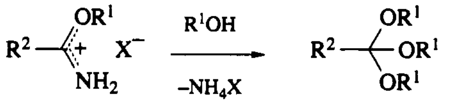
(190)



(408) **(409)**

(191)

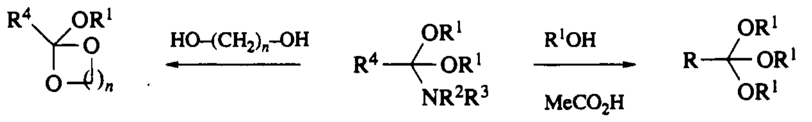
Pinner synthesis of orthoesters starting from alkoxymethyleneiminium salts (**410**; equation 192) (imino ester hydrohalides) is a standard procedure, which has been reviewed several times.[15,16,22,24,27] For some more recent results see ref. 7. Closely related to this reaction is the alcoholysis of *N*-alkyl- and *N*,*N*-dialkyl-alkoxymethyleneiminium salts[7] or acid amide–acid halide adducts.[883] Orthoesters are formed *via* *N*,*N*-dialkylalkoxymethyleneiminium salts when amide acetals (**411**; Scheme 74) are alcoholyzed in the presence of acetic acid.[7,214,884]



$$R^2C(OR^1)(NH_2)^+ X^- \xrightarrow[-NH_4X]{R^1OH} R^2C(OR^1)_3$$

(410)

(192)

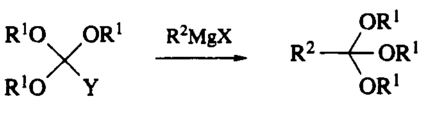


(411)

Scheme 74

2.7.4.1.5 *From orthocarbonic esters and related compounds (including trialkoxycarbenium ions)*

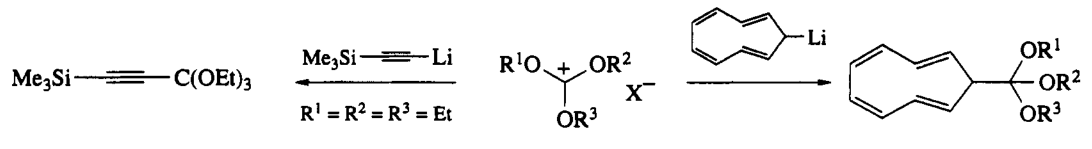
Orthocarbonates react with Grignard reagents to give orthocarboxylates (**412**; equation 193) in usually only moderate yields, because the orthoesters thus formed can react further with the Grignard reagent yielding acetals or ethers.[7,22,24,27,885,886] This side reaction can be suppressed by the use of trialkoxyacetonitriles instead of orthocarbonates.[887] From organolithium compounds and trialkoxycarbenium salts orthoesters (**413**) and (**414**) (Scheme 75) were synthesized.[888–890] The action of organolithium compounds on trialkoxyacetonitriles furnishes α-iminoorthocarboxylates (**415**; equation 194).[891] The reaction of tetraethylorthocarbonate with phenylacetylene can be catalyzed by $ZnCl_2$ and gives the phenylorthopropiolate (**416**; equation 195) in low yields.[22,24]



$$(R^1O)_3CY \xrightarrow{R^2MgX} R^2C(OR^1)_3$$

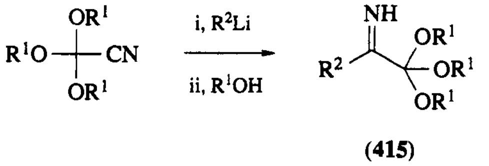
Y = OR, CN **(412)**

(193)



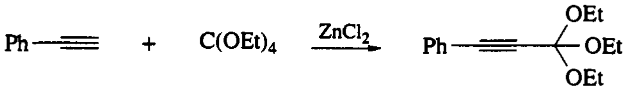
(413) **(414)**

Scheme 75



(194)

(415)

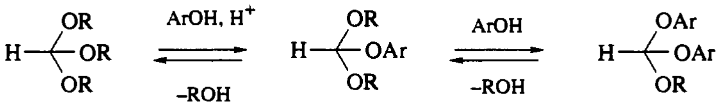


(195)

(416)

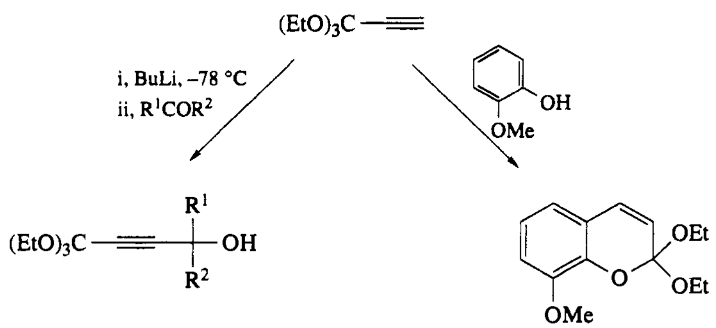
2.7.4.1.6 From orthoesters

The preparation of orthoesters from orthoesters by acid-catalyzed transesterification is a standard procedure, which has been reviewed several times.[7,22–27] Advantageous starting compounds are the methyl- or ethyl-orthoesters. Transesterification works well if primary alcohols are used whereas with secondary alcohols complete exchange of all alkoxy groups is difficult to achieve. Mixed substituted orthoesters are the products if tertiary[7] or sterically hindered[892] alcohols are used for transesterification. By this method mixed substituted orthoesters with aryloxy[7,893] or vinyloxy groups,[7,894,895] *e.g.* (**417**; equation 196), have been prepared. With diols and triols transesterification proceeds rapidly,[7,865,896,897] therefore it is not surprising that even acyloins (as 'endiols'),[898] nucleosides,[899,900] dihydroxylactones,[901] inositol,[902] alkaloids (germine),[903] *etc.* have been incorporated into the orthoester function. In a pyridine-catalyzed bromination orthoesters can be brominated to give α-bromo orthoesters, from which esters of orthoalkynecarboxylic acids can be prepared.[904] Triethylorthopropiolate has been used in alkynylation reactions giving orthoesters (**418**; Scheme 76).[905] From orthoacrylic and orthopropiolic acid triethyl ester and catechol



(196)

(417)

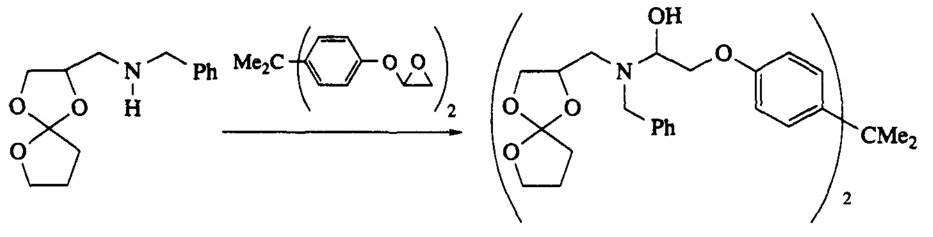


(418)

(419)

Scheme 76

monomethyl ether cumarin derivatives (**419**) are accessible.[906] A reactive bis(spiro)orthoester (**420**; equation 197) was synthesized from a trioxaspirononane.[907]

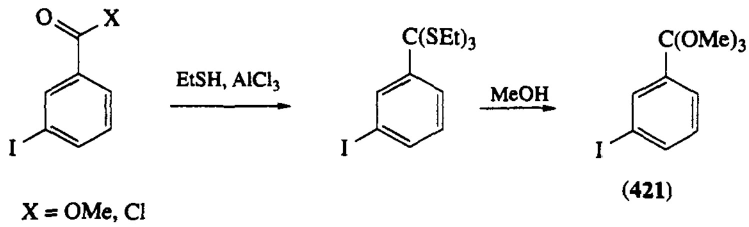


(197)

(**420**)

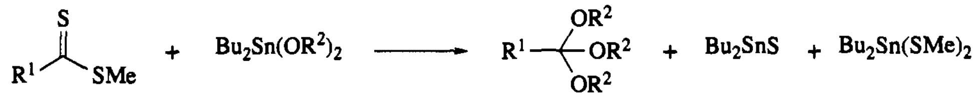
2.7.4.1.7 Miscellaneous methods

3-Iodotriethylorthotrithiobenzoate, a readily accessible compound, on reaction with methanol loses ethanethiol to give the methylorthobenzoate (**421**; equation 198).[908] Dialkoxydibutylstannanes convert dithiocarboxylic acid esters to orthoesters (**422**; equation 199).[909] From orthoesters and chloral the orthoesters (**423**; equation 200) can be synthesized.[910]



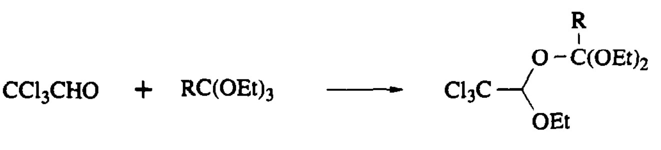
(198)

(**421**)



(199)

(**422**)



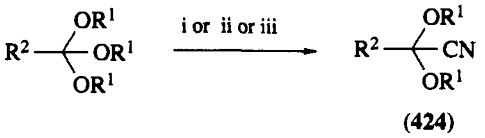
(200)

(**423**)

2.7.4.2 2,2-Bis(dialkoxy)carbonitriles

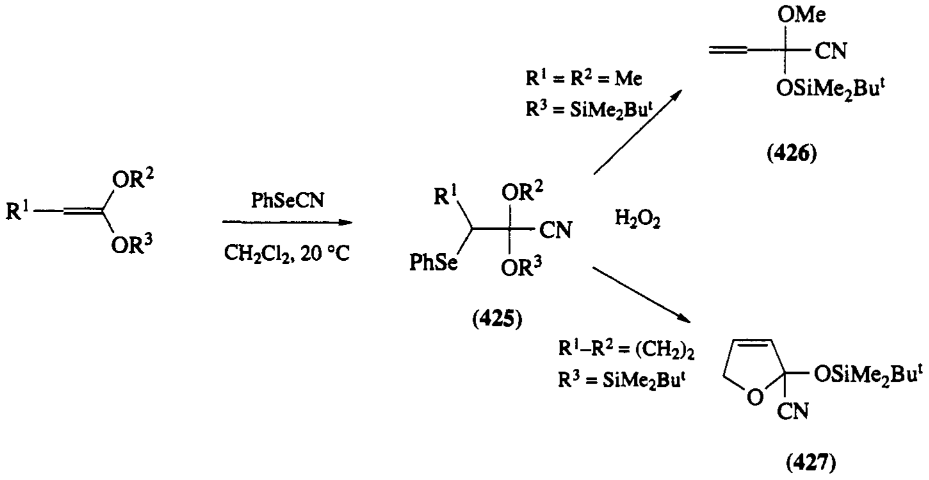
2.7.4.2.1 From orthoesters, ketene O,O*-acetals and cyanating reagents*

Orthoesters react with hydrocyanic acid, catalyzed by $ZnCl_2$, to give 2,2-dialkoxycarbonitriles (**424**; equation 201).[911] These nitriles can also be obtained by treatment of orthoesters with acyl cyanides[912] or trimethylsilyl cyanide in the presence of Lewis acids (BF_3, $SnCl_2$).[913–915] Cyanoselenation of ketene *O,O*-acetals affords the nitriles (**425**; Scheme 77),[916,917] from which other compounds of this type can be prepared, *e.g.* (**426**) and (**427**), by splitting off the phenylselenyl group. The acetonitrile derivative (**428**; equation 202) is a byproduct (23%) in the photochemical cycloaddition of ketene diethylacetal to 6-cyanouracil.[918]

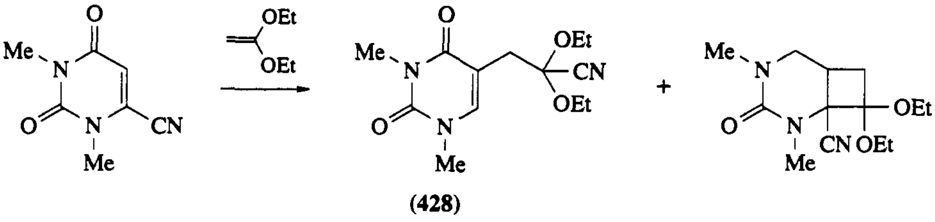


(201)

i, HCN, ZnCl$_2$; ii, R^{3}COCN; iii, Me$_3$SiCN, SnCl$_2$



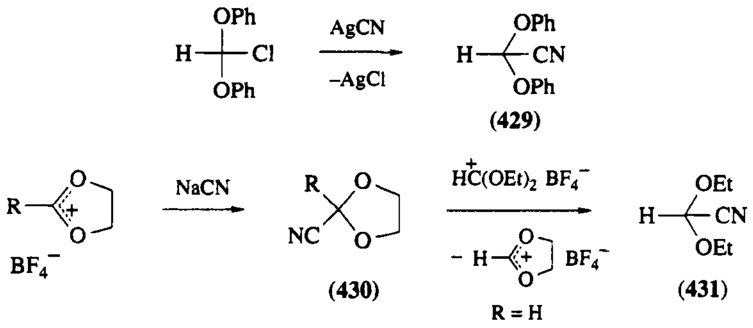
Scheme 77



(202)

2.7.4.2.2 *From dialkoxyhalomethanes or dialkoxycarbenium salts*

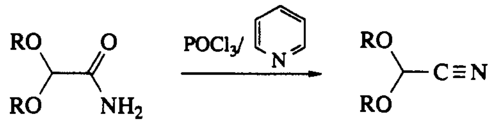
Chlorodiphenoxymethane[919] as well as 1,3-dioxolanylium salts[920] react with suitable cyanides to give the corresponding nitriles (**429**) and (**430**) (Scheme 78), respectively. The cyanodioxolanes (**430**) can serve as cyanide carriers to noncylic carboxonium ions giving, for example, diethoxyacetonitrile (**431**).[921]



Scheme 78

2.7.4.2.3 Dehydration of 2,2-dialkoxycarboxylic acid amides

The dehydration of 2,2-dialkoxyacetamides can be achieved by means of $POCl_3$/pyridine or trifluoroacetic anhydride and furnishes 2,2-dialkoxyacetonitriles (**432**; equation 203).[922–926]



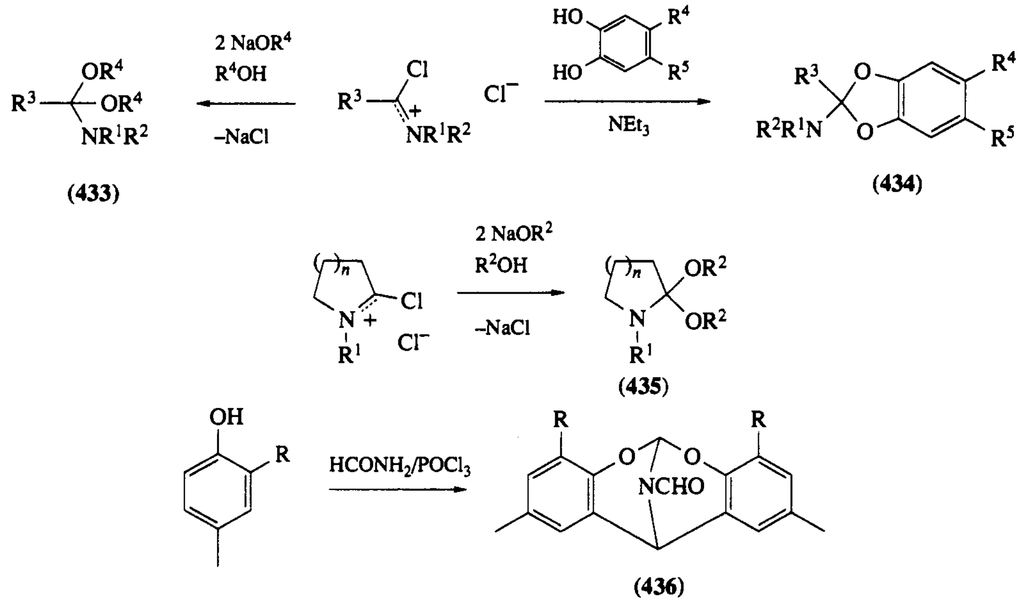
(432)

(203)

2.7.4.3 Amide Acetals (Including Lactam Acetals)

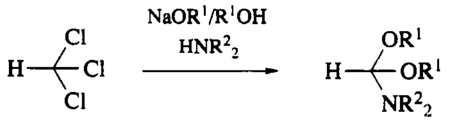
2.7.4.3.1 From amide halides (halomethyleneiminium salts)

N,N-Disubstituted chloromethyleneiminium chlorides (compare Section 2.7.2.2) react with alcoholic alkoxides at temperatures below 0 °C to give amide acetals (**433**; Scheme 79, yields 30–70%).[7–9,24,28,30,32,35] By the same method lactam acetals (**435**) are accessible. From dimethylformamide chloride and catechols the amide acetals (**434**) were prepared.[7,28,32,35] The bicyclic amide acetals (**436**) have been obtained from phenols, formamide and $POCl_3$.[927]



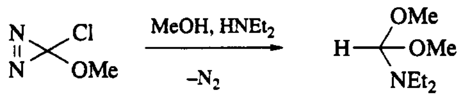
Scheme 79

In a usually less favorable procedure formamide acetals (**437**; equation 204) are accessible from chloroform or trichloroacetic acid esters and mixtures of secondary amines and alkoxides;[7,28,35] dichlorocarbene is thought to be an intermediate. Chloromethoxycarbene, generated from the diazirine (**438**; equation 205) inserts into the NH bond of diethylamine to yield the amide acetal (**439**).[928] The undissociated α,α-difluorotrialkylamines (**440**; Scheme 80) react with the alkali metal salts of diols to afford 1,3-dioxanes or 1,3-dioxolanes.[7,9,28,32,35,929,930] Noncyclic amide acetals can be prepared in the same manner.



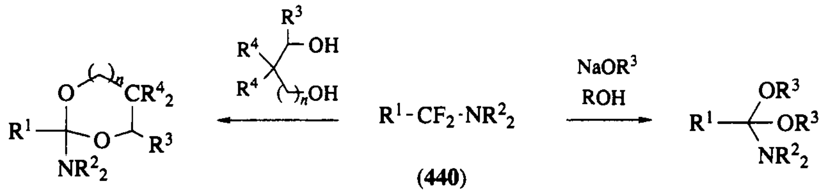
(437)

(204)



(438) (439)

(205)



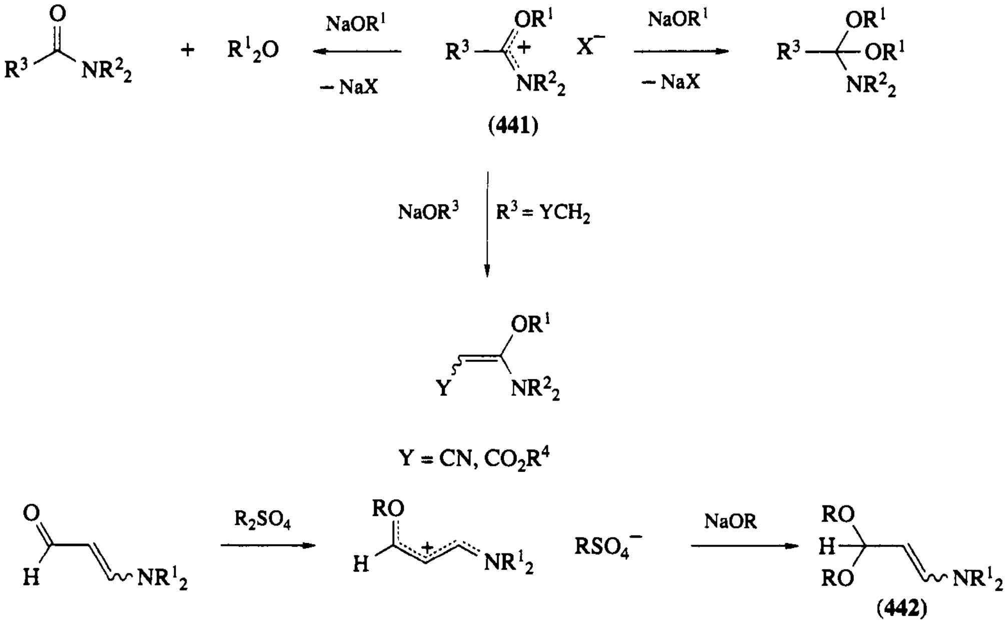
(440)

Scheme 80

2.7.4.3.2 *From alkoxymethyleneiminium salts*

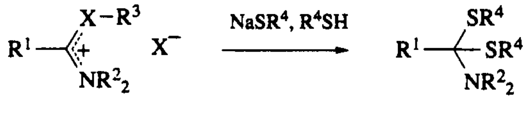
N,*N*-Disubstituted alkoxymethyleneiminium salts are converted by alkoxides to amide acetals.[7,10,24,28,32,35,634,829,931] Usually the alkoxides are applied in alcoholic solution; however, if alkoxymethyleneiminium salts having aromatic or electron-attracting groups bound to nitrogen are used, it is favorable to use alcohol-free alkoxides suspended in solvents of low polarity, *e.g.* diethyl ether or THF, to avoid orthoester formation. Since alkoxymethyleneiminium salts are easy to obtain (see Section 2.7.2.3) this procedure is the most convenient method for the preparation of amide acetals and lactam acetals and has found widespread application.

One side reaction, which is regarded as thermodynamically controlled, in this synthesis can be ether formation by dealkylation of the alkoxymethyleneiminium salt (**441**; Scheme 81). This type of reaction dominates if bulky groups are present in the iminium compound or if the reaction temperature (which should be kept below 0 °C) was chosen too high. Another side reaction is ketene *O*,*N*-acetal formation by deprotonation of the iminium salt, which can become the main reaction provided acidifying groups are present in the α-position to the iminium group. By the same reaction sequence vinylogous amide acetals (**442**) have been synthesized.[28,32]



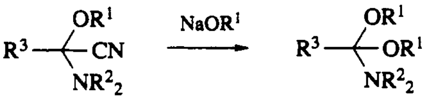
Scheme 81

Alkylmercaptomethyleneiminium salts as well as alkoxymethyleneiminium salts are transformed to amide thioacetals (**443**; equation 206) by alkali metal thiolates and thiols.[7,28,32,35] The action of alcoholic alkoxides on 2-alkoxy-2-dialkylaminocarbonitriles (**444**; equation 207) produces amide acetals.[7,634] Spirocyclic amide acetals (**446**; Scheme 82) were prepared from oxazolium salts (**445**) and substituted salicyl aldehydes.[932,933] The addition of alcohols to the 1,3-oxazolium-4-olate (**447**) affords heterocyclic amide acetals (**448**).[934]



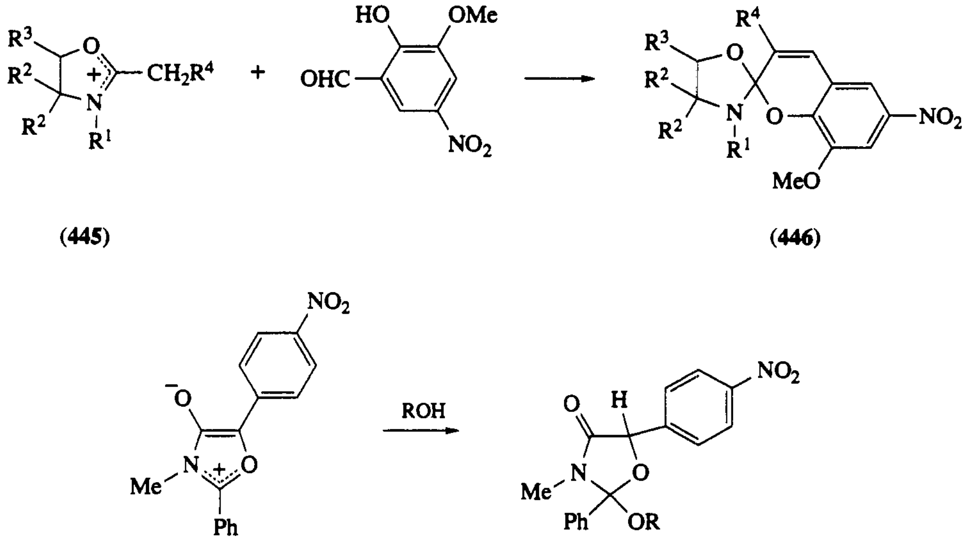
(**443**)

(206)



(**444**)

(207)



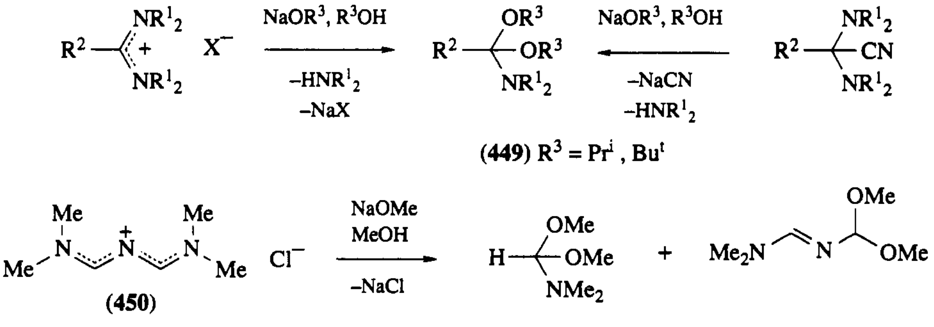
(**445**) (**446**)

(**447**) (**448**)

Scheme 82

2.7.4.3.3 From amidinium salts

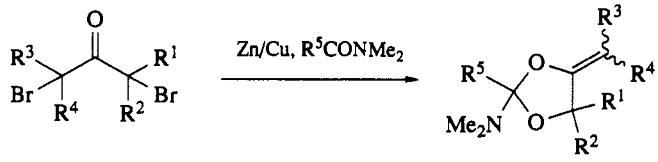
An important synthesis for formamide acetals with bulky alkoxy groups or with *N*-aryl substituents starts from the corresponding formamidinium salts or from bis(dialkylamino)acetonitriles; the reaction with alcoholic alkoxides furnishes the amide acetals (**449**; Scheme 83).[7,14,28,32,35] In the reaction of the azavinylogous formamidinium salt (**450**) with methanolic methoxide a mixture of *N*,*N*-dimethylformamide dimethyl acetal and its azavinylogous derivative is produced.[14,28,29]



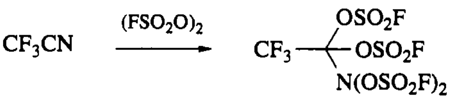
Scheme 83

2.7.4.3.4 *By acetalization of amides; by addition reactions to nitriles, lactim ethers or* N*-acylimino esters*

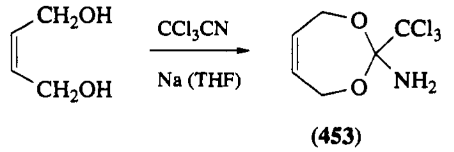
The action of a Zn/Cu couple on 1,3-dibromo ketones and secondary amides yields 2-dialkylamino-1,3-dioxolanes (**451**; equation 208).[935] Fluorosulfonic peracid anhydride adds to trifluoroacetonitrile to give an 'amide acetal' (**452**; equation 209).[936] In the addition of (*Z*)-2-butene-1,4-diol to trichloroacetonitrile, catalyzed by sodium, the 1,3-dioxepin (**453**; equation 210) is produced.[937] Bicyclic amide acetals (**454**; equation 211) are byproducts in the reaction of lactim ethers with diketene.[938] The methyl esters of perfluorinated carboxylic acids react with diethanolamine to afford bicyclic amide acetals (**455**; equation 212).[939] Heating of maleic anilides (**456**; equation 213) with acetic acid anhydride/sodium acetate gives heterocyclic compounds (**457**) containing an amide acetal structure.[940]



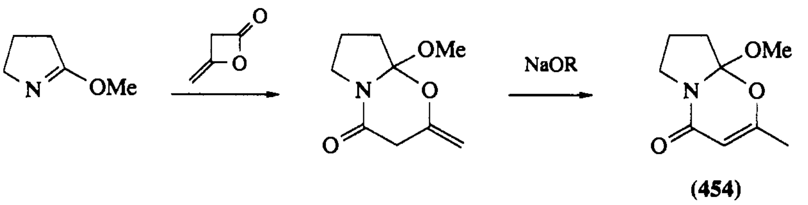
(**451**) (208)



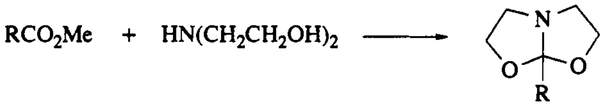
(**452**) (209)



(**453**) (210)

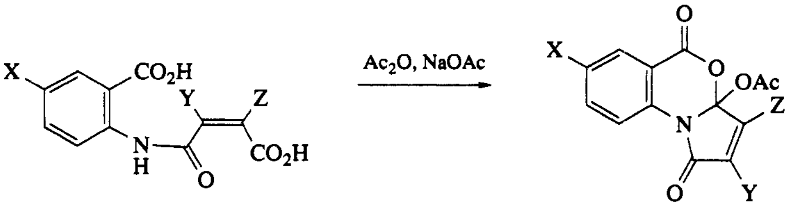


(**454**) (211)



(455) $R = CF_3, C_7F_{15}$

(212)

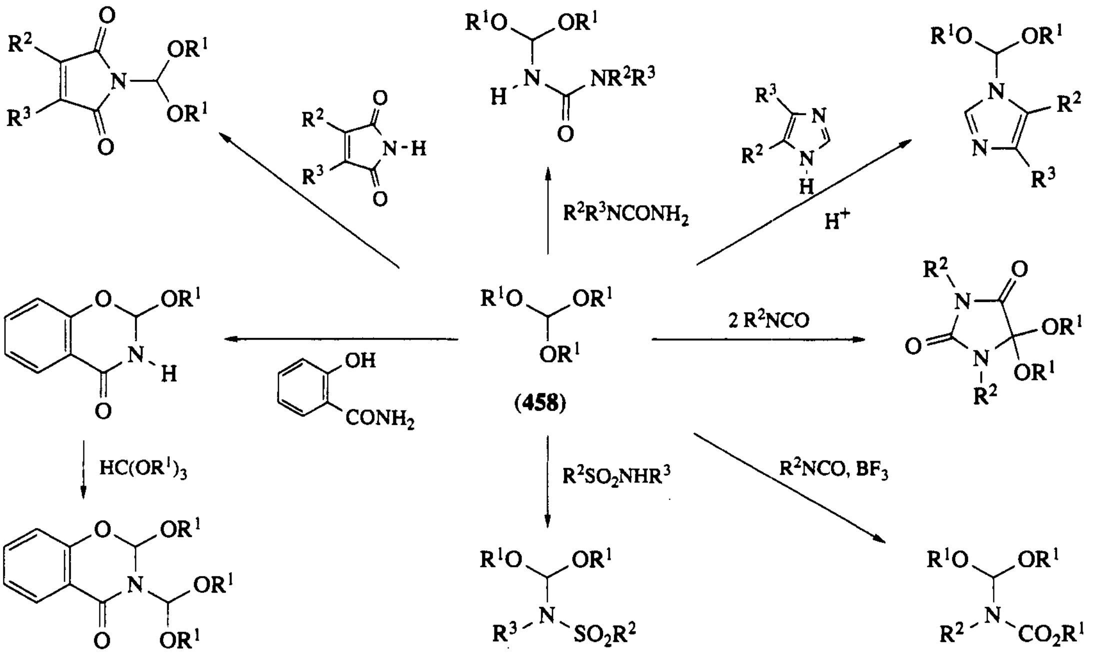


(456) (457)

(213)

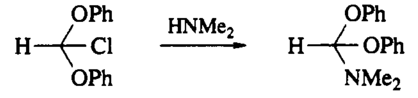
2.7.4.3.5 From orthoesters and related compounds

In orthoesters (**458**; Scheme 84) one alkoxy group can be replaced by aminoacyl groups, by aminosulfonyl groups or by the 1-imidazolyl group on reaction with ureas,[941,942] imides,[943,944] salicylamide,[945] *N*-alkylsulfonamides[946,947] in the presence of Lewis acids[948,949] or with imidazoles[944,950,951] under acid catalysis.[950,951] Excess aryl isocyanates convert orthoformates to acetals of parabanic acid.[952]



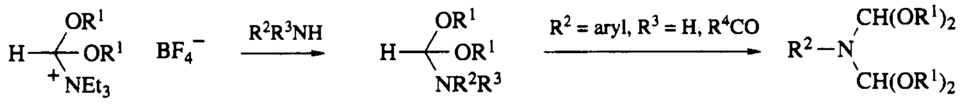
Scheme 84

The reaction of chlorodiphenoxymethane with dimethylamine yields the amide acetal (**459**; equation 214).[953] Dialkoxymethyl groups can be transferred by means of dialkoxyalkyltriethylammonium tetrafluoroborate (**460**; equation 215) to primary amines and amides, amidines, secondary amines and amides once or twice to give amide acetals (**461**) and (**462**).[7,28,29] Azodiazoles, *e.g.* (**463**) and (**464**) (Scheme 85), add to ketene dimethylacetal to give lactam acetals.[954,955]



$$\mathrm{HC(OPh)_2Cl \xrightarrow{HNMe_2} HC(OPh)_2NMe_2}$$ (214)

(459)



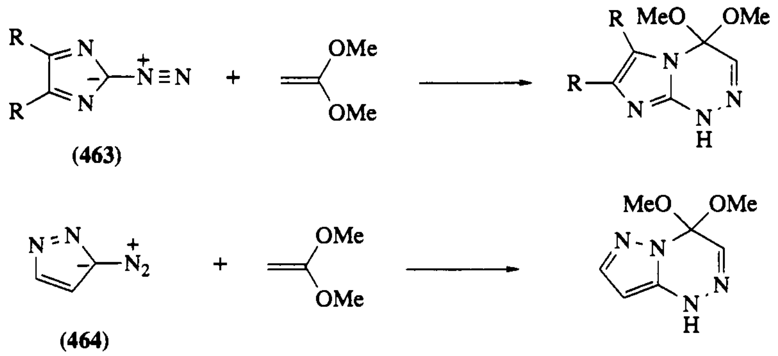
$$\mathrm{HC(OR^1)_2\overset{+}{N}Et_3\ BF_4^- \xrightarrow{R^2R^3NH} HC(OR^1)_2NR^2R^3 \xrightarrow{R^2 = aryl,\ R^3 = H,\ R^4CO} R^2{-}N[CH(OR^1)_2]_2}$$ (215)

(460) **(461)** **(462)**

$R^2 = R^3 = $ alkyl;

$R^2 = $ alkyl, $R^3 = $ CH=NR;

$R^2 = $ alkyl, $R^3 = $ COR



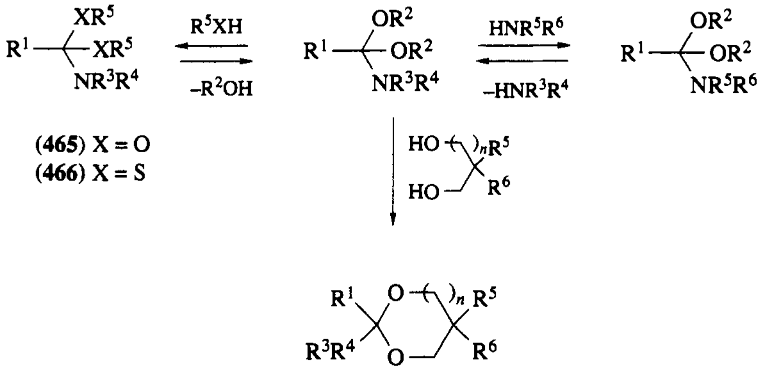
(463)

(464)

Scheme 85

2.7.4.3.6 *From orthoamide derivatives and related compounds*

Transacetalization, usually starting from the dimethyl acetal, is an important method for the preparation of amide acetals (**465**; Scheme 86) with long chain or secondary alkyl groups.[7,24,28,31,32,35] Recently a method was described which allows the preparation of even the di-*t*-butyl acetal of DMF by transacetalization.[956] To achieve good yields it is necessary to drive the equilibrium reaction to completion by distilling off the alcohol formed. Cyclic acetals (**467**) or dithioacetals (**466**) can be more easily synthesized by transacetalization.[7,24,28,31,32,35]



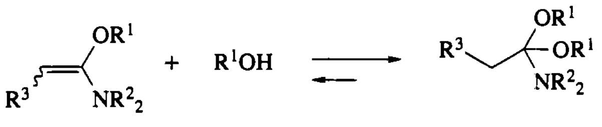
(465) X = O

(466) X = S

(467)

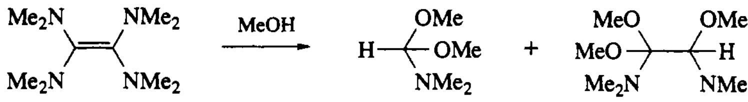
Scheme 86

Transamination of amide acetals is possible and of synthetic value if high boiling, strongly nucleophilic secondary amines are to be introduced.[7,957] Ketene *O*,*N*-acetals add alcohols to yield amide acetals (**468**; equation 216).[7,27–29,35] From tetrakis(dimethylamino)ethylene and methanol a mixture of amide acetals, *e.g.* (**469**) and (**470**; equation 217), is formed.[7,28,29,35] Azavinylogous formamide acetals (**471**; equation 218) are accessible by the action of formide acetals on tris(formylamino)methane[958] or formamide.[796]



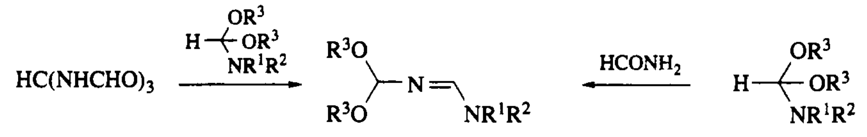
(216)

(468)



(217)

(469) **(470)**

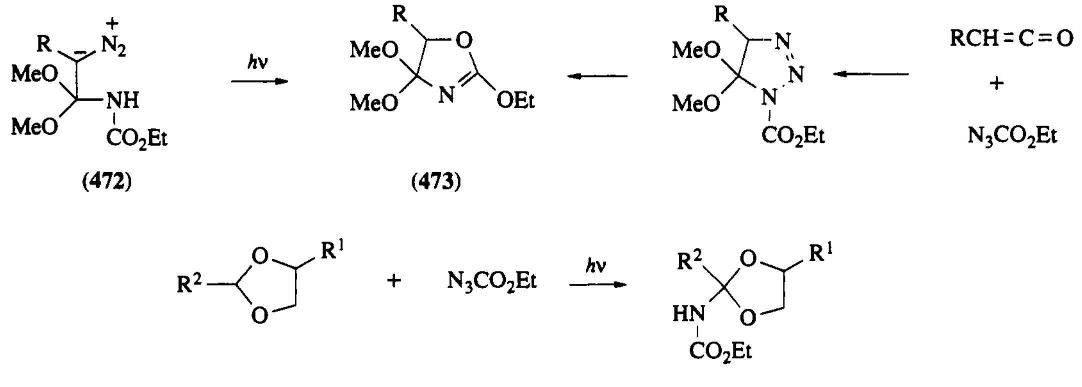


(218)

(471)

2.7.4.3.7 Miscellaneous methods

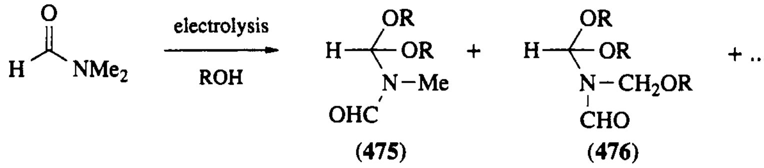
Photodecomposition of the diazo group containing acetals (**472**; Scheme 87) furnishes lactam acetals (**473**); similar compounds are accessible from ketenes and azidoformates.[7,27–29,35] From 1,3-dioxolanes and azidoformate the aminodioxolanes (**474**) were prepared.[7,27–29,35]



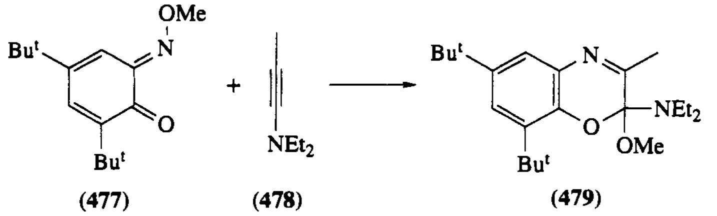
(472) **(473)** **(474)**

Scheme 87

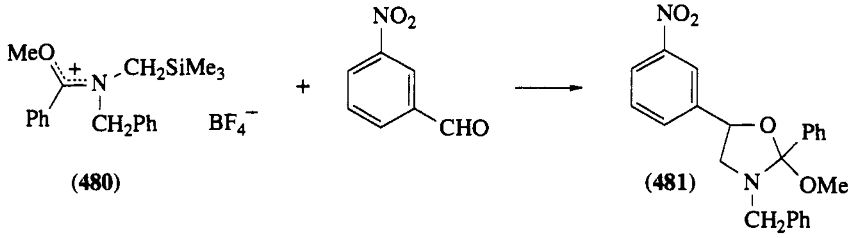
The electrolysis of DMF in alcohols affords a product mixture in which amide acetals, *e.g.* (**475**) and (**476**) (equation 219), are present.[959] The heterocyclic amide acetal (**479**; equation 220) was obtained by reaction of the ynamine (**478**) with the *o*-quinonimine derivative (**477**).[960] An azomethine ylide, generated *in situ* from the iminium salts (**480**; equation 221), transforms *m*-nitrobenzaldehyde to the oxazolidine derivative (**481**).[961]



(219)



(220)

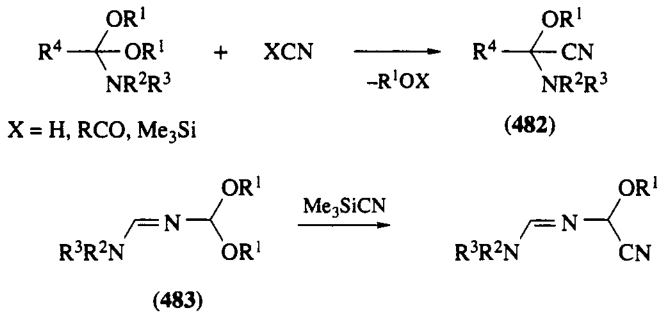


(221)

2.7.4.4 2-Alkoxy-2-dialkylaminocarbonitriles

2.7.4.4.1 From amide acetals and cyanating reagents

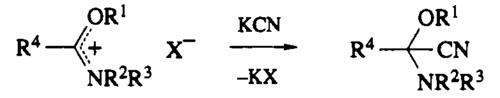
Amide acetals on treatment with hydrocyanic acid,[28,29,35,962] acyl cyanides[28,29,45] or trimethylsilyl cyanide[963] yield 2-alkoxy-2-dialkylaminocarbonitriles (**482**; Scheme 88). A similar cleavage has been performed with azavinylogous amide acetals (**483**).[798]



Scheme 88

2.7.4.4.2 From alkoxymethyleneiminium salts and alkali metal cyanides

In the most favorable preparative method for the synthesis of nitriles (**482**; equation 222) alkoxymethyleneiminium salts serve as starting materials, their reaction with alkali metal cyanides in a two-phase system (water/benzene or water/cyclohexane) affords the desired compounds in good yields.[28,29,35,962] An analogous reaction has been performed in acetonitrile.[964]



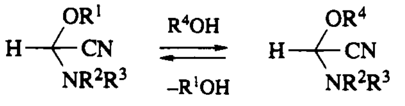
X = MeSO$_4$, BF$_4$

(482)

(222)

2.7.4.4.3 *From alkoxydialkylaminoacetonitriles*

On heating with higher boiling alcohols alkoxy group exchange occurs in the nitriles (**484**; equation 223), thus furnishing new nitriles (**485**).[962]



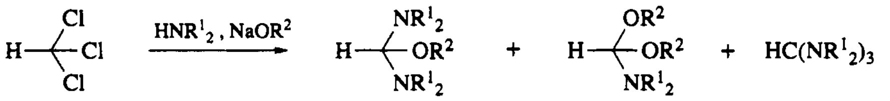
(484) **(485)**

(223)

2.7.4.5 Aminal Esters (Bis(dialkylamino)alkoxyalkanes)

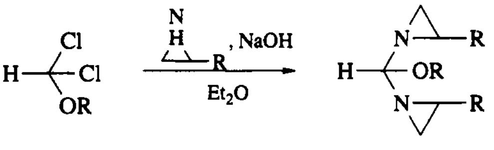
2.7.4.5.1 *From 1,1,1-trihaloalkanes or orthoesters*

In the presence of alkoxides chloroform reacts with secondary amines or aziridines to yield a mixture of aminal esters (**486**), amide acetals (**487**) and tris(dialkylamino)methanes (**488**; equation 224). Predominantly aminal esters (**489**; equation 225) are formed in the reaction of dichloromethyl ether with aziridines and sodium hydroxide.[7,28,29,35] The heterocyclic aminal ester (**491**; equation 226) was prepared from the perimidine (**490**) and triethyl orthoformate.[965]



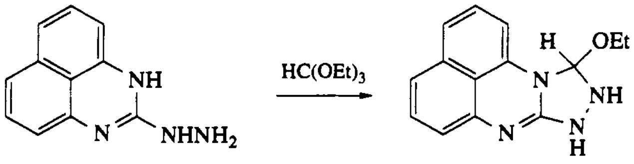
(486) **(487)** **(488)**

(224)



(489)

(225)

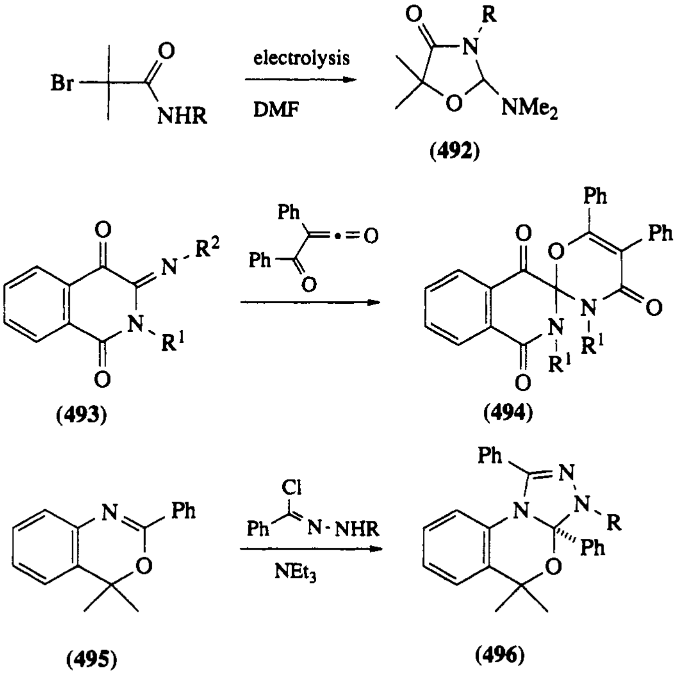


(490) **(491)**

(226)

2.7.4.5.2 From acid amides, lactamidines and cyclic imino esters

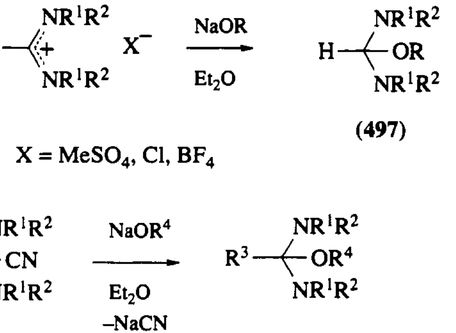
By electrolysis of 2-bromoamides in DMF the aminal esters (**492**; Scheme 89) are accessible.[966] In the reaction of benzoylphenyl ketene with the isoquinolinedione (**493**) the heterocyclic aminal ester (**494**) is formed.[967] Another heterocyclic aminal ester (**496**) was obtained from a hydrazinoyl chloride and a benzoxazine derivative (**495**).[968]



Scheme 89

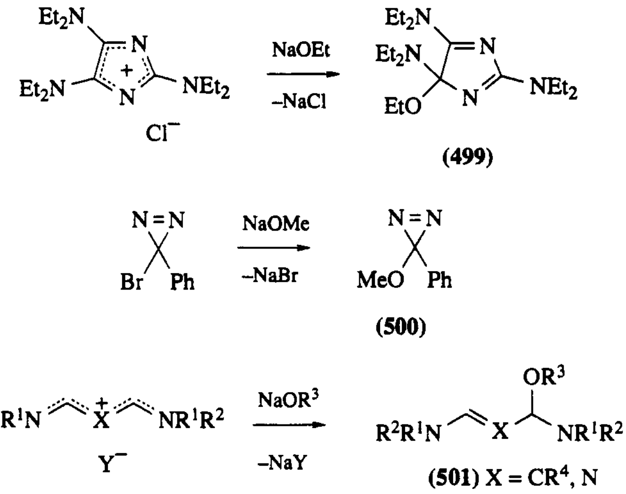
2.7.4.5.3 From amidinium salts and related compounds

N,N,N′,N′-Tetraalkylformamidinium salts[7,28,29,35] and *N,N′*-dimethyl-*N,N′*-diphenylformamidinium tetrafluoroborate[7,28,29,35] in ether, hexane, benzene or cyclohexane, have been treated with alcohol-free alkoxides to yield aminal esters (**497**; Scheme 90). By a similar procedure aminal esters (**498**) were obtained from 2,2-bis(dialkylamino)carbonitriles in good yields.[7,28,29,35]



Scheme 90

2,4,5-Tris(diethylamino)imidazolium chloride adds ethoxide to give the heterocyclic aminal ester (**499**; Scheme 91).[969,970] Treatment of 3-bromo-3-phenyldiazirine with methoxide at low temperatures affords the labile 3-methoxy-3-phenyldiazirine (**500**),[971] which can be regarded, from its substitution pattem, as an aminal ester. From vinylogous[7,28,29,35,972] and azavinylogous amidinium salts[973] the corresponding aminal esters (**501**) are accessible.



(**499**)

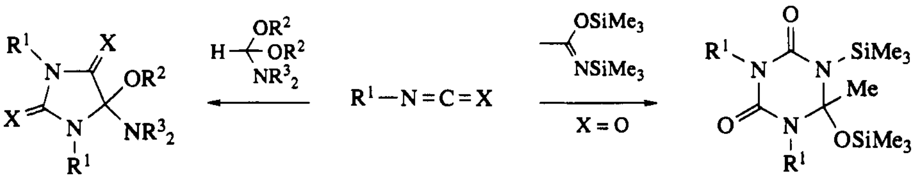
(**500**)

(**501**) X = CR^4, N

Scheme 91

2.7.4.5.4 *From orthoamide derivatives and related compounds*

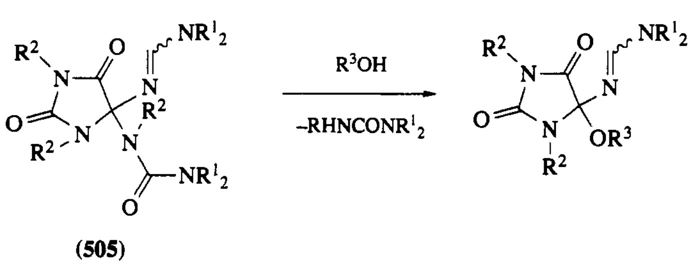
Amide acetals react with isocyanates and isothiocyanates to form *O,N*-acetals of parabanic acid (**502**) or dithioparabanic acid (**503**; Scheme 92).[7,28,29,35] The same type of compounds can be prepared from isocyanates and 2-alkoxy-2-dialkylaminoacetonitriles.[802] From bis(trimethylsilyl)acetamide and isocyanates the heterocyclic aminal esters (**504**) were obtained.[974] Alcoholysis of trisaminoalkane derivatives furnishes aminal esters.[974] This method is only of interest if the trisamino compound is easy to prepare, *e.g.* (**505**; equation 227).[801,802] In transamination reactions of amide acetals aminal esters (**506**) and (**507**) (equation 228) are formed among other products.[7,28,29,35,975]



(**502**) X = O
(**503**) X = S

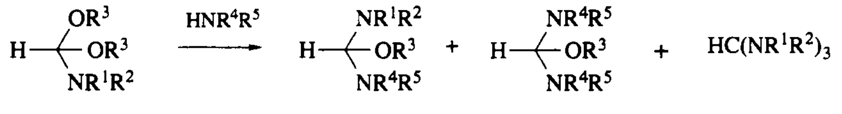
(**504**)

Scheme 92



(**505**)

(227)

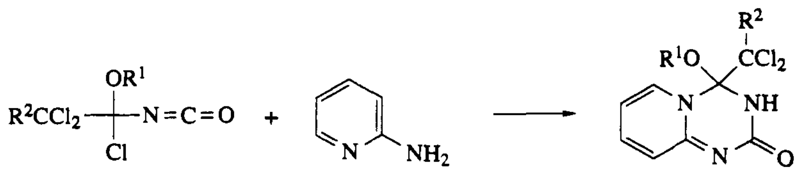


(**506**) (**507**)

(228)

2.7.4.5.5 Miscellaneous methods

2-Aminopyridine reacts with α-alkoxy-α-chloroalkyl isocyanates (**508**) to give heterocyclic aminal esters (**509**; equation 229).[976]



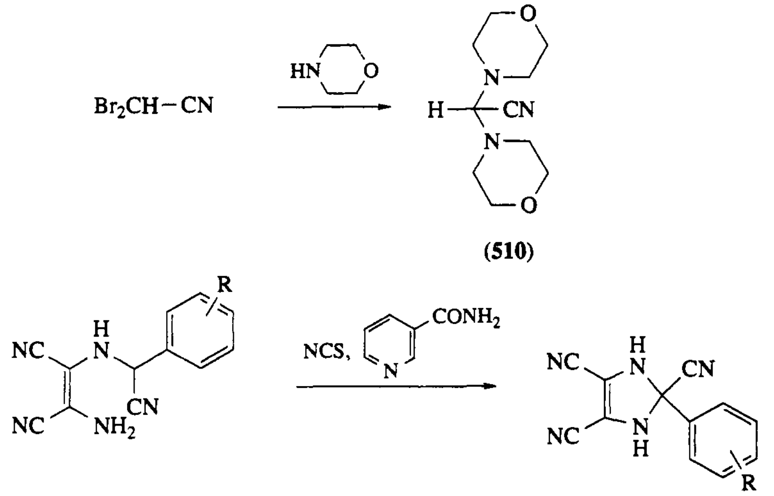
(508) **(509)**

(229)

2.7.4.6 2,2-Bis(dialkylamino)carbonitriles

2.7.4.6.1 From 2,2-dihalocarbonitriles and amines

Dibromoacetonitrile reacts with morpholine to form bis(morpholino)acetonitrile (**510**; Scheme 93).[28,29,35,977] The acrylonitriles (**511**) are cyclized to the imidazolines (**512**) by treatment with NCS and nicotinic acid amide.[978]



(510)

(511) **(512)**

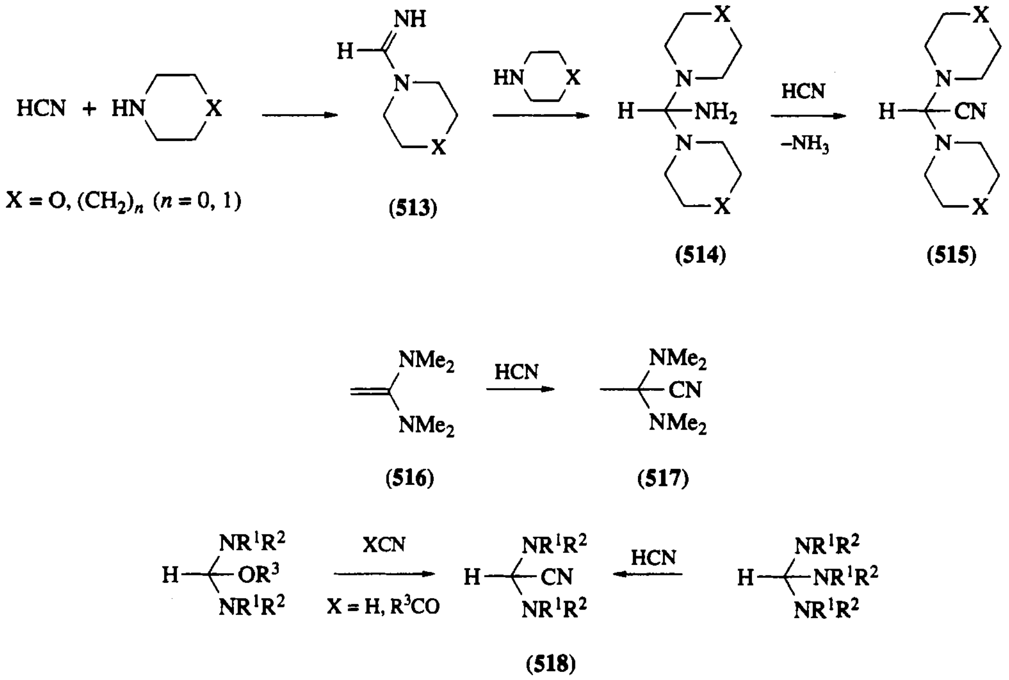
Scheme 93

2.7.4.6.2 From secondary amines and hydrocyanic acid

Alicyclic amines react with water-free HCN, probably *via* amidines (**513**; equation 230) and trisaminomethanes (**514**), to yield the corresponding bis(dialkylamino)acetonitriles (**515**).[28,29,35,977,979]

2.7.4.6.3 From ketene aminals, aminal esters and tris(dialkylamino)alkanes

Hydrocyanic acid adds to bis(dimethylamino)ethylene (**516**) to give 2,2-bis(dimethylamino)propionitrile (**517**; Scheme 94).[28,29,35,977] By cleavage of aminal esters with acyl cyanides or hydrocyanic acid α,α-diaminonitriles (**518**) are accessible; trisaminomethanes have also been cleaved by HCN to give nitriles (**518**).[28,29,35,977]

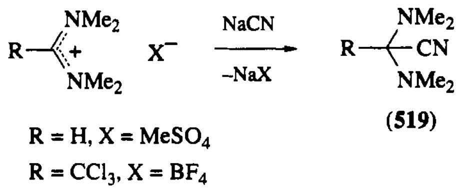


(230)

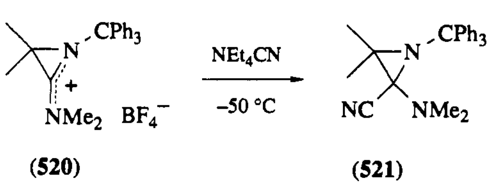
Scheme 94

2.7.4.6.4 *From amidinium salts and alkali metal cyanides*

In a two-phase system (water/cyclohexane) amidinium salts react with alkali metal cyanides to form bis(dialkylamino)carbonitriles (**519**; equation 231).[28,29,35,977] With the aid of tetraethylammonium cyanide the aziridinium salt (**520**; equation 232) was transformed to the nitrile (**521**).[980]



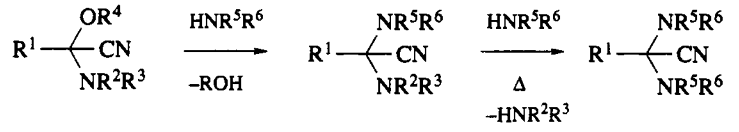
(231)



(232)

2.7.4.6.5 *From 2-alkoxy-2-dialkylaminocarbonitriles and related compounds*

On treatment with secondary amines 2-alkoxy-2-dialkylaminocarbonitriles readily exchange their alkoxy groups *versus* dialkylamino groups; mixed substituted nitriles (**522**; equation 233) can be prepared in this way.[28,29,35,977] At elevated temperatures an exchange of the amino group occurs additionally. This procedure is useful in the preparation of nitriles bearing alicyclic amino groups.[28,29,35,977,981]

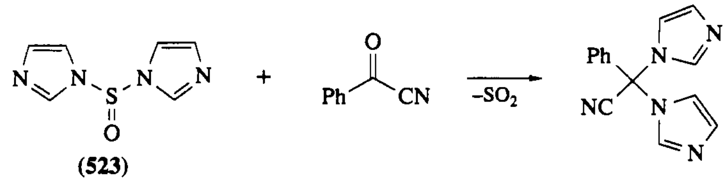


(522)

(233)

2.7.4.6.6 Miscellaneous methods

Thionylbisimidazolide (**523**) reacts with benzoyl cyanide to give α,α-bis(imidazolyl)benzyl cyanide (**524**; equation 234).[982]



(523)

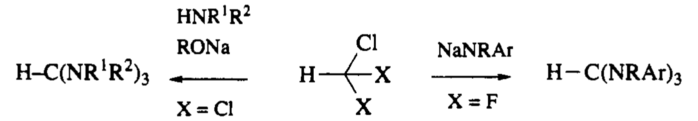
(524)

(234)

2.7.4.7 Tris(dialkylamino)alkanes

2.7.4.7.1 From 1,1,1-trihaloalkanes, amide halides and related compounds

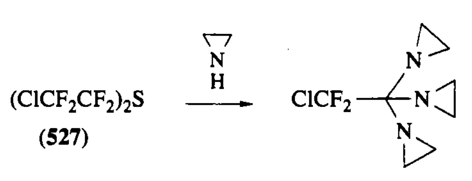
The reaction of chloroform with imidazoles,[983,984] benzimidazoles[985] and secondary amines (especially alicyclic amines) in the presence of alkoxides or hydroxides, as well as the reaction of chlorodifluoromethane with sodium *N*-alkyl-*N*-arylamides furnishes trisaminomethanes (**525**) and (**526**) (Scheme 95), respectively.[7,28,29,35] Aziridine transforms fluorodialkyl sulfide (**527**) to the orthoamide (**528**; equation 235).[7]



(525)

(526)

Scheme 95



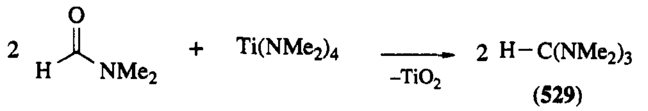
(527)

(528)

(235)

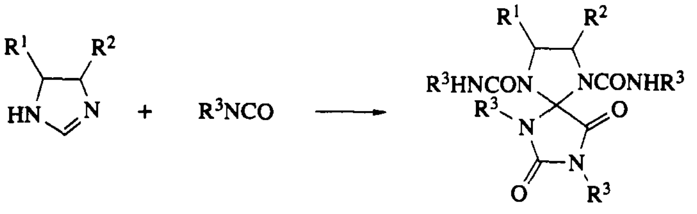
2.7.4.7.2 From amides, amidines and imidates

Tetrakis(dimethylamino)titanium converts DMF to tris(dimethylamino)methane (**529**; equation 236).[7,28,29,35] This compound is also formed in the reaction of *N,N,N',N'*-tetramethyloxamide with the titanium reagent,[7] whereas amides which have α-CH bonds are converted to ketene aminals.[7,28,29,35] Cyclic and spirocyclic compounds, containing the substitution pattern of a trisamino compound, are formed in the reaction of *N,N*-dialkylformamides or *N'*-aryl-*N,N*-dialkylformamidines with aryl isocyanates.[7] Similar compounds, *e.g.* (**530**; equation 237), are produced in the reaction of imidazolines[986] or lactamidines[987] with isocyanates.



(529)

(236)

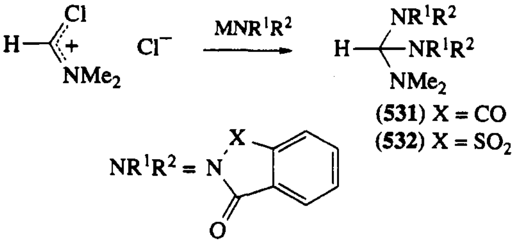


(530)

(237)

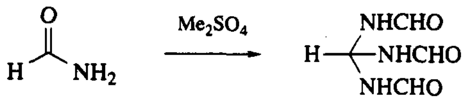
2.7.4.7.3 *From amide halides and related compounds*

N,*N*-Dimethylformamide chloride reacts with the alkali metal salts of phthalimide, saccharin or dimethylamine to give trisaminomethanes, *e.g.* (**531**), (**532**) and (**529**), respectively.[7,28,29,35] The preparation of tris(formamido)methane (**533**; equation 239) proceeds *via* iminium salts, which are formed as intermediates in the reaction of alkylating reagents (dialkyl sulfates, sulfonic acid esters, oxonium salts) or acylating reagents ($POCl_3$, PCl_3, SO_2Cl_2) with formamide.[7,28,29,35]



(**531**) X = CO
(**532**) X = SO_2

(238)

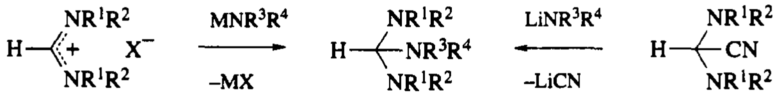


(533)

(239)

2.7.4.7.4 *From amidinium salts or 2,2-bis(dialkylamino)carbonitriles*

N,*N*,*N'*,*N'*-Tetrasubstituted formamidinium salts as well as bis(dialkylamino)acetonitriles have been reacted with alkali metal amides of secondary amines to give tris(dialkylamino)methanes (**534**; Scheme 96).[7,28,29,35]

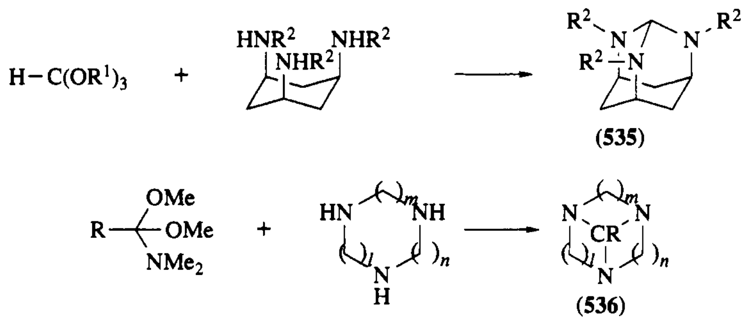


(534)

Scheme 96

2.7.4.7.5 From orthoesters, orthoamides and related compounds

Orthoformates have been reacted with secondary aliphatic amines,[7,28,29,35] *N*-alkylanilines,[7] 1,3,5-triaminocyclohexanes[7] and cyclic triamines[988,989] to afford trisaminomethane derivatives, *e.g.* (**535**) and (**536**) (Scheme 97), usually in unsatisfactory yields. Better results have been reported when orthoformates were replaced by amide acetals.[988,990,991]

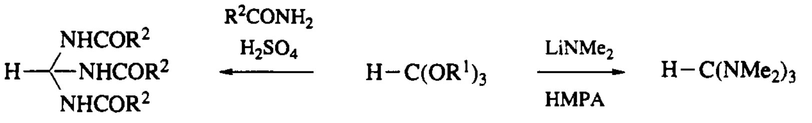


(**535**)

(**536**)

Scheme 97

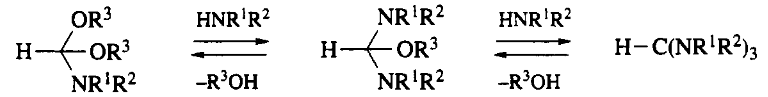
In the acid-catalyzed reactions of orthoformates with primary carbon acid amides or urethanes tris(acylamino)methanes (**537**; Scheme 98) are formed with good yields.[7,28,29,35] Dimethylaminodi(phthalimido)methane (**531**) is accessible from phthalimide and DMF diethyldithioacetal.[7] Lithium dimethylamide, prepared *in situ* from lithium and dimethylamine in HMPA converts orthoformates to tris(dimethylamino)methane (**529**).[28]



(**537**) (**529**)

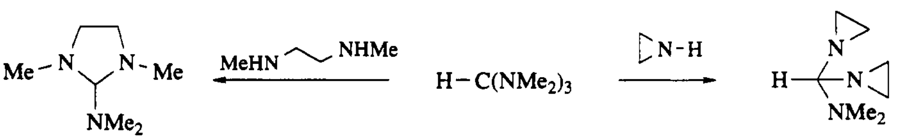
Scheme 98

On heating amide acetals (**538**; equation 240), or better aminal esters, with amines (preferably alicyclic amines) an equilibrium with the corresponding trisaminomethane is established. To achieve good yields of the orthoamide it is necessary to distill off the alcohol formed. Tris(dimethylamino)methane (**529**) is readily transaminated with high-boiling amines to give orthoamides, *e.g.* (**539**) and (**540**) (Scheme 99).[7] Parabanic acid aminals (**541**; equation 241) are formed in good yields in the reaction of 2,2-bis(dialkylamino)acetonitriles with isocyanates.[801,802]



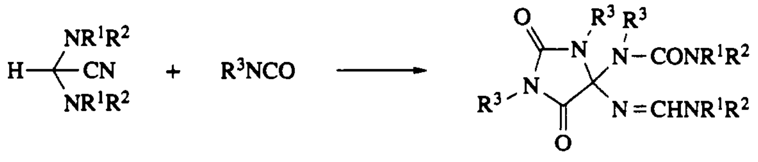
$$\mathrm{H{-}C(OR^3)_2(NR^1R^2)} \underset{\mathrm{-R^3OH}}{\overset{\mathrm{HNR^1R^2}}{\rightleftharpoons}} \mathrm{H{-}C(OR^3)(NR^1R^2)_2} \underset{\mathrm{-R^3OH}}{\overset{\mathrm{HNR^1R^2}}{\rightleftharpoons}} \mathrm{H{-}C(NR^1R^2)_3} \qquad (240)$$

(**538**)



(**539**) (**540**)

Scheme 99

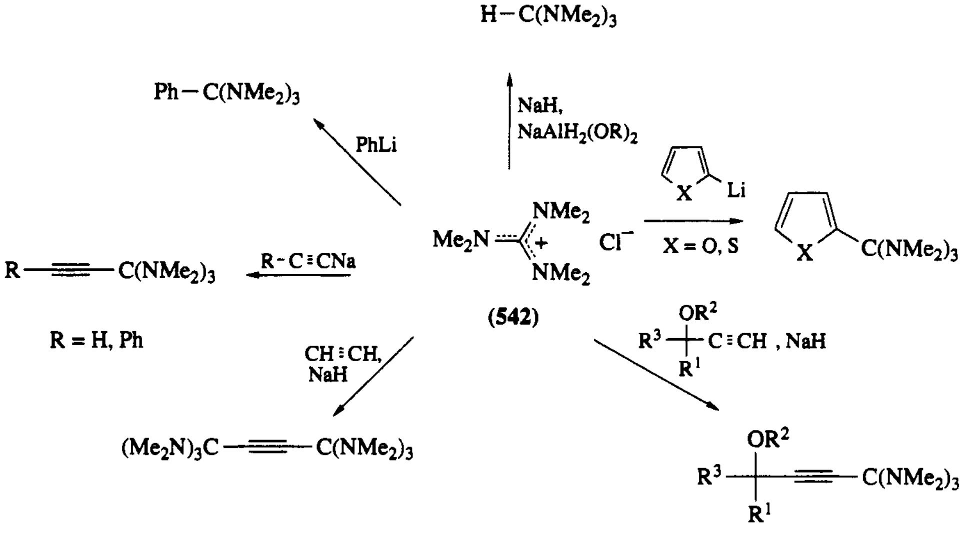


(541)

(241)

2.7.4.7.6 *From guanidinium salts or orthocarbonic acid derivatives*

N,*N*,*N*′,*N*′,*N*″,*N*″-Hexamethylguanidinium chloride (**542**; Scheme 100) is readily reduced by means of NaH in the presence of sodium alkoxyaluminates, boronic acid esters or aluminum alkoxides.[7] Organometallic derivatives such as phenyllithium, 2-thienyllithium or 2-furanyllithium or sodium acetylides add to the guanidinium salt to give the corresponding orthoamides. From tetrakis(dimethylamino)methane and phenylacetylene 1-phenyltris(dimethylamino)-1-propyne (**543**; equation 242) was prepared.[992]



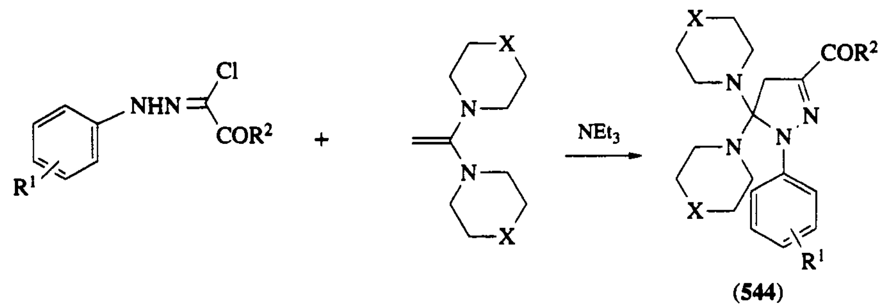
Scheme 100

$$\mathrm{C(NMe_2)_4} \xrightarrow{\mathrm{Ph{-}{\equiv}}} \mathrm{Ph{-}{\equiv}{-}C(NMe_2)_3} \qquad (242)$$

(543)

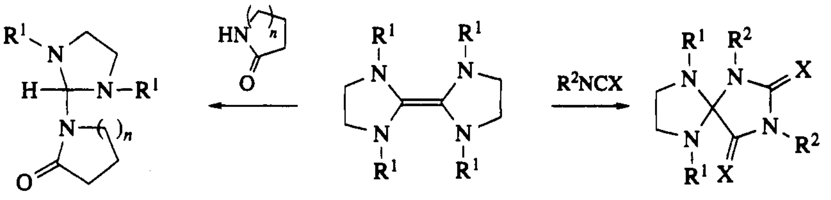
2.7.4.7.7 *From ketene aminals*

Hydrazinoyl chlorides react with ketene aminals in the presence of triethylamine to give diaminopyrazolines (**544**; equation 243).[993] From tetraaminoethylenes and amines or amine derivatives or heterocumulenes tris(amino)methane derivatives, *e.g.* (**545**) and (**546**) (Scheme 101) are formed. Reactions of this type have been reviewed.[994]



(544)

(243)



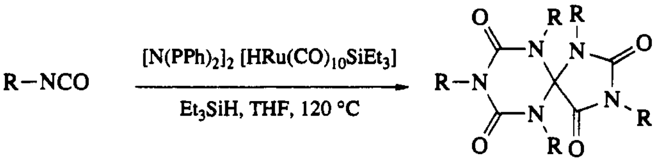
(545)

(546)

Scheme 101

2.7.4.7.8 Miscellaneous methods

Heterocyclic compounds possessing the structural pattern of orthoamides were obtained by spirocyclization of isocyanates in the presence of triethylsilane catalyzed by a ruthenium cluster (equation 244).[995,996]



(244)

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2.8

Inorganic Acid Derivatives

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2.8.1 INTRODUCTION

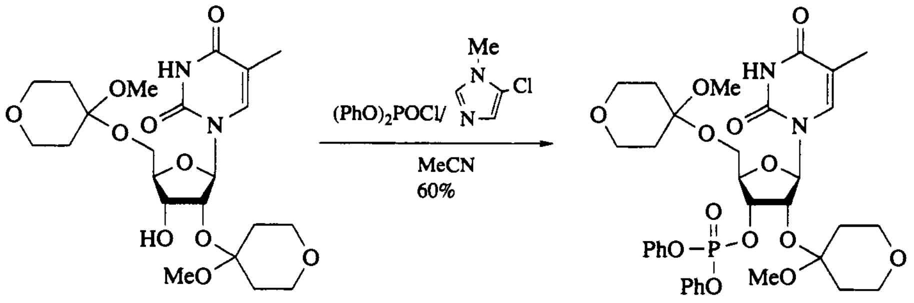
An organic phosphoric acid is a well recognized structural unit appearing in a number of biologically important substances such as nucleic acids, phospholipids, and inositol phosphates, and, accordingly, efforts to construct the structure have extensively been made so far, providing many ways to the organic phosphoric acid derivatives.[1] Among the existing methods, the most straightforward and synthetically useful one is phosphorylation of protic substances. In phosphorylation, of great importance is discovery of effective phosphorylating agents. In addition, invention of the protecting groups for a phosphoric acid moiety is sometimes an essential problem, because the many important classes of biochemical substances discussed above are phosphomonoesters or phosphodiesters, which generally are derived by deprotection of the corresponding phosphotriester precursors. This chapter describes methods of phosphorylation, which are classified by the type of phosphorylating agents employed, and makes brief discussion on the protecting groups.

2.8.2 USE OF PENTAVALENT PHOSPHORUS REAGENTS

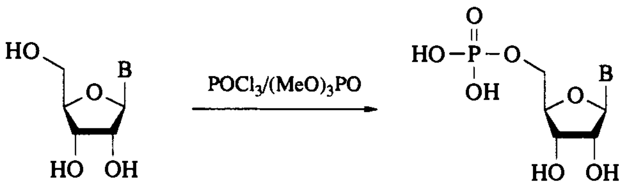
Pentavalent phosphorus compounds with a suitable leaving group, listed below, serve effectively as phosphorylating agents for some protic substrates such as alcohols, phenols, primary and secondary amines, thiols, phosphates, *etc.*

2.8.2.1 Halophosphates

Three types of chlorophosphates, *i.e.* phosphorus oxychloride ($POCl_3$), phosphorodichloridates [$(RO)POCl_2$], and phosphorochloridates [$(RO)_2POCl$], are among the most widely employed phosphorylating agents for the synthesis of organic phosphoric acid derivatives.[2] The reaction with chlorophosphates is usually promoted by tertiary amines, including trialkylamines, pyridine and its analogs, DBU, *N*-alkylazoles, *etc.* Use of 1-methyl-5-chloroimidazole effects phosphorylation of sterically hindered alcohols (equation 1).[3] In place of amines, molecular sieves can be used as acid scavengers.[4] Trialkyl phosphates also assist the phosphorylation (equation 2).[5] Less reactive phosphorofluoridates are usable for some limited cases. The reagents cannot be activated by the ordinarily used amines such as trialkylamines, pyridine and related compounds,[6] but are effected by use of DBU as a base (equation 3).[7] There is little example of phosphorylation using bromophosphates.



(1)



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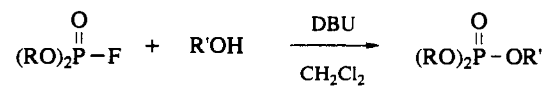
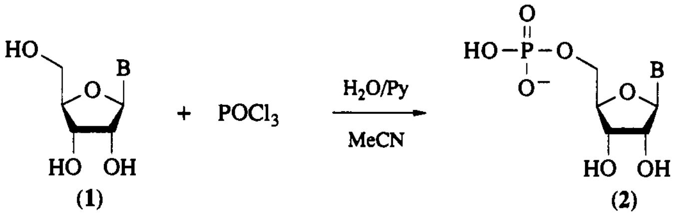


$$(RO)_2\overset{O}{\overset{\|}{P}}-F + R'OH \xrightarrow[CH_2Cl_2]{DBU} (RO)_2\overset{O}{\overset{\|}{P}}-OR' \qquad (3)$$

Phosphorus oxychloride is a suitable reagent for preparation of the symmetrically substituted phosphotriesters of type $(RO)_3PO$. The preparation is easily achieved by treatment of phosphorus oxychloride with 3 equiv. of alcohols or their metal salts. The reaction is generally promoted by a base or acid. Titanium trichloride is a particularly effective catalyst for the reaction.[8] Conversion of $POCl_3$ to unsymmetrically substituted phosphotriesters is achievable with difficulty. Phosphorochloridates and phosphorodichloridates have been used for the preparation of mixed tertiary phosphoric esters of type $(RO)_mPO(OR')_n$ ($m = 1$, $n = 2$, or $m = 2$, $n = 1$) in a very wide variety.[9] Reaction of phosphorus oxychloride and 1 or 2 equiv. of alcohols followed by hydrolysis forms phosphomonoesters or phosphodiesters, respectively. The hydrolysis may be generally effected by dilute aqueous alkali. Some phosphorodichloridate intermediates are easily hydrolyzed by water. For example, the phosphorylation of a ribonucleoside (**1**; equation 4) with phosphorus oxychloride in an aqueous pyridine–acetonitrile mixture furnishes the nucleoside 5′-monophosphate (**2**) in excellent yield.[10]

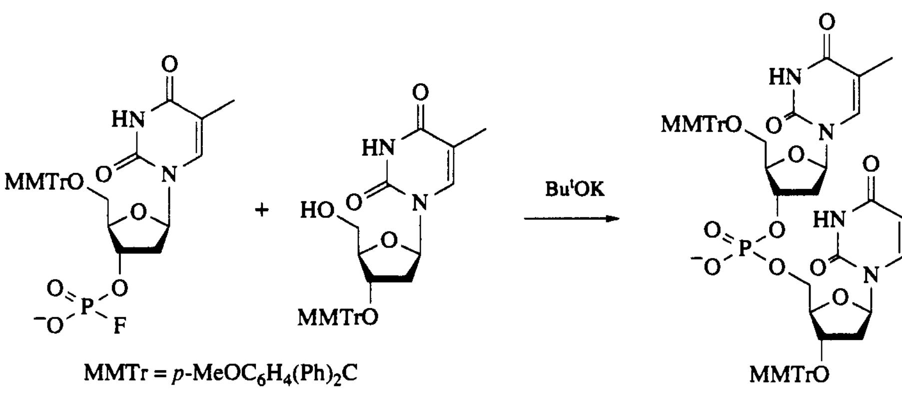


(4)

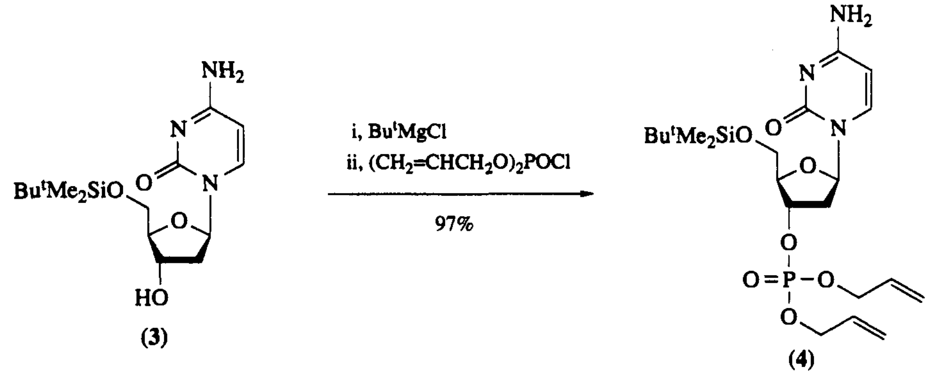
When alcohols are activated as the alkoxides, the phosphorylation is greatly accelerated. Activators employable are potassium *t*-butoxide,[11,12] thallium ethoxide,[13,14] alkyllithiums,[7,11,14] *t*-butylmagnesium chloride,[15] dibutylstannoxane,[16] *etc.* Phosphorylation *via* an aluminum alkoxide like $LiAl(OAr)_3(OR)$ or $Al(OAr)_2(OR)$, where Ar is *o*-chlorophenyl or *p*-nitrophenyl, also proceeds smoothly.[17] The lithium[7] and potassium[12] alkoxides react with not only chlorophosphates but also phosphorofluoridates (equation 5). The hydroxy activation procedure frequently reverses the reactivity of nitrogen and oxygen atoms toward the phosphorochloridate. Thus, this approach is often efficient for nucleotide synthesis. Particularly useful is the activation as the magnesium or aluminum alkoxides, and the phosphorylation of *N*-unprotected nucleosides proceeds in a perfect *O*-selective manner. No protection of amino function is necessary. For instance, when the cytidine derivative (**3**; equation 6) is treated with 1 equiv. of *t*-butylmagnesium chloride followed by $(CH_2{=}CHCH_2O)_2POCl$ in THF, the phosphate (**4**) is obtained in quantitative yield.[15] Choice of the activator is important in phosphorylation of an anomeric hydroxy of a carbohydrate. The stereochemistry of the product is highly dependent on the activator and reaction conditions employed. When the 1α-hydroxylaminosugar (**5**) is phosphorylated with dibenzyl phosphorochloridate by the aid of thallium ethoxide in acetonitrile, anomerization occurs to afford the β-glycosyl phosphate (**6**; equation 7). By contrast, the reaction promoted by *n*-butyllithium in hexane, which can generate the carbohydrate alkoxide at lower temperature (–70 °C), brings about no anomerization to give the α-phosphate (**7**; equation 8).[14] On the other hand, in phosphorylation of the thallium alkoxide of glucopyranose (**8**; equation 9) the solvent affects the stereochemistry of the product.[13] Formation of the α-anomer predominates in acetonitrile. On the other hand, the β-anomer is a major product in benzene. Phosphorylation of hydroxyaryl compounds is also accelerated by hydroxy activation. Preparation of triaryl phosphates can be readily achieved by reacting phosphorus oxychloride with the sodium salt of the hydroxyaryl compound in a two-phase system using a phase-transfer catalyst, tricaprylmethylammonium chloride.[18]

2.8.2.2 Phosphoric–Arenesulfonic Anhydrides

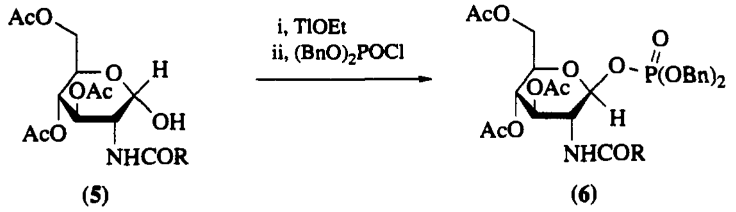
Mixed anhydrides of phosphoric acids and arenesulfonic acids, which are intermediately generated by the condensation of phosphodiesters and arenesulfonyl chlorides[19,20] or arenesulfonyl amides,[21–25] are more reactive phosphorylating agents than chlorophosphates. Arenesulfonylamides generally give higher coupling yields than arenesulfonyl chlorides. Benzenesulfonyl, 2,4,6-trimethylbenzenesulfonyl, 2,4,6-triisopropylbenzenesulfonyl (TPS), *p*-nitrobenzenesulfonyl, *etc.*, are effective as arenesulfonyl parts. Azoles such as imidazole,[21] *N*-methylimidazole,[25] triazole,[22,23] 3-nitrotriazole,[24] and tetrazole[24] are usable as the amine of the sulfonylamides (equation 10). In general, the phosphorylation proceeds



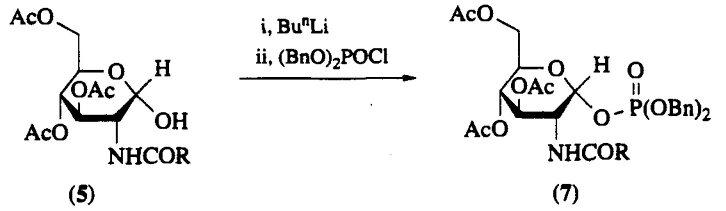
(5)



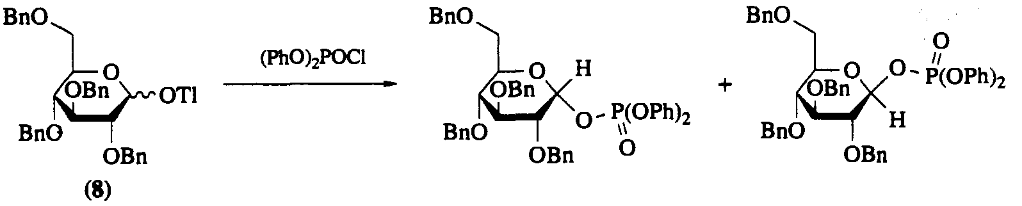
(6)



(7)



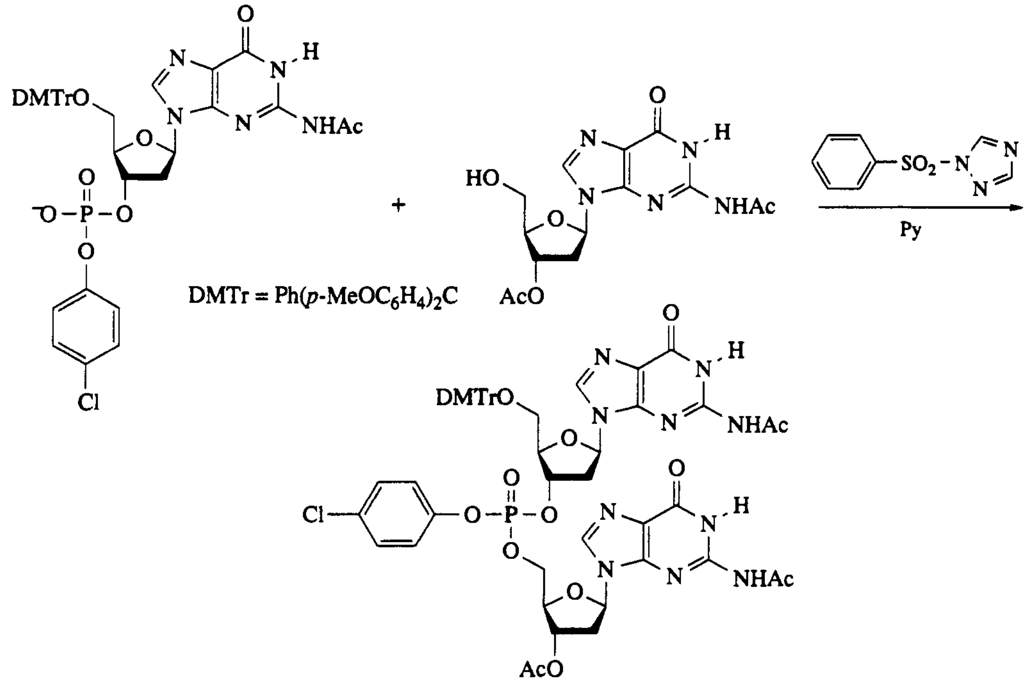
(8)



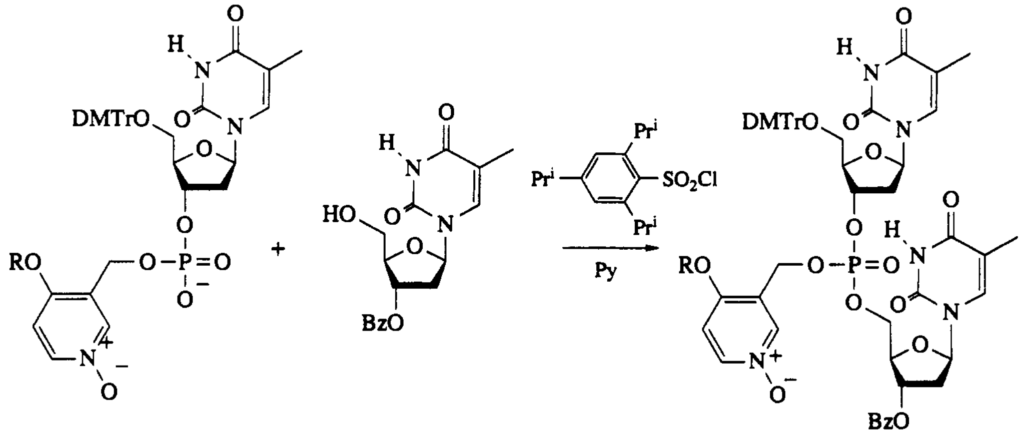
(9)

MeCN	100	0
C_6H_6	15	85

smoothly with the assistance of tertiary amines at room temperature or below it. According to this procedure, sulfonylation of alcohols competes with the phosphorylation.[26] The undesired reaction can be prevented to a considerable extent by the use of bulky sulfonyl reagents such as TPS derivatives.[26] Certain 4-substituted pyridine *N*-oxides promoted phosphorylation using arenesulfonyl chlorides. The 1-oxido-4-alkoxy-2-picolyl protecting group of phosphodiesters greatly accelerates the internucleotide bond formation with arenesulfonyl chlorides (equation 11).[27] A similar effect is observed with 4-alkoxy-2-picolyl,[27] 1-oxido-2-picolyl,[27] or a 2-(1-methylimidazole-2-yl)phenyl group.[28,29] The sulfonyl amide (**9**)[30] greatly accelerates the internucleotide linkage formation in pyridine. In nucleotide synthesis, use of a condensing agent that is easily separable from the product is essential for obtaining a high yield. Quinonesulfonyl chloride (**10**)[31] and the disulfonyl dichlorides (**11**)[32] and (**12**)[33] in the presence of 1*H*-tetrazole are such activators. The internucleotide bond formation with the sulfonylamide (**13**) proceeds in a diastereoselective manner to give the phosphotriester (**14**; equation 12) as a single isomer.[34]



(10)



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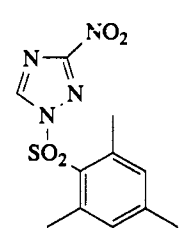

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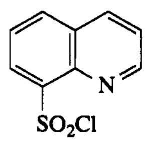

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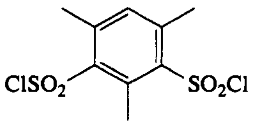

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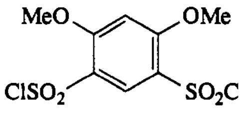
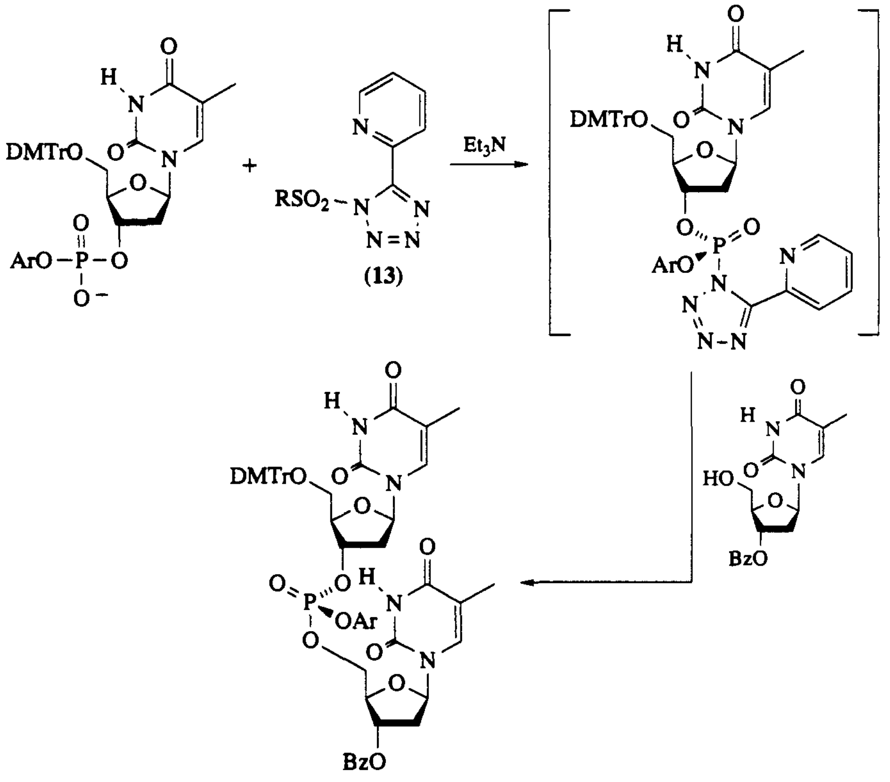


(12)

2.8.2.3 Pyrophosphates

Free pyrophosphoric acid (phosphoric anhydride) and P^1,P^2-pyrophosphoric diesters are stable under standard basic conditions and serve as phosphorylating agents only in some limited cases. An example is the trichloroacetonitrile-aided phosphorylation using a *syn*-dialkyl pyrophosphoric diester (equation 13).[35] The tetraalkyl esters contrast with the dissociated compounds, being convenient phosphorylating agents. Among the tetraalkyl pyrophosphates, symmetrical derivatives are widely employable as the monophosphorylating agents (equation 14).[36,37] The unsymmetrical pyrophosphates are not always

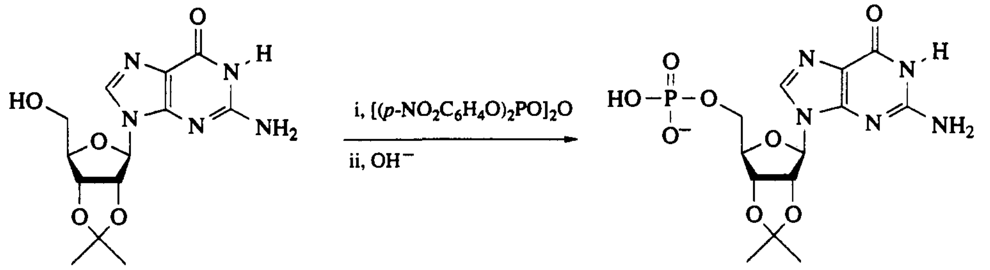


(14) Ar = o-ClC_6H_4

(12)

useful, because they react usually at two reactive sites to give a mixture of phosphates. In such cases, the selective preparation may be realized by designing the structure of a phosphoryl moiety which acts as the leaving group. In unsymmetrical pyrophosphates, the more acidic phosphate moiety generally acts as a leaving group. Reagents designed according to such consideration are the diaryl phosphorochloridates (**15**) or (**16**). The reagent (**16**) assists condensation of the thiophosphodiester (**17**; equation 15) and the 5′-free nucleotide (**18**) in the presence of 3-nitrotriazole to give exclusively the dinucleoside phosphate (**19**).[38] In this phosphorylation, the mixed phosphoric anhydride is the intermediate. The reagent (**20**)[39] has a similar effect. Pentavalent phosphorous trichlorides (**21**)[40] and (**22**)[41] and the dichloride analog (**23**)[41] are also useful condensing agents. Preparation of the nucleoside diphosphate (**24**; equation 16) and triphosphate (**25**; equation 16) is achieved using $Bu^n{}_2PSBr$. The reaction is believed to proceed *via* a mixed pyrophosphate-type intermediate.[42]

$$PhO-\overset{O}{\underset{O^-}{P}}-O-\overset{O}{\underset{O^-}{P}}-OPh + ROH \xrightarrow{Cl_3CCN} PhO-\overset{O}{\underset{O^-}{P}}-OR \qquad (13)$$



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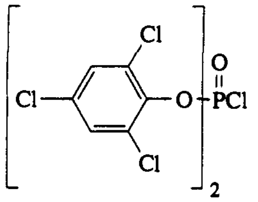

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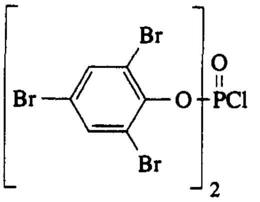

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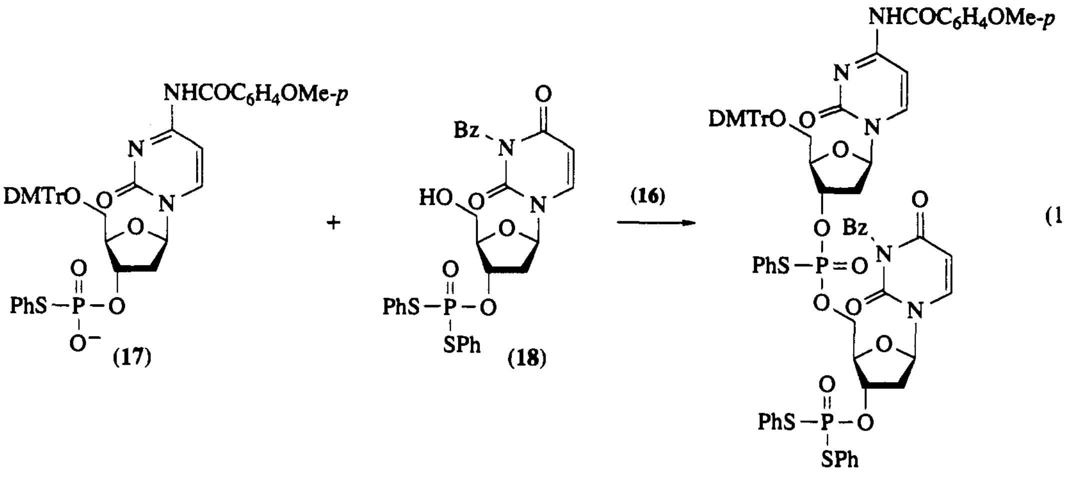

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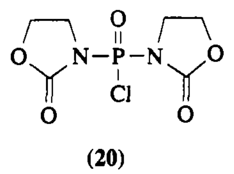
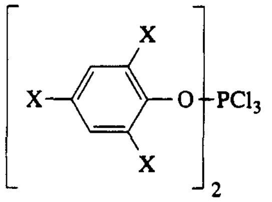
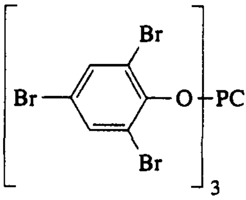
(19)



(20)



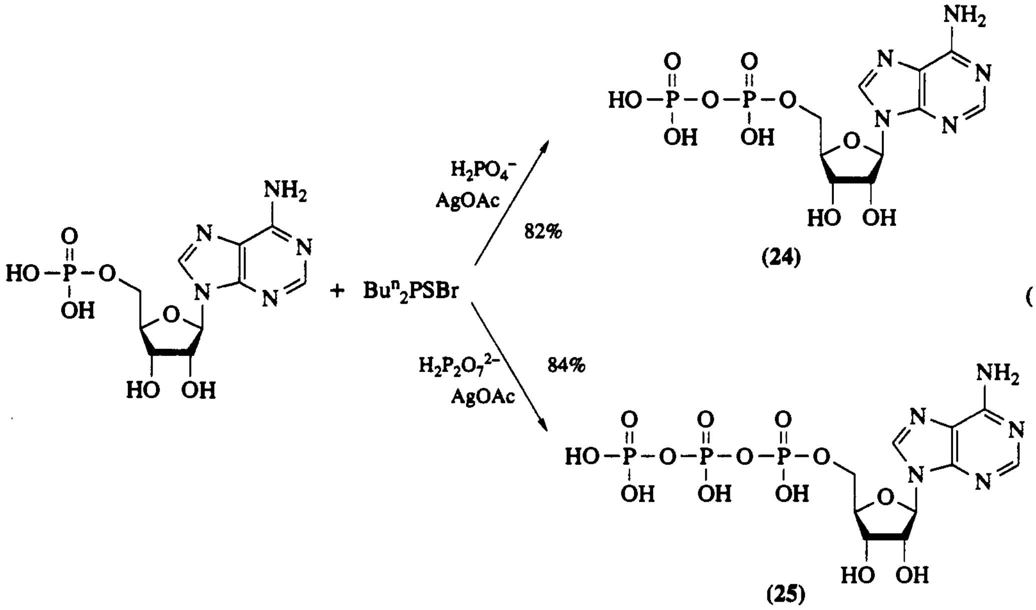
(21) X = Cl
(22) X = Br



(23)

2.8.2.4 Acyl Phosphates

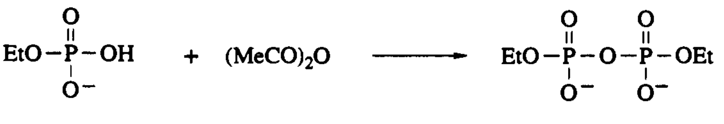
Nucleophilic attack of alcohol to acyl phosphates usually occurs predominately at the carbonyl carbon atom, producing carboxylic esters but not phosphates.[43] In contrast, some kinds of phosphoric monoesters or amines react with the mixed anhydrides at the phosphorus atom. An example is when monoethyl phosphate is treated with acetic anhydride or acetyl chloride in pyridine, the acetyl phosphate occurs intermediately, which in turn condenses with the second ethyl phosphate to give diethyl phosphate (equation 17).[44] A similar reaction is conducted by use of ketene dimer in place of the acetylating reagents (equation 18).[45] Triethylamine-promoted reaction of dialkyl phosphates and trifluoroacetic anhydride produces tetraalkyl pyrophosphates.[46] These reactions are presumed to involve an acyl phosphate as the intermediate. Both methods cannot be used for specific synthesis of unsymmetrical pyrophosphates. Condensation of the acyl phosphate (**26**; equation 19) and aniline exclusively occurs with a P—O bond fission to give the phosphoramidate (**27**).[47] Reaction of protection-free 2′-deoxyribonucleoside 5′-monophosphate with mesitylenecarbonyl chloride followed by methanol in pyridine gives the methyl ester of the nucleotide (equation 20).[48] This procedure is applicable to the 3′-phosphate of oligonucleotide, dCpApAp.[48]



(24)

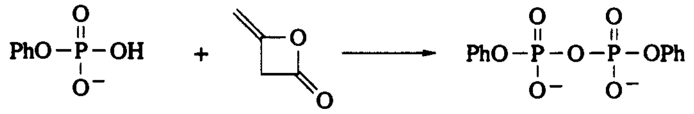
(25)

(16)



$$\mathrm{EtO-\overset{\overset{O}{\|}}{\underset{\underset{O^-}{|}}{P}}-OH} + (\mathrm{MeCO})_2\mathrm{O} \longrightarrow \mathrm{EtO-\overset{\overset{O}{\|}}{\underset{\underset{O^-}{|}}{P}}-O-\overset{\overset{O}{\|}}{\underset{\underset{O^-}{|}}{P}}-OEt}$$

(17)



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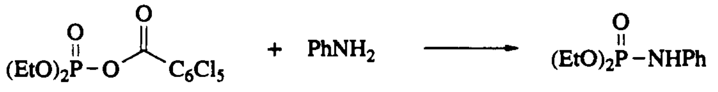
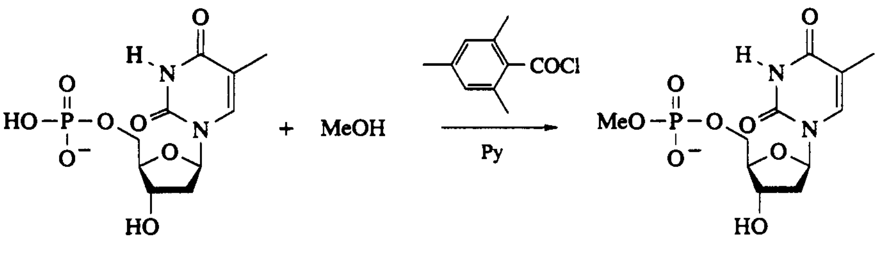


(26)

(27)

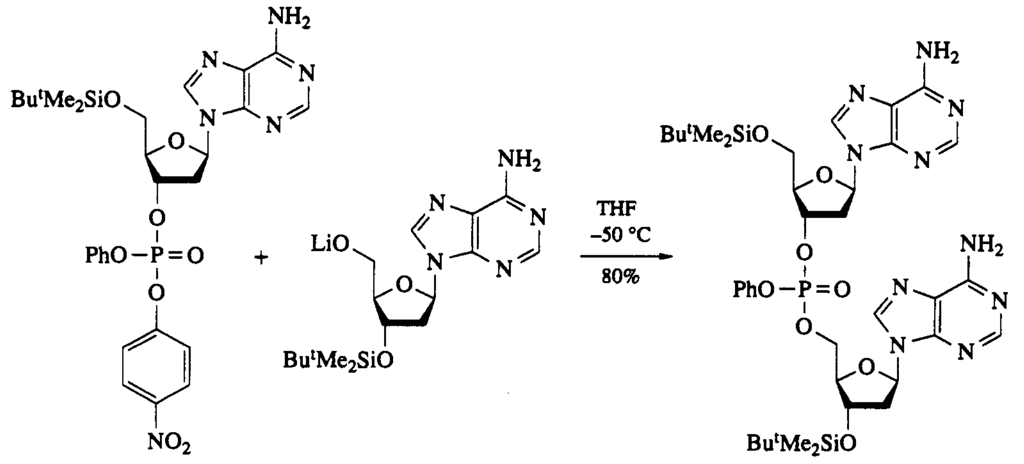
(19)



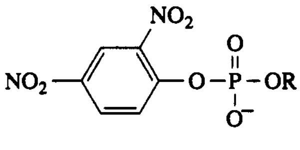
(20)

2.8.2.5 Phosphoryl Phenoxides and Related Compounds

Some kinds of phosphoryl phenoxides (phenyl phosphates) are useful and easily handled phosphorylating agents. Although a phosphoryl 4-nitrophenoxide does not serve as an efficient phosphorylating agent for alcohols in an ordinary procedure using a tertiary amine as an activator, because of the low reactivity, the phenoxide reacts very smoothly with the alkoxide to give the corresponding phosphate in high yield (equation 21).[8,11] The 2,4,6-trinitrophenoxide analog (**28**) is also a potential phosphorylating agent.[49] The alkyl-2-chloromethyl-4-nitrophenyl hydrogen phosphate (**29**; equation 22) is activated by pyridine to condense with an alcohol, giving the phosphodiester (**30**).[50] Similarly, the phosphoryl phenoxide (**31**; equation 23) reacts with cytidine 5′-monophosphate in the presence of triethylamine to form the diphosphate (**32**).[51]



(21)



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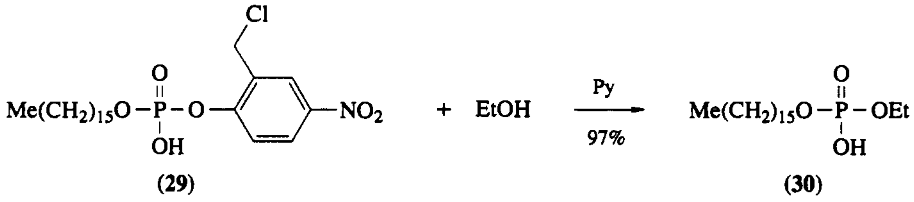
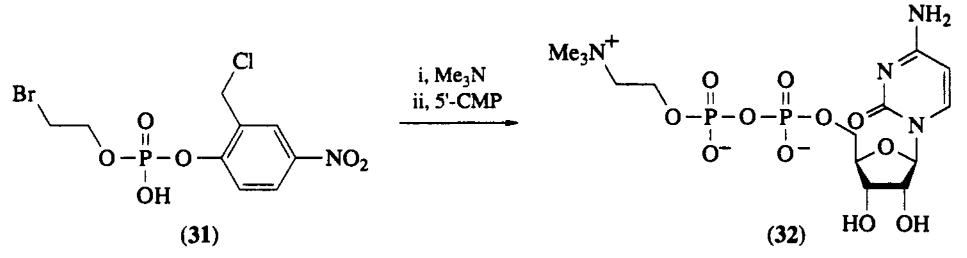
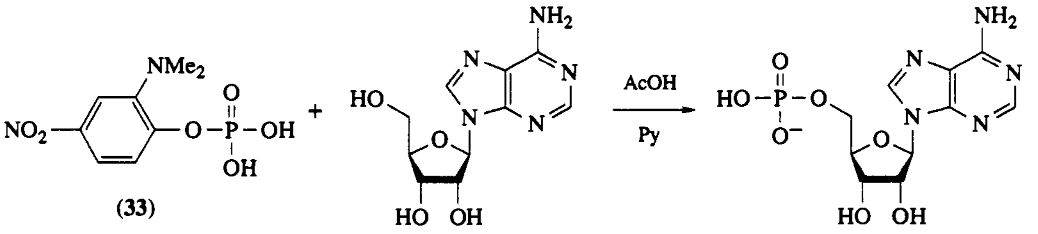


(29) **(30)** (22)



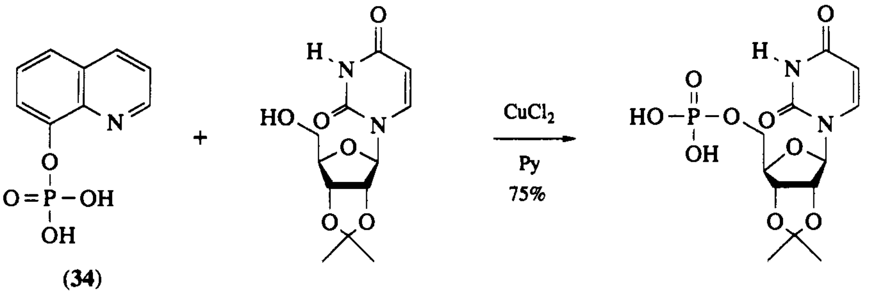
(31) **(32)** (23)

2-Dimethylamino-4-nitrophenyl dihydrogen phosphate (**33**; equation 24) in the presence of an acidic promotor such as acetic acid, trifluoroacetic acid, or BF_3–etherate in pyridine, is also a useful reagent.[52] The phosphorylation using (**33**) proceeds selectively on primary alcohols. Furthermore, it is noteworthy that (**33**) shows no interaction with the amino group in the reaction of amino alcohols. Thus, ribonucleoside 5′-monophosphates are directly prepared from amino-free nucleosides.[53] Phosphorylation using the 8-quinolyl phosphate (**34**; equation 25), in which the quinolyl moiety is activated by copper(II) ion through chelation, takes place readily with the assistance of copper(II) chloride.[54] Similarly, the aryl phosphate (**35**; equation 26) is activated by a Cu^{II} salt. Condensation of (**35**) and the phosphodiester (**36**) gives the pyrophosphoric ester (**37**).[55] The coupling of 5-chloro-8-quinolyl phosphate (**38**; equation 27) and the ribonucleoside (**39**) is promoted by cesium fluoride in acetonitrile to give the dinucleoside phosphate (**40**).[56] Oxidation of the monophosphate of a naphthaquinol (**41**; equation 28) by bromine generates metaphosphate, serving as a highly reactive phosphorylating agent.[57] This method is applicable to formation of 2′,3′-*O*-protected adenosine 5′-diphosphate from the corresponding monophosphate.[58] The 2-hydroxypyridyl phosphoric diester (**42**) in the presence of pyridine or tertiary amines is usable for phosphorylation of amines, alcohols, and phosphomonoesters, giving phosphoramidates, phosphodiesters, and unsymmetrical pyrophosphates, respectively.[59] For example, the reagent (**43**; equation 29) reacts with the nucleoside 5′-monophosphate (**44**) in pyridine to give the diphosphate (**45**).[60] The aryl phosphate (**46**), derived as an intermediate by the condensation of cyanuric chloride and phosphomonoester, acts similarly.[61]



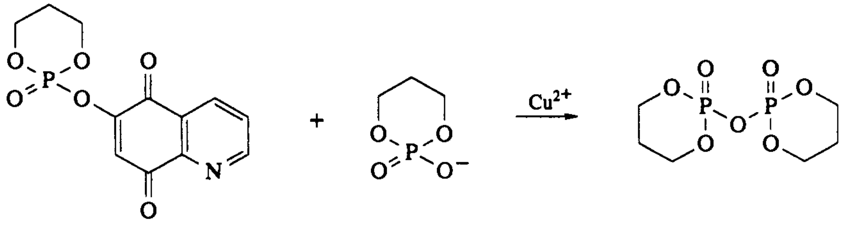
(**33**)

(24)



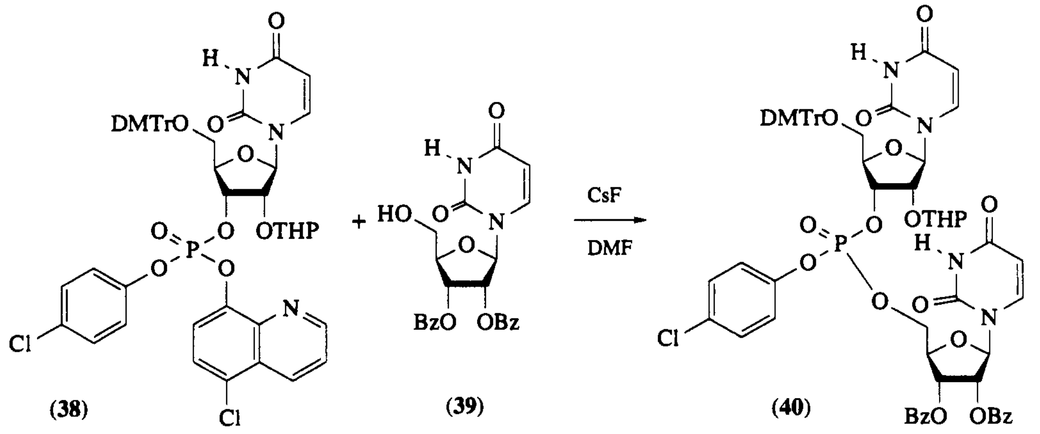
(**34**)

(25)



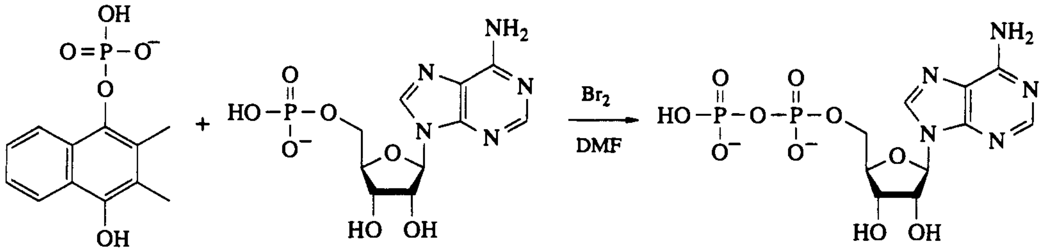
(**35**) (**36**) (**37**)

(26)



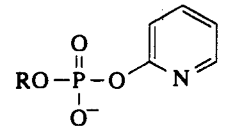
(**38**) (**39**) (**40**)

(27)



(41)

(28)



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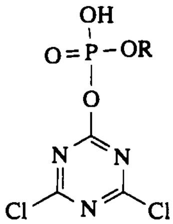

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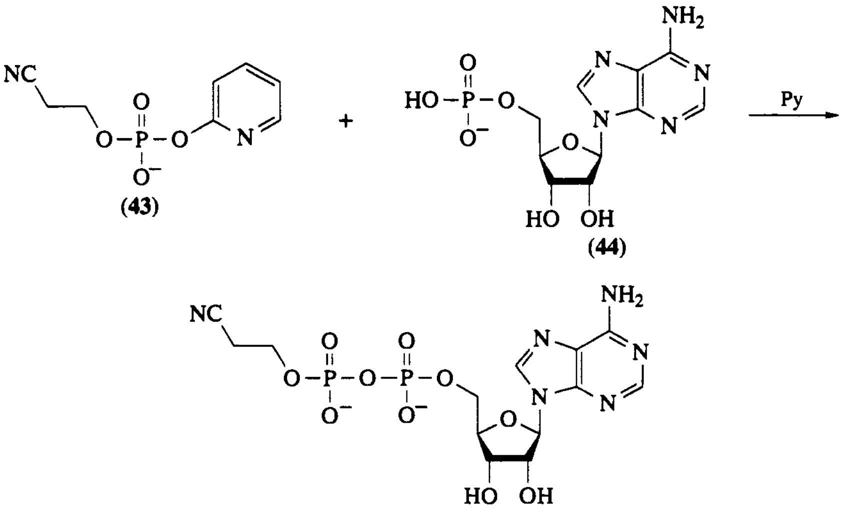


(43)

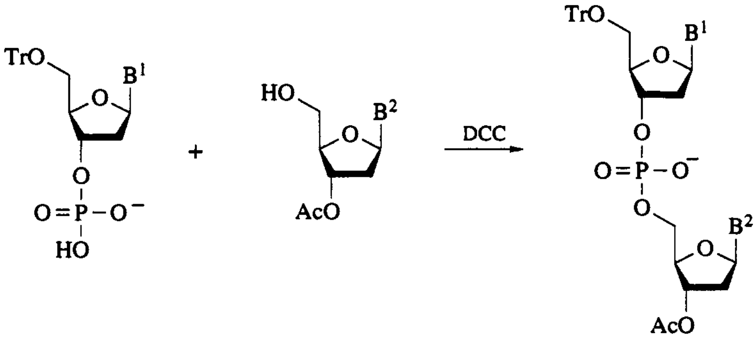
(44)

(45)

(29)

2.8.2.6 Vinyl Phosphates and Related Compounds

Vinyl phosphates, including imino ether-type derivatives, easily undergo transesterification with alcohols with the aid of a base or an acid to give new phosphoric esters.[62] In some cases, the vinyl phosphates are not isolable and thus the intermediates prepared *in situ* are used without purification. Condensation of phosphomonoesters and hydroxylic substrates with DCC in the presence of amines such as triethylamine, pyridine, *etc.*, belongs to this category.[63] This method has been widely employed in oligonucleotide synthesis (equation 30).[64] The reaction, however, particularly of hindered alcohols is very slow. For example, condensation of the ribonucleoside 3′-phosphate (**47**; equation 31) and 5′-free ribonucleoside (**48**) requires more than 4 d.[64] In contrast, a similar reaction with TPS chloride is completed within 6–7 h.[65] Preparation of unsymmetrical pyrophosphates with DCC has invariably led to the formation of mixed products.[66] Cyclohexyl isocyanide is capable of activating phosphomonoesters in a similar way to DCC, assisting the coupling with alcohols (equation 32).[67] Imidoyl phosphates (**49**; equation 33), formed as reactive intermediates by treatment of phosphoric monoesters with trichloroacetonitrile in pyridine, react with alcohols to give unsymmetrical diesters.[68] This method is also effective for the preparation of pyrophosphates. Aryl cyanates behave similarly to trichloroacetonitrile. When a phosphomonoester is treated with the cyanate, dimerization of the phosphates occurs to afford a pyrophosphate (equation 34). The pyrophosphate is activated again by the cyanate to react with an alcohol or an amine, giving an unsymmetrical phosphodiester or a phosphoramidate, respectively.[69] Condensation of DMF and a phosphorochloridate or a phosphorodichloridate also gives an imino ether-type active ester (**50**; equation 35; X = OR or Cl), which acts, in the presence of a tertiary amine, as the phosphorylating agent for phosphomonoesters, carboxylic acids, amino acids, *etc.*[70] An example is the reaction of (**50**; X = OEt) and triethylammonium benzoate to give the mixed anhydride (**51**). The internucleotide linkage formation using *N*-ethyl-5-phenylisoxazolium fluoroborate (**52**; equation 36) goes through a similar pathway.[71,72] The alkoxyvinyl ester of phosphoric acid (**53**), prepared by the addition of a phosphodiester to an alkoxyalkyne, is also an active phosphorylating agent.[73,74] Rapid phosphorylation of alcoholic, phenolic and nucleosidic hydroxy groups, phosphoric acids, amines, and carboxylic acids is achievable with (**53**).[73] This reaction is catalyzed by an $\mathrm{Hg^{II}}$ salt.[73] Reaction of a trialkyl phosphite and α-bromocyanoacetamide gives a vinyl or iminyl phosphate intermediate, (**54**) or (**55**), both of which serve as phosphorylating agents toward alcohols, phosphodiesters, and amines.[75] Dibromomalonamide in place of bromocyanoacetamide is also employable.[76] The ketene acetal-type phosphates (**56**) or (**57**), derived from trichloroacetic acid and diethyl bromomalonate, respectively, in a similar manner, react with acetic acid to give the phosphoric–acetic mixed anhydrides.[77]



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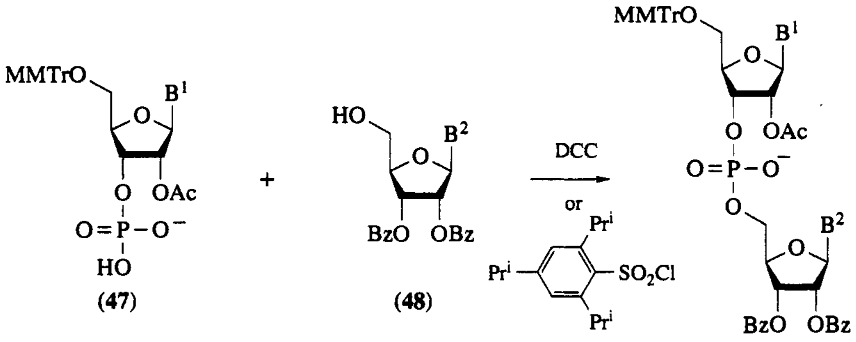

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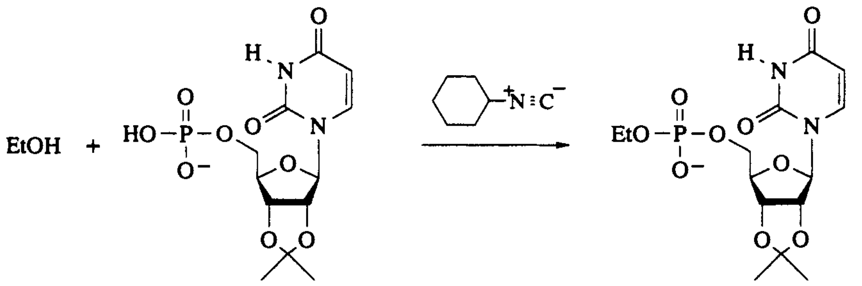

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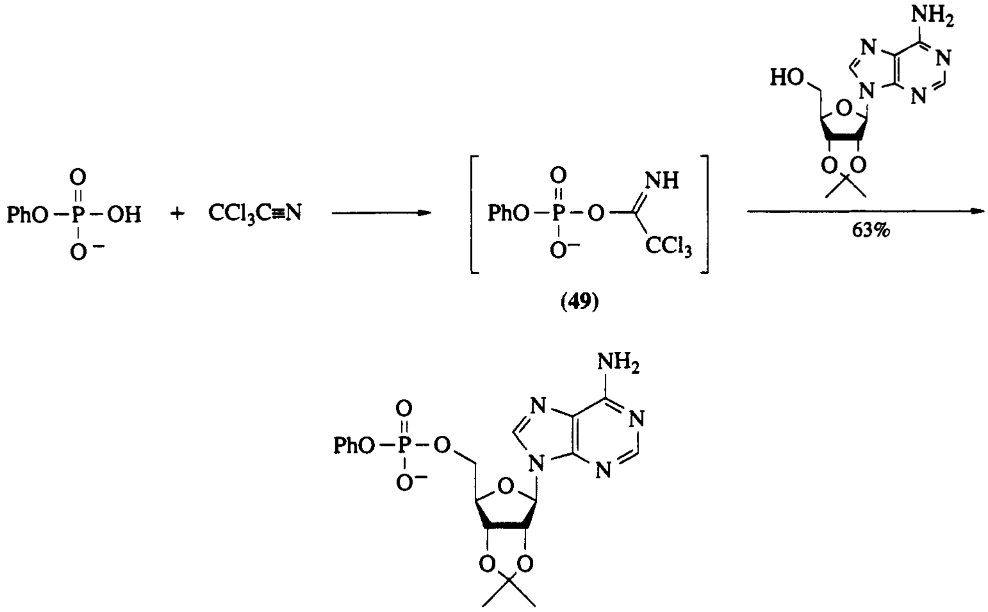
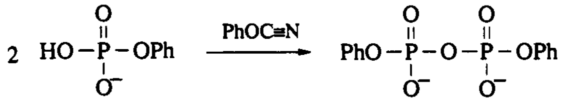


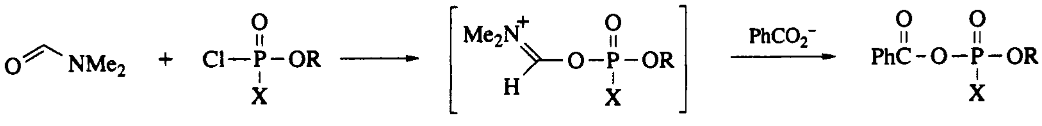
(49)

(33)



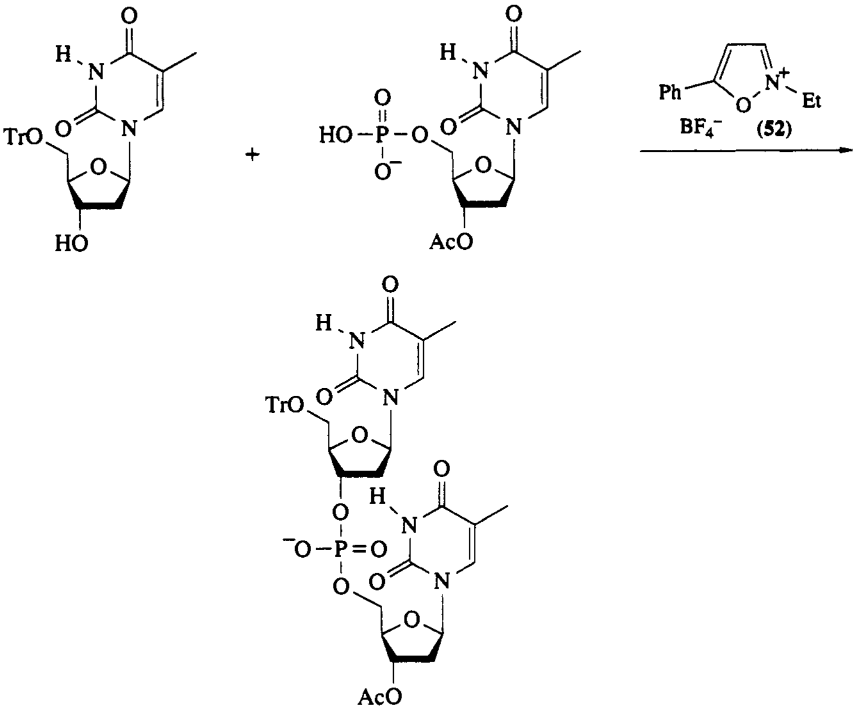
$$2\ \mathrm{HO{-}\overset{O}{\underset{O^-}{P}}{-}OPh} \xrightarrow{\mathrm{PhOC{\equiv}N}} \mathrm{PhO{-}\overset{O}{\underset{O^-}{P}}{-}O{-}\overset{O}{\underset{O^-}{P}}{-}OPh}$$

(34)



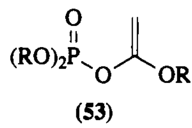
(50) **(51)**

(35)

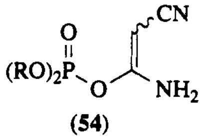


(52)

(36)



(53)



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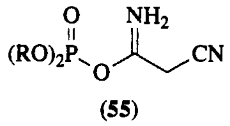

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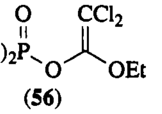

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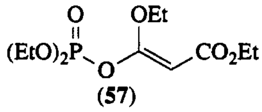
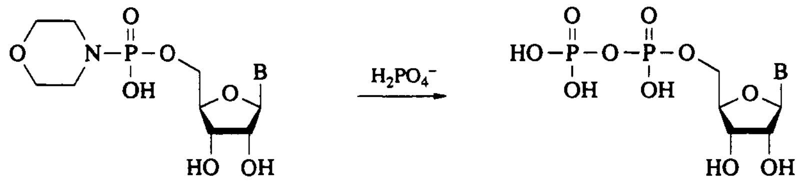


(57)

2.8.2.7 Phosphoramidates and Related Compounds

Aliphatic amides of phosphoric acid (phosphoramidates) are rather stable and do not react with alcohols. On the other hand, condensation of some of the amidates and phosphates takes place easily to give pyrophosphates. Thus, the phosphoramidates serve as useful reagents for the preparation of unsymmetrycal pyrophosphates.[78–80] Among the amidates, the morpholidate is the most useful reagent, because of ready accessibility and high reactivity.[80] This approach is effective for the synthesis of the nucleoside 5′-triphosphates by coupling of nucleoside 5′-monophosphates and pyrophosphate (equation 37).[81,82] *N*-Acylphosphoramidates, in contrast to the free amidates, phosphorylate alcohols under neutral or acidic conditions (equation 38).[83] The phosphoryloxazolides (**58**) and (**59**) are activated by Zr(acac)$_4$, serving as useful reagents for the phosphorylation of alcohols.[84] The phosphorohydrazidate (**60**) is oxidized by iodine or NBS to generate an active species capable of phosphorylating phosphate anions.[85] High yields of unsymmetrical pyrophosphates can be obtained by this method. Similarly, oxidative phosphorylation is accomplished using the phosphoramidate (**61**; equation 39), where triphenylmethyl fluoroborate or cerium(IV) ammonium nitrate is used as the oxidizing agent.[86] Photochemical oxidative phosphoryl transfer to alcohols is also achievable with (**61**).[86] Although unlike other systems containing a phosphorus–nitrogen bond, the phosphoroguanidates (**62**; equation 40) show remarkable chemical stability, the compounds undergo nucleophilic attack at the phosphorus atom with consequent phosphoryl transfer by the action of zinc and manganese(II) cations. Thus, the cross coupling between benzyl hydrogen phosphoroguanidate (**62**; R = PhCH$_2$) and phenyl dihydrogen phosphate is effectively promoted by zinc acetate to afford the pyrophosphate (**63**).[87] Related *N*-acylphosphoroguanidates (**64**) function as phosphorylating agents under weakly basic conditions.[88] *N*-Phosphorylimidazoles are highly reactive, particularly under acidic conditions, being capable of transferring a phosphoryl group to protic compounds. Reactivity of the phosphorylimidazole to phosphate or pyrophosphate anions is usually higher than to alcohols and therefore the reagent is widely employed for the preparation of diphosphates (equation 41)[89–92] or triphosphates.[93,94] Phosphoryltriazoles are also good phosphorylating agents.[95,96] Oligoadenylates with a 2′–5′ phosphoric linkage are prepared by Pb^{2+} ion catalyzed condensation of adenosine 5′-phosphorimidazolide.[93] The trimer (**65**; equation 42) is a major product.



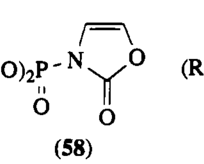
(37)

$$\mathrm{PhCONH{-}\overset{\displaystyle O}{\underset{\displaystyle O^-}{\overset{\|}{\underset{|}{P}}}}{-}OH} \;+\; \mathrm{EtOH} \;\xrightarrow{\mathrm{Et_3N}}\; \mathrm{EtO{-}\overset{\displaystyle O}{\underset{\displaystyle O^-}{\overset{\|}{\underset{|}{P}}}}{-}OH} \qquad (38)$$

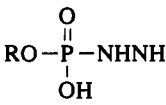
2.8.2.8 Phosphorothioates

The nucleoside phosphorothioate (**66**; equation 43) reacts with tributylammonium phosphate in the presence of silver nitrate to give the nucleoside 5′-diphosphite (**67**).[97]

(58)

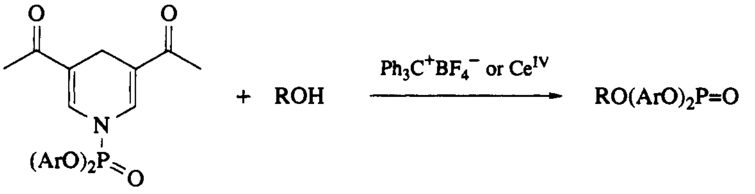


(59)



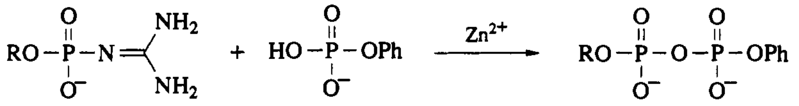
$RO-\overset{O}{\overset{\|}{P}}(OH)-NHNH_2$

(60)



(61)

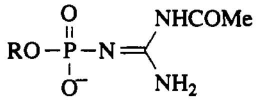
(39)



$$RO-\overset{O}{\overset{\|}{P}}(O^-)-N{=}C(NH_2)_2 + HO-\overset{O}{\overset{\|}{P}}(O^-)-OPh \xrightarrow{Zn^{2+}} RO-\overset{O}{\overset{\|}{P}}(O^-)-O-\overset{O}{\overset{\|}{P}}(O^-)-OPh$$

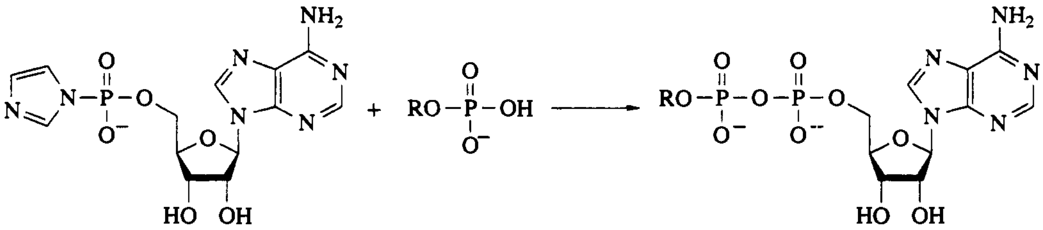
(62) **(63)**

(40)



$RO-\overset{O}{\overset{\|}{P}}(O^-)-N{=}C(NHCOMe)(NH_2)$

(64)



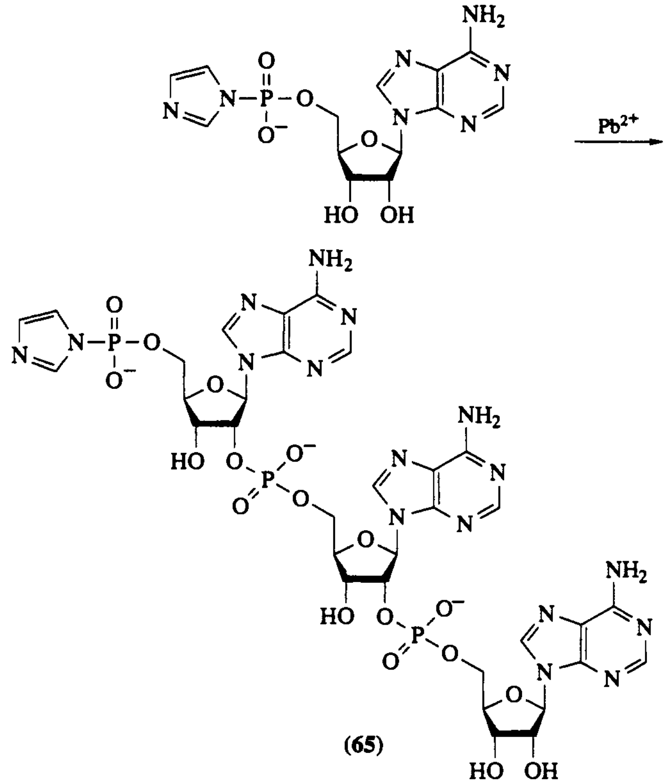
(41)

2.8.2.9 Triphenylphosphonium Salts of Phosphoric Acid Esters

Phosphorylation of alcohols and amines forming mixed esters of phosphoric acid and phosphoramidates, respectively, is effected by triphenylphosphine and 2,2′-dipyridyl disulfide.[98] The reaction passes through a triphenylphosphonium phosphate of type (**68**; equation 44) as an active intermediate. Formation of an internucleotide linkage can be achieved by this method.[99,100] Dimerization of monoesters of phosphoric acid producing dialkyl pyrophosphates is achieved using tributylphosphine and dibenzoylethylene or *p*-quinonedibenzimide (equation 45). A phosphonium phosphate is the active intermediate of this reaction.[101]

2.8.2.10 Miscellaneous

Esterification of dialkyl phosphates is carried out with diethyl azodicarboxylate and triphenylphosphine (equation 46).[102] This condensation is applicable to phosphorylation of pyrimidine nucleosides. The trichloromethanephosphonic acid derivative (**69**; equation 47) serves as a phosphorylating agent of ribonucleosides, affording the 2′- and 3′-monophosphates.[103] Ethyl vinyl ether assisted the dimeric condensation of diethyl hydrogen phosphate giving tetraethyl pyrophosphate (equation 48).[45]



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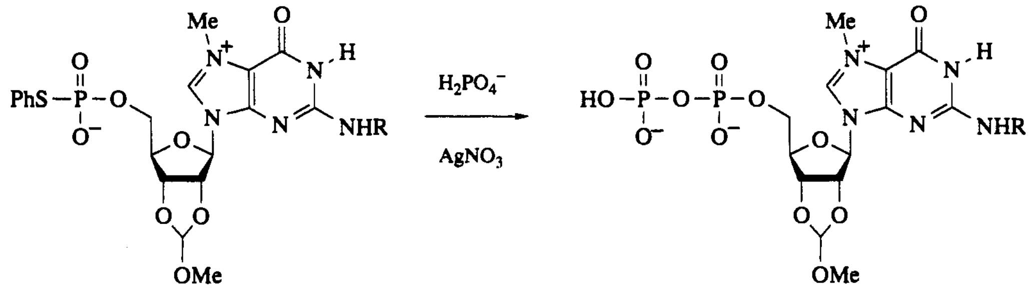


(66) R = $(p\text{-}MeOC_6H_4)_3C$

(67)

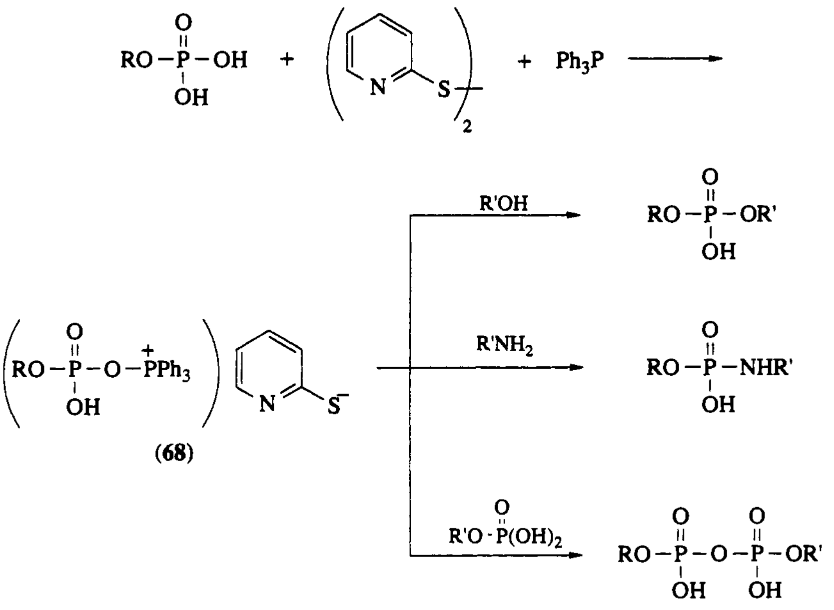
(43)

2.8.3 USE OF TRIVALENT PHOSPHORUS REAGENTS

Phosphorylation of alcohols can also be achieved through the phosphitylation with some kinds of trivalent phosphorus reagents followed by oxidation. The phosphitylating agents are generally more reactive than the corresponding pentavalent analogs. Thus this approach has been used very frequently for the preparation of phosphoryl derivatives of less reactive alcohols, such as nucleosides.[104]

2.8.3.1 Phosphorochloridites (Chloroalkoxyphosphines) and Related Compounds

Phosphorochloridites are highly reactive reagents, undergoing condensation with alcohols in the presence of an acid scavenger at low temperature. For instance, reaction of the 2′,3′-*O*-protected ribonucleoside (**70**; equation 49) with phosphorus trichloride in the presence of trimethyl phosphate takes place at 0 °C, to afford, after oxidation with chlorine followed by hydrolysis, the nucleoside 5′-monophosophate (**71**).[105] Preparation of alkyl dihydrogen phosphates is performed through condensation of an alcohol and diethylthiochlorophosphine, giving (**72**; equation 50), followed by oxidation and hydrolysis uisng aqueous iodine.[106]



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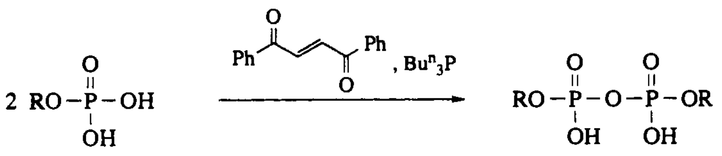

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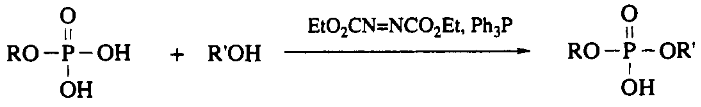

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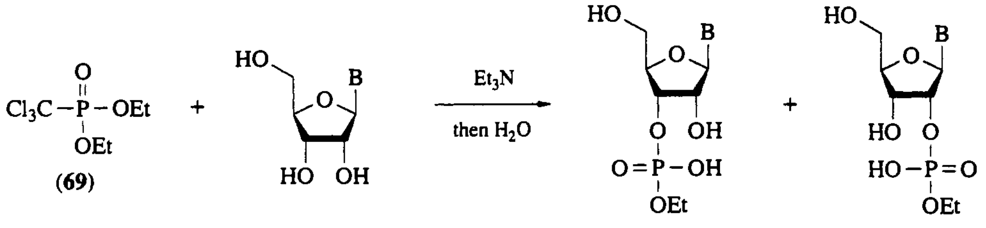

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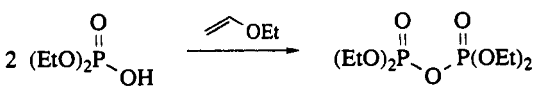

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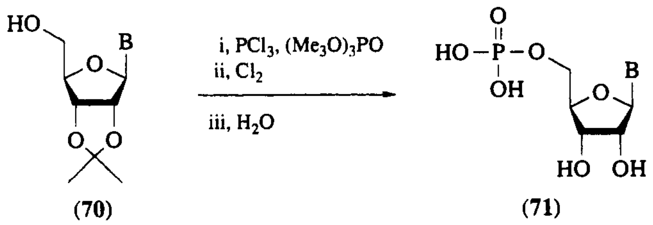

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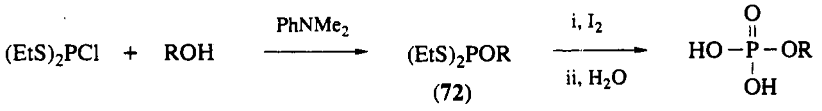
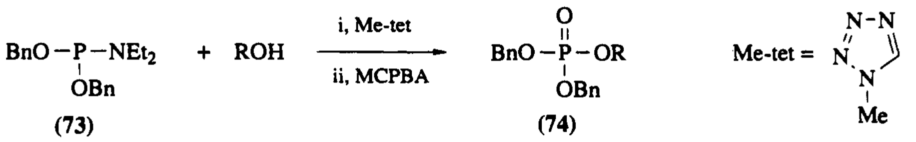


(50)

2.8.3.2 Phosphoramidites (Dialkylaminodialkoxyphosphines)

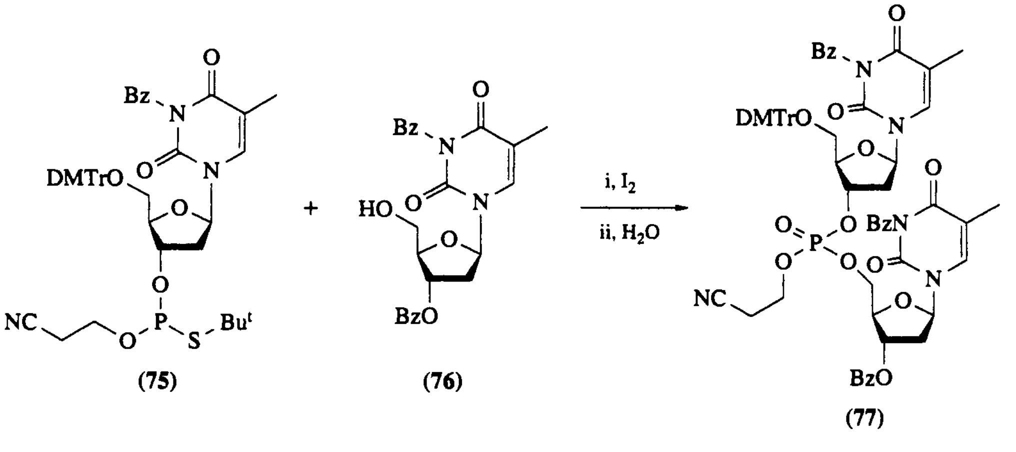
When phosphoramidites are activated by weak acids such as *N*-methylanilinium trifluoroacetate,[107] 1*H*-tetrazole,[108] 5-methyltetrazole,[109] 5-methylthiotetrazole, 5-(4-nitrophenyl)tetrazole,[110] *etc.*, the reagents react with alcohols, forming phosphites, which can be transferred to the phosphates by oxidation. For example, the methyltetrazole-assisted condensation of phosphoramidite (**73**; equation 51) and an alcohol followed by oxidation with MCPBA gives the phosphate (**74**).[111] Use of DMAP as an additive accelerates the reaction.[111] Choice of amino group of the amidite reagents affects the reactivity and stability. From the synthetic point of view, diethylamidites, diisopropylamidites, and morpholidites are most efficient reagents. In general, the phosphoramidites are more stable than the corresponding phosphorochloridites and some of the reagents can be purified by silica gel chromatography. Thus the reagents are frequently employed for the synthesis of oligonucleotides.



(51)

2.8.3.3 Phosphorothioites (Alkylthiodialkoxyphosphines)

The dinucleoside phosphate (**77**; equation 52) is prepared by oxidative coupling of the nucleoside phosphothioiten (**75**) and the nucleoside (**76**) using iodine followed by aqueous treatment.[112]



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2.8.4 BIFUNCTIONAL PHOSPHORYLATING AGENTS AND RELATED REAGENTS USEFUL FOR SYNTHESIS OF FULLY UNSYMMETRICAL PHOSPHOTRIESTERS

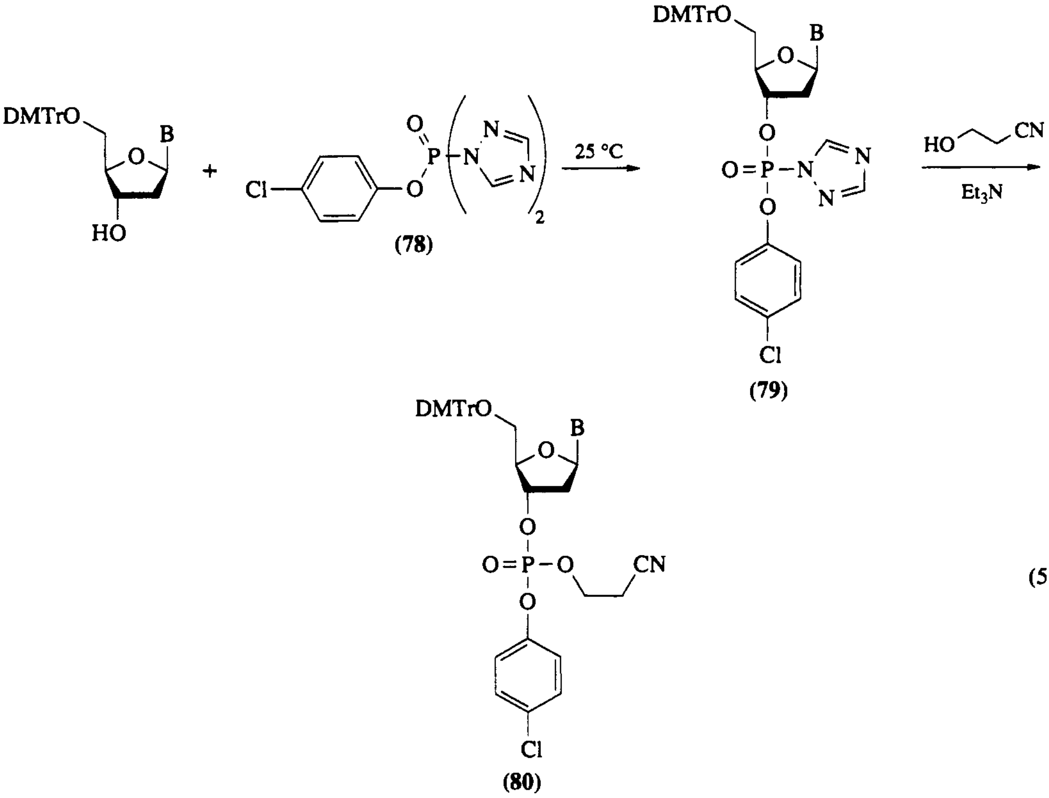
Preparation of the fully unsymmetrical phosphotriesters (RO)(R′O)(R″O)PO is very important for the synthesis of oligonucleotides, but it is far from easy. Reaction of $POCl_3$ or PCl_3 and three kinds of alcohols generally occurs at random to give a mixture of possible trialkyl phosphates or trialkyl phosphites, respectively. In contrast, use of bifunctional phosphorylating or phosphitylating agents like $(RO)POX_2$, (RO)POXY, $(RO)PX_2$, and (RO)PXY, where X and Y are leaving groups, sometimes brings about success. According to this approach, the desired phosphotriesters can be prepared in one pot without isolation of the intermediate formed by condensation of the first alcohol.

2.8.4.1 $(RO)POX_2$-type Reagents

The phosphorobistriazolide (**78**; equation 53) reacts with 1 equiv. of an alcohol without any activator to give the corresponding monotriazole (**79**), which then condenses the second alcohol with the aid of an amine to give the fully unsymmetrical phosphotriester (**80**).[113,114] A similar stepwise condensation is achieved by use of the phosphorobis(nitrobenzotriazolide) (**81**)[115] or phosphorobis(1-hydroxybenzotriazolide) (**82**).[116] The phosphorobis(oxazolide) (**83**; equation 54) also serves as the bifunctional reagent. In this case, Mn(acac)$_3$ and Zr(acac)$_4$ catalyze the first and second steps, respectively.[83]

2.8.4.2 (RO)PX$_2$-type Reagents

In general, monoesterification takes place in the reaction of a phosphorodichloridite and 1 equiv. of an alcohol in the presence of an amine at low temperature. The condensation with the second alcohol requires an elevated temperature. Thus, an internucleotide bond can be constructed *via* the coupling of (**84**; equation 55) and a nucleoside, forming the phosphorochloridite intermediate (**85**), and the subsequent condensation with another nucleoside.[117] 1*H*-Tetrazole-promoted esterification of the bisphosphoramidite of type (**86**) with two kinds of alcohol occurs in a similar manner.[118,119] The latter procedure is much more efficient for the synthesis of oligonucleotides, because the phosphorodichloridite reagent is too labile in air and cannot be stored for a long period without decomposition. Long sequences of DNA can be prepared by a procedure based on the bisphosphoramidite method.[120]



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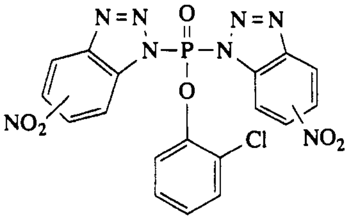

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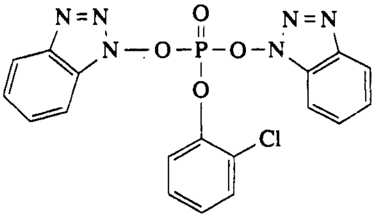

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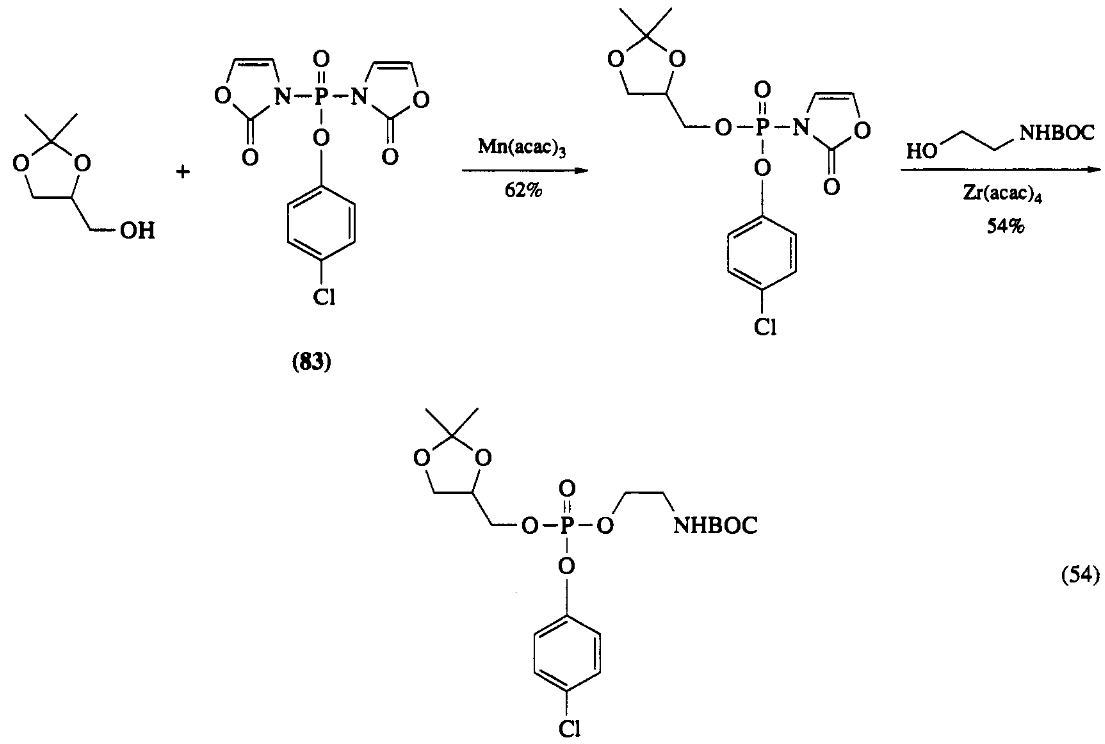


(54)

2.8.4.3 (RO)POXY-type Reagents

When the cyclic enediol ester of phosphoric acid (**87**; equation 56)[121] is reacted with the diol (**88**), the cyclic phosphate (**89**) is obtained in a single step.[122] Use of the chlorophosphoryl analog (**90**; equation 57) effects the two-step preparation of the phospholiposterol (**91**).[121,123] The pyrophosphate-type compound (**92**) has a similar reactivity.

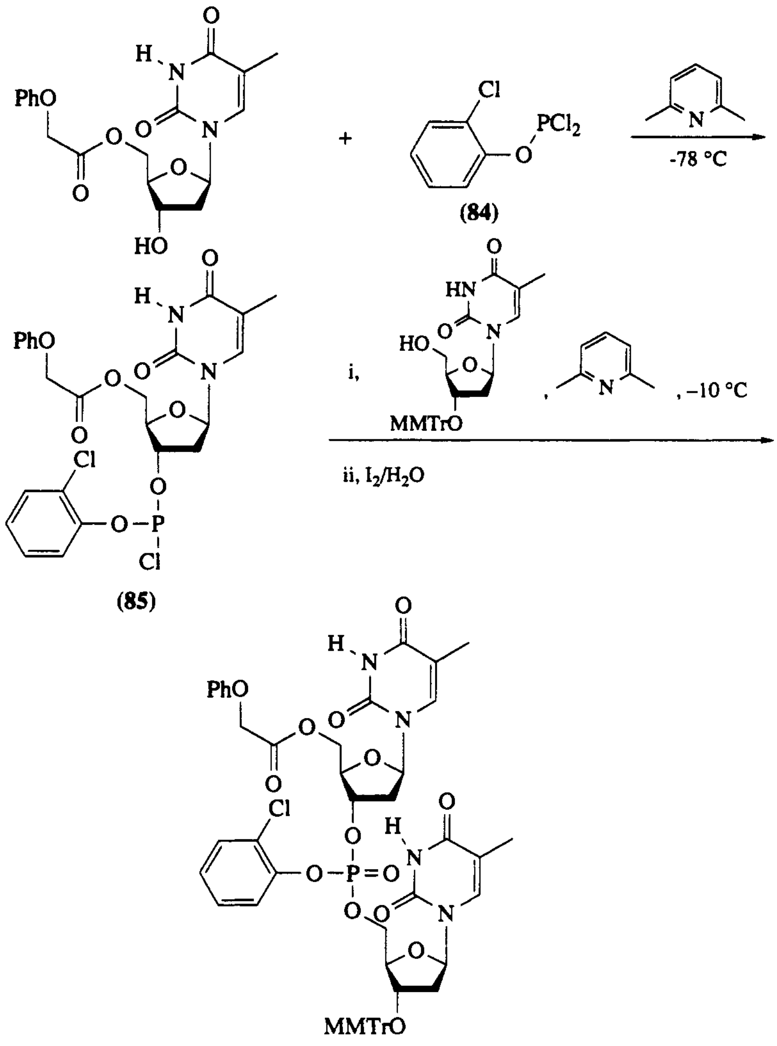
The method using (**90**) or (**92**) is applied to the synthesis of many phospholipids and their analogs, oligonucleotides, *etc.*[121,124–127] Interribonucleotide bond formation is accomplished by the successive condensation of the chlorophosphorylnitrobenzotriazolide (**93**; equation 58) and the 3′-free ribonucleoside (**94**) assisted by pyridine, followed by the 5′-free derivative (**95**) promoted by 2,6-lutidine, affording (**96**).[128]

The *p*-nitrophenyl phosphorochloridate (**97**; equation 59) acts as the bifunctional phosphorylating agent when used with 2 equiv. of magnesium alkoxide. The internucleotide linkage formation *via* alcohol activation does not require protectors on all the amino groups of the nucleoside bases.[129] The chlorophosphoromorpholidite (**98**) is a usable bifunctional reagent for the preparation of nucleoside di- and tri-phosphates.[130]

2.8.4.4 (RO)PXY-type Reagents

The chlorophosphoramidite (**99**; equation 60)[131] reacts with 1 equiv. of an alcohol in the presence of a tertiary amine to form the unsymmetrical phosphoramidite (**100**), which in turn condenses another alcohol, by the assistance of 1*H*-tetrazole to afford, after oxidation, the unsymmetrical phosphorotriester (**101**). This method has been successfully applied to the synthesis of long DNA sequences. The *H*-phosphonate (**102**; equation 61) exists in an equilibrium mixture with the valence tautomer, phosphite ester (**103**). The phosphite ester (**104**; equation 62) can be activated by pivaroyl chloride in the presence of pyridine to form the mixed anhydride, which reacts with an alcohol to give, after iodine oxidation, the phosphodiester (**105**).[132,133]

The phosphite method is effective for the synthesis of DNA oligomers, because the preparation requires no protection of the phosphoric acid moieties.[132,133]



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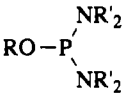
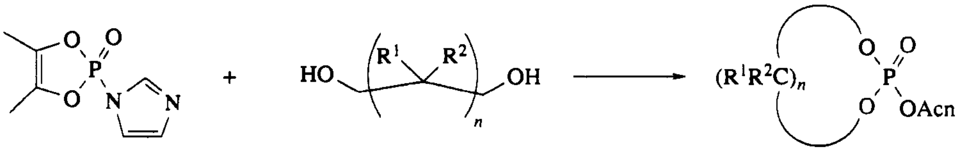


$RO{-}P(NR'_2)_2$

(86)

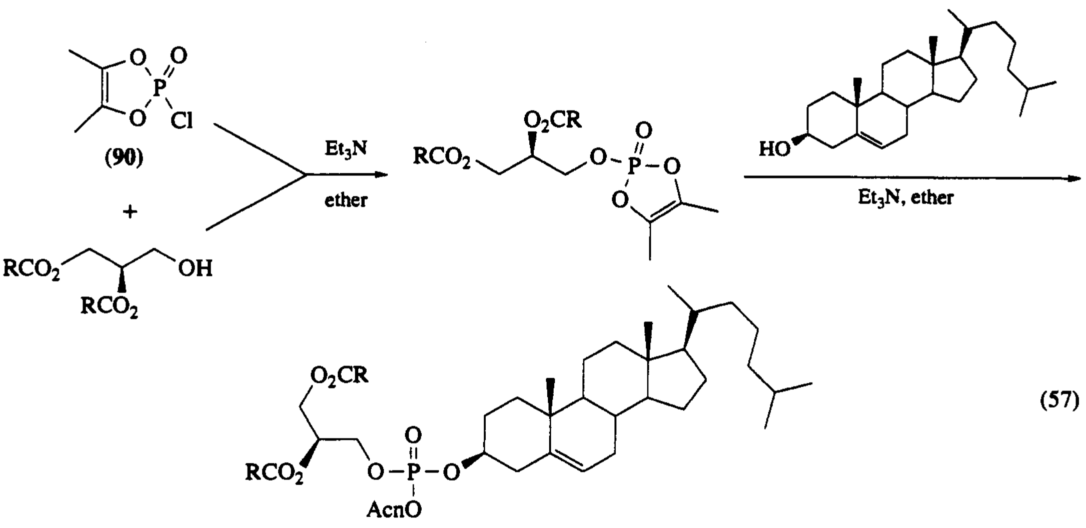
2.8.5 PROTECTING GROUPS OF PHOSPHORIC ACID

When the preparation of phosphomonoesters or -diesters is exemplified, two types of protecting group are conceivable. One is the protector removed *via* a P—O bond fission and the other through a C—O bond cleavage. In the former case, there is the possibility that a P—O bond fission between undesired positions competes. Use of the latter protector may prevent such side reaction. Thus, at present, the protecting groups belonging to the latter strategy are much more widely employed.



(56)

(87) **(88)** **(89)** Acn = CH(Me)COMe



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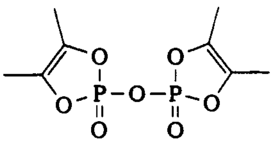
(91)



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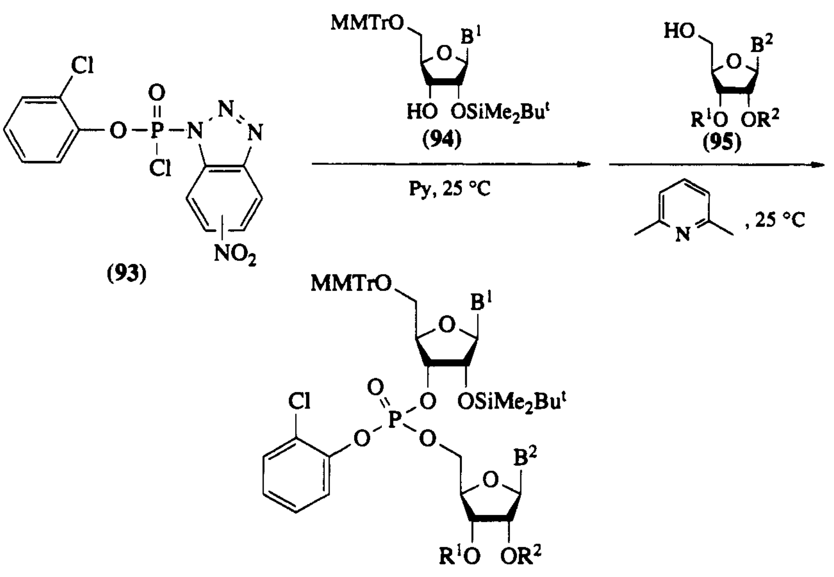
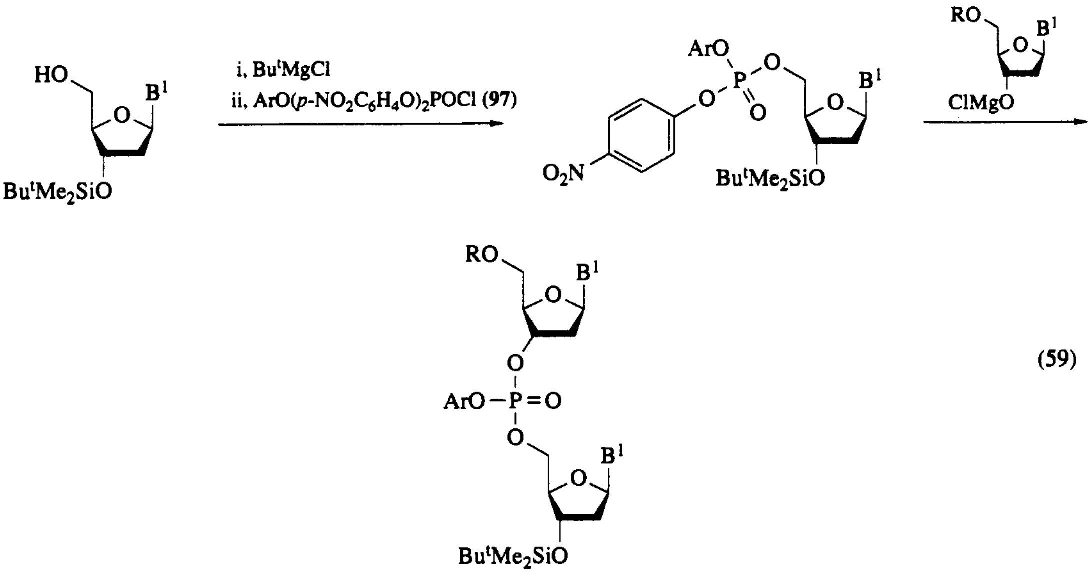


(58)

(96)

2.8.5.1 Aryl Groups

Aryl groups are widely employed as the protector. Some kinds of phenyl derivatives can be removed by basic hydrolysis. The removal, particularly from phosphodiesters, frequently requires high temperature.[134,135] For example, the 4-chloro-2-nitrophenyl ester (**106**; equation 63) is hydrolyzed by sodium



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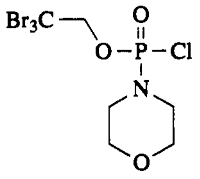

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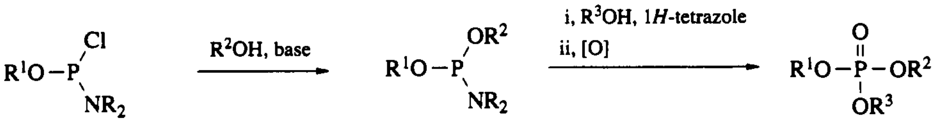
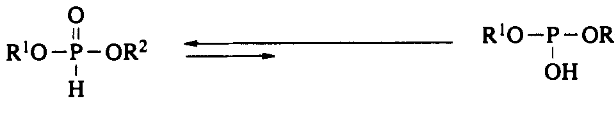
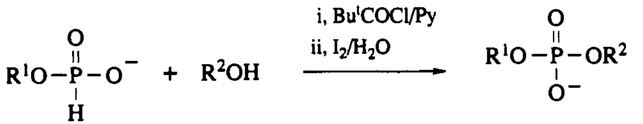


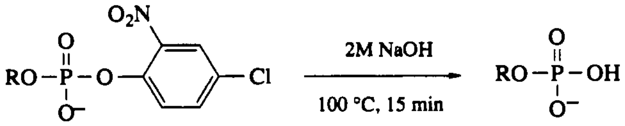
(99) **(100)** **(101)** (60)



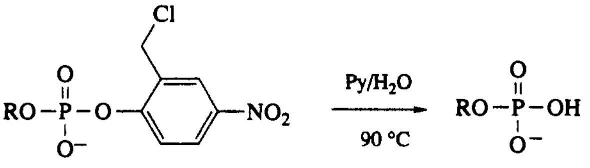
(102) **(103)** (61)



(104) **(105)** (62)



(106) (63)

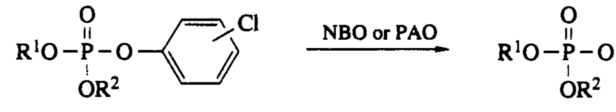


(107)

(64)

hydroxide at 100 °C.[136] Similarly, hydrolysis of the 2-chloromethyl-4-nitrophenyl analog (**107**; equation 64) takes place using aqueous pyridine at 90 °C.[137]

The base hydrolysis under harsh conditions very often brings about undesired cleavage of phosphates. In contrast, removal of an *o*- or *p*-chlorophenyl protecting group by N^1,N^1,N^2,N^2-tetramethylguanidinium *syn*-*p*-nitrobenzaldoxymate (NBO) (**108**; equation 65) or *syn*-pyridin-2-aldoxymate (PAO) (**109**) is achievable at room temperature and no side reaction occurs.[129,138] The 8-quinolyl phosphate (**110**; equation 66) is also hydrolyzed under mild conditions with the assistance of a stoichiometric amount of $ZnCl_2$ or $CuCl_2$ salt.[139]



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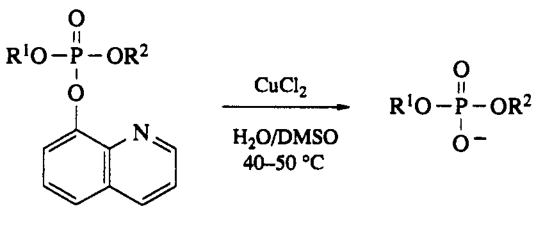
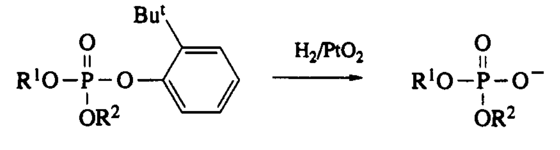


(110)

(66)

The 2-*t*-butylphenyl group, which is removed by hydrogenolysis on platinum oxide, is usable in some limited cases (equation 67).[140] 2-Hydroxyphenyl is a useful protecting group in conversion of phosphodiesters to phosphomonoesters. The deprotection is carried out by the oxidative treatment.[141]

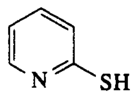


(67)

2.8.5.2 Alkyl Groups

Methyl is an easily employable protecting group. Deprotection is effected by thiophenol/triethylamine,[142] metal thiophenoxides,[143,144] dimethyl sulfide/methanesulfonic acid,[145] *t*-butylamine,[146] *etc.* (equation 68). The reaction using potassium thiophenoxide is greatly accelerated by addition of a catalytic amount of dicyclohexyl-18-crown-6.[144] When the demethylation of the methyl ester of nucleoside 5′-phosphoric acid is carried out with thiophenol in the presence of triethylamine, attack of the thiophenoxide to the 5′-carbon of the nucleoside takes place competitively.[142] This side reaction can be prevented to a considerable extent by use of 2-thiopyridine (**111**), 2-thiobenzoxazole (**112**), or 2-thiobenzothiazole (**113**) in place of thiophenol.[147] An allyl group is an excellent protector, removable using a palladium(0) catalyst in the presence of nucleophiles such as primary or secondary amines, and their salts of formic acid (equation 69).[15,120,148] Removal of the allyl protector is effected by sodium iodide in hot acetone.[149] The allyl protection is successfuly applied in oligo-DNA synthesis.[120] Benzyl is the protecting group and is removable by hydrogenolysis, using platinum or palladium metal as the catalyst (equation 70).[101,150] An *o*-nitrobenzyl group is a photolabile protector (equation 71). The reaction conditions do not affect purine or pyrimidine bases of nucleosides.[151] A 1-oxido-2-pyridylmethyl group is also use-

(68)



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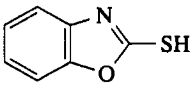

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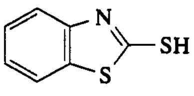

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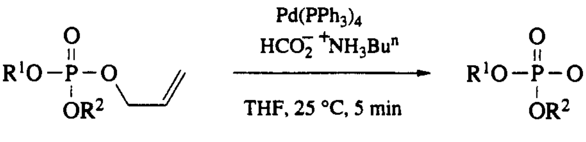

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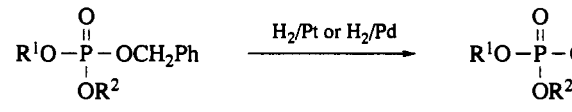

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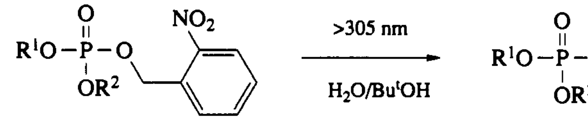

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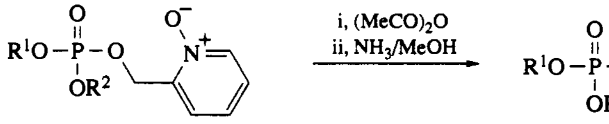
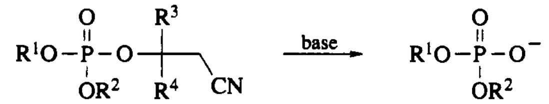


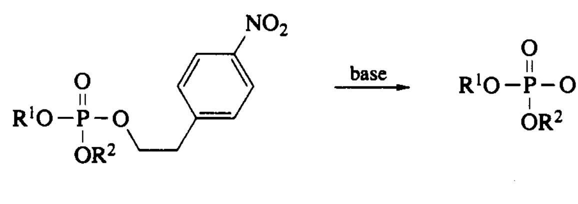
(72)

ful for protection of phosphoric acid, which is deblocked by treatment with acetic anhydride followed by methanolic ammonia (equation 72).[152]

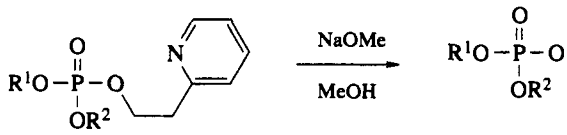
Protecting groups that are removed through a β-elimination mechanism are widely used in oligonucleotide synthesis. 2-Cyanoethyl (equation 73) and related protection can be deprotected by treatment with a base encompassing methanolic ammonia, DBU, *etc.*[146,153] 2-*p*-Nitrophenyl,[154] 2-pyridylethyl,[155] 2-(arylaminocarbonyl)ethyl[156] and 2-(arylsulfonyl)- or 2-(alkylsulfonyl)-ethyl groups[156,157] are similarly usable (equations 74–76). The sulfonylethyl function is usually generated from an arylthioethyl analog by oxidation with sodium periodate or NBS. The fluorene-9-methyl group is another example belonging to this category.[158] Deprotection is conducted by treatment with pyridine containing concentrated ammonia (equation 77). The 2,2,2-trichloroethyl[159,160] or 2,2,2-tribromoethyl groups[131] are protectors reductively removed by treatment with a Zn/Cu couple (equation 78).[159,160] The presence of acetylacetone as an additive in DMF greatly promoted the reaction.[161] A similar effect is observed with anthranic acid in pyridine.[160] The 2,2,2-trichloro-1,1-dimethyl group is also a useful protector, which can be removed with a mixture of triethylamine, tributylphosphine, and DMF (equation 79).[162] A 1-acetylethyl group is readily removed under mild basic conditions (equation 80).[121,163]



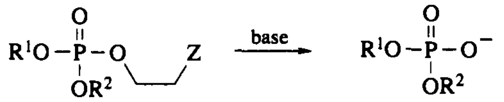
(73)



(74)

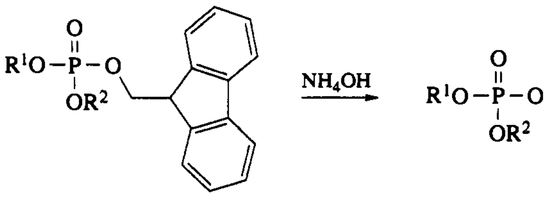


(75)

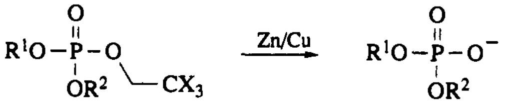


(76)

Z = CONHC$_6$H$_4$R^3, SO$_2$R^3

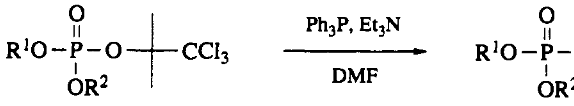


(77)

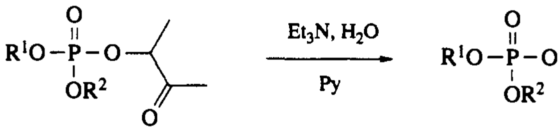


(78)

X = Cl, Br



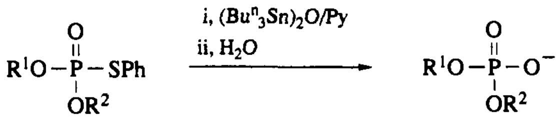
(79)



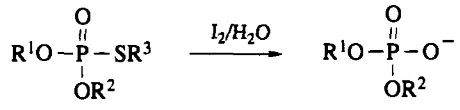
(80)

2.8.5.3 Miscellaneous

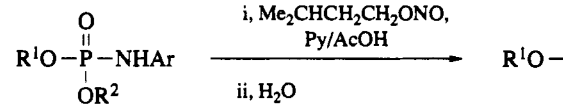
Thiophosphates can be converted to the phosphates by treatment with tributyltin oxide followed by water (equation 81).[164] Accordingly, the thiophenol is regarded as the protecting group in a formal sense. The transformation is also achieved by oxidative reaction with aqueous iodine (equation 82).[165] Certain kinds of amines also act formally as the protector. When phosphoramidates are treated with isoamyl nitrite in a mixture of pyridine and acetic acid, followed by water, hydrolysis occurs to give the phosphates (equation 83).[166,167] 2,2′-Diaminobiphenyl serves as a bifunctional protecting group deprotectable under similar conditions. Thus, the phosphorodiamidate (**114**; equation 84) is hydrolyzed to the phosphomonoester (**115**).[168] The deprotection is remarkably accelerated by addition of silver acetate and benzoic anhydride.



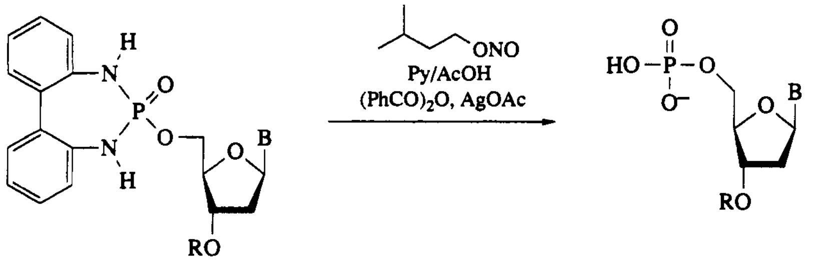
$$\mathrm{R^1O-\underset{\underset{OR^2}{|}}{\overset{\overset{O}{\|}}{P}}-SPh} \xrightarrow[\text{ii, } \mathrm{H_2O}]{\text{i, } \mathrm{(Bu^n{}_3Sn)_2O/Py}} \mathrm{R^1O-\underset{\underset{OR^2}{|}}{\overset{\overset{O}{\|}}{P}}-O^-} \quad (81)$$



$$\mathrm{R^1O-\underset{\underset{OR^2}{|}}{\overset{\overset{O}{\|}}{P}}-SR^3} \xrightarrow{\mathrm{I_2/H_2O}} \mathrm{R^1O-\underset{\underset{OR^2}{|}}{\overset{\overset{O}{\|}}{P}}-O^-} \quad (82)$$



$$R^1O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OR^2}{|}}{P}}-NHAr \xrightarrow[\text{ii}, H_2O]{\text{i}, Me_2CHCH_2CH_2ONO,\ Py/AcOH} R^1O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OR^2}{|}}{P}}-O^- \qquad (83)$$



(84)

(114) **(115)**

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3.1
Protecting Groups

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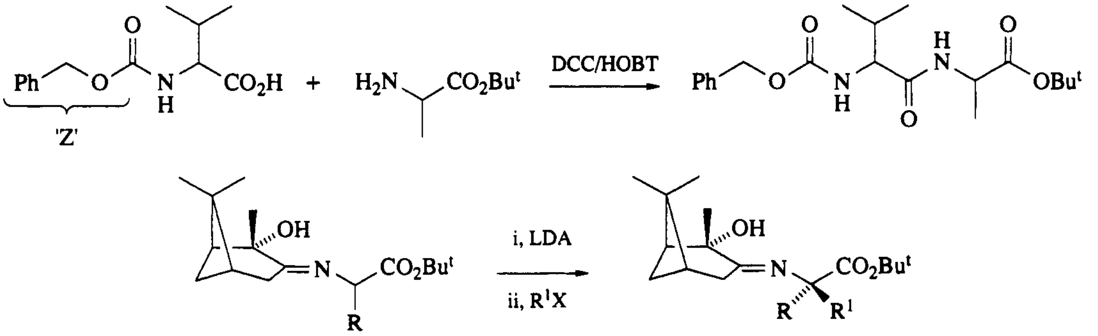
3.1.1 PRINCIPAL DEMANDS FOR AND ON FUNCTIONAL GROUP PROTECTION

There is hardly any area of preparative organic chemistry in which the proper use of protecting groups is not a prerequisite for the successful achievement of the goals aimed at. For this reason such blocking functions have been developed for nearly 100 years by numerous researchers from all disciplines of organic chemistry, and consequently solutions to the existing problems have been devised, making use of various synthetic transformations. It was Fischer who, among his many important contributions to chemistry, first realized that the application of protecting functions is often a necessity for a successful synthesis. Thus, he introduced the isopropylidene ketal in carbohydrate chemistry[1] (see Section 3.1.3), and for the first time used both the chloroacetyl moiety and a urethane, namely the ethoxycarbonyl group, as

N-terminal-protecting groups (see Section 3.1.2.1) in the selective synthesis of peptides.[2] However, although Fischer tackled the problem, he could not provide reliable blocking functions to address the prevailing synthetic problems in peptide chemistry. It was not until 1932 that the decisive breakthrough for the invention of easily and selectively removable protecting groups was achieved. In this year Bergmann and Zervas reported on the use of the benzyloxycarbonyl (Z, Cbo) group (see Section 3.1.2.1) in peptide synthesis[3] and thereby opened up this new field of organic chemistry. Since then the discipline has continued to grow steadily.

During the past decades the highly selective construction of polyfunctional molecules, *e.g.* nucleotides, oligosaccharides, peptides and glycopeptides, and complex natural products like alkaloids, the macrolide and polyether antibiotics and the prostaglandins, has seen dramatic improvements in the state of the art. These achievements were only possible through the extensive use of protecting groups, which in numerous cases had to be newly designed to overcome the emerging difficulties in the experimental realization of the synthetic plans. The studies aiming at the successful total synthesis of palytoxin,[4] the most complex acyclic compound known to date, provide an impressive example of this. Today, therefore, protecting group chemistry is more important than ever. This review intends to summarize the most practical and commonly used blocking functions, and to offer to the interested reader solutions to prevailing problems, rather than to be a complete summary of all protecting groups described.[5] Very detailed and helpful compilations of the developments reported in the literature up to 1979 are available,[5] and the data collected by Greene in this book have provided the basis for a computerized method to choose the correct protecting group combination in retrosynthetic analysis.[6]

A good protecting group has to meet numerous demands, which themselves heavily depend on the chemical nature of the function to be protected, the other structural elements present in the compound to be transformed and especially the types of reaction to be carried out in subsequent steps. Thus, the benzyloxycarbonyl (Z) group is very efficient for the protection of the amino group during the formation of peptide bonds. If, however, an alkylation of the α-carbon of an amino acid *via* the corresponding enolate is desired it cannot be used, and the nitrogen is best converted to an imine. The second example depicted in Scheme 1 also demonstrates that by a proper choice of the reagent used for protection, further directing effects, like the introduction of sterical bias, can be exerted.



Scheme 1

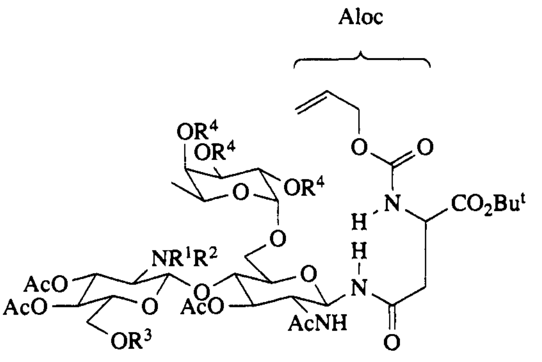
The major criteria that must be fulfilled by a protecting group are that: (i) it must exclude the protected functional group from participating in the reaction to be carried out; (ii) it must ensure that the protected functional group is not damaged during the projected synthetic transformation; (iii) it must itself be stable during the projected reaction, but at the same time must be removable after this reaction under conditions which will cause no damage to the newly synthesized structure; and (iv) it should not exhibit a destabilizing, but rather a stabilizing, influence on the compound to be protected (*e.g.* epimerizations and racemizations should be suppressed).

For practical reasons a blocking group should, in addition, display the following properties: (i) it should be easy to introduce and to remove, and the reagents for introduction and removal should be readily available, stable and easy to handle; (ii) the protected compound should be easy to characterize, in particular the protecting group should neither possess nor introduce a chiral center; (iii) the solubility of the protected product should be favorably influenced; (iv) it should be put on, and removed from, a functional group in high yields and, after deprotection, the reaction products should be readily separable from the freed compound; and (v) a participation of the protecting group during the reaction must be either unequivocal or excluded.

If several blocking functions are present in a given compound it may be desirable to remove them all in one step. However, the more demanding task, which usually has to be fulfilled in a reaction sequence, is that each single protecting group must be selectively removable, leaving the other blocking functions intact. This strategy has been addressed as 'the principle of orthogonal stability' of protecting groups.[7]

These criteria are highly demanding and, not surprisingly, most of the blocking groups which have been introduced fail to meet them all. On the other hand this is not always necessary. Depending on the synthetic problem to be addressed it is often sufficient that the protecting functions used display only some of the desired properties.

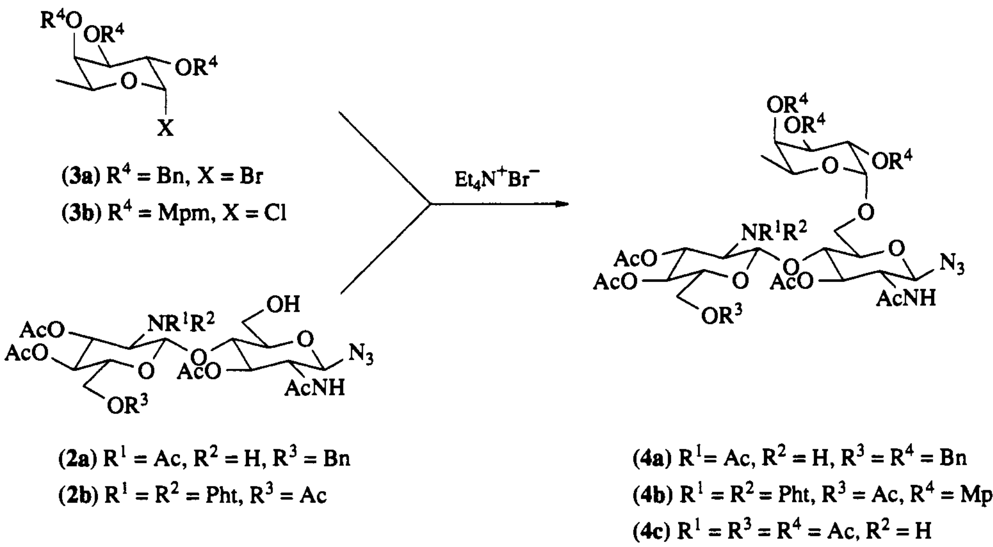
In the synthesis of complex molecules containing numerous different functional groups the interdependence of protecting groups extended by regio- and stereo-chemical requirements creates multidimensional problems which can only be solved by means of a subtle and versatile blocking group strategy. Frequently the overcoming of one problem creates a new one, as, for instance, had to be learned in attempting the synthesis of glycopeptides of type (**1**), representing partial structures of virus envelope glycoproteins and containing the α-fucosyl chitobiose core.[8] For immunological evaluations of such glycoprotein segments all blocking functions must be removable. Furthermore, the exactly specified extension of the peptide part and the coupling of the nondeformed glycopeptide to carrier proteins is highly desirable. This can only be achieved with N- and C-terminal-protecting groups which are orthogonally stable to each other, and which can be selectively removed without affecting the blocking functions and the sensitive glycosidic bonds in the saccharide part. However, the task is even more complex, because the construction of the saccharides themselves involves numerous regio- and stereo-chemical problems.



(**1a**) $R^1 = Ac, R^2 = H, R^3 = R^4 = Bn$

(**1b**) $R^1 = R^3 = R^4 = Ac, R^2 = H$

For syntheses of saccharide side chains of *N*-glycopeptides it is generally advantageous to use the anomeric azide group as the blocked form of the amino function, as can be demonstrated for the chitobiose derivatives (**2**). The azide does not usually interfere with ester formations and cleavages, nucleophilic substitutions, acetal formations, acetal reductions and acetal hydrolyses, or interfere with glycosylation reactions. A precondition for the construction of the α-fucoside linkage in (**1**) is that the fucosyl donor (**3**), to be connected with the chitobiose acceptor (**2**), carries nonneighboring group active blocking functions, *i.e.* ether-type protection. This is most commonly achieved with *O*-benzyl-protected fucosyl halides (**3a**). Thus, under *in situ* anomerization conditions[9] (**3a**) and (**2a**) give the desired α-fucosyl chitobiosyl azide (**4a**) with complete stereoselectivity.[8] As a consequence of the benzyl ether protection, the azide in (**4a**) cannot be reduced to the required glycosylamine by usual hydrogenation with palladium or platinum catalysts. The reduction is, however, accomplished using neutral Raney nickel. The amine thus obtained is then condensed with *N*-allyloxycarbonyl (Aloc) aspartic acid α-mono *t*-butyl ester to furnish the conjugate (**1a**). The selective removal of the Aloc group by means of the palladium(0)-catalyzed allyl transfer to dimedone allows N-terminal peptide chain extension without destruction of the complex conjugate. The planned subsequent removal of the C-terminal *t*-butyl ester from the trisaccharide peptide (**5a**) was expected to open the way for the coupling of the synthetic glycopeptide to a carrier protein. However, in contrast to the safe and selective removal of the Aloc group, the treatment of (**5a**) with trifluoroacetic acid resulted in complete cleavage of the fucoside bond. After a synthesis of about 30 steps this result was quite discouraging. It illustrates the fatal consequence of the fact that, although all other demands on selective protecting group chemistry are fulfilled, the sensitivity of the fucoside bond in (**5a**) is incompatible with a selective *t*-butyl ester cleavage. In this situation, two principally different ways could lead to the aimed selective carboxy deprotection of (**5**). The first, and probably more generally applicable one, would consist in a substitution of the carboxy protecting group by another blocking function. Of course, the properties of this substitute may necessitate a modification of the whole synthetic strategy to avoid new undesired interferences. On the other hand, for glycopeptide syntheses a further property of a correctly chosen fucoside-protecting group might advantageously be exploited: the stabilizing effect towards acids exerted by acyl protection in the carbohydrate.

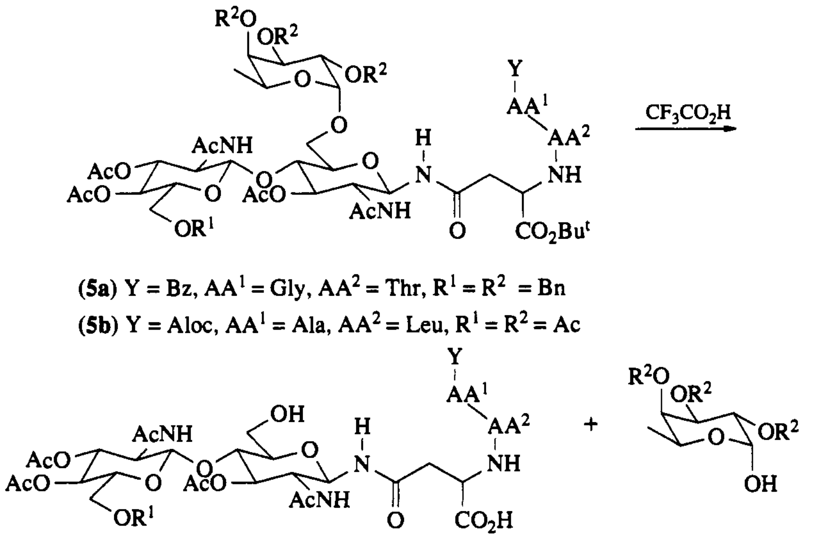


(3a) R^4 = Bn, X = Br
(3b) R^4 = Mpm, X = Cl

(2a) R^1 = Ac, R^2 = H, R^3 = Bn
(2b) R^1 = R^2 = Pht, R^3 = Ac

(4a) R^1= Ac, R^2 = H, R^3 = R^4 = Bn
(4b) R^1 = R^2 = Pht, R^3 = Ac, R^4 = Mpm
(4c) R^1 = R^3 = R^4 = Ac, R^2 = H

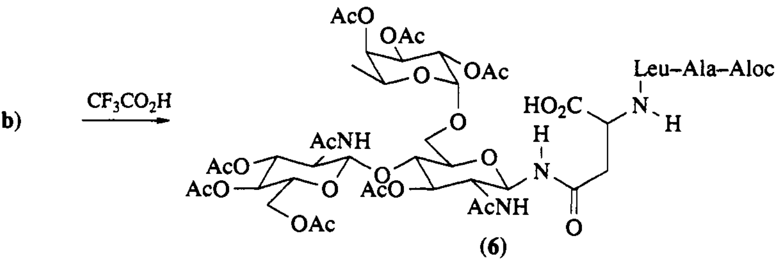
(1)



(5a) Y = Bz, AA^1 = Gly, AA^2 = Thr, R^1 = R^2 = Bn
(5b) Y = Aloc, AA^1 = Ala, AA^2 = Leu, R^1 = R^2 = Ac

(2)

Experiences in glycopeptide synthesis suggested that acyl protecting functions in the saccharide part enhance the stability of intersaccharidic bonds towards acids.[10] Therefore a new concept was developed, based on the exchange of the fucose-protecting groups in (**4b**) immediately after formation of the α-fucosidic bond. The acid sensitive 4-methoxybenzyl (Mpm) ether protection requires a special construction of the fucosyl donor (**3b**). However, after linking to the acceptor (**2b**) the ether protecting groups are removable from the trisaccharide (**4b**) by means of an oxidation method which does not affect the azide group. Subsequent hydrazinolysis of the phthaloyl moiety and acetylation of the free amino and hydroxy groups furnishes the fully acetylated trisaccharide (**4c**). After hydrogenation the liberated amine is transformed into the conjugate (**1b**) which after N-terminal deblocking is chain-elongated to give the trisaccharide tripeptide (**5b**). The removal of the *t*-butyl ester protection from (**5b**) can now be achieved with complete selectivity by using trifluoroacetic acid. The selectively deblocked compound (**6**) allows for C-terminal chain extension as well as for coupling to a protein carrier.[8] The successful deblocking of (**5b**) as opposed to (**5a**) illustrates the manifold interdependency of properties in protecting group chemistry. It is also a highlighting example which demonstrates that the protecting group (here the acetyl group) not only serves to mask a functionality (in **5b** the hydroxy groups of fucose) but also may strongly influence other structures present (in this example the fucoside bond). Therefore, the realization of a planned synthesis aiming at a complex structure critically depends on the protecting group strategy chosen.



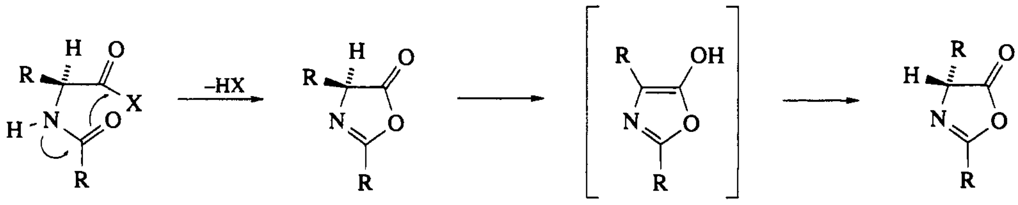
(3)

3.1.2 AMINO-PROTECTING GROUPS

Amino-protecting groups are extensively used in peptide chemistry.[11] During the formation of a specific peptide bond between two amino acids, one amino function has to remain blocked to ensure the formation of only a single amino acid sequence. Together with the reversible masking of the nucleobases in nucleotide synthesis[12] and the protection of nitrogen atoms in alkaloid synthesis, this constitutes the most important area of application for amino-protecting groups.[5]

3.1.2.1 Urethane Protecting Groups

In peptide synthesis the use of a suitable protection for the N-terminal amino group is required not only to prevent the formation of a complex mixture of oligo- and cyclo-peptides, but an additional demand on the functionality applied for this purpose is that it should prevent possible racemization of the activated amino acid. Racemization usually takes place *via* an intermediate oxazolone (**7**) that forms readily from *N*-acyl-protected amino acids (Scheme 2). This side reaction can be mostly suppressed by using a carbamate as an N-terminal-protecting group. Therefore, nearly all blocking functions currently applied in this field are of the urethane type.

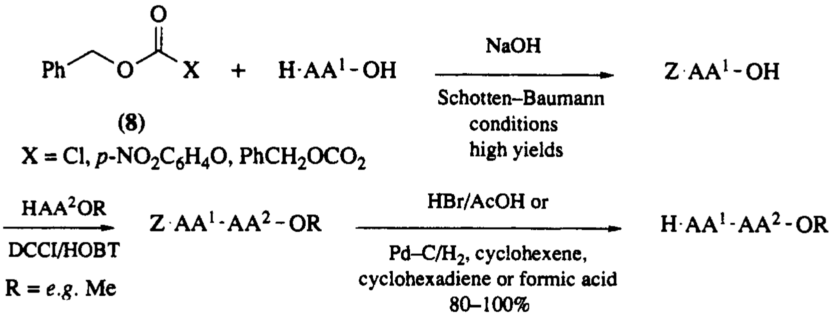


(7)

Scheme 2

Since their invention by Bergmann and Zervas in 1932, benzyl carbamates have been widely used as protecting groups. They are easily introduced *via* the corresponding chloroformates[3,11] or the *p*-nitrophenyl carbonates (**8**; Scheme 3).[13] The benzyloxycarbonyl (Z, Cbo) group[3] is stable during the formation of the peptide bond, but can be selectively removed under a variety of conditions. Thus, hydrogenolysis over palladium catalysts in the presence of hydrogen (or hydrogen donors like cyclohexene,[14a] cyclohexadiene[14b] or formic acid)[15] is effective. Furthermore, the group can be cleaved off using sodium in liquid ammonia, or strong acids like HBr/HOAc[17a] and 70% HF/pyridine.[17b] It is, however, stable to hydrazine, to warm acetic acid and to trifluoroacetic acid at room temperature, *i.e.* the conditions used to cleave *t*-butyl carbamates and *t*-butyl esters.

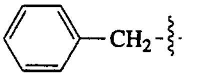
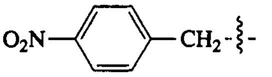
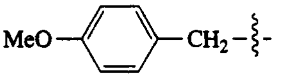
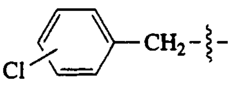
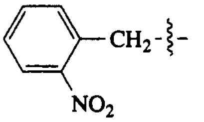
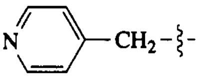
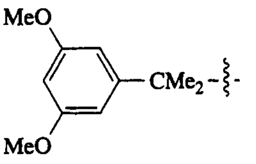
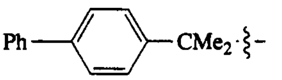
By introducing substituents into the benzylic system, its stability towards acids or reduction can be varied. Electron-withdrawing substituents in the aromatic ring increase acid stability and may accelerate the cleavage by hydrogenolysis. Thus, the 4-nitro-Z group (NZ)[18] and the (isonicotinyl)oxycarbonyl group (Inoc)[23] are stable towards HBr/HOAc but are more quickly removed by hydrogenation than the Z group. On the other hand introduction of electron-donating substituents promotes acid sensitivity, *e.g.* the 4-methoxy-Z group (MOZ)[19] is attacked by trifluoroacetic acid at 0 °C, conditions under which a benzyl



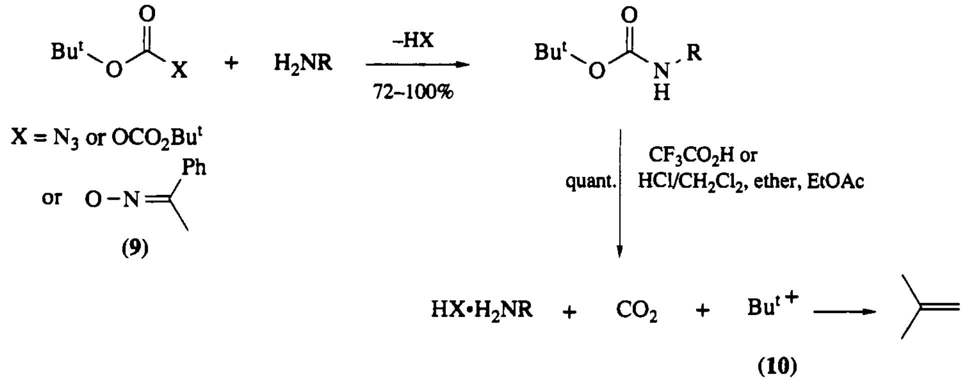
Scheme 3

carbamate is stable. The even more electron-rich 2-(3,5-dimethoxyphenyl)-2-propoxycarbonyl (Ddz) group (see Table 1)[24] is cleaved by 5% TFA in methylene chloride. Table 1 shows a selection of the most commonly used benzyl-type urethane protecting groups. For an extensive compilation of the numerous variants of the Z group see especially Wünsch in ref. 11a.

Table 1 Selected Benzyl Urethane-type Protecting Groups

Benzylic system	*Abbreviation*	*Stable to*	*Removal by*	*Ref.*
	Z	Base, TFA, H_2NNH_2	H_2/Pd, Na/NH_3, Et_3SiH, $PdCl_2$/Et_3N	13–17
	NZ	Base, TFA, HBr/AcOH	H_2/Pd increased, e^-/1.2 V, $R_4N^+ X^-$	18
	MOZ	Base	H_2/Pd, TFA	19
	CZ	Base, TFA	HBr/AcOH, decreased; H_2/Ph	20, 21
	(2-NO_2)Z	Base, TFA	Like NZ, *hv*	22
	Inoc	Base, TFA	H_2/Pd, Zn/AcOH	23
	Ddz	Base	5% TFA/CH_2Cl_2, *hv*	24
	Bpoc	Base	80% AcOH/H_2O	25

It is not only benzyl-type urethanes which are widely used for the blocking of amino groups. This goal may also successfully be achieved by the application of alkyl urethanes. Among these, the *t*-butoxycarbonyl group (t-BOC or Boc), introduced in 1957,[26] deserves special mention. Today it probably is the most frequently used amino-protecting function in peptide synthesis. The t-BOC group can be easily introduced using *t*-butoxycarbonyl azide,[27] the commercially available pyrocarbonate[28] or an oxime reagent (t-BOC-ON; **9**).[29]

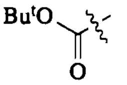
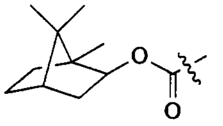
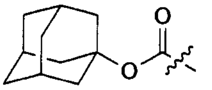
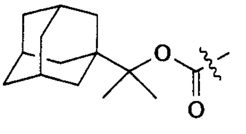
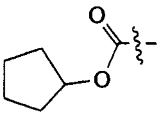


Scheme 4

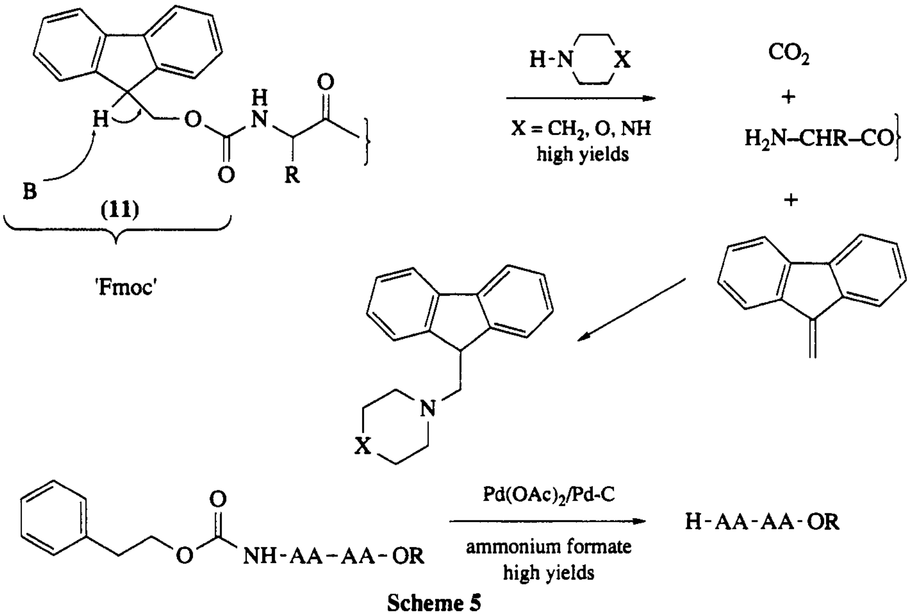
It is stable towards bases and reduction with hydrogen and sodium in liquid ammonia. Its removal can be accomplished with the aid of hydrochloric acid in dichloromethane, ether and ethyl acetate[30] or by using trifluoroacetic acid (neat or dissolved in dichloromethane).[31] Under these conditions the Z group remains unaffected, so that the t-BOC group appears to be an ideal complement to it. During the acid-catalyzed cleavage the *t*-butyl cation (**10**) is formed, which then eliminates a proton to give isobutene (Scheme 4). If, however, nucleophilic reagents are present, *e.g.* mercapto groups as in cysteine, they may be attacked by the cation giving rise to undesired side products. To circumvent this difficulty thiophenol or ethanedithiol should be added as scavengers.[31] Deprotection of t-BOC amino acids and peptide derivatives is also achieved by treatment with trimethylsilyl trifluoromethanesulfonate,[32a–c] and the reagent generated from phenol and trimethylsilyl chloride.[32d]

The underlying principle for the advantageous properties of the t-BOC group, that is the stabilization of the cation formed during acid-catalyzed deprotection by adjacent substituents exerting +I effects, was also adopted for the development of similar blocking functions with varied acid sensitivity. The most important ones among them are presented in Table 2. Once more, introduction of –I substituents causes increased acid stability. In addition, the Ddz and the 2-(4-biphenyl)-2-propoxycarbonyl (Bpoc) groups mentioned in Table 1 may be considered as intermediates between t-BOC- and Z-type protection.

Table 2 Selected Acid Labile Protecting Groups

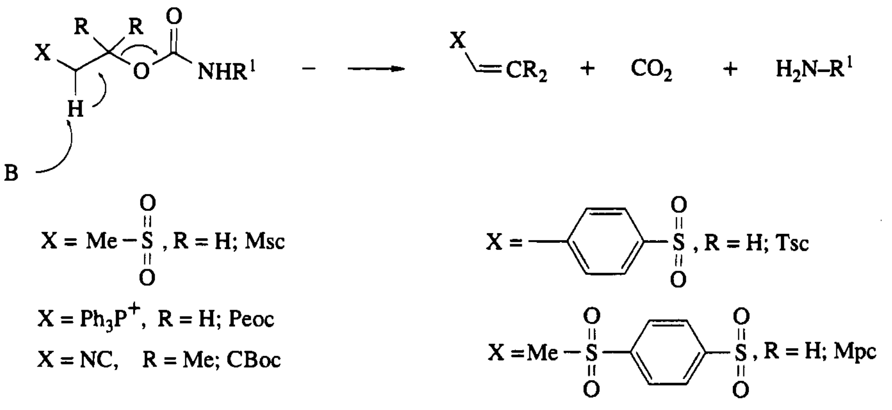
Protecting group	*Abbreviation*	*Removal by*	*Ref.*
	t-BOC	TFA, HCl/solvent, Me_3SiOTf	26–32
	Iboc	TFA	33
	Adoc	TFA	34
	Adpoc	3% TFA/CH_2Cl_2	35
	Cpc	HBr/AcOH	36

Whereas the Z- and the t-BOC-based urethane protecting groups are characterized by their sensitivity towards hydrogenation and/or acids, in recent years a new class of protecting functions which are removable by treatment with bases has been developed. In 1970 Carpino and coworkers introduced the 9-fluorenylmethoxycarbonyl (Fmoc) group for N-terminal protection in peptide synthesis (Scheme 5).[37] Fmoc-protected amines and amino acids are easily formed in the reaction of the amino compound with the chloroformate. After condensation to dipeptides the amino function can be liberated by treatment with bases like piperidine, morpholine, ammonia or ethanolamine. Acids, such as HBr/HOAc or TFA, however, do not affect the Fmoc group. The ease of removal of the Fmoc group has allowed for a new strategy in solid-phase peptide synthesis which is becoming increasingly popular.[38] A certain drawback of the Fmoc methodology, however, is that the protected derivatives (**11**) are sometimes not easily soluble in organic solvents and that the amino group liberated can react with the dibenzofulvene formed, giving rise to undesired side products. The latter reaction can be prevented by using cyclic amines in the deprotection step. In addition, the Fmoc function can be removed by hydrogenolysis. Here, the homobenzylic position is attacked by hydrogen in the presence of a freshly prepared Pd catalyst. This type of reaction appears to be general, since the parent 2-phenylethoxycarbonyl group is also sensitive to hydrogenation and can too be used as an N-terminal-protecting group for the synthesis of peptides (Scheme 5).[39]

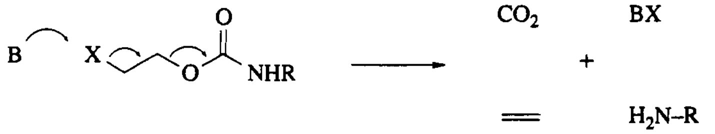


Scheme 5

The underlying principle in the cleavage of the Fmoc protecting group is that the base abstracts the bisbenzylic proton from the cyclopentadiene part. The aromatic fluorenyl carbanion generated undergoes an *E*1*cB* β-elimination reaction. Similar processes are also exploited in several other protecting techniques. Thus, in the tolyl-[40] and methyl-sulfonylethyl[41] carbamates the acidifying functionality is a sulfone (equation 4). The protecting groups can be removed by treatment with bases of the strength of dilute NaOH, but are not attacked by strong acids. Compared to the Fmoc group, these protecting functions are less sensitive to bases. They are stable towards primary and secondary amines in aprotic solvents. Therefore, Tesser and coworkers[41b] designed the 2-[4-(methylsulfonyl)phenylsulfonyl]ethoxycarbonyl (Mpc) group as a new amino-protecting group which is only slightly more stable than the Fmoc group, resists hydrogenation and whose cleavage product does not polymerize spontaneously. The triphenylphosphonioethoxycarbonyl (Peoc) function[42] is even more base labile than the Fmoc group and is cleaved at pH 8.4. Its extreme acid stability allows the preparation of Peoc amino acid chlorides which appear to be very useful in the synthesis of strained cyclic depsipeptides.[43] Acid-stable analogs of the t-BOC group were created following these guidelines, resulting in the use of the 'Cyano-Boc' (CBoc)[44] and the β-trichloro-Boc (TcBoc)[45] groups. Both are stable to trifluoroacetic acid. The CBoc protection is lost at pH 10 (see equation 4) and the TcBoc function can be removed reductively with zinc in acetic acid (see equation 5) or using the supernucleophile lithium cobalt(I) phthalocyanine. The nucleophilic attack at a heteroatom in the β-position of a substituted ethyl carbamate, exploited in the deprotection of the TcBoc group, also forms the basis for the cleavage of 2-haloethyl carbamates[46] and the 2-trimethylsilylethyl carbamate.[47]



(4)



(5)

X = Cl, B = Zn/AcOH or cobalt(I) phthalocyanine (ref. 46a)

X = Br, B = Zn/AcOH, electrolysis or cobalt(I) phthalocyanine (ref. 46b)

X = I, B = Zn/MeOH (ref. 46d)

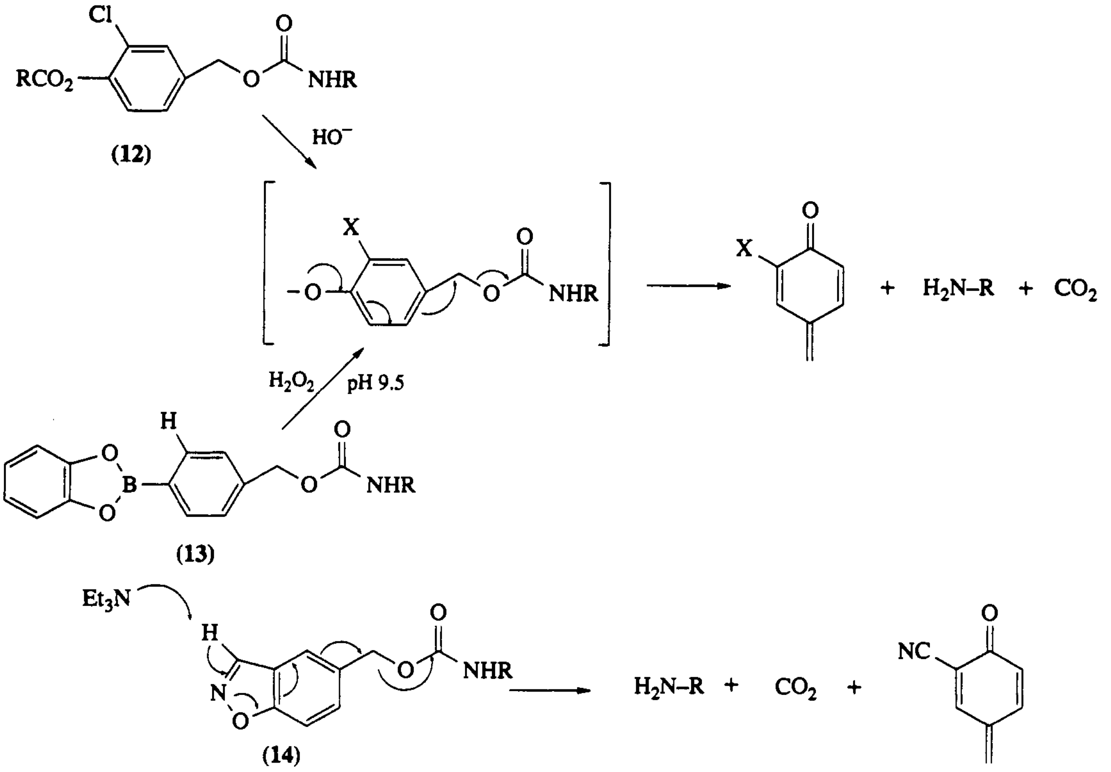
X = Me_3Si, B = KF or $Bu_4N^+F^-$ (ref. 47)

Not only β-elimination reactions were introduced for fragmentation-induced deblocking. The *m*-chloro-*p*-acyloxybenzyl carbamates (**12**),[48] the *p*-(dihydroxyboryl)benzyl carbamate (**13**)[49] and the 5-benzisoxazolylmethoxycarbonyl group (**14**)[50] can all be regarded as substituted Z groups. On the one hand they can be cleaved by hydrogenolysis. Alternatively, however, treatment with base (for **12** and **14**) or H_2O_2 at pH 9.5 (for **13**) results in the formation of a phenolate which then decomposes to a quinomethane, CO_2 and the free amine (Scheme 6).

An inherent disadvantage of the very base- and acid-labile protecting groups is that their reactivity retained during the projected synthetic steps (which make the protection necessary) must be considered. Therefore, side reactions and unwanted loss of the blocking groups become possible. In particular, when several protecting functions of comparable sensitivities are present at the same time, the selective liberation of one functionality may be complicated. These difficulties can be overcome by applying protecting groups which are introduced in a chemically stable form, and which, if deprotection is desired, are modified to yield a chemically sensitive structure. Protecting functions of this type are called 'two-step protecting groups'. This principle was first developed in the form of the 2-methylthioethyl ester as a carboxy-protecting group.[51] On the basis of this concept, the 2-(methylthio)ethoxycarbonyl (Mtc)[52] and the (1,3-dithian-2-yl)methoxycarbonyl (Dmoc)[53] groups were designed for amino protection (Scheme 7). Both are relatively stable towards acids and bases, but, after oxidation of the sulfurs to sulfones, base-induced β-elimination liberates the amino function. The acidifying influence exerted by the oxidized Dmoc group is so strong that the deprotection occurs at pH 7.5.

Applying the same principle, 2- and 4-pyridylethoxycarbonyl (2- and 4-Pyoc)[54] structures can be sensitized by methylation of the pyridine nitrogen. Subsequent treatment with the weak base morpholine ($pK_a \approx 8.3$) in dichloromethane already induces fragmentation and the formerly protected amino group is liberated (Scheme 8). This method proved to be successful in the synthesis of acid- and base-sensitive *O*-glycopeptides with tumor-associated antigen structure.[53b]

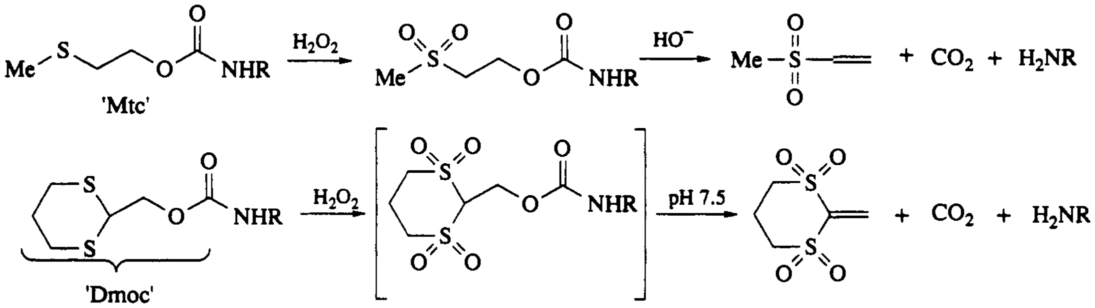
Further examples for this type of protecting group strategy were developed for amides and esters (*vide infra*; levulinyl esters, azidobutyryl esters and *o*-nitrophenylpropionyl amides). Although the two-step protecting groups circumvent the presence of potentially labile structures for protection, they require the use of further chemical transformations which might also harm other parts of the molecule to be deprotected (*e.g.* the methylations of the Pyoc groups and the oxidations of the Dmoc and the Mtc groups de-


(12)

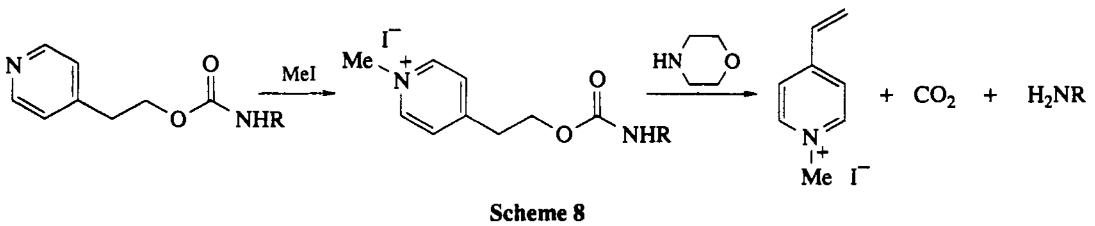
(13)

(14)

Scheme 6



Scheme 7

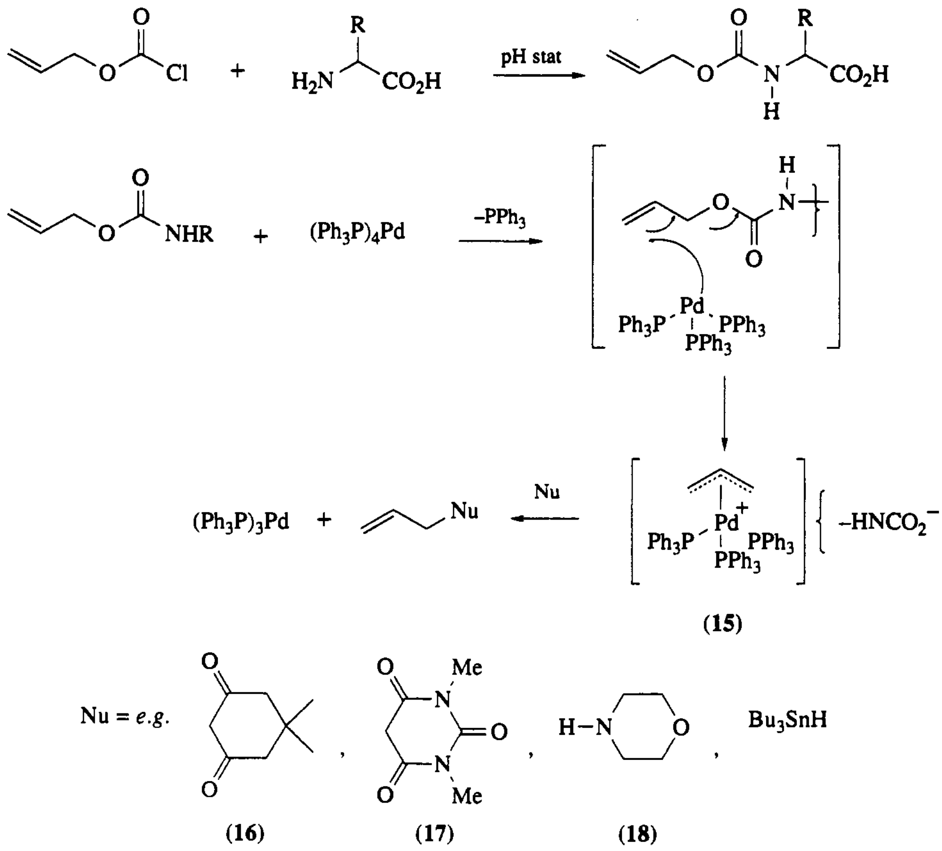


Scheme 8

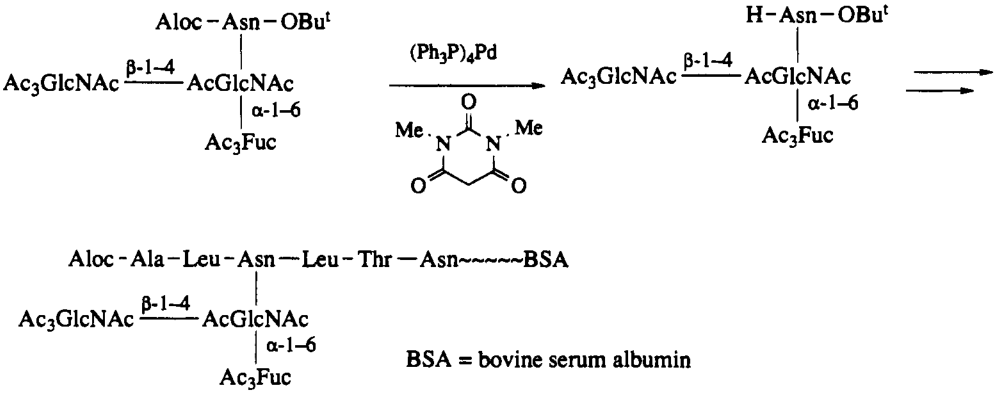
scribed above cannot be performed in the presence of methionine, cysteine or tryptophan). This disadvantage may be overcome by initiating the protecting group removal through the action of a reagent which is unreactive towards the other functionalities present, but at the same time regio- and chemoselectively activates the desired group without performing a chemical transformation. This principle could be realized in the allyl esters (see Section 3.1.5.1) and the allyloxycarbonyl (Aloc) group (Scheme 9).[55] This long-known amino-protecting function[56] is easily introduced using chloroformic acid allyl ester and is stable towards bases and strong acids. The removal of the Aloc group can be accomplished under nearly neutral conditions by palladium(0)-catalyzed allyl transfer to weakly basic nucleophiles like morpholine (**18**) or CH-acidic compounds like dimedone (**16**) and *N*,*N*′-dimethylbarbituric acid (**17**).[57]

Recently, tributyltin hydride was described as the allyl-trapping reagent in this amino-deblocking reaction.[58] The earlier reported method,[59] unknown at that time in peptide chemistry, consisted in the use of 2-ethylhexanoic acid ions as the allyl-trapping nucleophiles. However, this nucleophile is not generally applicable for amino deblocking because of the more rapidly occurring competing reaction of the liberated amino group itself as the allyl-accepting nucleophile. During the deprotection reaction the palladium catalyst interacts as the electron donor with the allylic system and forms a π-allylpalladium complex (**15**) which then is attacked by the nucleophile, liberating the Pd^0 compound again. This protecting principle proved to be particularly advantageous for the construction of biologically important and chemically very sensitive glycopeptides.[10] An example in which the removal of the Aloc group was carried out in the presence of complex structures being sensitive to acids and bases is mentioned in Section 3.1.1. One of the decisive applications of the Aloc protecting principle is shown in Scheme 10.[8]

Allyl-type protection is becoming increasingly popular. In addition to the use of Aloc amino acids in peptide synthesis,[8,55–58] it has been applied to the blocking of alcohols, phenols, phosphates and carboxylic acids (see the respective chapters and references given in ref. 58) and also for the introduction of a new linking principle for solid-phase peptide synthesis, making removal of the synthesized peptide under nearly neutral conditions possible.[60] Several modifications of the parent system as well as the allyl-trapping reagents have been described.[58–61] However, the most reliable and advantageous nucleophile for the removal of the Aloc moiety appears to be *N*,*N*′-dimethylbarbituric acid (**17**).[57] It not only undergoes no side reactions (the tin hydride may reduce enones; dimedone may form enamines with amino groups) but it also protonates liberated amino groups, thereby protecting them from further electrophilic attack. Its anion is a very weak base unable to cause racemization. In other developments no additional nucleophile is needed since the substituted allylic moiety under the conditions applied eliminates a β-hydrogen (in boiling dioxane) to form a diene[61] or is attacked by the liberated carboxylate (see Section 3.1.5.1). Among the substituted modifications of the Aloc group, the cinnamyloxycarbonyl analog[62] shows an increased acid sensitivity and is not reliably stable during *t*-butyl ester cleavage. In contrast, the *p*-nitrocinnamyloxycarbonyl (Noc) group[57] is not only completely stable towards trifluoroacetic acid but also resists rhodium(I)-catalyzed isomerization of the allyl system which is used for allyl ester deblocking.[63]



Scheme 9

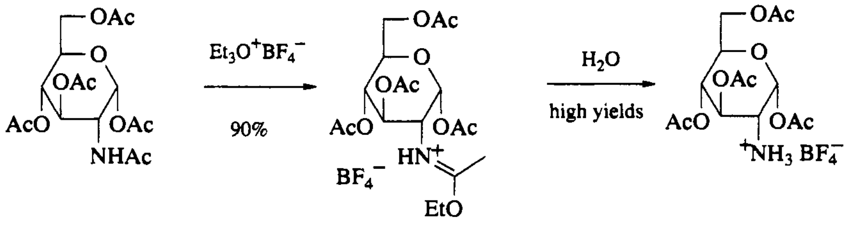


Scheme 10

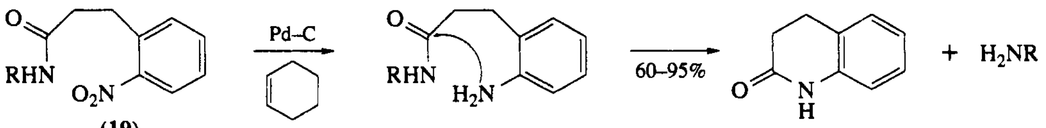
3.1.2.2 Acyl Protecting Groups

Amides can in most cases be readily synthesized from activated derivatives of carboxylic acids and amines. They are fairly stable and often need harsh conditions for their removal. On the one hand this prompted a search for advanced methods for their selective cleavage; on the other, however, amides generally are used for the protection of chemically stable compounds, *e.g.* in nucleotide chemistry. In more recent developments, acceleration of the deprotection reaction by intramolecular attack and the advantageous properties of amido hydrolases have been exploited.

The most simple amide function is the *N*-formyl group, used by Fischer.[64] Its removal could be carried out using acid or base, but newer methods have applied oxidation with H_2O_2[65] or reduction to an acetal.[66] Acetamides also usually require strongly acidic or basic conditions for their hydrolysis. However, a much milder method, which leaves *O*-acetates untouched, consists of the *O*-alkylation of the amide group with oxonium salts, followed by hydrolysis of the imidate formed (Scheme 11).[67] Substituted acetates in many cases can be cleaved by much milder processes. Thus, mono-, di- and trichloro- as well as trifluoro-acetamides[68] are more easily hydrolyzed by acids or bases. The removal of a further class of substituted acetamides is based on the generation of a nucleophile in the molecule followed by its intramolecular attack on the amide group. In such a transformation *o*-nitrophenylacetamides after hydrogenation to the corresponding amino compounds break down to the free amine and the cyclic amide.[69] The same principle is realized in the *o*-nitrophenoxyacetamide,[70] the 3-(*o*-nitrophenyl)propionamide (**19**)[71] and the *o*-nitrocinnamide (Scheme 12).[72] A particularly interesting example of this type consists of the removal of the chloroacetyl group, applied by Fischer,[73] but only as a precursor for glycine, after treatment with *N*-thiocarbamoylpiperidine.[74]



Scheme 11

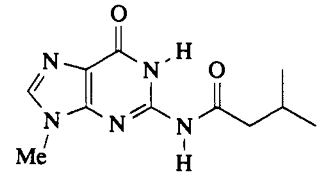


(19)

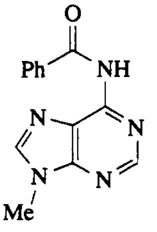
Scheme 12

In nucleotide chemistry amide-type protecting functions have proven to be very useful and are widely used. The amino group in guanine is usually blocked as the isobutyramide (**20**), adenine is masked as the

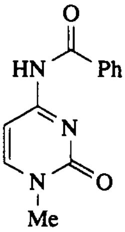
N-benzamide (**21**) and cytosine as the benzamide (**22**) or the 4-methoxybenzamide.[12,75] These derivatives all must be cleaved with strong bases, *e.g.* 9 M NH_3.



(20)



(21)

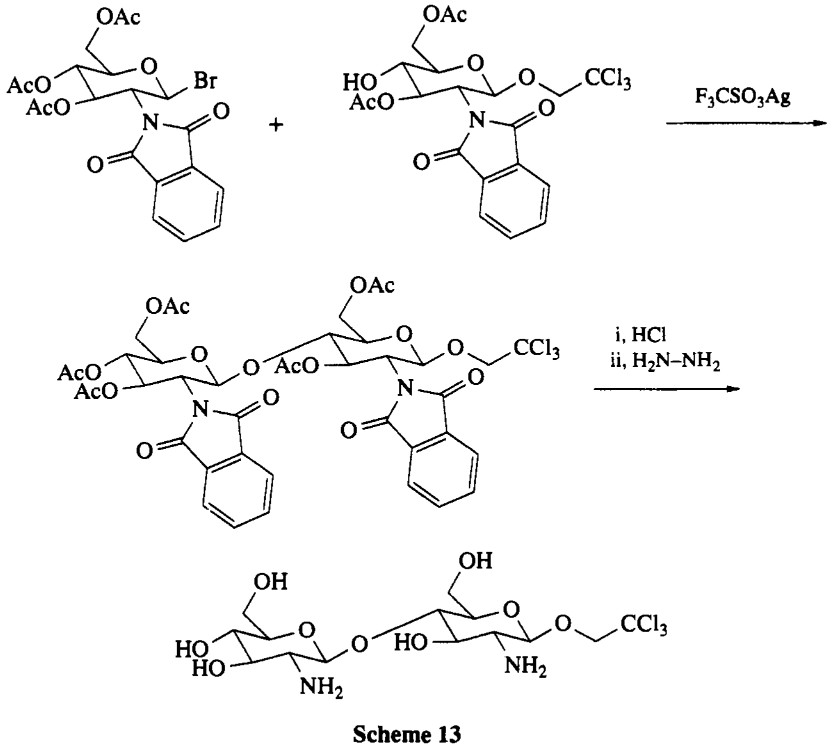


(22)

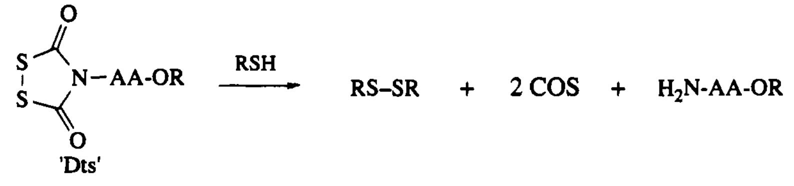
In peptide, as well as in carbohydrate chemistry, phthalimides (Pht) are applied for the temporary protection of primary amino functions.[76] They are easily introduced *via* phthalic anhydride or *N*-ethoxycarbonylphthalimide.[77] The Pht group is stable to acids and provides neighboring group assistance in glycosylations. It can finally be removed with hydrazine or hydrazine acetate (Scheme 13). Among analogous diacylamide protections the dithiasuccinyl (Dts) group (equation 6) should be mentioned.[78] It resists acids, but is easily cleaved by thiols and obviously has advantageous properties in solid-phase synthesis. The introduction of the Dts group requires several steps. Furthermore, the protected form exhibits remarkable carbonyl activity, which limits its application.

The great chemical stability and lack of reactivity under mild conditions for deprotection has greatly hampered the widespread application of amides in protecting group chemistry. However, recent developments in this area may suggest that proteases and amidohydrolases of broad substrate specificity can serve to overcome these drawbacks. Thus, 3-phenylpropionamides and *N*-benzoylphenylalanine amides are attacked by chymotrypsin (pH 7, 37 °C).[79] The application of penicillin acylase for the selective removal of the phenylacetamido residue from peptides (**23**; equation 7) and carbohydrates[80] is also promising.

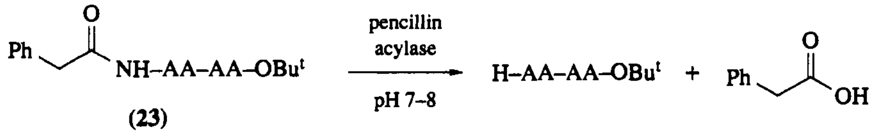
Besides the protecting groups based on carboxylic acid amides, the attention should also be drawn to derivatives of other acids. Arylsulfonamides are stable to bases and to catalytic reduction, but may be cleaved with sodium in liquid ammonia or butanol and heating in strong acids. The most commonly used



Scheme 13



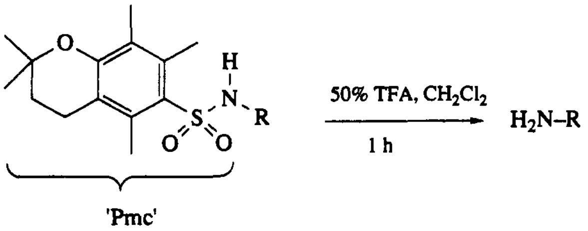
(6)



(23)

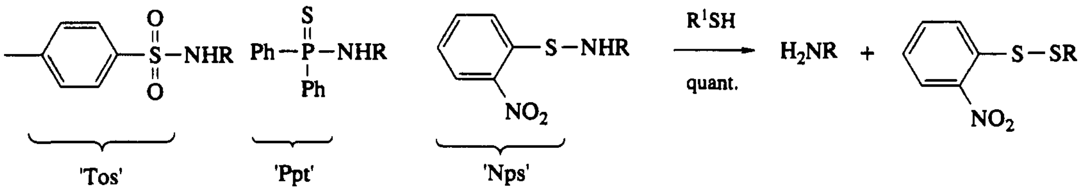
(7)

sulfonamide is the tolylsulfonyl (Tos) group which can also be removed by photolysis and cathodic reduction.[81] A modern alternative, especially recommended for the protection of the arginine guanidino function, is the 4-methoxy-2,3,6-trimethylphenylsulfonyl (Mtr) group[82] which can be cleaved off with trifluoroacetic acid. The acid sensitivity of this group has been even more enhanced by conformational optimizing of the +M effect in the form of the 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc) group[83] shown in equation (8).



(8)

Among the phosphorus-containing blocking functions the diphenylphosphinyl (Dpp)[84] and the diphenylthiophosphinyl (Ppt)[85] groups were advantageously applied in peptide synthesis. Both are resistant to mild alkaline hydrolysis, hydrazinolysis and hydrogenation, but are readily cleaved with trifluoroacetic acid without intermediary formation of carbocations. *N*-Sulfenyl derivatives of amines are conveniently prepared from the sulfenyl halides. They can be cleaved by acid hydrolysis, nucleophiles and Raney Ni/H_2. Here the *o*-nitrophenylsulfenyl (Nps) group,[86] which has extensively been used in peptide chemistry,[87] is the most representative example (Scheme 14).



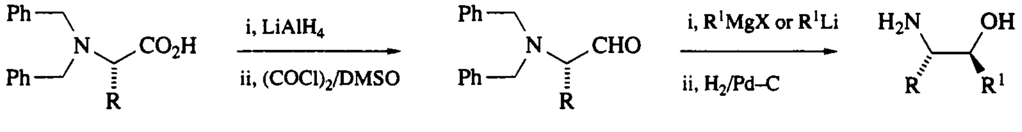
Scheme 14

3.1.2.3 Alkyl and Alkylidene Protecting Groups

In numerous applications the presence of acyl protecting groups cannot be tolerated. In these cases *N*-alkyl protection often provides a viable alternative. For instance, the *N*-benzyl group proved to be the only reliable choice for amino protection in the racemization-free synthesis of α-amino aldehydes (**24**) from amino acids (Scheme 15).[88] Its removal is best accomplished by catalytic transfer hydrogenolysis[89] or with sodium in liquid ammonia.[90]

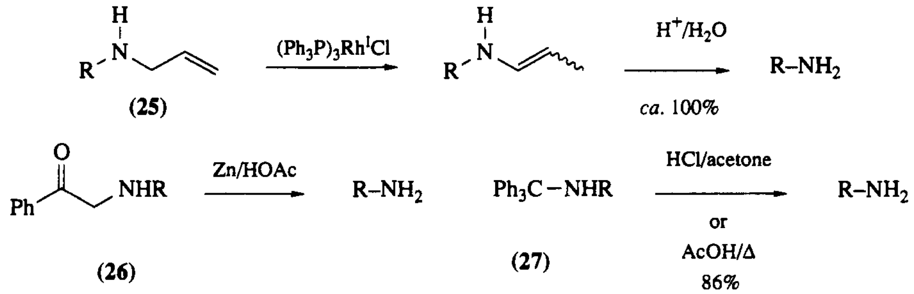
Allyl- (**25**) and phenacyl-amines (**26**) are also practical alternatives. They can be cleaved after isomerization of the allyl moiety to the acid sensitive vinyl amines,[91] or with zinc in acetic acid.[92] The bulky triphenylmethyl (Tr) group (**27**), readily removed by mild acid hydrolysis, possesses advantageous shielding properties and has found applications in the protection of amino acids (Scheme 16).[93]

Amines and β-keto carbonyl compounds form enamines in high yields. This reaction has been used to protect amino acids and amino acid esters (Scheme 17).[94] Enamines (**28**) from acyclic β-dicarbonyl com-



(24)

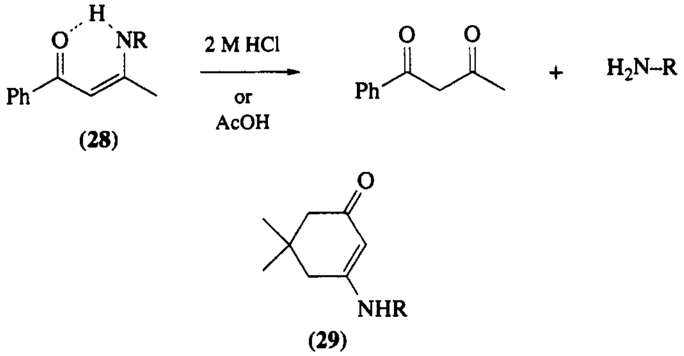
Scheme 15



(25) (26) (27)

Scheme 16

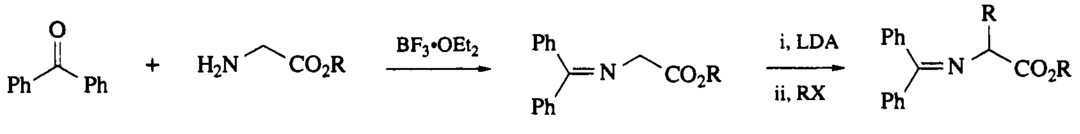
pounds are sensitive to acid hydrolysis, but those derived from cyclic carbonyl compounds (**29**) are more stable because of the missing intramolecular hydrogen bonding.[94b]



(28) (29)

Scheme 17

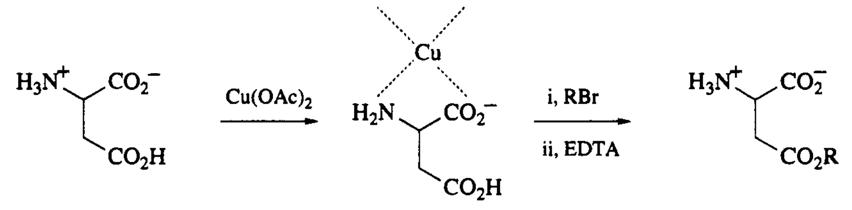
Imines were extensively applied for the protection of the amino group in the synthesis of unusual amino acids. They have been used in both chiral and achiral form (see Scheme 1), and in the first case high asymmetric induction was achieved.[95] The most common derivative is the *N*-benzylideneimine[96] but ketones have also been used for this purpose,[97] as is demonstrated in Scheme 18.



Scheme 18

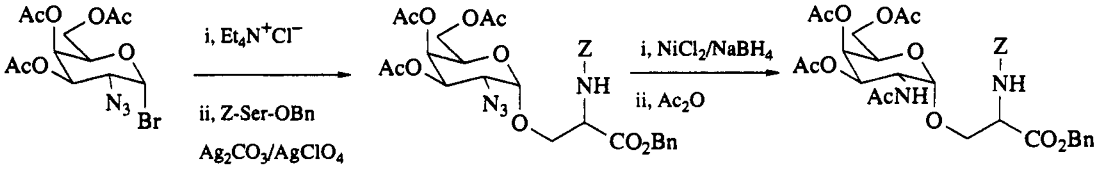
3.1.2.4 Special Amino-protecting Groups

Amines are known to coordinate to various metal ions and this has been exploited for their temporary protection, *e.g.* as zinc and copper(II) chelates.[11,98] For the selective functionalization of the ε-amino group of lysine, the phenolic hydroxy group of tyrosine or the side chain carboxylic acids in aspartic and glutamic acid, the α-amino and the α-carboxy groups are protected as copper chelates. After the desired reaction has been carried out, the metal ion is removed with 2 M HCl or even better with thioacetamide, EDTA or hydrogen sulfide (Scheme 19).



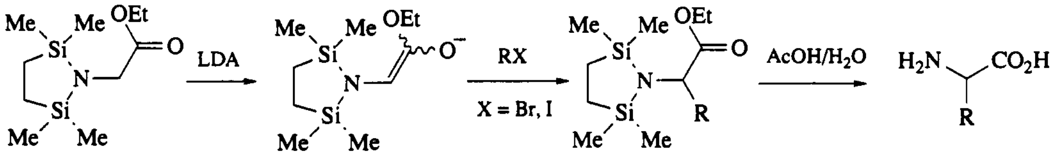
Scheme 19

Azido groups constitute protected forms and precursors for amines and have been used in this sense, for instance, in carbohydrate chemistry. Here for the stereoselective synthesis of α-glycosides a non-neighboring group active substituent in the 2-position of the glycosyl donor is needed and the azido group serves well (Scheme 20).[99] After the glycoside has been constructed, the azide is reduced to the amine with nickel boride,[99b] thioacetic acid,[100a] H_2S[100b] or tertiary phosphines in the presence of water.[10,101] In addition, the anomeric center of carbohydrate amines can be masked in the form of a 1-azide which is stable under a variety of conditions.[8,102] For a further example see the use of 4-azidobutyryl esters (Section 3.1.5.1).



Scheme 20

Recently silicon-based protection has matured into a new broad area of protecting group chemistry (see Section 3.1.3.2) and amines can also be conveniently blocked with appropriate silicon reagents. In organometallic syntheses, *e.g.* in the alkylation of amino acid enolates, the so-called stabase adducts (**30**) serve to temporarily protect the α-amino group (Scheme 21).[103] In the absence of hard nucleophiles, in particular of O-nucleophiles, the Si—N bonds are stable, but deprotection is readily effected in the presence of water and acids.



(**30**)

R = *e.g.* methyl, allyl, propargyl

Scheme 21

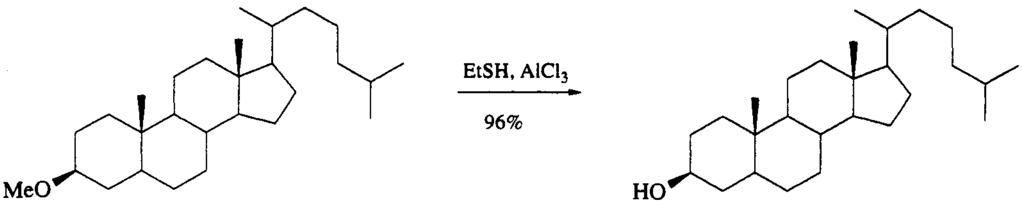
3.1.3 ALCOHOL-PROTECTING GROUPS[104]

In carbohydrate and nucleotide chemistry one of the regularly arising problems is the selective protection and liberation of a specific hydroxy function in the presence of several others of comparable reactivity. Also, in steroids, hydroxy acids and some amino acids alcoholic functions frequently have to be masked. In addition, for the successful completion of most total syntheses of complex natural products, in particular macrolide and polyether antibiotics and prostaglandins, numerous problems of hydroxy protection have to be solved, and many new developments stem from this area. Isolated hydroxy groups are generally protected as ethers, acetals and esters, while 1,2- and 1,3-diols are best masked *via* the formation of cyclic acetals and ketals. Whereas simple alkyl ethers are resistant to mild cleavage conditions, acetals are hydrolyzed under mild acid catalysis. In general, benzyl-type protecting groups are removed by hydrogenolysis, silyl ethers by reaction with fluoride ions or under slightly acidic conditions and several 2-substituted ethyl ethers can be cleaved by β-elimination reactions.

3.1.3.1 Ether and Acyclic Acetal Protecting Groups[104]

Ethers usually are prepared by the Williamson ether synthesis, *i.e.* by nucleophilic displacement on alkyl halides or sulfates. The system silver oxide/alkyl halide is also efficient. The numerous variations in ether-forming reactions cannot be outlined in this survey. They are covered in extensive reviews.[104] Among the more recent contributions the acceleration of etherifications by phase transfer catalysis[105] and the ether formation with methyl triflate in pyridine[106] should be noted. The cleavage of simple alkyl ethers by acids occurs only under drastic conditions; therefore, they have mainly been used, not as protecting groups, but rather as a means of functionalization to obtain more favorable properties for analytical techniques. Thus, after permethylation, carbohydrates can be analyzed conveniently by gas chromatography and mass spectrometry.[107] Recently the introduction of iodotrimethylsilane for the cleavage of methyl ethers,[108] shown in equation (9), offered new opportunities. Disadvantages of this method are that the relatively aggressive reagent also attacks other functionalities (esters, urethanes, other ethers) and that alkyl iodides are formed. This can be overcome by using $SiCl_4$/NaI or $SiMeCl_3$/NaI.[109] Further milder methods for the cleavage of methyl ethers involve combinations of Lewis acids with soft nucleophiles, *e.g.* BF_3/thiol and $AlCl_3$/EtSH (equation 10).[110]

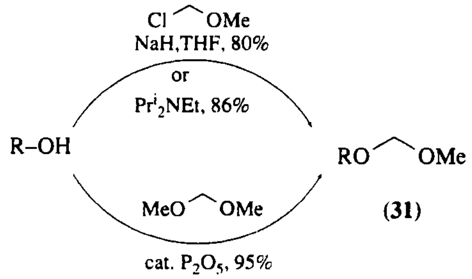
$$\text{R–OMe} \xrightarrow[\text{ii, H}_2\text{O} \;\; 70\text{–}80\%]{\text{i, Me}_3\text{SiI}} \text{R–OH} + \text{MeOH} \qquad (9)$$



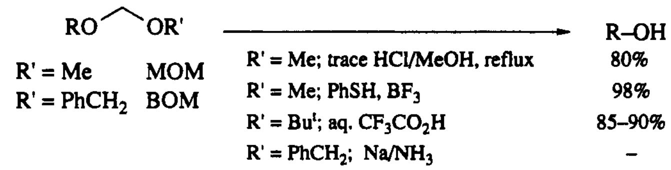
(10)

To overcome the difficulties encountered in the application of simple alkyl ethers, suitably substituted ether variants were introduced. Many of these systems were developed by Corey and Bock.[111] and are nowadays widely used in natural product synthesis. In general, these groups protect the hydroxy functions as acyclic acetals. The most common ones are derived from formaldehyde and synthesized by a Williamson reaction with halomethyl alkyl ethers (Scheme 22). According to this method methoxymethyl (MOM) ethers (**31**) are formed in yields of 80–86%.[112a] They may alternatively be obtained from formaldehyde dimethyl acetal by transacetalization.[112b] The MOM group is readily removed under acidic conditions or again by transacetalization with thiophenol.[113] The benzyloxymethyl (BOM)[114] and *t*-butyloxymethyl groups[115] can be similarly introduced. The BOM group is cleaved by hydrogenolysis or with sodium in ammonia, the *t*-butyl acetal hydrolyzes readily in aqueous trifluoroacetic acid (Scheme 23).

The methylthiomethyl (MTM) ethers (**32**), mainly applied in natural product synthesis, represent thioacetals of formaldehyde. These ethers again are formed by Williamson-type reactions; however, the

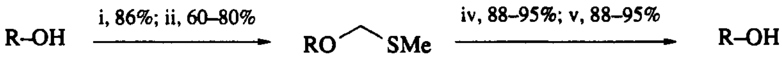


Scheme 22



Scheme 23

chloromethyl acetal must be converted *in situ* to the iodide[111] or activated with Ag^+.[116] Further methods for MTM introduction consist of a Pummerer rearrangement with dimethyl sulfoxide (DMSO) and acetic anhydride[117a] or treatment of the respective alcohol with dimethyl sulfide in the presence of dibenzoyl peroxide (Scheme 24).[117b]

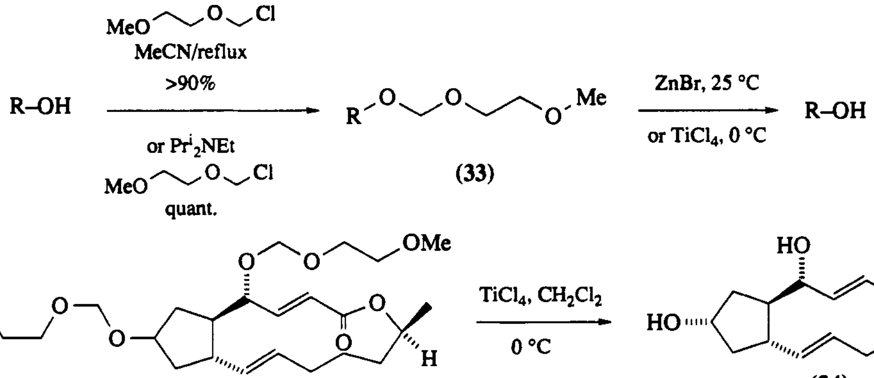


(32)

i, NaH then NaI/$ClCH_2SMe$; ii, $ClCH_2SMe$, $AgNO_3/NEt_3$; iii, DMSO, Ac_2O, AcOH, r.t; iv, $HgCl_2$, $MeCN/H_2O$, r.t.; v, $AgNO_3$, THF/H_2O, r.t.; vi, MeI, $NaHCO_3$, acetone/H_2O

Scheme 24

Formaldehyde acetals are effectively labilized by Lewis acids like $ZnBr_2$ or $TiCl_4$ if a second oxygen atom in a β-position promotes the coordination of the metal. This is used in the removal of the 2-methoxyethoxymethyl (MEM) ethers (**33**; Scheme 25).[118] They were designed to protect alcohols with formation and cleavage under aprotic conditions and were advantageously used in syntheses of brefeldin A (**34**)[118] and gibberelic acid.[119] A variant of this type of protecting group is the 2-methoxyphenoxymethyl moiety.[120]



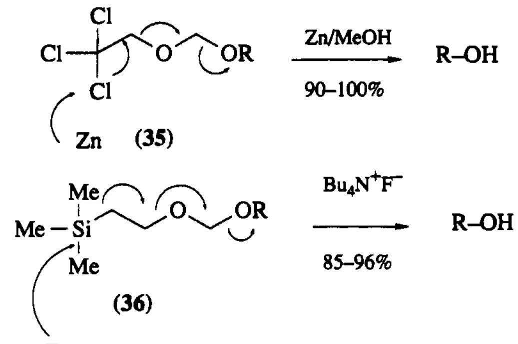
(33)

(34)

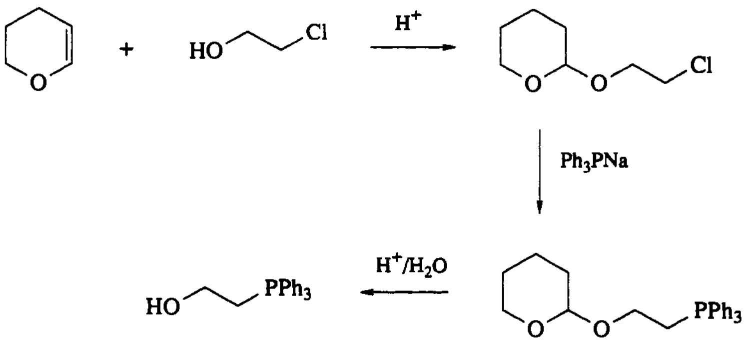
Scheme 25

For the liberation of acetal-masked alcohols under nonacidic conditions, β-eliminations, already mentioned in Section 3.1.2.1, were adopted. Following this concept the 2,2,2-trichloroethoxymethyl (**35**)[121] and the 2-(trimethylsilyl)ethoxymethyl (SEM) ethers (**36**)[122] were proposed. Both are introduced *via* Williamson syntheses and their removal is initiated by treatment with Zn or Zn/Cu in methanol[121] or by fluoride-induced β-elimination[122] respectively. Similarly, the trichloroethyl ether had already been applied in carbohydrate chemistry (Scheme 26).[123]

Before all these acetal-based protecting groups were introduced, the tetrahydropyranyl (THP) ether had found extensive use in organic synthesis.[124] It can easily be synthesized from a variety of hydroxy-containing compounds like carbohydrates, amino acids, steroids and nucleotides by the acid-catalyzed reaction with dihydropyran. It is stable to bases, but the protection is removed through acidic hydrolysis with hydrochloric acid, toluenesulfonic acid or acidic ion-exchange resin (Scheme 27). In the case of acid sensitive substrates, *e.g.* containing an epoxide or a further acetal, pyridinium *p*-toluenesulfonate should be applied for particularly mild deprotection conditions.[125]

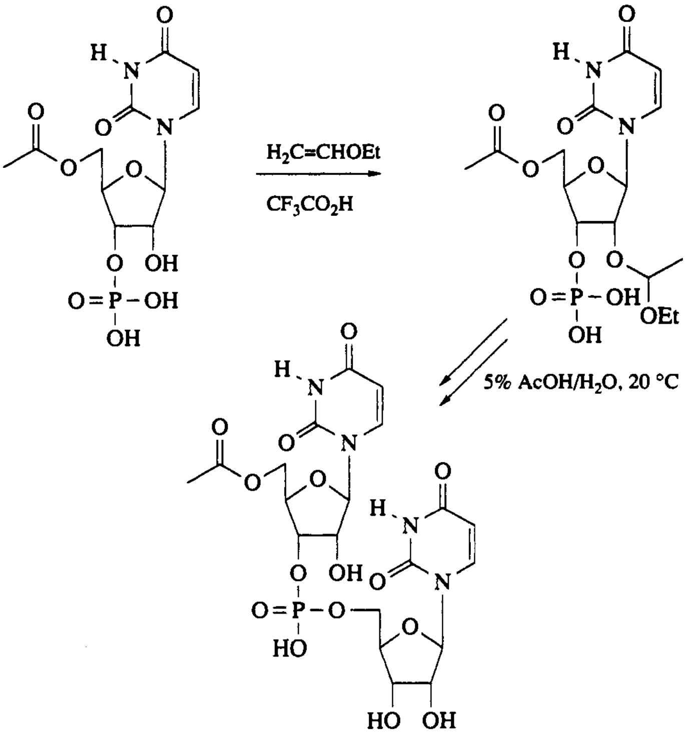


Scheme 26



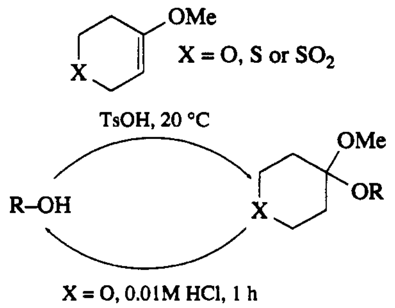
Scheme 27

As a similar protecting function the 1-ethoxyethyl ether, formed by reaction of the alcohol with ethyl vinyl ether, was introduced (Scheme 28). It displayed advantageous properties for the construction of oligonucleotides since it could be cleaved with 5% acetic acid without affecting the internucleotide bond.[126]



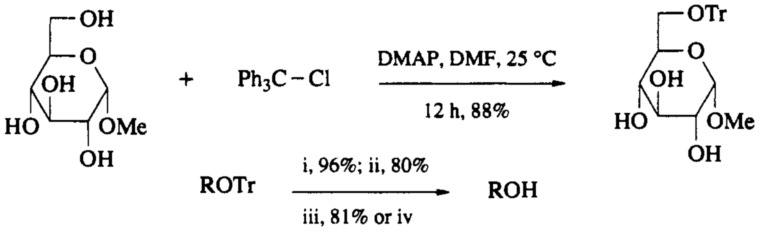
Scheme 28

An inherent disadvantage of the THP and acetaldehyde acetals is that they contain a new chiral center, giving rise to mixtures of diastereomers if chiral alcohols are involved. This can be overcome by the use of 4-methoxytetrahydropyranyl ethers (Scheme 29).[127] They are extensively applied in oligonucleotide synthesis. The analogous thiopyranyl compounds are hydrolyzed five times more quickly, but their *S*,*S*-dioxides 2000 times more slowly, than the corresponding oxygen compounds.



Scheme 29

An important family of acid labile ether protecting groups consists of the trityl (Tr) group and its substituted variants. Due to their high steric demand, trityl ethers are mainly used to selectively mask primary alcohols in the presence of secondary ones. Consequently, the major fields of their application are carbohydrate and nucleotide chemistry. Thus, in the presence of pyridine, trityl chloride selectively reacts with the 6-OH group of glucose (Scheme 30),[128] and also other mono- and di-saccharides can be selectively substituted. The Tr protecting function is also introduced using a variety of other reagents, *e.g.* 1-tritylpyridinium tetrafluoroborate or tritylated pyridones.[128] The latter reagents in particular react with high substrate selectivity and allow the protection under neutral conditions. The removal of the trityl group is carried out with the aid of mineral acids, Lewis acids ($ZnCl_2$) or, most mildly, with silica gel.[129] Although the conditions for trityl removal cannot be described as harsh, they were not mild enough to prevent hydrolysis of *N*-glycosidic bonds when this protecting group was used for the protection of the 5′-OH group of purine nucleosides. Therefore, Khorana introduced the monomethoxytrityl (Mmt) and the dimethoxytrityl (Dmt) groups,[130] which are widely applied in nucleotide chemistry. The addition of each *p*-methoxy substituent increases the rate of hydrolysis by about one order of magnitude. The times required for the hydrolysis of the uridine derivatives (37) in 80% aqueous acetic acid at 20 °C are given in Scheme 31. As is evident, the Mmt and the Dmt ether[131] are the most advantageous protecting groups because they are not too sensitive, but at the same time are readily removed. An interesting variant of the trityl group, also suitable for the blocking of primary hydroxys, is the 'tritylon' group (Scheme 32). It is more stable towards acids, but removable with hydrazine in an interesting 1,6-elimination reaction.[132]

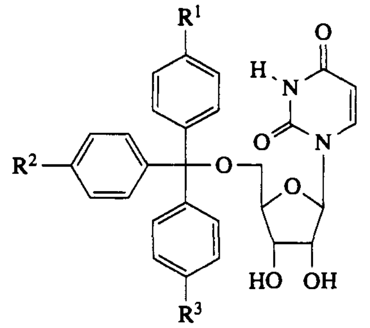


i, HOAc, 56 °C; ii, $BF_3 \cdot Et_2O$, thiol; iii, SiO_2, PhH, 25 °C; iv, TsOH, MeOH, 25 °C

Scheme 30

In amino acid chemistry *t*-butyl ethers are also used successfully for the protection of the serine and threonine hydroxy groups.[133a] They are formed by the addition of the alcohols to isobutene and are cleaved with TFA and HBr/AcOH. *t*-Butyl trichloroacetimidate is also a convenient reagent for their introduction.[133b] However, the preparation of *O*-*t*-butyl serine and threonine themselves requires several steps including methyl or *p*-nitrobenzyl esters as intermediates.[133c]

Acidic conditions for hydroxy deprotection can be avoided if benzyl-type ethers are used as the blocking functions. They can be prepared from the alcohols by alkylation with benzyl halide/sodium hydride in DMSO or benzyl halide/silver(I) oxide in DMF (the silver salt does not cause acyl migration as a side



(37)

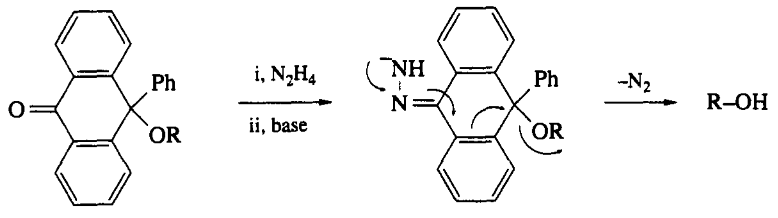
$R^1 = R^2 = R^3 = H$ Tr, 48 h

$R^1 = OMe, R^2 = R^3 = H$ Mmt, 2.2 h

$R^1 = R^2 = OMe, R^3 = H$ Dmt, 1.15 min

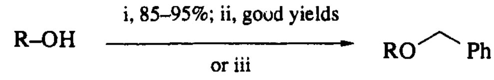
$R^1 = R^2 = R = OMe,$ 6 s

Scheme 31



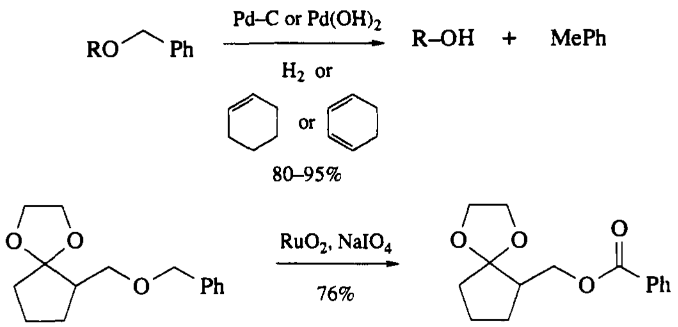
Scheme 32

reaction).[134] For base labile compounds benzyl trichloroacetimidate is the reagent of choice (Scheme 33).[135] Also regioselective benzylation of 1,2-diols can be achieved from an intermediary dibutylstannylidene acetal (see Section 3.1.3.4). Benzyl ethers are stable to bases and weak acids, as used to cleave acetals. Their removal can, however, be easily accomplished by catalytic reduction with palladium[136a–c] or better with $Pd(OH)_2$ (Pearlman's catalyst),[136d] although steric hindrance sometimes poses a problem.[136] Furthermore, iodotrimethylsilane, the system thiol/$BF_3{\cdot}OEt_2$ (*vide supra*) and electrochemical methods are effective. The benzylic CH_2 group can also be oxidized using, for instance, ruthenium dioxide/sodium periodate to furnish base labile benzoic acid esters (Scheme 34).[137]



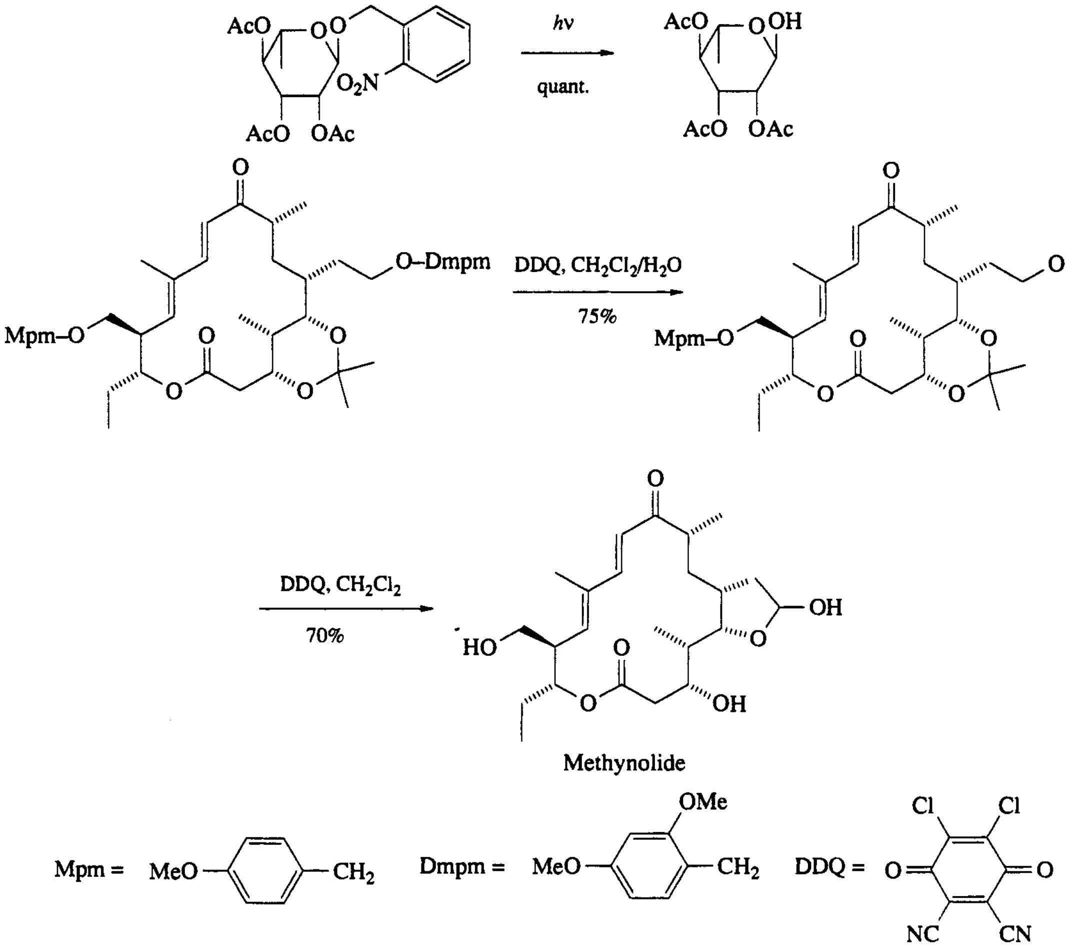
i, $PhCh_2Cl$, NaH (or $NaNH_2$, NaOH)/DMSO, 20 °C, 1–3 h; ii, $PhCH_2Cl(Br)$, Ag_2O, DMF, 25 °C;
iii, $BF_3{\bullet}OEt_2$, $CCl_3C(=NH)OCH_2Ph$

Scheme 33



Scheme 34

Introduction of substituents into the aromatic ring makes the benzylic system prone to further deblocking methods. Thus, *o*-nitrobenzyl ethers, available from *o*-nitrobenzyl bromide, are cleaved photolytically[138] and the mono- and di-methoxybenzyl groups (Mpm and Dmpm) are removable by oxidation with ammonium cerium nitrate[139] or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[140] An example chosen from a chiral pool synthesis is given in Scheme 35.



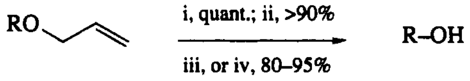
Scheme 35

The major areas of application for benzyl-type protecting groups are polyol, nucleotide, and, in general, carbohydrate chemistry. In this latter field these ethers do not only serve to effect protection, but also function as nonneighboring group active substituents in the stereoselective construction of α-glycosides.[141]

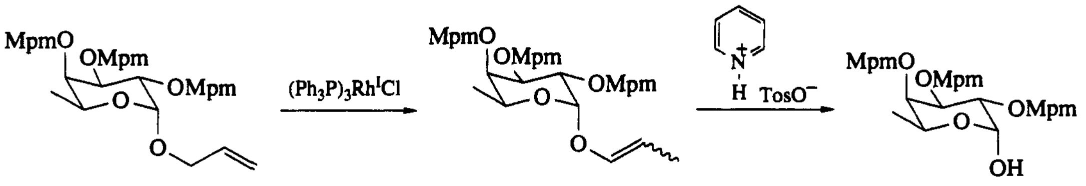
A protecting group which is gaining increasing importance is found in the allyl ethers (Scheme 36). They are also synthesized *via* alkylation with allyl bromide and base, or under acidic conditions with allyl trichloroacetimidate.[142] The advantage of this group lies in the possibility to isomerize it to very acid labile propenyl ethers using either potassium *t*-butoxide[143] or, even better, a rhodium(I)[144] or iridium complex.[145] This method for the removal of allyl ethers is often used in carbohydrate chemistry. This deblocking principle allowed, for instance, the selective cleavage of the allyl fucoside (**38**) in the presence of the very acid sensitive Mpm ether groups.[8] The isomerization of the allyl system can also be carried out with palladium on carbon in the presence of acids.[146] These conditions are so mild that benzyl ethers, nitriles, epoxides, esters and α,β-unsaturated structures remain intact.

3.1.3.2 Silyl Protecting Groups[147]

The arsenal for hydroxy protection has been considerably enriched by the introduction of silyl ethers in the early 1970s and many of the decisive developments in this area were made by Corey *et al.* Since then a boom of applications has emerged, and in numerous complex total syntheses to date a silyl protecting group has been involved. Natural product synthesis, in particular the construction of prostaglan-



i, $KOBu^t/DMSO$, 100 °C, then 0.1 M HCl or $HgCl_2/HgO$; ii, $(Ph_3P)_3Rh^ICl$, DABCO, EtOH, H_2O, reflux then Hg^{II}, pH 2; iii, $[Ir(COD)(PMePh_2)]^+PF_6^-$ then H^+; iv, Pd/C–H_2O, MeOH, 60–80 °C, cat. TsOH or $HClO_4$



(38)

Scheme 36

dins but also nucleoside and, increasingly, carbohydrate chemistry, is the major discipline in which protection by silyl groups is applied.

The widespread use of these blocking groups is due to the widely adjustable stability which different trialkylsilyl groups can exhibit towards acid- and base-induced hydrolysis and towards fluoride ion mediated cleavage. The ease of hydrolysis of silyl ethers is mainly influenced by the steric bulk of the ligands at silicon. The more bulky the substituents are, the higher is the stability of the silyl ether to acidic and basic hydrolysis. Furthermore, in silyl ethers silicon is prone to react with hard nucleophiles, whereas at the same time electrophiles can attack the oxygen atom. Therefore, electron-withdrawing groups at the silicon increase the stability of a silyl ether to acidic hydrolysis and decrease the stability to basic hydrolysis, and *vice versa* for electron-donating substituents. The general stabilities of trialkylsilyl ethers $R^1R^2R^3SiO$ towards acid-catalyzed and base-catalyzed solvolysis were determined and found to be in agreement with these general considerations (Scheme 37).[147,148]

Relative stabilities of trialkylsilyl ethers towards acid-catalyzed solvolysis

$Me_3Si \approx PhMe_2Si \approx Ph_2MeSi < Et_3Si \approx Pr^iMe_2Si \approx Pr_3Si \approx Bu_3Si < Ph_3Si < Pr^i_2MeSi < Bu^tMe_2Si <$
$thexylMe_2Si < Pr^i_3Si < Bu^tPh_2Si < TrMe_2Si < Bu^t_2MeSi$

Relative stabilities of trialkylsilyl ethers towards base-catalyzed solvolysis

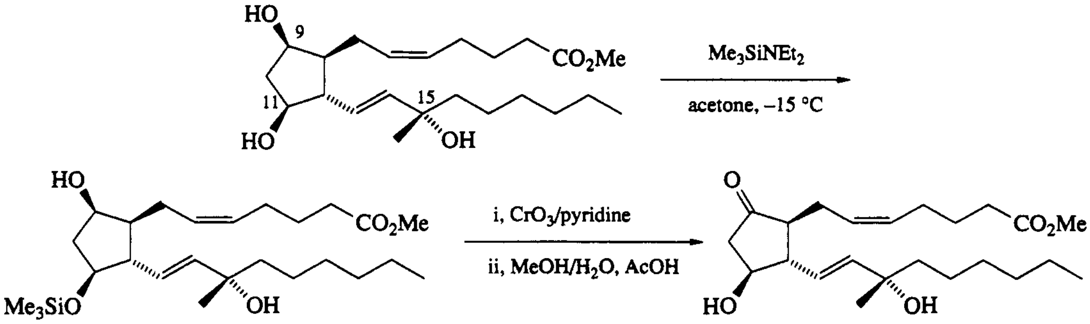
$PhMe_2Si \approx Ph_2MeSi \approx Ph_3Si \approx Me_3Si < Pr^iMe_2Si \approx Et_3Si < Pr_3Si < Bu_3Si < Pr^i_2MeSi < Bu^tPh_2Si \approx$
$Bu^tMe_2Si < thexylMe_2Si < Pr^i_3Si < Bu^t_2MeSi$

Scheme 37

The rate of cleavage with fluoride ions, *e.g.* tetrabutylammonium fluoride, approximately parallels the orders given for basic hydrolysis.

Trimethylsilyl (TMS) ethers have been widely used for the protection of alcohols and even today it is probably the most important silyl blocking group. The TMS group can be introduced under basic, neutral or acidic conditions by choosing the appropriate reagent.[149] As shown in equation (11), the silylation is achieved with trimethylsilyl chloride in the presence of a base like pyridine or triethylamine. The reaction can be accelerated by the addition of DMSO, hexamethyl phosphoric acid triamide, DABCO or imidazole. Alternatively, hexamethyldisilazane[150] and trimethylsilyldiethylamine can be used. The latter reagent is very sensitive to the steric environment of the hydroxy group to be masked. In the cyclohexane series, for instance, it attacks only equatorial alcohols and it effectively differentiates between hydroxy groups in prostaglandins (see Scheme 38).[151]

$$R{-}OH \; + \; Cl{-}SiMe_3 \; \xrightarrow[\text{THF or ether}\atop \textit{ca. } 90\%]{\text{base}} \; R{-}O{-}SiMe_3 \qquad (11)$$

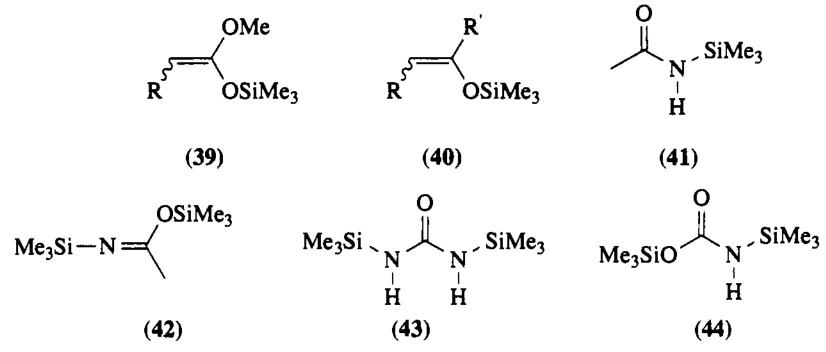


Order of reactivity: 11 > 15 >> 9

Scheme 38

For the introduction of the TMS group under neutral conditions, trimethylsilyl chloride can be activated with lithium sulfide.[152] Also trimethylsilylketene acetals (**39**), silyl enol ethers (**40**) (in particular those of pentane-2,4-dione), *N*-trimethylsilylacetamide (**41**), *N*,*O*-bis(trimethylsilyl)acetamide (**42**), *N*,*N*′-bis(trimethylsilyl)urea (**43**) and *N*,*O*-bis(trimethylsilyl)carbamate (**44**) are effective silylating agents under neutral conditions (Scheme 39).[147]

$$\text{R-OH} + \text{Li}_2\text{S} + \text{Cl-SiMe}_3 \xrightarrow[75\text{–}95\%]{\text{MeCN, 25 °C}} \text{R-OSiMe}_3 + 2\,\text{LiCl} + \text{H}_2\text{S}$$

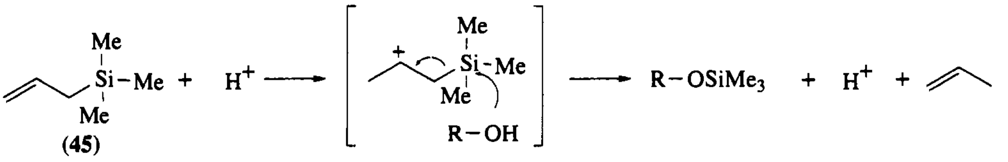


(39) (40) (41)

(42) (43) (44)

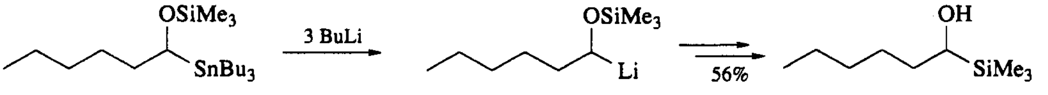
Scheme 39

For the introduction of TMS groups under acidic conditions, trimethylsilyltriflate, hexamethyldisilazane and also allyltrimethylsilane (**45**)[153] have been successfully applied. The allylsilane offers the advantage of being stable to hydrolysis. The mechanism proposed for its reaction with alcohols is shown in equation (12). It involves an initial protonation of the double bond. The 1-silylisopropyl cation formed is then attacked by the alcohol at the silicon to produce the silyl ether and propene.



(45) (12)

The TMS group is stable under a variety of conditions, *e.g.* Grignard reactions, Wittig reactions, reductions with DIBALH, Collins oxidation[154] and epoxidations with MCPBA. However, strongly basic conditions occurring in organometallic reactions as, for instance, in the treatment of (**46a**) with butyllithium, may result in a silyl migration (**46b** to **46c**; Scheme 40; reverse Brook rearrangement).[155] A severe drawback of the TMS group is its tendency to hydrolyze, which also prevents chromatography on silica gel. Because of this sensitivity the deprotection of the TMS ethers can be achieved readily by basic or acidic hydrolysis or alcoholysis. Alternatively, the use of fluorides, *e.g.* tetrabutylammonium fluoride in anhydrous THF,[156] is the method of choice (see equation 13).



(46a) **(46b)** **(46c)**

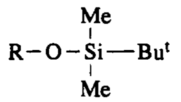
Scheme 40

$$\mathrm{R{-}OSiMe_3} \xrightarrow[\text{iii or iv}]{\text{i, 100\%; ii, 100\%;}} \mathrm{R{-}OH} \qquad (13)$$

i, MeOH/AcOH or citric acid, 20 °C; ii, $MeOH/K_2CO_3$, 0 °C; iii, MeOH/THF; iv, $Bu^n_4N^+F^-$/THF or KF/DMF

It should finally be pointed out that trimethylsilyl ethers can also be transformed directly into other functionalities. Oxidation with NBS leads to ketones and aldehydes,[157] treatment with $LiAlH_4/AlCl_3$ results in deoxygenation of the alcohol,[147] reaction with carboxylic acid anhydrides in the presence of $BF_3{\cdot}OEt_2$ produces esters[158] and on treatment with $Ph_3P{\cdot}Br_2$ acid bromides are formed directly from TMS esters.[159]

The *t*-butyldimethylsilyl (TBDMS) group was introduced by Stork[160] and Corey,[156] and since then has become one of the most popular hydroxy-protecting groups. It is more stable to hydrolysis than the TMS group but can still be removed selectively. TBDMS ethers can be formed with the aid of a variety of introducing reagents (equation 14). The one most often applied is *t*-butyldimethylsilyl chloride with imidazole in DMF,[156] with $DMAP/Et_3NH$ in DMF or with silver nitrate in pyridine.[161] In addition, the same types of reagents already described for the formation of TMS ethers can be used for the introduction of the TBDMS group. Thus, under acidic conditions the corresponding silylketene acetals, silyl enol ethers and allyl-*t*-butyldimethylsilane are applied. TBDMS-Cl can, too, be activated with lithium sulfide under essentially neutral conditions. Also *N*-methyl-*N*-(*t*-butyldimethylsilyl)-acetamide and -trifluoroacetamide and the analogous *N*,*O*-bis(*t*-butyldimethylsilyl) derivatives deliver the TBDMS group under neutral conditions. These reagents show markedly better silylating properties than the silyl chloride and serve to overcome problems with low reactivity towards hindered secondary and tertiary alcohols. Exceptionally reactive introducing reagents are TBDMS triflate and perchlorate.

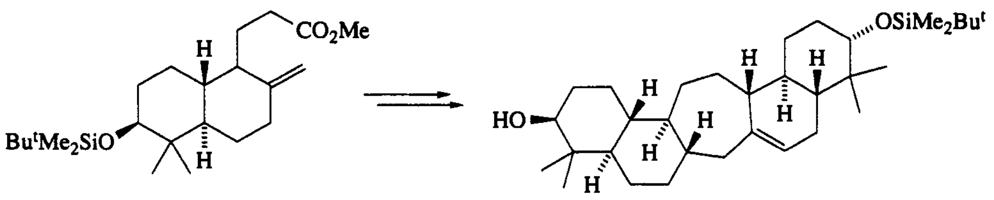


$$\mathrm{R{-}OH} \xrightarrow[\text{iii, 100\%; iv, 70–80\%; or v, 75–95\%}]{\text{i, high yield; ii, 60–90\%;}} \mathrm{R{-}O{-}\overset{\displaystyle Me}{\underset{\displaystyle Me}{Si}}{-}Bu^t} \qquad (14)$$

i, Bu^tMe_2SiCl/imidazole, DMF; ii, Bu^tMe_2SiCl/DMAP, NEt_3, DMF;
iii, $Bu^tMe_2SiOClO_3$/pyridine; iv, $Bu^tMe_2SiCH_2CH{=}CH_2$, TsOH, MeCN;
v, Bu^tMe_2SiCl, Li_2S, MeCN, 25 °C. For further introducing reagents see text

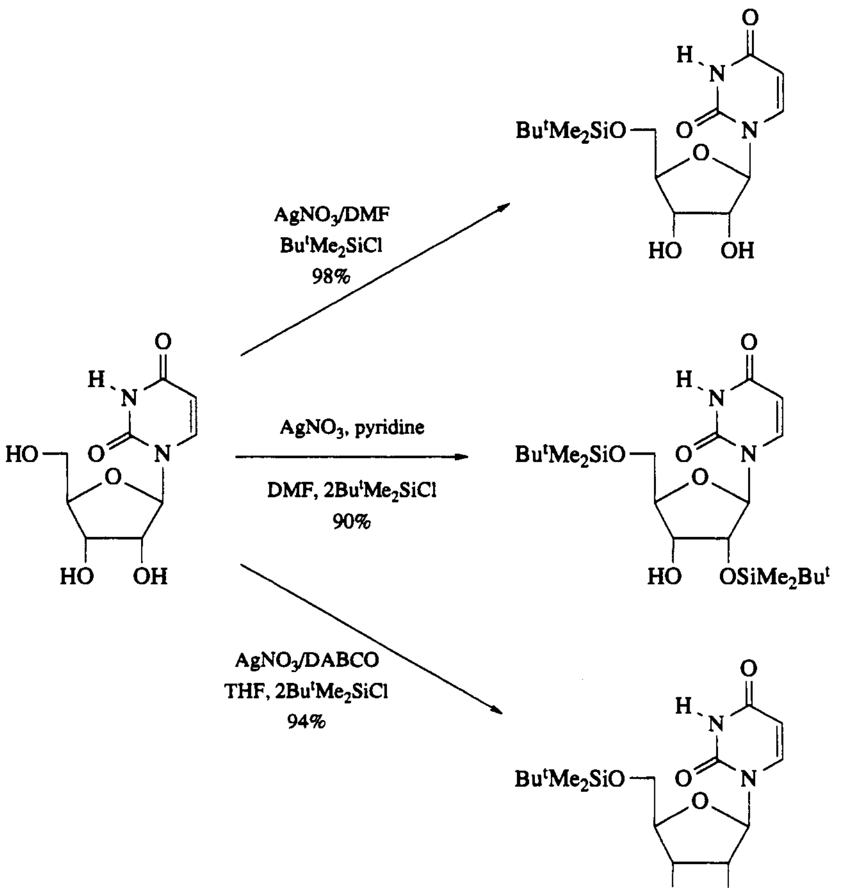
TBDMS ethers are stable under a great variety of conditions, some of which are Wittig reaction, reduction with Zn/MeOH, H_2/Pd–C, Na/NH_3 and DIBAL-H, oxidation with CrO_3/pyridine,[162] H_2O_2/OH^- or RuO_2, MeI/Ag_2O, K_2CO_3/MeOH, acidic removal of a THP ether,[163] reactions with organocopper reagents, mesylation, treatment with $KOBu^t$/DMF or Pr^iMgI/−78 °C and even the elimination of the β-trimethylsilyl ethyl ester protecting group with fluoride.[164a] This resistance has allowed the application of this silyl protecting group in numerous syntheses (an example is given in Scheme 41).[164b] It found a particularly broad application in the chemistry of prostaglandins[165] and carbohydrates.[166] Thus, the TBDMS group is the most popular silyl protecting group in nucleoside chemistry.[147,167] It is useful for the selective protection of the 5′-OH group or for the simultaneous masking of the 2′- and the 5′-OH groups. Also 3′,5′-diprotected compounds were obtained (Scheme 42).

t-Butyldimethylsilyl ethers can be cleaved by methods similar to those reported for the trimethylsilyl group (Scheme 43). The usual reagent is tetrabutylammonium fluoride at 25 °C.[156] However, the fluoride ion is a strong base and may cause severe side reactions. In these cases either mixtures of aqueous HF/MeCN or $THF/H_2O/AcOH$[156] can alternatively be applied. Acetic acid may be replaced by weakly acidic ion-exchange resins. Alternative sources of fluoride are BF_3 and tetrafluoroborates. In addition, $Ac_2O/FeCl_3$ cleaves the silyl ethers to produce the corresponding acetates. One of the problems arising



The Bu^tMe_2Si group was cleaved with tetra-*n*-butylammonium fluoride in THF at 70 °C for 12 h

Scheme 41



Scheme 42

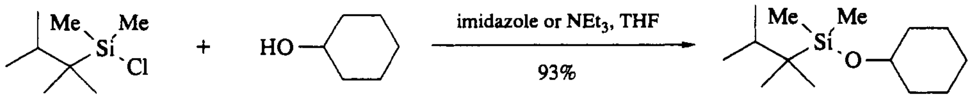
during the removal of the TBDMS blocking group is that in acylated substrates, particularly under basic conditions, the acyl groups and also the silyl group itself may migrate.[168]

$$\mathrm{R{-}OSiMe_2Bu^t} \xrightarrow[\text{iii, high yields; iv, high yields; or v, 70–90\%}]{\text{i, 100\%; ii, 90–100\%}} \mathrm{R{-}OH}$$

i, $Bu^n_4N^+F^-$, THF, 25 °C; ii, aq. HF/MeCN (95:5), 20 °C; iii, $AcOH/H_2O/THF$, 20–80 °C;
iv, Dowex 50W-X8, MeOH, 20 °C; v, $BF_3{\bullet}OEt_2$, 0–25 °C

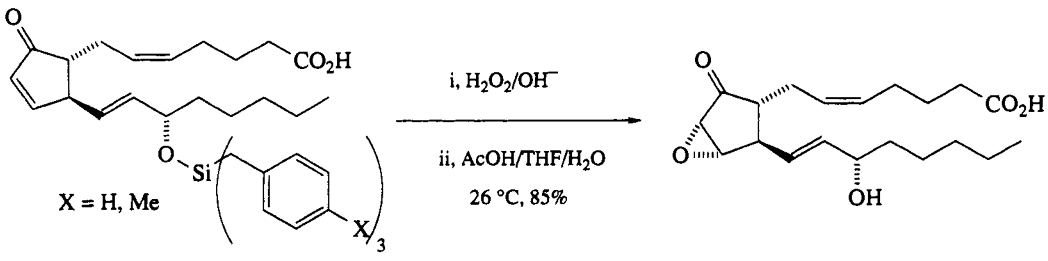
Scheme 43

Silyl protecting groups other than TMS and TBDMS are usually applied only if a modified acid stability is wanted. Thus, the triethylsilyl (TES) group[169] shows a sensitivity to hydrolysis and nucleophilic attack intermediate between the TMS and the TBDMS groups. The triisopropylsilyl (TIPS),[170] the *t*-butyldiphenylsilyl (TBDPS)[171] and the thexyldimethylsilyl (TDS)[172] groups are considerably more stable towards 1% HCl and aqueous NaOH than the TBDMS group. The TDS group can, in addition, be regarded as a replacement for the TBDMS protecting group since the silyl chloride used for its introduction is less expensive and easier to handle (equation 15).



(15)

The respective introducing reagents may also be sterically more demanding and give better selectivities in the protection of polyfunctional molecules. This is mainly exploited in nucleotide chemistry. Also, stereochemical bias may be introduced with the aid of appropriate silyl protection. As shown in equation (16), tribenzylsilyl and tri-*p*-xylylsilyl ethers were used to control the stereochemistry of epoxidation in prostaglandin syntheses.[173]

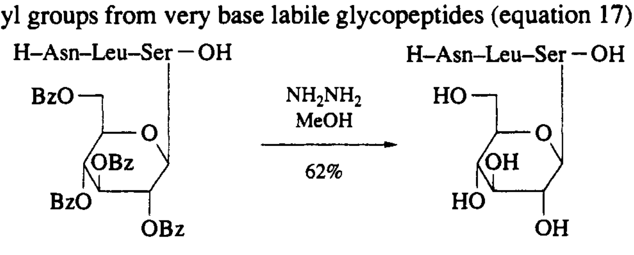


(16)

3.1.3.3 Ester and Carbonate Protecting Groups

Esters can be prepared from alcohols and activated forms of carboxylic acids by a variety of methods.[174] Carboxylic acid esters are mainly base labile and, therefore, they complement the acid sensitive ether protecting groups. A variety of esters can be used for simpler and for more complex problems. Here, only the most practical groups will be treated. The application of esters as protected forms is frequently complicated by the possibility of acyl migration which may occur under basic, acidic and also neutral conditions.[175]

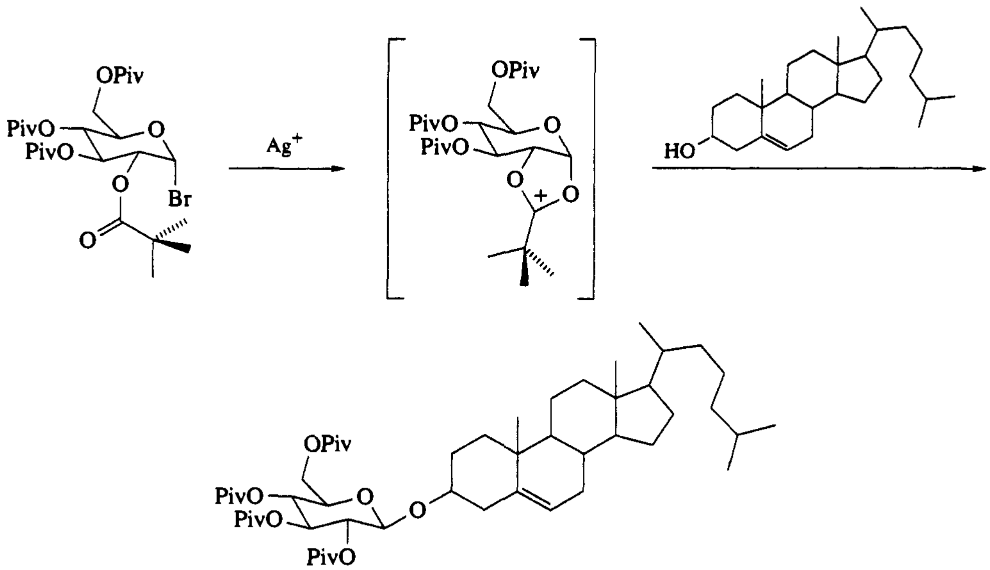
Acetates and benzoates are widely used in carbohydrate chemistry. Their introduction is readily achieved *via* the acyl chlorides or the anhydrides. The reactivity of these reagents is greatly enhanced by the addition of 4-dimethylaminopyridine, and unreactive alcohols can usually be acylated this way.[176] The removal of these ester blocking groups can be carried out in several ways. Alkaline saponification, treatment with K_2CO_3 in aqueous methanol, ammonia in methanol and, as a particularly mild method, KCN in ethanol[177] are effective for the cleavage of acetates. In addition, hydrazine in methanol is a very advantageous reagent to achieve this aim. Its use proved to be the method of choice for the removal of *O*-acetyl and *O*-benzoyl groups from very base labile glycopeptides (equation 17).[178]



(17)

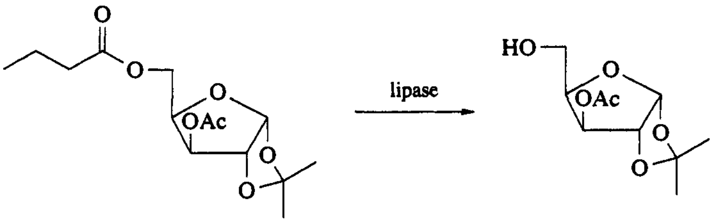
Acetates and benzoates not only serve to mask the OH groups in sugars, they also display neighboring group assistance in the stereoselective construction of 1,2-*trans*-glycosides.[141]

The major side reaction in this glycosylation reaction is the formation of an orthoester. This can, however, be suppressed if the sterically demanding pivaloyl group is used as the blocking group of the 2-hydroxy function of the glycosylating compound. Here the *trans*-glycosides are isolated in high yields without orthoester formation (Scheme 44).[179] Even earlier pivaloates had been introduced for the selective masking of 5′-hydroxys in nucleosides.[180] For their removal transesterification with sodium methylate in methanol or, according to Gassman *et al.*, 'anhydrous hydroxide' ($KOBu^t/H_2O$ 8:2, 20 °C, 3 h, 94%) has to be applied.[181] Under these conditions tertiary amides also are hydrolyzed.



Scheme 44

Recently the enzyme-catalyzed hydrolysis of pivaloates from carbohydrates was reported.[182] In general, enzymatic methods could prove to be viable alternatives to traditional chemical transformations since enzymes mostly operate under exceptionally mild conditions and with selectivities which are otherwise hard to achieve.[183] An example is given in equation (18). Also trypsin and chymotrypsin may be applied.[184]



(18)

By introducing substituents into the acetyl or benzoyl groups the stability of the derived esters towards basic hydrolysis can be varied. In accordance with the Hammett principle, the order of increasing reactivity given in Scheme 45 is valid.

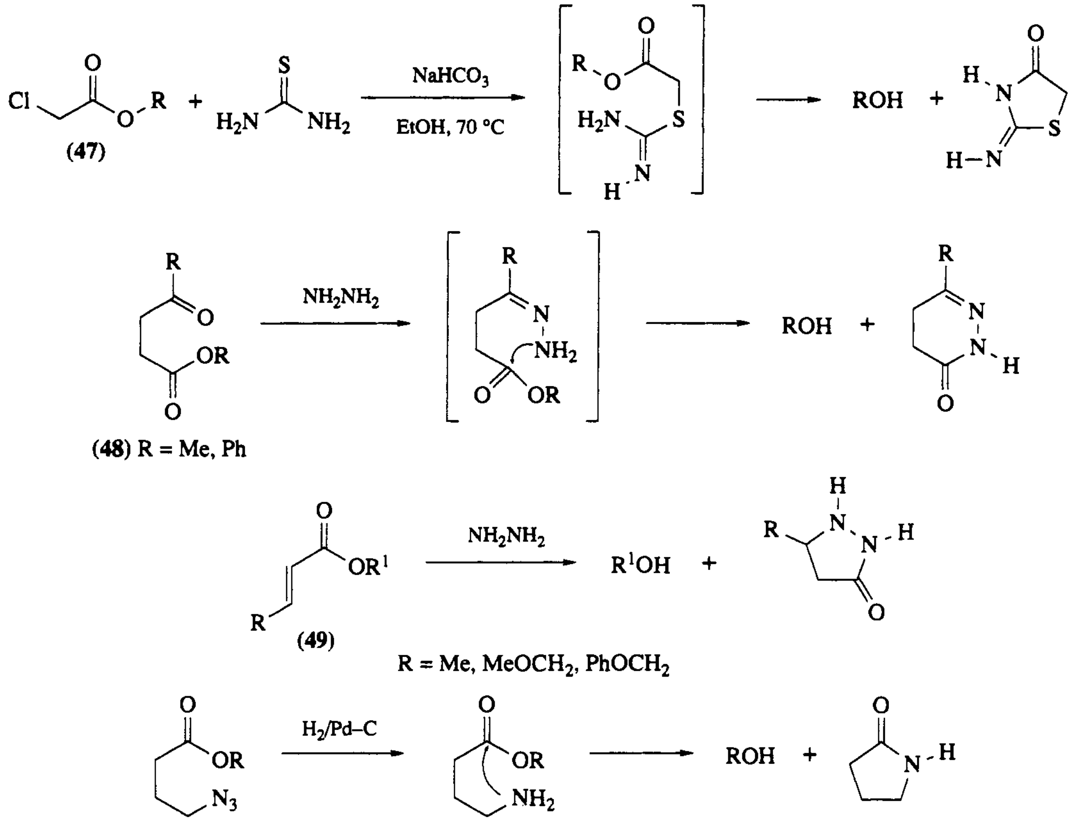
$\mathrm{Bu^tCO} < \mathrm{MeCO} < \mathrm{MeOCH_2CO} < \mathrm{PhOCH_2CO} < \mathrm{HCO} < \mathrm{ClCH_2CO} < \mathrm{Cl_2CHCO} < \mathrm{Cl_3CCO} < \mathrm{F_3CCO}$

$\mathrm{PhCO} < p\text{-}\mathrm{NO_2C_6H_4CO} < o\text{-}\mathrm{BrC_6H_4CO} < \mathrm{MeCO}$

Scheme 45

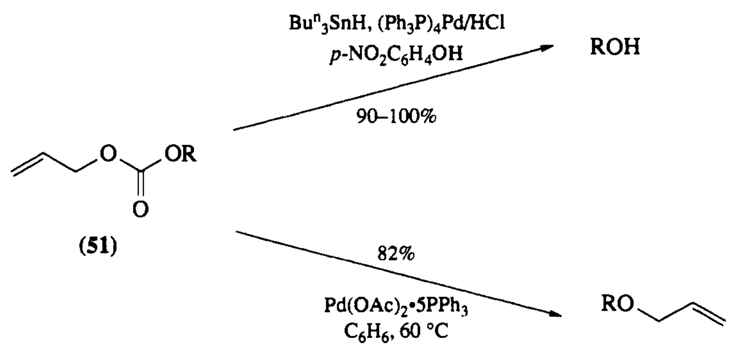
Methoxyacetates and phenoxyacetates serve as protecting groups in nucleoside synthesis.[185] They are cleaved by aqueous ammonia 20 and 50 times faster respectively than acetic acid esters. In the aromatic series the *p*-nitrobenzoates often show the advantageous tendency to crystallize.

In analogy to methods developed in peptide chemistry, acyl groups can be removed *via* a secondary intramolecular transformation (Scheme 47). For instance, chloroacetyl esters (**47**) are cleaved with thiourea[186a] or hydrazinedithiocarbonate[186b] by the formation of a heterocycle. Similarly γ-oxo carboxylic acid esters (**48**) are labile towards hydrazine. This is the basis for the cleavage of the benzoylpropionates and the levulinic acid esters.[187] Under nearly neutral conditions initially a hydrazone is formed, which then intramolecularly attacks the ester bond. By this method a levulinic group can be selectively removed in the presence of acetates. Alternatively, the levulinates can also be cleaved by initial reduction of the ketone with $\mathrm{NaBH_4}$, to an alcohol.[188] Similarly, crotonates and methoxycrotonates (**49**) first undergo a Michael addition with hydrazine followed by an intramolecular reaction.[189] Further methods for the generation of a nucleophile which then attacks intramolecularly consist in the reduction of a nitro or an azido group in 4-nitro and 4-azido carboxylic acid esters (**50**).[190]



Scheme 46

Several of the urethane protecting groups described in Section 3.1.2.1 can analogously be used as carbonates for the protection of alcohols, too.[5,104] Thus, the 2-arylsulfonylethyl[191] (deblocking with ammonia), the 9-fluorenylmethyl[192] (deblocking with ammonia), the 2-phosphonioethyl[43,193] (deblocking with dimethylamine in methanol), the benzyl and substituted benzyl,[194,195] the allyl (deblocking by Pd^0-catalyzed hydride transfer,[196] trapping with 2-ethylhexanoate[59] or catalyzed isomerization[144]), the 2,2,2-trichloroethyl[46c,197a] (deblocking by reduction) and the 2-(trimethylsilyl)ethyl carbonates[197b] have been applied successfully. Allyl carbonates (**51**) prove to be particularly valuable. On the one hand they can be removed completely using Pd^0 and tri-*n*-butylstannane, or on the other hand they can be decarboxylated to give the corresponding allyl ethers (Scheme 47).[196]

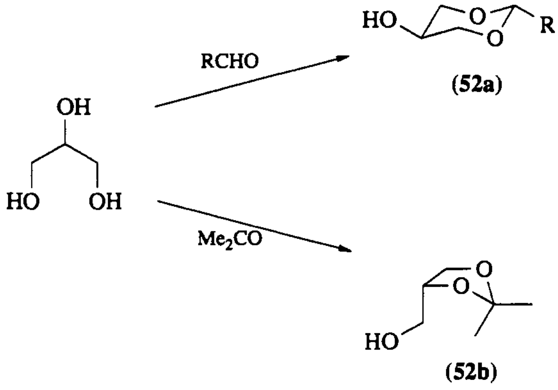


Scheme 47

3.1.3.4 Protecting Groups for 1,2- and 1,3-Diols

Compounds bearing *cis*-1,2-diols and *cis*- and *trans*-1,3-diols can be protected as cyclic acetals and ketals or cyclic orthoesters. As has been shown for ethers, these blocking groups are stable to bases but are labile to acids. Diol protection as cyclic esters, sensitive to basic conditions, is also possible. More recent developments have involved cyclic silylene, siloxanylidene and stannoxane derivatives.

Cyclic acetals and ketals are of particular importance in carbohydrate chemistry. They can be formed by the reaction of the diol and a carbonyl component in the presence of an acid or a Lewis acid.[2,198] Also transacetalization of a ketal or acetal with the diol can be carried out. Finally geminal dibromides and dichlorides can be used as introducing reagents. In the acid-catalyzed acetalizations polyols can give rise to five-, six- or seven-membered rings. Here different carbonyl reagents prefer different ring sizes. As an empirical rule, aldehydes like formaldehyde, acetaldehyde and aromatic aldehydes react to give 6-ring acetals (1,3-dioxanes; **52a**), and aliphatic ketones like acetone, cyclopentanone and cyclohexanone form 5-ring ketals (1,3-dioxolanes; **52b**) (Scheme 48).[198] However, the particular method for the introduction as well as the acid catalyst may also influence which product is preferred. Thus, in the reaction of glycerol with benzaldehyde dimethyl acetal only the formation of the 1,3-dioxolane derivative is observed, but on prolonged standing it isomerizes to the 1,3-dioxane. With benzaldehyde itself, however, a mixture of both isomers is isolated.[199]



Scheme 48

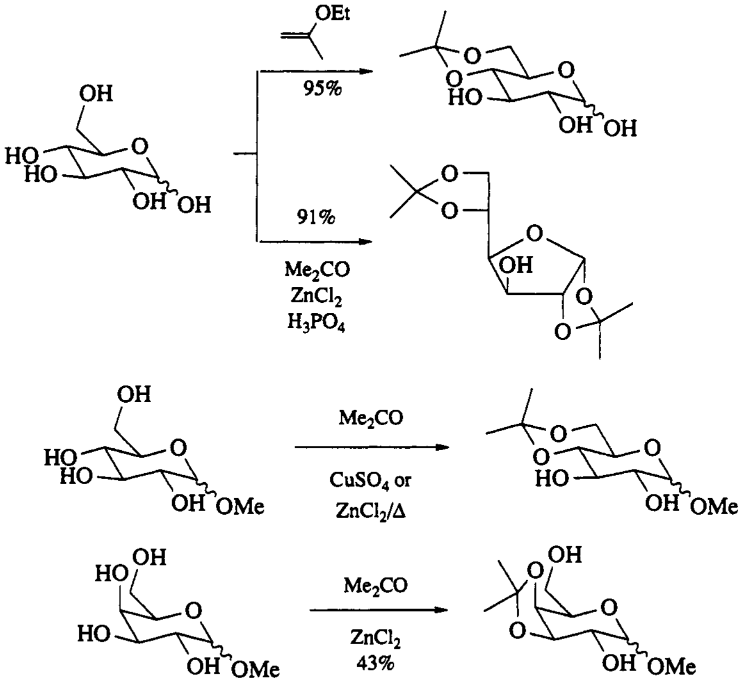
The most important and widely used ketal is the acetonide.[2] It is prepared by the reaction of the diol with acetone[200] or acetone dimethyl acetal[201] and an acid catalyst. Also 2-alkoxy and 2-silyloxy propenes can be applied for this purpose (Scheme 49).[202] In the reactions with carbohydrates furanose rings are formed if possible, but under kinetically controlled conditions also 1,3-dioxanes may be constructed. In the cases of hexoses which do not contain *cis*-1,2-diols the reaction usually involves the 6-OH group.

For the removal of the isopropylidene ketal a variety of acid-catalyzed hydrolyses have been described. Typical conditions are: Dowex 50-W $(H^+)/H_2O$, 70 °C and 60–80% HOAc, 25 °C or reflux.

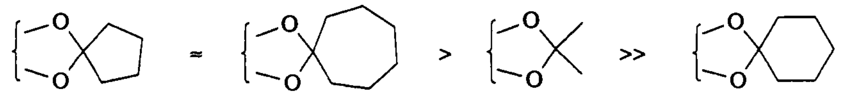
Other ketals which are frequently used if a modified acid stability is wanted are the cyclopentylidene, the cyclohexylidene and the cycloheptylidene ketals. They are readily prepared by the reaction of a diol and the cycloalkanone in the presence of ethyl orthoformate and mesitylenesulfonic acid.[203] The relative rates of their acid-catalyzed hydrolysis are given in Scheme 50.

The most important acetal protecting function is the benzylidene group. It is formed from the diol and benzaldehyde or its dimethyl acetal under acidic catalysis (Scheme 51).[104,204] The Williamson reaction of the diols with benzylidene bromide in the presence of pyridine is also effective.[204,205] The benzylidene group constitutes an important blocking and regiodifferentiating principle in carbohydrate chemistry. This is due to the fact that it can be easily removed by acidic hydrolysis and hydrogenation and that, on the other hand, it can be regioselectively opened, thereby providing a route for the selective liberation and protection of OH groups. As is shown in Scheme 52, by treatment with $NaCNBH_3$ in the presence of acids in THF the 4,6-*O*-benzylidene function in protected glucose is converted to the 6-benzyl ether (**53**).[206] Alternatively the application of $LiAlH_4/AlCl_3$ produces the 4-benzyl ether (**54**).[207] Whereas the former method can be used with ester- and ether-protected carbohydrates, only ether protecting groups are tolerated in the second case. In similar reactions NBS transforms the benzylidene group to the 4-benzoate.[208] In analogous reactions 4-methoxybenzylidene acetals can be regioselectively opened and oxidized with dichlorodicyano-*p*-quinone (DDQ)[209] or ammonium cerium nitrate[139] to give the *p*-methoxybenzoates or deprotected compounds.

In addition to the ketals and the acetals, cyclic orthoesters are sometimes used for the protection of 1,2-diols. They are more readily cleaved by acids than the acetonides. In nucleoside chemistry formic acid, acetic acid and benzoic acid orthoesters were applied to temporarily mask the carbohydrate part.[210] Also the methoxyacetic acid orthoester (**55**) was useful because it allowed the selective liberation of the 3′-



Scheme 49

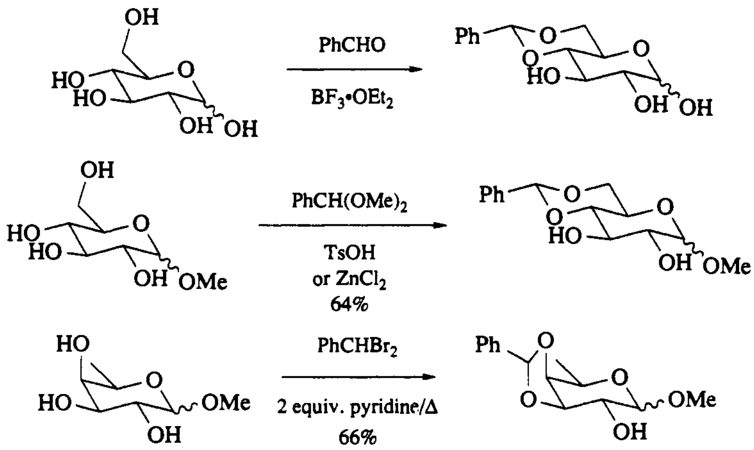


e.g. 8 : 10 : 20 : 124

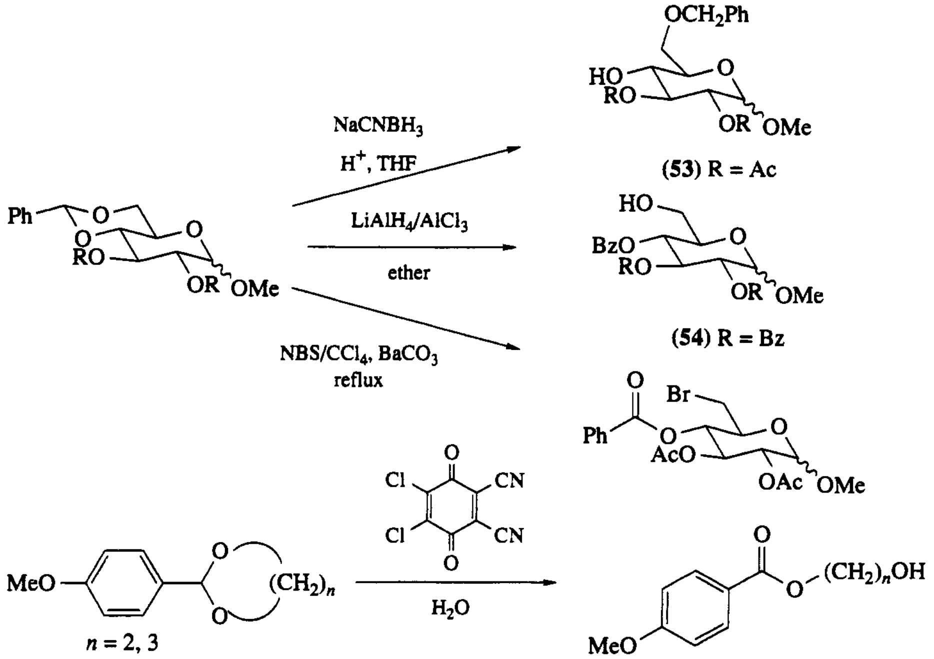
for 1,2-*O*-alkylidene-α-D-glucopyranoses

Scheme 50

and the 2′-hydroxy groups.[211] During its cleavage the protecting function is converted to the base labile ester (**56**; Scheme 53).



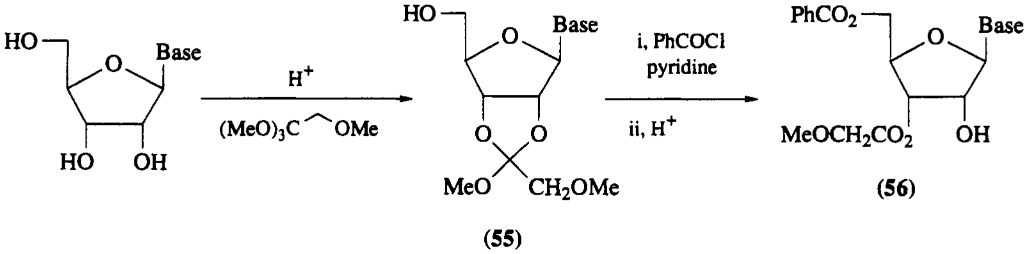
Scheme 51



(53) R = Ac

(54) R = Bz

Scheme 52



(55)

(56)

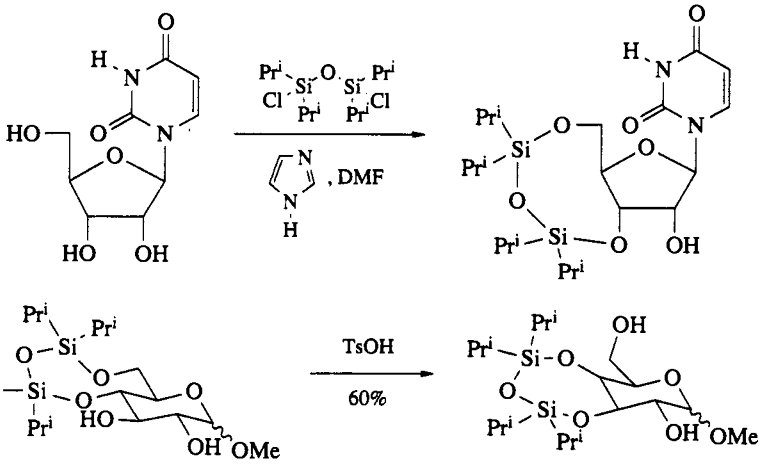
Scheme 53

Besides the many acid sensitive derivatives, base labile protecting groups for 1,2-diols were also recommended. With phosgene or a chloroformate, cyclic carbonates are formed from *cis*- and *trans*-diols.[210,212] They are stable to the conditions that hydrolyze acetals but are readily removed by saponification. Cyclic boronates may also be used, but their application is limited because they hydrolyze very rapidly.[213]

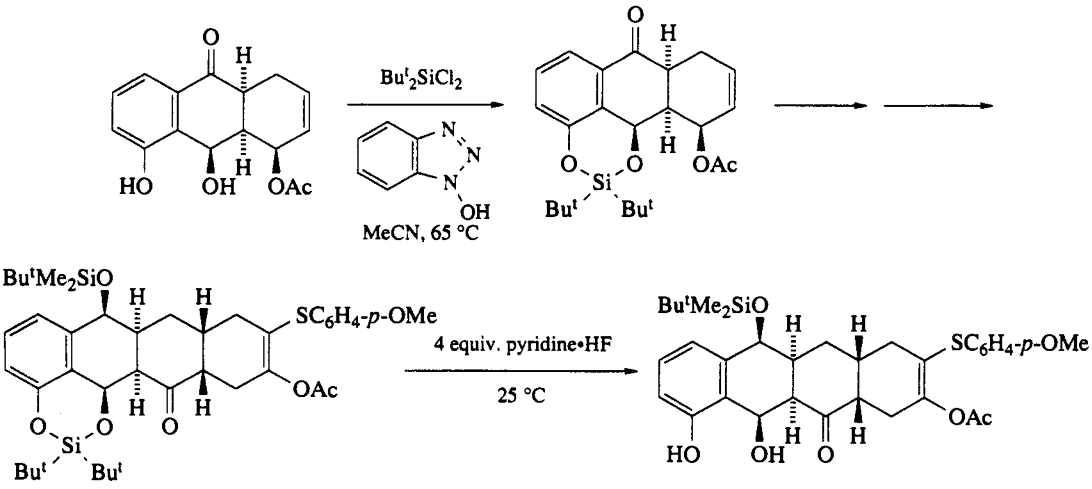
Finally, silicon and tin reagents offer the possibility to protect diol systems. The 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene) (TIPDS)[214] group is introduced *via* the 1,3-dichloro derivative. With 1,3-diol structures of nucleosides, carbohydrates or glycerol it forms eight-membered rings (Scheme 54). This protecting group is stable to water, 0.3 M TosOH, 10% TFA/CHCl$_3$, amines, the conditions for the introduction of THP, sulfonyl and trityl groups and the isomerization of an allyl to a propenyl ether. Its removal is accomplished with tri- or tetra-*n*-butylammonium fluoride, 0.2 M HCl/MeOH and 0.2 M NaOH in dioxane/water. In addition the 3′- and the 5′-OH groups of nucleosides can selectively be liberated and the siloxanylidene group can be isomerized under acidic conditions (see Scheme 54).[214]

Diisopropyl- and di-*t*-butyl-silylene (DTBS) derivatives constitute further interesting protecting groups for 1,2-, 1,3- and 1,4-diols. These compounds are obtained from the dichlorosilanes or the ditriflates.[215] An example for the use of the di-*t*-butylsilylene group is given in Scheme 55. It demonstrates that the blocking group is cleaved under mild acidic conditions with pyridinium fluoride. The TBDMS ether, the 4-methoxyphenyl sulfide and the sensitive β-ketol system present remain unaffected.

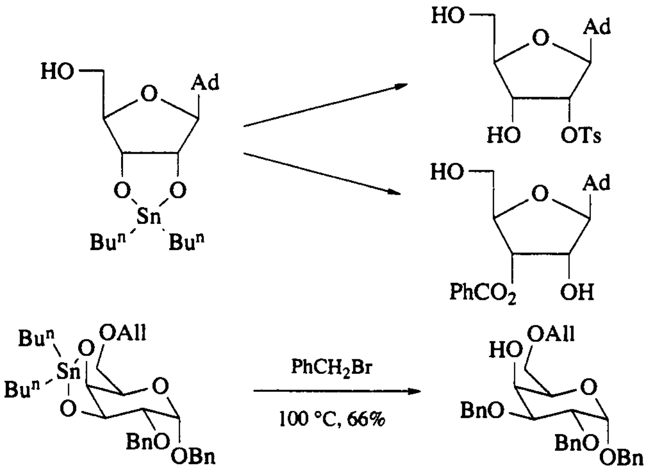
More sensitive than silicon-derived compounds are dialkoxystannanes.[216] They are formed in good yields on treatment of the respective diols with dibutyltin oxide. The particular advantage offered by this protecting technique is that it allows for regioselective acylations and alkylations of diol structures.[217] Two examples are given in Scheme 56.



Scheme 54



Scheme 55

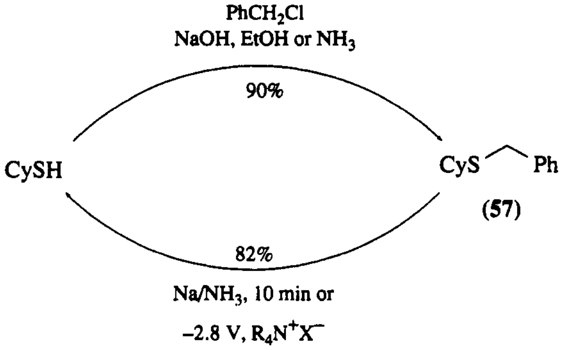


Scheme 56

3.1.4 THIOL-PROTECTING GROUPS[5,218]

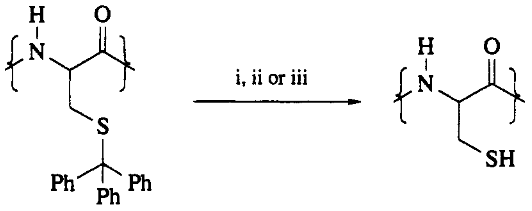
The protection of the thiol group is a serious problem in peptide synthesis if cysteine is involved. Blocking can be achieved as a thiol ester, a sulfide or as a disulfide from which the thiol must be regenerated by reduction. The protection of cysteine through *S*-acyl or *S*-alkoxycarbonyl derivatives embodies the danger of β-elimination under formation of alkenic structures. Also these thiol ester derivatives display considerable acylating properties towards amines and alcohols. Therefore, *S*-alkyl protecting groups and disulfides are used almost exclusively.

Due to the pronounced nucleophilicity of the SH group, the *S*-benzyl ether (**57**) can directly be prepared from cysteine and benzyl chloride in high yield. It is stable towards acid, but removable with sodium in ammonia[16,219] or electrolysis.



Scheme 57

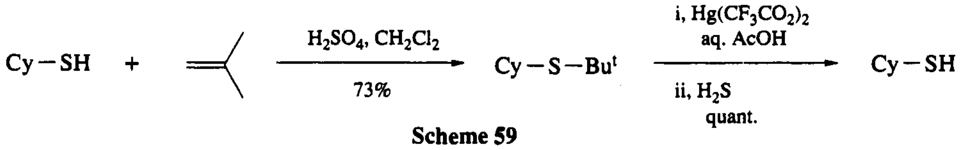
Also the trityl group was applied for the masking of SH functions.[220] The sulfides were prepared by the reaction of the thiol with trityl chloride (75% yield) or from trityl alcohol and the thiol in the presence of anhydrous TFA (85–90% yield). The cleavage of this group can be carried out under several conditions (Scheme 58).[221] It is sensitive to acids (*e.g.* trifluoroacetic acid/ethanethiol 1:1) and to heavy metals. Thiocyanogen (SCN)$_2$ oxidizes *S*-trityl ethers to the disulfides and iodine converts *S*-tritylcysteine derivatives to cystine structures.



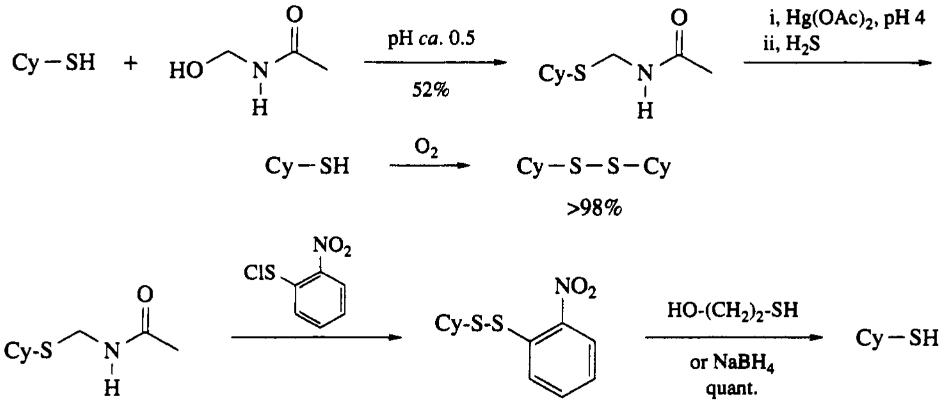
i, HCl/aq. AcOH, 90 °C; ii, Hg(OAc)$_2$/EtOH/Δ then H$_2$S; iii, AgNO$_3$/EtOH/pyridine, 90 °C then H$_2$S

Scheme 58

t-Butyl sulfides, like *t*-butyl ethers, are formed from the thiol and isobutene under acidic conditions.[222] They are stable to HBr/AcOH and TFA but are cleaved with HF/anisole. Mercury salts in combination with acids also liberate the thiol function (Scheme 59).[222] In addition to these *S*-alkyl protecting methods, several of the acetalic blocking groups used for alcohols can be applied to the SH function (*e.g.* BOM, MOM, THP). An advantageous thioacetal is found in the *S*-acetamidomethyl (Acm) protecting group (Scheme 60).[223] Cysteine can be masked with this function under acidic conditions and its removal is accomplished with Hg^{2+} in aqueous acid. Alternatively with *o*-nitrobenzenesulfenyl chloride the disulfide is obtained, which must be cleaved with mercaptoethanol or NaBH$_4$.[224]

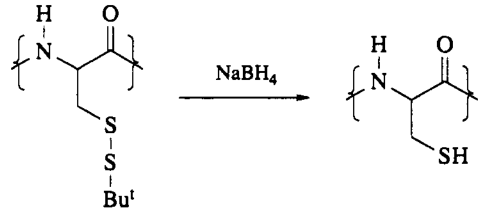


Scheme 59



Scheme 60

Disulfides can also, in general, be prepared from a thiol by oxidation (O_2, H_2O_2, I_2). The symmetrical or unsymmetrical disulfides must finally be reduced, for instance with other thiols, $NaBH_4$ or $LiAlH_4$, to liberate the SH group again. The unsymmetrical disulfide with *t*-butyl thiol has been used for the protection of cysteine in peptides.[225] As is shown in equation (19) its cleavage was successfully achieved with $NaBH_4$.



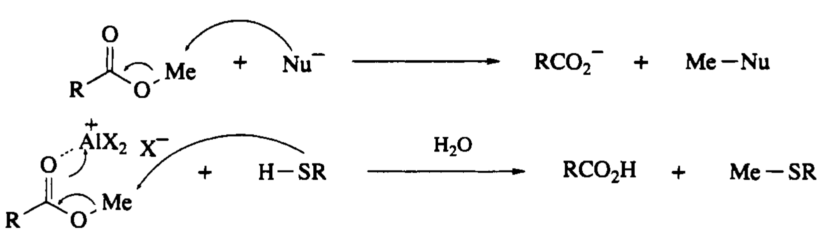
(19)

3.1.5 CARBOXY-PROTECTING GROUPS[5,11c,11d,226,227]

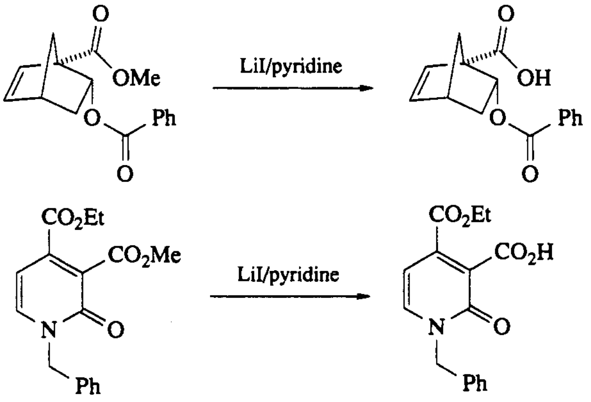
The carboxylic acid group represents one of the central functionalities in organic chemistry and, due to its reactivity, it must be protected in the majority of reactions involving other parts of a given molecule. In comparison to amino protection the masking and liberation of carboxylic acids pose less severe problems. Usually esters are chosen for this purpose, and the great variety of methods for their formation is well documented.[174,227] In contrast to amides and urethanes, esters can be hydrolyzed under relatively mild acidic or basic conditions. The ester cleavage often can be carried out without racemization of optically active compounds. Therefore, in numerous cases simple alkyl esters fulfill the demands for the temporary protection of carboxylic acid groups. However, for the cases in which milder deprotection techniques are required, nearly all the reliable methods already described as urethane protection principles for the amino function can be applied in the form of the analogous esters. Therefore, they are presented in this section mainly in tabular surveys. For detailed discussions see Section 3.1.2.1. In addition to chemical methods, increasing numbers of reports on enzymes attacking esters and amides under mild conditions can be found in the recent literature,[228] and it must be expected that these techniques will receive more and more attention for the selective removal of ester protecting functions.

3.1.5.1 Ester Protecting Groups

The most simple esters are the methyl and higher *n*-alkyl esters which can be prepared by numerous methods.[226,227] They usually are cleaved by saponification with base but also the application of trimethylsilyl iodide is efficient.[229] This reaction belongs to the mildest methods for ester cleavage, which generally consist in the treatment with nucleophiles effecting an S_N2 displacement of the carboxylate (Scheme 61).[227,229,230] For this transformation various anions (iodide, chloride, cyanide, thiocyanate, thiolate) or neutral molecules (thiols, amines) are applied in dipolar aprotic media. In the reaction of trimethylsilyl iodide with esters the silyl group acts as an activating Lewis acid, while the iodine attacks as the nucleophile. If thiols are used, the reaction can also be accelerated by adding a strong Lewis acid ($AlCl_3$, $AlBr_3$, BCl_3) which complexes the carbonyl oxygen and thereby activates the ester group (Scheme 61).[231] Of the metal halides employed in this deprotection technique the use of lithium iodide in pyridine is probably the method of choice for S_N2 dealkylation of esters. It also allows differentiations between similar esters in a given molecule because the accessibility of the ester alkyl carbon atom determines the ease of these ester cleavages (Scheme 62). If electron-withdrawing groups are bound to the methyl group of methyl esters, functionalities are generated which are considerably more reactive towards nucleophiles. Thus, the phenacyl ester, easily prepared by reaction of a carboxylate with phenacyl bromide, is cleaved with zinc in acetic acid[232] or sodium thiophenoxide.[233] Furthermore, the α-methylphenacyl ester can be removed photolytically or by hydrazinolysis.[234] The phthaloylmethyl group is also attacked by thiophenoxide[232a] or zinc, or alternatively by hydrazine or diethylamine in methanol (see Table 3). As the carboxy group generally is a much better leaving group than an alcohol, acetal-type protecting functions corresponding to those mentioned in Section 3.1.3.1 can also be used in the form of the α-alkoxyalkyl esters. They are in most cases synthesized in good yields by nucleophilic substitution of the halogen at the respective halomethyl alkyl ether by a carboxylate. For the cleavage of these groups, methods similar to those reported for the acetal-type protection of alcohols were devised. A selection of the proven blocking groups belonging to this class and conditions for their removal is given in Table 3.



Scheme 61



Scheme 62

In analogy to the β-substituted ethyl urethanes the corresponding β-substituted ethyl esters are cleaved in reductive fragmentations and β-elimination reactions. This allows deprotections under very mild conditions using various reagents (Table 4, see Sections 3.1.2.1 and 3.1.3.1), which can often be applied as alternatives to each other. It should be noted that the methylthioethyl,[51] the pyridylethyl[244] and the 1,3-dithianylmethyl esters[245] are two-step protecting groups which offer the additional advantage of being stable during the synthetic transformations of the protected compounds. After chemoselective labilization they can be removed under very mild conditions. To this category of protecting functions the cinnamoyl esters (**58**) must be added, since they can be cleaved in nearly neutral media by a method which is also based on a β-elimination (Scheme 63).[247] After methoxymercuration, the organomercury intermediate is fragmented by attack of thiocyanate at the thiophilic Hg atom. β-Substituted ethyl ester groups proved to be particularly well suited for the construction of sensitive glycopeptides. An example in which a synthesis of *N*-glycopeptides is highlighted is depicted in Scheme 64.[248] Here, the selective C-terminal deblocking and the subsequent extension of the peptide chain are achieved with the aid of the dithianylmethyl ester as a two-step protecting group. After oxidation of the sulfurs to the disulfones, the whole ester becomes so labile that it immediately hydrolyzes under the weakly basic reaction conditions (pH 7–8).

Table 3 Substituted Methyl Esters, R—COO—R′, as Carboxy-protecting Groups

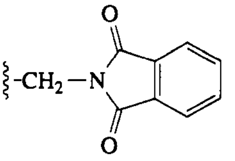
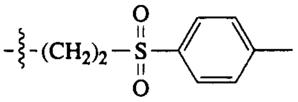
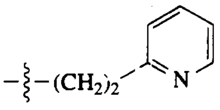
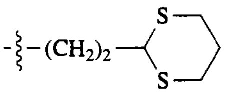
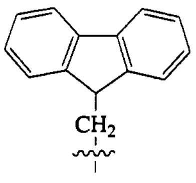
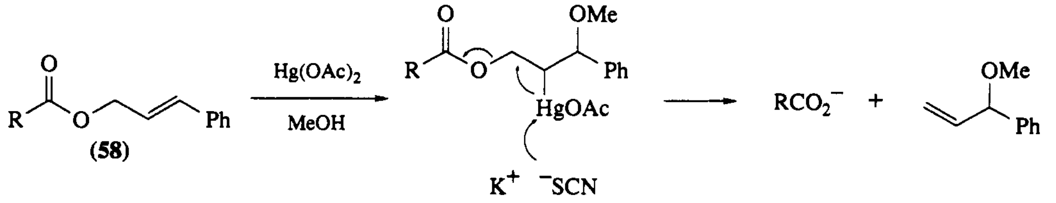
R′	*Abbreviation*	*Removal by*	*Ref.*
Me	Me	HO^-; LiI/pyridine; Me_3SiI if possible	174, 229–231
$CH_2C(O)Ph$	Pac	NaSPh; Zn/AcOH; hν	232–234
	Ptm	Zn/AcOH; NH_2—NH_2; HCl or HBr/EtOAc	235
CH_2OMe	MOM	R_3SiBr, trace MeOH	236
$CH_2O(CH_2)_2OMe$	MEM	3 M HCl, THF	237
CH_2OCH_2Ph	BOM	H_2/Pd-C, EtOH	238
CH_2SMe	MTM	i, $HgCl_2$/MeCN-H_2O; ii, H_2S if possible or i, MeI or H_2O_2; ii, NaOH	239

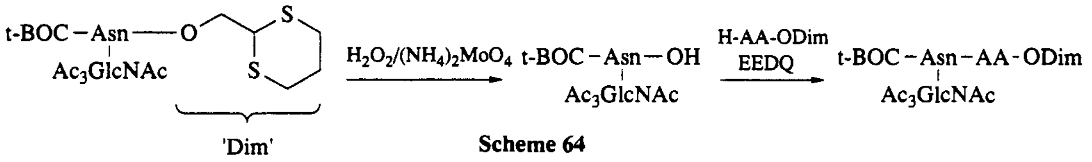
Table 4 β-Substituted Ethyl Esters, RCO_2R', as Carboxy-protecting Groups

R′	*Abbreviation*	*Removal by*	*Ref.*
	Tse	1 M NaOH; KCN or Na_2CO_3, dioxane/H_2O	240
-§-$(CH_2)_2$—S—Me	Mte	i, H_2O_2; ii, pH 10–11	51
-§-$(CH_2)_2$—$SiMe_3$	Tmse	R_4N^+ F^-	241
-§-CH_2—CCl_3	Tce	Zn/AcOH or THF; electrolysis	242
-§-$(CH_2)_2$—Br(I)	Br(I)Et	Zn/AcOH; S^{2-} or $^-S(CH_2)_2S^-$; electrolysis; Co(I)-phthalocyanine	243
	2-Pet	i, MeI; ii, morpholine	244
	Dim	i, H_2O_2; ii, pH 7–8	245
	Fm	Et_2NH	246

Of great importance in peptide chemistry are the *t*-butyl, benzyl and substituted benzyl esters.[11c,11d,174,226] They are more stable to acids than the corresponding urethanes. Benzyl and substituted benzyl esters can be prepared by azeotropic esterification with the respective benzyl alcohol, by activating the carboxy group, *e.g.* with dicyclohexylcarbodiimide (DCC) or by reacting a carboxylate with a benzyl halide (Scheme 65). The latter S_N2-type ester formation is particularly efficient if cesium carboxylates are employed.[249] Under the conditions required for this reaction the racemization of α-chiral car-

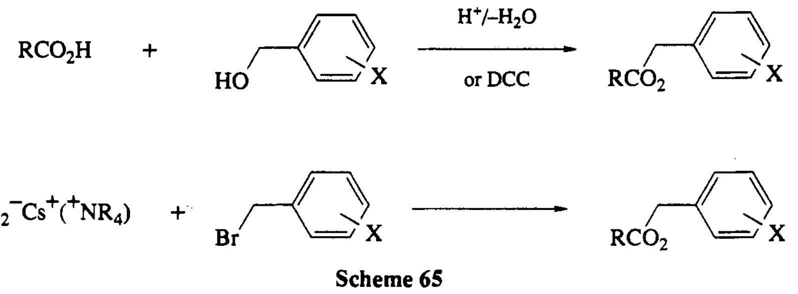


Scheme 63



Scheme 64

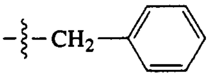
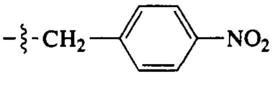
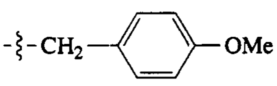
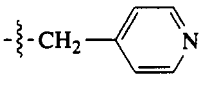
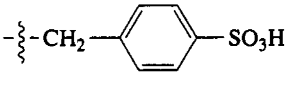
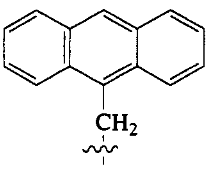
boxylic acids can be minimized. All benzyl-type esters are cleaveable by hydrogenolysis. Furthermore, it should be noted that catalytic transfer hydrogenation can be useful to remove these groups from sulfur-containing compounds.[250] Whereas simple unsubstituted benzyl esters are hydrolyzed by HBr/AcOH, the properties of the substituted variants depend on the substituent in the aromatic ring (see Section 3.1.2.1). Electron-withdrawing groups, *e.g.* the nitro group,[251] enhance the acid stability of the esters. In contrast, electron-donating substituents induce an increased sensitivity towards acids. Thus, the 4-methoxybenzyl esters are already cleaved by trifluoroacetic acid at 0 °C.[252] In addition, the substituents can serve to introduce solubilizing properties as is the case for 4-sulfobenzyl esters[253] and for 4-picolyl esters.[254] The picolyl ester, furthermore, is resistant towards acids and allows the protected compound to be purified by ion-exchange techniques. Since the hydrogenation of picolyl esters may be very slow, the electrochemical reduction at a mercury electrode at least in some cases appears to be more favorable. Benzyl esters also form the basis for several photosensitive protecting groups. Thus, for instance, *o*-nitrobenzhydryl and 2,4-dinitrobenzenesulfenyl esters can be photolyzed under neutral conditions.[255] As is to be expected, the 9-anthrylmethyl ester is also an acid sensitive protecting function. Interestingly, it is very reactive towards thiolate anions in hexamethyl phosphoric triamide.[256] The most commonly used benzyl-type esters are shown in Table 5. Phenyl esters, or aryl esters in general, constitute blocking groups of carboxylic acids of only limited applicability. For most purposes their acylating ability is too high. They are readily removed, exploiting the α-effect of peroxide anions in moderately basic media.[257]



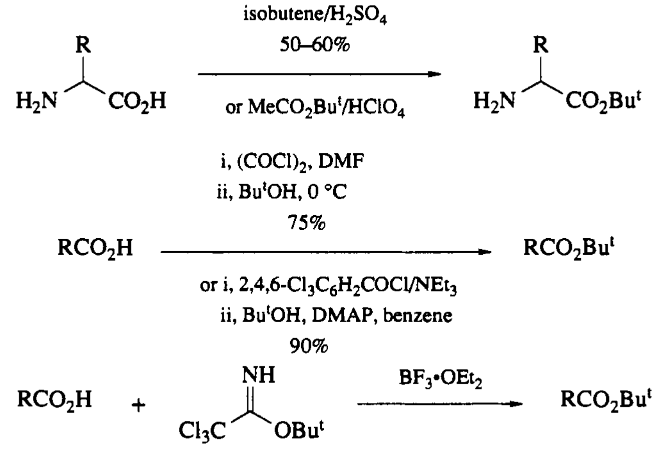
Scheme 65

t-Butyl esters[11c,11d,226,227] are among the most important carboxy-protecting groups. They are stable under basic conditions and towards hydrazine and ammonolysis. The *t*-butyl ester protection is readily removed with trifluoroacetic acid, HBr/AcOH, formic acid or toluenesulfonic acid. The formation of these esters is most frequently carried out by the reaction of the acid with isobutene under acidic catalysis (Scheme 66).[258] However, transesterification of acetic acid *t*-butyl ester catalyzed by perchloric acid[259] and the reaction of an acid chloride or the mixed anhydride with 2,4,6-trichlorobenzoic acid[260] with *t*-butyl alcohol are effective (Scheme 66). A very mild method consists in the recently described esterification using *t*-butyl trichloroacetimidate.[261] *t*-Butyl esters are completely stable under conditions required for hydrogenolytic removal of benzyloxycarbonyl and related groups. The acidolysis of *t*-butyl esters can selectively be achieved in the presence of the N-terminal Z, and suitably substituted Z, groups. These orthogonal stabilities form the basis for numerous successful peptide syntheses. Under the weakly acidic conditions used for the acidolytic removal of the 2-(4-biphenyl)-2-propoxycarbonyl (Bpoc) group, the *t*-butyl ester remains untouched.[262] However, this acid stability is not reliably sufficient to allow the

Table 5 Substituted Benzyl Esters, RCO_2R', as Carboxy-protecting Groups

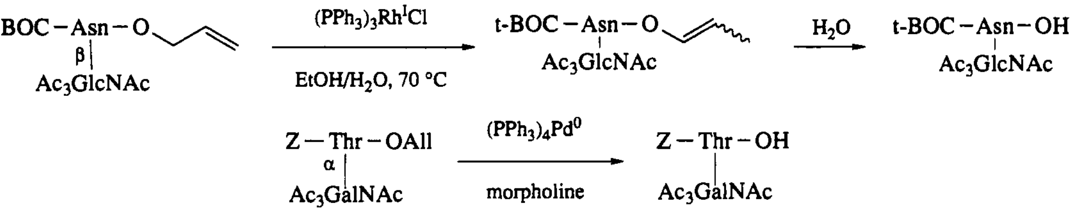
R'	*Abbreviation*	*Removal by*	*Ref.*
	Bn	Pd–C, H_2, HCO_2H/MeOH, cyclohexadiene or cyclohexene; OH^-; HBr/AcOH; $NaNH_3$ liq.	11c, 11d, 226, 227
	Nb	H_2/Pd–C; OH^-; Na/NH_3 liq.; stable to HBr	251
	Mob	H_2/Pd–C; Na/NH_3 liq.; CF_3CO_2H, 0 °C	252
	Pic	H_2/Pd–C; electrolysis; very stable towards acids	254
	—	H_2/Pd; NaOH/H_2O/dioxane	253
	Anm	HBr/AcOH; 0.1 M NaOH; NaSMe/HMPA	256

selective removal of N-terminal *t*-butyloxycarbonyl groups.[263] It seems that the treatment with trimethylsilyl perchlorate[32a] can provide a possibility for the chemoselective differentiation between Boc and *t*-butyl ester protection. It should also be noted that the application of one equivalent of *p*-toluenesulfonic acid in ether/ethanol mixtures results in the selective cleavage of the N-terminal Boc group, while the C-terminal *t*-butyl esters remain intact.[264] As is well known, these esters are quite resistant towards nucleophilic attack. One severe exception to this generalization is observed in the synthesis of peptides involving aspartic acid β-*t*-butyl ester units. On treatment with alkali, amines or hydrazine, cyclization to the corresponding aspartimide derivatives occurs. The analogous side reaction is also observed for glutamic acid γ-*t*-butyl esters, but only to a lesser extent.[265]

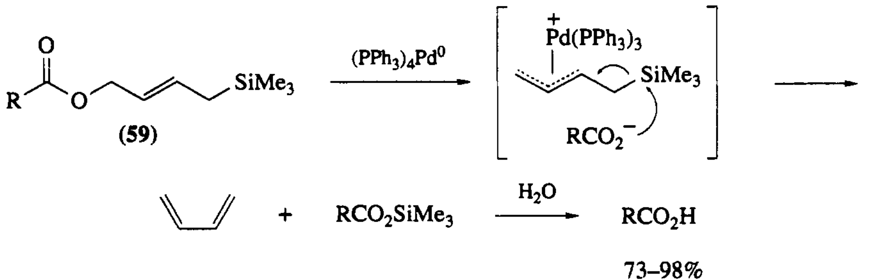


Scheme 66

As has already been detailed for the allyloxycarbonyl (Aloc) moiety, allyl esters also proved to be very versatile and useful carboxy-protecting groups. They can be easily constructed by azeotropic esterification or nucleophilic displacement on allylic halides.[63,266] For the cleavage of these esters lithium dimethylcuprate can be used. However, a much milder method is found in the Rh^{I}-catalyzed isomerization of the allyl moiety to a propenyl ester which immediately hydrolyzes under the reaction conditions (Scheme 67).[63,267] Even milder is the Pd^0-catalyzed allyl transfer to morpholine as an accepting nucleophile.[10,266,267] The removal of allyl ester protection has earlier been used in particular in β-lactam antibiotic synthesis in the sense of a Pd^0-mediated transesterification.[59] By applying a substituted derivative, the addition of an external nucleophile can be circumvented. Thus, 4-(trimethylsilyl)-2-buten-1-yl esters (**59**)[268] react with Pd^0 to form a π-allylpalladium complex. This species then undergoes desilylation by the liberated carboxylate to give butadiene and a trimethylsilyl ester (Scheme 68).



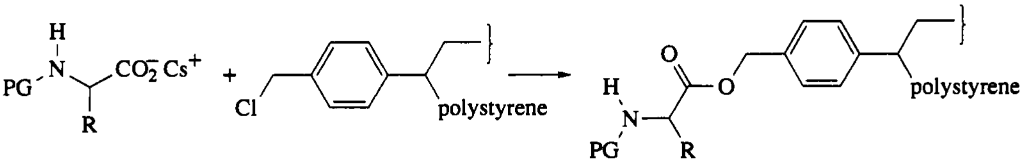
Scheme 67



Scheme 68

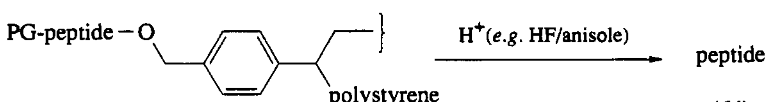
3.1.5.2 Polymer Esters as Protecting and Anchoring Groups

One of the milestones in preparative organic synthesis is certainly the concept of synthesizing peptides on a solid supporting phase, invented by Merrifield.[269] Therefore, polymer-linked protecting groups[270] shall be briefly discussed here. In the original form as well as in most of the commonly applied variants of this principle, the C-terminal amino acid is attached to a resin *via* a benzyl ester-type linkage. The coupling to the polymer is preferably carried out by reacting the salts of *N*-protected amino acids with benzyl halide groups of the polymer, in the most simple case with chloromethyl polystyrene (**61**).[269] As shown in equation (20), a particularly efficient anchoring without racemization is accomplished if the cesium salts (**60**) are used.[249] Alternative condensations of *N*-protected amino acids with polymeric benzyl alcohols often suffer from the partial racemization of the activated amino acid derivative. As the selectively removable amino-protecting group (PG) in this concept, the *t*-butyloxycarbonyl function (t-BOC, see Section 3.1.2.1) is most commonly used. Its removal from the polymer-linked amino acid derivative (**62**) is achieved with trifluoroacetic acid without affecting the polymer benzyl ester bond. After construction of the desired peptide (**63**) by sequential chain extension,[271] the final detachment of the free peptide (**64**) requires treatment with strong acids which simultaneously cleave off the N-terminal and side chain protecting groups. A mixture of liquid hydrogen fluoride and anisole[272] is widely used for this aim. It often yields the peptides almost quantitatively. The anisole serves as a suitable scavenger for the generated carbocations and thus prevents their reaction with nucleophilic functionalities of the peptide (equation 21). Numerous efforts to optimize the concept of solid-phase synthesis[270,271] involve the application of different N-terminal and side chain blocking groups, generation of improved accessibilities of functional groups by using polyamides,[38] or even soluble polyethylene glycol as the polymeric backbone,[273] and modified benzyl ester anchorages. The acid stability of this benzyl ester linkage is increased by electron-withdrawing substituents in the aromatic ring.[269] In this sense, a useful method was developed on the basis of the *p*-hydroxymethylphenylacetic acid,[274] which, furthermore, provides an improved anchoring strategy using preformed benzyl esters (**65**) of the *N*-protected amino acids ('handle strategy', see equation 22). The separately synthesized handle ester (**65**) can be purified and its condensation with aminomethyl polystyrene is not accompanied by racemization. Compared with the simple benzyl ester (**63**), the Pam-linked benzyl ester in (**66**) displays about a 100-fold greater stability towards acids. In contrast, electron-donating substituents enhance the acid sensitivity of polymer benzyl esters as has been demonstrated for *p*-alkoxybenzyl ester anchoring groups.[275] Even more acid labile are the dialkoxybenzyl ester linkages[276,277] which are already cleaved by 1% trifluoroacetic acid in dichloromethane. Solid-phase peptide syntheses on these resins are carried out with the N-terminal Fmoc group[37,38] (see Section 3.1.2.1), which is selectively removable under weakly basic conditions.



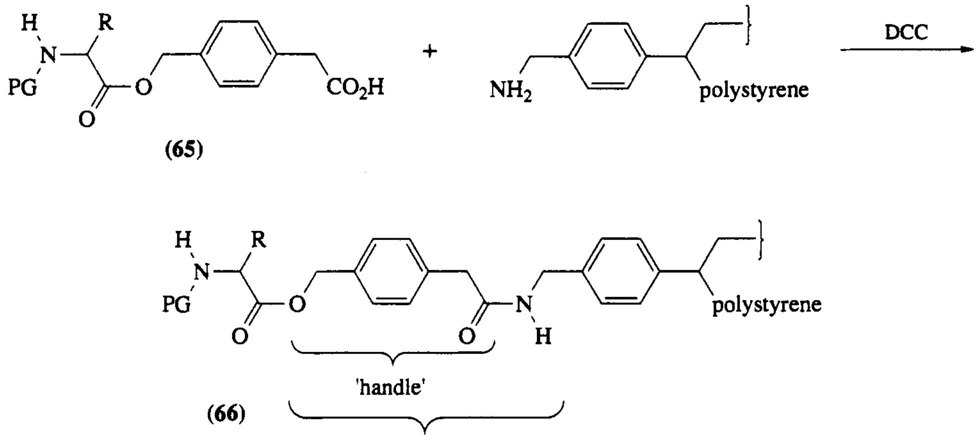
(**60**) (**61**) (**62**)

(20)



(**63**) (**64**)

(21)

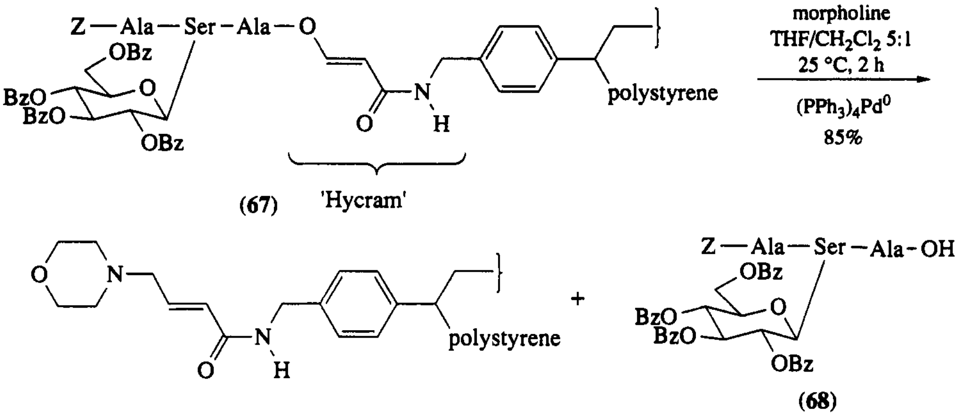


(**65**) (**66**)

(22)

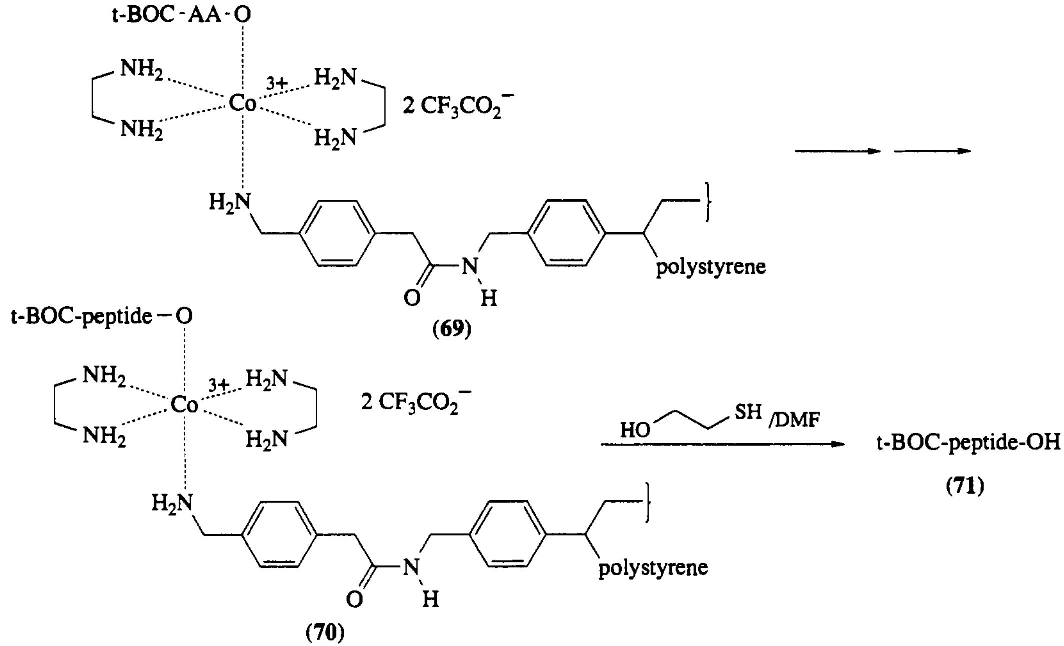
A new type of anchorage, stable towards trifluoroacetic acid, and at the same time cleavable under almost neutral conditions was developed on the basis of the allyl ester and its palladium(0)-catalyzed removal. For instance, the very acid and base sensitive *O*-glycosyl serine peptide (**68**) can be selectively released from its polymer-protected derivative (**67**), bound to hydroxycrotonyl aminomethyl polystyrene (Hycram resin)[60] by application of the Pd^0-catalyzed allyl transfer to morpholine[55,266] or a different suitable weakly basic nucleophile.[57,278] The stability of the allylic anchoring group allows the use of the acid sensitive t-BOC or, alternatively, the base labile Fmoc group as temporary amino protection. Under the neutral detachment conditions (equation 23) *N*- and side chain protecting groups remain unaffected. The obtained peptide fragments can immediately be used for fragment condensations.

As has been demonstrated in Section 3.1.2.4, complexation of amino groups offers a quite different concept for reversible protection. Making use of this principle, the coordination of chromium carbyne complexes with amino acids was described as a new amino protection.[279] Similarly, bis(ethylenediamine)cobalt(III) complexes of amino acids constitute a new interesting method for protection[280] which recently was extended to the development of a new type of anchoring in solid-phase synthesis (Scheme 69).[281] First, a t-BOC amino acid is condensed with the aquabis(ethylenediamine)cobalt(III) complex of *p*-aminomethylbenzoic acid. The handle obtained in this way is then linked to aminomethyl polystyrene to give the anchored amino acid (**69**). Due to the sufficient stability of the complex towards



(23)

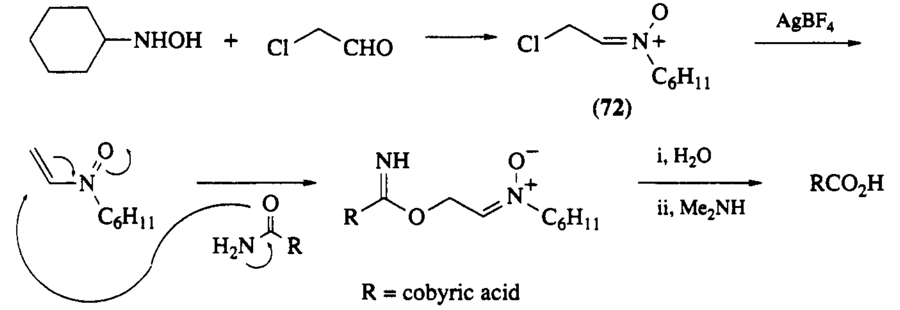
acids, the t-BOC group can be selectively removed. Subsequent chain extension delivers the polymer-linked peptide (**70**) from which the *N*-t-BOC peptide (**71**) is released by destruction of its cobalt complex with mercaptoethanol. Both allyl ester anchoring and amino acid complexation need further testing in syntheses of larger peptides.



Scheme 69

3.1.5.3 Amide Protecting Groups

Amides are only in isolated cases employed as blocking groups for carboxylic acids. However, their use may be advantageous since they can be removed easily by *O*-alkylation[282] and subsequent hydrolysis of the imidate formed (Scheme 70). An alternative, known for a long time,[283] consists of nitrosation and hydrolysis of the diazonium intermediate. These strategies were applied by Woodward[284] and Eschenmoser,[285] respectively, in their syntheses of vitamin B_{12}. Nitrosation can be achieved by using N_2O_4, butyl nitrite, nitrosyl chloride or nitrosonium tetrafluoroborate. The conversion to imidates usually is effected with Meerwein salts[286] or, following Eschenmoser's method, using the extremely reactive *N*-alkyl-*N*-vinylnitrosonium ion, derived from the α-chloronitrone by treatment with $AgBF_4$ (Scheme 70). Alkyl diphenyl sulfonium salts have also been described as *O*-alkylating reagents for amides.[287] An additional method for the cleavage of tertiary amides consists in the use of 'anhydrous hydroxide' (see Section 3.1.3.3).[181]



R = cobyric acid

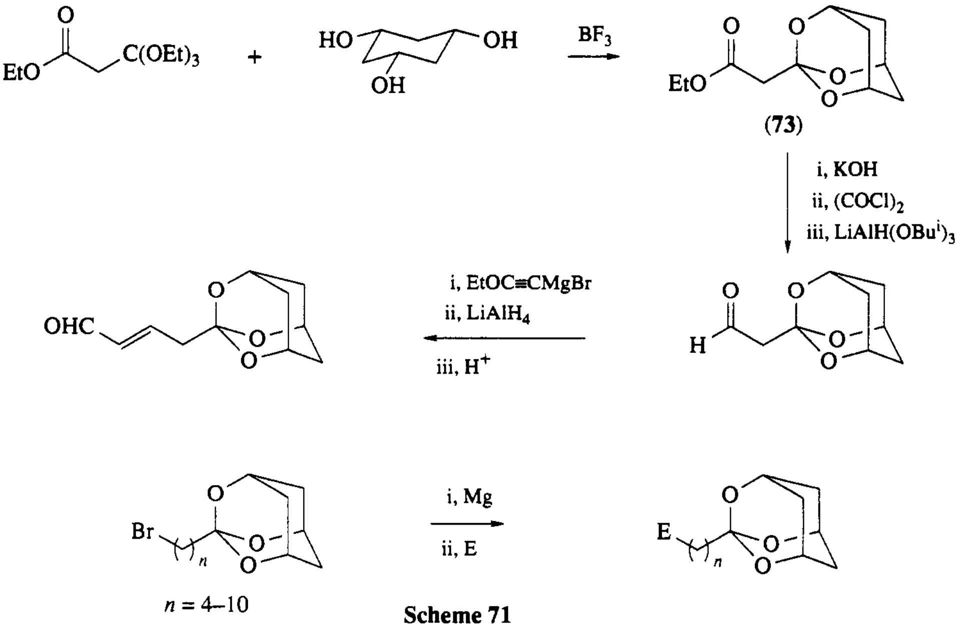
Scheme 70

3.1.5.4 Protection of Carboxylic Groups in Organometallic Transformations

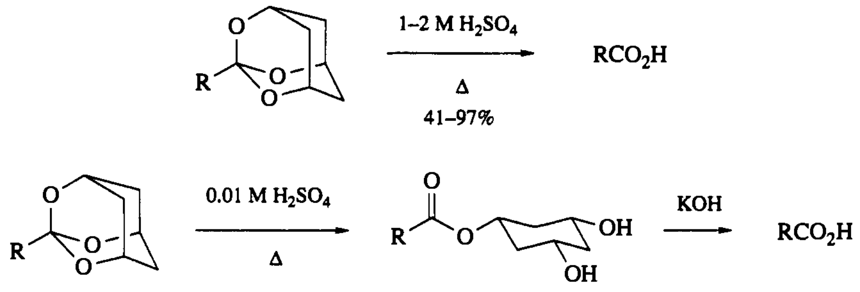
Carboxylic acids and esters frequently must be protected against the attack of organometallic reagents, *e.g.* metal alkyls and hydrides, and reducing agents like $LiAlH_4$. For this purpose they usually are converted to orthoesters, oxazolines or oxazoles.

Acyclic orthoesters can be used for the masking of carboxylic acids; however, they are very sensitive to hydrolysis and are affected by Grignard reagents. Therefore, the more stable 3,4,10-trioxa-3-adamantyl group (**73**), derived from *cis*-phloroglucit (*r*-1,*c*-3,*c*-5-trihydroxycyclohexan) and orthocarboxylic acid trimethyl or triethyl esters, was introduced (see Scheme 71).[288] It is resistant to treatment with Grignard compounds, reduction with $LiAlH_4$, and can be converted to Grignard reagents,[289] ready for reactions with various electrophiles like acetaldehyde, methyl vinyl ketone, alkyl halides and epoxides (Scheme 71). For the hydrolysis of these orthoesters to the free carboxylic acids heating with 1–2 M H_2SO_4/dioxane (1:1) is necessary (Scheme 72). Alternatively, heating with 0.01 M H_2SO_4 for 10 min leads to 3,5-dihydroxy-1-cyclohexyl esters, which can then be saponified with base.

The problems with the inaccessibility and relatively slow cleavage rates of these adamantoid orthoesters were overcome by the introduction of cyclic ortho esters (**74**) derived from 2,2-bishydroxymethyl-1-propanol.[290] They are prepared either from trialkylorthoesters by ortho ester exchange[290] or, most advantageously, directly from the carboxylic acids by esterification with 3-methyl-3-hydroxyethyl oxetane (obtained from the triol $MeC(CH_2OH)_3$ and subsequent rearrangement with $BF_3{\cdot}OEt_2$; Scheme 73).[291] The oxabicyclo[2.2.2]octyl ortho esters (OBO esters; **74**) thus obtained are still stable during chromatography but can be readily removed in high yields by subsequent treatment with acid (pH 3) and a base to cleave the intermediately formed ester.[290,292] The advantageous properties of this ortho ester

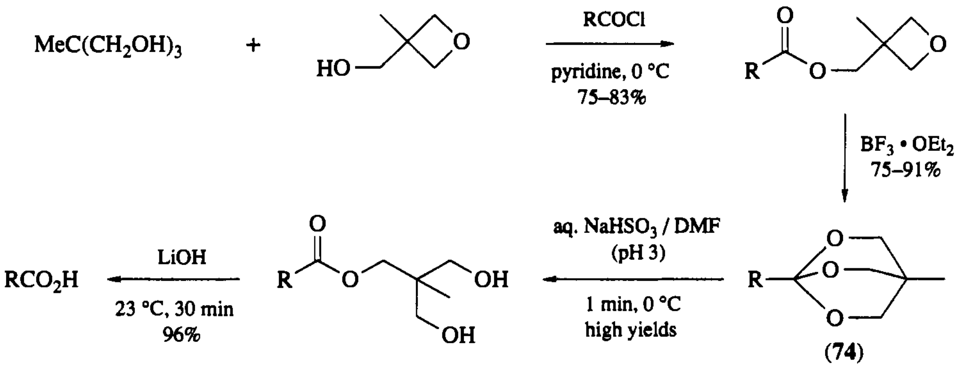


Scheme 71



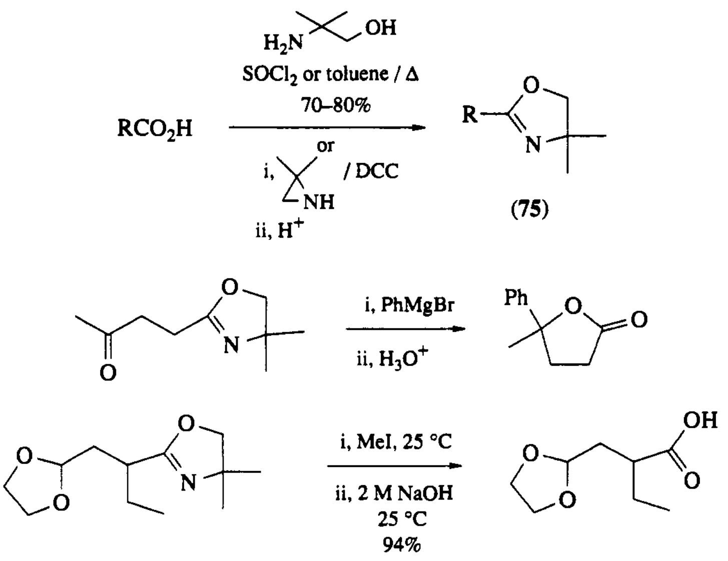
Scheme 72

protecting group were, for instance, exploited in the synthesis of a metabolite of prostaglandin D_2,[293] the eicosanoid hybridalactone[292] and ginkgolide B.[294]



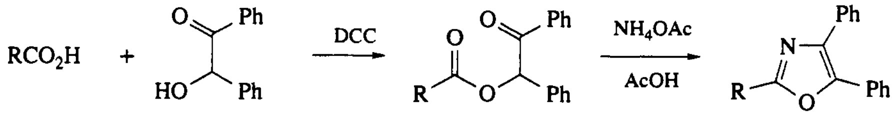
Scheme 73

Oxazolines (**75**) may be formed from carboxylic acids by condensation with either 2-amino alcohols or aziridines (Scheme 74). They are stable to Grignard reagents and to $LiAlH_4$ and are cleaved either by acid-catalyzed hydrolysis or alcoholysis.[295] A disadvantage of the oxazolines is that they retain reactivity towards alkylating reagents. On the other hand, this forms the basis for an alternative deprotection in the presence of acid sensitive structures. After methylation the oxazolines can be hydrolyzed to the free acids with 2 M NaOH (94% yield).[296]

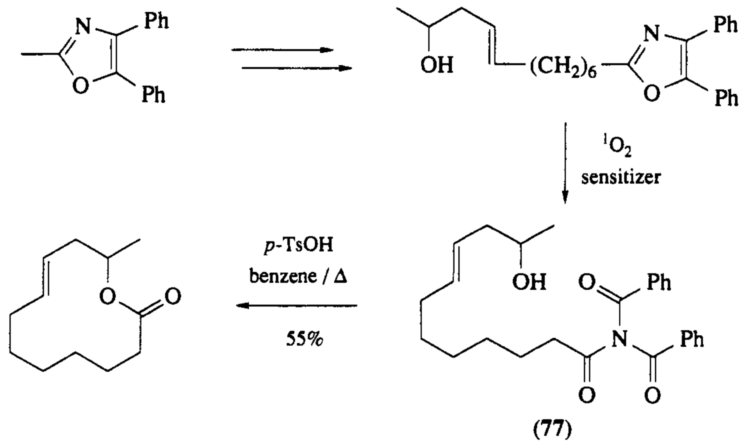


Scheme 74

4,5-Diphenyl oxazoles (**76**)[297] may be prepared from carboxylic acids and benzoin by esterification, followed by treatment with ammonium acetate in glacial acetic acid in overall yields of 80–85% (Scheme 75). The heterocycles thus obtained can be functionalized in numerous ways (alkylations, Friedel–Crafts reactions, reduction with $NaBH_4$, *etc.*). If desired, the original carboxylic function may be regenerated in a reaction with singlet oxygen in high yields. In fact, what is obtained from this reaction is a triamide (*e.g.* **77**) which represents an activated acylating agent and which may be used directly for lactonizations and lactam formations. As an example for this conversion a synthesis of recifeiolide is detailed in Scheme 76.



Scheme 75



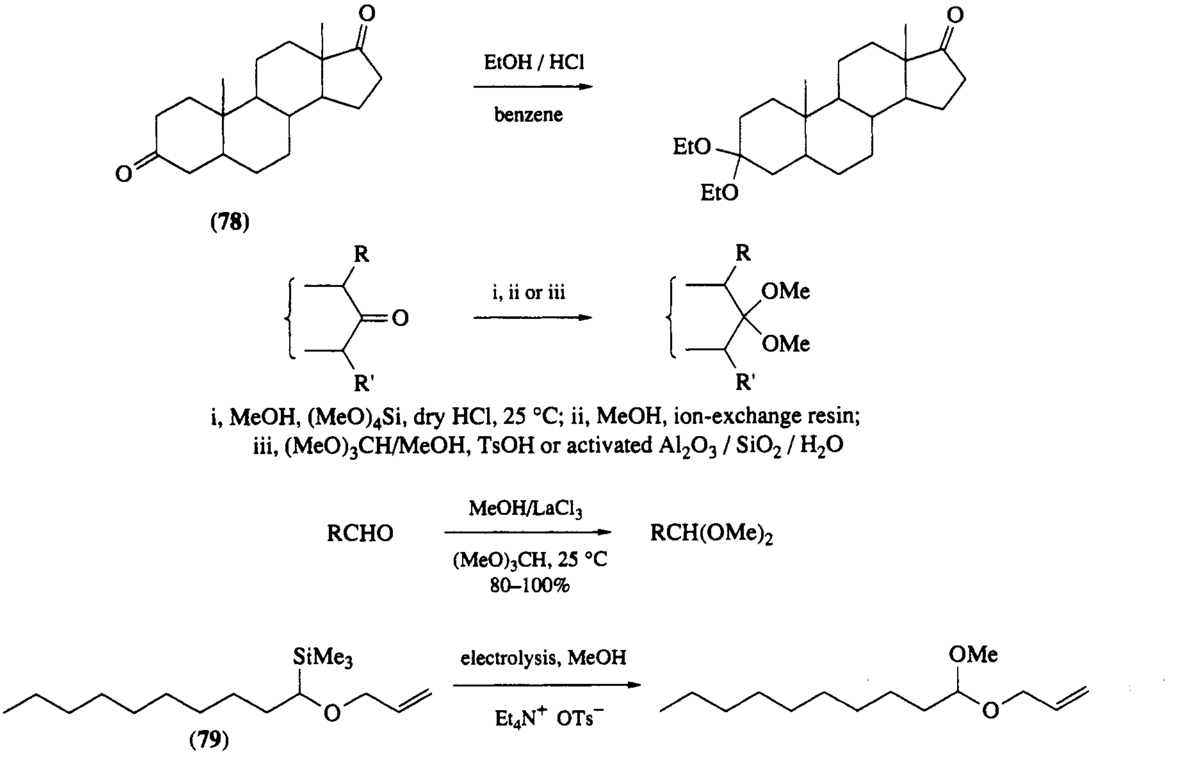
Scheme 76

3.1.6 CARBONYL-PROTECTING GROUPS[5,298]

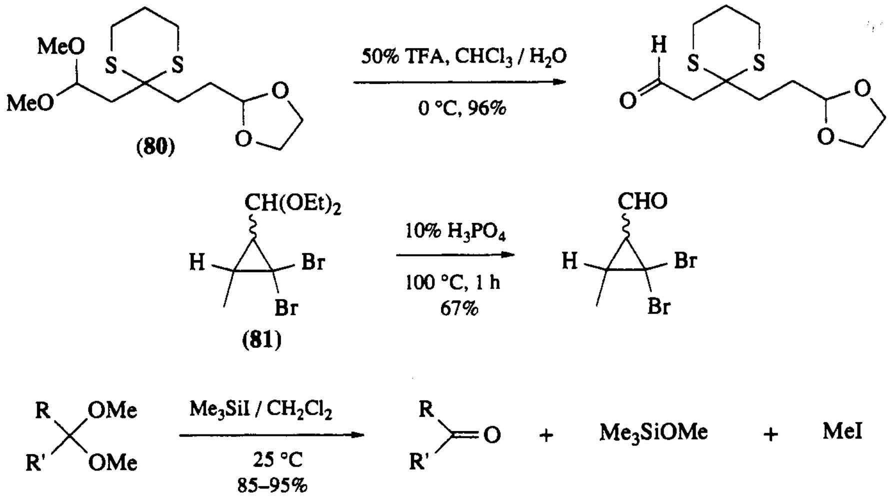
In the course of complex syntheses, for instance in total syntheses of natural products, carbonyl groups often must be protected against nucleophilic attack, *e.g.* by organometallic compounds and strong bases, reduction, and sometimes also oxidation. To achieve this aim, the carbonyl functions generally are transformed into suitable acetals, thioacetals, hydrazones, oximes and cyanohydrins. In addition, they can be converted to enamines, enol ethers and silylenol ethers. In these derivatives the carbonyl function is desensitized towards attack under neutral and basic conditions. Most of the protecting groups can be removed by treatment with acids or Lewis acids. In particular, the oxygen acetals and ketals are readily cleaved by acidic hydrolysis and are stable to oxidants and heavy metal ions. In contrast, thio-acetals and -ketals are cleaved by a wide range of oxidants and, under neutral conditions, by mercury(II), silver(I) or copper(II) salts. Due to the pronounced differences in reactivity between the different carbonyl groups, in many cases a reactive C═O group may be protected selectively in the presence of less reactive ones.

3.1.6.1 Acyclic and Cyclic Acetals and Ketals

Dialkyl acetals and ketals can easily be formed from carbonyl compounds with alcohols under acidic conditions. Some representative examples for the great variety of methods available for this transformation are given in Scheme 77. As is demonstrated, both simple alcohols themselves or formic acid ortho esters can be used for acetal formation in the presence of hydrochloric acid,[299] toluenesulfonic acid[300] or activated alumina (Montmorrilonite clay K-10).[301] Owing to different carbonyl reactivities, regio- and chemo-selective differentiation is often realizable, as has been shown, for example, on androstane-3,17-dione (**78**). Acid-catalyzed acetalization selectively delivers the 3-ketal, whereas the sterically hindered 17-carbonyl function remains unaffected. Under neutral conditions the reactions are promoted by catalysis with lanthanide ions.[302] An interesting acetal formation consists of the electrochemical oxidation of α-silyl ethers, *e.g.* (**79**).[303] The classical method for the cleavage of acetals is acidic hydrolysis.[304] With trifluoroacetic acid the dimethyl acetal (**80**) is selectively hydrolyzed while the cyclic acetal and the dithioacetal remain intact.[304] The acid sensitivity of dimethyl or diethyl acetals, *e.g.* in (**81**), allows the regeneration of the carbonyl group even in the presence of a cyclopropane structure.[305] However, transacetalization[306] and, in particular, the cleavage with trimethylsilyl iodide[307] offer alternatives (Scheme 78).



Scheme 77

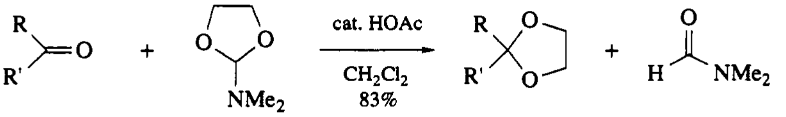


Scheme 78

More popular than the acyclic acetals are 1,3-dioxanes and 1,3-dioxolanes in carbonyl protection. A great variety of techniques, mainly based on the acid-catalyzed reaction of the respective diol with the carbonyl compound, were developed.[308] Recently an improved procedure was described in which trimethylsilyl chloride was used as the condensing reagent.[309] Particularly mild conditions are found in the transacetalization with 2-dimethylamino-1,3-dioxolane (**82**), which has been extensively used for the regioselective functionalization of steroid ketones (see equation 24).[310] As a rule, 1,3-dioxolanes and -dioxanes are more stable than acyclic acetals (see Scheme 78).[304] This has been exploited, for instance, in the synthesis of the manoalide analog (**84**) from the precursor (**83**; Scheme 79).[311] The hydrolysis of these acetals is usually carried out with dilute acid[312] or by acid-catalyzed transketalization, as for example in the synthesis of walburganal (**85**; Scheme 80).[314] As a general rule, for the hydrolysis of cyclic acetals it was found that 1,3-dioxanes derived from ketones hydrolyze faster than the corresponding 1,3-dioxolanes. For aldehyde derivatives the reversed order is commonly observed.[315] The acidolytic regeneration of ketones from their dioxolanes takes place under relatively mild conditions. Even acid sensitive structures, *e.g.* the cyclopropane in (**86**), can be conserved. This has been used in the synthesis of sirenine.[312] Since the dioxane and dioxolane protection are reliably stable to strong nucleophiles and bases, organometallic reactions can be performed on compounds protected in this way, without destruction of the blocked form (see, for example, the transformation of (**87**) to (**88**)[313] shown in equation 25). Much milder and nonacidic conditions for the deprotection can be applied if functionalized acetals and ketals are introduced. Thus, bis(2,2,2-trichloroethyl) acetals, 5,5-dibromo-1,3-dioxanes and 4-bromomethyl-1,3-dioxolanes can be removed with zinc in organic solvents.[316] The synthesis of the bis(trichloroethyl) acetals is favorably carried out by an acid-catalyzed exchange reaction with the corresponding dimethyl or diethyl acetals.[316a] From acyclic[317] and cyclic dibenzyl acetals and ketals, as for instance (**89**),[318] the carbonyl group can be regenerated by hydrogenation. Interestingly, the seven-membered cyclic dibenzyl acetal is removable with conservation of the cyclopropane, which is usually prone to hydrogenolytic ring opening.[318a] The cyclic benzyl-type acetal also proved to be an efficient carbonyl-protecting group in pheromone synthesis.[318b] In addition, 5-methylene-1,3-dioxanes[319] can be regarded as cyclic allyl ethers which are cleaved under mild conditions either after isomerization or with the aid of oxidizing reagents. Finally, the deprotection principle used for amino protection in the 2- and 4-Pyoc urethanes (see Section 3.1.2.1) has been adapted for the design of acetals being labile after methylation of the pyridine nitrogen (Scheme 81).[320]

3.1.6.2 Acyclic and Cyclic Dithioacetals and Dithioketals

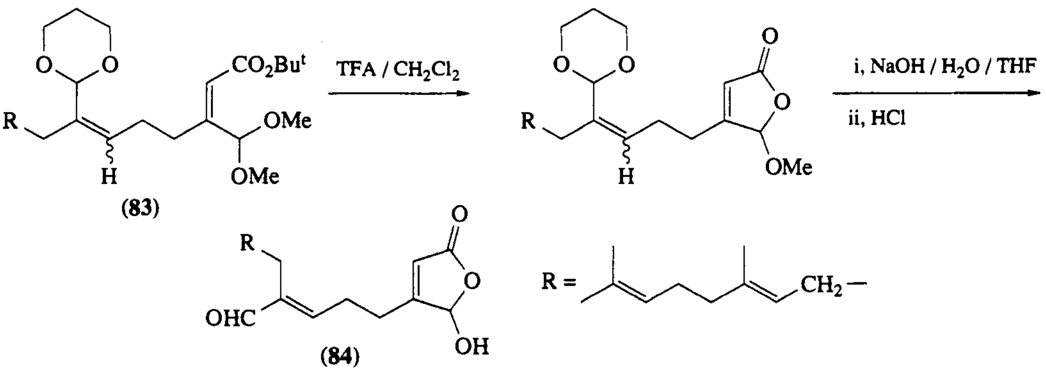
Carbonyl functions often are protected as thioacetals, because these derivatives are stable to acids and bases. Dithio-acetals and -ketals generally are prepared by reaction of the carbonyl compound with a thiol in the presence of an acid catalyst. This transformation has been used in carbohydrate chemistry for a long time to lock aldoses in their acyclic forms (see equation 26).[322] In recent years, this blocking principle for carbohydrates has been exploited in several chiral pool syntheses.[323] Several other methods for



(24)

(**82**)

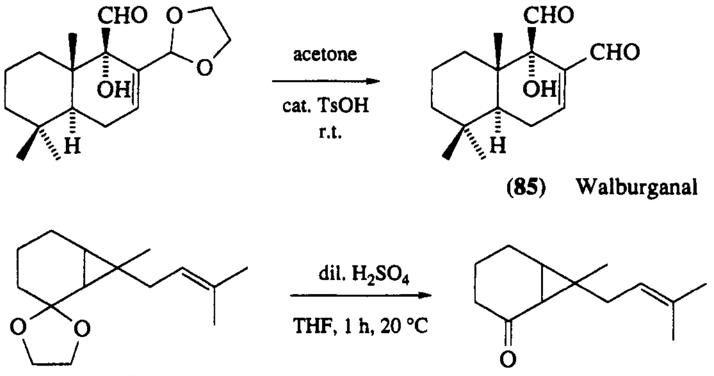
R–R' = C$_3$ keto steroid



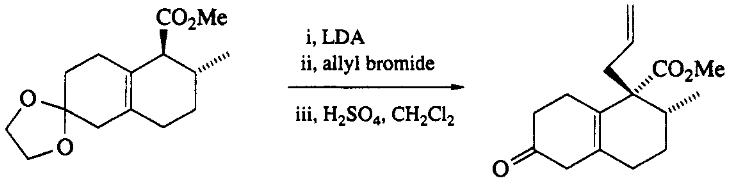
(**83**)

(**84**)

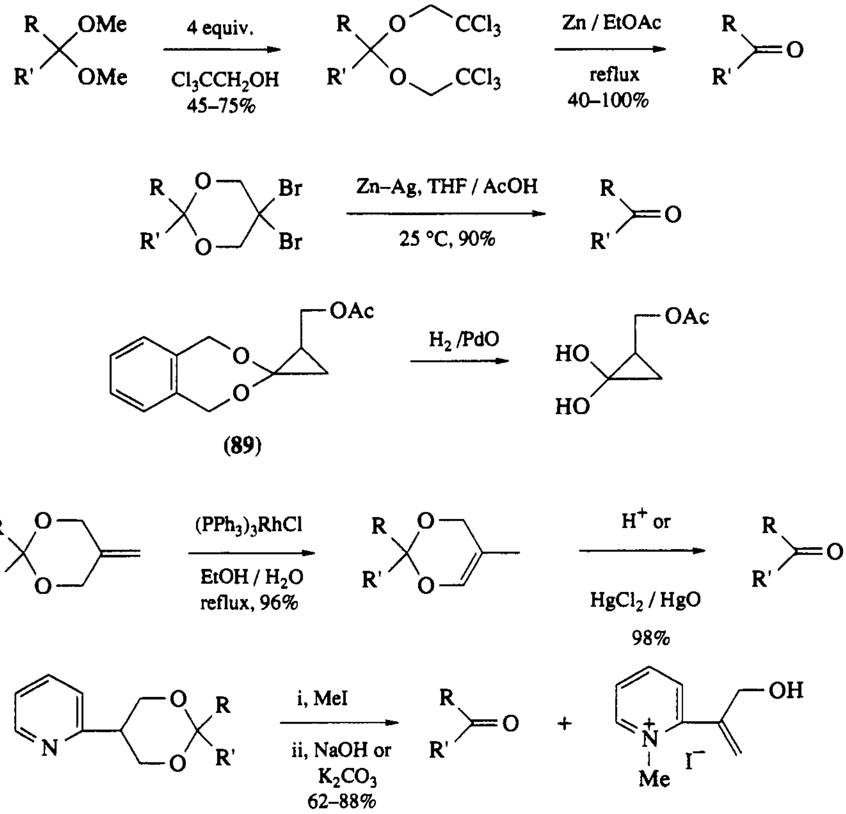
Scheme 79



Scheme 80

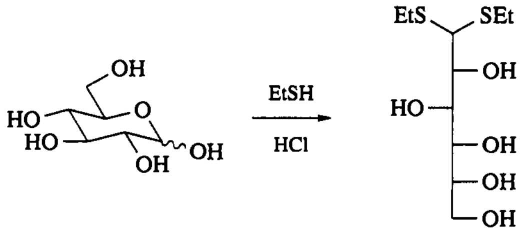


(87) (88) (25)

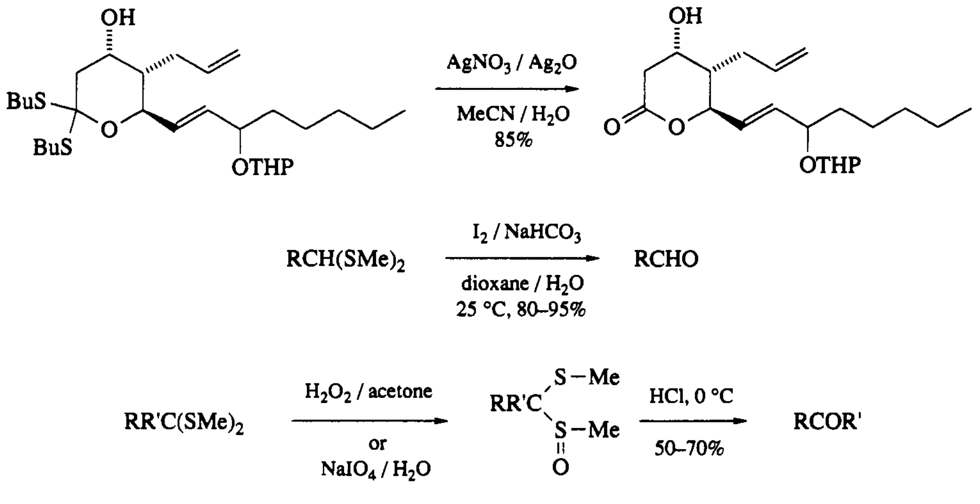


Scheme 81

the execution of this reaction are available,[5,321] including the use of $BF_3{\cdot}OEt_2$ or $ZnCl_2$ as Lewis acids, the application of thiol esters of boric acid and a combination of trimethylsilyl chloride with thiols. In general, the thioacetals are cleaved by the action of silver, copper or mercury salts.[324] Electrophilic attack or oxidation of the sulfurs are also recommended.[321,325] Some representative examples are given in Scheme 82.



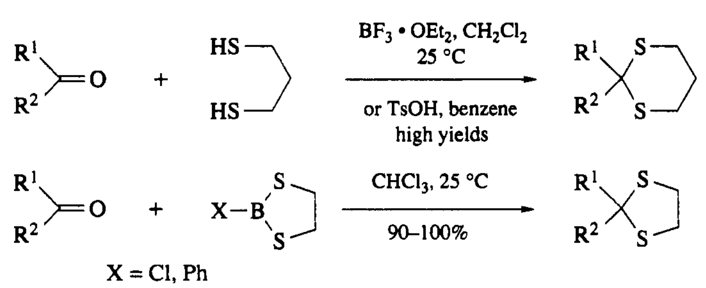
(26)



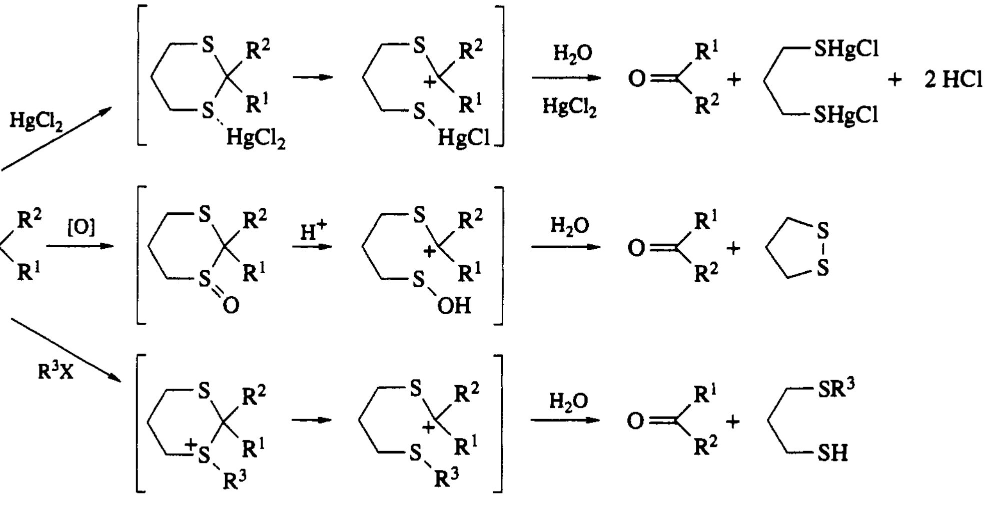
Scheme 82

Very popular and widely used protected forms of aldehydes and ketones are found in the dithiolanes and dithianes. The use of these blocking groups has raised a new strategy for electrophilic substitutions at the carbonyl carbon. This method was developed and introduced by Corey and Seebach[326] and is termed 'umpolung of the reactivity'.[321,326,327] The cyclic dithioacetals are easily formed from the carbonyl compounds and the dithiols under the influence of Lewis acids, acids and boron reagents (Scheme 83). Several methods are available for the subsequent liberation of the carbonyl groups from these very acid-stable ketals and acetals. They all are based on the conversion of the sulfurs to better leaving groups, followed by hydrolysis (Scheme 84).[321] The modification of the sulfides can be achieved by complexation with thiophilic heavy metal ions like Ag^+, Hg^{2+} and Cu^{2+}, by oxidation of the sulfurs, with, *e.g.* iodine, halosuccinimides, ammonium cerium nitrate, $NaIO_4$, chloramine T, singlet oxygen, and also by their conversion to sulfonium salts through alkylation with methyl iodide or oxonium salts.[321] Finally, transthioacetalization under weakly acidic conditions is successful (Scheme 85).[328]

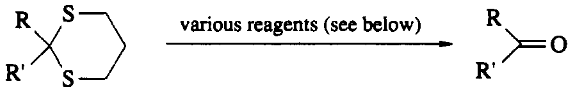
The dithiane method is extensively applied in the construction of complex molecules. Some representative examples[329] are given in Scheme 86. The diastereoselective attack of the 2-methyl-1,3-dithianyl anion at the *si*-face of the ulose (**90**) is a crucial step in a synthesis of methylaldgaroside B (**91**).[329a]



Scheme 83

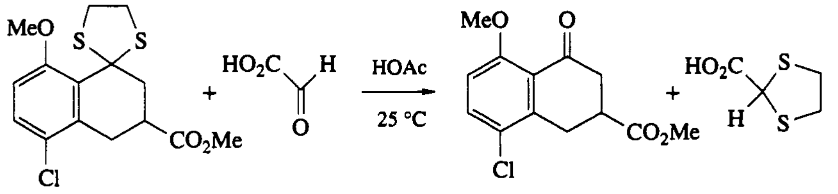


Scheme 84



$CuCl_2$ / CuO, acetone, Δ, 85%
$AgNO_3$, EtOH / H_2O, 50 °C, 55%
HgO, BF_3, THF / H_2O, 86%
NBS, H_2O / MeCN or acetone, 70–100%
I_2, DMSO, 90 °C, 75–85%

isopentyl nitrite, 65%
$Ce(NH_4)_2(NO_3)_6$, MeCN / H_2O, 70–87%
O_2 / $h\nu$, 60–80%
MeI, MeOH / H_2O, Δ, 60–80%
$Et_3O^+BF_4^-$, 3% aq. $CuSO_4$, 81%

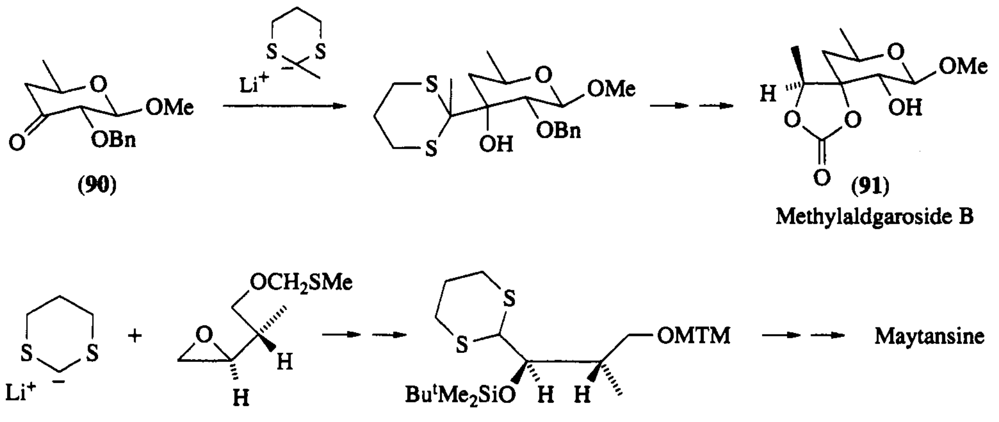


Scheme 85

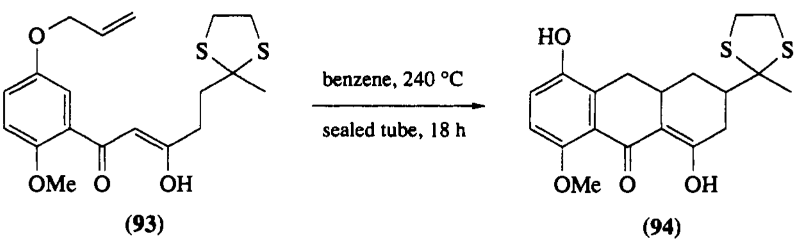
The second example involves the diastereoselective reaction of the dithianyl anion with the epoxide (**92**) to achieve the construction of maytansine.[329b] However, not only the opportunities offered by the umpolung concept are of preparative interest. The high stability of the cyclic dithioacetals is also a very valuable property for syntheses of complex compounds. This has recently been demonstrated in the construction of 11-deoxydaunomycin and its analogs.[330] The hydroquinone monoallyl ether derivative (**93**) contains a carbonyl function protected as the dithiolane, whereas the enolized β-dicarbonyl structure is underivatized (equation 27). At 240 °C this compound undergoes a Claisen rearrangement which induces a cascade of reactions, including an intramolecular Diels–Alder reaction and a double bond isomerization. The tricyclic compound (**94**) thus formed serves as a key intermediate in the synthesis of daunomycin derivatives.[330] After oxidation of ring B, the regeneration of the ketone from the dithiolane allows the annelation of the fourth ring to furnish the complete daunomycin skeleton.

1,3-Oxa-thiolanes and -thianes combine the properties of oxygen and sulfur acetals. Thus they can be cleaved with mercury salts and are also more labile towards acids than the sulfur analogs.[331] In addition, oxazolidines, imidazolidines and thiazolidines can be used for the protection of aldehydes and ketones;[5] however, they have not found a broader use in protecting group chemistry.

An acid-resistant protecting principle for carbonyl groups consists of the α,α-dicyanoethylene derivatives (**96**). They are obtained from carbonyl compounds, *e.g.* pyrrole aldehydes (**95**), by Knoevenagel condensation with malodinitrile.[332] In general, mineral acids and Lewis acids, which are used in Friedel–

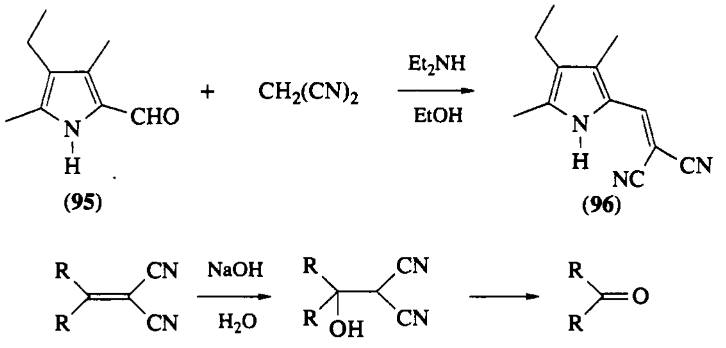


Scheme 86



(27)

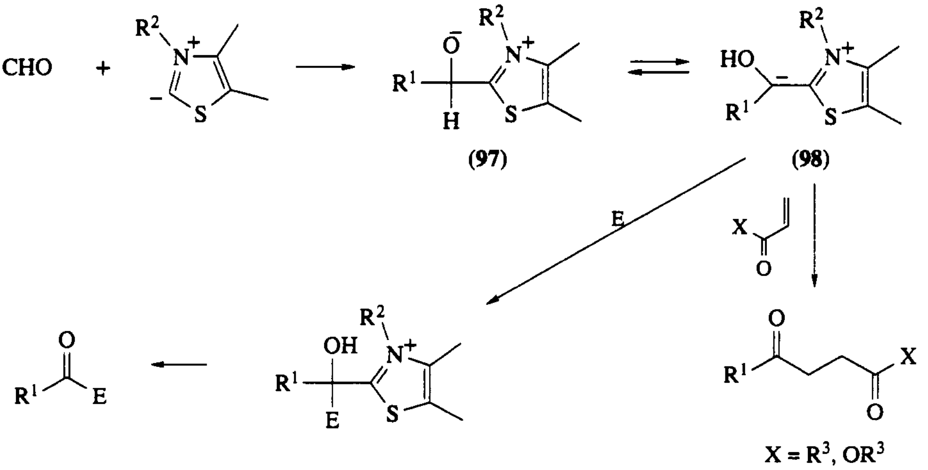
Crafts reactions, and oxidizing reagents like chlorine do not destroy this protection. The regeneration of the carbonyl functions has to be carried out with concentrated aqueous alkali and proceeds as a tandem hetero Michael addition/retro aldol reaction (Scheme 87). Although these drastic conditions set a limit to the general application of this protecting group, it has successfully been used in porphyrine total syntheses.[332]



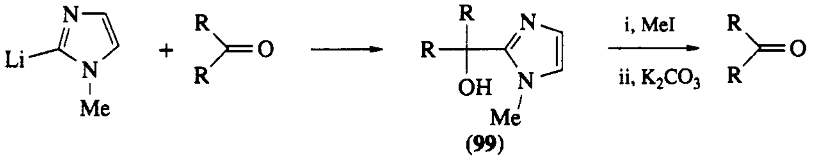
Scheme 87

3.1.6.3 *O*-Substituted Cyanohydrins[147]

Cyanohydrins of aldehydes and ketones may be considered as protected forms of the carbonyl compounds. If they are further *O*-alkylated with vinyl ethers, the acetals formed constitute base resistant protection. Such *O*-acetals and aldehyde cyanohydrins have been subjected to deprotonation and umpolung transformations.[333] Actually, the benzoin condensation[334] has to be considered as the first reaction based on umpolung at the carbonyl carbon. In benzoin condensations the cyanide ion can further be substituted by thiazolium salts.[335] Their anions react with aldehydes to give the aldol-type adducts (**97**). After the following crucial transfer of the proton from the carbonyl carbon to the oxygen (enabled by the electron-withdrawing effect of the thiazolium group), electrophiles can attack. In contrast to the cyanide-catalyzed reaction, aliphatic aldehydes can be used here. The preparative value of this group was increased still further when it could be demonstrated that α,β-unsaturated ketones, esters and nitriles undergo vinylogous addition with the intermediate (**98**). Thus, they deliver 1,4-diketones, keto esters and keto nitriles (Scheme 88).[336] The principle demonstrated in these chemical transformations is also of fundamental biological relevance. For example, the reaction of the intermediate, corresponding to (**98**), formed from pyruvate (acetaldehyde) and thiamine pyrophosphate (vitamin B_1) with lipoic acid is a key step in the pathway which links glycolysis and the citric acid cycle. A protecting group related to the thiazolium adduct has recently been found in the hydroxyalkylation products (**99**) of *N*-methyl imidazole.[337] After activation by *N*-alkylation, the carbonyl compounds are regenerated by treatment with aqueous base (see Scheme 89).



Scheme 88



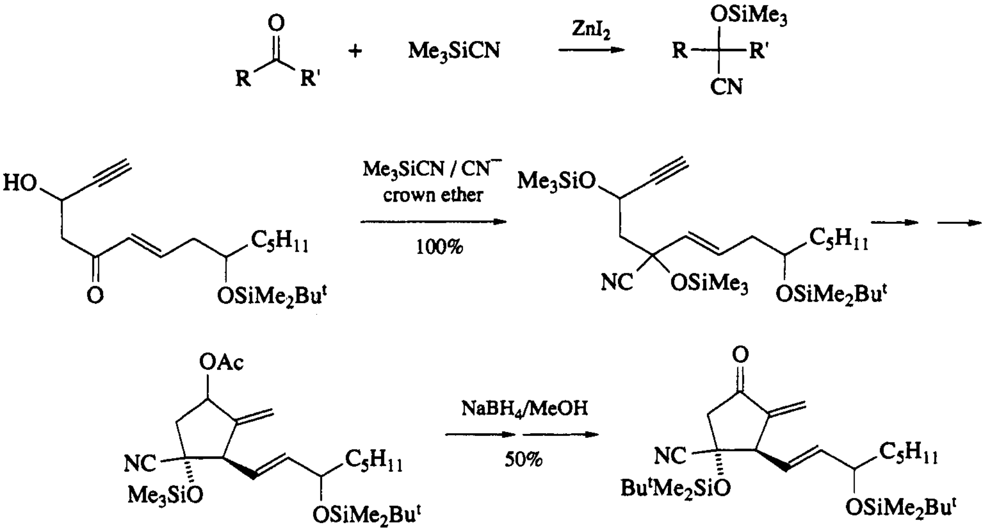
(**99**)

Scheme 89

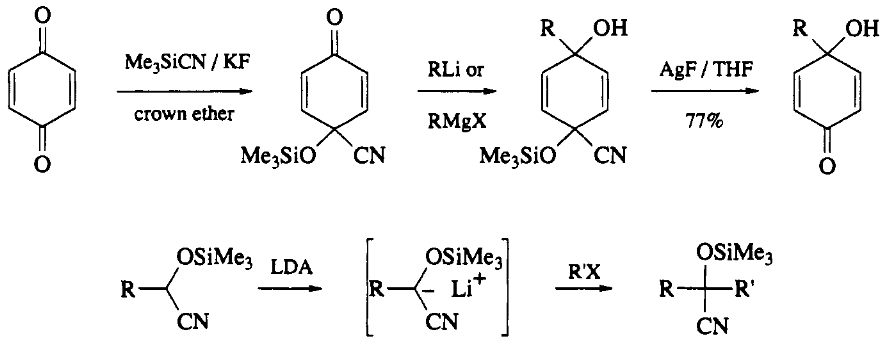
Aldehydes and ketones can also be protected as *O*-trimethylsilyl cyanohydrins by reaction with trimethylsilyl cyanide under catalysis with zinc iodide, cyanide ions, tetra-*n*-butylammonium fluoride or triphenylphosphine.[338] The resulting silyl cyanohydrins are stable to sodium hydride, amines, hydrogenation with Lindlar's catalyst, $NaCNBH_3$, CrO_3/pyridine and thionyl chloride and can therefore be advantageously used in multistep synthesis. An example which shows a synthesis of partial structures of prostaglandins is depicted in Scheme 90.[339] Here, the cleavage is carried out with $NaBH_4$ in methanol. *O*-Trimethylsilyl cyanohydrins are particularly useful for the monoprotection of *p*-benzoquinones,[340] because they allow the functionalization of the remaining unprotected carbonyl group, *e.g.* by addition of organometallic reagents (Scheme 91). Furthermore, if an α-hydrogen is present, the silylated cyanohydrins offer an additional possibility for umpolung of carbonyl groups, *e.g.* alkylation of the former carbonyl carbon (Scheme 91).[340] The reformation of the carbonyl groups from the protected forms can usually be achieved in dilute aqueous acid or base and with fluoride ions, *e.g.* silver fluoride in aqueous THF.

3.1.6.4 Substituted Hydrazones and Oximes[5]

For decades oximes and hydrazones have been used for the derivatization of carbonyl compounds and are mainly applied for carbonyl group characterization in analytical procedures. However, they can also be applied as viable protecting groups in complex reaction schemes. For instance in the synthesis of erythronolide A[341] a carbonyl group had to be converted to an oxime to allow the selective removal of the remaining isopropylidene protecting group without side reactions. The reconversion of the oxime to the carbonyl compound proceeds by *N*-nitrosation (Scheme 92). The previously attempted removal of the

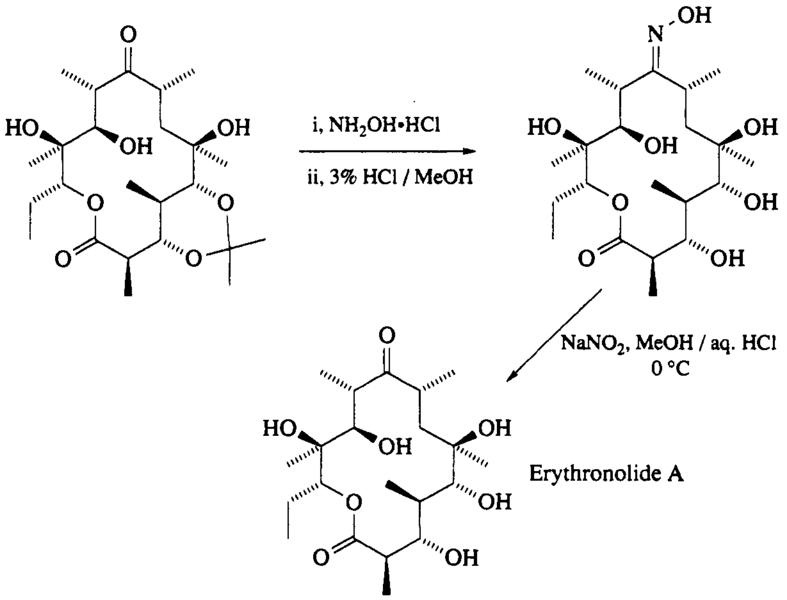


Scheme 90



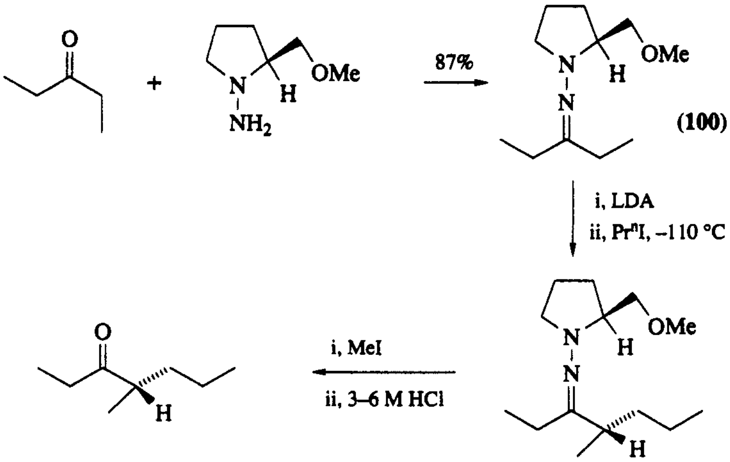
Scheme 91

isopropylidene protecting function in the presence of the unprotected keto group could not successfully be carried out. Oximes are mainly cleaved by oxidation, reduction or hydrolysis.



Scheme 92

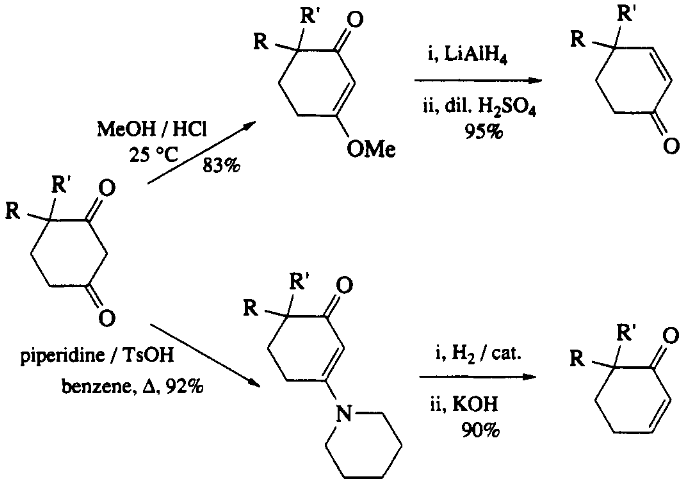
N,*N*-Dialkylhydrazones are often converted into the carbonyl form by a variety of oxidative methods. The respective compounds (like **100**) shown in Scheme 93, derived from proline-based systems (RAMP and SAMP), are widely used as potent chiral auxiliaries and have provided a very versatile method for the diastereoselective α-alkylation of ketones.[342] SAMP and RAMP hydrazones can be cleaved with O_3, by reductive techniques and by hydrolysis with strong acids.



Scheme 93

3.1.6.5 Monoprotection of Dicarbonyl Compounds

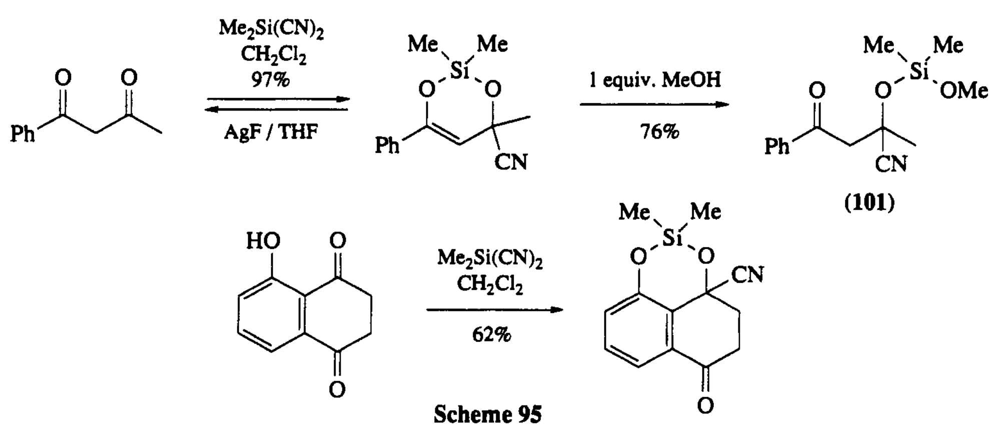
β-Diketones often are protected as enol ethers or enamines and these selectively functionalized compounds may be subjected to complementary transformations (Scheme 94).[343] Also silylenes can be prepared from diketones and β-hydroxycarbonyl compounds by reaction with dimethyldicyanosilane.[344] Naturally, these blocking groups are relatively sensitive to hydrolysis. On the other hand, partial solvolysis can open a route to monoprotected derivatives (*e.g.* **101**), usually blocked at the sterically less demanding carbonyl function as *O*-silyl cyanohydrins (see Scheme 95). Deprotection is finally achieved with silver fluoride in THF.



Scheme 94

3.1.7 PROTECTION OF ALKENES AND ALKYNES[345]

Unsaturated carbon–carbon bonds are central structural elements of numerous chemical entities. The construction of these bonds can be carried out by a variety of reactions. In many chemical transform-



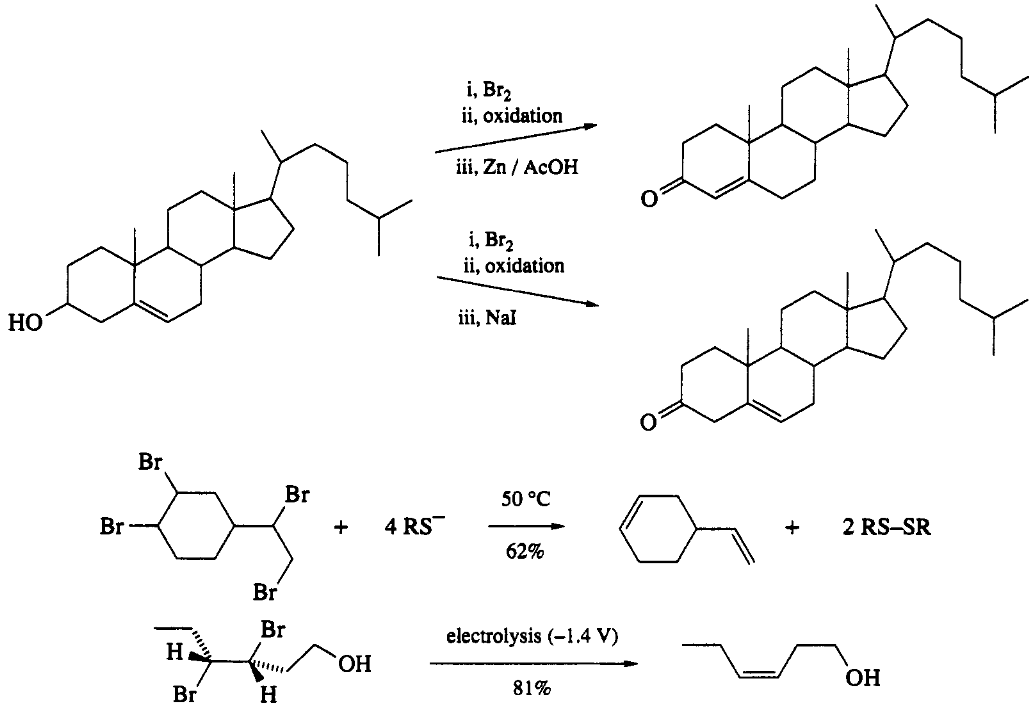
Scheme 95

ations a special masking of double and triple bonds is not necessary. However, the high reactivity of π- and π^*-orbitals of these bonds, particularly against soft electrophiles or nucleophiles, makes them sensitive to oxidation, reduction and addition processes. Although modern mild variants of such reactions which were harmful to double and triple bonds have been introduced in the last decades, this reactivity still demands effective methods for multiple bond protection. In most cases this goal can be achieved by conversion of alkenes to addition products from which the double bonds can be regenerated. Alternatively, complexation by transition metals can also be utilized for the temporary protection of alkenes, 1,3-dienes and alkynes.

3.1.7.1 Protection of Alkenes[345,346]

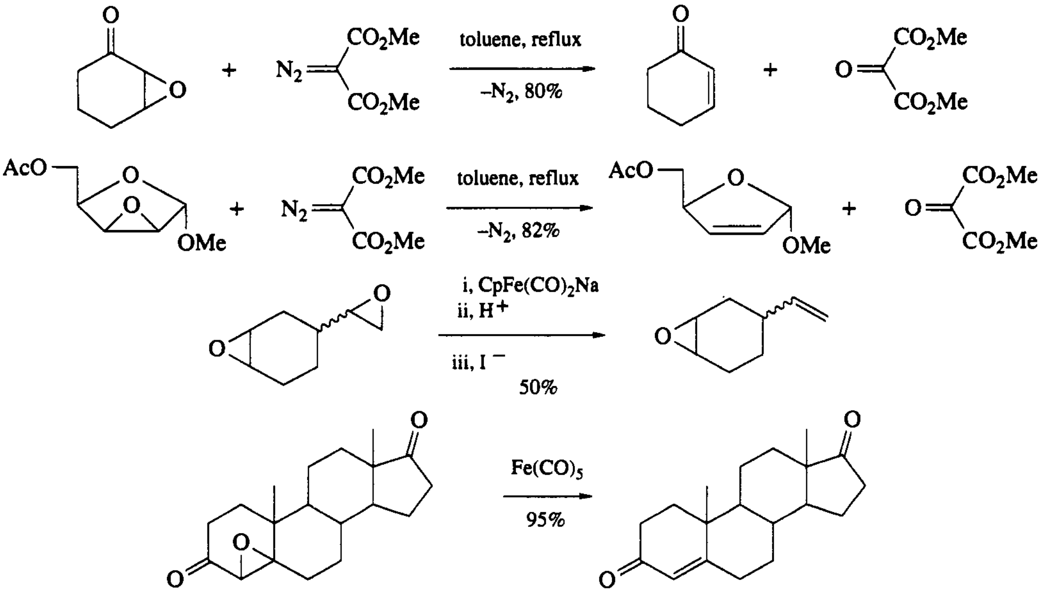
The ease and the stereospecificity of bromine addition to alkenes, together with the possibility of regeneration of the double bond under conservation of the original stereochemistry, render the bromination reaction one of the most common methods for protection of alkenes. The dibromides of alkenes are conveniently obtained by using bromine itself or reagents like pyridinium hydrobromide perbromide ($C_5H_5N{\cdot}HBr_3$).[347] These bromo adducts are, for instance, stable during reactions with ozone, CrO_3, $KMnO_4$ and OsO_4. They are also efficiently protected forms during addition reactions and hydrogenolysis.[345] For the regeneration of the double bond numerous methods are available,[345,348,349] *e.g.* treatment of the dibromides with metals[345] (zinc, magnesium, sodium, lithium or sodium amalgam, iron graphite[350]), metal ions of sufficient electron-donating potential[345,351] (Cr^{II}, Fe^{II}, Ti^{II}, Co^{II}, Ni^{II}, Sn^{II}) and various nucleophilic reagents[345] (halides,[352] thiolates,[353] selenides,[354] tellurides,[355] phosphites, phosphines, $LiAlH_4$, Grignard reagents). Also electrochemical methods are often effective.[356] Some selected examples for the protection of double bonds in the form of dibromides and for their reconversion to the alkenic structures under different conditions are shown in Scheme 96. Most of these methods are stereospecific and proceed through an *anti* elimination of the bromides. The most widely employed reagent for this conversion is zinc dust. The reaction is usually carried out in acetic acid or in ethanol.[345,346,357] However, problems frequently arise by possible side reactions of the solvent with the substrate (*e.g.* acetylation of alcohols). In these cases the other methods described above offer viable alternatives to achieve the synthetic goals. Problems caused by debromination at higher temperatures or instability of the dibromides in a reduction step can be overcome by employing dichlorides[358] or halohydrins[359] as protecting groups. In addition halohydrin acetates may serve as the blocked forms. They are obtained by treatment of the alkene with aqueous *N*-bromosuccinimide and subsequent acetylation. They are relatively stable to acid, mild alkali and oxidation with chromic acid. The alkene can be regenerated from the β-haloalkyl acetate by using a zinc–copper couple.[360]

Alkenes are converted to epoxides by oxidation with peroxy acids, and thereby they are protected with regard to certain chemical transformations. Alkaline hydrogen peroxide selectively attacks enone double bonds in the presence of other alkenes. The epoxides can be transformed back to alkenes by reduction–dehydration sequences[361] or using triphenylphosphine,[362] chromous salts, zinc, or sodium iodide and acetic acid.[363] A more advantageous and fairly general method consists, however, of the treatment of epoxides with dimethyl diazomalonate in the presence of catalytic amounts of binuclear rhodium(II) carboxylate salts.[364] This deoxygenation proceeds under neutral conditions and without isomerization or cyclopropanation of the liberated alkene (Scheme 97). Furthermore, epoxides can be converted to alkenes with the aid of various metal carbonyl complexes. Thus, they may be nucleophilically opened with



Scheme 96

$CpFe(CO)_2^-$ Na^+ and after treatment with acid and decomplexation with sodium iodide in acetone the free alkene is isolated (Scheme 97).[365] In addition, certain metal carbonyls like $Co_2(CO)_8$,[366] $Fe(CO)_5$[367] and $Mo(CO)_6$[368] effectively deoxygenate epoxy-esters and -ketones. Also low-valent tungsten species[369] and metallocenes[370] may be used for the regeneration of alkenes.



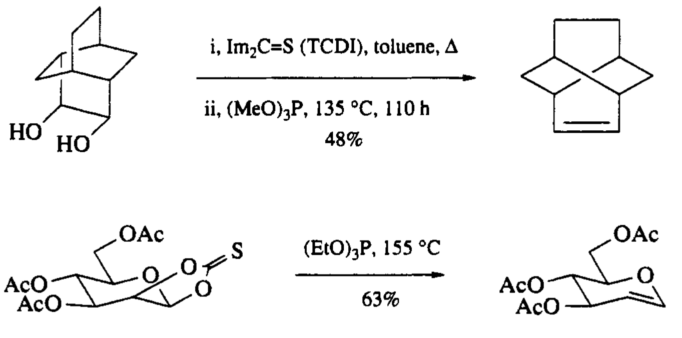
Scheme 97

1,2-Diols are easily accessible from alkenes by the reaction with osmium tetroxide, and constitute another protection of the double bond since a variety of methods for the reformation of the alkenes from them is available.[371] Among the important methods which proceed stereospecifically, the desulfurization of 2-thioxo-1,3-dioxolanes (*e.g.* **102**, Corey–Winter reaction),[372] the acid-catalyzed decomposition of

2-ethoxy- or 2-dialkylamino-1,3-dioxolanes (Eastwood procedure)[373] and the base-induced fragmentation of 2-phenyl-1,3-dioxolanes[374] must be mentioned. In the Corey–Winter method cyclic thioxocarbonates, readily prepared from vicinal diols by reaction with thiophosgene or *N*,*N*′-thiocarbonyldiimidazole, are fragmented by heating with trivalent phosphorus compounds, commonly with trialkyl phosphites (Scheme 98). Although this transformation requires prolonged heating at elevated temperatures and, occasionally, undesired side reactions are observed, it often is superior to the other methods. Thus, it can be advantageously used for the preparation of unsaturated sugars (*e.g.* **103**). However, bicyclo[2.2.1]hept-2-enes and related alkenes cannot be synthesized by this method. For their construction the thioxocarbonates can instead be decomposed with other reagents (Raney Ni, $Fe(CO)_5$, Ni^0 complexes) in good yields.[371] In the Eastwood deoxygenation, vicinal diols are treated with ethyl orthoformate at elevated temperatures (100–180 °C), followed by continued heating at higher temperatures (160–220 °C) in the presence of a carboxylic acid. In this reaction sequence, 2-ethoxy-1,3-dioxolanes (**104**) are formed initially. In the following acid-catalyzed reaction they eliminate ethanol and the resulting carbocation captures the carboxylate. Finally rearrangement to the desired alkene takes place (Scheme 99). Lower reaction temperatures are needed if first 2-dialkylamino-1,3-dioxolanes are formed by reaction of the diols with dimethylformamide dimethyl acetal. In the presence of acetic anhydride or after alkylation with methyl iodide the alkenes are obtained at temperatures around 90–115 °C. The reaction even proceeds at 20–50 °C if a combination of trifluoromethanesulfonic anhydride with diisopropylethylamine is used (Scheme 99).[375] The mechanism proposed for this reaction involves the attachment of the anhydride at the nitrogen and the subsequent formation of a nitrogen ylide intermediate which fragments to the alkene. The Eastwood procedure possesses the advantage of being a one-pot alkene synthesis, but the strongly electrophilic conditions and the high temperatures usually required are limiting for its application. The third procedure mentioned, the rearrangement of 2-phenyl-1,3-dioxolanes, requires the use of *n*-butyllithium. This circumstance makes the method inapplicable to many substrates and, consequently, it has found only a few applications in organic synthesis. In addition to these fairly stereospecific alkene syntheses several other procedures are available for the formation of a double bond from 1,2-diols.[345] Among them are the reduction–elimination of cyclic phosphates and phosphoramidates,[376] as well as titanium- and tungsten-mediated deoxygenations (Scheme 100).[377] Also, the treatment of vicinal sulfonate esters (*e.g.* **105**) with nucleophiles (Scheme 100, Tipson–Cohen reaction),[378] which is often used in carbohydrate chemistry, the reductive elimination of vicinal dimesylates[379] and the radical decomposition of vicinal dixanthates (*e.g.* **106**) induced by tri-*n*-butyl tin hydride[380] allow the regeneration of alkenes from vicinal diols (Scheme 100). The latter reaction occurs under neutral and relatively mild conditions and gives predominantly the more stable isomer of the alkene. This method is also mainly applied in the construction of unsaturated carbohydrates.

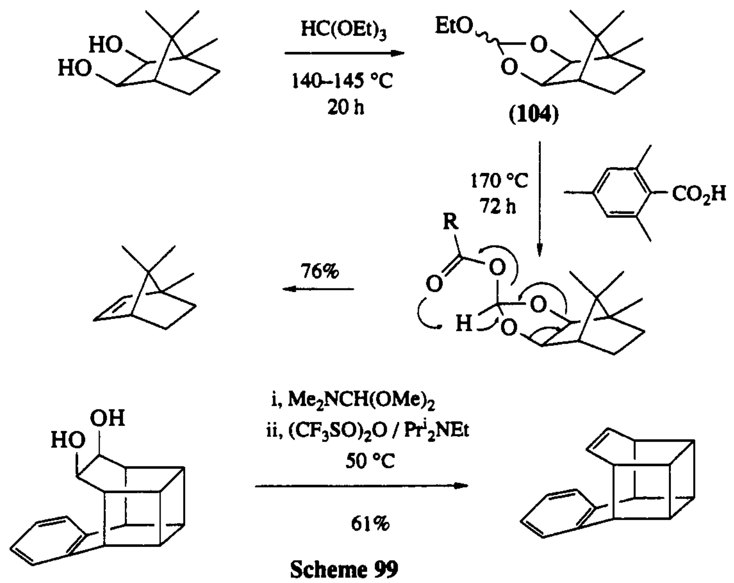
The double bonds of enones easily undergo Michael additions and this may be used for their temporary masking. Thus dimethylamine[381] or, better, propanethiol[382] may be added to the conjugated system. From the adducts thus formed, the alkene may finally be recovered *via* pyrolysis of the derived methiodide. In a recent development the silylcuprate derived from dimethylphenylsilyllithium and copper iodide is added to the β-position of enones. The silyl ketones (**107**) produced in this way can conveniently be used for further syntheses. The double bond may be reobtained by bromination followed by desilylbromination (Scheme 101).[383] The sequence was, for instance, successful in syntheses of carvone (**108**) and dehydrojasmone.

Alkenes and dienes react with each other in Diels–Alder reactions to form cyclic adducts and the reversal of this transformation can be exploited for the regeneration of the desired alkenes at a later stage

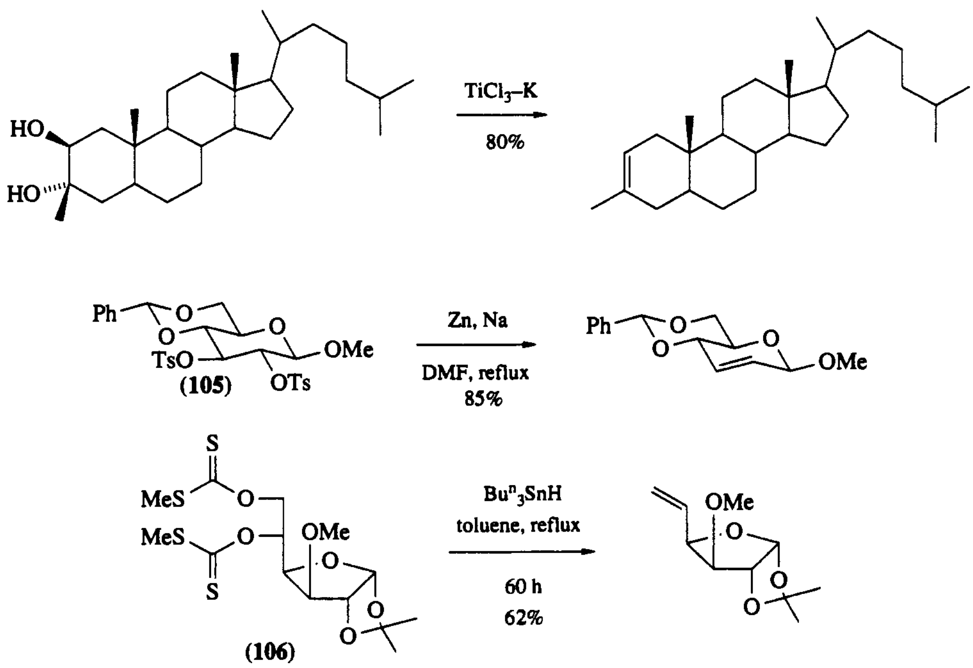


(102) **(103)**

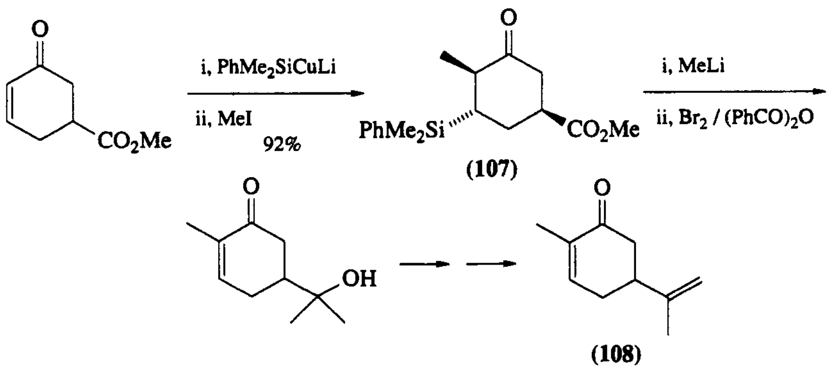
Scheme 98



Scheme 99

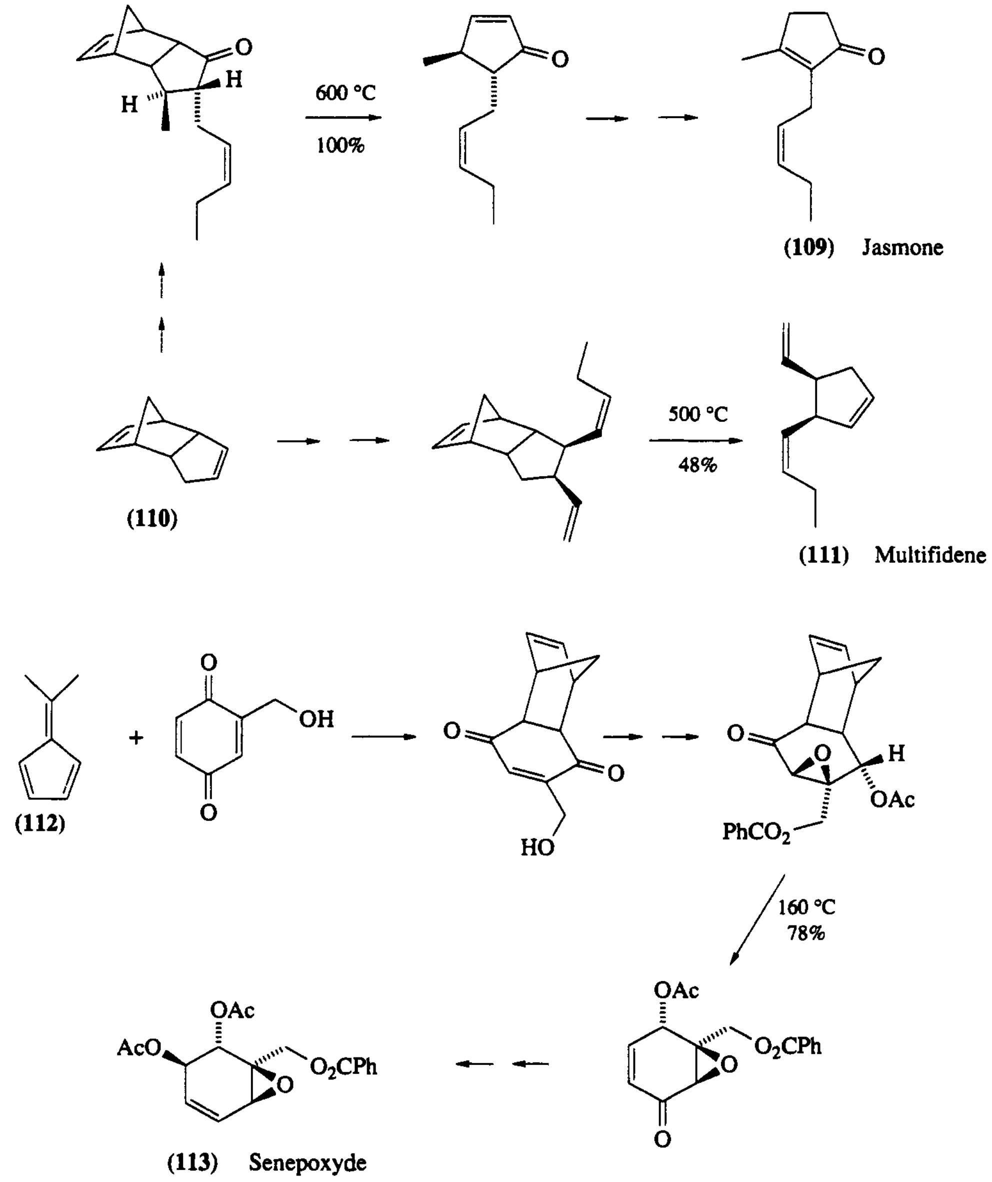


Scheme 100



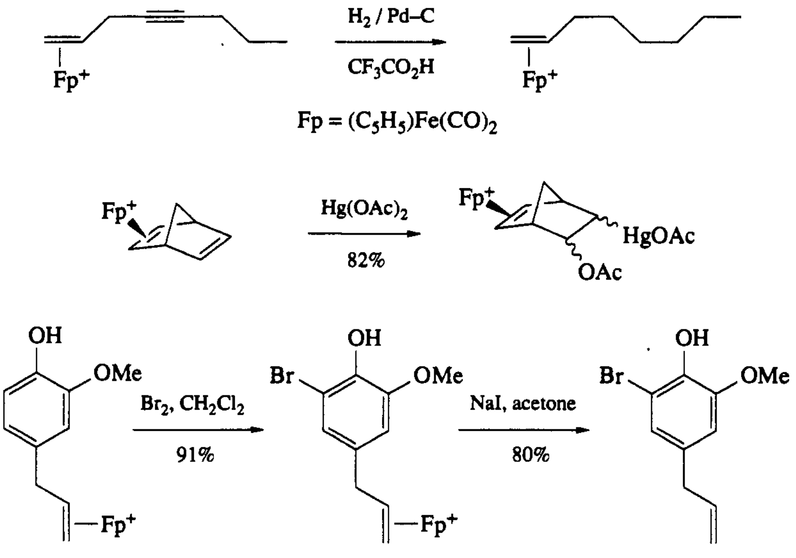
Scheme 101

of a synthesis. The retro Diels–Alder reaction usually requires high temperatures to proceed. This has for a long time hampered the application of this methodology as a strategy for protection. However, the correct choice of the dienes employed in the reaction and the invention of new techniques, like flash vacuum pyrolysis and infrared laser beams, have allowed to use the [4π + 2π] cycloreversion as a key step in the generation of complex natural products.[384] The dienes which are often used to protect double bonds are anthracene, cyclopentadiene, dimethylfulvene and 1-methoxy-1,3-cyclohexadiene. In Scheme 102 some applications of these protecting techniques are given. Dicyclopentadiene (**110**) serves, for instance, as the starting material for a synthesis of jasmone (**109**),[385] a cyclopentenoid compound. Numerous other cyclopentenones, for example multifidene (**111**), have been generated in this way. The elimination of dimethylfulvene (**112**) has been applied in the construction of quinone epoxides which were converted into natural products, as is briefly illustrated for senepoxyde (**113**).[386] Although the activation energy for the retro Diels–Alder reaction involving cyclopentadiene is relatively low (*e.g.* E_A for the retroreaction of *endo*-bicyclo[2.2.1]hept-2-ene-5-carbaldehyde is 33.6 kcal mol^{-1}),[387] dimethylfulvene is ejected even more easily (at temperatures of 150–190 °C). Anthracene also is an easily available protecting group for a double bond. It can, for example, be used for the synthesis of butenolides like tuli-



Scheme 102

paline A.[388] In addition to the chemical derivatizations described above, alkenes may be protected by the formation of complexes with some metals or their ions. Thus, coordination to silver ions protects double bonds from hydrogenation.[389] Alternatively, iron tricarbonyl complexes were used to mask double bonds during oxidation of an alcohol to a ketone.[390] Coordination of an alkene to the cyclopentadienyliron dicarbonyl cation to give the cations $CpFe(CO)_2(alkene)^+$ reduces its reactivity towards electrophilic attack and this may be used as a convenient protection method.[346] This masking can be introduced by ligand exchange reactions in which the alkene substitutes for the isobutene of the corresponding isobutene complex. In polyenes selective coordination of the most strained or the terminal double bond can be achieved. Double bonds masked in this way withstand hydrogenation,[391] treatment with mercury(II) acetate,[392] and bromination (Scheme 103).[391,392] Reactions of these types may, therefore, be performed selectively on the unblocked multiple bonds of the same polyenes. The release of the alkene is simply effected by treatment with sodium iodide in acetone. Terminal alkenes can be selectively and reversibly functionalized by alkyl exchange with organoaluminum compounds to form an aluminum alkyl, which must finally be decomposed again in a second exchange reaction with another alkene (*e.g.* 1-dodecene).[393]

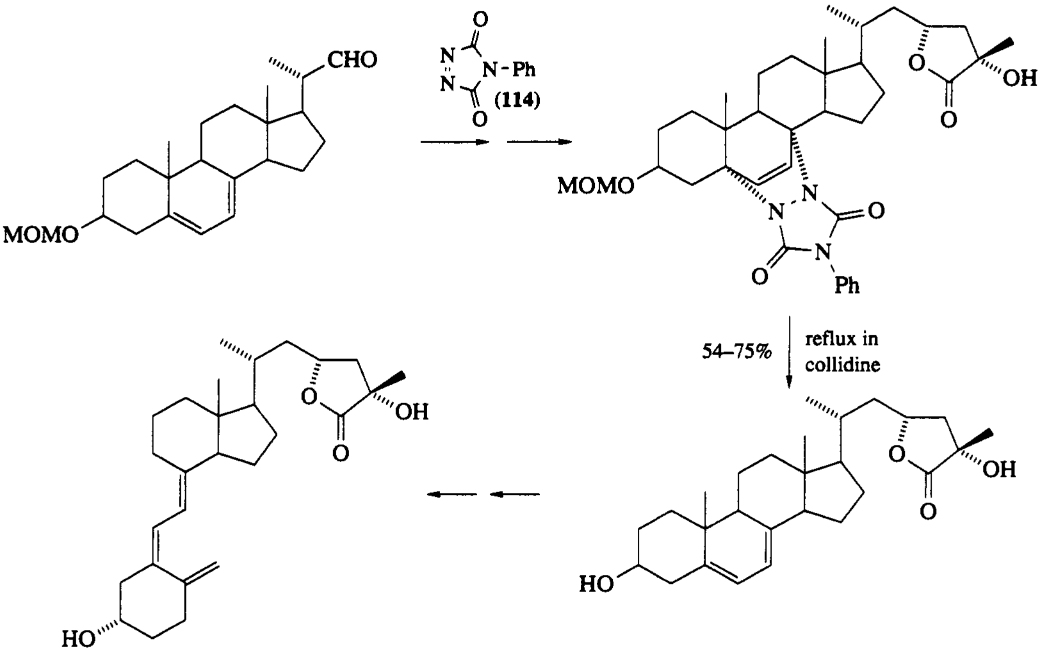


Scheme 103

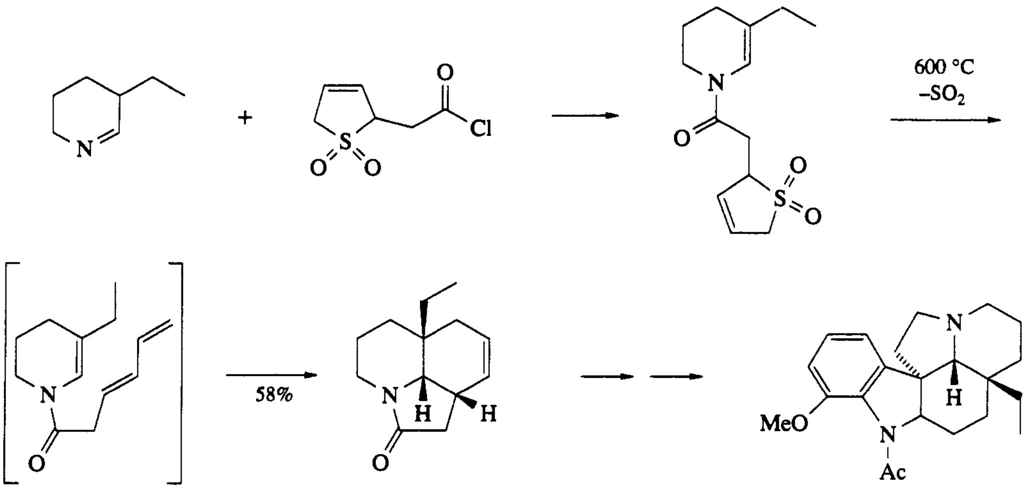
3.1.7.2 Protection of 1,3-Dienes[346,384]

Dienes may be protected as their Diels–Alder adducts and, like the dienophiles, they can be regenerated from the adduct by pyrolysis. Thus, conjugated steroidal dienes have been masked by reaction with 4-phenyl-1,2,4-triazoline 3,5-dione (**114**).[394] The parent systems are reobtained[384] after treatment of the cycloadduct with $LiAlH_4$, with K_2CO_3 or by using tetramethylguanidine or 1,3,5-collidine at relatively low temperatures. This methodology was, for instance, successfully applied in syntheses of metabolites of vitamin D_3, starting from ergosterol or provitamin D_3 (Scheme 104).[394,395] Also, dienes may be protected as cyclic sulfones and reobtained from their sulfur dioxide adducts in a cheletropic reaction. This approach has become important in the construction of various natural products like terpenes, steroids, alkaloids and pheromones[384] (as an example the synthesis of aspidospermine (**115**) is outlined in Scheme 105).[396]

Conjugated as well as nonconjugated dienes can be converted to irontricarbonyl complexes by reaction with iron carbonyls like $Fe(CO)_5$, $Fe_2(CO)_9$ and $Fe_3(CO)_{12}$.[397] In these complexes their reactivity differs from that of the uncomplexed ligand. This phenomenon can be exploited as a means of the protection of 1,3-dienes under varying conditions.[346,399] 1,3-Diene complexes of this kind are not affected during hydroboration,[398,399] reductions[398–400] with $LiAlH_4/AlCl_3$, $NaBH_4$, and with H_2/Pd–C or H_2/PtO_2. They also withstand oxidation with OsO_4, treatment with SO_3/pyridine, Sharpless epoxidations $(VO(acac)_2/Bu^tO_2H)$[399,401] as well as Friedel–Crafts acylations, treatment with cyanogen bromide, cyclopropanation conditions[400,402] and treatment with strong bases[401–403] as for example lithium alkyls, Grignard compounds and Wittig reagents. Furthermore, they do not participate in Diels–Alder reactions and



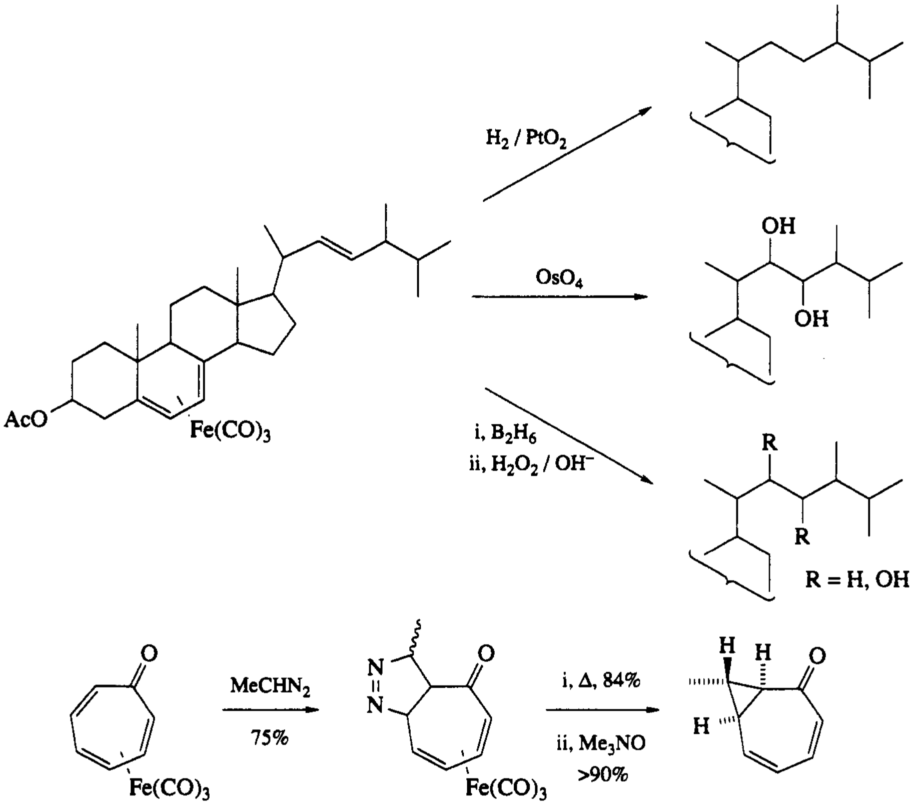
Scheme 104



(115) Aspidospermine

Scheme 105

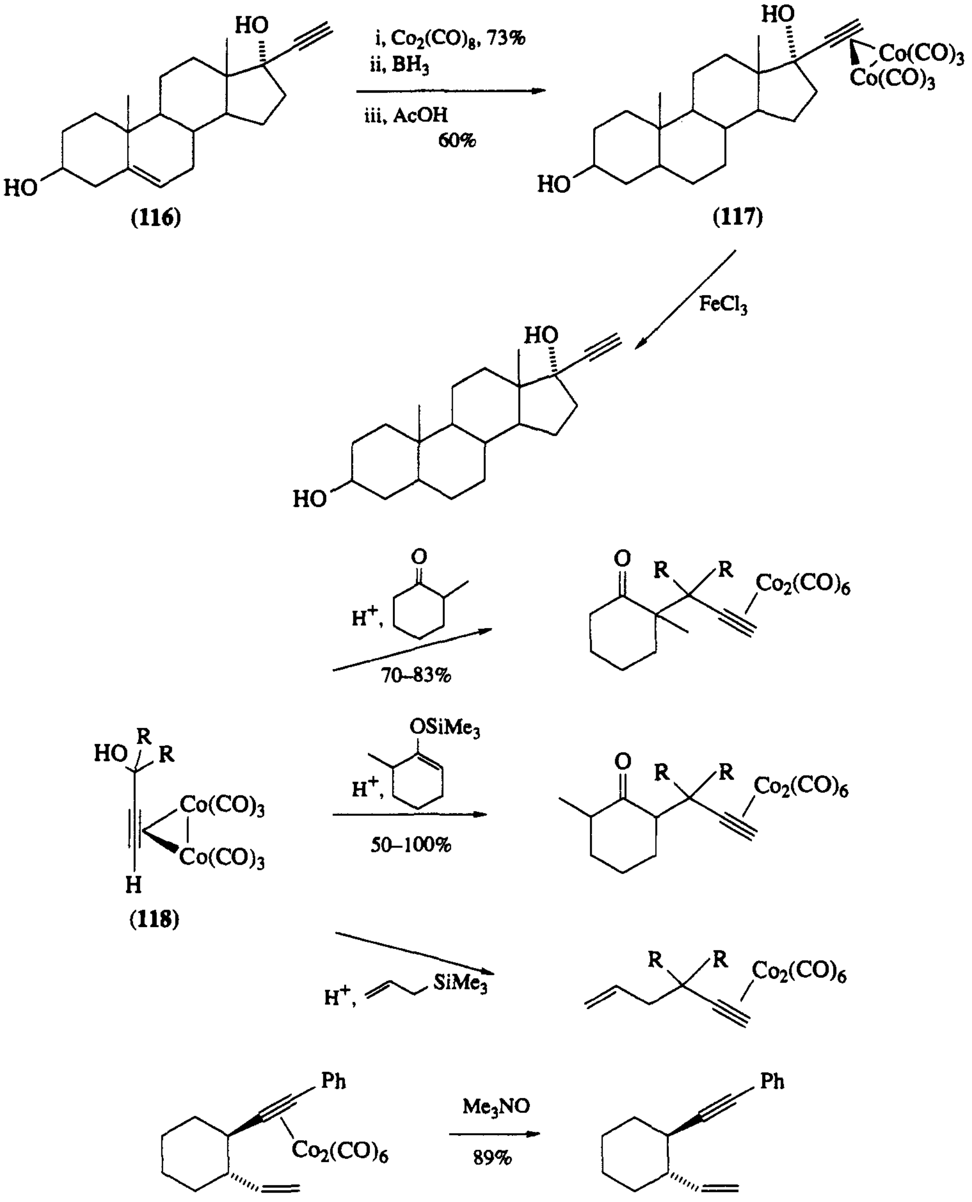
1,3-dipolar cycloadditions.[404] Selected examples, illustrating the efficiency of this selective diene protection, are depicted in Scheme 106. The blocking of the diene structure of ergosterol opens a route for the selective hydrogenation, oxidation and hydroboration of the isolated side chain double bond.[399] Protection of the diene part of tropone opens the way for cycloaddition reactions on the remaining unmasked double bond. In contrast, unprotected tropone would undergo ring expansion reactions with diazomethane.[404b] In particular, it should be noted that in the $Fe(CO)_3$ complexes the dienes are not only protected but even stabilized. Thus, for instance, 1,3-butadien-1-ol and -2-ol are prevented from rearranging to their respective keto tautomers by coordination to $Fe(CO)_3$.[405] In addition, the highly reactive cyclobutadiene can be isolated as its complexes with transition metals. The dienes may be regenerated from their complexes by treatment with oxidizing agents, *e.g.* Fe^{III}, Cu^{II} or Ce^{IV} salts, trimethylamine *N*-oxide and pyridinium chlorochromate.[397-404]



Scheme 106

3.1.7.3 Protection of Alkynes[346]

Like the double bond, the carbon–carbon triple bond is susceptible to many of the common addition reactions. In some cases, such as reduction, hydroboration and acid-catalyzed hydration, it is even more reactive. A very efficient method for the protection of the triple bond is found in the alkynedicobalt hexacarbonyl complexes (*e.g.* **117** and **118**), readily formed by the reaction of the respective alkyne with dicobalt octacarbonyl.[406,407] In eneynes this complexation is specific for the triple bond. The remaining alkenes can be reduced with diimide or borane[407] as is illustrated for the ethynylation product (**116**) of 5-dehydro androsterone in Scheme 107. Alkynic alkenes and alcohols complexed in this way show an increased structural stability. This has been used for the construction of a variety of substituted alkynic compounds uncontaminated by allenic isomers (Scheme 107) and in syntheses of insect pheromones.[408] From the protecting cobalt clusters, the parent alkynes can easily be regenerated by treatment with iron(III) nitrate,[407] ammonium cerium nitrate[406] or trimethylamine *N*-oxide.[409]



Scheme 107

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4.1
Carbonyl Group Derivatization

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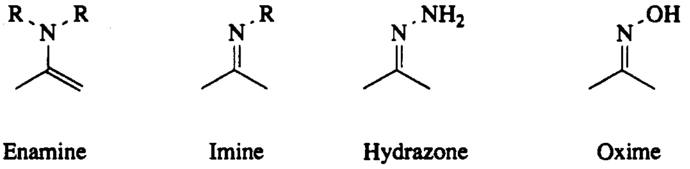
4.1.1 INTRODUCTION

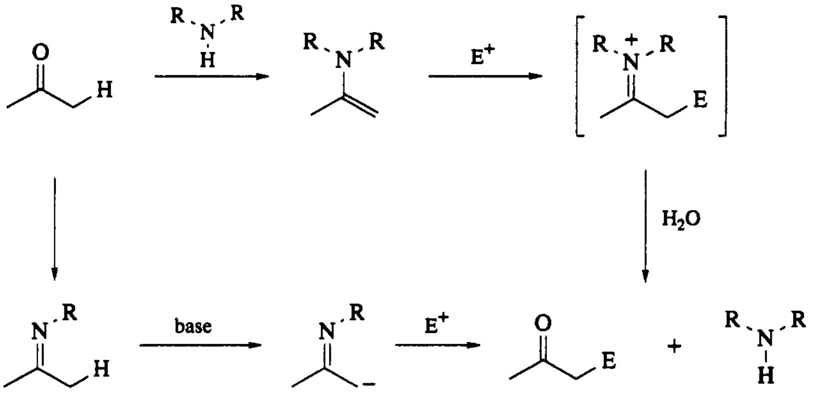
Enamines, imines, hydrazones and oximes represent the common nitrogen derivatives of ketones and aldehydes (Scheme 1). Both hydrazones and oximes were of importance before the availability of modern spectral techniques for the conversion of liquid carbonyl-containing compounds into solid materials that could be correlated with known samples by melting point and mixed melting point methods. While these applications have all but disappeared, these derivatives, as well as enamines and imines, have emerged as important intermediary species in overall transformations that effect substitution α to the original carbonyl group. Much of this work is based on the seminal contributions of Stork.[1–4]

While enamines are structurally distinguished from the other three derivatives by the absence of the carbon–nitrogen double bond, they serve in substitution reactions in the same conceptual way: that is, the



Scheme 1

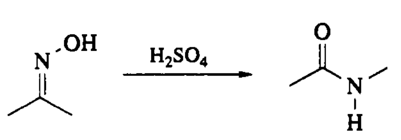
substitution process involves, overall, the replacement of a hydrogen atom by a different atom, usually carbon, and these species provide an avenue for removal of the α-hydrogen as the first operation. Thus, direct formation of enamines from aldehydes and ketones involves removal of this hydrogen, while reactions that proceed through the other derivatives involve separate steps, usually treatment with a strong base (Scheme 2). The resulting anions are structurally similar to enamines and, indeed, have been referred to as metalloenamines.



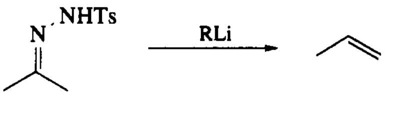
Scheme 2

There are other applications of these derivatives. For example, imines can be reduced to amines (equation 1),[5] oximes can undergo rearrangement under strongly acidic (or dehydrating) conditions to form amides (equation 2),[6] and the treatment of tosylhydrazones with strong bases can provide an excellent method for reductive elimination to form alkenes (equation 3).[7]

(1)



(2)



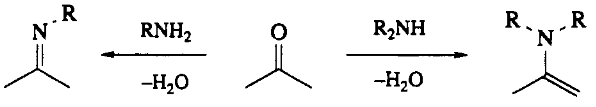
(3)

A number of comprehensive reviews of enamine and imine chemistry have appeared.[8-17] Sections in other volumes of this series will concentrate explicitly on carbon–carbon bond forming reactions that use these species. They will be treated here mainly from the perspectives of methods for their formation and of their unique structural features.

4.1.2 ENAMINES

4.1.2.1 Formation

The reaction between all classes of amines (except tertiary) and either ketones or aldehydes is usually straightforward and generally leads to imines in the case of primary amines and to enamines with secondary amines, which bear only one labile proton on nitrogen (equation 4).

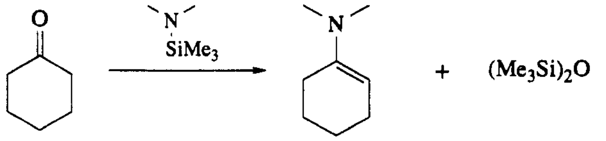


imine enamine

(4)

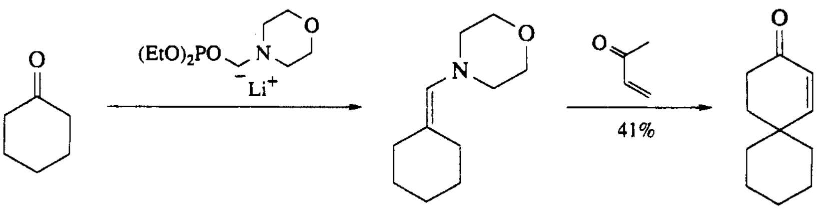
It is generally conceded that some method of removal of the water that is coproduced in both reactions is required to effect maximal conversion of ketones to imines or enamines. Indeed, the variations between the different methods for enamine formation center on the techniques employed for driving the reaction to completion. The simple method of azeotropic removal of water when effecting reaction in a hydrocarbon solvent such as benzene or toluene in the presence of an acid catalyst represents the classical method for enamine formation. Qualitative rates of reaction of three commonly used amines are in the order: pyrrolidine > morpholine > piperidine. The rate of reaction of pyrrolidine with various ketones proceeds in the following order: cyclopentanone > cyclohexanone > cycloheptanone > 2-methylcyclohexanone > acetone.[18,19] Alternatively, chemical drying agents can be employed with the advantage that the conversion to enamine can be effected more rapidly and that elevated temperatures (reflux) need not be employed. Molecular sieves not only provide a means for water removal but have also been shown to have catalytic, rate-enhancing effects on enamine formation,[20–22] most likely as the result of the binding agent.[21] Reaction between simple secondary amines and hindered ketones, including the relatively unreactive methyl ketones, can be quite slow. Titanium tetrachloride has been used in such cases as both a strong Lewis acid and a powerful dehydrating agent,[23] and an extensive study has been carried out in order to find optimum conditions for its application.[24] Two significant conclusions from this latter study are that: (i) complexation of the amine and titanium tetrachloride before addition to the ketone provides enhanced rates; and (ii) a large excess of amine is required, presumably to effect deprotonation of an intermediate complex.

In a similar vein, 3 equiv. of trimethylsilyldimethylamine have been used at room temperature to form the enamine from cyclohexanone, conditions under which the water is presumably consumed as hexamethyldisiloxane (equation 5).[25] This method has been extended to the formation of *N,N*-dimethylenamines from unsaturated aldehydes.[26] Alternatively, enamines have also been obtained by converting the carbonyl compound to a ketal before reaction with the amine.[27] The first process is endothermic but can be readily driven to completion and provides the driving force for formation of the enamine.

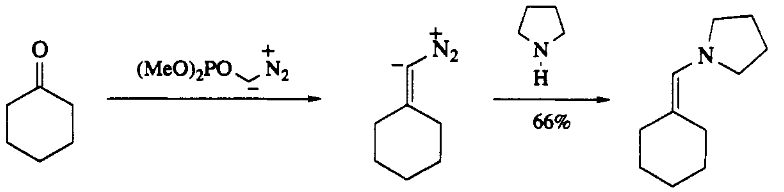


(5)

Two unusual and useful methods for enamine formation involving carbon–carbon bond formation[28–36] have been developed from the pioneering work of Martin[28–30] and are illustrated in equations (6)[28] and (7).[36] The moderate overall yields in both processes are offset by the complexity of alternative pathways for accomplishing the same transformation.

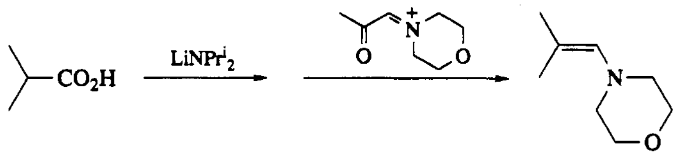


(6)



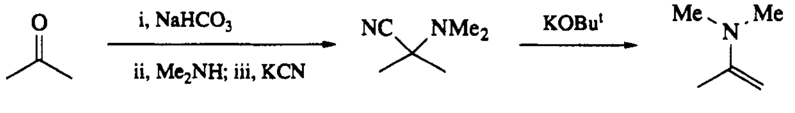
(7)

The transformation illustrated in equation (8) effects a net conversion of an acid to the enamine of the corresponding aldehyde, but does so by decarboxylation (rather than by reduction).[37]



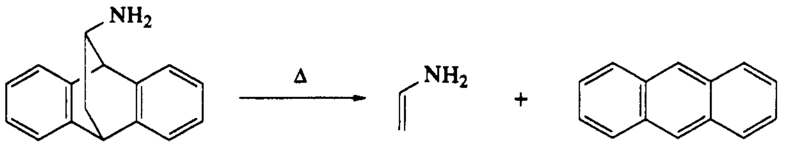
(8)

The formation of enamines from acyclic methyl ketones is often complicated by reaction of the enamine with the ketone. In a cleverly devised process, Ahlbrecht first converted acetone to a cyanoamine, which is then transformed into the enamine by potassium *t*-butoxide induced loss of hydrogen cyanide (equation 9).[38]



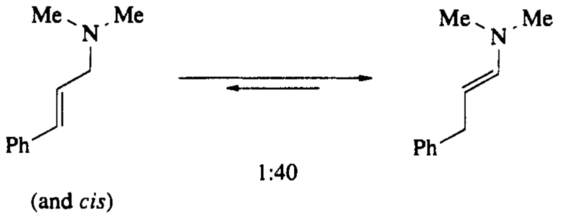
(9)

Enamines that would formally be derived from ammonium cannot be formed by any process that would expose the product to either acid or base, since the conversion to the imine is exothermic as both the carbon–nitrogen π-bond (74 kcal mol^{-1}; 1 cal = 4.18 J) and carbon–hydrogen bond (99 kcal mol^{-1}) are stronger than the carbon–carbon π-bond (63 kcal mol^{-1}) and nitrogen–hydrogen bond (93 kcal mol^{-1}). However, ethenamine and several substituted analogs have been prepared for spectral analysis (at low temperature) by retro-Diels–Alder reactions (equation 10).[39]



(10)

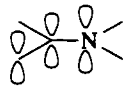
As will be further detailed in Section 4.1.2.2, it is possible to effect equilibration of allylamines and the corresponding enamines (for example, equation 11). Such a procedure obviously lacks generality, as in the majority of cases the allylamine would be more difficult to prepare than the enamine. Furthermore, and more importantly, such a sequence for forming enamines removes the ketone functionality from its central role in the synthetic sequence.



(11)

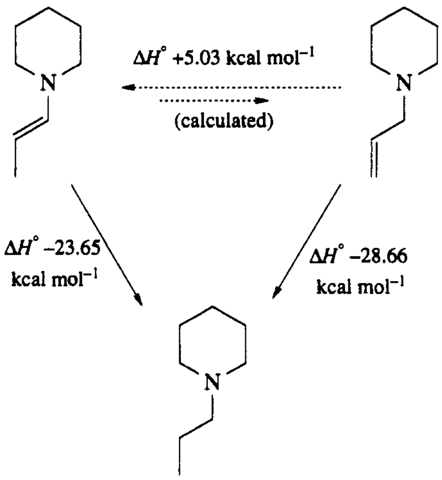
4.1.2.2 Structure and Chemical Properties

The structure of enamines, on first inspection, would seem straightforward, and, indeed, most elementary texts present a simplistic picture in which the nitrogen is fully sp^2-hybridized with complete p-orbital overlap between nitrogen and the carbon–carbon π-bond system (**1**).

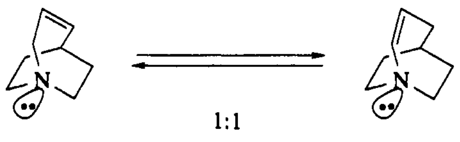


(**1**)

The energetic significance of this overlap can be concluded from a combined analysis of a number of studies. The energy difference between *N*-allyl- and *N*-propenyl-piperidine was determined indirectly by heats of hydrogenation to be 5.0 kcal mol^{-1} (in favor of the enamine form) (Scheme 3).[40] Approximately 2.5 kcal mol^{-1} of this difference can be attributed to the greater stability inherent in the more substituted alkene isomer.[41] Doering has pointed out that the remaining difference of 2.5 kcal mol^{-1} could, in principle, be the result of either nitrogen lone pair, π-system overlap or a change in the energy of the σ-bond between nitrogen and either an sp^2 or sp^3 carbon.[42] In an imaginative experiment, he determined the equilibrium ratio between the allylamine and enamine below (equation 12) to be nearly 1:1, demonstrating that there is essentially no difference in energy between the allylamine and enamine in the absence of lone pair, π-system overlap. (The bridgehead lone pair must be orthogonal to the carbon–carbon π-bond in this system.)

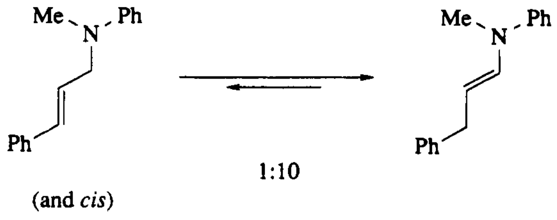


Scheme 3

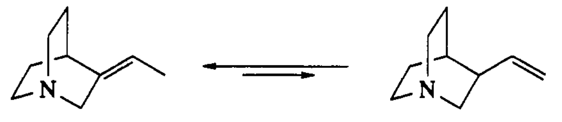


(12)

Other determinations of the energy difference between an allylamine and an enamine include the equilibration of the species in equations (11),[44] (13)[43] and (14).[45,46]



(13)

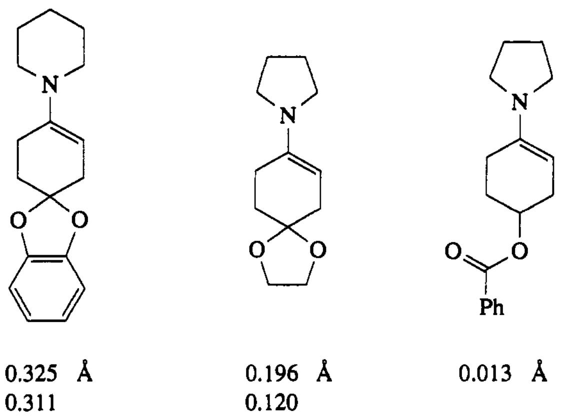


(14)

16:1

In theory, the energetic advantage that results from lone pair π-system overlap could be directly assessed by determining the barrier to rotation about the carbon–nitrogen σ-bond. Unfortunately, the barrier appears to be too low for determination by NMR spectroscopic techniques. Philipsborn has shown that there is a good correlation between the barrier to rotation about this bond and the ^{15}N NMR chemical shift for enamines with extended conjugation, resulting in higher and measurable barriers (vinylogous amides, for example).[47] Extrapolation of these observations to simple enamines leads to a predicted barrier of 5 kcal mol^{-1}, corresponding well with a barrier of 6 kcal mol^{-1} calculated by Dixon using PRDDO and *ab initio* calculations with a variety of basis sets.[48] The chemical shift of the vinylic hydrogen can be correlated in a similar fashion.[49]

An extensive collection of single-crystal, X-ray structural determinations resulting from a collaboration between Eschenmoser and Dunitz on a variety of enamines provides interesting insight into the conformation about the nitrogen–carbon σ-bond as well as the degree of planarity (hybridization) at nitrogen.[50] The three examples shown in Scheme 4 illustrate the range of possibilities found, with nitrogen varying from nearly perfectly planar to nearly pyramidal. (The values provided are a measure of the degree, in angstroms, to which the nitrogen atom lies out of the plane defined by its three attached carbon atoms.)



Scheme 4

Caution should always be exercised in extrapolating solid state structural information to the analysis of arrangements in solution and, indeed, the unit cells of two of the crystals contain different molecules with significant differences in arrangements. Nonetheless, the large number of examples in this study provide a statistical basis for concluding that the energetics of overlap are affected in only a minor way by the hybridization state at nitrogen. Further, the energetics of alignment of the lone pair with the π-system appears to be quite soft and overridden by an apparent favoring of arrangements in which the bond from nitrogen to one of the two substituents of the amine moiety is nearly eclipsed with the carbon–carbon double bond (Figure 1).[50]

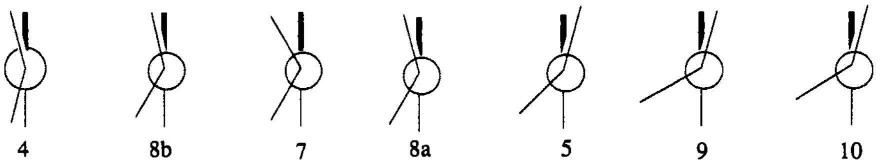
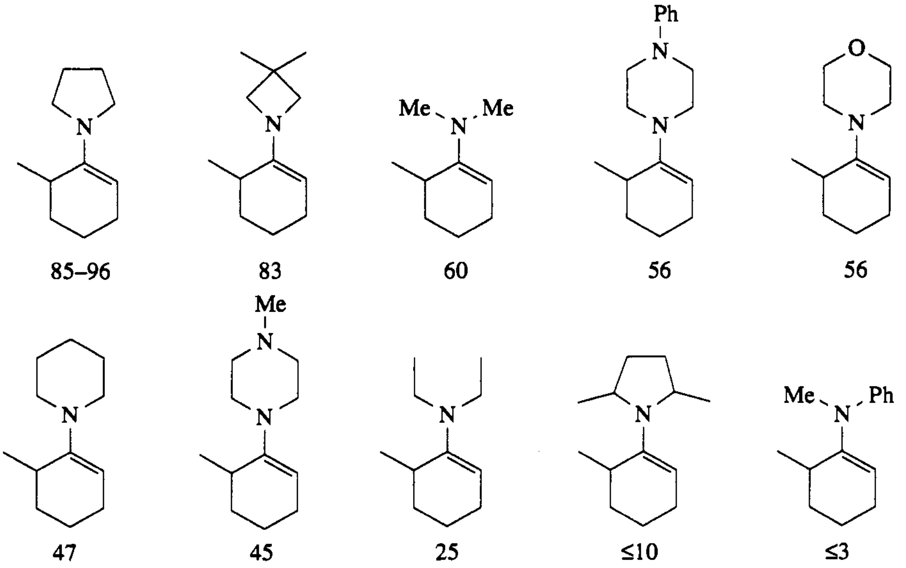


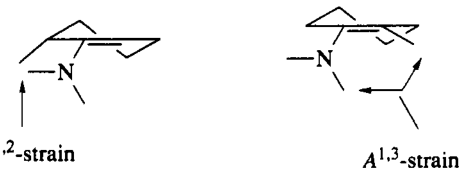
Figure 1 Newman projections of various enamines looking down the N–C bond (the C=C bond is maintained in the vertical position throughout)[50]

For applications of enamines as reactive derivatives of ketones and aldehydes, the major structural question for those derived from unsymmetrical ketones is that of regiochemistry. The ratio of less to more substituted forms for a series of 10 enamines derived from various amines and methylcyclohexanone has been summarized by Thompson from various literature studies (Scheme 5).[51]

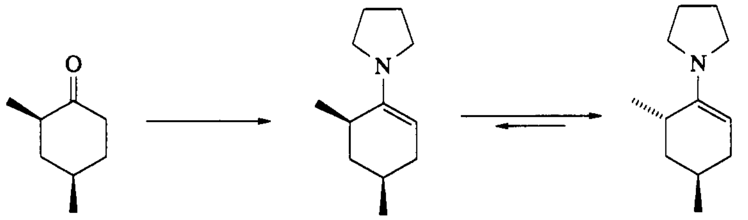


Scheme 5

While it is probably reasonable to draw general trends from this series, it should be kept in mind that most of the data came from different laboratories, as indeed there are four different reports for the simple pyrrolidine enamine that account for the range from 85 to 96%. Some of the factors that contribute to determining the regioisomeric composition of enamines are A^{1,3}-strain, which destabilizes the more substituted isomer, and A^{1,2}-strain, which destabilizes the less substituted isomer (Scheme 6).[52] The former effect was used by Johnson to effectively convert *cis*-2,4-dimethylcyclohexanone to the *trans* isomer through formation of the less substituted pyrrolidine enamime, where a pseudo-axial orientation of the 2-methyl group reduces the level of A^{1,2}-strain (equation 15).[53,54]

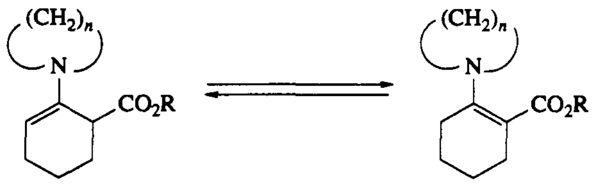


Scheme 6



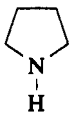
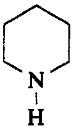
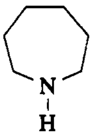
(15)

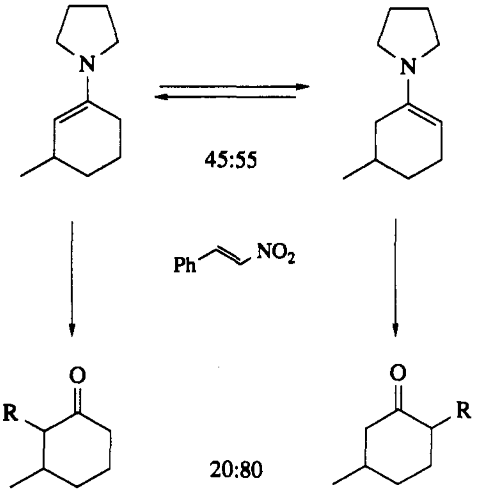
The degree to which each of the effects will impact the respective isomer will depend not only on the amine substituents but also on the specific structure of the ketone involved. For example, and rather surprisingly, it has been shown that A^{1,3}-strain can be sufficiently greater that A^{1,2}-strain so as to favor the less substituted enamine, even when the substituent is an alkoxycarbonyl group capable of adding stability to the more substituted form through extended conjugation (equation 16).[55,56] Further, it has been established, at least with some enamines, that interconversion of the two regioisomers occurs at a rate competitive with alkylation and, therefore, that the ground state composition of the starting enamine does not directly correlate with product composition. For example, the two regioisomeric enamines derived from 3-methylcyclohexanone (Scheme 7) have been shown to be in rapid equilibrium, providing a product ratio upon reaction with β-nitrostyrene that differed markedly from that of the starting enamine.[57–59]



(16)

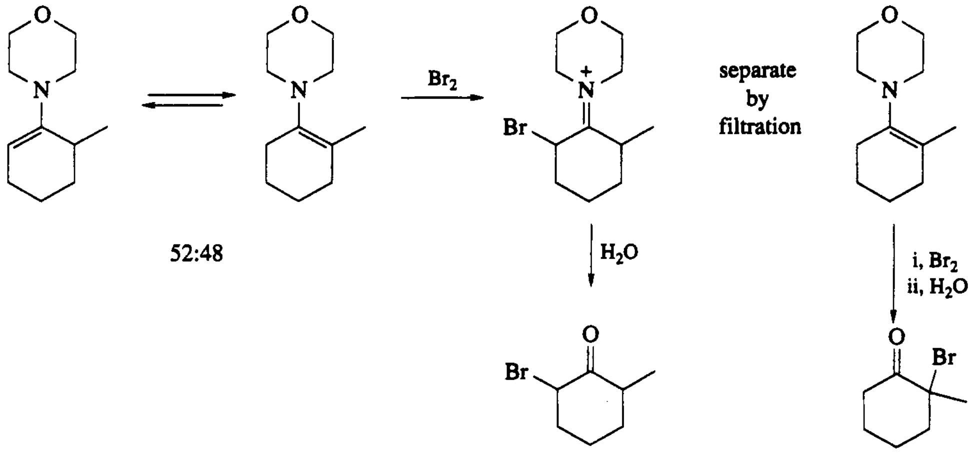
Percentage of more substituted isomer

			
R = Me	95	34	75
R = Et	88	25	64
R = Pr^i	85	25	64



Scheme 7

Interpretation of these studies, as well as those involving reaction with methyl acrylate and acrylonitrile as electrophiles,[60] are complicated by the possibility that these reactions are reversible. Conversely, reaction with molecular bromine is considerably faster than regioisomerization, an observation that has been used to prepare separate samples of 2-bromo-6-methyl- and 2-bromo-2-methyl-cyclohexanone.[61] Thus, in the reaction of a nearly one to one mixture of the less and more substituted enamines derived from methylcyclohexanone with 0.5 equiv. of bromine, only the less substituted isomer is converted to the intermediate immonium ion, which precipitates from ether solution at –50 °C (Scheme 8). Separation, and then addition of more bromine to the filtrate, then effected reaction of the more substituted isomer.



Scheme 8

4.1.2.3 Spectral Properties

4.1.2.3.1 Photoelectron spectra

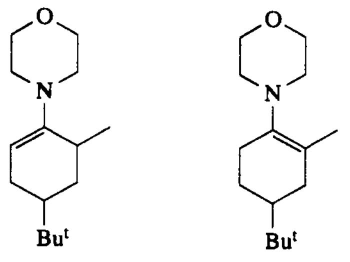
Extensive measurements of ionization potentials of various enamines by photoelectron spectroscopy from a number of separate investigations[62–66] have been nicely tabulated by Hickmott[67] and, more recently, by Vocelle.[68] Conclusions from these data concerning the degree of lone pair, π-system conjugation for different enamines seem valid as they are consistent with other spectroscopic and chemical observations. On the other hand, the presumption that the nitrogen is pyramidal because the first ionization band is quite broad as a result of a large geometry change between the neutral ground state and the radical cation is more speculative.

4.1.2.3.2 Ultraviolet spectra

The UV absorption spectra of simple enamines as well as those with extended carbon–carbon π-conjugation are quite broad. A correlation with photoelectron spectra has also been made.[69]

4.1.2.3.3 Infrared spectra

The π-bond stretching of enamines is only slightly affected by interaction with the nitrogen lone pair.[8] It might be argued that the relatively greater shift of the absorption for the less substituted isomer as compared with the more substituted isomer (relative to a tri- or tetra-substituted alkene[70] at 1670 cm^{-1}) is an indication of greater lone pair delocalization in the former (Scheme 9).

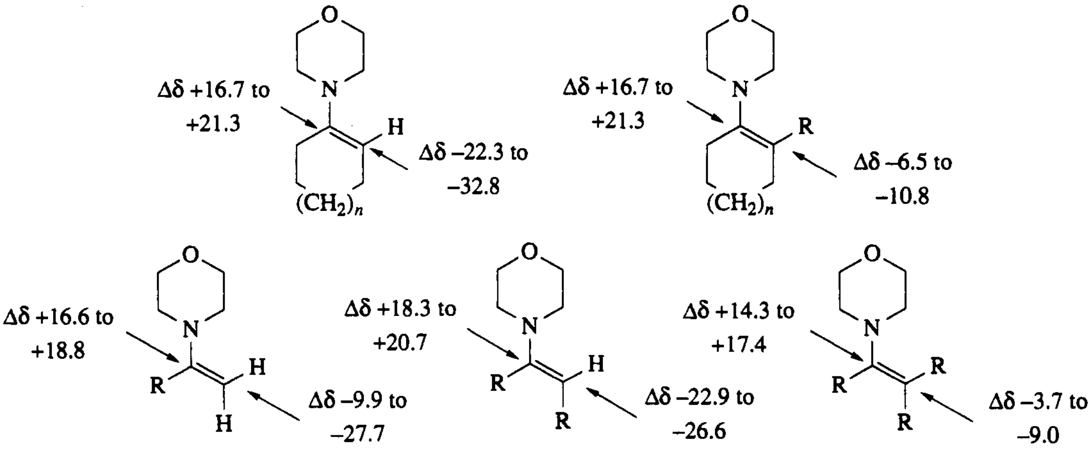


1639 cm^{-1} 1677 cm^{-1}

Scheme 9

4.1.2.3.4 Carbon NMR spectra

A number of early studies established the value of carbon NMR spectroscopy for the analysis of the composition of enamines, especially with regard to regiochemistry for those derived from unsymmetrical ketones and to stereochemistry for enamines of acyclic ketones as well as of aldehydes.[71-73] A more recent survey by Paquer provides valuable information for the prediction of the expected chemical shift for new systems.[74] While only morpholine enamines were directly examined, the anticipated shift corrections for those derived from both pyrrolidine and piperidine are given. Two approaches are provided by these authors; the first provides appropriate shift-of-shift values for both the α- and β-carbon relative to the corresponding alkene (Scheme 10).[75] These are quite consistent for the α-carbon, ranging from +16.7 to +21.3 δ for the α-carbon of enamines derived from five-, six-, seven- and eight-membered ring ketones. Similarly, the shift-of-shift values for the β-carbon relative to the corresponding alkene ranged from –22.3 to –32.8 when the β-carbon had one hydrogen and from –6.5 to –10.9 when the β-carbon was fully substituted. Both the relatively large variation in the shift-of-shift of the β-carbon and the decrease in this value upon further substitution by carbon correlate well with the degree of anticipated delocalization of the nitrogen lone pair. Similar observations were also made for a series of eight enamines derived from acyclic ketones. These results are also summarized in Scheme 10.



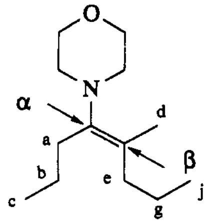
Scheme 10

An alternative process for predicting the chemical shifts of both the α- and β-carbons without reference to the parent alkene is also provided. This latter method is amazingly accurate and will find use especially where the spectrum for the appropriate alkene is not available. Notice the large shift of shift effect on both the α- and β-carbons for added substituents on the β-carbon. Thus, analysis of ratios and assignment of regiochemistry to enamines derived from unsymmetrical ketones becomes a trivial matter by ^{13}C NMR spectral analysis. There is also a large difference in the shift of shift value for the β-carbon for adding an additional substituent either *cis* (23.4) or *trans* (13.3) to the nitrogen, permitting ready and reliable assignment of stereochemistry about the enamine π-bond for those derived from aldehydes and acyclic ketones (Scheme 11).

4.1.2.3.5 Proton NMR spectra

The proton NMR spectra of enamines have been examined for some time,[76,77] and represented the first reliable technique for assigning the regiochemistry of those enamines derived from unsymmetrical ketones, although of course there will be no vinylic hydrogen absorption for enamines upon formation of the π-bond toward the side of the ketone that is disubstituted. Shown in Scheme 12 are shift values for the vinylic hydrogen of enamines derived from a variety of ketones and amines.[76]

The shift values obtained in $CDCl_3$ are at approximately 0.1 p.p.m. lower field. The large upfield shift of this proton from simple alkenes is, of course, the result of lone pair electron delocalization into the π-system, resulting in an increase in electron density at the β-carbon. The ease with which this delocalization can occur crudely correlates with the kinetic reactivity of the various enamines where the most reactive are generally the pyrrolidine enamines.[12,77,78] A similar analysis of the proton spectra for enamines derived from 2-butanone and a variety of amines has also been made.[79] Again, the pyrrolidine enamine absorption occurs upfield from both the piperidine and morpholine enamines. The vinylic



For C-α

To base of 147.00 p.p.m. add for nonhydrogen

a 4.68	e −5.93
b 4.30	g −1.46
c −0.92	j −1.25
d −6.26	

For five-membered ring add 5.88

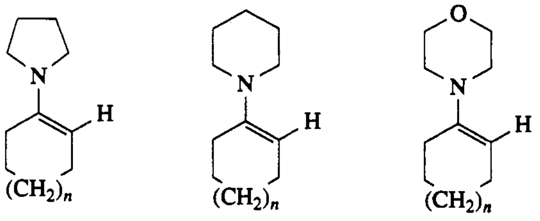
For C-β

To base of 84.40 p.p.m. add for nonhydrogen

a 0.45	e 13.29
b 0.51	g 6.10
c 1.06	j −4.79
d 23.37	

For five-membered ring add −2.12

Scheme 11



Chemical shift of the vinylic hydrogen in p.p.m.(δ) downfield from TMS

n			
0	3.92	4.25	4.35
1	4.13	4.53	4.57
2	4.37	4.75	
3	4.08	4.48	
5	3.97	4.30	

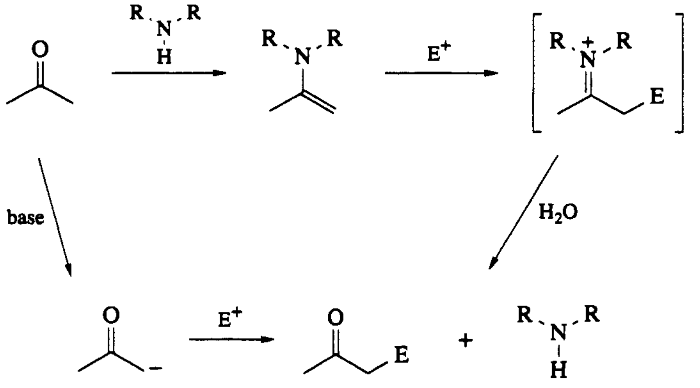
Scheme 12

hydrogen of the (*E*)-isomer is found to be consistently (0.1 to 0.7 p.p.m.) upfield from the (*Z*)-isomer and it is probable that this also results from greater lone pair delocalization in the former since overlap in the (*Z*)-isomer can be inhibited as the result of $A^{1,3}$-strain. A similar study of enamines of propiophenone has also been reported.[80a]

The configuration about the carbon–carbon π-bond of enamines derived from acyclic ketones can, at least in principle, be derived from NOE enhancement between the carbons α to the nitrogen and the vinylic hydrogen.[80b] For example, that of the enamine derived from propiophenone and dimethylamine (where the hydrogen is *cis* to the amine unit, *i.e.* the (*E*)-isomer) exhibits an enhancement of 23% in the vinylic hydrogen upon irradiation of the methyl groups attached to nitrogen. The generality of this observation has not been demonstrated and, further, in those cases where only the (*Z*)-isomer was obtained the evidence would be negative. In summary, it would appear that carbon NMR spectral analysis represents by far the best technique for determining the regio- and stereo-chemistry of enamines.

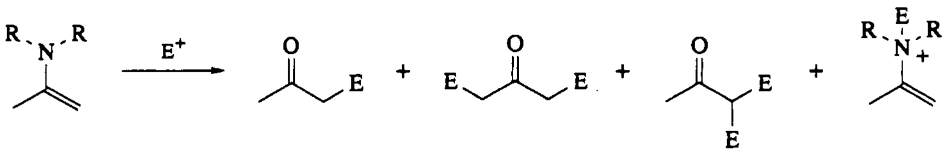
4.1.2.4 General Reactions

Enamines are employed in the majority of cases as a means of activating the α-carbon as a nucleophile for reaction with an electrophilic carbon partner (Scheme 13). In the historical picture of the development of methods for α-alkylation of ketones and aldehydes, they represented a significant advance over the use of alkaline earth metal enolates, which had been employed up to that point. More recently developed techniques that involve the formation of enolates (as well as imine and hydrazone anions, *vide infra*) with lithium amide bases have proved superior in most cases both in terms of regiochemical control and in limiting the process to monosubstitution. Nonetheless, these methods universally involve strongly basic reactions, and enamine alkylation stands uniquely apart from other methods in being essentially neutral.



Scheme 13

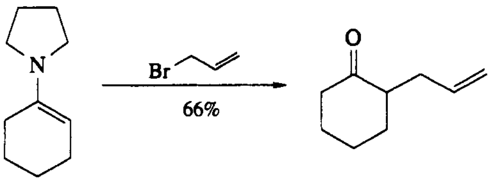
There are a number of side processes in the reactions of enamines that can divert material from the (usually) desired monoalkylation product at the less substituted side. These include *N*-alkylation (which in rare cases is reversible), reaction at the more substituted α-carbon, and di- and higher alkylation (equation 17). Furthermore, conditions for maximum conversion to monoalkylation relative to dialkylation product generally result in incomplete alkylation of the enamine which is then converted, upon hydrolysis, to the original ketone or aldehyde.



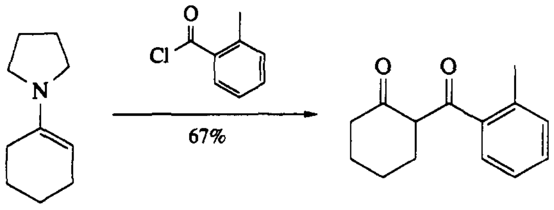
(17)

A variety of secondary amines have been used for enamine alkylation.[81-83] Nonetheless, the three most commonly used, pyrrolidine, piperidine and morpholine, appear to still represent the best compromise between ease of access to the amine and formation of the enamine and the degree of conversion to monoalkylated product.[81] Pyrrolidine appears to be the best amine for the specific case where the electrophilic partner for the enamine is a Michael acceptor, such as an α,β-unsaturated ester,[84,85] and enamines derived from this base are generally more reactive than the piperidine and morpholine analogs.[3] The use of optically active amines for asymmetric induction will be covered in Section 4.1.2.5.

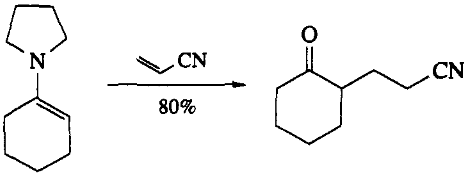
A range of electrophilic partners have been employed in reactions with enamines, ranging from simple alkyl halides (and sulfonates) to acylating agents such as carboxylic acid chlorides and to electrophilic alkenes such as the aforementioned unsaturated esters. Specific examples are provided in equations (18), (19) and (20). Appropriately, all three examples are from Stork.[3] The reaction with α,β-unsaturated ketones has special significance as a variant of the Robinson ring annelation technique[86] (equation 21).[87] in which the second stage is the cyclization of a diketone through formation of the enamine of one ketone group. This process can be effected with a high degree of asymmetric induction with the amino acid proline as a catalyst. This aspect will be covered in detail in Section 4.1.2.5.



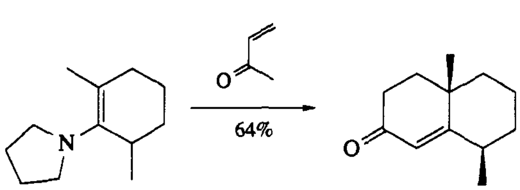
(18)



(19)

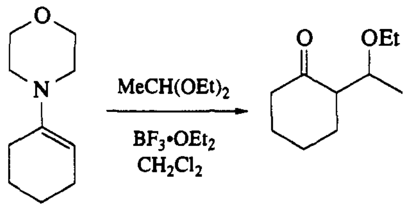


(20)



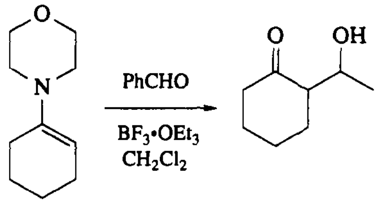
(21)

Recent reports from Takazawa[88–90] provide the background for the reaction of enamines with aldehydes and acetals as well as with orthoesters in the presence of Lewis acids (equations 22[89] and 23[90]). For these reactions it was found that the enamine from morpholine provided the highest yield as did the use of boron trifloride etherate as a Lewis acid (in stoichiometric amounts).



(22)

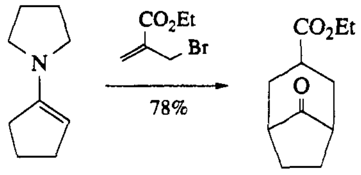
76% (mixture of diastereomers)



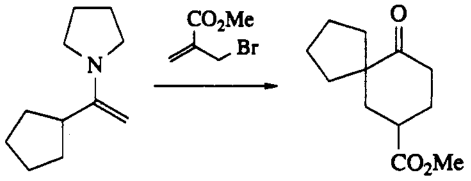
(23)

92%; *erythro:threo* = 78:22

Sequential reaction at both positions α to a carbonyl group (as its enamine derivative) with a bifunctional electrophile provides for ring formation, as illustrated in equation (24) by the preparation of a bicyclo[3.2.1]octane bridged system from a cyclopentanone.[91] Alternatively, spiro systems can also be formed, as in equation (25).[92] A comprehensive study with a variety of bifunctional electrophiles has been reported recently.[93]

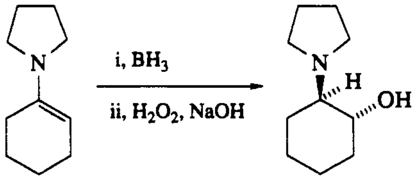


(24)

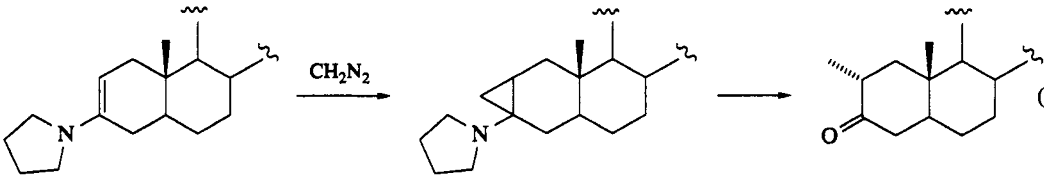


(25)

A number of atypical reactions of enamines have been developed. For example, hydroboration–oxidation affords stereochemically defined, vicinal amino alcohols (equation 26).[94] Similarly, enamines have been shown to undergo reaction with diazomethane to form substituted cyclopropanes. These materials can be further transformed to α-alkylated ketones by thermolysis followed by hydrolysis (equation 27).[95]



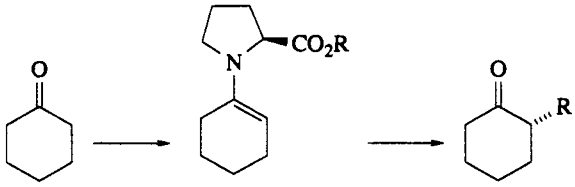
(26)



(27)

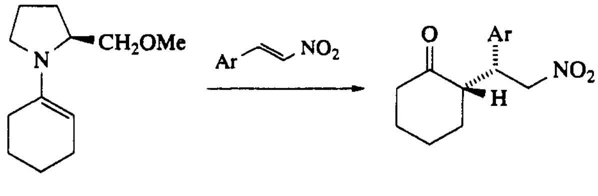
4.1.2.5 Stereochemical Features

Control of absolute stereochemistry in ketone alkylation through the use of chirality in the amine component of an enamine represents a nearly ideal case for asymmetric induction where the chiral auxiliary is present in an equimolar amount. The formation of enamines is generally straightforward, cleavage of the product immonium ion is trivial in most cases, and the amine can be readily separated from the prouct for recovery and reuse. Indeed, the first example of such a process was reported by Yamada in 1969 using proline esters as the chiral amine (equation 28).[96–98]

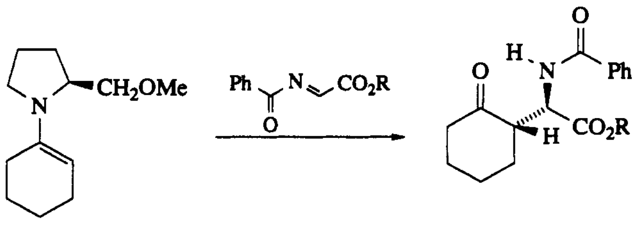


(28)

However, the maximum level of stereochemical control in these processes with a variety of electrophiles ($CH_2{=}CHCO_2Me$, $CH_2{=}CHCN$, $BrCH_2CH{=}CH_2$, $BrCH_2CO_2Et$) was below 60% optical purity (corresponding to a ratio no better than 4:1). These results appear to be the result of kinetic control in the transition state for carbon–carbon bond formation. On the other hand, reactions with methyl vinyl ketone can be run under either kinetic or thermodynamic control and the level of stereochemical control is higher under the latter conditions.[99,100] Likewise, the enamine from 2-methoxymethylpyrrolidine (derived from proline) adds in a Michael fashion to nitrostyrenes (equation 29)[101–103] and in a simple addition mode to acyliminoacetates (equation 30)[104] with very high levels of asymmetric induction.

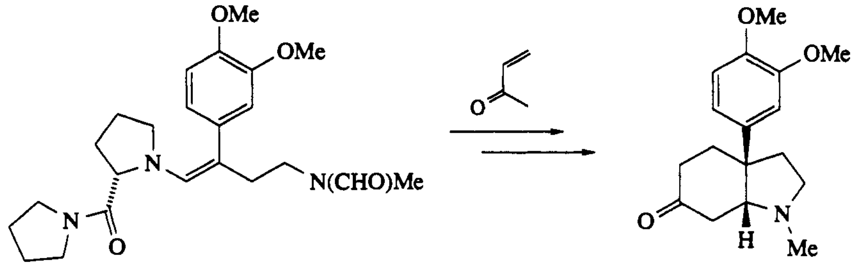


(29)



(30)

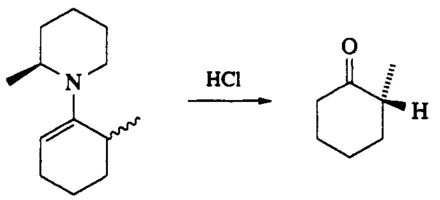
Similarly, reaction of an enamine derived from the pyrrolinylamide of proline with methyl vinyl ketone afforded an entry to the natural product mesembrine (equation 31).[105–107]



(31)

Mesembrine

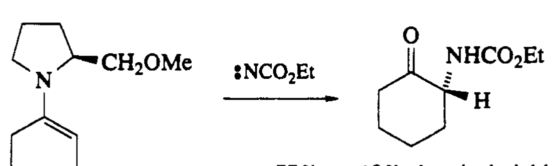
In an analogous fashion, the enamine derived from cyclohexanone and trimethylsiloxymethylpyrroline undergoes reaction with methyl acrylate with good levels of stereochemical control, while enamines derived from a noncyclic chiral amine gave poorer results.[108] Protonation of enamines under both thermodynamic and kinetic control has provided optically active products, though generally at less than practical levels.[109] The 'deracemization' illustrated in equation (32) represents an interesting example of this process.[110] Likewise, reaction of a chiral proline-derived enamine with a nitrene led to reasonable levels of stereochemical control but to poor chemical yield (equation 33).[111]



(32)

from racemic ketone

20% *ee*

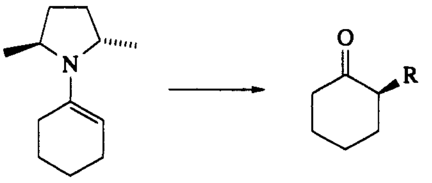


(33)

77% *ee*; 18% chemical yield

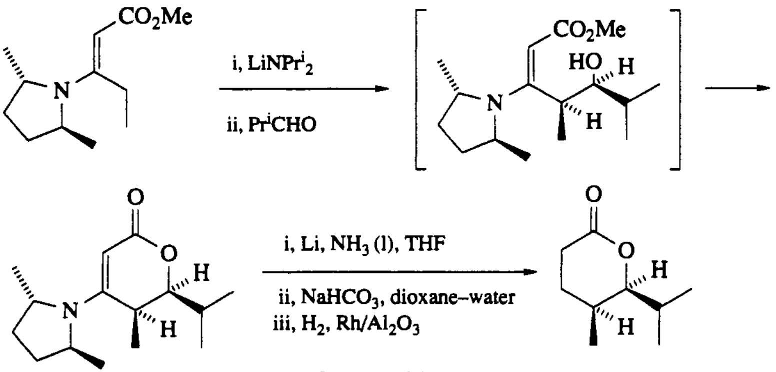
In 1977, we proposed that use of an unsymmetrical amine in such a reaction would lead to reaction from both rotational isomers (about the nitrogen–carbon formal single bond), reducing the level of stereochemical control.[112] As an alternative, the C_2 symmetrical amine *trans*-2,5-dimethylpyrrolidine was prepared in optically pure form and shown to be superior (equation 34). Other applications of this amine have followed from other research groups, including the alkylation of a vinylogous ester enolate derived from a β-keto ester vinylogous amide (Scheme 14).[113] We have recently introduced a new tricyclic chiral amine (**2**) and demonstrated its superior stereochemical directing ability in the same sequence.[114]

Schreiber has recently demonstrated excellent control of asymmetric induction in the intramolecular reaction of *in situ* prepared aldehyde enamines with unsaturated aldehydes (equation 35).[115,116] The

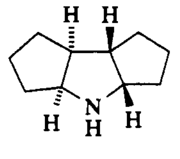


(34)

	ee (%)
R = Me	83
Pr^n	93
$CH_2CH{=}CH_2$	82

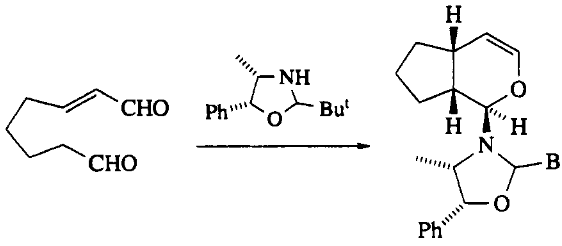


Scheme 14



(2)

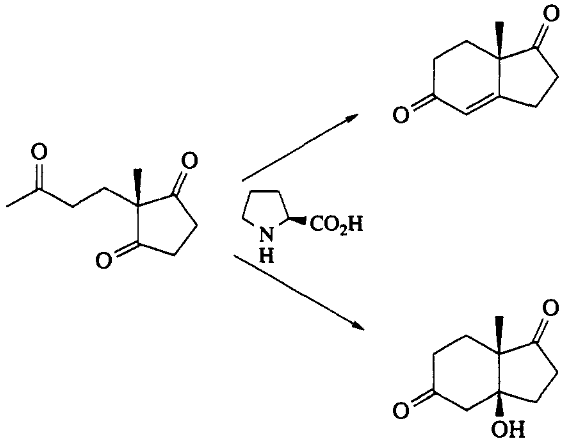
five-membered amine used has the feature that one of the carbons α to nitrogen bears a bulky *t*-butyl substituent that disfavors reaction from one of the two enamine rotamers.



(35)

The most interesting and practical asymmetric induction process that involves enamines is the proline-catalyzed conversion of the prochiral triketone in Scheme 15 to the cyclic aldol condensation product[117] or to the aldol product.[118] The course of the reaction is determined by the presence (or absence) of a strong acid such as hydrochloric acid as a cocatalyst. As a result of both the practical significance of the product(s) as synthetic intermediate(s) and the catalytic nature of this process, there has been a high level of interest directed at establishing the mechanistic pathway for these reactions.[119–124]

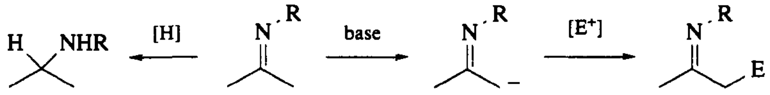
The most interesting observation relative to the mechanism of stereochemical control is that the level of asymmetric induction is *not* linear with the enantiomeric excess of the proline catalyst.[124] From these observations it can be concluded that (at least) two molecules of proline are involved at the stage where the stereochemical outcome is determined. While the intermediacy of an enamine is not required by any of the observations made to date on this reaction, it would appear probable.



Scheme 15

4.1.3 IMINES AND DERIVED ANIONS

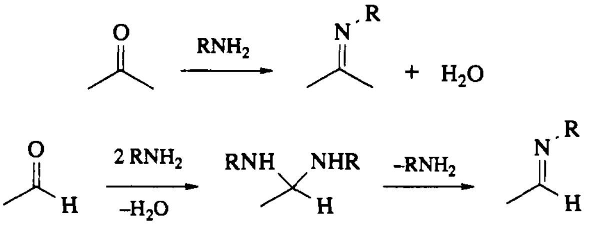
Use of imines as synthetic intermediates has been limited to mainly two processes: reduction to amines, and as precursors to azaallyl anions for reaction with a variety of electrophiles (equation 36). The former transformation can often provide the best access to highly substituted amines and the latter represents one of the highest yield methods for carbon–carbon bond formation α to the carbonyl group of an aldehyde or ketone. Thus, the following sections will deal not only with imines but also with the properties and chemical reactions of the derived anions. Several reviews are available (in addition to those that cover both enamine and imine anion chemistry)[15-17] as the result of recently uncovered methods for asymmetric induction through reactions of the anions.[125,126]



(36)

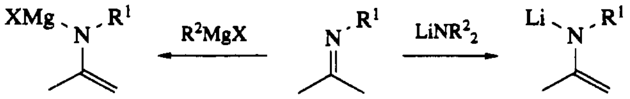
4.1.3.1 Formation

The reaction of a primary amine with a ketone to form an imine is generally quite straightforward, with the techniques typically used for water removal in the formation of enamines (see Section 4.1.2.1) also applicable here. As with the formation of enamines from aldehydes, preparation of the corresponding aldehyde imines can be difficult, especially with relatively unhindered aldehydes where formation of the double amine addition product can occur. However, these aminals often undergo loss of one amine unit thermally (typically during distillation) to generate the imine (Scheme 16).[127]



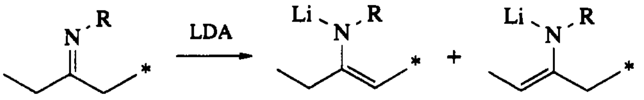
Scheme 16

Reaction of an imine with a strong base represents the most straightforward avenue for the formation of imine anions. The first bases used were lithium dialkylamides and Grignard reagents (equation 37) employed in the seminal studies of Wittig[128] and Stork.[129] The rate of deprotonation with both reagents is relatively low (for example in comparison to the reaction of ketones with dialkylamide bases) and the use of Grignard reagents requires elevated temperatures. Interestingly, the rate of deprotonation of a secondary amine by an alkyllithium is faster than reaction of the alkyllithium with the imine. Thus, the amine can be used in less than stoichiometric amounts.[128] Furthermore, it has been shown that methyllithium acts preferentially as a base with imines, providing little of the addition product.[128]



(37)

Formation of an imine from a symmetrical ketone effects a desymmetrization of the two α-carbons. The deprotonation of such imines has been extensively investigated by Bergbreiter and Newcomb.[125,130] In general, there is little observed selectivity for deprotonation by lithium dialkylamide bases, as, for example, with the 3-pentanone imine in equation (38).

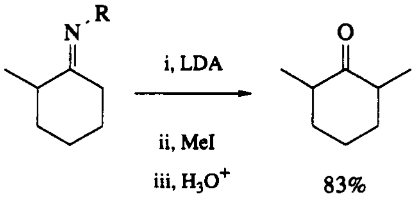


(38)

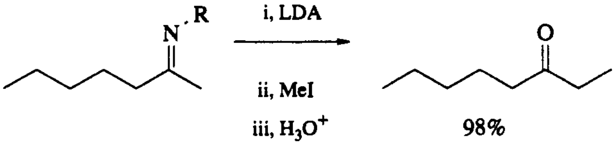
* = ^{13}C

R = Bu^t 30 : 70
= c-C_6H_{11} 53 : 47

The regiochemistry of deprotonation of imines derived from unsymmetrical ketones is of special significance for the synthetic applications of these anions for carbon–carbon bond formation. This selectivity is sensitive to both the amine moiety and the base used. With imines derived from cyclohexyl- or *t*-butylamine, deprotonation with either Grignard reagents or lithium dialkylamide bases will result in high selectivity (>98:2) for removal of the proton on the less substituted α-carbon as in equations (39)[128] and (40).[131]

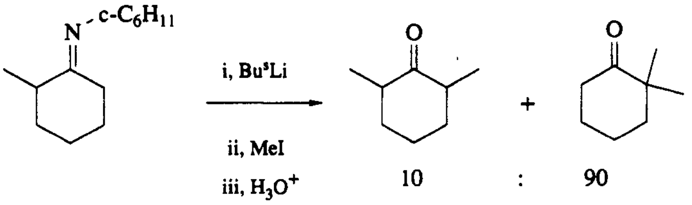


(39)



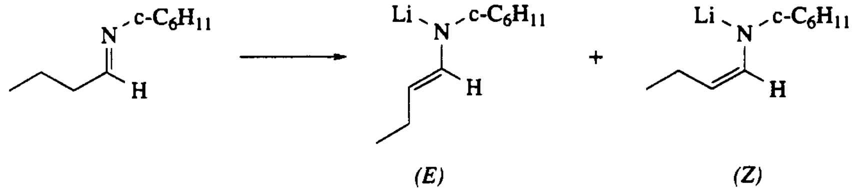
(40)

Conversely, Hosomi and Sakurai have shown that deprotonation with alkyllithium reagents occurs predominantly at the more substituted side of the cyclohexylimine of 2-methylcyclohexanone (equation 41).[132] However, the low yield in this sequence (as compared with, for example, equations 39 and 40) places this route to 2,2-disubstituted systems only equal with other techniques such as those that employ the more stable enolate-derived 2-alkyl cyclic ketones. Further, in no case did deprotonation of an unsymmetrical, acyclic ketone imine with an alkyllithium result in synthetically usable selectivity for the more substituted carbon.



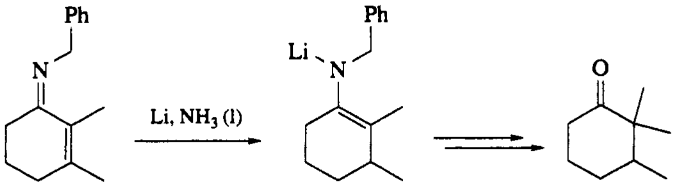
(41)

Knorr has studied both the kinetic and thermodynamic selectivity for the two geometric isomers about the carbon–carbon π-bond system in anions derived from acyclic ketones and aldehydes.[133] Thus, deprotonation of imines at –70 °C with lithium diisopropylamide in THF led to a mixture of (*E*)- and (*Z*)-anions where a small but consistent preference for the former was observed (equation 42). No change was observed upon heating these mixtures at 60 °C, although addition of an excess of the original imine, as a proton source, led to slow but essentially quantitative conversion of the (*E*)- to the (*Z*)-isomer. For the one aldehyde-derived system studied, the (*E*)-isomer was favored. The half-life for this isomerization varied with substituents from less than 10 min to 5 h at room temperature. The half-life for the example given in equation (42) was 30 min. It was also demonstrated that protonation of these anions occurred on nitrogen with apparent kinetic control and that the resulting secondary amine derived enamines were sufficiently stable (relative to rearrangement to the isomeric imines) for spectral analysis.



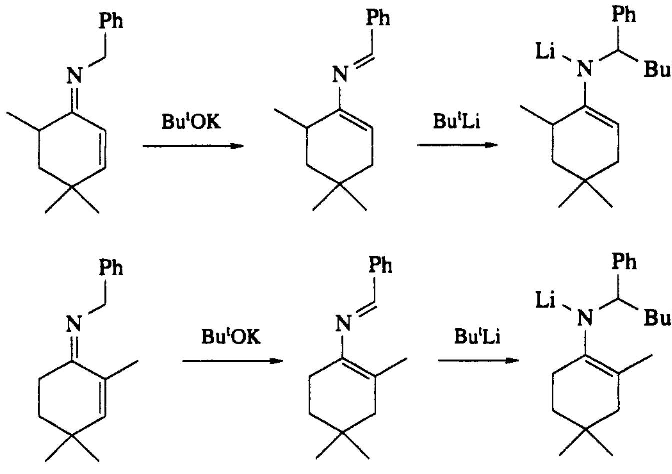
(42)

There are a number of indirect, yet valuable, methods for the preparation of imine anions. The more important of these provide convenient access to regiochemically defined anions, especially those that would otherwise be derived by deprotonation at the more substituted α-carbon. For example, Wender reported that reduction of imines derived from α,β-unsaturated ketones leads to lithium substituted anions, in analogy to the reduction of the ketones themselves (equation 43).[134]

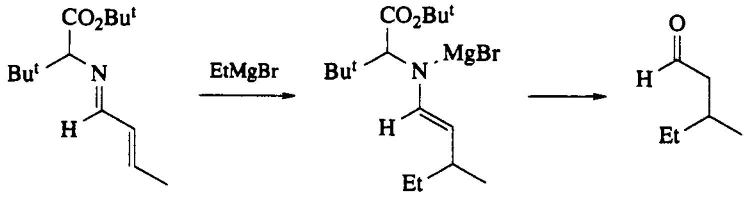


(43)

Imines derived from benzylamine and α,β-unsaturated ketones which represent 1-azadiene systems can be isomerized to the corresponding 2-azadienes with potassium *t*-butoxide. Addition of *t*-butyllithium occurs smoothly to afford simple imine anions that undergo alkylation in the usual fashion.[134,135] The two examples provided in Scheme 17 illustrate the power of this method to provide either α,α- or α,α'-substitution. On the other hand, reaction of similar 1-azadiene systems with Grignard reagents results in addition to form the imine anion directly (equation 44).[136] This example represents one of the early contributions to asymmetric induction in this area and will be elaborated in Section 4.1.3.5.

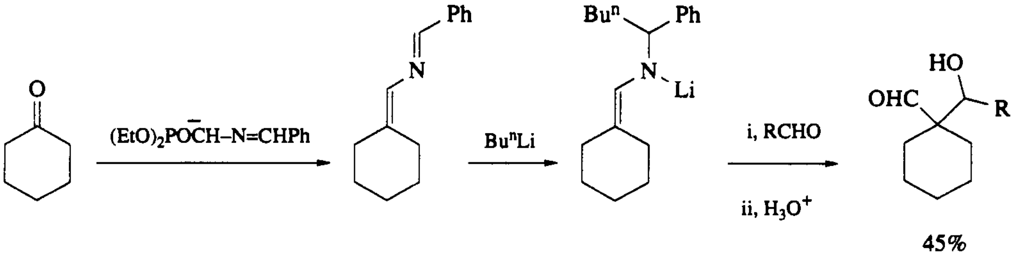


Scheme 17



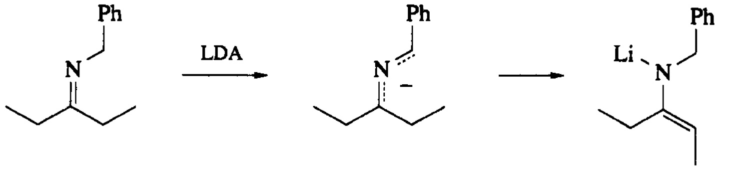
(44)

Martin has provided a useful procedure for geminal disubstitution at the carbonyl carbon of ketones.[137,138] Reaction of, for example, cyclohexanone (equation 45) with a phosphonate anion provides an alternative to Wender's route to 2-azadienes described above.



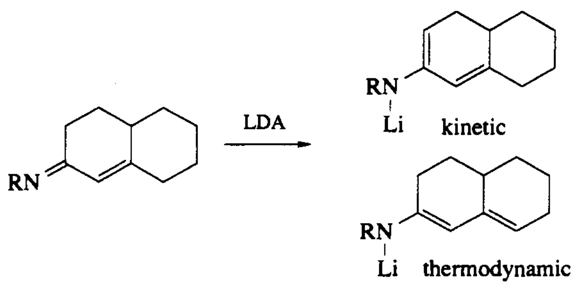
(45)

Bergbreiter and Newcomb have shown that the benzylamine imine of 3-pentanone is deprotonated by lithium diisopropylamide selectively at the benzylic position of a 2-azaallyllithium system that slowly isomerizes by a protonation–deprotonation sequence to afford the 1-azaallyl system (equation 46).[139]



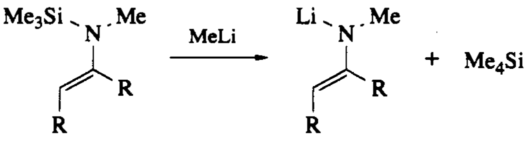
(46)

Stork has demonstrated that, in analogy with enolate chemistry, deprotonation of α,β-unsaturated imines with butyllithium under kinetic control produces the 'cross-conjugated' anion.[140] Conversely, use of slightly less than 1 equiv. of lithium diisopropylamide leads ultimately (by equilibration) to the conjugated system (equation 47).



(47)

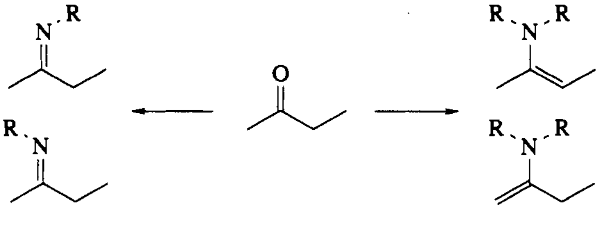
Enders[141] has shown that *N*-trimethylsilyl enamines[142,143] [*N*,*N*-bis(trimethylsilyl) enamines have also been prepared[144]] undergo reaction with methyllithium to afford imine anions (equation 48).



(48)

4.1.3.2 Structure and Chemical Properties

The structures of imines are generally devoid of the subtleties that permeate the same discussion of enamines. While two regiochemically distinct enamines can be derived from unsymmetrical ketones (each with two possible geometric isomers in the case of acyclic ketones), the corresponding imines show only geometric isomerism (equation 49). As would be expected, the preferred isomer is generally that which disposes the substituent on nitrogen *anti* to the larger carbon substituent.



(49)

On the other hand, the conversion of imines to their anions raises issues of regio- and stereo-chemistry (geometric) and is fully as complex an issue as the formation of enamines. The structural analysis of imine anions is further complicated by questions relating to the nature of bonding to the metal. In addition to extensive investigations by NMR spectroscopic techniques (see Section 4.1.3.3.2), there exists one single-crystal X-ray structural determination (Figure 2).[145] Unfortunately, the imine anion is significantly different to those used for synthetic purposes in that the nitrogen is directly substituted with a benzene ring. Thus, the orientations about bonds and the nature of the coordination to lithium that are present in this example may not be of use in explaining the properties and reactions of the imine anions derived from cyclohexyl- and *t*-butyl-amine. Note especially the coordination of lithium to the aromatic ring. The presence of a dimeric structure with two lithium atoms associated with each azaallyl anion unit is consistent with at least some of the spectral studies and is, indeed, quite reasonable. The ultimate usefulness of such ground state structural details to an understanding of the reactions of these species will probably not be resolved in the near future since dissociation pathways can be expected to be rapid. These reactions thus provide pathways for reactions occurring *via* higher energy monomeric species or, conversely, *via* even more highly aggregated clusters.

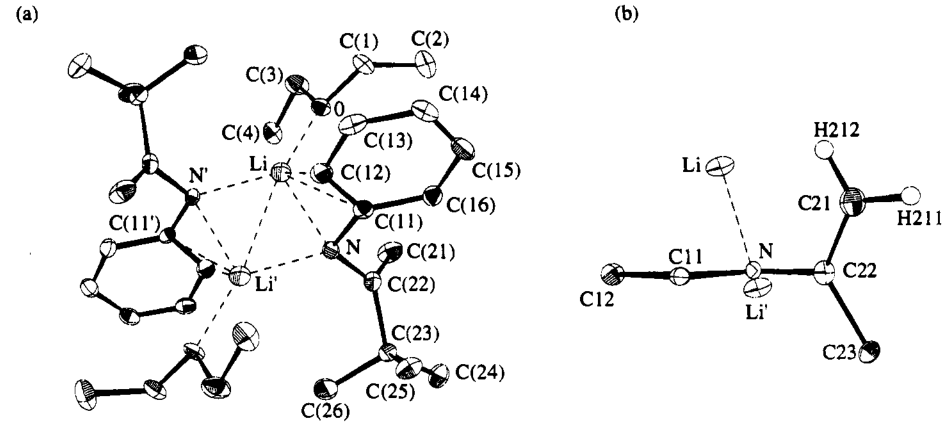


Figure 2 (a) Molecular structure of the dimer [CH$_2$C=CBu^{t}NPh)Li(OEt$_2$)]$_2$. Ellipsoids correspond to 50% probability. Distances: Li—Li', 2.544(2); Li—N, 2.076(2); Li—N', 2.000(2); Li—O, 1.937(2); Li—C(11), 2.437(2); N—C(11), 1.380(1); N—C(22), 1.436(1); C(22)—C(21), 1.326(1); O—C$_{av}$, 1.443 Å. Angles: Li—N—C(11), 87.28(7); Li—N'—C(11), 119.36(7); Li—N—Li', 77.22(7); N—Li—N', 102.78(7); N—Li—O, 121.93(9); N'—Li—O, 134.7(1); C(22)—N—C(11), 116.61(7)°. (b) Partial structure of the monomer viewing the dimer shown in (a) from the right and along the bisector of the angle C(22)—N—C(11)[145]

A number of investigators have examined the ease of isomerization about the formal carbon–carbon bond in imine anions.[133,146–149] Bergbreiter and Newcomb determined an energy barrier of approximately 17 kcal mol^{-1} for rotation about this bond in both the lithium imine anions derived from cyclohexyl- and *t*-butyl-amine addition to acetaldehyde.[146] The barrier for rotation for the corresponding anion derived from propionaldehyde was approximately 23 kcal mol^{-1}. Similar observations for the magnesium anions were made by Koga.[148] On the other hand, theoretical calculations (*ab initio*) by Fraser and Houk provide predicted barriers for the carbon–nitrogen bond of 16 kcal mol^{-1} and for the carbon–carbon bond of 45 kcal mol^{-1}.[150]

4.1.3.3 Spectral Properties

The unusual regiochemical and stereochemical features that are part of both the formation of imine anions and their subsequent reaction as nucleophiles have spawned considerable interest in deriving details of the bonding, especially of the metal, in these species.

4.1.3.3.1 Infrared spectra

The carbon–nitrogen double bond behaves in the IR region as would be expected, exhibiting stretching absorptions in the range 1690 to 1640 cm^{-1}.[151] No IR spectra for imine anions appear to have been reported.

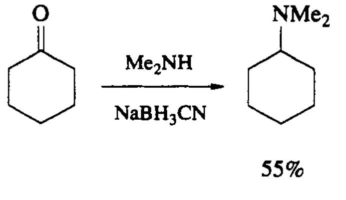
4.1.3.3.2 Carbon and proton NMR spectra

^{13}C NMR spectroscopy has served as the major tool for investigating the solution structure of imine anions. Analysis of these spectra is made difficult by the number of possible isomers and by the complication of an unknown state of aggregation. Thus, interpretation of the significance of these various observations and possible application to new systems is best done through reference to the original literature.[141,152–156]

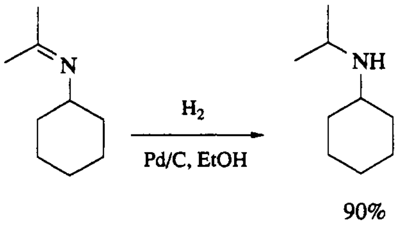
4.1.3.4 General Reactions

The two major synthetic applications of imine derivatives of ketones and aldehydes are: (i) for reduction to amines; and (ii) for formation of carbon–carbon bonds at the α-position to the original carbonyl group. Both topics are covered extensively in other volumes in this series and thus will be treated only briefly here.

A variety of reducing agents have been used for the conversion of imines to amines.[157–164] The examples in equations (50)[162,163] and (51)[157] are typical. The relatively slow destruction of sodium cyanoborohydride in slightly acid aqueous solutions allows the process of imine formation to be carried out simultaneously with reduction.[162–164] Apparently, the protonated imine is the species that is reduced and this process occurs significantly faster than reduction of the original carbonyl compound by this reagent. A recent report by Nose indicated that diborane in methanol will reduce only imines and no other functionality.[165] Apparently, the diborane reacts rapidly with methanol to form a derived reagent.



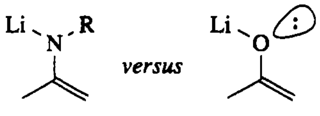
(50)



(51)

The alkylation of carbonyl groups through imine anions as the reactive nucleophile often represents (along with the corresponding chemistry of hydrazone anions) the very best procedure for accomplishing carbon–carbon bond formation α to a carbonyl group.[15,17,125,126] Indeed, in those cases where comparisons have been made, both the yield of the process and the level of conversion are superior with imine anions, as compared to reactions using enolate chemistry. The sole exceptions to this general rule are those systems where other functionality prevents the use of the strongly basic conditions required by all methods for formation of the anions. In such cases, enamine alkylation represents the method of choice.

In general, formation of the anion from an imine will occur at the least substituted α-carbon, and thus the overall process of alkylation *via* imine anions is generally limited to substitution at a methylene or methyl group. There are, however, alternative techniques for the formation of these anions that provide some access to more substituted species (see Section 4.1.3.1). It would appear that the comparative success of imine anion alkylations is the result of a comparatively slow rate of proton exchange between the product imine and the anion and to an almost total lack of reaction at nitrogen. Indeed, both of these factors may be the result of the same feature of imine anions that contrasts with corresponding enolates: given heteroatom coordination to the metal from an sp^2 lone pair on nitrogen, the remaining unshared electron density is delocalized in the π-system. In contrast, a similar bonding arrangement in enolates leaves one sp^2 lone pair 'free' to act as a base or a nucleophile (Scheme 18).



Scheme 18

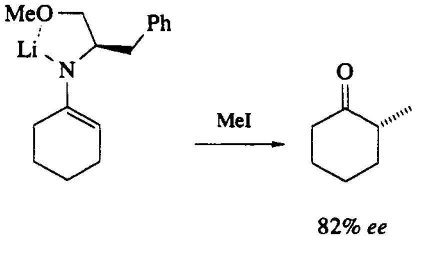
Recently, Hickmott has reported an unusual reaction in which methyl acrylate underwent reaction with the relatively small amount of enamine present in equilibrium with the imine of a 2-methylcyclohexanone.[166] In all cases the major product was the 2,2-disubstituted isomer, although the reaction yields were in general low (13–64%). Previous reports of this unusual carbon–carbon bond forming reaction are rare.[167]

4.1.3.5 Stereochemical Features

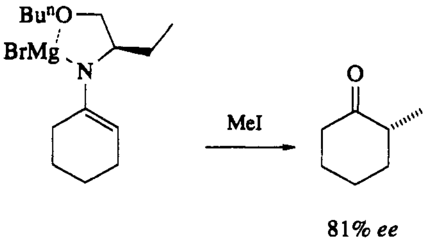
The synthetic implications of carbon–carbon bond formation *via* imine anions gained additional significance with the first report by Horeau[168] of asymmetric induction in the alkylation of the anion derived from isobornylamine and cyclohexanone.[126] However, the degree of stereochemical control in the formation of 2-methylcyclohexanone by this process (72% *ee*) was below the synthetically useful level. Additionally, incorporation of other alkyl groups afforded even lower levels of asymmetric induction. Further studies by Yamada with a variety of chiral amines did not improve on these results.[169]

Both Meyers[170,171] and Whitesell[172] independently ascribed the less than ideal level of asymmetric induction to the possibility that reaction was taking place from two or more rotamers of the anion and designed chiral amines incorporating a second, oxygen ligand for the metal involved (equations 52 and 53). These ideas came from previous[173] and concurrent[112] activities in each group to design more rigid systems for asymmetric induction. Both of these methods for the alkylation of cyclohexanone afforded improved and practical levels of control and amazingly consistent results given the difference in the metal involved (lithium *versus* magnesium).

Similar studies have been carried out for control of absolute stereochemistry in the alkylation of aldehydes *via* imine anions. Fraser examined the reactions of the imine anion derived from α-phenylethylamine with lithium as the counterion where optimum conditions afforded approximately 70% optical



(52)

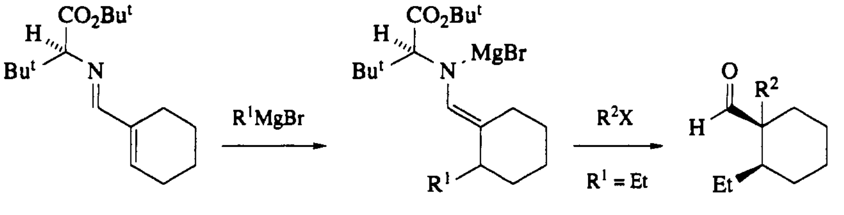


(53)

purities.[174] Meyers extended his studies with chelating chiral auxiliaries and found, surprisingly, that alkylation of octanal afforded optimized levels of control (17 to 54%) inferior to those observed in the alkylation of cyclohexanone.[175] Examination of a range of chelating auxiliaries (all *trans*, vicinal alkoxyaminocyclohexane derivatives) led to improved but still less than practical levels of control (75%).[176]

Other chelating auxiliaries for imine anion alkylation have been developed. Hashimoto and Koga used *t*-butyl esters of the amino acids leucine and valine, where the chelating functionality is presumably the ester carbonyl oxygen.[177,178] Saigo examined the influence of the metal counterion and found large differences, with zinc species providing the highest levels of control with 2-methoxy-1,2-diphenylethylamine as auxiliary.[179] Asymmetric induction in the reactions of imine anions with tin as the counterion has also been examined.[180] McArthur has shown that the chiral auxiliary can be bound to a polymer, thus facilitating recovery for reuse.[181,182]

In an unusual variation, Hashimoto and Koga found that Grignard reagents add to the β-carbon of imines derived from α,β-unsaturated aldehydes (rather than acting as base to form the anions).[183,184] High levels of asymmetric induction (91 to 95%) were observed with the *t*-butyl ester of leucine as the chiral auxiliary (equation 54).



(54)

4.1.4 HHYDRAZONES, OXIMES AND DERIVED ANIONS

The synthetic uses of hydrazones and oximes for carbon–carbon bond formation differ little from those of imines as their anions represent enolate equivalents except for certain methods that have been developed for asymmetric induction. Conversely, the formal replacement of the carbon substituent of imines by a heteroatom (nitrogen for hydrazones and oxygen for imines) opens reaction pathways such as the Beckmann rearrangement of oximes and the Wolff–Kishner and Shapiro reductions of hydrazones that have no analogy in the chemistry of imines.

4.1.4.1 Formation

Methods for the preparation of hydrazones and oximes differ little from those used for the synthesis of imines from ketones and aldehydes in that the appropriate nitrogen species and the ketone are mixed. However, the equilibrium for the majority of reactions of ketones and aldehydes with hydrazines and hydroxylamine favor the product hydrazones and oximes and removal of the water formed by the condensation is not required.[185,186] Acid catalysis is complicated by the basicity of the reagent and, for example, the maximum rate of oxime formation is at approximately pH 4.[187] Complicating reactions can occur such as the 1:2 combination of hydrazine with two ketones or aldehydes to form azines but this is not a problem with the substituted hydrazines that are used for asymmetric induction.

Of special importance to the applications of hydrazones and oximes to carbon–carbon bond formation is the observation that these derivatives are considerably more resistant to hydrolysis than are either enamines or imines. Thus, methods for mild regeneration of the carbonyl group from these derivatives are especially significant. Among the reagents/systems developed are: oxidation with bromine;[188] reaction with thallium[189] or sodium nitrate in trifluoroacetic acid;[191] reaction with dinitrogen tetroxide;[190] oxidation with periodate;[192,193] and oxidation with *m*-chloroperbenzoic acid.[194]

4.1.4.2 Structure and Chemical Properties

Many of the same features of imine and imine anion structure previously discussed (Section 4.1.3.2) are apparent with hydrazones and their anions and with oxime ether anions. A number of investigations of the structure of *N*,*N*-dialkylhydrazone and oxime ether anions as well as oxime dianions have been carried out, Most notable are the experimental studies of Collum and Clardy,[195–198] and the theoretical treatment by Glaser and Streitwieser.[199,200] As might be expected, and as was observed for lithiated imine anions (*vida supra*), lithiated hydrazones exist in the solid as aggregates, with two lithiums coordinated to the aza anion system (Figure 3).[195]

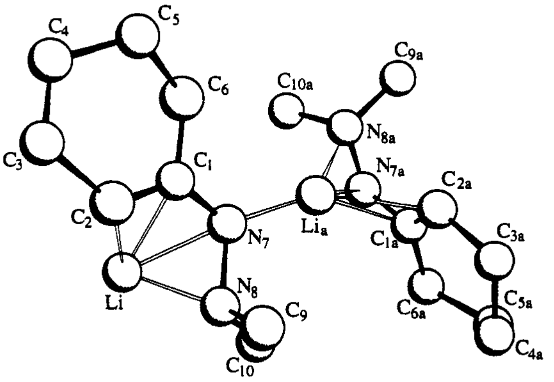


Figure 3 Molecular structure of the asymmetric unit of lithiated cyclohexanone dimethylhydrazone polymer (hydrogen positions have been left off for clarity)[195]

Note that one of the lithiums is associated with the nitrogen sp^2 lone pair, while the other is π-bound to the three atoms of the allylic anion. As with the structure of imine anions, there appears to be no simple answer for the unusual properties of these anions, especially in asymmetric induction, and the interested reader is referred to the original literature.

4.1.4.3 Spectral Properties

4.1.4.3.1 *Infrared spectra*

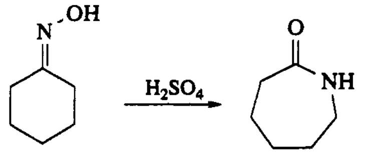
A systematic survey of the IR spectra of hydrazones and oximes has been carried out and summarized by Bellamy.[201] Values for the carbon–nitrogen double bond do not differ greatly, and are surprisingly similar for oximes and imines.

4.1.4.3.2 *Proton NMR, carbon NMR and ultraviolet spectra*

A very complete treatment of the proton and carbon NMR spectra as well as the UV absorption spectra of *N*,*N*-dialkylhydrazones has been reported by Grundemann.[202]

4.1.4.4 General Reactions

In addition to carbon–carbon bond forming reactions of derived anions, hydrazones and oximes are important derivatives of carbonyl groups for the Beckmann rearrangement (of oximes to amides, equation 55)[203,204] and the Shapiro reaction (tosylhydrazones to alkenes, equation 56).[205,206] Of historical significance is the Wolff–Kishner reduction of ketones *via* their hydrazones (equation 57).[207] The procedure is rarely employed since the conditions of this procedure are considerably harsher than those of more recently developed sequences.



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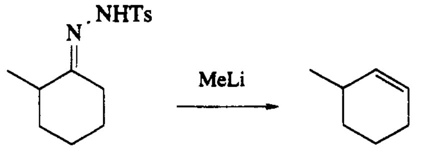

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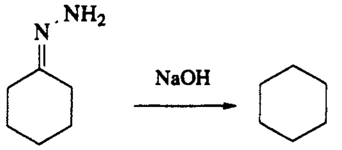
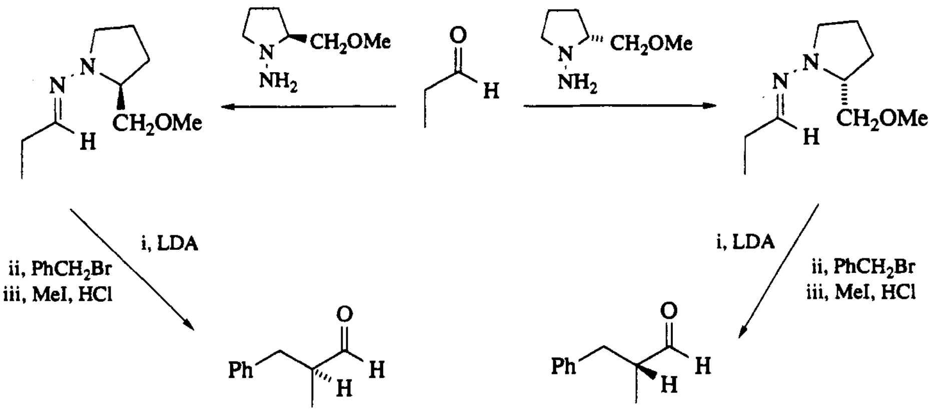


(57)

4.1.4.5 Stereochemical Features

The application of hydrazone and oxime anions for carbon–carbon bond formation generally offers no advantages to the use of imine anions and, significantly, the hydrolysis of the hydrazone or oxime products to form the product carbonyl group is substantially more difficult than is the cleavage of an imine. The notable exception is in the area of asymmetric induction where powerful direction has been obtained with chiral hydrazone anions. This area has been explored fully by Enders[208–213] following initial observations of Enders and Corey.[214,215] Enders has recently reviewed these contributions.[211,212]

The basic concept, although most likely not the detailed mechanism, of the Enders asymmetric induction follows from the chelation-controlled asymmetric alkylation of imine anions introduced by Meyers[170,171] and Whitesell.[172] The hydrazones derived from either the (*S*)- or the (*R*)-enantiomer of *N*-amino-2-methoxymethylpyrrolidine (SAMP and RAMP, derived from the amino acid proline) can be converted to anions that undergo reaction with a variety of electrophiles. After hydrolysis of the product hydrazones, the alkylated ketones can be obtained with good to excellent levels of optical purity (Scheme 19).



Scheme 19

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4.2

Use of Carbonyl Derivatives for Heterocyclic Synthesis

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4.2.1 INTRODUCTION

The carbonyl group and its derivatives occupy a central position in synthetic organic chemistry. In the preparation of heterocyclic compounds, they may play a multiple role: they provide the reactive species required for the crucial ring-closing bond formation and, simultaneously, act as valuable sources for the heteroatom in the ring produced.

In view of the vast scope of this synthetic field, the present review is not intended to provide a complete account of this subject, but rather to emphasize certain selected points. As already indicated by the title, only carbonyl derivatives will be dealt with, particularly heteroatom-type or positively charged analogs of carbonyl groups, not carbonyl compounds themselves (unless they serve as starting material for the carbonyl derivatives). In addition, carbonyl derivatives with more than one heteroatom (such as the aldehyde-derived nitrones), which can be utilized for 1,3-dipolar cycloadditions,[1] had to be omitted, due to the restricted space.

For the chosen examples, the, inevitably subjective, emphasis was laid preferentially on the synthetic use of the presented reactions and on their applicability to the synthesis of natural products or other important molecules which prove difficult to synthesize, rather than on mechanistic or theoretical aspects, unless these are essential for the prediction of the chemo-, regio- or stereo-selective outcome of the reaction.

The article is subdivided according to the gross reaction types and the reactive species involved, for the convenience of the reader. Wherever possible, not only the carbonyl derivatives and their reactions are presented, but also modern synthetic trends and strategies which benefit from them.

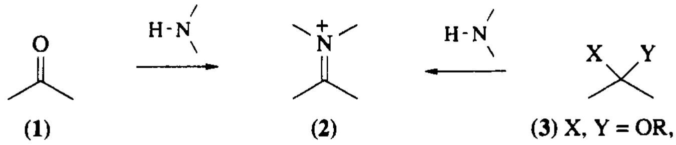
4.2.2 CYCLIZATION REACTIONS INVOLVING NUCLEOPHILIC ATTACK ON CARBONYL DERIVATIVES

4.2.2.1 Reactions Involving Imines or Iminium Ions

4.2.2.1.1 Creation of the reactive species and general aspects

For a long time, iminium ions (**2**; Scheme 1) have been recognized as useful functional groups in the synthesis of important and demanding heterocyclic ring systems. Milder methods of iminium preparation, efficient modern strategies (such as tandem techniques, intramolecular reactions, *etc.*) and the use of attractive new counter-nucleophiles demonstrate the still-increasing value of these nitrogen-containing carbonyl derivatives as indispensible synthetic tools.[2]

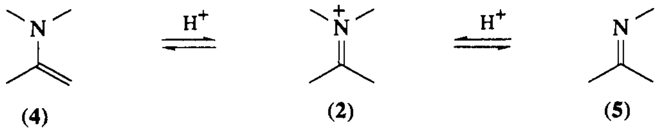
Iminium salts (**2**) can commonly be prepared from the reaction of amines with aldehydes or ketones (**1**; Scheme 1). With formaldehyde as the carbonyl precursor, Eschweiler–Clark-type methylation reactions may occur when using reducing acids such as formic acid.[3,4] Alternatively, other sp^3-type, nitrogen-free carbonyl derivatives (**3**), such as acetals[5] and hemiacetals,[6,7] can be used, where this is favorable. Highly electron-poor carbonyls, such as chloral (*cf.* Scheme 10),[8] may show distinctly decreased reactivity in aqueous solution, due to the extended hydrate formation.



(**1**) (**2**) (**3**) X, Y = OR, OH

Scheme 1

Furthermore, iminium ions (**2**) can be generated from enamines (**4**) and imines (**5**), by reaction with electrophiles such as H^+ (Scheme 2; for corresponding acylation reactions, see Section 4.2.2.2).[9]

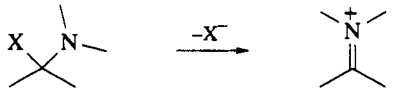


(**4**) (**2**) (**5**)

Scheme 2

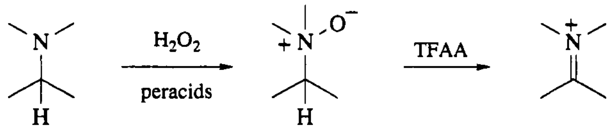
Other sp^3-type, nitrogen-containing carbonyl derivatives (**6**), such as α-amino alcohols,[10] α-amino ethers[11] (*e.g.* oxazolidines[12]), α-amino sulfides (*e.g.* thiazolidines[13]) and α-amino nitriles,[14] are efficient sources for iminium ions (Scheme 3).

Similarly, though not starting from carbonyl precursors, iminium ions can be prepared from tertiary amines (**7**) by oxidative *N*-functionalization and subsequent β-elimination,[15] as employed in the Polonovski reaction (*cf.* Section 4.7),[16] and by decarbonylation of α-amino acids (Scheme 4).[17,18]



(6) X = NR$_2$, OR, CN

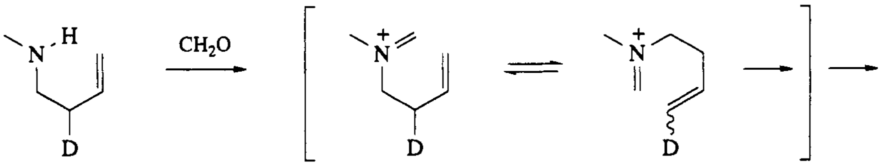
Scheme 3



(7)

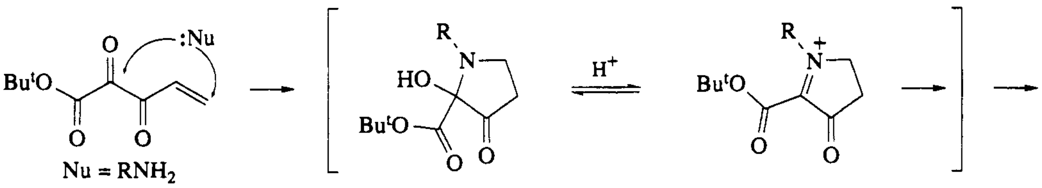
Scheme 4

Increasing importance has to be attributed to modern 'tandem' (or 'cascade') techniques—reaction sequences that can be performed as a one-pot procedure because the first reaction step creates the arrangement of functional groups needed for the second to occur. Schemes 5–7 present some *in situ* preparations for iminium species, which can then react further with appropriate nucleophiles that are already present (preferably in the same molecule). Most elegantly, *in situ* generation of iminium ions for tandem processes was performed by a 3,3-sigmatropic (aza-Cope-type) rearrangement (Scheme 5),[19] but also by initial Michael-type addition reactions to vinyl-substituted 1,2,3-tricarbonyls (Scheme 6)[10] or to electron-deficient alkynes *via* enamines (Scheme 7).[20]



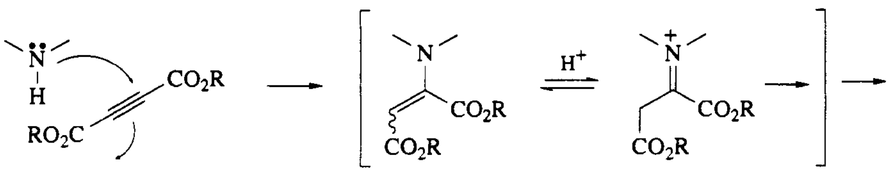
D = donor substituent

Scheme 5



Nu = RNH$_2$

Scheme 6



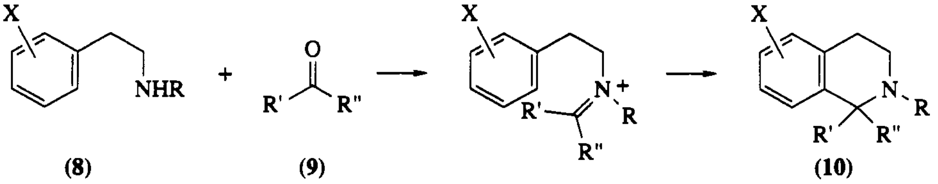
Scheme 7

Iminium cations are comparatively weak electrophiles and consequently require quite reactive nucleophiles. This limitation offers the advantage that intramolecular reactions, which lead to heterocyclic ring systems, are strongly favored over intermolecular ones.

4.2.2.1.2 Cyclization reactions

(i) With aromatic nucleophiles

The most prominent intramolecular reaction of iminium ions with aromatic C-nucleophiles is the long-known Pictet–Spengler condensation[21] of 2-phenylethylamines (**8**) with reactive carbonyl compounds (**9**)—by far the most important route to natural and synthetic tetrahydroisoquinolines (**10**; Scheme 8).

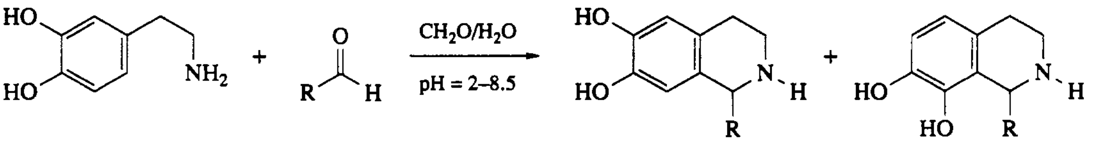


(8) **(9)** **(10)**

Scheme 8

Plants have taken advantage of this successful synthetic principle for their enzymatic production of isoquinoline[22] (as well as β-carboline[23]) alkaloids.[24] In the chemical laboratory, this synthetic approach has been exploited for nearly 80 years in numerous biomimetic-type syntheses.[25] This special form of the Mannich reaction requires electron-rich aromatics, if possible with free phenolic oxygen functions in *ortho* or *para* positions (Scheme 9). As for the carbonyl compound, aldehydes or 1,2-dicarbonyls (and very recently 1,2,3-tricarbonyls[26,27]) are preferred. Due to the mild 'physiological' reaction conditions required with such ideally reactive partners (often pH = 7, room temperature, aqueous medium), this condensation was also found to play a role in human organisms, leading to endogenous 'mammalian alkaloids'.[28,29,22]

Pictet–Spengler reactions with dopamine-type 2-arylethylamines (**11**) usually proceed with high regioselectivity, *para* to the activating group, thus leading to 6,7-dihydroxytetrahydroisoquinolines (**12**; Scheme 9). Only for smaller aldehydes, especially formaldehyde (R = H), have appreciable amounts of *ortho*-cyclized products (**13**) been reported, especially at neutral pH.[30]

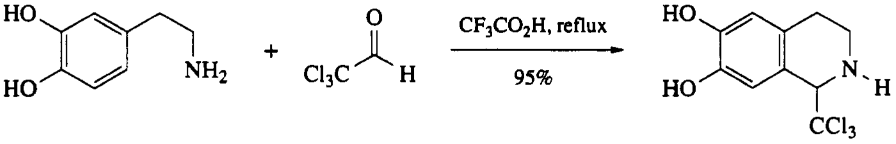


(11) **(12)** **(13)**

R	*pH*	*Ratio (12):(13)*	*R*	*pH*	*Ratio (12):(13)*
H	2	87:13	Me	2	100:0
H	7	50:50	Me	7	75:25

Scheme 9

Some aldehydes require special reaction conditions, *e.g.* chloral (**14**), which, due to extended hydration, does not undergo a Pictet–Spengler reaction with dopamine (**11**) in aqueous solution but can be condensed very efficiently in organic acids, such as trifluoroacetic acid, to give the 1-trichloromethyltetrahydroisoquinoline (**15**) in high yield (Scheme 10).[8]



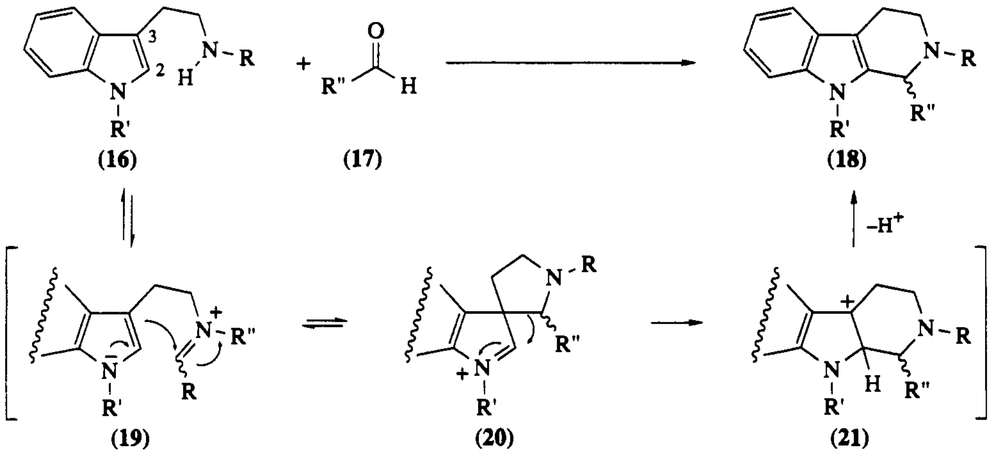
(11) **(14)** **(15)**

Scheme 10

Furthermore, nonaqueous, especially nonprotic, solvents allow Pictet–Spengler condensation reactions to occur with acid-labile aldehydes[31] (*e.g.* when bearing additional acetal functions) and may significantly influence the stereoselectivity (see below).

Isotope-labeling experiments and the secondary formation of regioisomers show that the Pictet–Spengler condensation may be reversible under more vigorous conditions.[32]

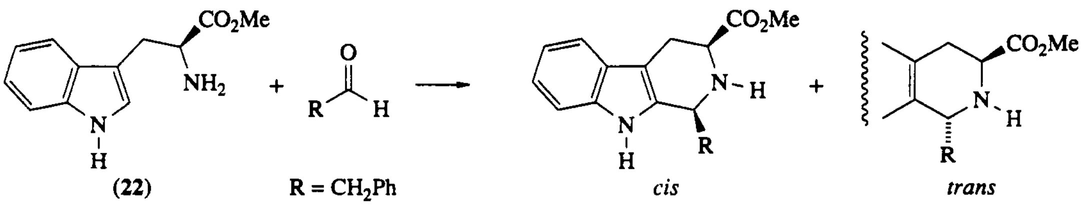
Starting from (3-indolyl)-2-ethylamines (**16**), such as tryptamine, and aldehydes (**17**), the Pictet–Spengler reaction has been broadly extended to the synthesis of tetrahydro-β-carbolines (**18**), the most important synthetic access to such indole alkaloids (Scheme 11). Early findings[33–36] and newer results[37] suggest an initial attack of the iminium salt (**19**) at the reactive 3-position (Scheme 11), rather than the expected 'direct' ring closure at C-2. The intermediate spiroindolenine (**20**) (which can be trapped by *in situ* hydrogenation[38]) is thought to undergo a Wagner–Meerwein-type rearrangement to (**21**).



Scheme 11

In view of the multifold important biological activities[39] of isoquinoline and β-carboline alkaloids, increasing efforts have been made to perform Pictet–Spengler reactions stereoselectively. The most obvious chiral auxiliary to induce asymmetric control is the stereogenic center of the corresponding aromatic amino acids, such as DOPA or tryptophan.

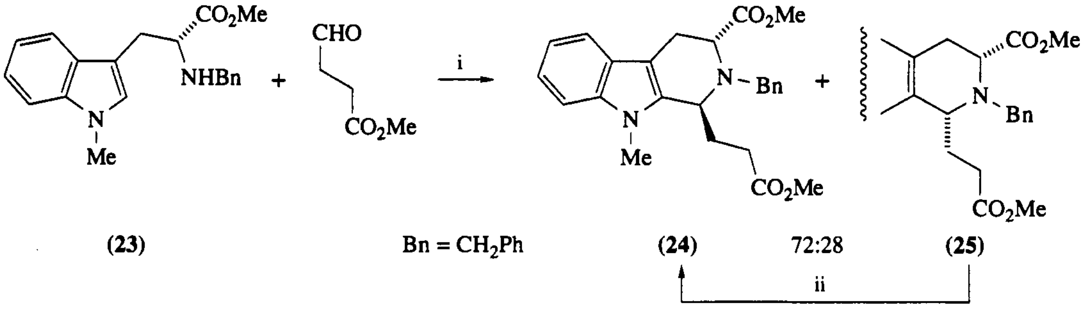
Thus, at low temperatures, tryptophan esters (**22**) with nonalkylated, primary amino functions condense with aldehydes to give tetrahydro-β-carbolines with predominantly *cis* configuration (Scheme 12).[40] At higher temperatures, *e.g.* in refluxing benzene, the diastereomeric ratio is reversed, giving mainly the *trans* product. Under these thermodynamically controlled conditions, however, extended racemization may become an additional serious problem.



Temperature	*Solvent*	*Yield (%)*	*cis/trans ratio*	*ee (%)*
0 °C	CH_2Cl_2	74	82:18	90
40 °C	CH_2Cl_2	72	45:55	
r.t.	Benzene	65	78:22	
80 °C	Benzene	76	37:63	11

Scheme 12

For an efficient, directed synthesis of *trans*-tetrahydro-β-carbolines such as (**24**), hydrocarbyl (*e.g.* benzyl) substituents at the amino function[41] and at the pyrrole nitrogen of the tryptophan ester, as in (**23**), are favored (Scheme 13).[42] Under kinetically controlled nonacidic conditions, small amounts of the corresponding *cis* isomer (**25**) are formed.[43] The latter can be completely converted into the *trans* product (**24**) by heating in methanolic HCl (1%). Alternatively, the Pictet–Spengler reaction can be carried out directly in an acidic medium, obviously under thermodynamic control (to give *trans* products almost exclusively).[42] Moreover, under these reaction conditions, the *N*-benzyl group allows a complete retention of optical purity, as the epimerization occurs at C-1 solely, not at C-3.



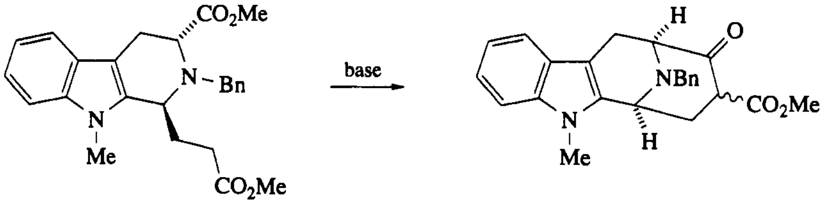
(**23**) (**24**) (**25**)

i, PhH, Δ, 10 h, 90%; ii, MeOH–HCl, Δ

Scheme 13

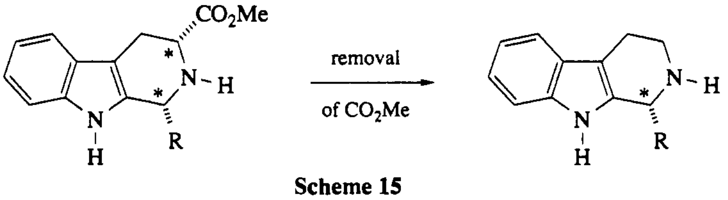
On the basis of a rapid and reversible[44] spiroindolenine mechanism, a pathway for the Pictet–Spengler reaction was proposed recently, which is consistent with all these stereochemical findings.[45]

The amino acid derived carboxy group can be utilized as a functionality for further synthetic manipulations, *e.g.* for cyclization reactions to 1,3-bridged β-carbolines, using the Dieckmann reaction, a promising stereocontrolled approach to macroline-related alkaloids (Scheme 14).[43,46]



Scheme 14

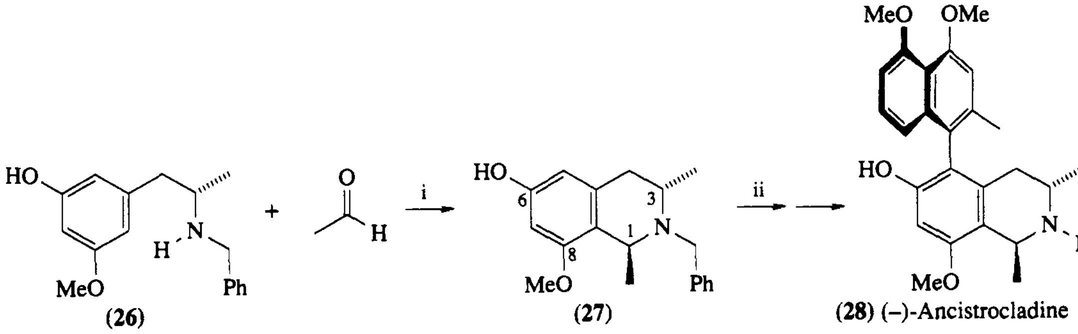
Alternatively, after having governed the stereochemistry at C-1, the carboxy group at C-3 can be eliminated (Scheme 15), *e.g.* according to Yamada's method.[47,48] Such as overall enantioselective synthesis of optically pure 1-alkyltetrahydro-β-carbolines from the 'chiral pool', optionally with (*R*) or (*S*) configuration, has been applied in numerous indol alkaloid syntheses.[49–51]



Scheme 15

A regio- and stereo-controlled Pictet–Spengler reaction in the field of tetrahydroisoquinolines is the condensation of the secondary amine (**26**) with acetaldehyde (Scheme 16). At pH 11.5, the *trans* product (**27**), with the free phenolic OH-group at C-6, a key intermediate in the total synthesis of the naphthylisoquinoline alkaloid (–)-ancistrocladine (**28**),[52–54] is obtained in good yield.[55] This yield can be further upgraded by epimerization at C-1 of the analogous *cis* diastereomer (6.5%). Alternatively, the corresponding 6-methoxy-8-hydroxy regioisomer, which was required for the first total synthesis of the related alkaloid ancistrocladisine,[56] can be attained as the main product by running the reaction at pH 2.[55]

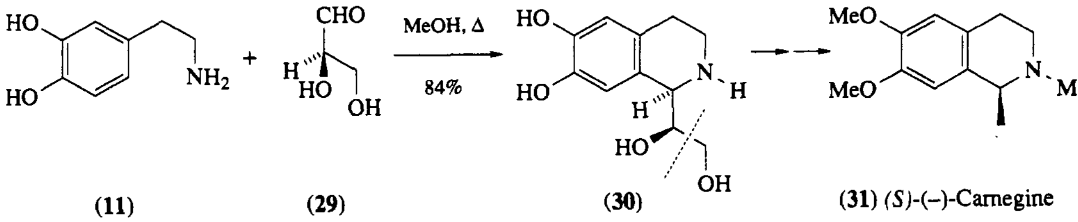
Besides these influences exerted by C(3)- and N-substituents, asymmetric induction may also be achieved by the use of chiral aldehydes. Thus, reaction of dopamine (**11**) with (*R*)-(+)-glyceraldehyde (**29**) affords the tetrahydroisoquinoline (**30**) in excellent yield (93%) and high diastereoselectivity (9:1; Scheme 17).[57] The broader synthetic applicability of this approach is exemplified by the oxidative cleav-



i, H_2O/Pr^iOH (2:1), pH = 11.5, 78%; ii, regio- and stereo-selective aryl coupling

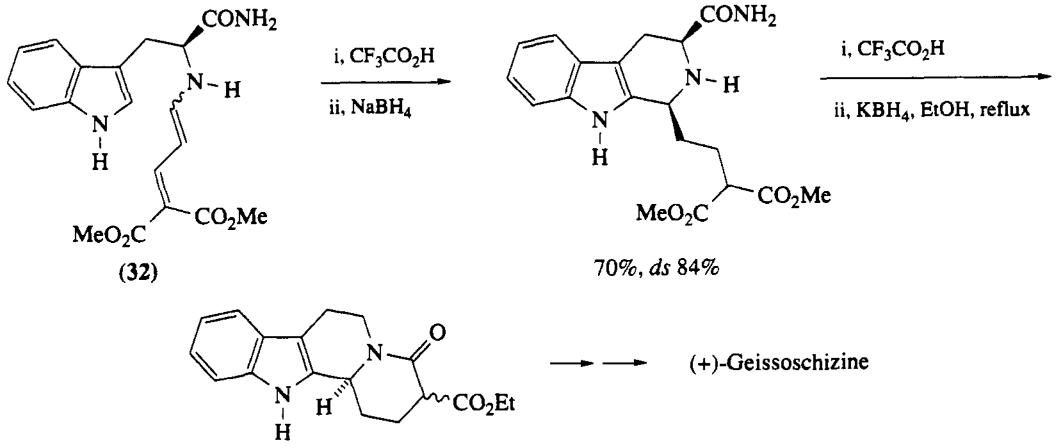
Scheme 16

age of the chiral auxiliary and the subsequent transformation into various optically active alkaloids, such as (*S*)-(–)-carnegine (**31**).[57]



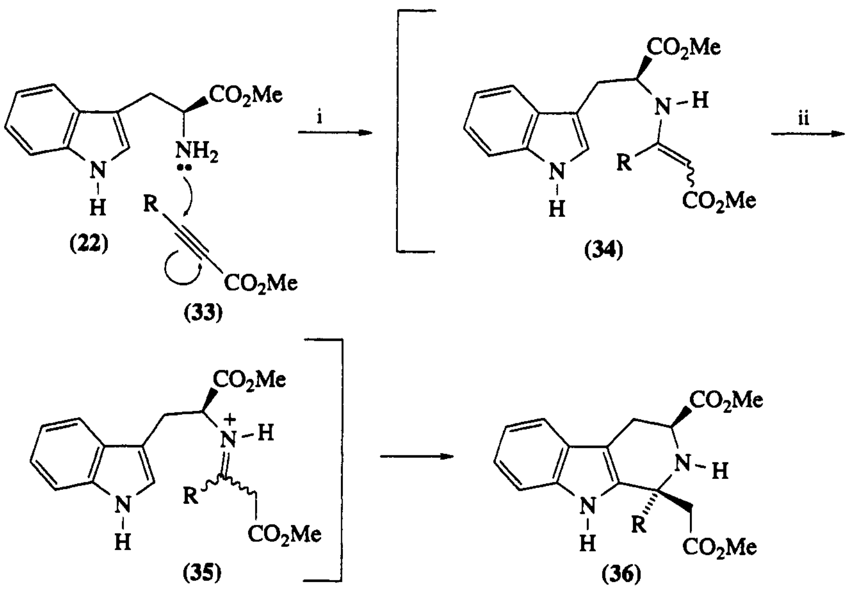
Scheme 17

Several modifications of the Pictet–Spengler reaction have been developed.[58] From these, only two, both relying on iminium salt generation from intermediate enamines, will be presented here. The first one is the acid-catalyzed cyclization of the dienamine (**32**), which is one of the key steps in an elegant total synthesis of (+)-geissoschizine and related alkaloids (Scheme 18).[59] As in previous similar cases,[50] the tryptophan-derived amide function governs the stereochemical outcome at C-1 much more efficiently than the analogous ester group. After the stereocontrolled ring closure, the amide can be removed by reduction of the corresponding nitrile.



Scheme 18

The second procedure worth presenting involves the Michael addition of tryptophan ester (**22**) to propynoate ester (**33**; R = H) to give (**34**; R = H), and subsequent acid-induced cyclization *via* the iminium salt (**35**; R = H; Scheme 19),[60,61] to afford tetrahydro-β-carboline (**36**; R = H), which could not be prepared by the 'simple' Pictet–Spengler reaction with malonic hemialdehyde.[20] Again, asymmetric induction can be achieved through the amino acid derived ester function. Extension of this procedure to dimethyl butynedioate (**33**; R = CO_2Me_3) lowers the diastereoselectivity (Scheme 19), but simultaneously strongly enhances the reaction rate and the yield, and gives rise to 1,1-disubstituted (formally, ketosuccinic acid derived) tetrahydro-β-carbolines (**36**; R = CO_2Me_3), which are key intermediates for the synthesis of alkaloids of the ajmaline group.



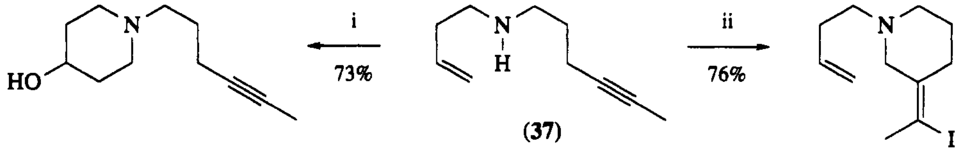
i, $CHCl_3$, r.t.; ii, TFA/$CHCl_3$, r.t.; 50%, *ds* 71% (R = H); 91%, *ds* 68% (R = CO_2Me)

Scheme 19

(ii) With vinylic and alkynic C-nucleophiles

Under the assistance of external nucleophiles, simple, nonactivated alkenes can undergo intramolecular attack to give nitrogen-containing heterocyclic compounds, *via* the iminium salt.

Alkynes are more susceptible than alkenes to external soft nucleophiles, as demonstrated in the reaction of (**37**) with formaldehyde, where an excess of NaI dramatically changes the cyclization mode (Scheme 20).[62]



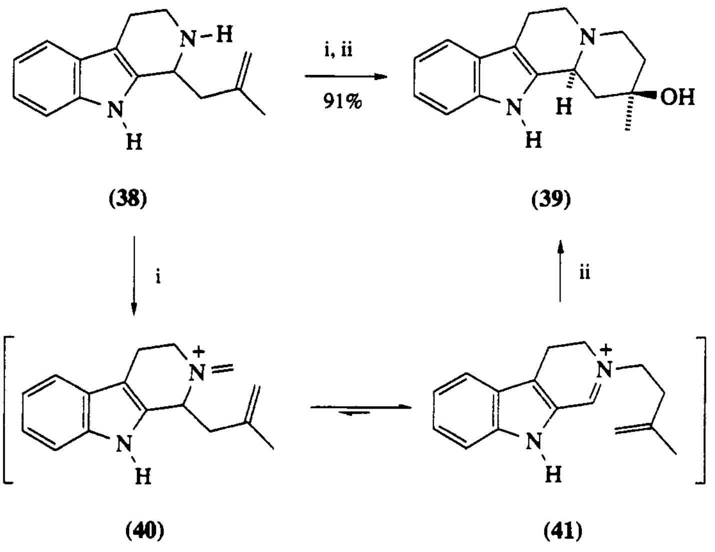
i, CH_2O, H_2O, camphorsulfonic acid (CSA); ii, as in i, excess NaI

Scheme 20

Starting from homoallylic amines (such as **38**; Scheme 21) and, for example, formaldehyde, the initially formed iminium species (**40**) may, before cyclizing to (**39**), suffer a rapid charge-accelerated 3,3-sigmatropic rearrangement to (**41**), the relevance of which was shown by reductive trapping.[63] More recent investigations with related optically active substances show that, depending on the electronic nature of the substrate, cyclization may occur with or without a preceding aza-Cope rearrangement.[64]

On the basis of this rearrangement, an efficient synthetic route to pyrrolidines such as (**46**) was developed by Overman, starting from oxazolidine (**42**), *via* hydroxylated homoallylic imines such as (**43**; Scheme 22).[19] Mechanistically, the formation of (**46**) may be explained as a tandem-type combination of a cationic aza-Cope rearrangement with a subsequent Mannich cyclization (route a) or, alternatively, as an alkene–iminium ion cyclization/pinacolic rearrangement sequence (route b).

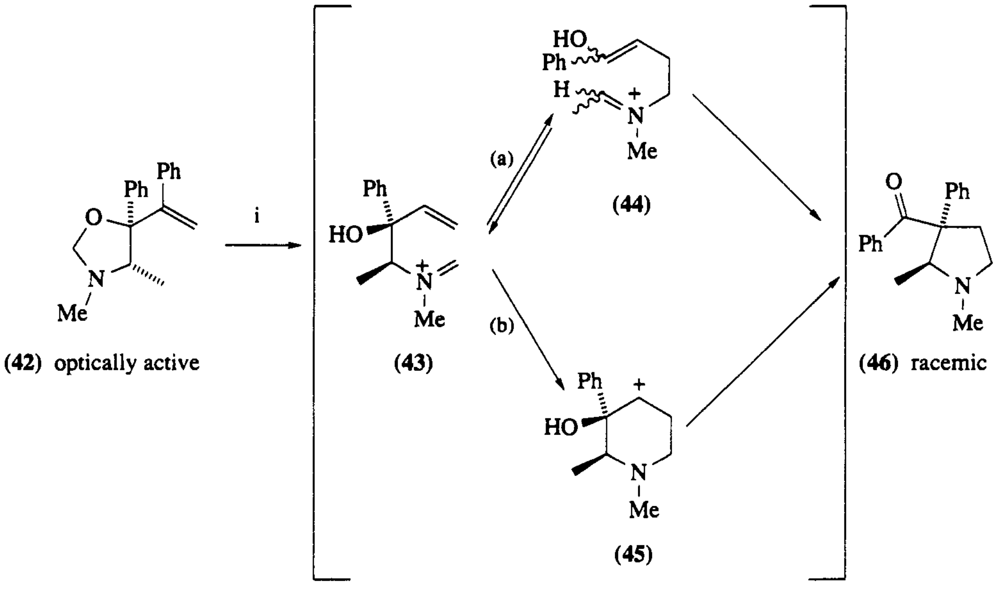
Some evidence for the mechanism being reaction mode (a) comes from the conversion of optically active oxazolidine (**42**) to a racemic mixture of pyrrolidine (**46**; Scheme 22),[19] obviously *via* the achiral intermediate (**44**), since in a pinacolic-type rearrangement *via* (**45**), the chiral information would have been



i, AcOH/H_2O, formalin, 3 h, r.t.; ii, H_2O, 24 h, r.t.

Scheme 21

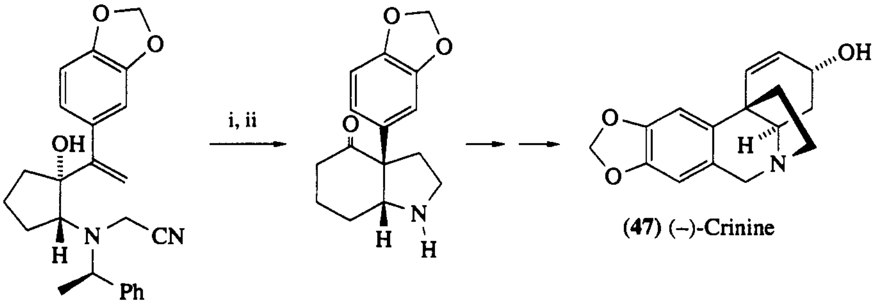
expected to be conserved. In consequence, this example reveals the limited stereochemical use of this strategy for the synthesis of enantiomerically pure compounds.



i, toluene, CSA, 60 °C, 1.5 h

Scheme 22

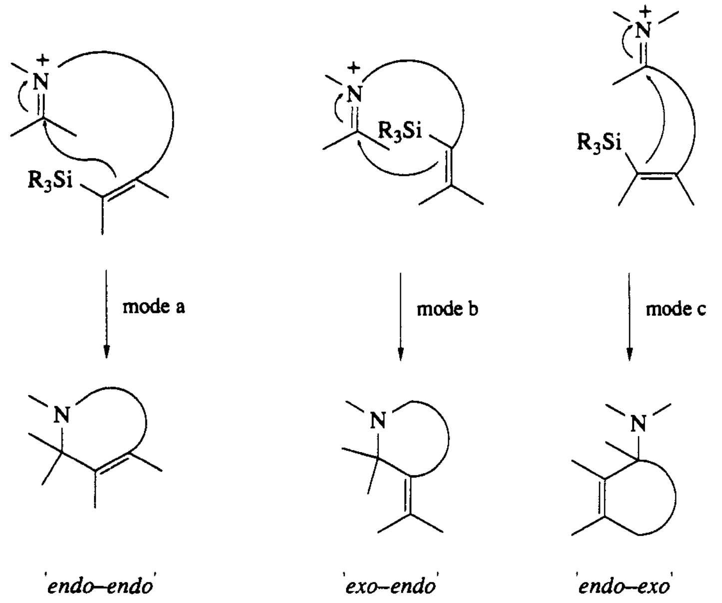
On the other hand, the alkaloid (–)-crinine (47) can be prepared in enantiomerically pure form by a similar approach (Scheme 23),[12,65] possibly due to the different reaction conditions applied or because of the additional chiral *N*-phenylethyl residue. This method also applied very well for other nitrogen-containing heterocycles,[66] including other ring sizes.



i, $AgNO_3$, EtOH, 25 °C, 3 h, 80%; ii, ammonium formate, Pd/C, 100 °C, 0.5 h, 94%

Scheme 23

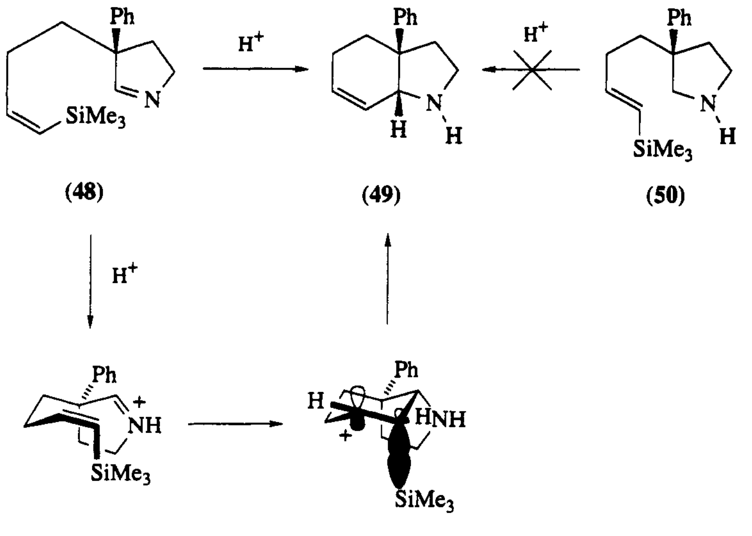
During the last few years, silyl-substituted alkenes in particular have emerged as potent 'terminators' for regio- and stereo-selective iminium ion initiated cyclization reactions.[67] In principle, such ring closure reactions proceed either in an endocyclic (types a and c) or exocyclic fashion (type b)[68] with respect to the terminating alkene, and in an endocyclic (types a and b) or exocyclic mode (type c) with respect to the iminium function (Scheme 24), with the C=C double bond being retained in its place and the silyl group substituted with retention of configuration.



Scheme 24

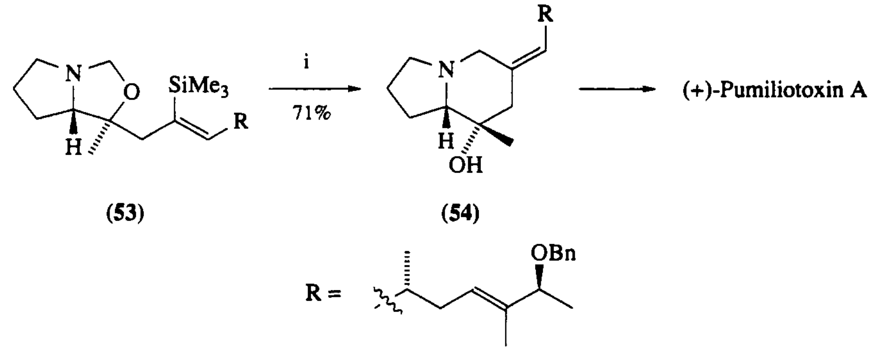
Correspondingly, this stereospecificity may inevitably require the correct configuration to exist in the starting material, as illustrated by comparative reactions of the diastereomeric vinylsilanes (**48**) and (**50**; Scheme 25).[69] While (**48**) smoothly cyclizes to give the hexahydroindole (**49**), reaction of (**50**) completely fails, proceeding at least 7000 times more slowly. This can be rationalized by considering the geometry of the ring-closed species (**52**) that is primarily formed. For steric reasons, only the β-silyl carbenium ion (**52**), as obtained from the (*Z*)-isomer (**51**), can profit from the 'β-effect', the typical stabilizing interaction of the empty carbenium *p*-orbital with the C—Si σ-bond.

The reverse case, a cyclization in an endocyclic fashion with respect to the iminium salt and in an exocyclic way with respect to the vinylsilane part, is represented by the first enantioselective synthesis of (+)-pumiliotoxin A (Scheme 26), which establishes, for the first time, the complete stereostructure of this famous cardiac-active poisonous alkaloid obtained from frogs.[70] The key step, the impressively stereo-



Scheme 25

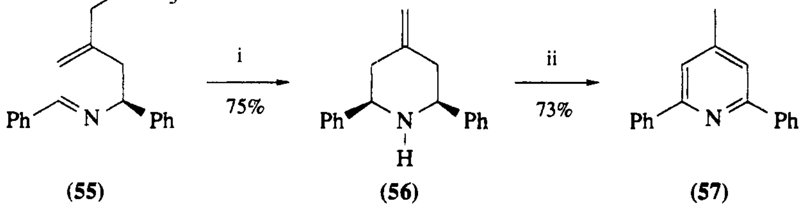
specific conversion of (**53**) into the alkylideneindolizidine (**54**), with the correct (*Z*)-configuration at the exocyclic double bond, is performed under near neutral conditions. Another impressive example is the stereocontrolled total synthesis of the indole alkaloid (+)-geissoschizine.[59]



i, pyridine–TsOH, MeOH, pH ≈ 4.5, 80 °C

Scheme 26

Trialkylsilyl groups may assist imine-initiated cyclization reactions as alkylic as well as vinylic substituents. Thus, in the presence of desilylating reagents, such as Bu_4NF or LiI, the allylsilane (**55**) is cyclized diastereoselectively to give the 2,6-disubstituted *cis*-4-methylenepiperidine (**56**), which can be dehydrogenated to give the aromatic pyridine (**57**; Scheme 27).[71]

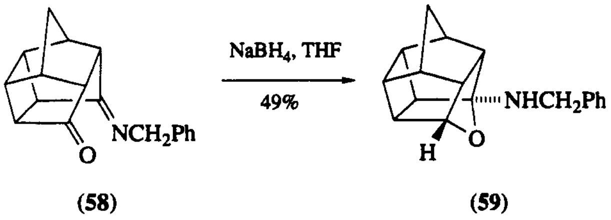


LiI, THF, 40 °C; ii, $Hg(OAc)_2$, AcOH, Δ

Scheme 27

(iii) With heteroatom nucleophiles

Far less important for the synthesis of important molecular frameworks are cyclization reactions involving attack of heteroatom nucleophiles on carbonyl derivatives, since these reactions are not concerned with carbon–carbon bond formation but rather with transforming the carbonyl derivatives into other carbonyl derivatives, such as the reductive cyclization of (**58**) to give the cyclic *O*,*N*-acetal (**59**; Scheme 28).[72]



Scheme 28

4.2.2.2 Reactions Involving Acyliminium Ions

4.2.2.2.1 Creation of the reactive species and general aspects

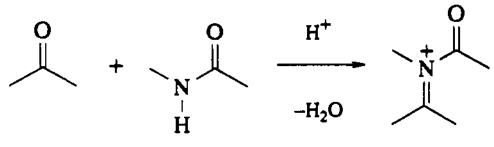
N-Acylated iminium ions have gained increasing importance in the past few years.[73] As the less electron-rich counterparts of the aforementioned 'softer' iminium ions, they offer strongly enhanced reactivities towards nucleophiles, combined with the attractive possibility of introducing additional functionalities (*e.g.* the amide group) into the desired heterocycles.

The sp^2-type hybridized ionic acyliminium species (**60**) are in chemical equilibrium with the corresponding covalently bound sp^3-type species (**61**; Scheme 29).[74]

(**60**) (**61**) X = OR, OH, Hal, *etc.*

Scheme 29

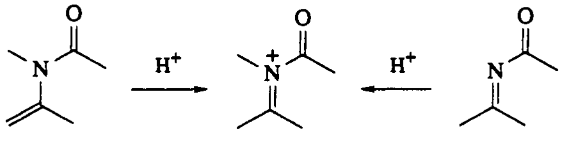
In analogy to the synthesis of iminium salts (Section 4.2.2.1.), acyliminium ions (**60**) can be obtained from carbonyl precursors (**1**), such as ketones or aldehydes, and carboxylic acid amides (**62**; Scheme 30). In addition, other amides can be used, such as *p*-toluenesulfonamides, which lead to the corresponding *N*-tosylated iminium salts.[75]



Scheme 30

Acyliminium ions can also be created by treatment of the easily accessible enamides (**63**) with protic acids (Scheme 31; see also Section 4.2.2.1). Alternatively, transformation of enamides (**63**) to (**60**) can be achieved with C-electrophiles, by simultaneous formation of carbon–carbon bonds (*cf.* Scheme 37).[76]

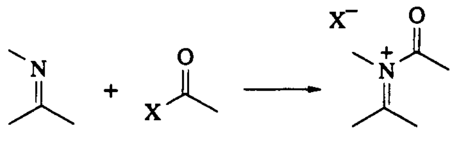
In contrast, considerably less importance can be attributed to the comparable preparation of (**60**) from acylimines (**64**; Scheme 31), by protonation for example,[77] due to their usually pronounced instability,



(63) **(60)** **(64)**

Scheme 31

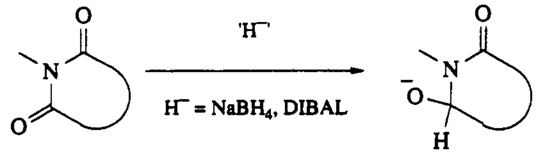
for which only few exceptions have been described.[78,79] Acyliminium ions (**60**) can also be generated by *N*-acylation of imines (**5**), *e.g.* with acyl halides (**65**; Scheme 32).



(5) **(65)** **(60)** X = Hal

Scheme 32

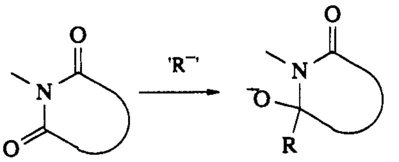
The preparation of acyliminium ions is not restricted to aldehyde or ketone derivatives as starting materials, but can also use the more highly oxidized carboxylic acid amides as precursors, *e.g.* reduction of imides (**66**) affords (**67**; Scheme 33).[80,81] For constitutionally unsymmetrical imides, regiocontrol can be achieved in many cases by the choice of the appropriate hydride-transfer reagent.[82]



(66) **(67)**

Scheme 33

Similarly, addition of C-nucleophiles 'R⁻'[83] (such as Grignard reagents) to cyclic imides (**66**) leads to acyliminium ions, *via* their sp^3-type precursors (**68**; Scheme 34). Again, regioselectivity is observed for unsymmetrical imides, which are attacked preferably at the less-hindered carbonyl group.[84] A disadvantage of this procedure may be seen in occasional side reactions, such as ring opening or over-alkylation.

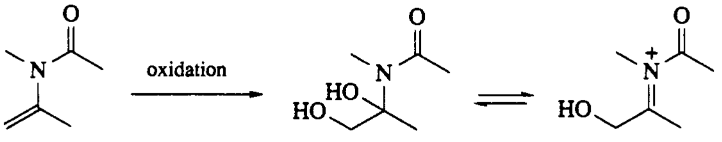


(66) **(68)**

Scheme 34

Other oxidative methods have been mentioned,[85,86] such as the transformation of enamides (**63**) to α-hydroxylated acyliminium salts (**70**), *via* the hemiaminals (**69**).[87]

Compared with the simple iminium ions, the enhanced reactivity of acyliminium salts opens up a greatly enlarged spectrum of counter-nucleophiles, which now includes alkenes and aromatic compounds possessing no donor substituents (see Section 4.2.2.2.2).



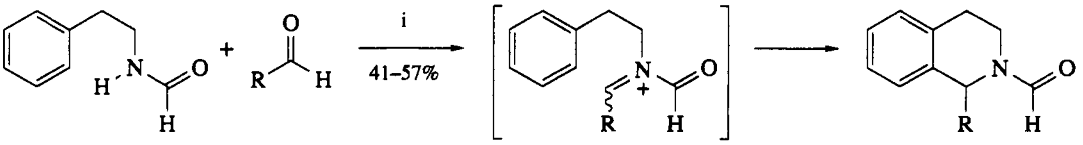
(63) **(69)** **(70)**

Scheme 35

4.2.2.2.2 *Cyclization reactions*

(i) With aromatic carbon nucleophiles

'Normal' Pictet–Spengler-type cyclization reactions of 2-arylethylamines and reactive carbonyl compounds require activated aromatic systems, ideally with unprotected phenolic oxygen functions in *ortho* and *para* positions (Section 4.2.2.1). The high reactivity of acyliminium salts, however, allows very effective analogous ring closure reactions, even for the oxygen-deficient 2-phenylethylamine *via* its formamide (**71**), which may be prepared *in situ* (Scheme 36).[88] Similar tetrahydroisoquinoline syntheses were achieved in good to excellent yields *via* the corresponding tosylamides.[75]



(71)

i, AcOH/TFA, 5–10 h, Δ; R = H, Me, Ph, 4-$O_2NC_6H_4$

Scheme 36

In a very elegant tandem-type combination of such a modified Pictet–Spengler condensation and an initial Pummerer reaction (*e.g.* Section 4.2.2.4), the polycyclic framework (**75**) of the erythrina alkaloid (**76**; Scheme 37) is formed diastereoselectively, in a single step, from (**72**) in 72% yield; the required acyliminium ion (**74**) is created by an intramolecular alkylation of the intermediate enamide (**73**).[76]

In addition analogous β-carboline syntheses with tryptamine and α,β-unsaturated aldehydes, hitherto impossible even under acid catalysis,[89] were found to proceed very smoothly *via* acyliminium salts (**78**), induced by *in situ* acylation of the intermediate imine (**77**) with methyl chloroformate,[90] allowing a first directed total synthesis of the indole alkaloid borrerine (**79**; Scheme 38).

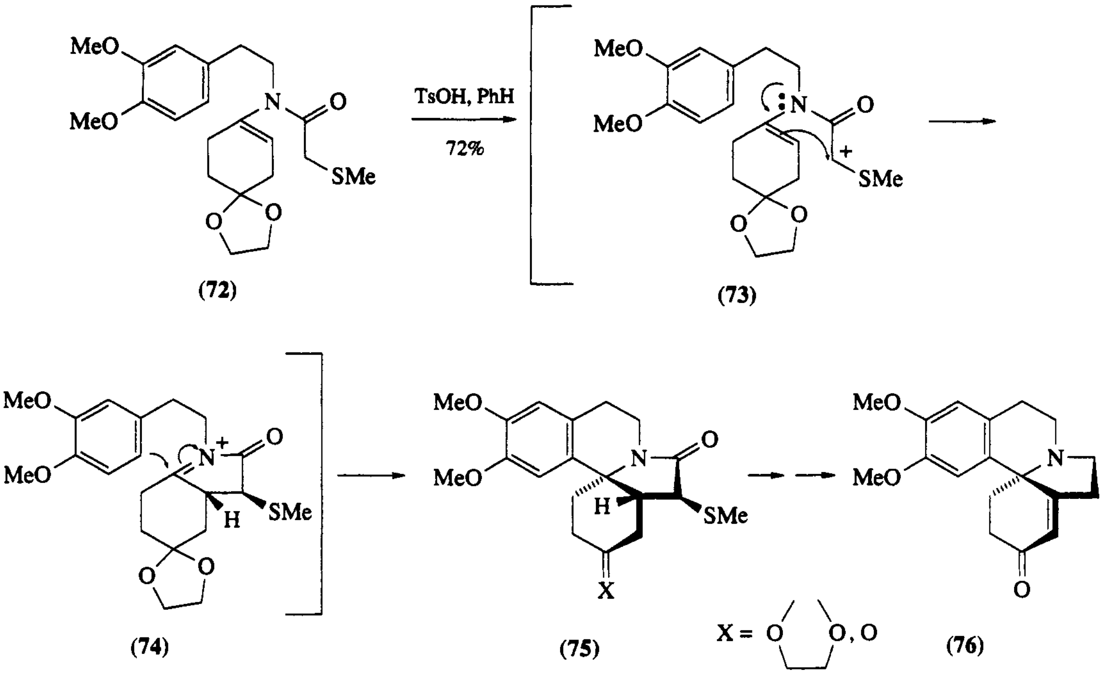
An impressive acyliminium ion initiated cyclization to the β-carboline system, combined with the simultaneous formation of an additional seven-membered ring, is found in the synthesis of the vasodilating alkaloid vincamine (**80**), as outlined in Scheme 39.[91]

(ii) With alkenic carbon nucleophiles

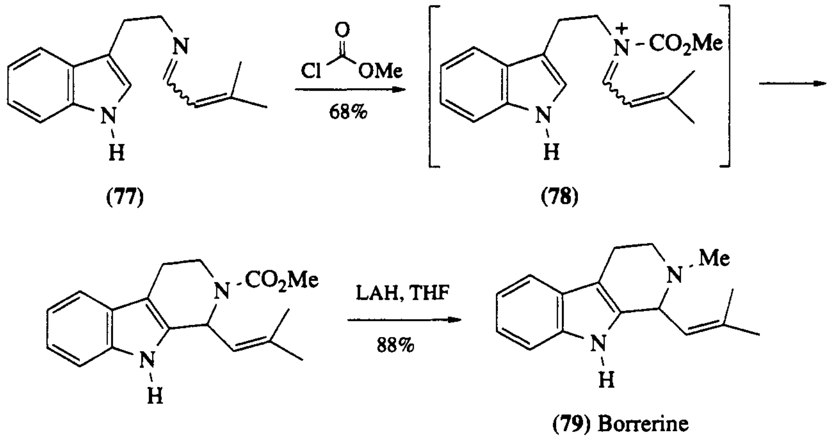
As mentioned previously, acyliminium ions are electrophilic enough to react intramolecularly even with nonactivated alkenic π-systems. These cyclization reactions have been recognized and elaborated as valuable tools in the stereoselective total synthesis of quinolizidine, indolizidine and pyrrolizidine alkaloids.[92,93] A typical example from Speckamp's laboratory is the highly stereospecific acid-catalyzed cyclization of (**81**) to (**83**; Scheme 40), presumably *via* the corresponding acyliminium ion (**82**).[94]

Analogously, other more complex natural products, such as the antiulcerogenically active alkaloid matrine (**85**), can be built up with high stereocontrol (Scheme 41), with an enol ether function as a more electron-rich nucleophile for the intermediate iminium ion (**84**).[95]

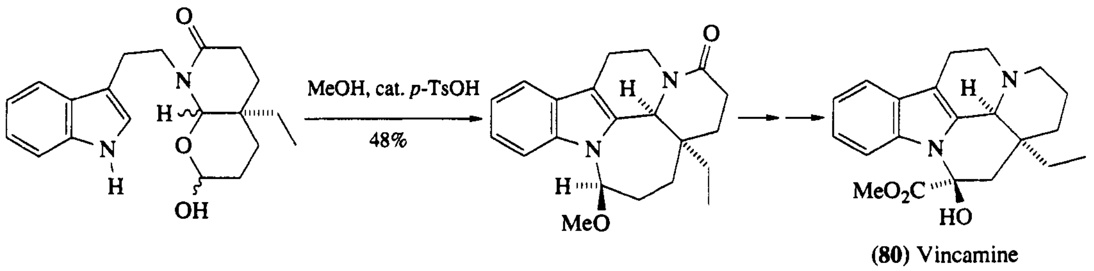
Special steric or electronic influences may thwart the expected reaction pathway, as in the regio- and stereo-selective conversion of (**86**) to the pyrrolizidine (**87**; Scheme 42).[96] This surprising formation of a five- instead of a six-membered ring is interpreted in terms of an aza-Cope equilibrium between the expected iminium salt (**88**) and its isomer (**89**). The latter finally cyclizes regioselectively in an exo-type mode to give (**87**). Further support for this assumption was obtained from quenching experiments with related compounds.[97]



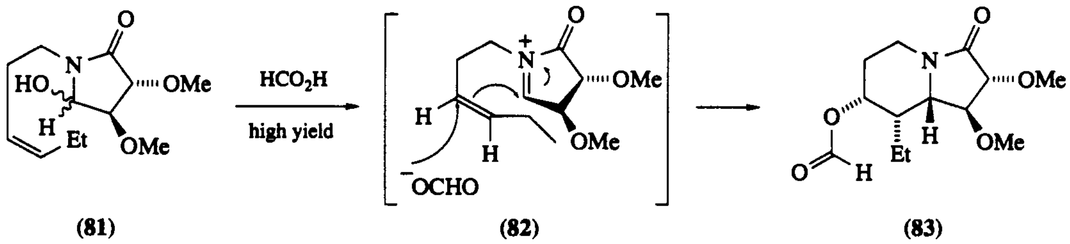
Scheme 37



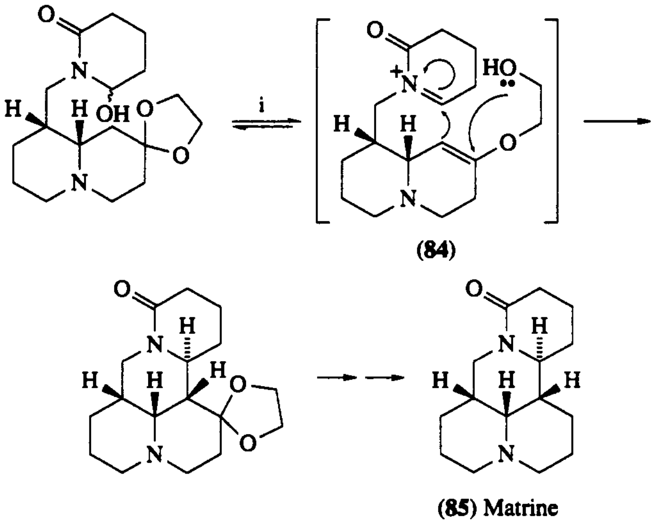
Scheme 38



Scheme 39

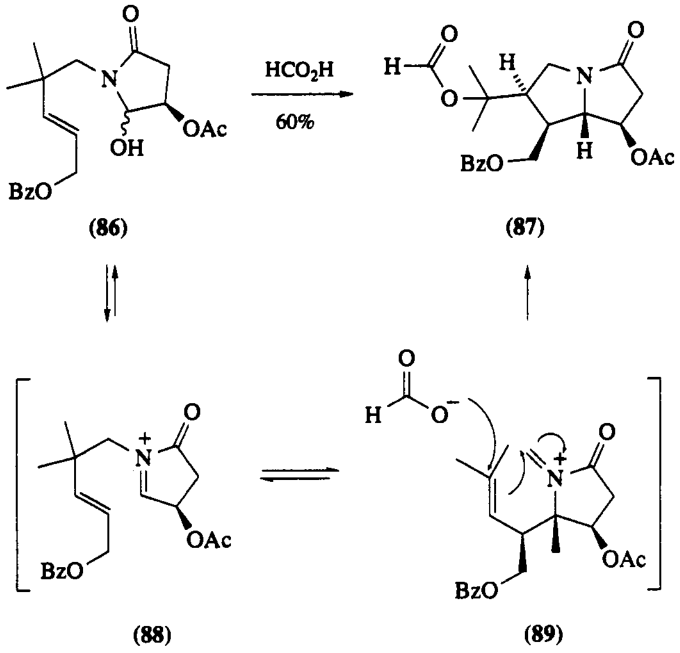


Scheme 40



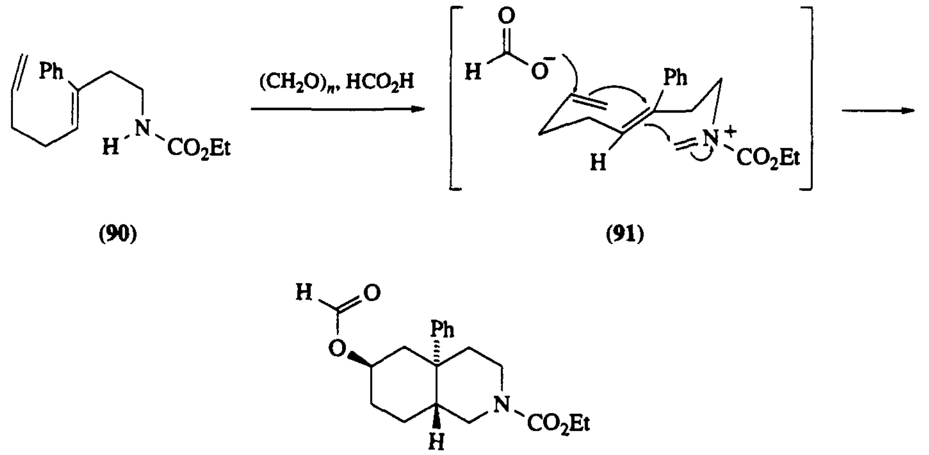
i, MSA, CHCl$_3$, 25 °C, 20 h

Scheme 41



Scheme 42

Instead of being captured by external or internal heteroatom nucleophiles as in the preceding examples, the cationic intermediate resulting from the initial ring closure can eventually undergo a further cyclization reaction with additional C-nucleophiles present in the same molecule. Such a tandem-type reaction cascade from (**90**) to (*92*), *via* the intermediate acyliminium salt (**91**), is presented in Scheme 43.[98]



(90) **(91)** **(92)**

Scheme 43

4.2.2.3 Reactions Involving Oxocarbenium Ions

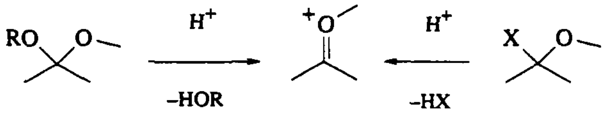
4.2.2.3.1 Creation of the reactive species

The use of oxocarbenium ions provides an efficient method for the preparation of heterocycles, especially of medium-sized cyclic ethers.

Most commonly, oxocarbenium ions (**94**) are formed from acetals (**93**), by treatment with either Brønsted or Lewis acids (Scheme 44).[99] In a similar way, α-halo ethers (**95**) have also been used as potent sources of oxocarbenium ions.[100]

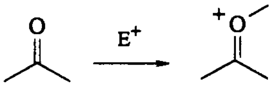
Alternatively, they can be prepared by an electrophilic attack of Brønsted or Lewis acids, or alkyl halides, at the carbonyl oxygen of, for example, ketones (**1**; Scheme 45.[101]

Although detectable by spectroscopic methods,[102] oxocarbenium ions are highly reactive intermediates, prone to nucleophilic attack.



(93) **(94)** **(95)**

Scheme 44



(1) **(94)**

$E^+ = H^+$, Lewis acids, carbon electrophiles

Scheme 45

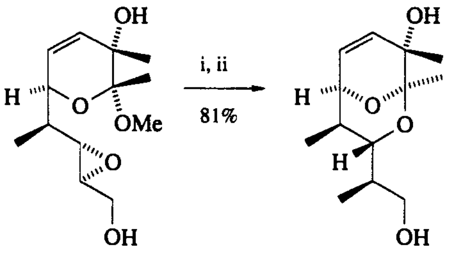
4.2.2.3.2 Cyclization reactions

Oxocarbenium ions may react with carbon and hetereoatom nucleophiles. In intramolecular reactions, the attacking nucleophile may be attached either to the oxygen or to the carbon atom of the oxocarbenium unit (Scheme 46), thus allowing ring closure reactions to occur in an endocyclic (type a) or exocyclic (type b)[68] fashion.

mode a mode b

Scheme 46

Exo- and endo-cyclic ring closure reactions using O-nucleophiles transform oxocarbenium ions into cyclic acetals. As an example of an endocyclic cyclization, epoxide ring opening of (**96**) with lithium dimethyl cuprate, and subsequent treatment of the resulting alcohol with acid, smoothly gives the bicyclic acetal (**97**),[103] a key intermediate in the total synthesis of tirandamycic acid (Scheme 47).[104]



(96) **(97)**

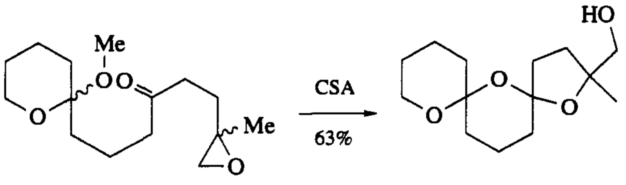
i, Me_2CuLi, Et_2O, 0 °C; ii, $CHCl_3$, TsOH (trace)

Scheme 47

Out of numerous endo-type multiple ring closure cascades, only the double cyclization of (**98**) is mentioned here. This leads to the bis(spiroacetal) entity (**99**; Scheme 48), which is present in polyether antibiotics, insect pheromones and other important natural products.[105]

Though intensively exploited (*e.g.* in carbohydrate chemistry), reactions of oxocarbenium ions with heteroatom nucleophiles will not be treated further in this chapter, since they all lead back to carbonyl derivatives such as acetals. Instead, particular emphasis is laid on syntheses of heterocycles that involve carbon–carbon bond formation.

However, for ring closure reactions that use C-nucleophiles in the exocyclic fashion, heterocyclic products can be expected only under special conditions, namely when an additional heteroatom is present within the ring-closing loop. The most important exo mode reaction of oxocarbenium ions with aromatic

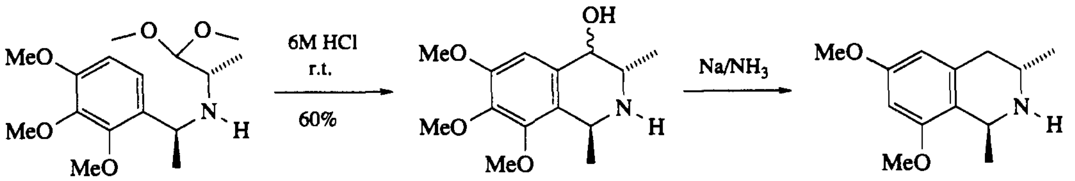


'one single diastereomer'

(98) **(99)**

Scheme 48

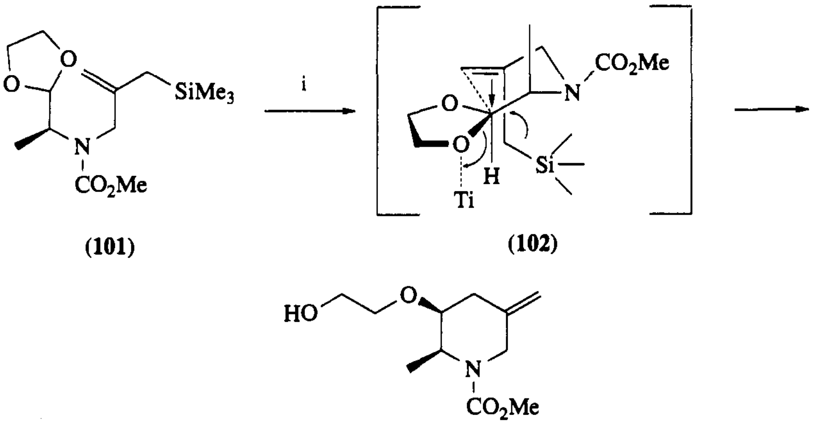
C-nucleophiles is the Pomeranz–Fritsch type synthesis of isoquinolines,[53] including Bobbit's improved modification.[106] For a mild ring closure without epimerization, electron-releasing *ortho* or *para* substituents are obligatory (Scheme 49); this situation nicely complements the substitution pattern required for corresponding Pictet–Spengler reactions (Section 4.2.2.1), due to the different ring closure site. For a given target molecule like (**100**; Scheme 49; *cf.* also Scheme 16), lack of reactivity can be compensated for by additional alkoxy groups, which can be removed selectively after the ring closure.[107]



(100)

Scheme 49

Similarly, the nucleophile may also be an activated alkene, such as the allylsilane moiety in (**101**; Scheme 50),[108] which cyclizes diastereoselectively, though under partial racemization, to the piperidine (**103**). The cyclization proceeds *via* the energetically favorable transition state (**102**), which avoids steric repulsion between the acetal oxygen and trimethylsilylmethyl group, and minimizes A-strain[109] with the methyl group.



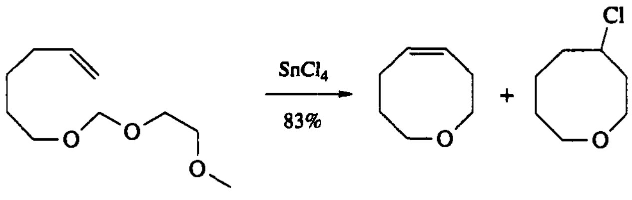
(101) **(102)**

(103)

i, TiCl$_3$(OPr^i), '100%' *de*, 82–83% *ee*

Scheme 50

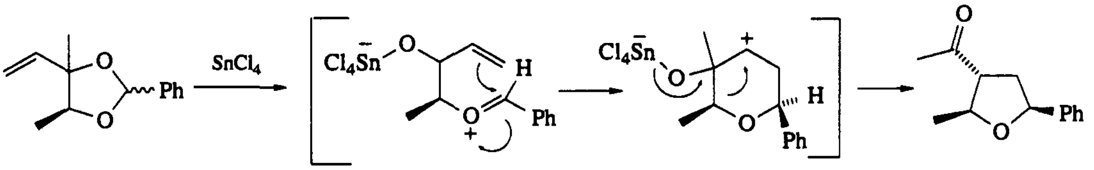
Considerably more important are reactions involving an endocyclic attack of C-nucleophiles. Besides rarer reactions with aromatic nucleophiles[110] (the oxa analog of the Pictet–Spengler reaction) the use of vinylic nucleophiles especially provides an efficient route to 'critical', medium-sized oxygen-containing heterocycles. Thus, even nonactivated alkenes like (**104**) readily undergo acid-catalyzed cyclization in remarkable yields (Scheme 51).[111]



(104) 2:1

Scheme 51

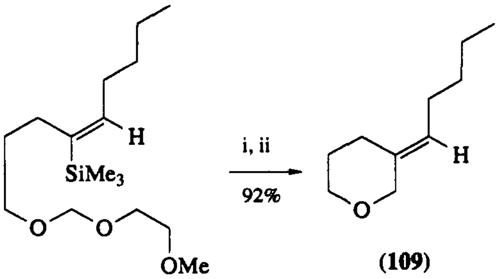
A different outcome in the presence of an additional vinylic oxygen was observed by Overman's group (Scheme 52).[112] The formation of the five-membered cyclic ether (**108**) is rationalized in terms of an $SnCl_4$-mediated acetal ring opening of (**105**), subsequent cyclization of (**106**) to (**107**), followed by a ring contraction to (**108**) by a pinacol-type rearrangement. This stereocontrolled reaction proved to be applicable to the synthesis of related natural products.[112]



(105) **(106)** **(107)** **(108)**

Scheme 52

Vinylsilanes as nucleophilic 'terminators' offer several additional advantages over ordinary nonactivated alkenes (*cf.* Section 4.2.2.1). The silyl group is readily substituted stereo- and regio-selectively by the electrophilic carbon atom of the oxocarbenium ion, as demonstrated in Overman's synthesis of alkylidenetetrahydropyran (**109**; Scheme 53).[113] This strategy was also applied to the preparation of five- and seven-membered cyclic ethers.[113]

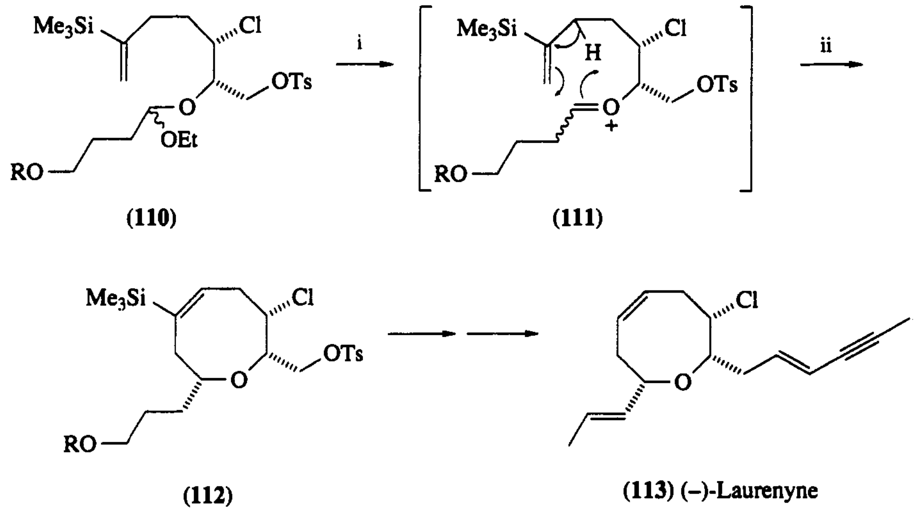


(109)

i, 2–8 equiv. $SnCl_4$, –20 °C; ii, aq. NaOH, –70 °C

Scheme 53

An impressive application is the highly stereocontrolled and enantioselective synthesis of (–)-laurenyne (**113**; Scheme 54).[114] The key step is the cyclization of the mixed acetal (**110**) to give the oxocene (**112**), with the required endocyclic unsaturation at the correct position. The formation of this eight-membered cyclic ether, instead of the corresponding seven-membered ring with an exocyclic double bond, may be rationalized[111] by an intramolecular ene-type reaction of the intermediate oxocarbenium ion (**111**).



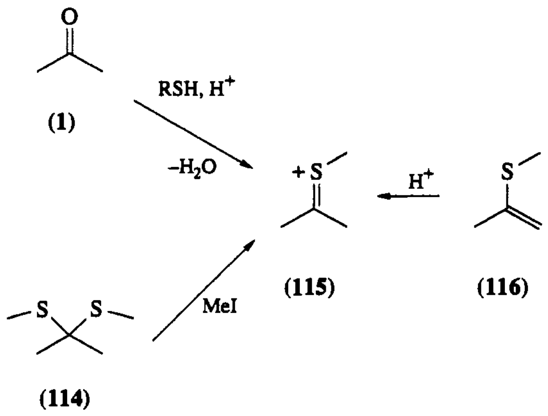
i, 2 equiv. $SnCl_4$, 0 °C, CH_2Cl_2; ii, $Bu^n{}_4NF$–THF

Scheme 54

4.2.2.4 Reactions Involving Thiocarbenium Ions

4.2.2.4.1 Creation of the reactive species

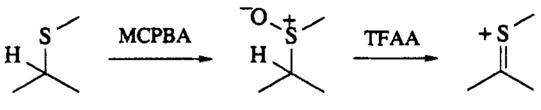
In analogy to the preparation of iminium salts, thiocarbenium ions (**115**) can be created by treatment of carbonyl compounds (**1**) with thiols,[115] by alkylating (or Lewis acid catalyzed) cleavage of dithioacetals[116] (**114**) or by protonation of vinyl sulfides (thio enol ethers) (**116**; Scheme 55).[116]



Scheme 55

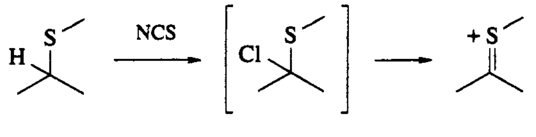
Most efficiently, however, thiocarbenium ions (**115**) can be prepared from sulfides (**117**), by *S*-oxidation, transformation of the introduced oxygen into a good leaving group (*e.g.* into the trifluoroacetate) and subsequent β-elimination—the Pummerer-type route (Scheme 56; see also Chapter 4.7).[117]

Alternatively, the sulfides can be *C*-oxidized (*e.g.* with *N*-chlorosuccinimide) to yield α-halo sufides (**118**), which easily decompose to afford the thiocarbenium salt (**115**; Scheme 57).[118]



(117) **(115)**

Scheme 56

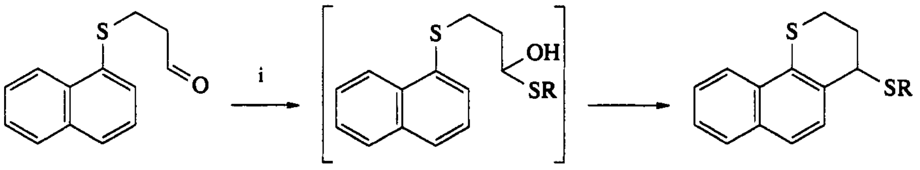


(118) **(115)**

Scheme 57

4.2.2.4.2 Cyclization reactions

As for the corresponding iminium and oxocarbenium ions, thiocarbenium salts can undergo endo- or exo-cyclic ring closure reactions. Again, carbon–carbon bond formation by exocyclic-type reactions lead to heterocyclic systems only 'by chance', namely when an additional heteroatom is located in the chain that will form the ring, *e.g.* the thiol-assisted annulation of **(119)** to give (**120**; Scheme 58).[115]

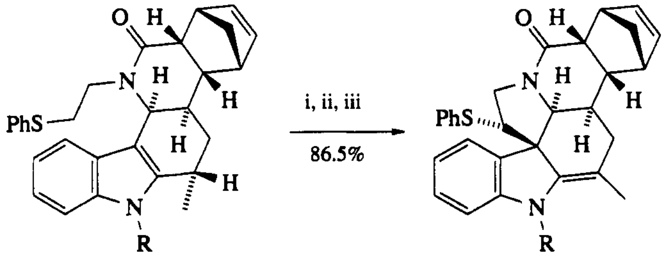


(119) **(120)**

i, RSH, 0.1M H_2SO_4, PhH, high yield

Scheme 58

Especially when combined with the Pummerer-type preparation, thiocarbenium species become valuable carbon electrophiles for various ring closure reactions. At nearly any time in the course of the synthesis, the thiocarbenium species can be set free, *e.g.* from the nonproblematical sulfide function under essentially mild, oxidative conditions, as demonstrated in the synthesis of the pentacyclic precursor **(122)** to aspidospermine alkaloids[119] from (**121**; Scheme 59). The sulfur, if not required for the target molecule, can be taken away reductively, after the ring closure reaction (*cf.* Scheme 37, Section 4.2.2.1).

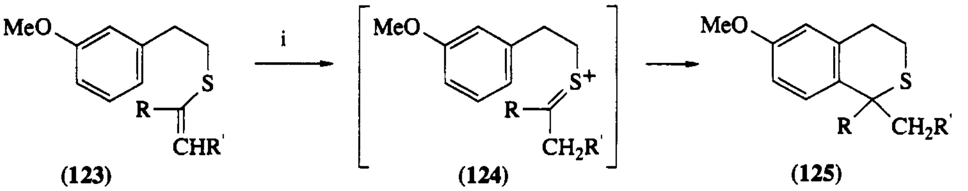


(121) **(122)**

i, MCPBA, $NaHCO_3$, CH_2Cl_2; ii, TFAA, CH_2Cl_2, 0 °C, 1 h; iii, toluene, 1.5 h, Δ

Scheme 59

Only very rarely have endo-type cyclization reactions triggered by thiocarbenium ions been achieved. One interesting example,[116] involving an aromatic C-nucleophile, is the sulfur analog of the Pictet–Spengler reaction, leading to (**125**), presumably *via* (**124**; Scheme 60). Besides the vinyl sulfide (**123**), the corresponding dithioacetal can also be utilized.



(**123**) (**124**) (**125**)

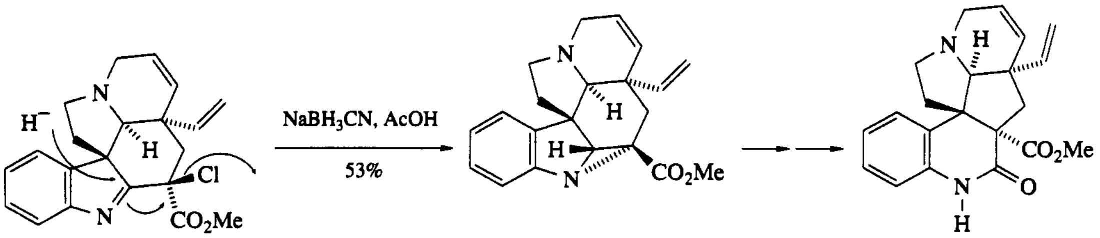
i, $HClO_4$ (70%), 25 °C, 2–3 h, 'high yield'

Scheme 60

4.2.3 CYCLIZATION REACTIONS INVOLVING ELECTROPHILIC OR RADICAL ATTACK ON CARBONYL DERIVATIVES

4.2.3.1 By Electrophilic Attack

Generally, cyclization reactions using carbonyl derivatives involve an intramolecular nucleophilic attack on the carbon atom of the heterocarbonyl group. Sometimes, especially in domino-type reaction cascades, (hetero)carbonyl groups undergo nucleophilic and electrophilic ring closure reactions 'simultaneously' (*cf.* Scheme 48, Section 4.2.2.3). Far less frequently, the cyclization reaction results exclusively from an intramolecular electrophilic attack on carbonyl derivatives, the reaction then usually being triggered by the attack of an external nucleophile. This is the case in the formation of the aziridine (**127**) from the α-haloimine (**126**; Scheme 61),[120] a key step in the first biomimetic synthesis of scandine (**128**) and the structurally related meloscine. A similar cyclization, albeit with a carbonyl group itself rather than a carbonyl derivative, is found in Scheme 28 (Section 4.2.2.1). However, compared with cyclization reactions by nucleophilic attack on heterocarbonyl groups, this reaction type has received only relatively marginal attention and will not be treated further in this chapter.

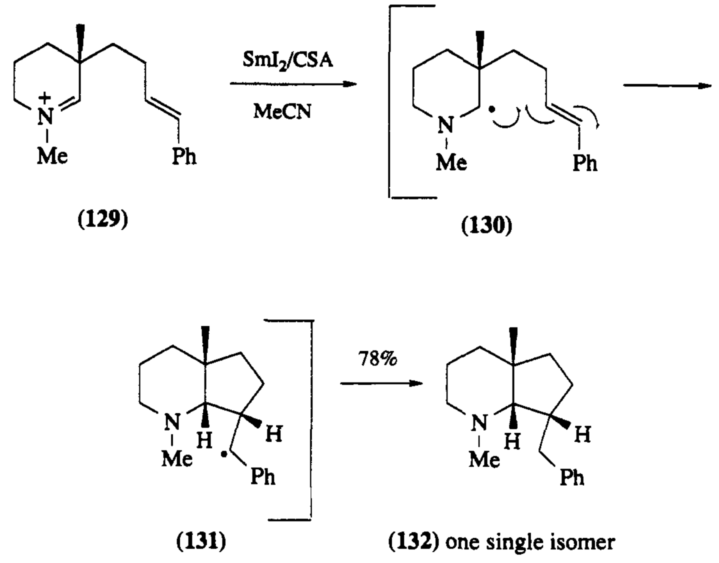


(**126**) (**127**) (**128**) Scandine

Scheme 61

4.2.3.2 By Radical Attack

Compared with the numerous efficient syntheses based on nucleophilic/electrophilic or concerted (*cf.* Section 4.2.4) cyclization reactions of carbonyl derivatives, very little synthetic applications have been described that rely on radical-induced ring closure reactions, such as the reductive cyclization of δ-unsaturated iminium salts like (**129**) using samarium diiodide, which affords (**132**) as the only bicyclic product (Scheme 62).[121] The reaction is believed to proceed by single electron transfer, going through the α-amino radical (**130**), which cyclizes in an exocyclic mode to give the denoted product (**132**) *via* the benzylic carbon radical (**131**).



Scheme 62

Besides such free radical induced reactions, cyclization reactions involving carbonyl derivatives may of course have partial or complete radical character (such as some [2 + 2] cycloaddition reactions[122]), but will be dealt with in Section 4.2.4 for reasons of lucidity and simplicity.

4.2.4 CONCERTED REACTIONS

4.2.4.1 [4 + 2] Cycloadditions (Hetero Diels–Alder Reactions)

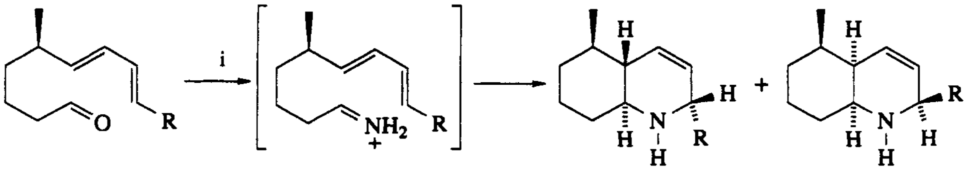
4.2.4.1.1 General aspects

During the last few years, pericyclic reactions, especially hetero [4 + 2] cycloadditions, have increasingly been utilized as pivotal steps in the total synthesis of heterocyclic natural products. This vast field of hetero Diels–Alder reactions has been thoroughly reviewed recently.[123] Because of the intentions (and limitations) of the present chapter, all that will be done is to highlight some of the modern trends, such as the control of regio- and stereo-selectivity by intramolecular processes, the *in situ* generation of highly reactive π-systems, *e.g.* by cycloreversion, and, finally, tandem-type strategies, such as ring contraction reactions subsequent to the cycloaddition.[124]

4.2.4.1.2 Carbonyl derivatives as dienophiles

From the numerous π-systems investigated, nitrogen-containing dienophiles[78] are the most typical carbonyl derivatives for hetero Diels–Alder reactions. Simple imines, however, are quite unreactive and require highly reactive dienes as counterparts.[125,126] In contrast, electron-deficient species, such as iminium salts (**134**; Scheme 63) or *N*-acylimines (**137**; Scheme 64), do undergo [4 + 2] cycloadditions with normal nonactivated dienes. Thus, the intramolecular Diels–Alder reaction of the iminium species (**134**), created *in situ* from the aldehyde (**133**) and ammonia, gives the octahydroquinoline (**135**), which can be hydrogenated to afford the 8a-epimer of pumiliotoxin C (Scheme 63).[127]

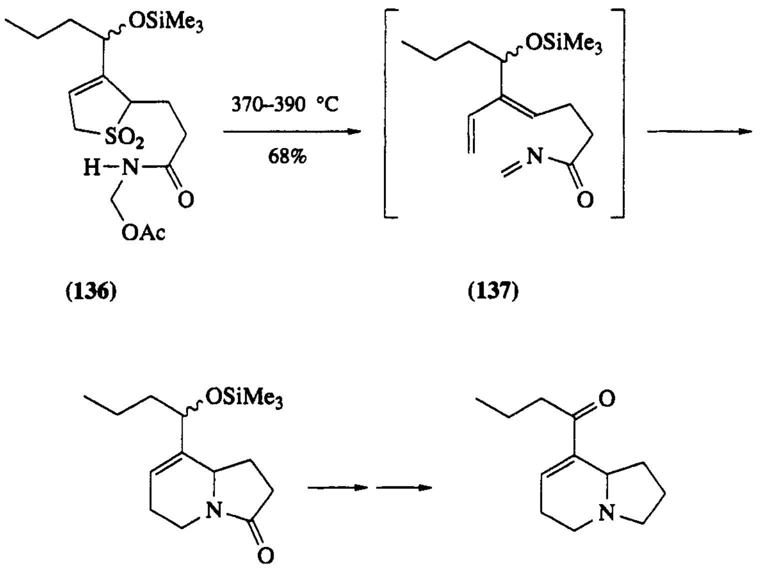
Both reaction partners, *i.e.* the diene and the dienophile, may simultaneously be set free *in situ*, as illustrated in the total synthesis of the indolizidine alkaloid elaeokanine A (**139**; Scheme 64).[128] Flash pyrolysis of (**136**) yields (**138**), presumably *via* the nonisolable dieneacylimine (**137**).



(133) R = Pr^n **(134)** **(135)** 2.2:1

i, NH_4Cl, H_2O–EtOH, 75 °C, 55%

Scheme 63



(136) **(137)**

(138) **(139)** Elaeokanine A

Scheme 64

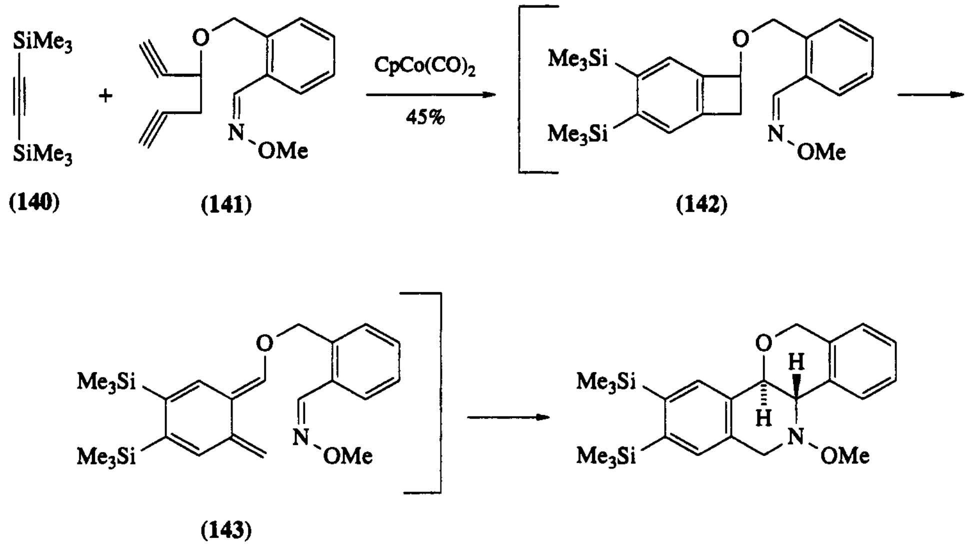
In the presence of very reactive dienes, such as *o*-quinodimethanes, even electron-rich dienophiles, such as oxime ethers, can be reacted, as exemplified in the intramolecular cycloaddition of (**143**; Scheme 65),[129] which is created *in situ* by an initial [2 + 2 + 2] cycloaddition reaction of (**140**) with (**141**) and subsequent electrocyclic ring opening of the resulting benzocyclobutene (**142**). This strategy has been applied recently to a novel isoquinoline synthesis.[130]

For such electron-rich dienophiles, Diels–Alder reactions with unfavorable electron demand become possible when assisted by intramolecularity and high dilution, as in Oppolzer's total synthesis of lysergic acid (Scheme 66),[131] where the labile transient diene is set free by cycloreversion.

4.2.4.1.3 Carbonyl derivatives as dienes

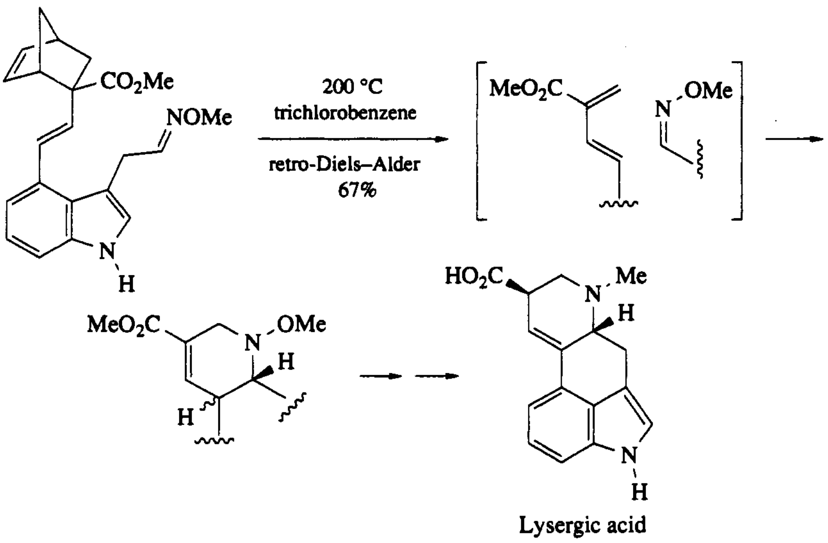
1-Azabutadiene systems, as more or less formal carbonyl derivatives, have been used for [4 + 2] cycloaddition reactions. The fluoride-induced stereoselective transformation of (**144**) to the polycyclic steroid-like system (**145**), obviously proceeding *via* the corresponding reactive aza-*o*-quinodimethane (Scheme 67),[132] shows the synthetic utility of such heterodienes.

Where no assistance can be expected from intramolecularity, or from a reactive rearomatizing *o*-quinodimethane system as above, [4 + 2] cycloadditions with inverse[133] electron demand are required. Thus, reaction of the 2-aza-1,3-butadiene (**146**) with the electron-rich enamine (**147**) at room temperature affords the octahydroisoquinoline (**148**) in high regio- and diastereo-selectivity (Scheme 68).[134]

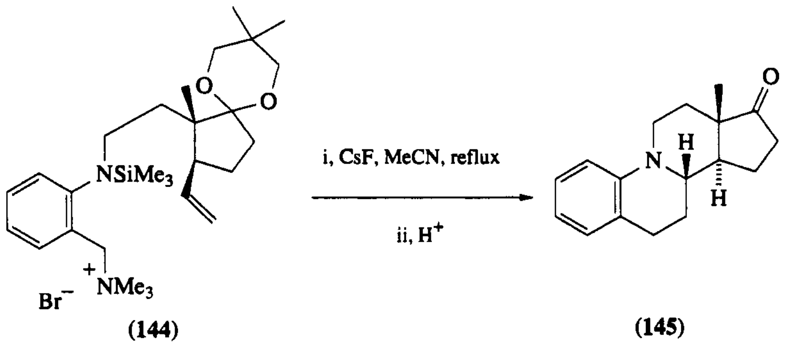


(140) **(141)** **(142)** **(143)**

Scheme 65

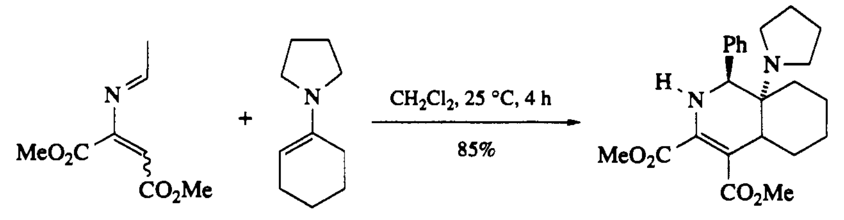


Scheme 66



(144) **(145)**

Scheme 67

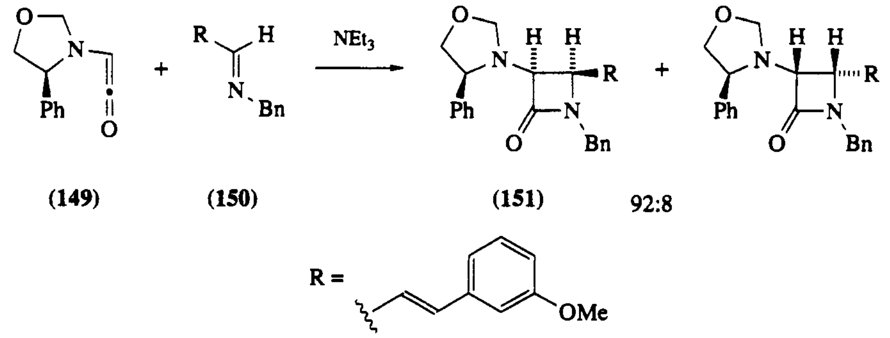


(146) **(147)** **(148)**

Scheme 68

4.2.4.2 [2 + 2] Cycloaddition Reactions

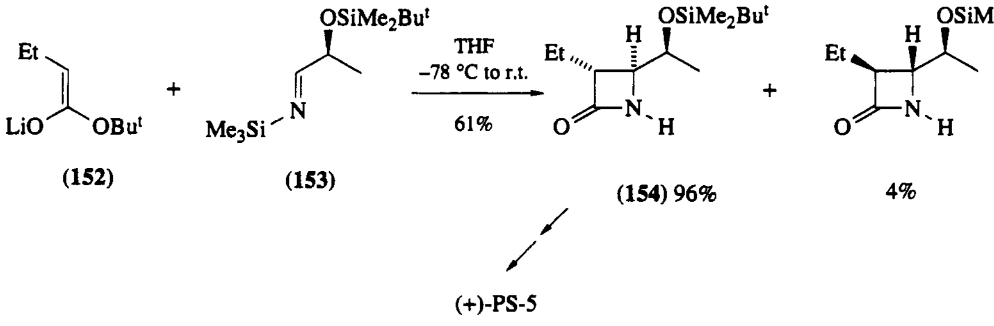
The most prominent hetero [2 + 2] cycloaddition reaction is the Paterno–Büchi reaction[135] of alkenes with carbonyl compounds, such as aldehydes or ketones. Among the corresponding reactions of carbonyl derivatives, the ketene–imine addition, the so-called Staudinger reaction, deserves particular attention, as it provides efficient straightforward access to the β-lactam system.[136] The synthetic value of this procedure not only comes from the diastereoselectivity concerning the relative configuration [(*E*)-imines usually afford *cis*-azetidinones; see Scheme 69], but also from the establishment of absolute stereochemical control, by using transient or permanent chiral auxiliary groups located, for example, in the ketene part. Thus, treatment of the imine (**150**) with the oxazolidine-substituted ketene (**149**; Scheme 69) mainly yields the β-lactam (**151**) with excellent 1,2-asymmetric induction (no formation of *trans*-azetidinones) and good diastereoselectivity (92:8) with respect to the chiral residue.[137,138] In the course of the further β-lactam synthesis, the phenylglycinol-derived chiral auxiliary is cleaved reductively. On the basis of this strategy, further β-lactams have been synthesized more recently.[139]



(149) **(150)** **(151)** 92:8

Scheme 69

For the preparation of optically active β-lactams (**154**) with relative *trans* configuration (*e.g.* for the synthesis of '(+)-PS-5'), the [2 + 2] cycloaddition of ester enolates such as (**152**) and *N*-trialkylsilylimines (**153**) is an appropriate strategy (Scheme 70).[140] In this case, chirality is introduced by the imino moiety.



(152) **(153)** **(154)** 96% 4%

Scheme 70

Apart from numerous similar β-lactam syntheses,[141–143] the very promising photolytic [2 + 2] cycloaddition of imines (or the corresponding hexahydro-1,3,5-triazenes respectively)[122] to chromium carbene complexes that leads to norcardicin precursors[144] merits special interest.

4.2.5 CONCLUDING REMARKS

Heterocyclic compounds are of great interest not only as useful synthetic auxiliaries but also as natural products (or merely synthetic compounds) of biological and medicinal relevance. This review was intended to demonstrate that carbonyl derivatives constitute versatile reactive species for the efficient regio- and stereo-controlled synthesis of demanding heterocyclic molecules. The different reactive carbonyl-derived species could not be covered exhaustively in a chapter of this size, but it is hoped that some salient features of this important subject have been highlighted.

ACKNOWLEDGEMENT

We are indebted to all those who have helped in the preparation of this review, especially to Torsten Geuder, for skilful technical assistance and useful comments.

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4.3

Functional Group Transformations *via* Carbonyl Derivatives

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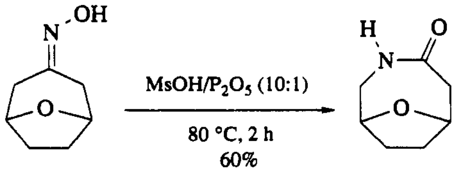
4.3.1 BECKMANN REARRANGEMENT

The Beckmann rearrangement is the skeletal rearrangement of aldoximes and ketoximes in the presence of certain acids, including Lewis acids, to give amides or lactams. Since the first discovery of this rearrangement by Beckmann in 1886,[1] successive investigations have largely clarified its scope, reaction mechanism, and the stereochemical configurations of the oximes employed. Accordingly, the Beckmann rearrangement has become an increasingly important synthetic tool in organic chemistry and it has been reviewed several times.[2–6] It is one of the most reliable ways of incorporating the nitrogen atom efficiently into both acyclic and alicyclic systems, thereby providing a powerful method for a variety of natural product syntheses.

4.3.1.1 Synthetic Utility of the Beckmann Rearrangement

Most ketoximes will undergo the normal Beckmann rearrangement under the proper acidic or neutral conditions to yield an amide or a mixture of amides, and a wide variety of examples are listed in reviews.[2,6] Polyphosphoric acid continues to be a common reagent for the Beckmann rearrangement. However, in view of the viscosity and utility in a large molar excess as a solvent, polyphosphoric acid has several drawbacks in the work-up step. A recent procedure suggests the use of xylene as a cosolvent.[7] Under these conditions the reaction temperature is easily controlled and the yields are the same or better than those obtained in polyphosphoric acid alone.

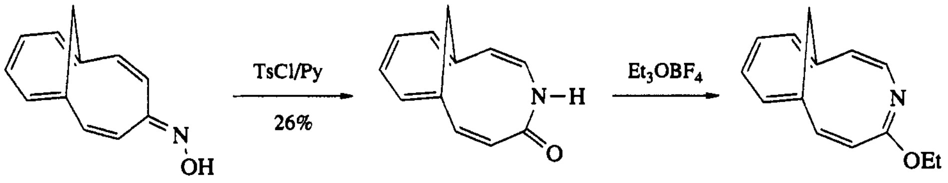
Several reagents for effecting the Beckmann rearrangement of the oxime (**1**) to give the lactam (**2**) have been evaluated with a view to the synthesis of a structural analog of the natural product, muscarine. The best results are obtained with a 10:1 mixture of methanesulfonic acid and phophorus pentoxide (equation 1).[8]



(1)

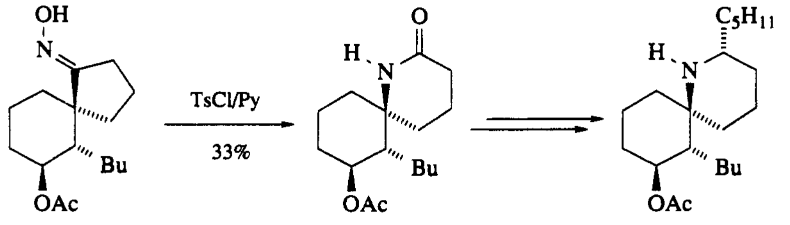
(1) **(2)**

The combination of benzenesulfonyl chloride and *p*-toluenesulfonyl chloride with base is highly effective for the Beckmann transformation. The oxime (**3**) of 4,9-methano[11]annulenone, when heated with *p*-toluenesulfonyl chloride in pyridine, gives the desired lactam (**4**) in 26% yield (equation 2).[9,10] Attempted rearrangement of (**3**) with PCl_5 is fruitless. Oximes that are prone to the Beckmann fragmentation can often be rearranged by use of these reagents. Spirooxime (**5**) successfully rearranges to the lactam (**6**; equation 3), the key intermediate for the synthesis of pharmacologically important alkaloid perhydrohistrionicotoxin.[11] An interesting case of regiochemical control has been observed in the Beckmann rearrangement of the oxime (**7**). Thus, heating of (**7**) in polyphosphoric acid produces exclusively the abnormal lactam (**8**), suggesting the acid-catalyzed *syn*/*anti* oxime isomerization prior to rearrangement. By contrast, solvolysis of the corresponding oxime tosylate (**9**) yields the normal Beckmann lactam (**10**) under essentially neutral conditions (equation 4).[12]



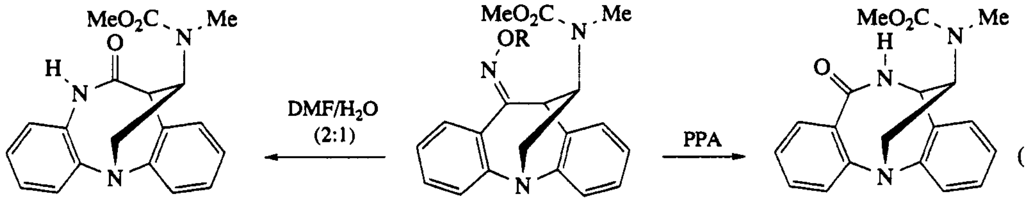
(2)

(3) **(4)**



(3)

(5) **(6)** Perhydrohistrionicotoxin



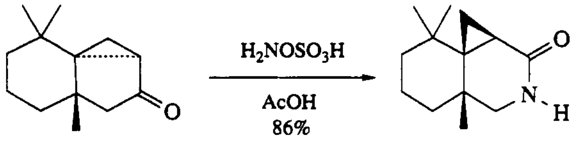
(4)

(10) **(7)** R = H

(9) R = Ts **(8)**

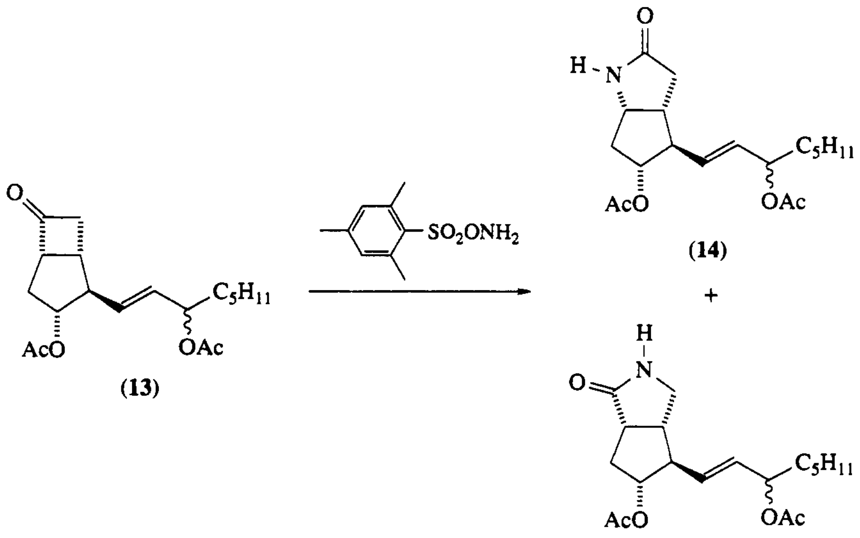
Hydroxylamine-*O*-sulfonic acid or *O*-mesitylenesulfonylhydroxylamine (Tamura's reagent)[13] are effective catalysts for the conversion of ketones directly to lactams. For example, the rearrangement of

C_5–C_{12} cycloalkanones with hydroxylamine-*O*-sulfonic acid produces the corresponding lactams in 80–83% yield.[14] Abnormal Beckmann rearrangement, where the migration of the more-substituted α-carbon takes place predominantly, is observed on treatment of cyclopropyl ketone (**11**) with hydroxylamine-*O*-sulfonic acid to furnish the lactam (**12**) as the sole isolable product in 86% yield (equation 5).[15] In contrast, heating of the oxime of (**11**) with polyphosphoric acid affords a mixture of (**12**) and its isomeric lactam. The utility of this reagent in the synthesis of various heterocycles has been reviewed by Wallace.[16] Although the Beckmann rearrangement of ketone (**13**) cannot be accomplished by standard methods, *O*-mesitylenesulfonylhydroxylamine enables the facile transformation of the ketone (**13**) to the crystalline lactam (**14**) in 55% yield along with 15% of the isomeric lactam (**15**; equation 6).[17]



(**11**) (**12**)

(5)

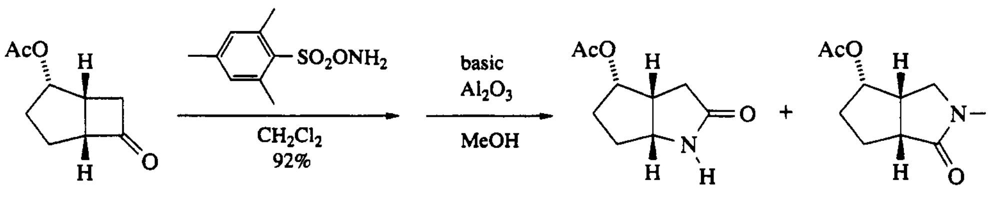


(**13**) (**14**) (**15**)

(6)

A regio- and stereo-selective ring expansion of the *O*-mesitylenesulfonyl oxime of an unsymmetrical cyclobutanone (**16**) has been observed under the influence of a basic alumina (equation 7).[18] In the rearrangement of *O*-mesitylenesulfonyl oxime (**17**) the activated alumina is found to be superior to basic alumina which causes the formation of oxazoline derivative (**18**) as a side product (equation 8).[19]

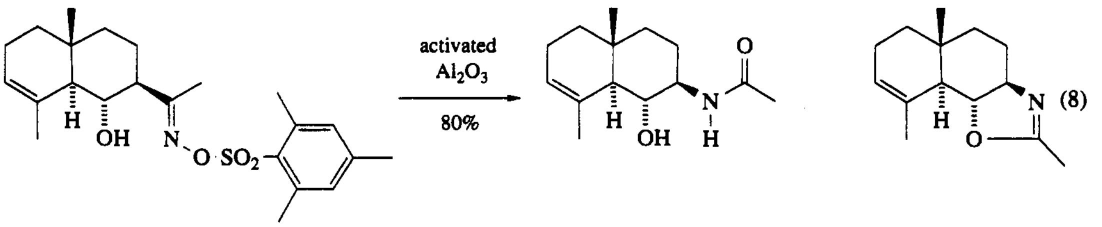
α-Hydroxy ketoximes are prone to undergo the Beckmann fragmentation with a variety of reagents which generally induce the Beckmann rearrangement. However, photoreaction of cyclic α-hydroxy ketoxime (**19**) in MeOH gives two structurally isomeric lactams, (**20**) and (**21**), possessing a hydroxy group



(**16**)

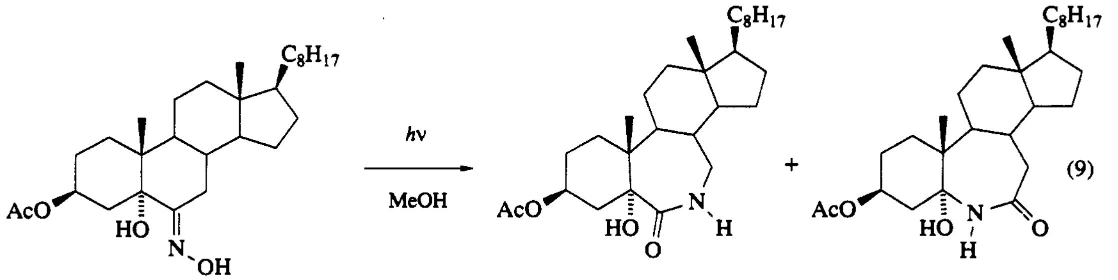
(7)

-10 °C, 5:1
25 °C, 2:1

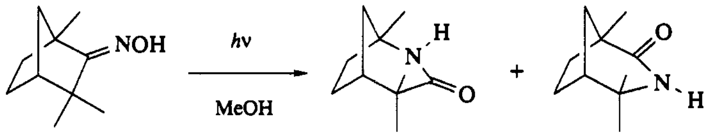


(17) **(18)** (8)

adjacent to the amide group (equation 9).[20] Another feature of the photoreactions of oximes is their reluctance towards the Beckmann fragmentation, as demonstrated in equation (10).[21]

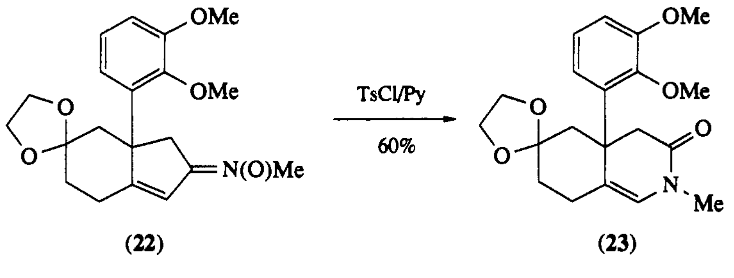


(19) **(20)** 15% **(21)** 21% (9)



13% 13% (10)

Beckmann rearrangement of α,β-unsaturated oximes usually gives rise to α,β-unsaturated lactams. However, treatment of unsaturated *N*-methyl nitrone (**22**) with *p*-toluenesulfonyl chloride in pyridine leads to selective migration of the vinylic rather than the alkyl bond, producing enamide (**23**) in 60% yield (equation 11).[22]

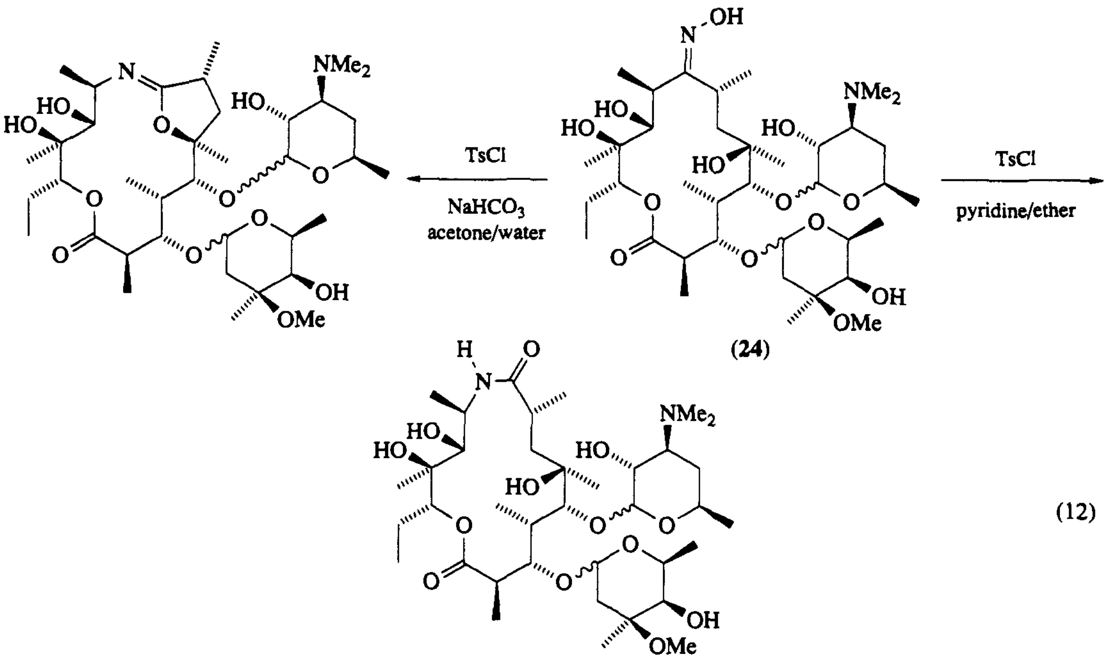


(22) **(23)** (11)

4.3.1.2 Trapping of the Beckmann Intermediate with Heteroatoms

One synthetically interesting development in the Beckmann rearrangement is the trapping of the intermediate nitrilium ion with heteroatom nucleophiles other than water, since the resulting imine derivatives may be further manipulated into various amine derivatives.

Intramolecular participation of a neighboring hydroxy group is observed in the rearrangement of erythromycin A oxime (**24**) with *p*-toluenesulfonyl chloride and sodium hydrogencarbonate in acetone–water (equation 12).[23] Interestingly, with the same reagent in pyridine–ether only the normal rearrangement product (**25**) is formed.

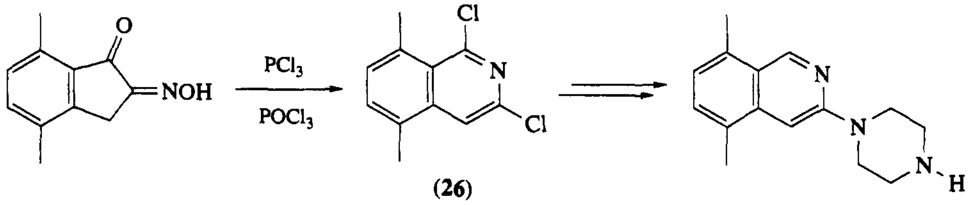


(24)

(25)

(12)

Preparation of imidoyl chlorides is usually effected by using phosphorus pentachloride or triphenylphosphine–carbon tetrachloride.[24] A recent example indicates the utility of imidoyl chloride (**26**) in the synthesis of the potential antidepressant (**27**; equation 13).[25]



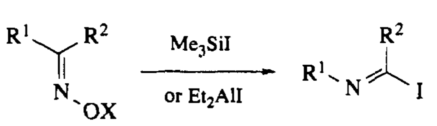
(26)

(27)

(13)

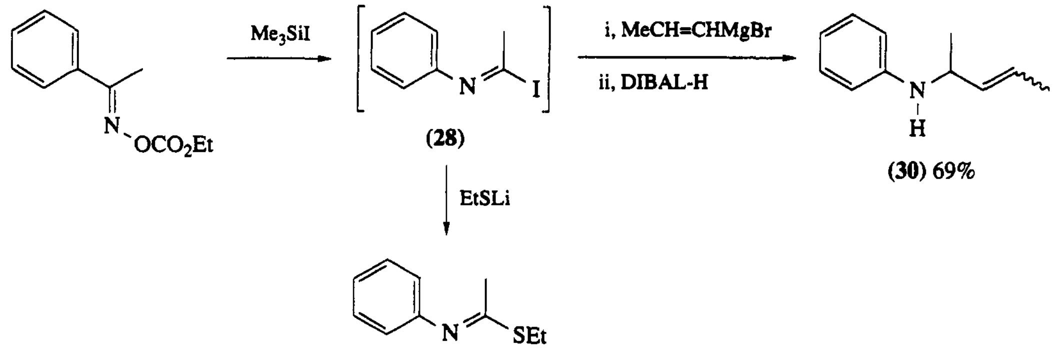
Although imidoyl iodides are chemically labile, their *in situ* generation from oxime derivatives with trimethylsilyl iodide or diethylaluminum iodide has been ascertained spectroscopically (equation 14).[26,27] The synthetic utility of these reactive species has been demonstrated by further reacting them with external nucleophiles such as thiolates or Grignard reagents. For example, the imidoyl iodide (**28**), generated from acetophenone oxime carbonate with trimethylsilyl iodide, is further transformed to ethylthioimidate (**29**) and α-alkylated amine (**30**), respectively (Scheme 1 and equation 15).

A highly efficient and general approach for the synthesis of thioimidates from oxime sulfonates has been developed which involves the use of dialkylaluminum thiolates both as initiators of the Beckmann rearrangement and as trapping agents, *via* thiolate nucleophiles, of the intermediate nitrilium ions. The regiochemistry of this reaction follows the general rule of the Beckmann rearrangement and preferential migration of the group *anti* to the oxime sulfonate is rigorously observed, as shown in equations (16) and (17).[28]



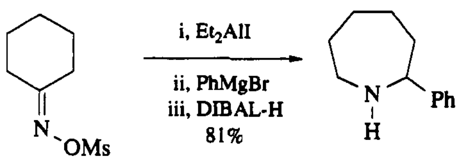
(14)

X = Ac, COPh, CO_2Et, Ms

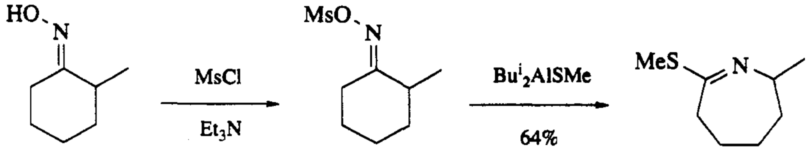


(29) 67%

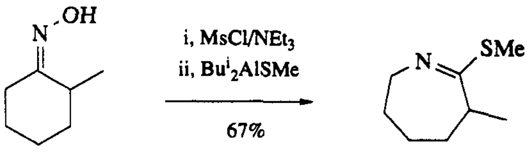
Scheme 1



(15)

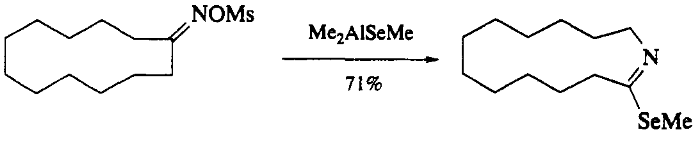


(16)



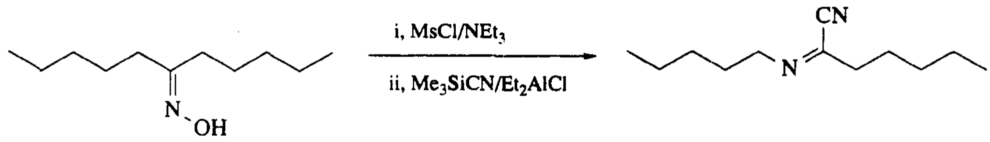
(17)

This aluminum method, in principle, is applicable to a synthesis of other heterosubstituted imino derivatives, since the preparations of various organoaluminum reagents of type R_2AlX are well established. For instance, treatment of oxime sulfonate (**31**) with dimethylaluminum selenomethylate yields methylselenoimidate (**32**) in 71% yield (equation 18).[28]



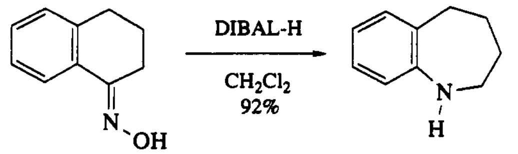
(**31**) (**32**) (18)

The combination of diethylaluminum chloride with trimethylsilyl cyanide has been successfully utilized for the general synthesis of imidoyl cyanides from various oxime sulfonates (equation 19).[28]



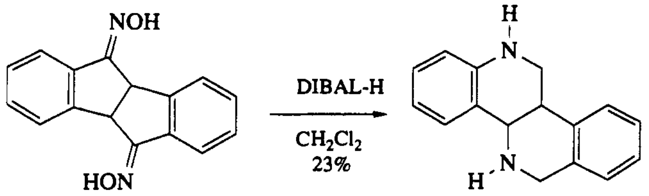
(19)

The reductive Beckmann rearrangement of oximes has been effected with several types of aluminum hydride reagents. Early examples exhibited only moderate regioselectivity, giving mixtures of primary amines and rearranged secondary amines. Recently, diisobutylaluminum hydride was reported to be most satisfactory for this type of transformation (equation 20).[29] Here dichloromethane is the solvent of choice, and attempted use of ethereal solvents results in the formation of a mixture of primary and secondary amines.[30]



(20)

An unexpected reductive rearrangement was observed in the reaction of the dioxime (33) with diisobutylaluminum hydride in dichloromethane, leading to the diamine (34; equation 21).[31] It should be noted that attempted reaction of (33) under various Beckmann rearrangement conditions resulted either in extensive decomposition or fragmentation.

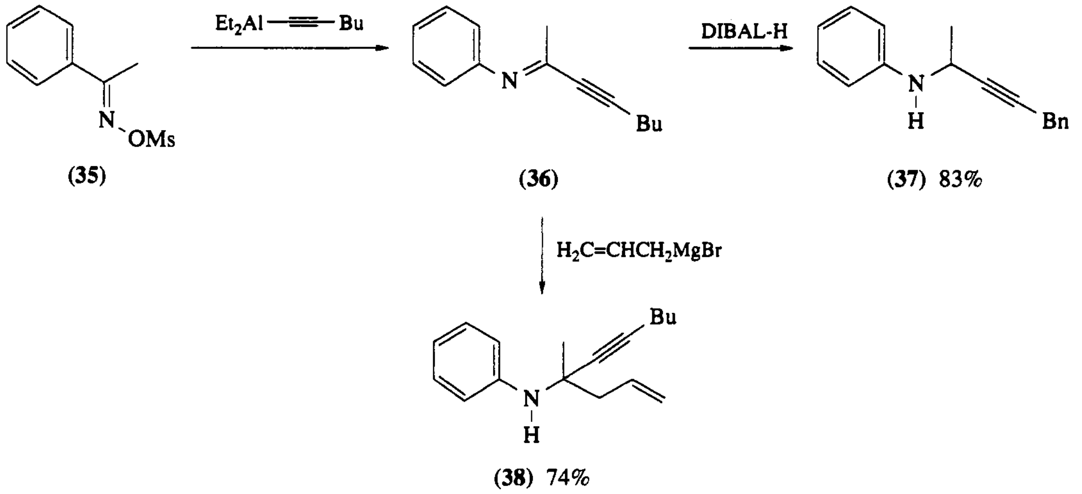


(33) (34)

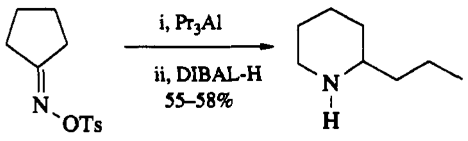
(21)

4.3.1.3 Beckmann Rearrangement–Alkylation Sequence

A most exciting advance in Beckmann rearrangement chemistry is the successive Beckmann rearrangement–alkylation sequence promoted by certain organometallic reagents. Here, organoaluminum reagents behave in an amphoteric manner, inducing the Beckmann rearrangement of oxime sulfonates as well as capturing the intermediate nitrilium ion with the carbon nucleophile from aluminum.[28,32] For example, treatment of oxime mesylate (35) with diethyl(1-hexynyl)aluminum in CH_2Cl_2 gives after reduction of the intermediate imine (36) with DIBAL-H, the amine (37) with rigorous regioselectivity (Scheme 2). Further alkylation is achieved with allylmagnesium bromide to furnish the amine (38). This approach possesses a vast potential in the area of alkaloid synthesis, as demonstrated by the facile synthesis of coniine and pumiliotoxin C (equations 22 and 23).

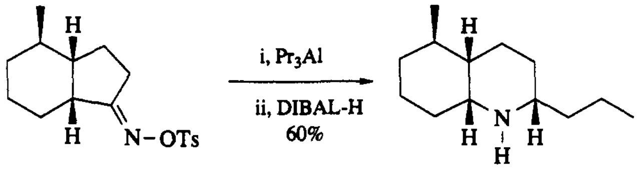


Scheme 2



Coniine

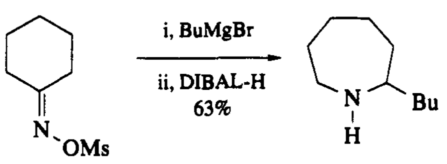
(22)



Pumiliotoxin C

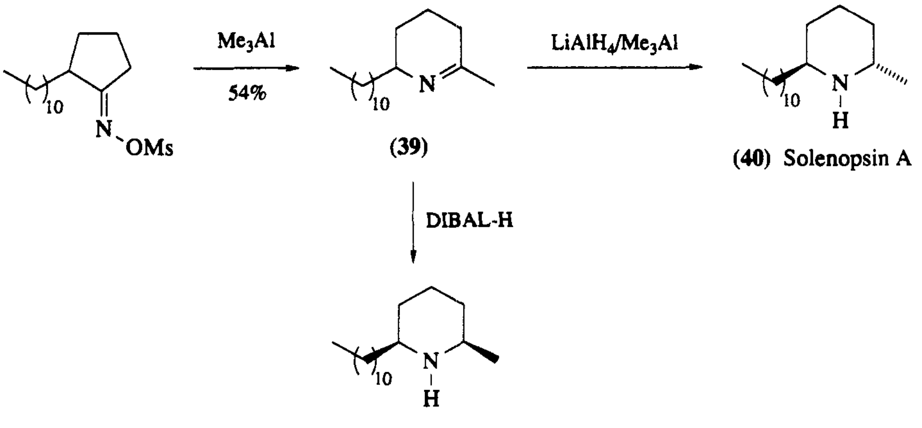
(23)

Grignard reagents have also been found to be effective for these types of transformations (equation 24), but not with cyclopentanone oxime sulfonate.[33]



(24)

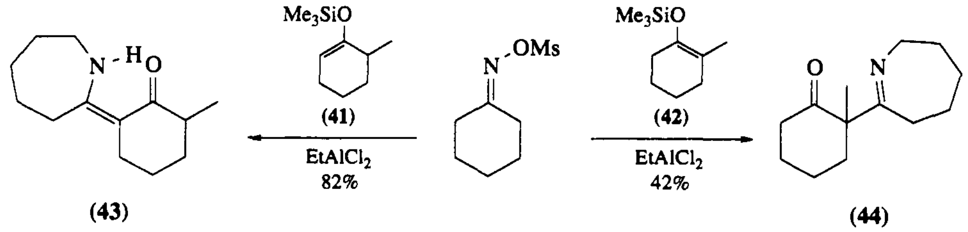
The isolable imine (**39**), which is obtainable by the rearrangement of 2-undecylcyclopentanone oxime mesylate with Me_3Al, can be transformed to either the *cis* or *trans* isomer with high stereoselectivity depending on the choice of the reducing agents (Scheme 3). Reduction of (**39**) with $Me_3Al–LiAlH_4$ completes a short synthesis of solenopsin A (**40**).[34]



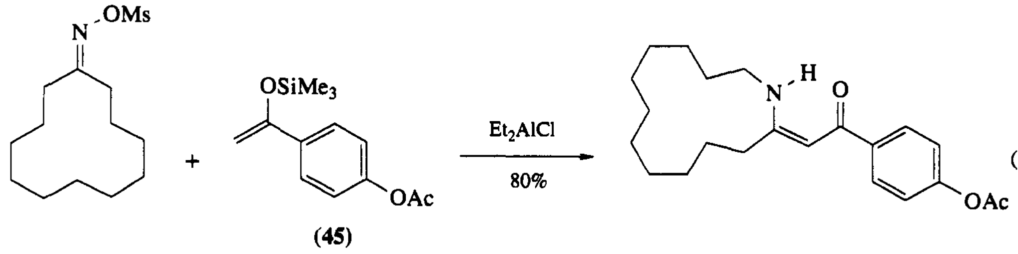
Scheme 3

Trapping of the Beckmann intermediates with enol silyl ethers affords facile entry to a variety of enamino ketones.[35] This condensation takes place with retention of regiochemical integrity in both oxime sulfonates and enol silyl ethers. Reaction of 6-methyl-1-(trimethylsiloxy)-1-cyclohexene (**41**) or 1-methyl-2-(trimethylsiloxy)-1-cyclohexene (**42**) with cyclohexanone oxime mesylate furnishes (**43**) or (**44**), respectively, as the sole isolable products (equation 25). Another striking feature of the reaction is the high chemospecificity. The condensation of the enol silyl ether (**45**), derived from *p*-acetoxyacetophenone, occurs in a chemospecific fashion with cyclododecanone oxime mesylate, the acetoxy moiety remaining intact (equation 26). Oxime sulfonates of aromatic ketones and cyclopentanones are not employable since complex reaction mixtures are formed.

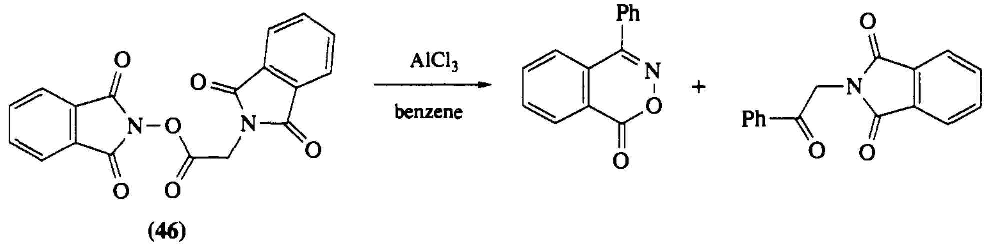
Beckmann rearrangement of phthalimide derivative (**46**) is induced by aluminum chloride in benzene and terminated by electrophilic aromatic substitution, as shown in equation (27).[36]



(25)



(26)



(27)

4.3.1.4 Beckmann Rearrangement–Cyclization Sequence

The efficient activation of oxime sulfonates by organoaluminum reagents enables the intramolecular cyclization of alkenic oxime mesylates, which involves the electrophilic addition of the intermediate nitrilium ion to the double bond. This results in the direct formation of a wide variety of structurally diverse carbocyclic and heterocyclic systems. Four distinct cyclization modes, *i.e.* *endo*(B)-*endo*, *endo*(B)-*exo*, *exo*(B)-*endo* and *exo*(B)-*exo* are possible, as shown in Scheme 4.[37] The values in parentheses refer to the yields obtained using SnCl$_4$.

The *endo*(B) cyclizations are highly useful in natural product syntheses. Solenopsin B can be prepared *via* the *endo*(B)-*endo* cyclization in two steps from a simple acyclic precursor (equation 28). Analogous *endo*(B) cyclizations have been utilized as key steps in synthetically important transformations (equations 29 and 30).[38]

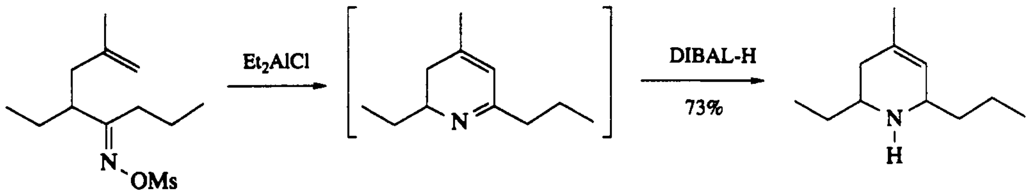
The alkenic cyclizations described above are terminated by deprotonation, yielding unsaturated imines. The intermediate carbocations, however, may also be captured by carbon nucleophiles to afford saturated imines. For example, treatment of the oxime mesylate (**47**) with Me$_3$Al followed by reduction with DIBAH predominantly produces the methylated product (**48**; equation 31).[37]

The similar *endo*(B)-*exo* cyclizations have been effected with phosphorus pentoxide and more recently with trimethylsilyl polyphosphate (equation 32 and 33).[39–41] The starting alkenic oximes are readily obtainable by the alkylation of the oxime dianion. Hence the overall process provides convenient access to the stereospecific synthesis of various heterocycles bearing substituents in the desired positions.

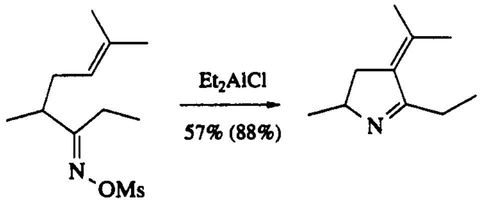
The Beckmann rearrangement–cyclization sequence terminated by aromatic moieties is fairly general. Recent examples of isoquinoline and dihydroisoquinoline synthesis exhibit two-step sequences using phosphorus pentachloride and phosphorus pentoxide *via* the cyclization of the intermediate imidoyl chlorides (equation 34).[42]

Indoloisoquinoline skeletons can be readily constructed, *via* intramolecular cyclization, by treatment of the indole aldoxime (**49**) with sulfuric acid in refluxing ethanol (equation 35).[43] This example is rather unusual, since the rearrangement of aldoximes to formamides is difficult to achieve.

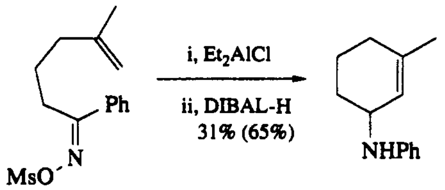
endo(B)–*endo* cyclization



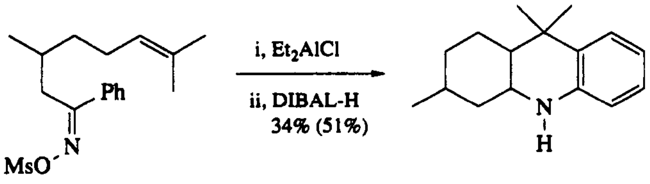
endo(B)–*exo* cyclization



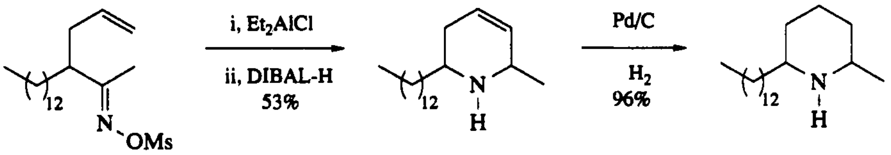
exo(B)–*endo* cyclization



exo(B)–*exo* cyclization

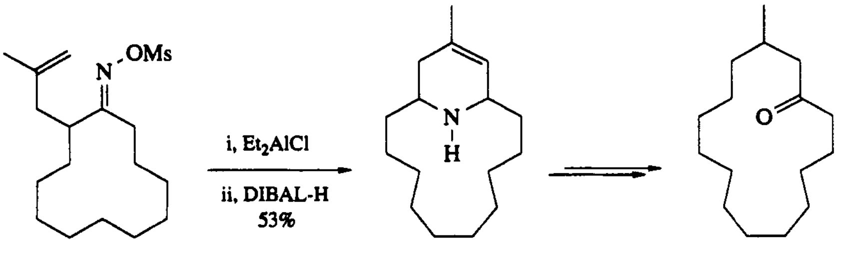


Scheme 4



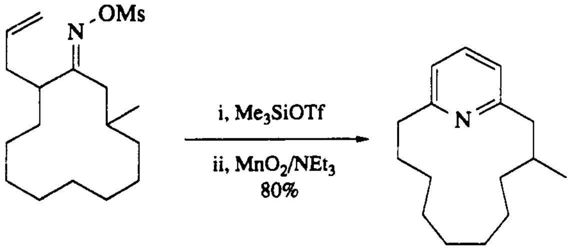
Solenopsin B

(28)



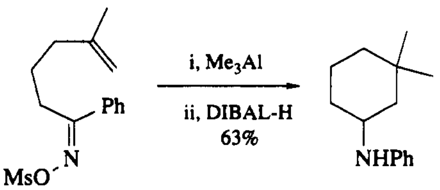
Muscone

(29)



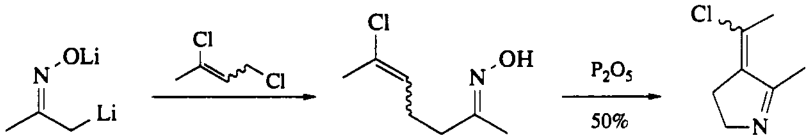
Muscopyridine

(30)

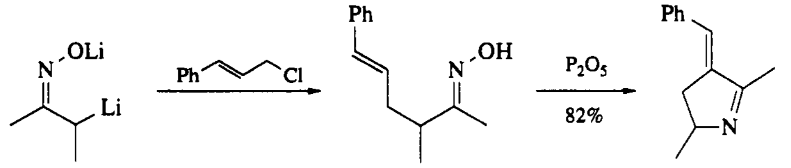


(47) **(48)**

(31)



(32)



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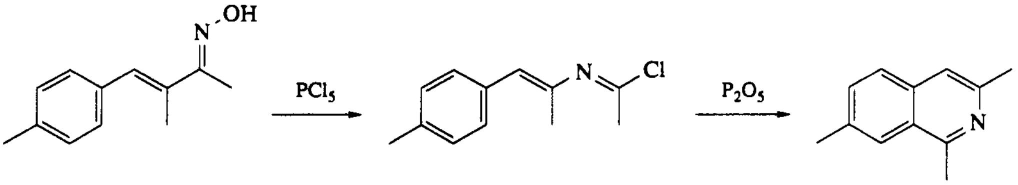

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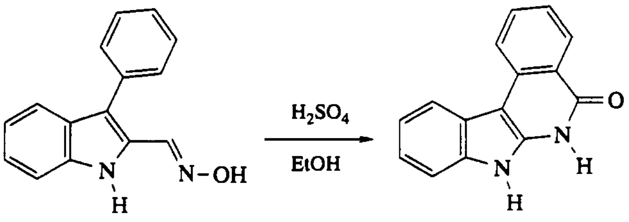
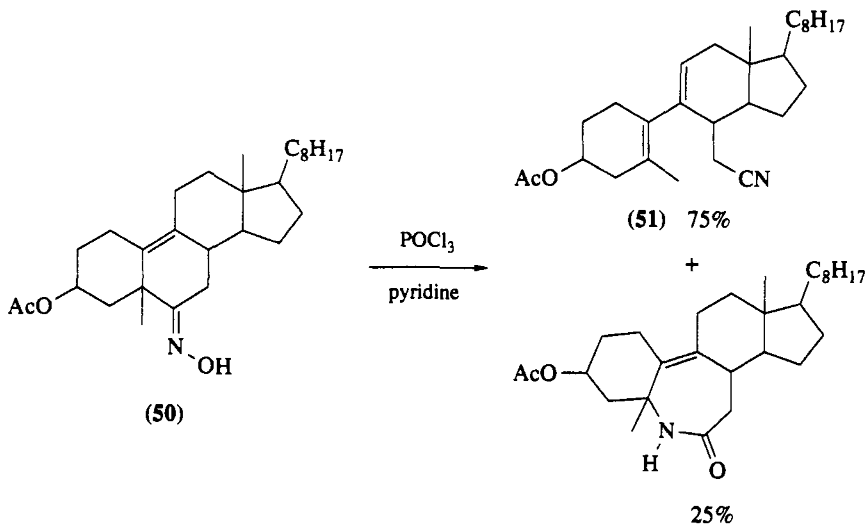


(49)

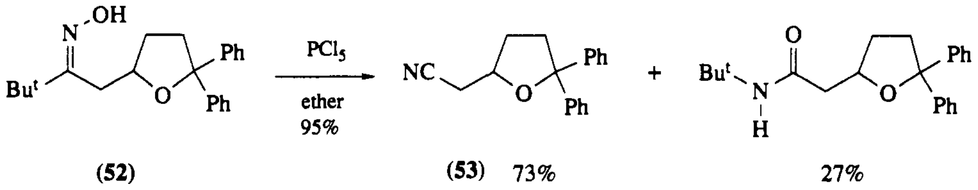
(35)

4.3.1.5 Beckmann Fragmentations

Oximes that have quaternary carbons adjacent to the oxime carbon are prone to undergo fragmentation as a major reaction pathway, furnishing nitriles. Steroidal ketoxime (**50**) and tetrahydrofuranyl ketoxime (**52**) give nitriles (**51**) and (**53**), respectively, as major products (equations 36 and 37).[44,45]

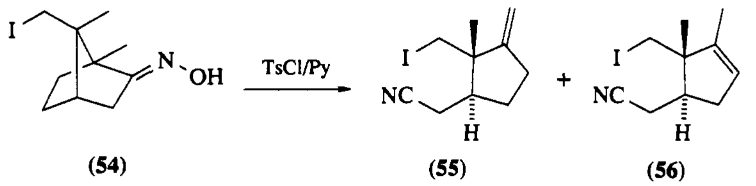


(36)



(37)

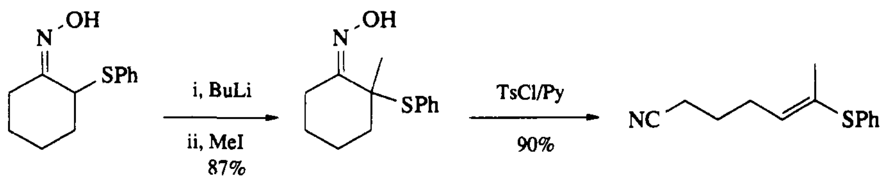
In the course of an asymmetric synthesis of steroids, iodocamphor oxime (**54**) was converted to a 1:1 mixture of chiral cyclopentenyl cyanides, (**55**) and (**56**), on treatment with *p*-toluenesulfonyl chloride in pyridine at 0 °C (equation 38).[46] Notably, equilibration of this mixture with anhydrous trifluoroacetic acid afforded essentially pure (**56**), in 81% yield, which was further elaborated in the synthesis of chiral *trans*-hydrindenone.



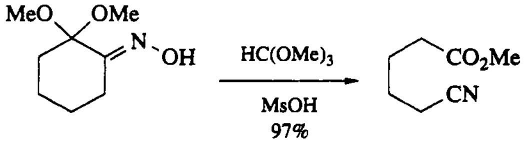
(38)

The presence of α-substituents such as carbonyl, amino, hydroxy, alkoxy or alkylthio groups on oxime substrates also promotes the Beckmann fragmentation to nitriles under thermal or acid-catalyzed conditions. A recent example demonstrates the synthesis of functionalized nitriles by the regioselective sulfenylation–alkylation of cyclic oximes *via* their dianions and subsequent regioselective ring cleavage (equation 39).[47] Acetals of 1,2-dione monooximes are susceptible to the Beckmann fragmentation in the presence of trimethyl orthoformate and methanesulfonic acid (equation 40).[48]

The trimethylsilyl group can rigorously control and direct the Beckmann fragmentation leading to the regio- and stereo-specific formation of unsaturated nitriles (equations 41 to 43).[49,50] Oxime acetate (**57**) fragments to the *cis*-alkenic nitrile (**58**) in 90% yield, whereas its epimer (**59**) affords the *trans*-alkenic nitrile (**60**) in 94% yield under the same conditions. Furthermore, fluoride-induced fragmentation can re-

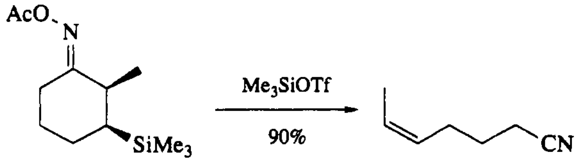


(39)



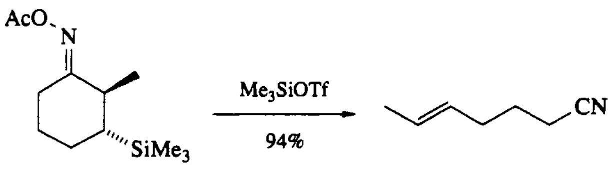
(40)

sult in the stereochemical reversal of the alkenic bond, as shown in the equation (43). This approach is applicable to the synthesis of some insect pheromones.



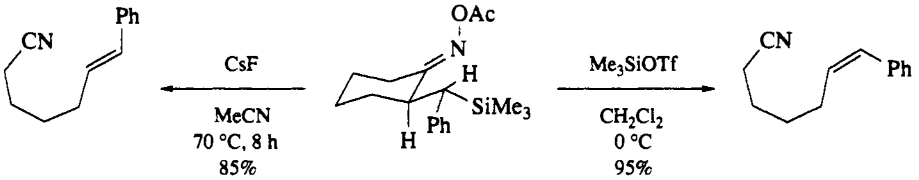
(41)

(57) **(58)**



(42)

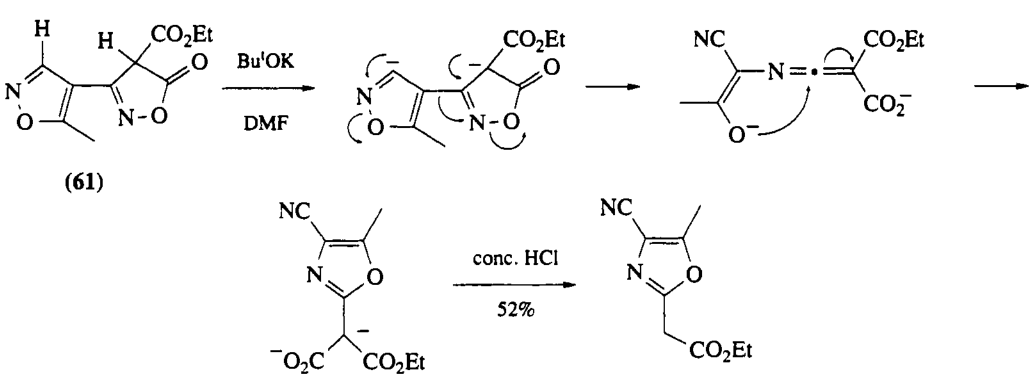
(59) **(60)**



(43)

Aldoxime fragmentation is a well-known process for nitrile synthesis, and numerous reagents have been developed for this purpose. Trimethylsilyl iodide was recently found to be effective as a dehydration agent.[27]

Closely related to the aldoxime fragmentation is the base-catalyzed ring cleavage of C(3)-substituted isoxazoles.[51] Quite recently a novel base-catalyzed isoxazole–oxazole ring transformation was realized in the conversion of ethyl 5-hydroxy-3-(5-methylisoxazol-4-yl)isoxazole-4-carboxylate (**61**) into ethyl 4-cyano-5-methyloxazol-2-ylacetate (**62**; Scheme 5).[52]



(61)

(62)

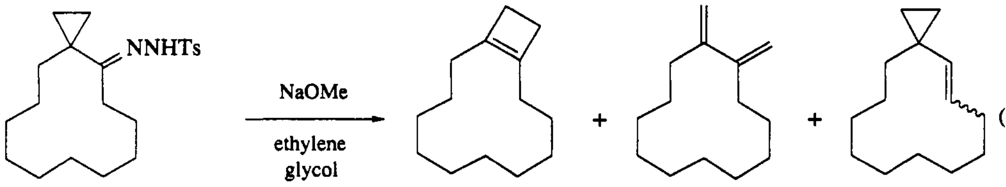
Scheme 5

4.3.2 BAMFORD–STEVENS REACTION

The Bamford–Stevens reaction is the base-catalyzed decomposition of arenesulfonylhydrazones of aldehydes and ketones, leading to the formation of alkenes and/or cyclopropanes. There are several important general reviews in this area of organic synthesis.[53–55] Since the reactions are mostly carried out either in protic or in aprotic solvents, the reaction types are divided into the protic and aprotic Bamford–Stevens processes. This section reviews recent examples in the synthesis of alkenes and cyclopropanes from arenesulfonylhydrazones, which is closely related to the following Shapiro reaction.

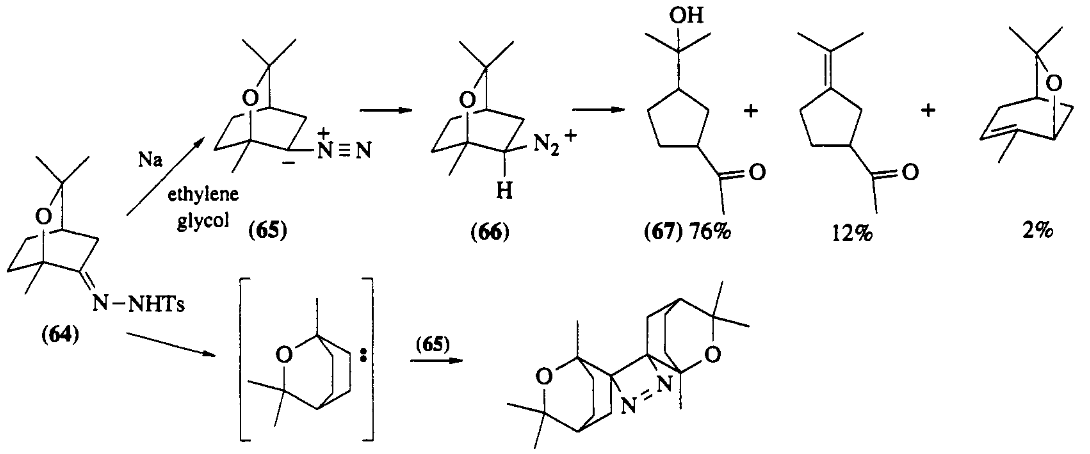
4.3.2.1 Protic Bamford–Stevens Process

The original Bamford–Stevens reaction employs protic solvents in the decomposition of a tosylhydrazone with a strong base. Ethylene glycol is the most popular and reliable solvent. The tosylhydrazone (**63**), bearing an adjacent cyclopropyl group, decomposes on treatment with sodium methoxide in ethylene glycol to give four alkenic products (equation 44).[56] Possible mechanisms in the formation of these products are in agreement with previous mechanistic conclusions concerning tosylhydrazone decompositions.[53] Very often different behavior is observed in the decomposition of tosylhydrazones of aliphatic ketones under protic or aprotic Bamford–Stevens conditions. For example, in the case of the protic medium, reaction of oxabicyclic ketone tosylhydrazone (**64**) with sodium in ethylene glycol at 115–120 °C yields hydroxy ketone (**67**), mainly *via* the intermediate diazo compound (**65**) followed by the *exo*-diazonium cation (**66**). In contrast, (**64**), subjected to the aprotic condition (excess sodium methoxide in diglyme at 135–140 °C), gives diazetine (**69**) *via* carbene intermediate (**68**; Scheme 6).[57]



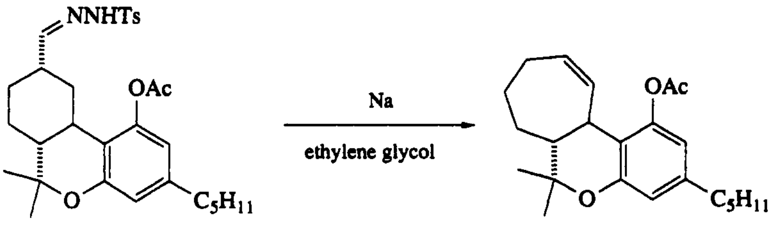
(44)

(63) 60% 10% 30%



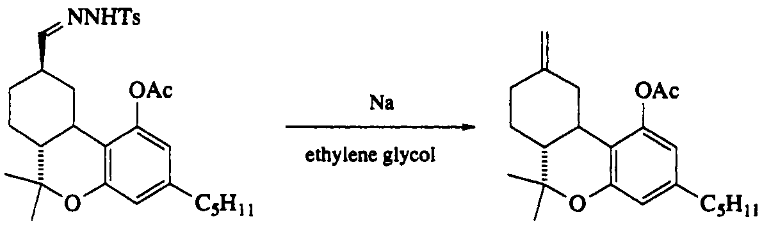
Scheme 6

Interesting stereochemical aspects of the protic Bamford–Stevens reactions of the epimeric 7-oxohexahydrocannabinol tosylhydrazone acetates (**70**) and (**72**) have been recently demonstrated. When the axial epimer (**70**) was added to sodium ethylene glycol, the ring expansion product (**71**) was obtained in 38% yield. On the other hand, reaction of the equatorial epimer (**72**) under the same conditions yielded (**73**) in 56% yield (equations 45 and 46).[58] Notably, the aprotic Bamford–Stevens reaction of the axial epimer (**70**) gave rise to (**73**) (30–40% yield) after acetylation.



(70) **(71)**

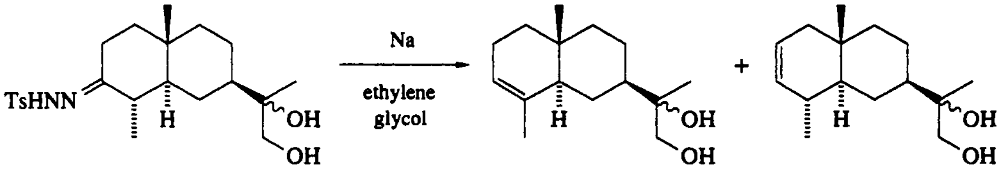
(45)



(72) **(73)**

(46)

The protic Bamford–Stevens reaction has been successfully utilized in the asymmetric synthesis of the naturally occurring sesquiterpenes (+)-α-eudesmol and (–)-α-selinene. Here, the more-substituted alkene was formed preferentially (equation 47).[59]



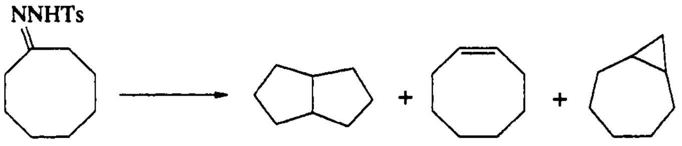
38% 17%

(47)

4.3.2.2 Aprotic Bamford–Stevens Process

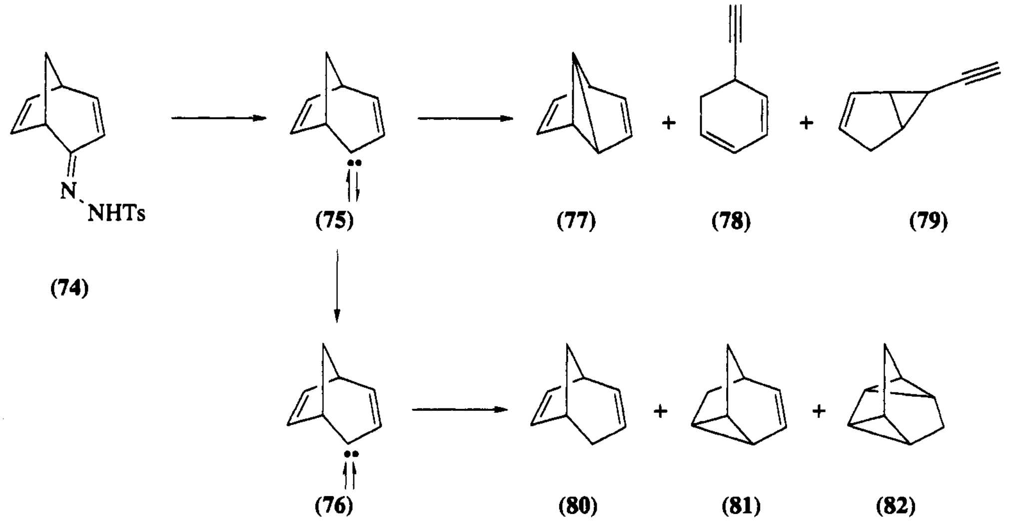
The aprotic reaction is usually executed with bases in a solvent of little or no proton-donating ability, such as diglyme or diethyl carbitol. These conditions provide convenient ways of carbene generation from tosyl hydrazones, which collapse to rearranged alkenes and insertion products as exemplified in the decomposition of cyclooctanone tosylhydrazone on treatment with sodium methoxide in diethyl carbitol or with KH/18-crown-6 in diglyme (equation 48).[60] In a more complex example, pyrolytic or photolytic decomposition of the lithium salt of the substrate (**74**; Scheme 7) results in the formation of (**77**) to (**82**).[60] The formation of (**77**) to (**79**) is thought to occur *via* the singlet carbene (**75**), while (**80**) to (**82**) are generated *via* the triplet carbene (**76**), or a closely related species.

A structurally intriguing dimethyl[6]ditriaxane (**84**) has been synthesized from the polycyclic diketone tosylhydrazone (**83**) by the aprotic Bamford–Stevens reaction *via* a carbenic intermediate (equation 49).[61]

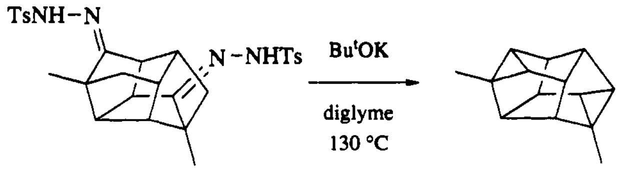


(48)

KH/18-crown-6	45%	47%	8%
NaOMe	46%	45%	9%

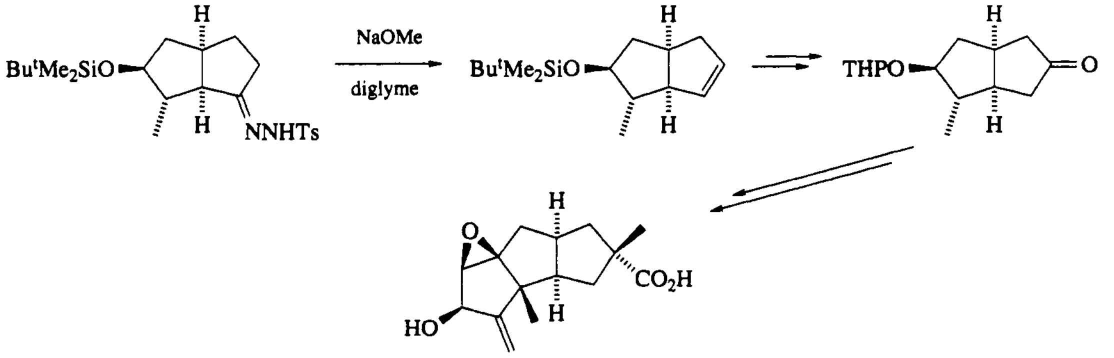


Scheme 7



(49)

The aprotic Bamford–Stevens reaction has been utilized for the development of a methodology towards 1,2-carbonyl transposition in natural product synthesis. The example in Scheme 8 illustrates the regiocontrolled alkene formation for the synthesis of hirsutic acid.[62]

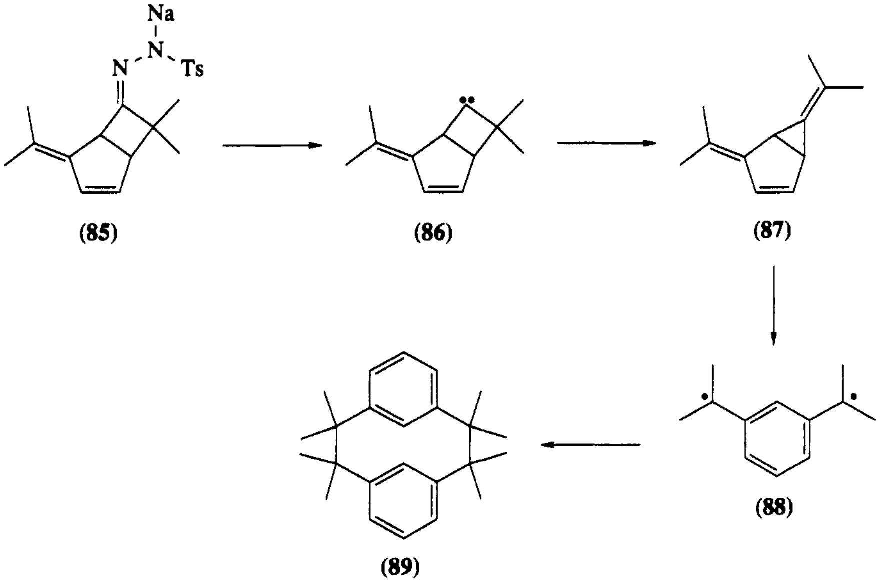


Hirsutic acid

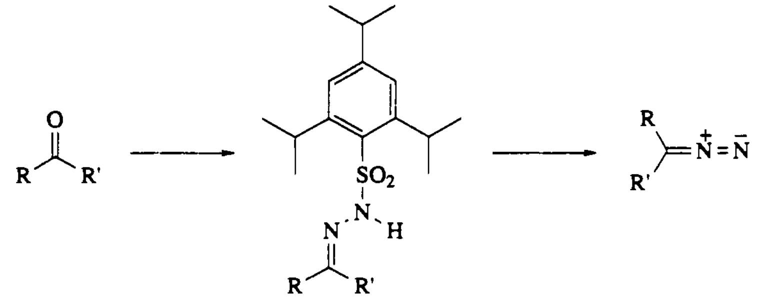
Scheme 8

A non-Kekule molecule, a *m*-xylylene (**88**), has been generated by the Bamford–Stevens reaction of a fulvene–ketene adduct (**85**), *via* the homofulvene (**87**) from the intermediate carbene (**86**). This unstable intermediate readily dimerizes to octamethyl[2.2]metacyclophane (**89**; Scheme 9).[63]

The Bamford–Stevens reaction is the key step in a convenient procedure for the conversion of aldehydes and ketones into the corresponding diazoalkanes. Here, the use of 2,4,6-triisopropylbenzenesulfonylhydrazone (trisylhydrazone) is far superior to the use of the more common tosylhydrazones (equation 50).[64] This behavior is attributed to the greater release of steric compression in the decomposition of *ortho*-substituted arenesulfonylhydrazones.



Scheme 9



(50)

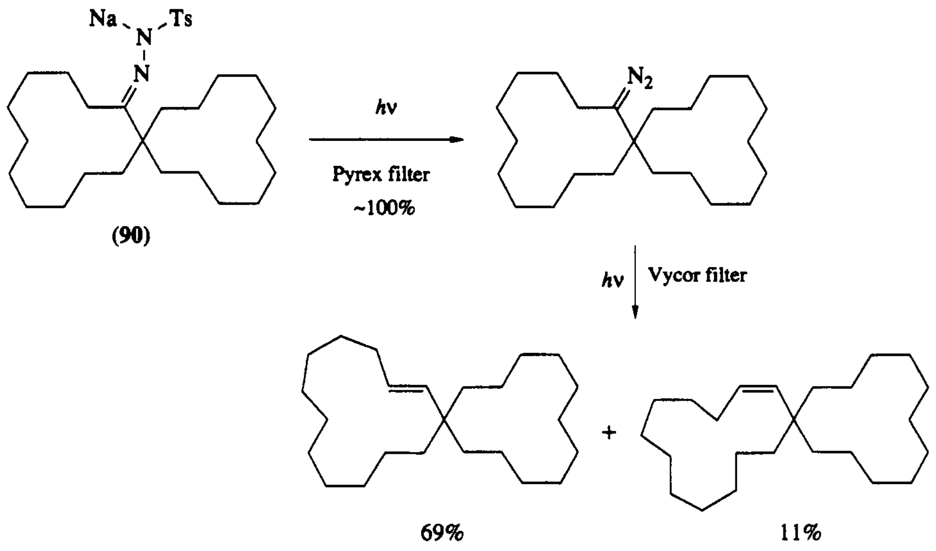
Mechanistic information on the photolytic Bamford–Stevens reaction is provided by the successful isolation of a diazo hydrocarbon as a reaction intermediate from the direct photolysis of a tosylhydrazone sodium salt (**90**; Scheme 10).[65] This study also clarifies that the 'carbene' derived thermally and that derived photolytically behave differently with respect to the stereoselectivity of the 1,2-hydrogen shift that produces the alkene.

The Bamford–Stevens reaction is particularly effective for the generation of 9-phenyl-1(9)-homocubene (**93**), the most twisted alkene yet known.[66] Thus, thermolysis of the cubyl phenyl ketone tosylhydrazone (**91**) in ethanolic sodium ethoxide or photolysis of the diazo compound (**92**) in ethanol both give good conversions to a 3:2 mixture of the isomeric ethers (**95**) and (**96**) (Scheme 11). The formation of (**96**) suggests the intervention of 1-phenyl-9-homocubylidene (**94**) *via* the rearrangement of (**93**).

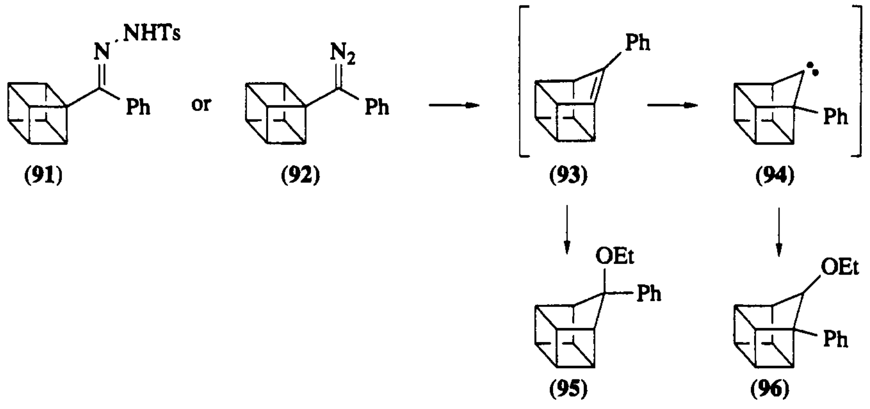
Mesitylene-2-sulfonylhydrazone is found to be particularly effective in the Eschenmoser fragmentation reaction. For example, reaction of the epoxy ketone of type (**97**) gives rise to the corresponding cycloalkynone in reasonable yield (equation 51).[67] The same reaction with tosylhydrazone failed, however.

4.3.3 SHAPIRO REACTION

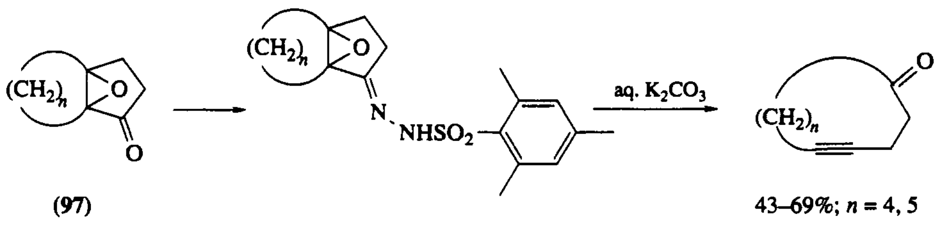
The title reaction represents the decomposition of arenesulfonylhydrazones with alkyllithium reagents to furnish unrearranged, less-substituted alkenes almost exclusively. The *in situ* generated alkenyllithium reagents can be further elaborated by reaction with an electrophile. Since the electrophile can be easily varied, the Shapiro reaction permits the convenient transformation of a ketone into a single substituted alkene in a synthetically useful way.[53,68] This section will highlight the versatility of this reaction in selective organic synthesis.



Scheme 10



Scheme 11

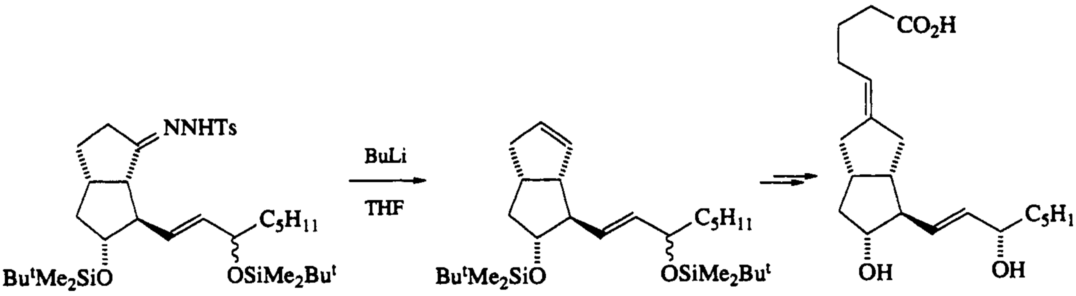


(51)

The original Shapiro reaction involves the preparation of unfunctionalized alkenes from ketone tosylhydrazones by quenching of the *in situ* generated alkenyllithium reagents with water. Recent applications of this reaction in natural product synthesis include the synthesis of 9(0)-methanoprostacyclin (Scheme 12),[62] the *in vitro* conversion of humulene to $\Delta^{8(13)}$-capnellene (Scheme 13),[69] the synthesis of the basic skeleton of isoatisirene (equation 52)[70] and the total synthesis of the eudesmanolides rothin A and rothin B (equation 53).[71]

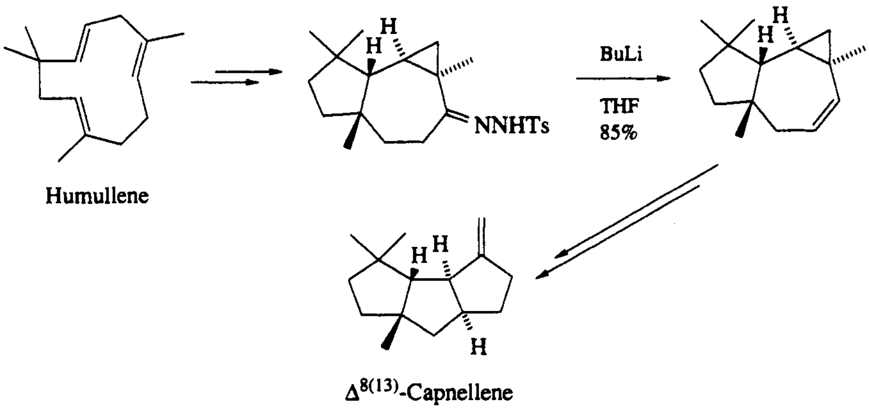
New methods for the 1,2-transposition and alkylative 1,2-transposition of carbonyl groups *via* vinylsilanes or vinyl sulfides have been explored which are based on the Shapiro reaction as the key reaction (Schemes 14 and 15).[72-74] These methodologies have been further extended to regiocontrolled enone transpositions.[75]

As already demonstrated in the Bamford–Stevens reaction, 2,4,6-triisopropylhydrazones (trisylhydrazones) are also found to undergo fragmentation more easily than the corresponding tosylhydrazones in

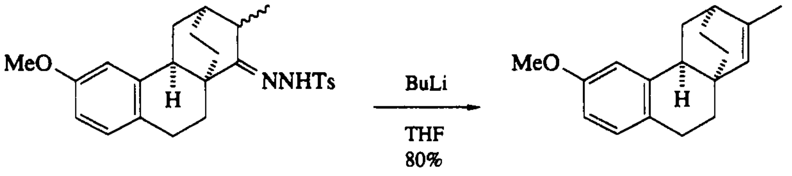


9(0)-Methanoprostacyclin

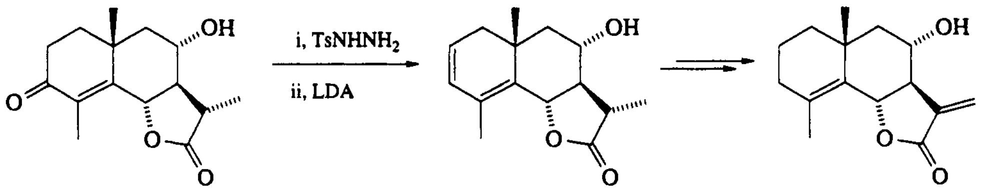
Scheme 12



Scheme 13



(52)



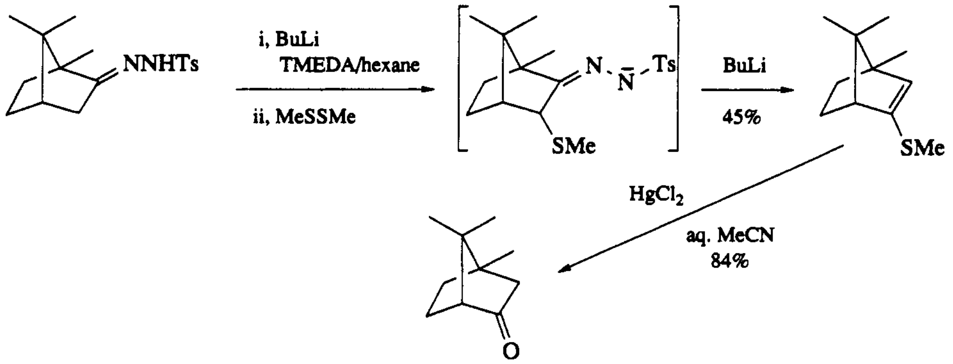
(53)

Rothin A

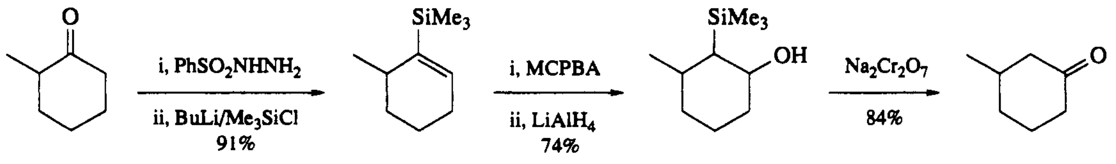
the Shapiro reaction.[76] In fact, the conversion of the hydrazone (**98**) to the annulene (**99**) is much improved by using trisylhydrazone (Scheme 16).[77]

The modified Shapiro reaction is quite effective for the regioselective generation of 1-octen-2-yllithium (**100**) from an (*E,Z*)-mixture of 2-octanone trisylhydrazones (Scheme 17).[78] Here, the use of hexane–TMEDA is crucial for regiospecifically obtaining the less-substituted alkenyllithium reagent. In THF the regioselectivity is controlled by the stereochemistry of the hydrazones, and the ratio of a 1-octene/2-octene product is identical with that of the original hydrazone mixture. In contrast, the more-substituted regioisomeric alkenyllithium reagent (**101**) has been successfully generated, as outlined in Scheme 18.[79] The regiospecifically generated alkenyllithium reagent can be trapped with a variety of electrophiles, as illustrated in Scheme 19.[78,80]

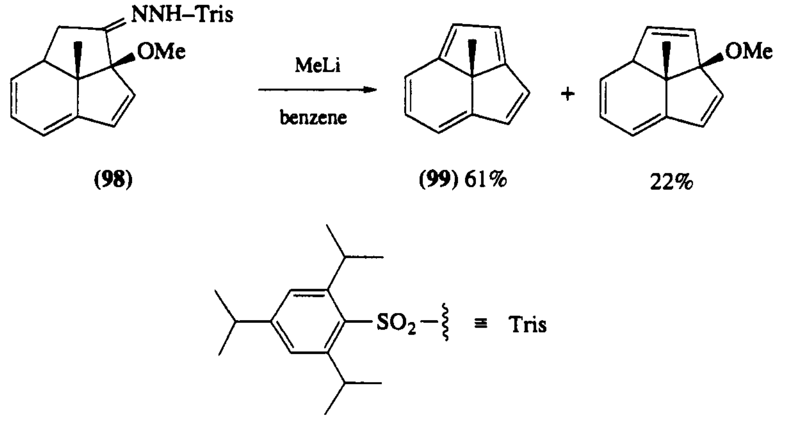
Reactive alkenyl anions prepared by the Shapiro reaction from trisylhydrazones of polyenones and their smooth 1,2-addition to polyenals provides a new route to the versatile synthesis of hydroxymethyl-



Scheme 14



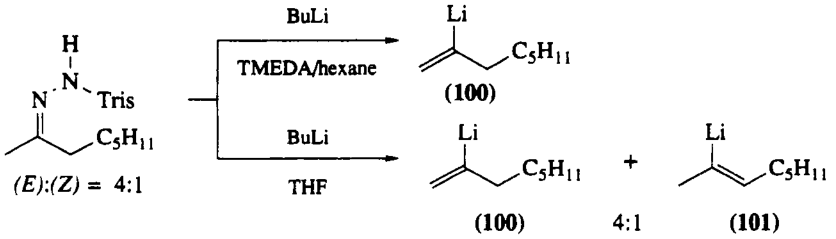
Scheme 15



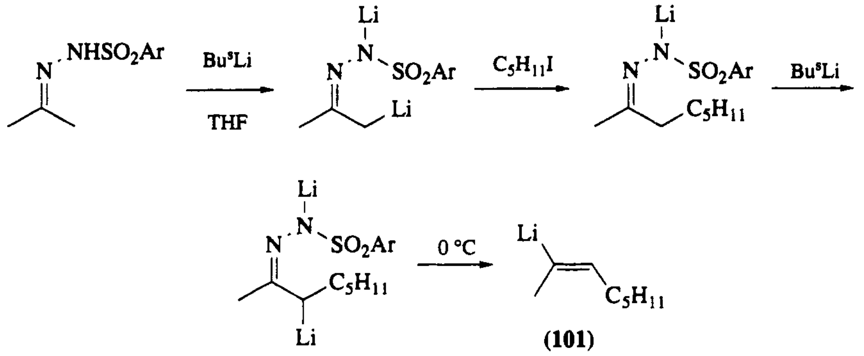
Scheme 16

carotenoids. A typical example is the facile synthesis of optically active carotenediol (**102**), a model compound structurally very close to loroxanthin (Scheme 20).[81]

A new enephosphinilation of ketones has been developed, based on the Shapiro decomposition of trisylhydrazones with BuLi followed by trapping with chlorodiphenylphosphine (Scheme 21).[82] Oxidation of the resulting vinylphosphines with 30% hydrogen peroxide or 40% peroxyacetic acid/sodium carbonate yields the corresponding phosphine oxides.

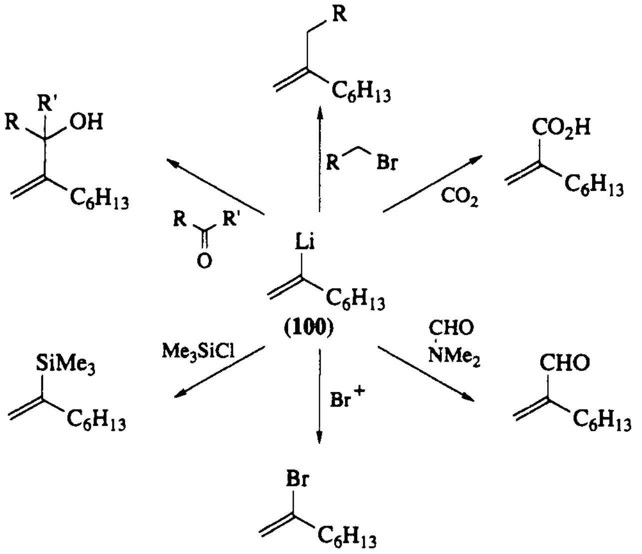


Scheme 17



(101)

Scheme 18



(100)

Scheme 19

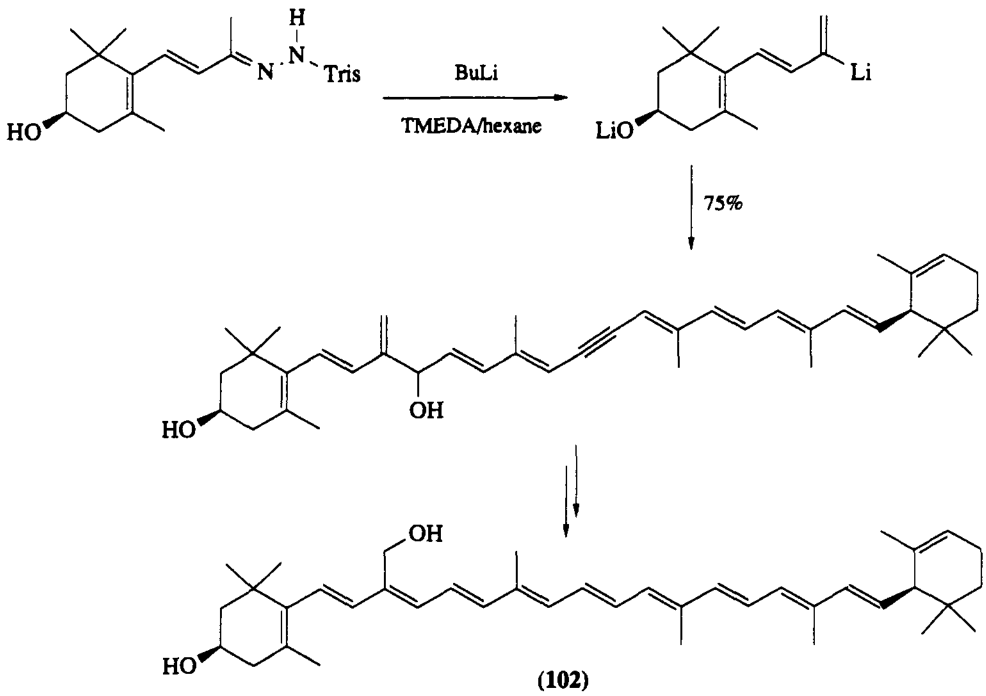
The modified Shapiro reaction usually requires the use of an excess of base along with a coordinating solvent such as TMEDA: this hampers the clean generation of alkenylcuprate reagents from trisylhydrazones. However, treatment of trisylhydrazones with 2 equiv. of Bu^{t}Li in THF successfully gives the desired alkenyllithium reagents. Subsequent transmetallation with phenylthiocopper affords the corresponding mixed alkenylcuprates which smoothly undergo conjugate additions to enones (equation 54).[83]

Intramolecular cyclization of an ω-chloro ketone trisylhydrazone *via* the *in situ* generated alkenyllithium has been achieved efficiently, thereby providing a new approach to the synthesis of various unsaturated carbocycles (equation 55).[84]

Amidorazones are very useful as acyl anion equivalents. For example, trisylamidorazones on treatment with Bu^{t}Li yield α-lithioenamines which subsequently react with electrophiles to give ketones (Scheme 22).[85]

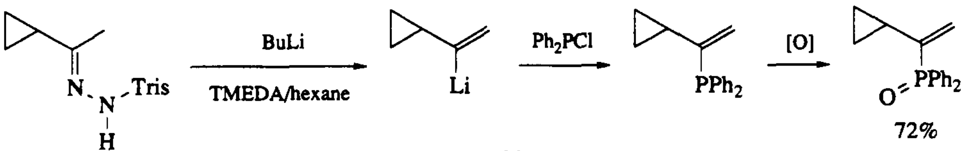
The synthon of the α-acrylate anion is available from a secondary α-keto carboxamide by the Shapiro reaction.[86] The secondary α-ketoamide trisylhydrazones are prepared in a 'one-pot' synthesis by reaction of the isocyanides with acid chloride, water and trisylhydrazine in sequence. In DME solvent, the hydrazone (**103**) is smoothly metallated with BuLi to give the trianion (**104**). Allylation of the trianion (**104**) gives the hydrazone (**105**). Alternatively, warming (**104**) up to room temperature yields the dianion (**106**) which can be intercepted with several electrophiles (Scheme 23). The adduct (**107**) is readily transformed into the *trans*-iodo lactone (**108**) stereospecifically (equation 56). This chemistry also has been applied to a new synthesis of β-lactams (Scheme 24).[87]

The ability of the trisylhydrazone dianion to undergo alkylation further enhances the synthetic potential of the Shapiro reaction. The initial carbonyl alkylation of acetone trisylhydrazone dianion, followed by fragmentation to the functionalized alkenyllithium reagent and subsequent trapping with carbon diox-

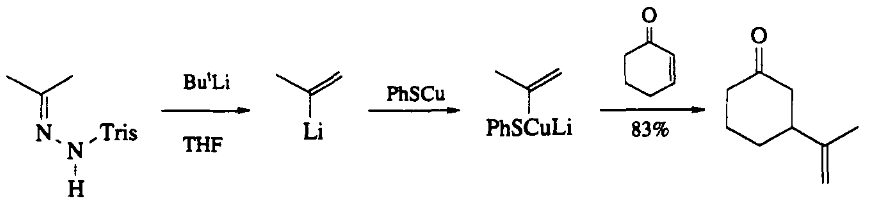


(102)

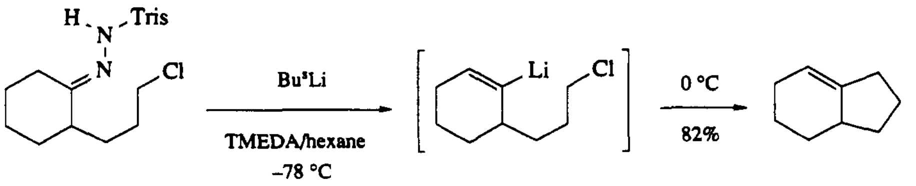
Scheme 20



Scheme 21



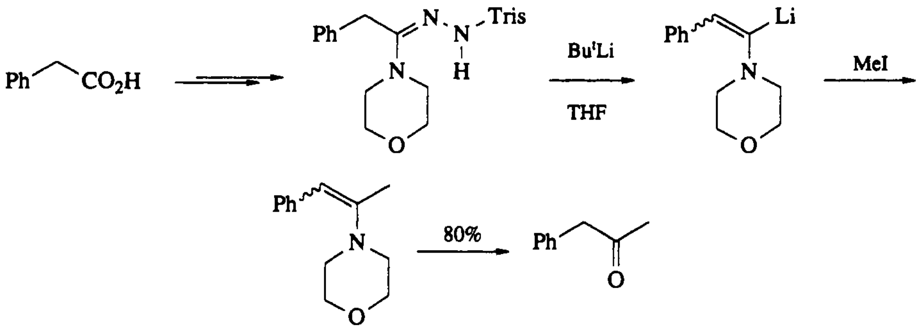
(54)



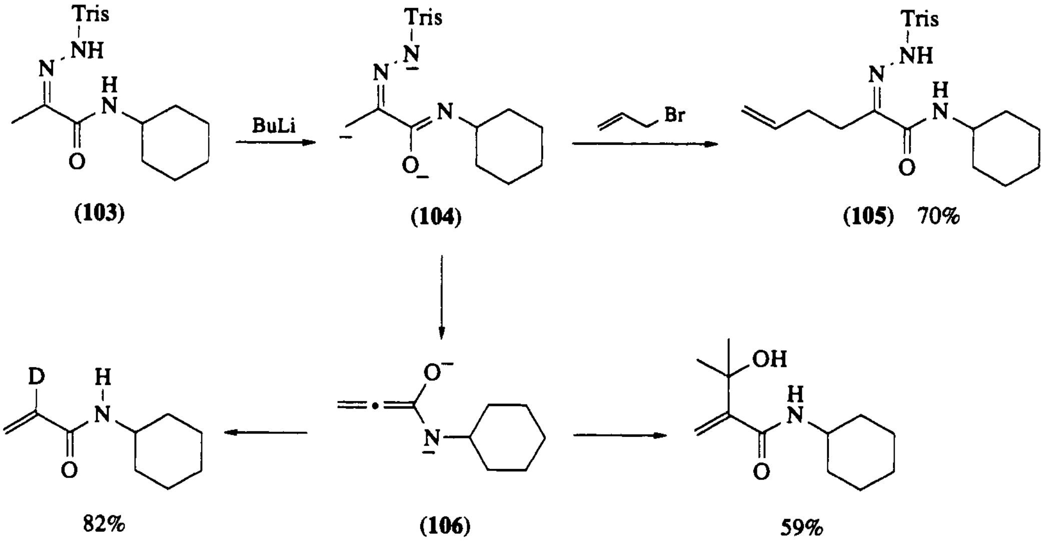
(55)

ide provides a novel route to α-methylene-γ-lactones (equation 57).[88] The important 3,5-dimethylene-tetrahydrofuran-2-one unit found in natural products such as obtsusilactones and mahubenolides is also available by this procedure (Scheme 25).[89,90] In the total synthesis of ovalicin, the vinylstannane (**109**) is obtained from acetone trisylhydrazone in a 'one-pot' synthesis (equation 58).[91]

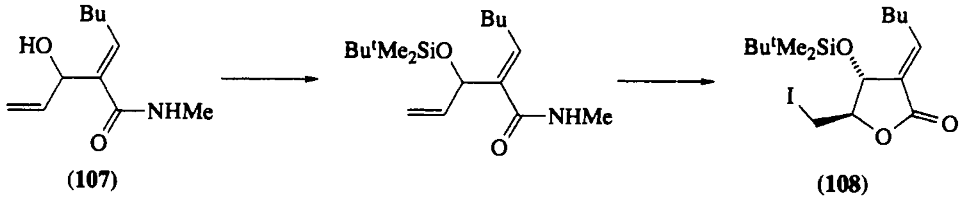
1,3-Diphenylacetone tosylhydrazone can be used as an indicator in the assay of organolithium reagents (equation 59).[92] Here, the end point, the formation of the orange dianion, is sharp and easily observed.



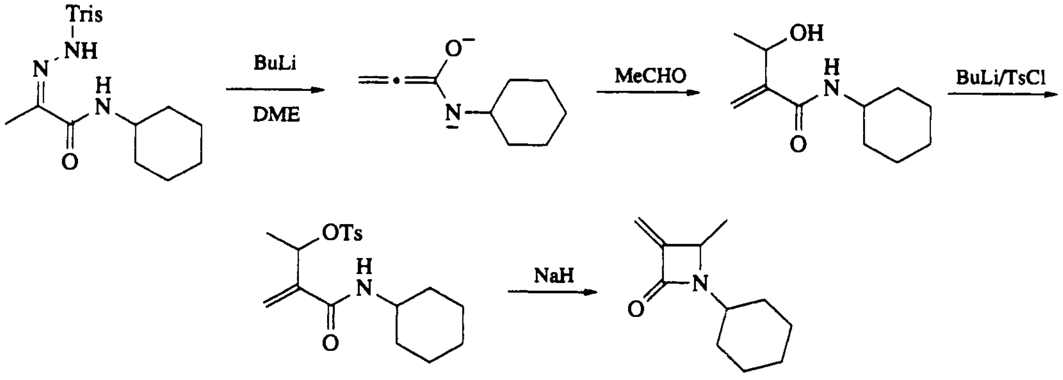
Scheme 22



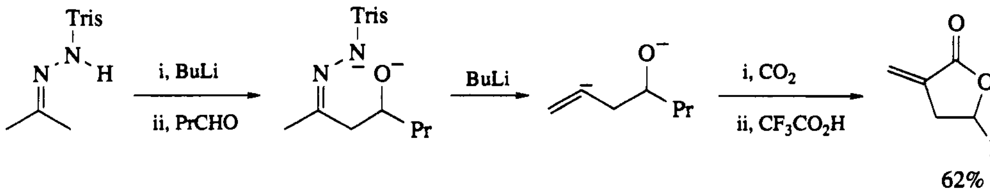
Scheme 23



(56)



Scheme 24



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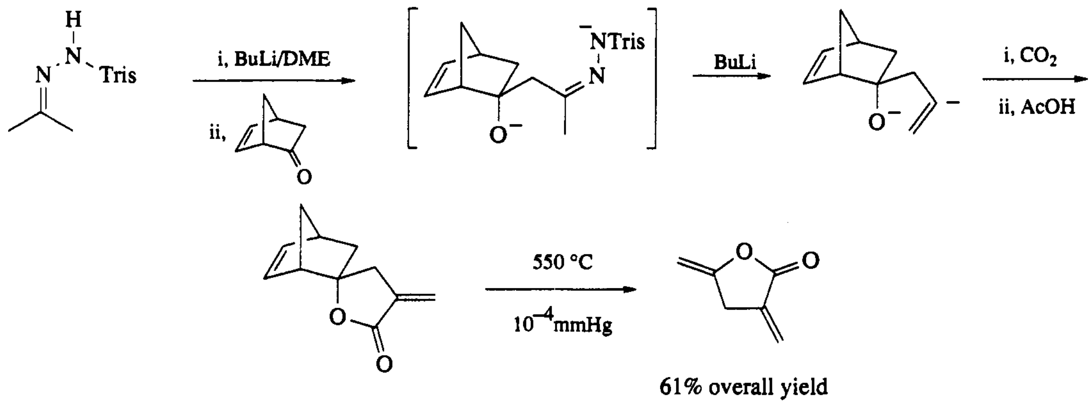
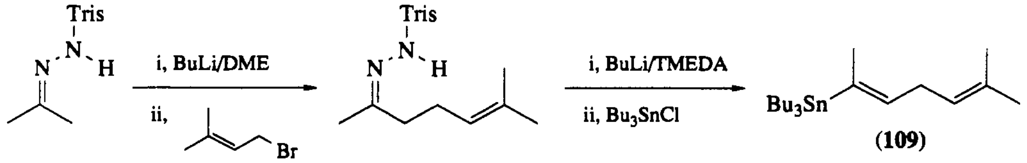
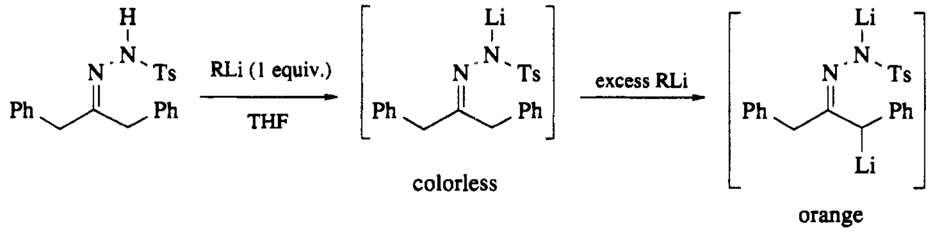


Scheme 25



(109)

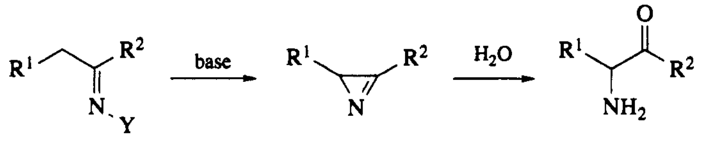
(58)



(59)

4.3.4 NEBER REARRANGEMENT

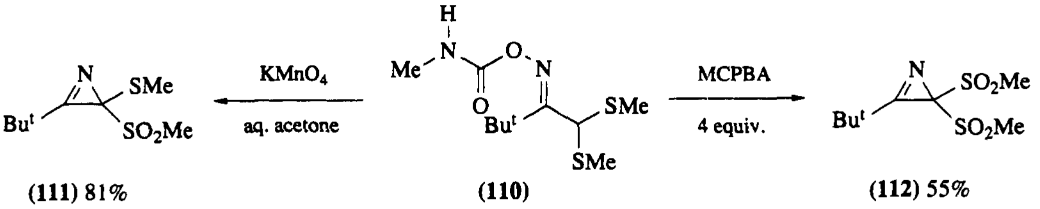
The Neber rearrangement involves the base-catalyzed conversion of oxime tosylates, quaternary salts of hydrazones or *N*-chloroimines to α-amino ketones *via* isolable azirine intermediates (equation 60).[93-95]



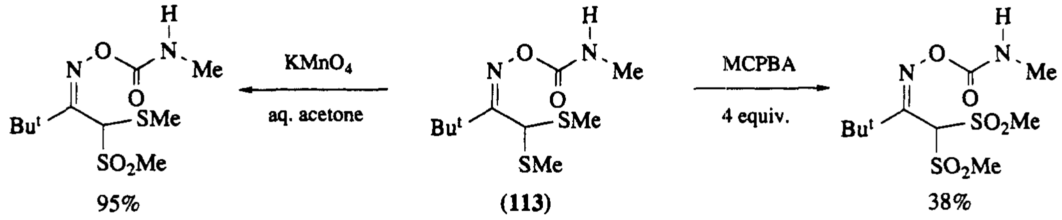
Y = OTs, NMe_3X, Cl

(60)

From mechanistic studies on the Neber reaction, the 2*H*-azirine has been shown to be a distinct intermediate formed by ring closure of a vinyl nitrene.[96] The evidence for the vinyl nitrene has resulted from the reported lack of stereospecificity in converting the (*E*)- and (*Z*)-isomers of *O*-tosyloximes to the same α-amino ketone. Although a vinyl nitrene has been suggested as a possible intermediate in the thermal and photochemical preparations of the azirine ring, direct evidence for such a species is lacking. In this context, the configurational stereospecificity in a modified Neber reaction has been studied with oxime carbamates in order to elucidate the mechanism of this reaction. Thus, oxidation of (*E*)-α,α-bis(methylthio)oxime carbamate (**110**) with $KMnO_4$ or MCPBA yields functionalized 2*H*-azirine derivatives (**111**) or (**112**) exclusively (Scheme 26).[97] On the other hand, reaction of the corresponding (*Z*)-isomer (**113**) results only in oxidation at sulfur (Scheme 27). These observations imply that the involvement of a vinyl nitrene intermediate seems unlikely in the conversion of the oxime carbamate to the 2*H*-azirine.



Scheme 26



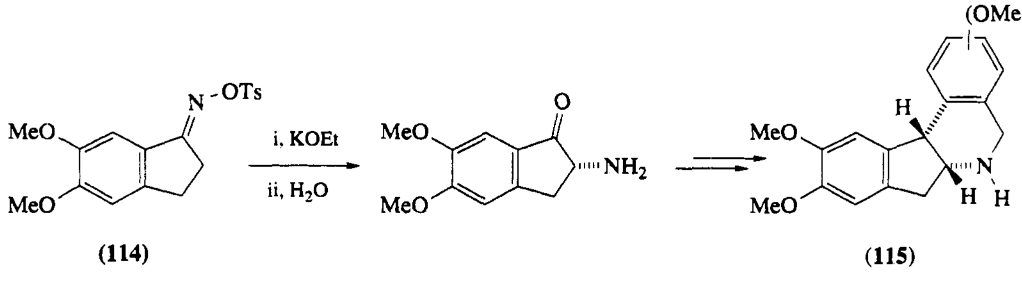
Scheme 27

Since α-amino ketones are useful intermediates for the preparation of a variety of heterocycles, including imidazoles, oxazoles and pyrazines, the Neber rearrangement is of high synthetic value particularly in the pharmacological fields. Tetrahydroindenoisoquinoline (**115**) has been synthesized *via* the Neber rearrangement of (**114**) in order to study the structural requirement necessary for interaction with dopamine receptor binding sites (equation 61).[98] Another example is the synthesis of a rigid dopamine congener, naphthoxazine (**117**), starting from methoxytetralone (**116**), *via* a seven-step sequence (equation 62).[99,100] In a search for a new structural type of β-adrenergic antagonist, a series of *trans*-2-(*N*-substituted amino)-1,2,3,4-tetrahydronaphthalen-1-ol (**118**) and 6-(*N*-substituted amino)-3-arylcyclohex-2-enol (**119**) derivatives have been synthesized by using similar methodologies (equations 63 and 64).[101,102]

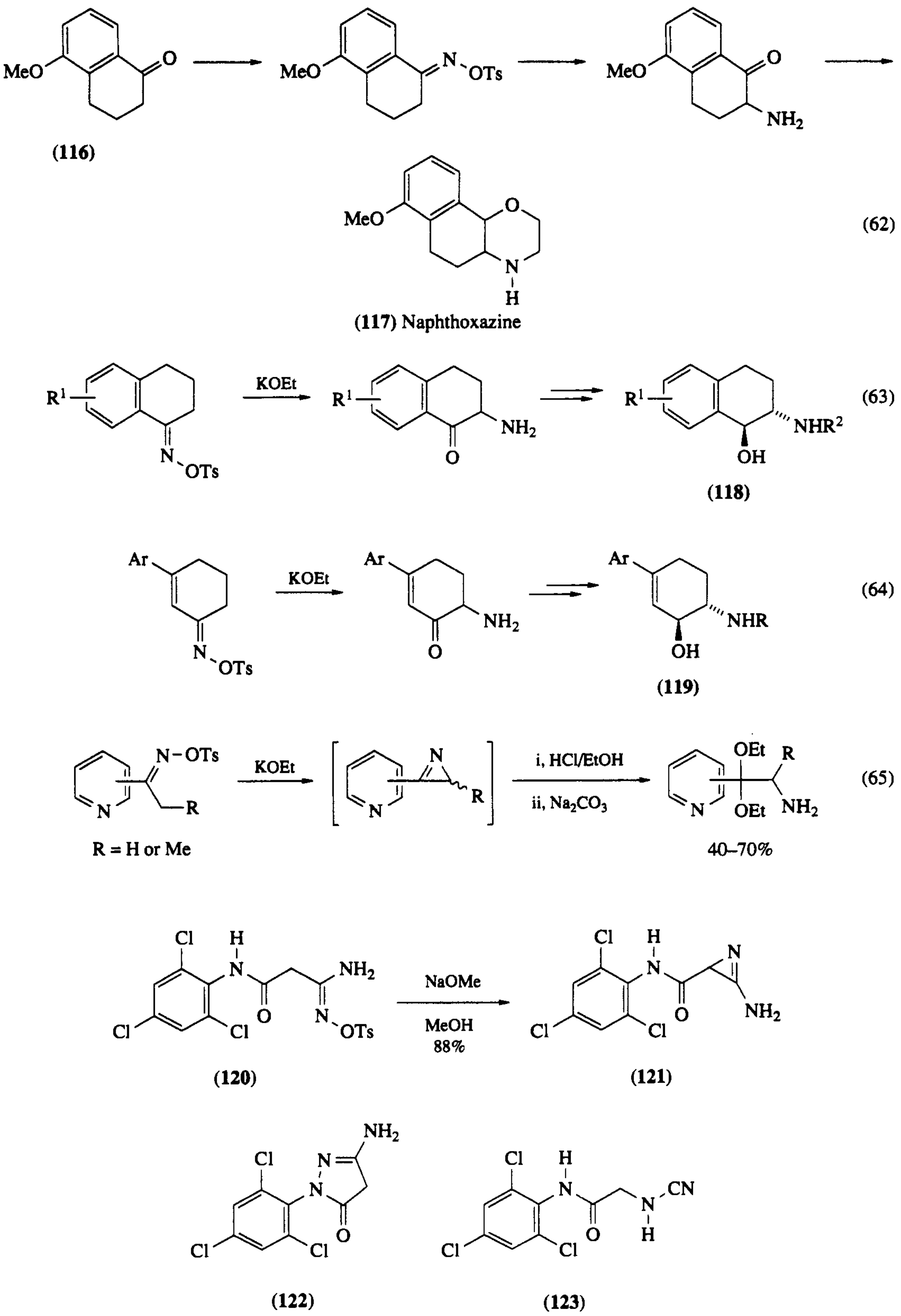
In the synthesis of various heterocycles from α-amino ketones, pyrazine formation can be a complicating side reaction due to the tendency of the α-amino ketone to dimerize. One way of avoiding this problem would be to generate the α-amino ketone in a protected form, specifically, as an α-amino acetal. Such derivatives allow the manipulation of the amino moiety as desired. Accordingly, the azirine intermediates derived from oxime tosylates by the Neber rearrangement are subsequently treated with acidic ethanol to furnish the corresponding α-amino acetals (equation 65).[103]

A new variant of the Neber rearrangement has been reported recently which involves the treatment of amidoxime-*O*-tosylate (**120**) with sodium methoxide affording 2-amino-1-aziridine (**121**), a useful intermediate for the synthesis of a large array of heterocyclic compounds. None of possible pyrazolone (**122**) or cyanamide (**123**) derivatives were detected in the reaction mixture (Scheme 28).[104]

The Neber rearrangement of dimethylhydrazone quaternary salts to α-amino ketones is a well-studied reaction. However, when this reaction is carried out at temperatures below those of normal Neber condi-

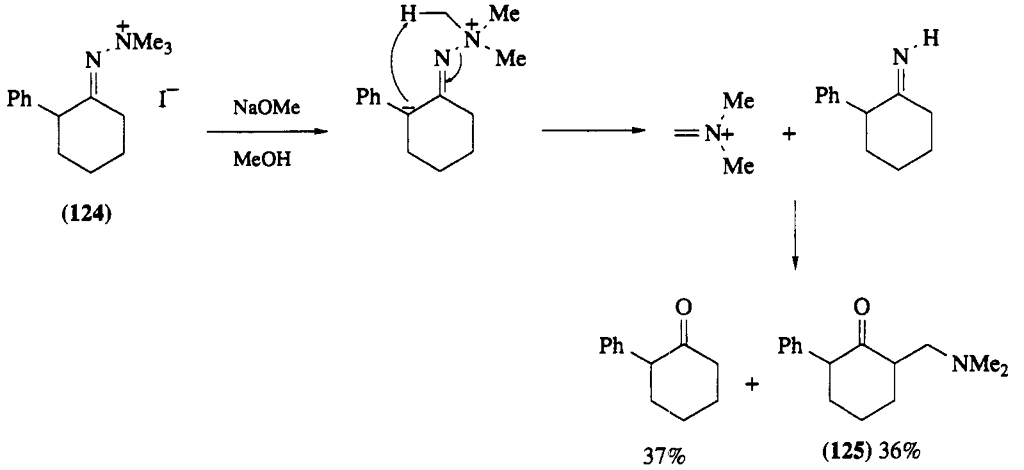


(61)


MeO
O
(116)
N
OTs
NH2
(117) Naphthoxazine
(62)
R1
KOEt
NHR2
OH
(118)
(63)
Ar
NHR
(119)
(64)
N-OTs
R
R = H or Me
i, HCl/EtOH
ii, Na2CO3
OEt
NH2
40–70%
(65)
Cl
H
NaOMe
MeOH
88%
(120)
(121)
CN
(122)
(123)

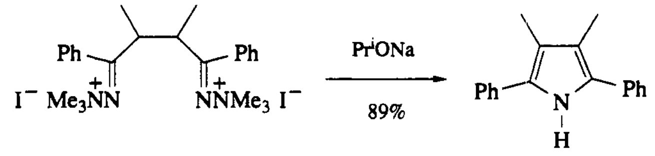
Scheme 28

tions, the methiodide (**124**) of 2-phenylcyclohexanone dimethylhydrazone gives varying amounts of 2-phenylcyclohexanone and the Mannich product (**125**) arising from this ketone (Scheme 29).[105] The normal Neber product can be made to predominate by adding the quaternary salt (**124**) portionwise to a refluxing solution of sodium ethoxide in ethanol.



Scheme 29

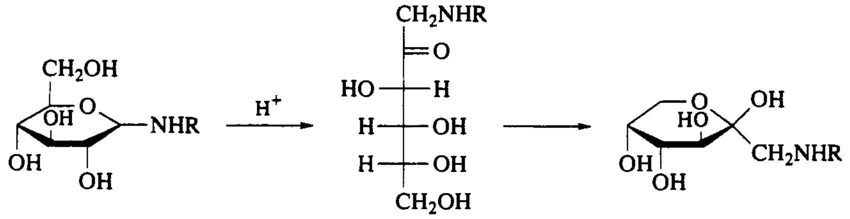
Attempted synthesis of the bis(2*H*-azirine) system from the 2,3-dimethyl-1,4-diphenyl-1,4-butanedione bis(hydrazonium) salt under basic conditions gives 3,4-dimethyl-2,5-diphenylpyrrole in 89% yield (equation 66).[106]



(66)

4.3.5 AMADORI REARRANGEMENT

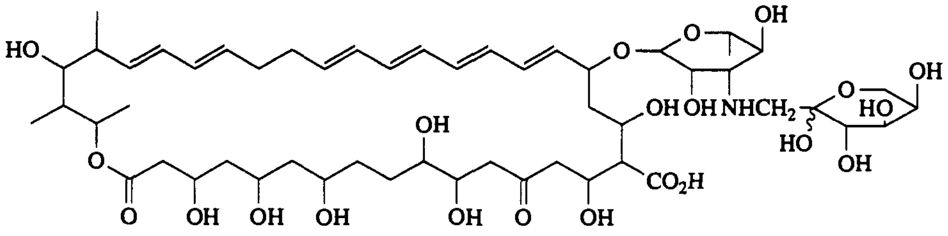
The Amadori rearrangement represents a conversion of *N*-glycosides of aldoses to *N*-glycosides of the corresponding ketones by acid or base catalysis, as shown in the preparation of 1-alkylamino-1-deoxy-(+)-fructose (**127b**) from (+)-glucosylamine (**126**; equation 67).[107,108] Compounds of the type (**127a**) and (**127b**) are known as 'Amadori compounds'. A variety of Lewis acids such as $CuCl_2$, $MgCl_2$, $HgBr_2$, $CdCl_2$, $AlCl_3$, $AsCl_3$, $FeCl_3$ and $SnCl_4$ have been employed as catalysts for the rearrangement of *N*-(+)-glucosylamines containing aromatic aglycons.[109]



(126) (127a) (127b)

(67)

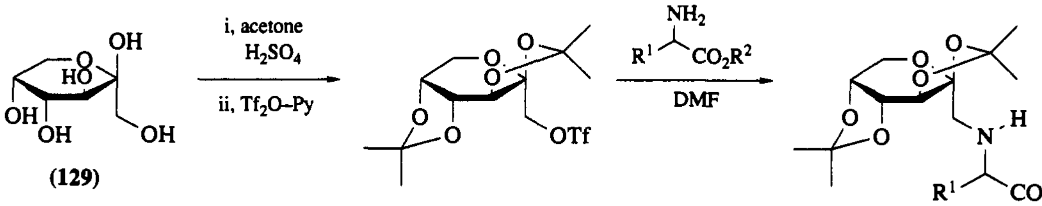
A recent example involves the synthesis of *N*-glycosyl derivatives of polyene macrolide antibiotics, such as the preparation of *N*-(deoxyfructosyl)nystatin (**128**) by reaction of nystatin with (+)-glucose (Scheme 30).[110]



(128)

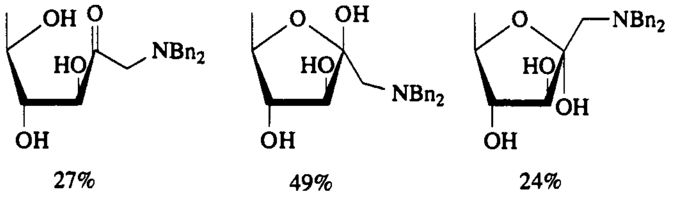
Scheme 30

In spite of their physiological and toxicological importance the Amadori compounds have been investigated until recently only in relatively few biological materials. This is due to the tedious procedures for their isolation and purification from the reaction medium. In this context, a new route to the Amadori compounds (**130**) has been developed starting from fructose (**129**; equation 68), thereby avoiding the formation of undesirable by-products from thermal degradation of amino acids, from Amadori compounds themselves, and due to sugar caramelization.[111]



(129) (68) **(130)**

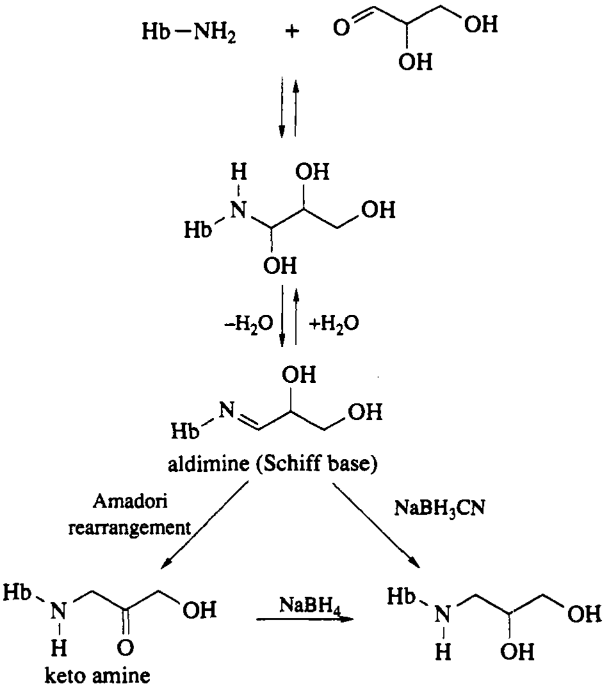
The equilibrium mixture of various Amadori products in dimethyl sulfoxide-d_6 has been studied qualitatively and quantitatively by ^{13}C NMR spectroscopy. The position of the equilibrium varies considerably depending on the substituents on the carbohydrates (Scheme 31).[112]



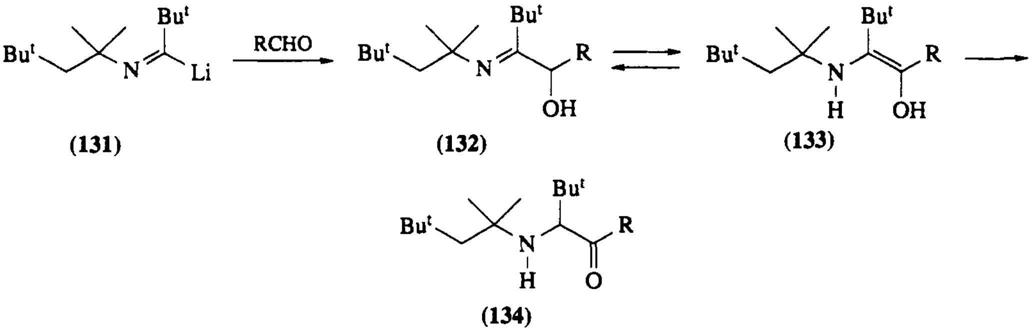
Scheme 31

The Schiff base adducts of glyceraldehyde with the amino groups of hemoglobin A are found to undergo Amadori rearrangement to give stable ketoamine adducts, a reaction analogous to the nonenzymic glycosylation of proteins (Scheme 32).[113–118] In the presence of sodium cyanoborohydride, the incorporation of glyceraldehyde into hemoglobin is faster than that in its absence, suggesting that Amadori rearrangement is the rate-limiting step in nonenzymic glycosylation.

Lithium aldimine (**131**), an acyl anion equivalent derived from an isocyanide and an organolithium reagent, adds to aldehydes giving, after quenching with water, α-amino ketones (**134**) *via* the Amadori rearrangement (Scheme 33).[119] The α-amino ketone (**134**) results from a double tautomerization of α-hydroxy imine (**132**), formed initially after quenching with water. Thus, the imine (**132**) isomerizes to enolamine (**133**), which in turn tautomerizes to the observed product (**134**).



Scheme 32



(131) (132) (133) (134)

Scheme 33

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4.4
Degradation Reactions

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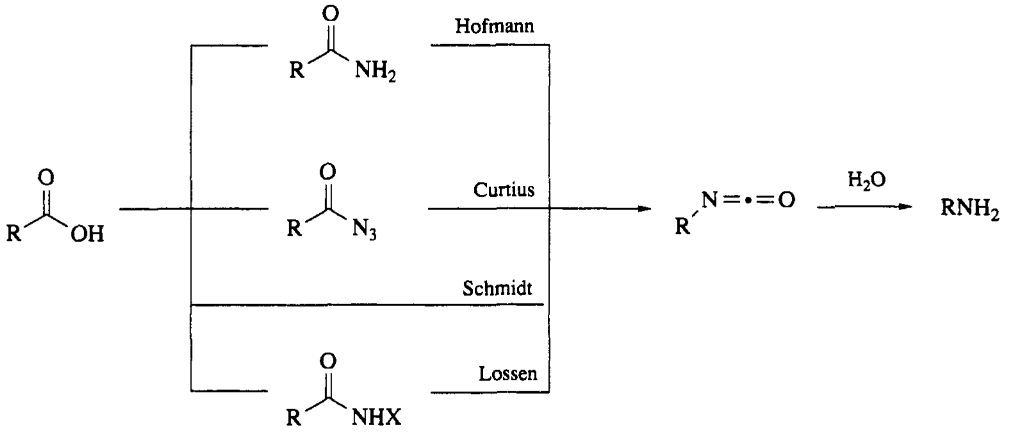
4.4.1 FROM CARBOXYLIC ACIDS TO AMINES

4.4.1.1 General Aspects

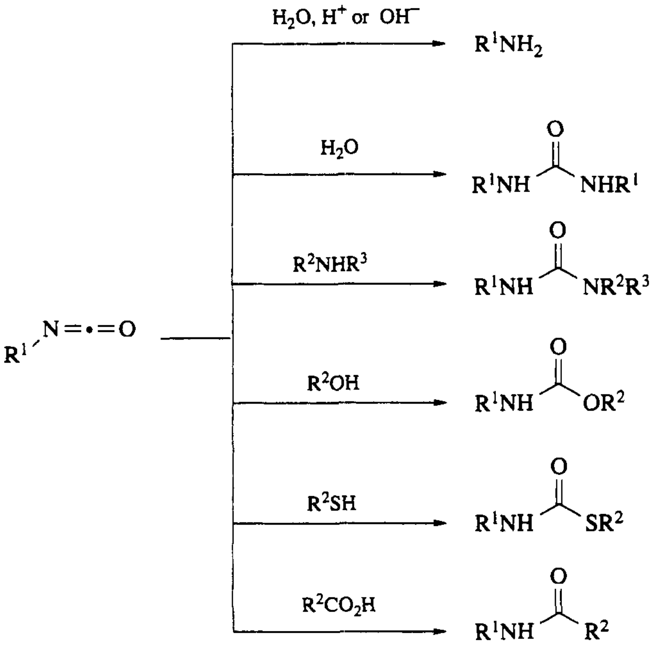
Degradation reactions of carboxylic acids and their derivatives to amines and their derivatives with one less carbon unit[1-5] involve rearrangements of a carbon to an electron deficient nitrogen atom as key steps, namely the Hofmann (H),[6,7] Curtius (C),[8,9] Schmidt (S)[10-13] and Lossen (L)[14,15] rearrangements, as shown in Scheme 1.

The overall process of going from carboxylic acids to amines is known as the Hofmann, Curtius, Schmidt or Lossen 'reaction', but these are quite often described as 'rearrangements' and sometimes called 'degradations'. These reactions were all discovered in the late 19th century (Hofmann, 1881; Curtius, 1890; Lossen, 1872) except for the Schmidt reaction (1923). Since these reactions provide a practical procedure for replacing a carboxy group by an amino group, they have been extensively used since their discoveries. Inspection of *Chemical Abstracts* between 1967 and 1988 has revealed that the numbers of papers related to these four rearrangement reactions are 233 for the Hofmann reaction, 522 for the Curtius reaction, 332 for the Schmidt reaction (including the Schmidt reaction of ketones, aldehydes and others) and 57 for the Lossen reaction.



Scheme 1

The common initial products of the rearrangements are isocyanates, which readily react with all types of compounds containing—OH, —NH or —SH functions, giving amines, ureas, urethanes, thiourethanes, amides *etc.* (Scheme 2).[16] Isolation of the isocyanates may be possible under some reaction conditions, especially in the Curtius reaction when the rearrangement is conducted in aprotic solvents, but usually the solvolytic conversion of isocyanates occurs to give amines or ureas.

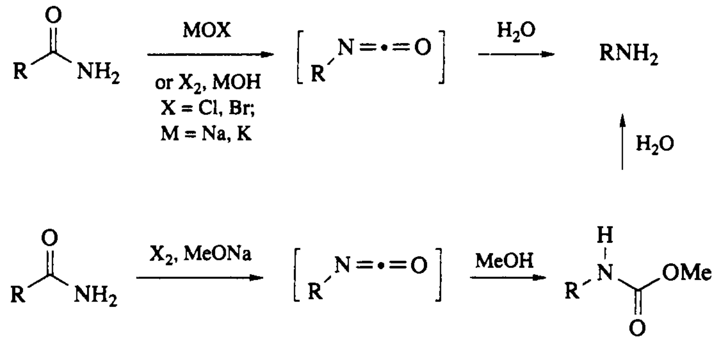


Scheme 2

The Hofmann reaction[6,7] involves the conversion of carboxylic primary amides to primary amines or their derivatives. Generally, alkaline hypohalites or a combination of halogens and alkaline hydroxides are used in aqueous solutions. The rearrangement generally occurs by heating. The intermediate isocyanates are easily hydrolyzed to amines under the reaction conditions, as shown in Scheme 3. When sodium methoxide in methanol is used in place of aqueous alkaline hydroxide, the corresponding methylurethanes are formed and may be hydrolyzed to yield amines.

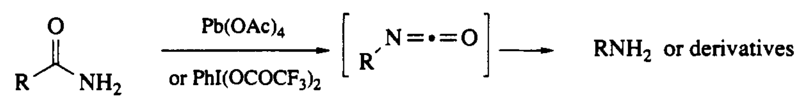
The Hofmann reaction is applicable to the preparation of a wide variety of aliphatic, aromatic and heterocyclic amines, and is suitable for large-scale preparative work, since it is safe and relatively inexpensive to carry out, especially when chlorine and sodium hydroxide can be used.

Oxidizing agents such as lead tetraacetate or [*I,I*-bis(trifluoroacetoxy)iodo]benzene can also be used for the Hofmann reaction. The usual Hofmann reaction shown in Scheme 3 proceeds under alkaline con-



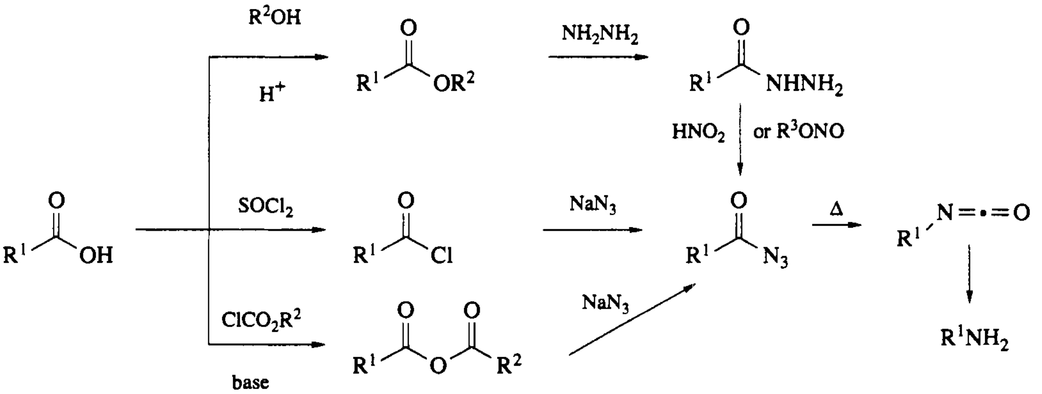
Scheme 3

ditions; hence, it can not be applied to compounds containing alkali labile functions. For these compounds, the alternative Hofmann reaction (equation 1) can be used, since it proceeds under mildly acidic conditions.



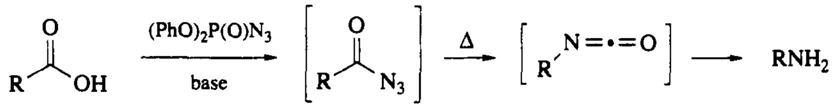
(1)

The Curtius reaction[8,9] involves the thermal rearrangement of acyl azides, with expulsion of nitrogen, to produce isocyanates. Although the rearrangement of acyl azides proceeds by photochemical means at lower temperatures, photolysis has no advantage over thermolysis from preparative points of view. Preparation of acyl azides is conducted in three ways, shown in Scheme 4. A common classical route to acyl azides involves the preparation of acyl hydrazides by the action of hydrazine on esters, followed by treatment of hydrazides with nitrous acid or alkyl nitrites. Interaction of acyl chlorides with sodium azide also gives acyl azides. Mixed anhydrides prepared from carboxylic acids and alkyl chloroformates are useful alternatives for acyl chlorides, giving acyl azides when reacted with sodium azide. The hydrazide method requires more steps and is less convenient than the other methods. Although the acyl chloride method is convenient, it is sometimes difficult to obtain pure acyl chlorides efficiently from acids, since decomposition or isomerization occurs in the presence of mineral acids. In contrast to these, the mixed anhydride method proceeds under mild reaction conditions and mostly gives satisfactory results. The overall process of converting carboxylic acids to amines or their derivatives through the corresponding acyl azides is commonly referred to as the Curtius reaction. Since the Curtius reaction proceeds under relatively mild conditions, it is suitable for sensitive compounds and can be carried out on a wide variety of acids.



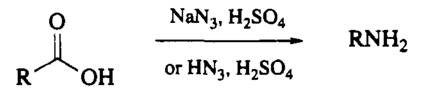
Scheme 4

One of the most useful variants of the Curtius reaction is the reaction of carboxylic acids with diphenyl phosphorazidate (DPPA; $(PhO)_2P(O)N_3$) in the presence of base, such as triethylamine (equation 2).[17,18]



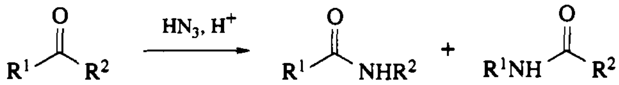
(2)

The Schmidt reaction[10–13] is the name given to a group of reactions which involve the addition of hydrazoic acid to carboxylic acids, ketones and aldehydes, alcohols and alkenes under strongly acidic conditions. The most common reaction is the reaction with carboxylic acids, which give amines in a single step (equation 3). Usually, a mixture of sodium azide and sulfuric acid is used to conduct the reaction, though the use of a solution of free hydrazoic acid together with sulfuric acid sometimes gives better results. The Schmidt reaction often gives higher yields than the other rearrangement reactions since it is a one-step reaction. However, the strongly acidic conditions preclude the use of carboxylic acids containing strongly acid labile or reactive functions. Advantages and drawbacks of the Hofmann, Curtius and Schmidt reactions carried out before 1946 have been discussed in ref.8.

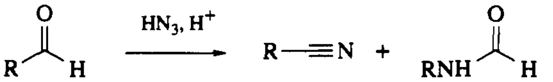


(3)

Reaction of ketones with hydrazoic acid proceeds similarly to the Beckmann rearrangement to give amides, while aldehydes yield nitriles and formamides under analogous reaction conditions (equations 4 and 5).

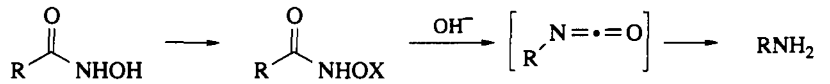


(4)



(5)

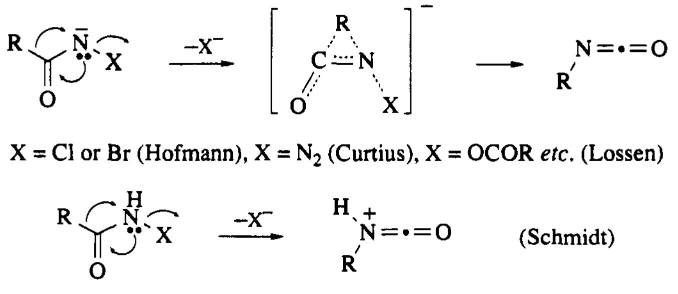
The fourth related rearrangement reaction is the Lossen reaction,[14,15] which generally occurs by base treatment of *O*-substituted hydroxamic acids which possess electron-withdrawing functions at the oxygen atom (*e.g.* *O*-acylhydroxamic acids), giving amines *via* isocyanates (equation 6). Preliminary *O*-activation (*e.g.* *O*-acylation) of hydroxamic acids is essential for a smooth rearrangement, otherwise it will not occur. The Lossen reaction is not as useful as the other three rearrangements since hydroxamic acids are not readily available.



(6)

4.4.1.2 Mechanism and Stereoselectivity

The Hofmann, Curtius, Schmidt and Lossen rearrangements generally involve nucleophilic migrations from a carbon to an electron deficient nitrogen center (Scheme 5), giving isocyanates as the initial products, which undergo further reactions as already shown in Scheme 2.

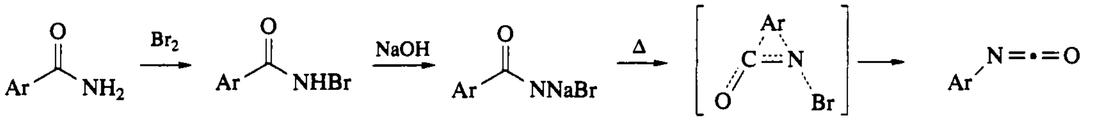


X = Cl or Br (Hofmann), X = N_2 (Curtius), X = OCOR *etc.* (Lossen)

Scheme 5

Mechanistic studies on these four rearrangements[2,3,9] have revealed that: (i) these are concerted intramolecular rearrangements; (ii) stereochemical configurations of the migrating groups are completely retained; (iii) the kinetics are first order; and (iv) neither free carbonium ions nor radical intermediates are formed during the rearrangements.

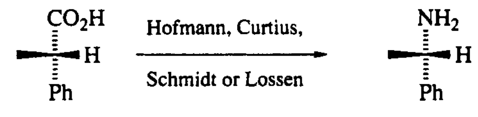
The first intermediates of the Hofmann reaction are *N*-haloamides (*e.g.* **1**), which are subsequently converted to alkaline salts (*e.g.* **2**). Both intermediates can be isolated under carefully controlled conditions. Kinetic evidence on both the substituent[19] and isotope[20] effects in the Hofmann rearrangement of various *N*-halobenzamides (**1**) in an aqueous sodium hydroxide solution strongly support a concerted mechanism, involving the bridged anion (**3**), shown in Scheme 6.



(1) **(2)** **(3)**

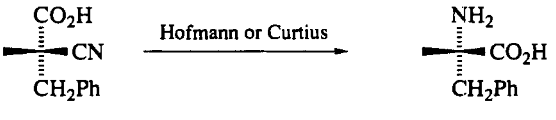
Scheme 6

Practically, the carbon–nitrogen rearrangements occur with almost complete retention of optical and geometrical configurations. (*S*)-(+)-2-Phenylpropionic acid (**4**) and its derivatives undergo the Hofmann, Curtius, Schmidt and Lossen rearrangements to give (*S*)-(–)-1-phenylethylamine (**5**) with more than 99% retention of configuration.[21,22] Strong alkaline conditions used in the Hofmann reaction cause some racemization (*ca.* 4%) before the rearrangement (equation 7).



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

Conversion of (*S*)-2-cyano-2-methyl-3-phenylpropionic acid (**6**) to (*S*)-α-methylphenylalanine (**7**) through the Hofmann and Curtius rearrangements followed by hydrolysis also proceed with nearly complete retention of configuration (equation 8).[23]

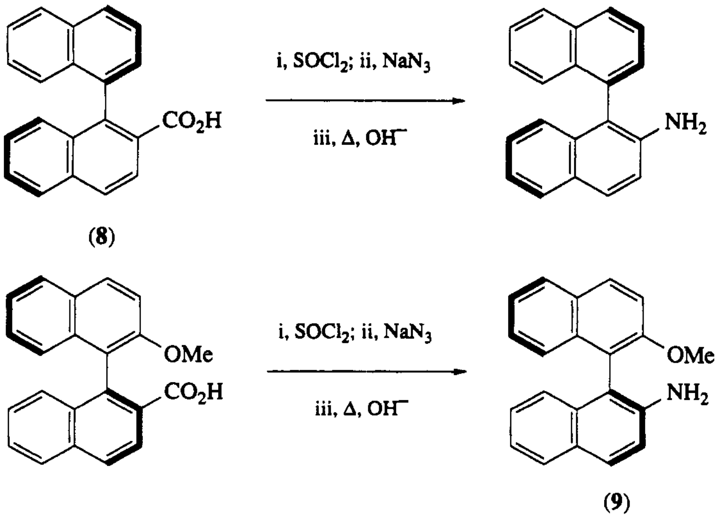


(6) (7) (8)

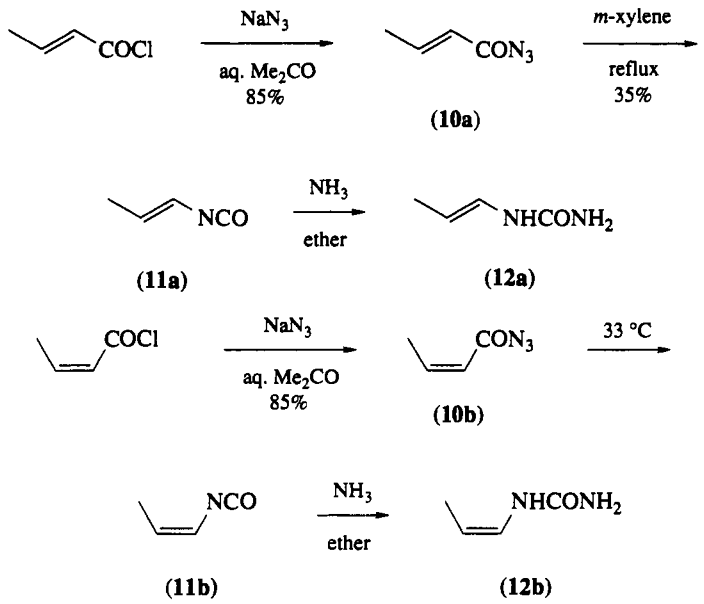
The four rearrangements may be utilized for the determination of absolute configurations by correlation to compounds of established configurations. Thus, the absolute configurations of two binaphthyl derivatives (**8** and **9**) have been determined by utilizing the Curtius rearrangement (Scheme 7).[24]

Perfect retention of the geometrical configurations has been observed in the Curtius rearrangement of *cis*- and *trans*-crotonyl azides (**10**), which respectively give *cis*- and *trans*-propenyl isocyanates (**11**), characterized as their urea derivatives (**12**; Scheme 8).[25] The *cis* isomers (**10b**) and (**11b**) tend to isomerize thermally to the *trans* isomers (**10a**) and (**11a**) respectively.

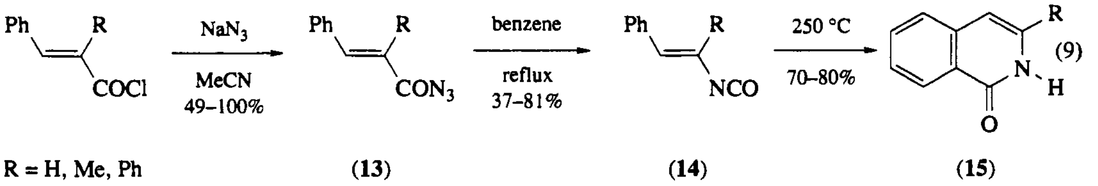
The Curtius rearrangements of some *trans*-cinnamoyl azides (**13**), obtained by treatment of the corresponding chlorides with sodium azide, smoothly give *trans*-β-styryl isocyanates (**14**), which are efficiently isomerized in an inert solvent at 250 °C to produce 1-isoquinolone derivatives (**15**; equation 9).[26] The isomerization proceeds more conveniently at 140 °C in the presence of iodine.



Scheme 7



Scheme 8



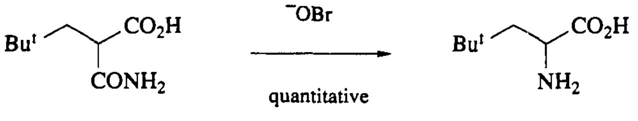
4.4.2 THE HOFMANN REACTION

4.4.2.1 Under Basic Conditions

The classical and most standard reaction conditions of the Hofmann rearrangement use sodium or potassium hypobromite (or bromine with sodium or potassium hydroxide) under aqueous conditions.

Sodium or potassium hypobromite may be replaced with the other alkaline hypohalites such as sodium hypochlorite, calcium hypochlorite or barium hypobromite. The other alternative reagent used under aqueous alkaline conditions is sodium bromite ($NaBrO_2$) in the presence of a catalytic amount of sodium bromide[27] or a calculated amount of benzyltrimethylammonium bromide ($PhCH_2N^+Me_3Br^-$).[28]

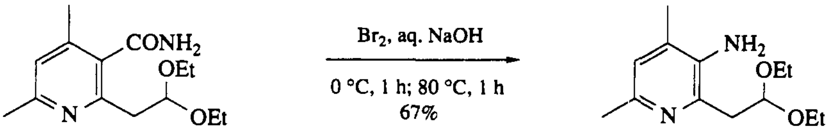
Neopentylglycine (**17**) is conveniently prepared from neopentylmalonamic acid (**16**) by the action of hypobromite (equation 10).[29] The method using the carbon–nitrogen rearrangements of malonic half-acid derivatives is one of the classical methods for the preparation of α-amino acids.



(10)

(16) **(17)**

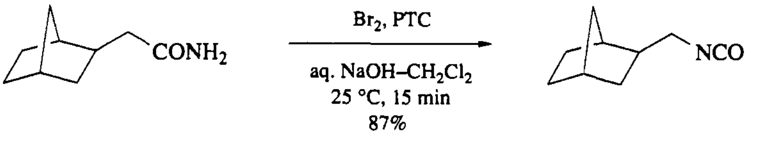
The Hofmann reaction under basic conditions is apparently suitable for degradation of acid sensitive compounds, *e.g.* acetals, without any change at their acid sensitive functions (equation 11).[30]



(11)

(18) **(19)**

Isocyanates, the initial products of the Hofmann rearrangement, usually undergo solvolysis to give amines, as described earlier (Section 4.4.1.1). However, a two-phase Hofmann reaction using phase transfer catalysts allows isolation of reactive isocyanates (equation 12).[31] The phase transfer catalyst is essential for the formation of primary and secondary isocyanates, while tertiary isocyanates are formed without the catalyst. Shorter reaction times at room temperature as well as high dilution conditions minimize the formation of by-products such as dialkylureas or acylalkylureas. Chlorine in place of bromine considerably decreases the yield of isocyanates.



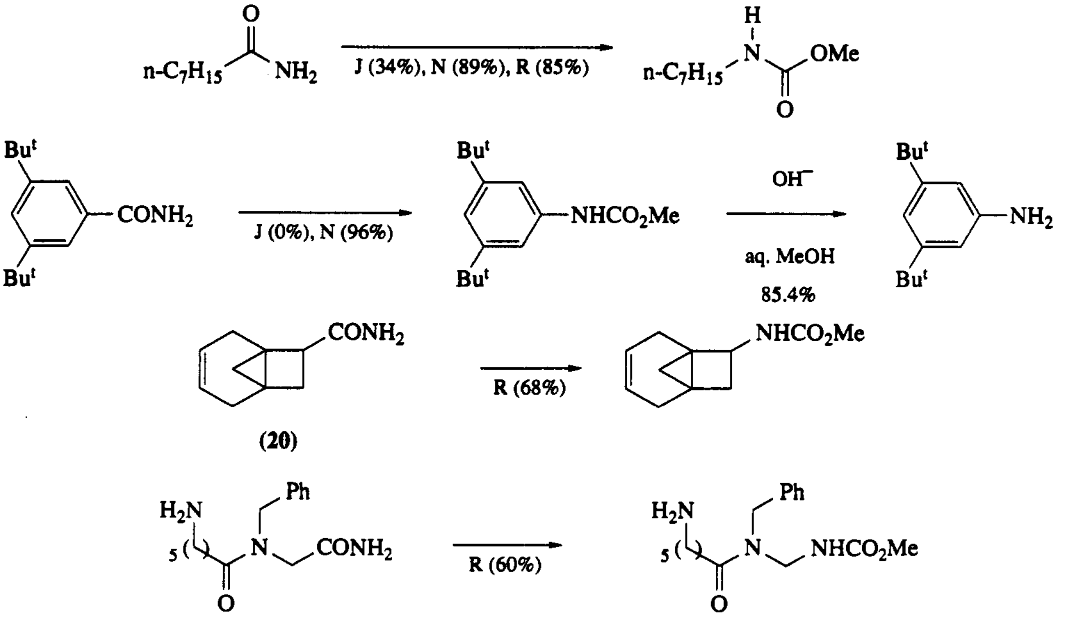
(12)

$PTC = Bu_4N^+HSO_4^-, PhCH_2N^+Et_3Cl^-, \text{or } Bu_4P^+Br^-$

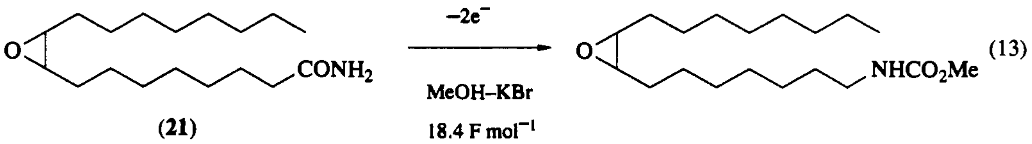
Although the Hofmann reaction is applicable to various amides under usual aqueous alkaline conditions, it sometimes proceeds sluggishly, especially in the rearrangement of hydrophobic amides such as aliphatic amides containing a longer carbon chain. However, use of bromine and sodium methoxide gives better results though the product is a methylurethane, as already shown in Scheme 3. This methoxide method is classified into three approaches according to the order of mixing reagents: (i) addition of bromine to a methanolic solution of an amide and sodium methoxide (the Jeffreys' method, J);[6,7,32] (ii) use of a methanolic solution of bromine in the Jeffreys' method (the Nagai–Matsuo method, N);[7,33,34] and (iii) addition of bromine to sodium methoxide in methanol to produce methyl hypobromite, followed by addition of amides (the Radlick and Brown method, R),[35,36] shown in Scheme 9. The last method is utilized for the amide (**20**), which is highly susceptible to electrophilic addition reactions.[35]

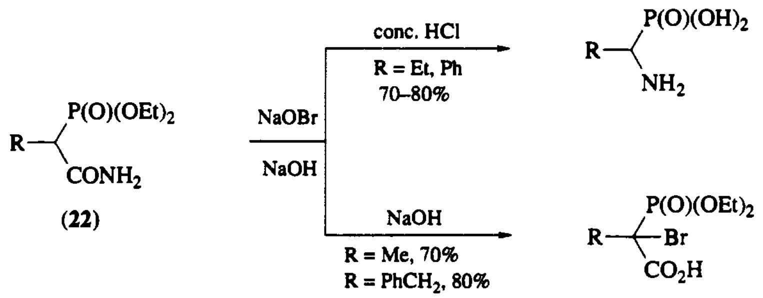
The electroorganic method also induces the Hofmann reaction, by use of potassium bromide as a catalytic mediator, giving methylurethanes.[37] Since the reaction proceeds without heating under neutral conditions, this method can be applied to a base labile epoxyamide (**21**), which gives unidentified products with no epoxide function when treated under the usual alkaline conditions of the Hofmann reaction (equation 13).

An attempted Hofmann reaction of phosphonoacetamides (**22**) with alkaline sodium hypobromite shows a dramatic substituent effect (Scheme 10).[38] The rearrangement occurs when the alkyl residue (R) is ethyl or phenyl, while only bromination occurs when R is hydrogen or benzyl.



Scheme 9





Scheme 10

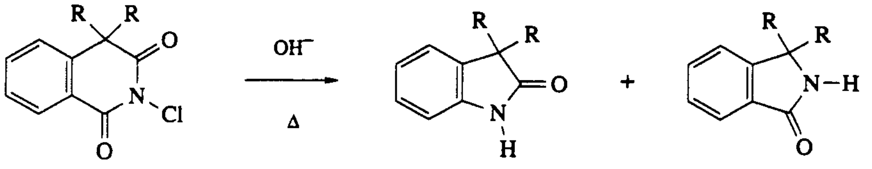
Phthalimides undergo the Hofmann reaction by an initial hydrolytic ring-opening, giving the *N*-haloamides formed from either of the free imides or the *N*-haloimides, followed by their rearrangement to give anthranilic acids.[39] The regioselectivity in the Hofmann rearrangement of *N*-chloro-4,4-dialkylhomophthalimides (**23**) is governed by the bulkiness of the 4,4-dialkyl groups.[40] The imides containing small substituents give rise to indolinones (**24**), while isoindolinones (**25**) are formed from the imides containing bulky substituents (equation 14).

(*S*)-*N*-Carbamoylalanine (**26**) also undergoes the Hofmann rearrangement to give (*S*)-*N*-aminoalanine (**27**), by use of sodium hypochlorite but not hypobromite (equation 15).[41]

4.4.2.2 Under Acidic Conditions

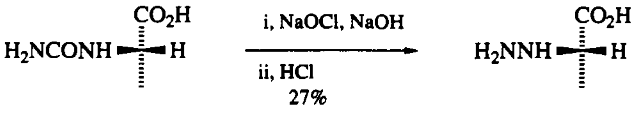
The oxidative Hofmann rearrangement of primary carboxamides occurs by use of lead tetraacetate (LTA) and several hypervalent organoiodine compounds IF_5 (**28**), $PhI(OCOCF_3)_2$ (**29**), PhI(OH)OTs (**30**) and PhIO (**31**) under mildly acidic conditions.

Although some conflicting results have been presented by Beckwith[42] and Baumgarten,[43] LTA is still an interesting reagent for the oxidative rearrangement. LTA in benzene converts primary amides to acyl-



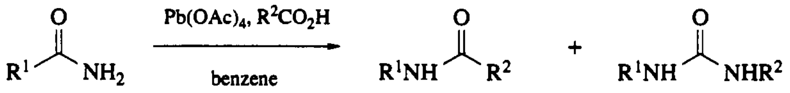
(23) (24) (25) (14)

	(24)	(25)
	%	%
R = Me	68	–
R = Et	–	58
R = $H_2C{=}CHCH_2$	47	31
R, R = $(CH_2)_4$	74	–



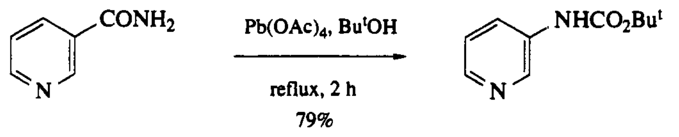
(26) (27) (15)

amines, together with a small amount of dialkylureas.[42] The reaction, which may also be conducted in acetic acid or benzene–acetic acid, is catalyzed by pyridine. Acetic acid may be replaced with other carboxylic acids (equation 16).

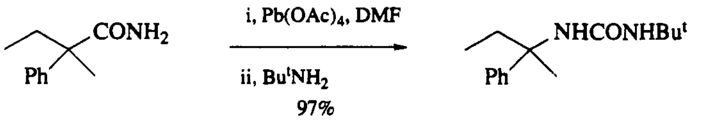


(16)

With LTA in refluxing *t*-butyl alcohol, *t*-butyl carbamates are conveniently produced from various amides (equation 17).[43] Triethylamine, tin(IV) chloride and dibutylstannyl dilaurate are effective catalysts for the reaction of the intermediate isocyanates and *t*-butyl alcohol. When the reaction is run in dimethylformamide, isocyanates can be isolated and easily converted to ureas with *t*-butylamine (equation 18).[43]



(17)



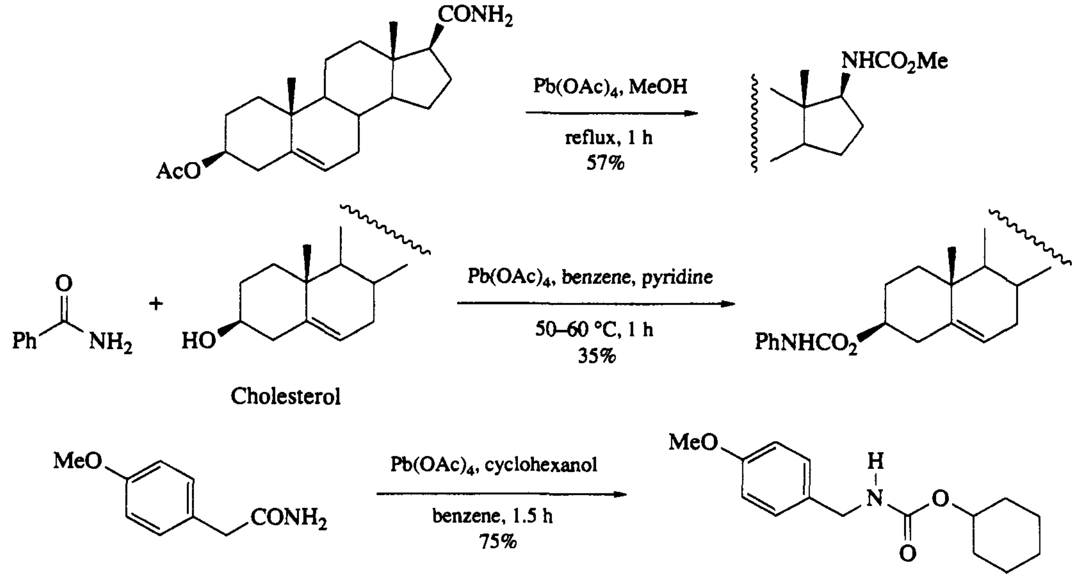
(18)

In addition, both primary and secondary alcohols can be used, alone or together with benzene.[42] Pyridine also serves as a catalyst. The method is applicable to a wide variety of amides and alcohols, including compounds containing alkenic, ester, aromatic and other reactive functions, as shown in Scheme 11.

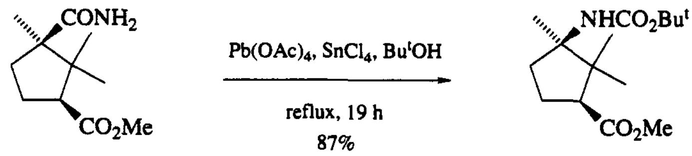
The oxidative rearrangement with LTA also proceeds with retention of configuration about the migrating carbon atom, as shown in equations (19)[43] and (20).[44]

Iodine pentafluoride (**28**) in hot pyridine works like LTA as a Hofmann reagent for aliphatic primary carboxamides (equation 21).[45] Iodination occurs together with rearrangement when benzamide is treated under similar reaction conditions.

[*I,I*-Bis(trifluoroacetoxy)iodo]benzene (PIFA; **29**) also brings about the facile oxidative rearrangement of aliphatic amides to amines in mildly acidic (pH 1–3) 50% aqueous acetonitrile at room temperature within several hours, as shown in equation (22).[46,47] The reagent cannot be applied to the formation of aromatic amines since the latter are further oxidized. The intermediates of the reaction are isocyanates, which are rapidly hydrolyzed to amines under mildly acidic conditions. The acidic conditions protect the



Scheme 11



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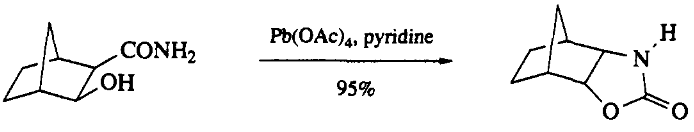
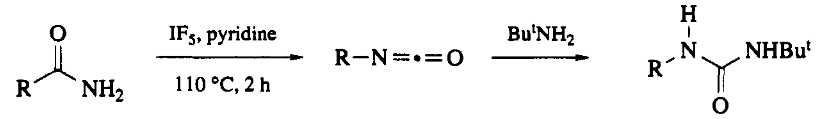


(20)



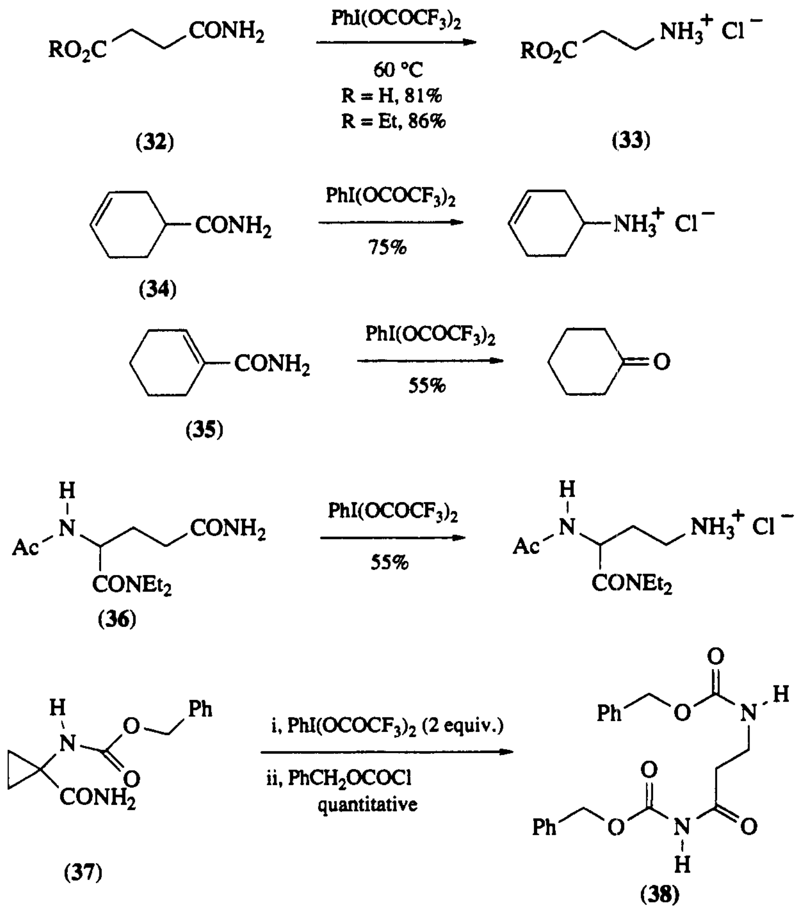
(21)

product amines from reacting with the intermediate isocyanates and forming ureas. The reaction is catalyzed by pyridine though this is not strictly necessary.

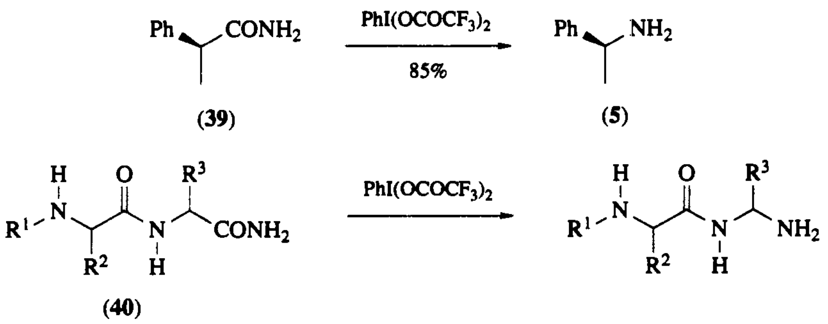
$$\underset{(29)}{\mathrm{RCONH_2 + PhI(OCOCF_3)_2}} + \mathrm{H_2O} \longrightarrow \mathrm{RNH_3^+ + CO_2 + PhI + 2CF_3CO_2^- + H^+} \qquad (22)$$

PIFA easily converts succinic acid derivatives (**32**) to β-alanine derivatives (**33**).[47] Limited use of PIFA (1 equiv.) allows the rearrangement of 3-cyclohexene-1-carboxamide (**34**) without oxidation of the double bond, as shown in Scheme 12. Cyclohexanone is obtained by the PIFA oxidation of 1-cyclohexenecarboxamide (**35**). Selective oxidation of the primary amide (**36**) occurs without effect on secondary or tertiary amides in the same molecule.[47] The rearrangement of the cyclopropane derivative (**37**) accompanies the ring cleavage to give the β-alanine derivative (**38**) after treatment with benzyloxycarbonyl chloride.[48]

Retention of configuration during the Hofmann reaction promoted with PIFA has been rigorously demonstrated in the rearrangements of (*S*)-(+)-2-phenylpropionamide (**39**)[47] as well as the peptide derivative (**40**),[49] as shown in Scheme 13. The latter reaction can be employed in the sequential degradation of carboxy terminal peptides[50] as well as modifications of peptides.[51]

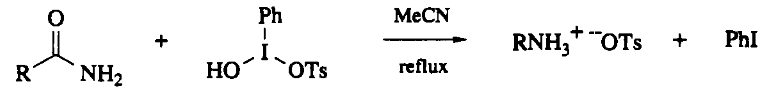


Scheme 12



Scheme 13

Hydroxy(tosyloxy)iodobenzene (HTIB; **30**) is another hypervalent organoiodine compound which acts as a Hofmann reagent,[52] converting aliphatic carboxamides to alkylammonium tosylates in refluxing acetonitrile (equation 23).

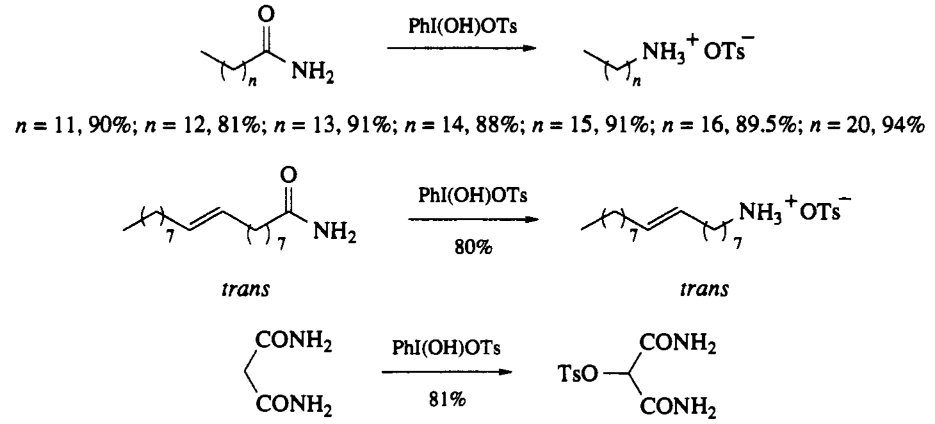


(30)

$$\mathrm{RCONH_2} + \mathrm{PhI(OH)OTs} \xrightarrow[\text{reflux}]{\text{MeCN}} \mathrm{RNH_3}^{+}\,{}^{-}\mathrm{OTs} + \mathrm{PhI} \qquad (23)$$

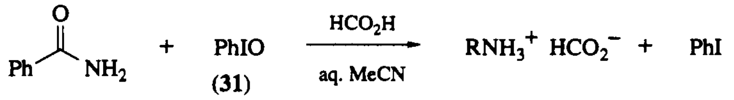
HTIB is particularly useful for the degradation of long chain amides,[53] in contrast to the classical Hofmann reaction under alkaline conditions (see Section 4.4.2.1). The double bonds remain intact with

HTIB. In the reaction with malonamide, however, only tosylation at the active methylene carbon occurs (Scheme 14).[52]



Scheme 14

Iodosylbenzene (**31**), together with formic acid, can also be used for the oxidative Hofmann reaction[54] in an acetonitrile–water mixture (3:1) at room temperature (equation 24). The reaction behavior of (**31**) is quite similar to that of PIFA.



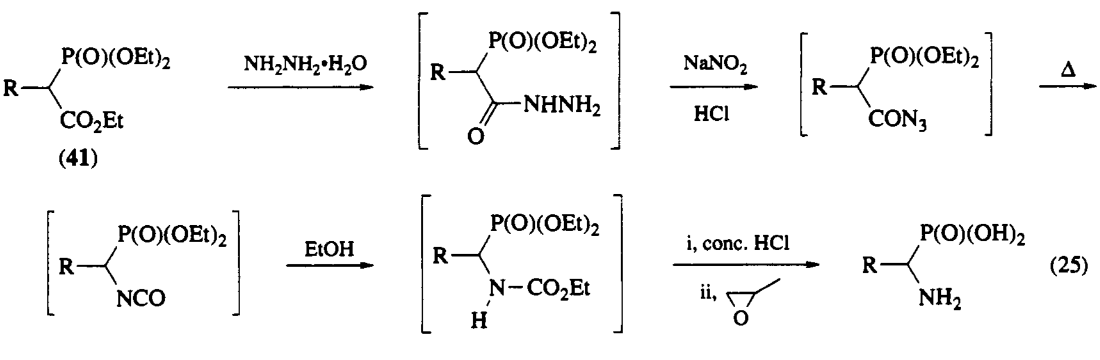
(24)

4.4.3 THE CURTIUS REACTION

4.4.3.1 *Via* Hydrazides

As described earlier (Section 4.4.1.1), the intermediates of the Curtius reaction are acyl azides, which thermally rearrange to isocyanates. One of the classical procedures[8,9] for the preparation of acyl azides consists of the formation of hydrazides from esters and hydrazine, followed by treatment of the hydrazides with nitrous acid, generated from sodium nitrite and acetic, hydrochloric or sulfuric acid. Acyl azides are commonly used in the crude state or in solution since they are thermally unstable and potentially explosive.

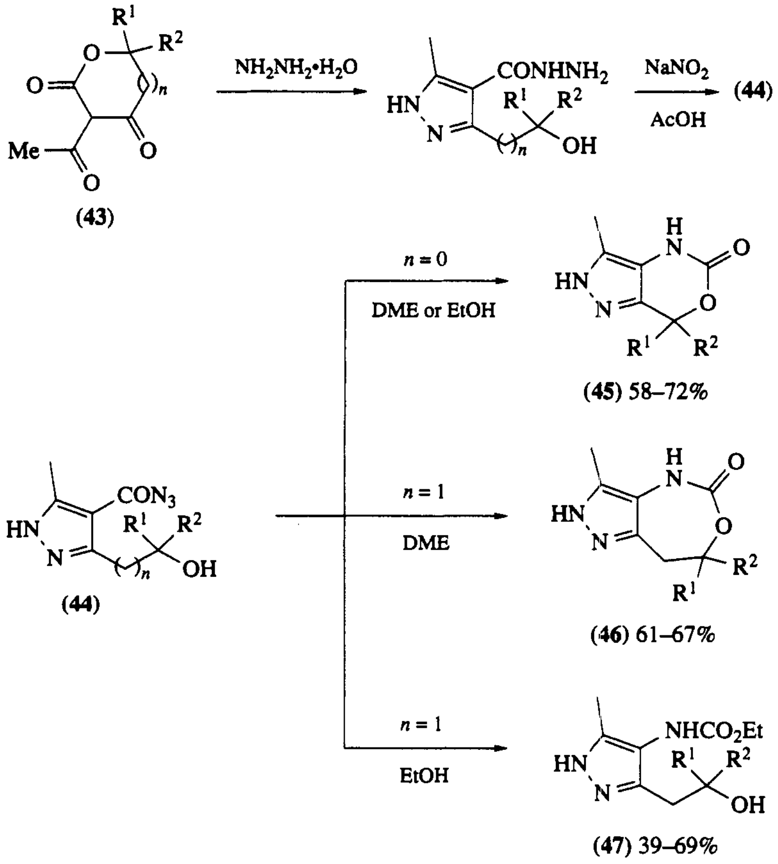
Conversion of phosphonoacetic esters (**41**) to aminophosphonic acids (**42**) is conveniently carried out by chemoselective reaction of (**41**) with hydrazine, followed by the Curtius rearrangement without isolation of any intermediates (equation 25).[55]



(25)

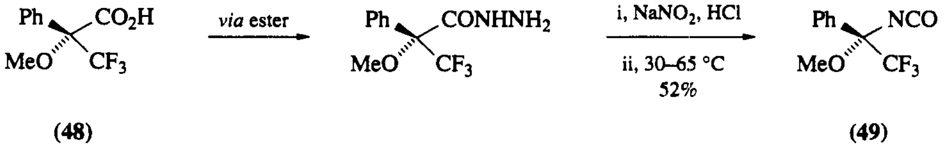
R = H, 54%; R = Me, 80%; R = PhCH2, 56% (**42**)

The pyrazole derivatives (**44**), prepared from the lactones (**43**), give the cyclized (**45** and **46**) or uncyclized products (**47**) by the Curtius rearrangement, depending on the substrates and reaction solvents (Scheme 15).[56]



Scheme 15

The Curtius rearrangement of the acyl azide derived from optically pure α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA; **48**) also proceeds with retention of configuration, giving α-methoxy-α-(trifluoromethyl)benzyl isocyanate (**49**; equation 26).[57] The isocyanate (**49**) is useful for the determination of the enantiomeric composition of optically active primary and secondary amines.

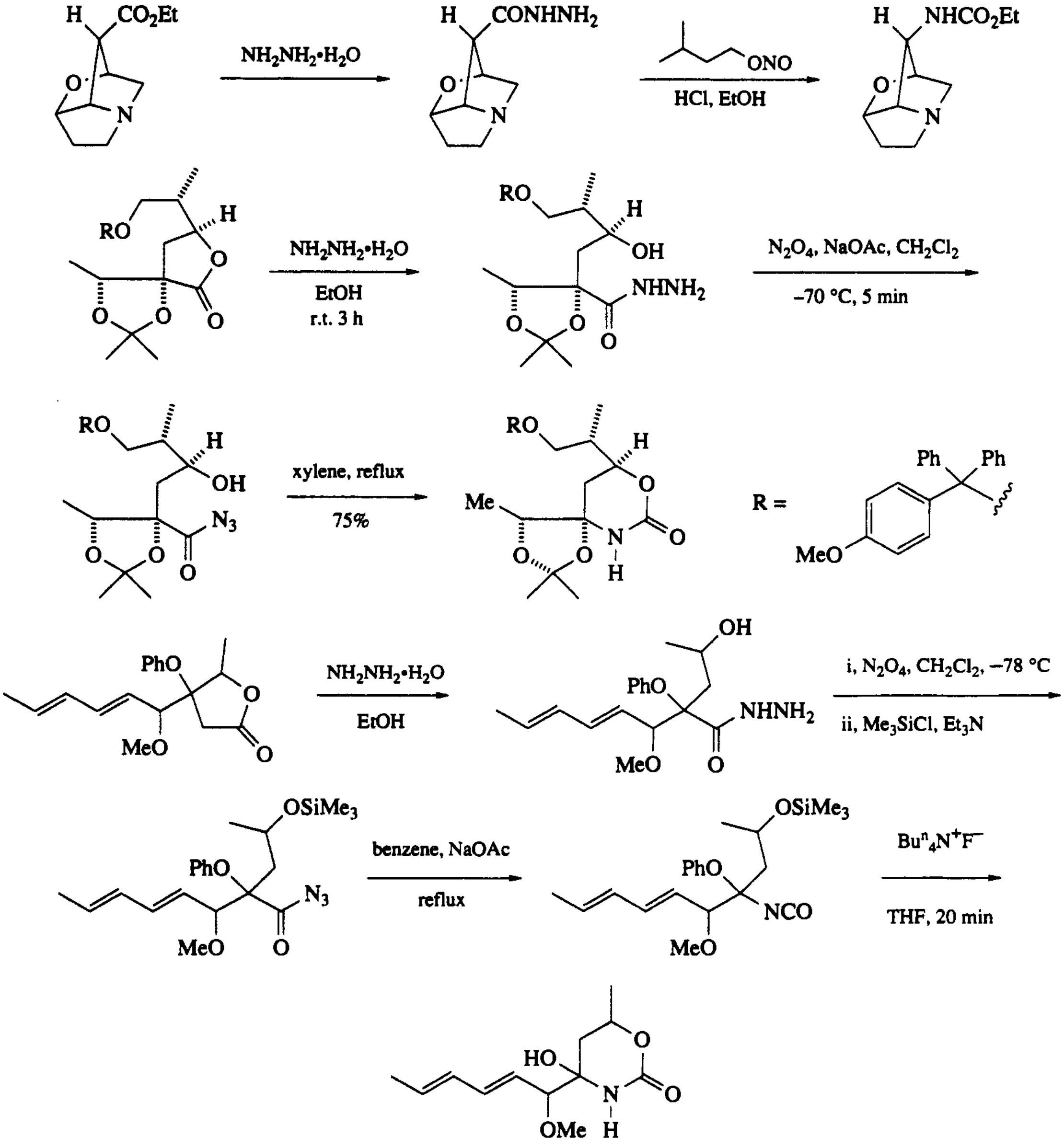


(26)

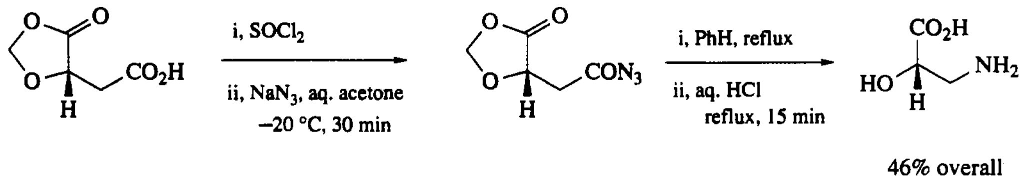
Alkyl nitrites[58] and nitrogen tetroxide[59,60] together with acid are also effective for the formation of acyl azides from hydrazides under anhydrous conditions. As shown in Scheme 16, the Curtius reaction is especially suitable for the formation of complex reactive molecules.

4.4.3.2 *Via* Acyl Chlorides

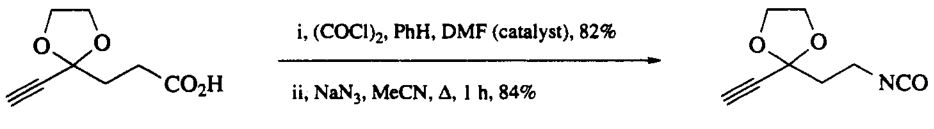
Formation of acyl azides from acyl chlorides is also a classical procedure[8,9] for the Curtius reaction. Sodium azide is used for the azidation under aqueous and anhydrous conditions, called the wet and dry methods respectively (equations 27[61] and 28[62]).



Scheme 16

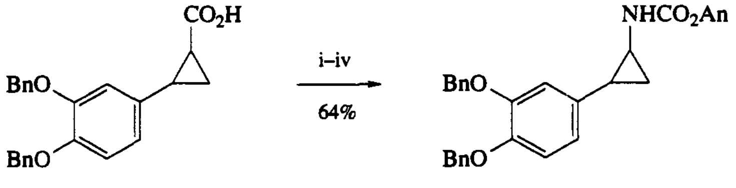


(27)



(28)

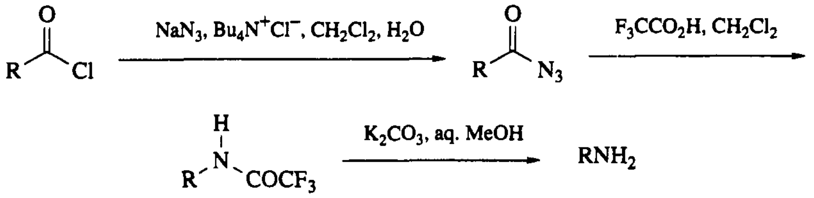
Trapping of isocyanates, the intermediates of the Curtius reaction, is usually carried out with methanol, ethanol, *t*-butyl alcohol or benzyl alcohol. Use of 9-anthrylmethanol (AnOH) gives the corresponding urethanes, which can be converted to amines by treatment with sodium ethanethiolate under neutral conditions (equation 29).[63]



(29)

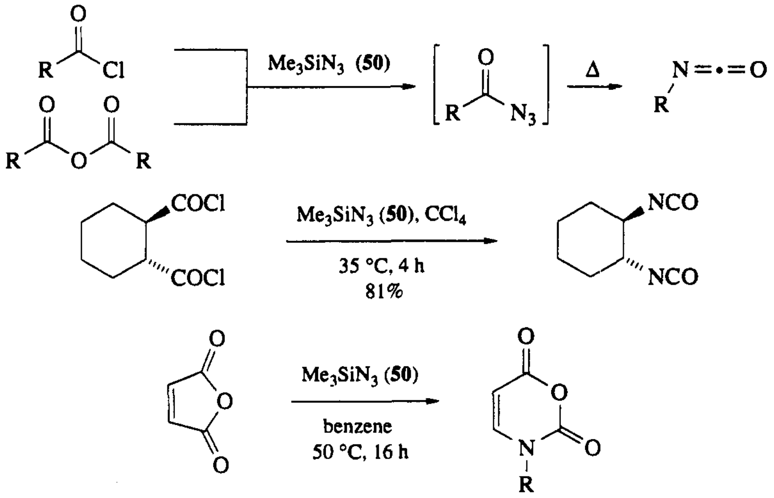
i, $SOCl_2$; ii, NaN_3; iii, Δ, toluene; iv, AnOH

A useful variant of the Curtius reaction comprises the reaction of acyl chlorides in dichloromethane with sodium azide under phase transfer conditions, followed by treatment of the dried dichloromethane solution, which contains acyl azides, with a slight excess of trifluoroacetic acid. The resulting trifluoroacetamides can easily be cleaved with potassium carbonate in aqueous methanol at room temperature, giving the amines (equation 30).[64]



(30)

In place of sodium azide, which has low solubility in common organic media, use of a mixture of hydrazoic acid and pyridine,[65] tetrabutylammonium azide[66] or tetramethylguanidinium azide[67] has been recommended. One of the most useful and safe alternatives is trimethylsilyl azide (**50**), which reacts with various acyl chlorides or anhydrides to give isocyanates directly, under thermal conditions (Scheme 17).[68,69]

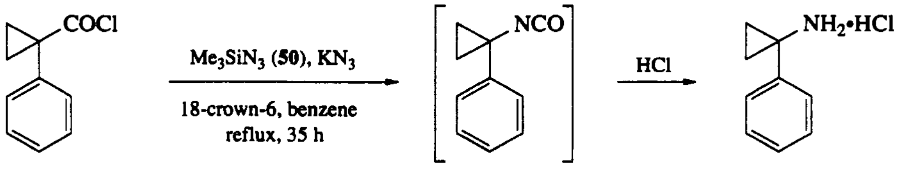


R = Me_3Si, 15%; R = H, 52%

Scheme 17

When the usual reaction conditions using trimethylsilyl azide (**50**) are not suitable for the Curtius reaction, addition of catalytic amounts of powdered potassium azide and 18-crown-6 is quite effective in conducting the reaction (equation 31).[70]

Tributylstannyl azide (**51**), prepared from tributylstannyl chloride and sodium azide, is also useful for the direct conversion of acyl chlorides to isocyanates (equation 32).[71] In addition, succinic anhydride



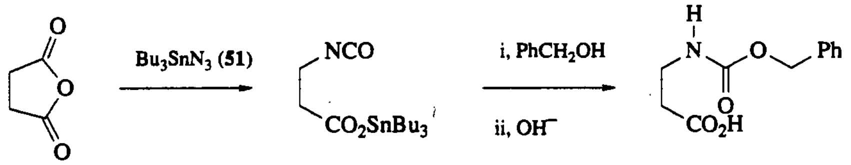
88% overall

(31)

reacts with (**51**) to give tributylstannyl 3-isocyanatopropionate (**52**), which on treatment with benzyl alcohol and then aqueous alkali affords *N*-benzyloxycarbonyl-β-alanine (**53**; equation 33).

(**51**)

(32)

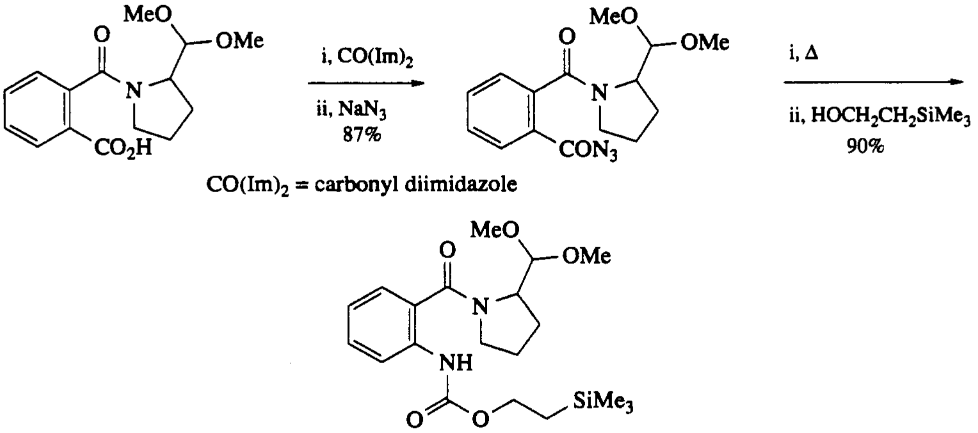


(**52**)

(**53**) 35% overall

(33)

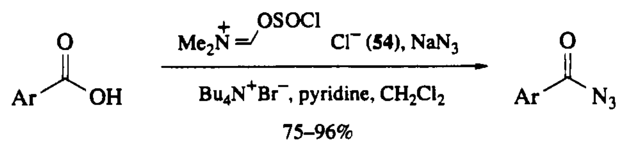
Acyl chlorides may be replaced with imidazolides, which react with sodium azide to give acyl azides. In the reaction shown in equation (34), 2-trimethylsilylethanol is used for trapping the isocyanate.[72] The resulting 2-trimethylsilylethyl ester is easily cleaved with tetra-*n*-butylammonium fluoride.



CO(Im)$_2$ = carbonyl diimidazole

(34)

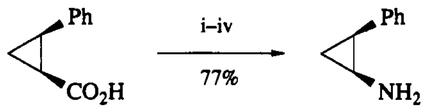
N,*N*-Dimethylchlorosulfitomethaniminium chloride (**54**), prepared from thionyl chloride and dimethylformamide, together with sodium azide is useful for the direct preparation of acyl azides from carboxylic acids (equation 35).[73]



(35)

4.4.3.3 *Via* Mixed Anhydrides

Mixed carboxylic–carbonic anhydrides, prepared from carboxylic acids and alkyl chloroformates in the presence of base, are easily converted to acyl azides by the action of sodium azide. Since the reaction sequence from carboxylic acids to acyl azides proceeds under mild conditions, it has a broad applicability. *cis*-2-Phenylcyclopropanecarboxylic acid (**55**) is easily converted to *cis*-2-phenylcyclopropylamine (**56**), without isomerization to the *trans* isomer, by consecutive treatment with: (i) ethyl chloroformate in the presence of triethylamine; (ii) sodium azide; (iii) refluxing toluene; and (iv) hydrochloric acid, without purification of the intermediates (equation 36).[74]

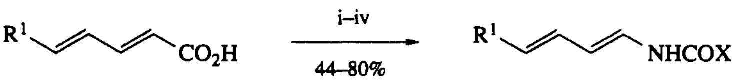


(36)

(**55**) (**56**)

i, $ClCO_2Et$, Et_3N, aq. Me_2CO, 0 °C, 30 min; ii, NaN_3 in water, 0 °C, 1 h; iii, toluene, reflux;
iv, 20% aq. HCl, reflux, 9 h

Various *trans*-1-*N*-acylamino-1,3-butadienes (**58**) are prepared from 2,4-pentadienoic acids (**57**) by the mixed anhydride method (equation 37).[75] The procedure is reproducible when *N*,*N*-diisopropylethylamine is used in place of triethylamine.

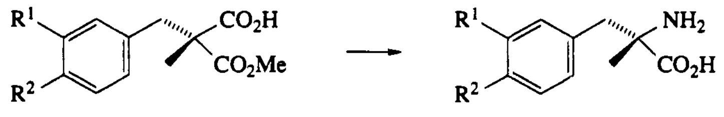


(37)

(**57**) (**58**)

i, $ClCO_2Et$, $Pr^i{}_2NEt$, 0 °C, 30 min; ii, NaN_3 in water, 0 °C, 30 min; iii, toluene;
iv, XH (R^2OH, R^3NHR^4 or R^5SH), reflux

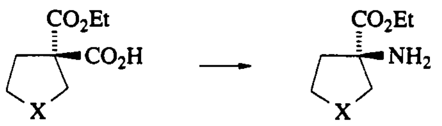
The mixed anhydride method is analogously and conveniently applied to the preparation of α-amino acids (**60**) from malonic acid half-esters (**59**; equations 38 and 39).[76,77]



(38)

(**59a**) (**60a**)

$R^1 = R^2 = H$, 86%; $R^1 = MeO$, $R^2 = H$, 63%; $R^1 = R^2 = Me$, 74%



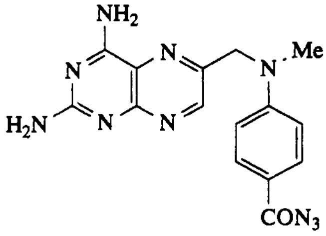
(39)

(**59b**) X = NH, S (**60b**)

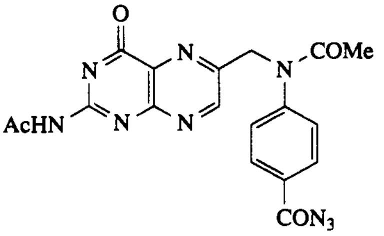
4.4.3.4 By Use of Diphenyl Phosphorazidate

Diphenyl phosphorazidate (DPPA; $(PhO)_2P(O)N_3$) is a useful and versatile reagent in organic synthesis,[78] and can be conveniently used for the Curtius reaction under mild reaction conditions, using carboxylic acids as a starting material.[17,18] Exchange of the azide group occurs from DPPA to carboxylic acids in the presence of base, *e.g.* triethylamine, giving acyl azides. When the reaction is conducted under thermal conditions, the rearrangement occurs *in situ* to give isocyanates in a single step. Addition of water, or preferably a mineral acid, to the reaction mixture containing isocyanates gives amines in a one-pot process, while addition of alcohols yield urethanes. When this modified Curtius reaction is carried out in refluxing *t*-butyl alcohol, *t*-butylurethanes are formed in a single process from carboxylic acids. The modified Curtius reaction using DPPA is similar to the Schmidt reaction in the sense that carboxylic acids yield amines or their derivatives in a one-pot process, but is more like the Curtius reaction from a mechanistic point of view.[18] Since the reaction proceeds under mild and neutral conditions, it has a broad applicability.

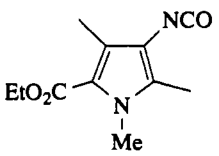
Acyl azides (**61**)[79] and (**62**)[80] and isocyanate (**63**),[81] the reaction intermediates of the modified Curtius reaction using DPPA, have been isolated in a pure state, since they are relatively thermally stable, and further converted to urethanes or ureas by the addition of alcohols or amines respectively.



(**61**)

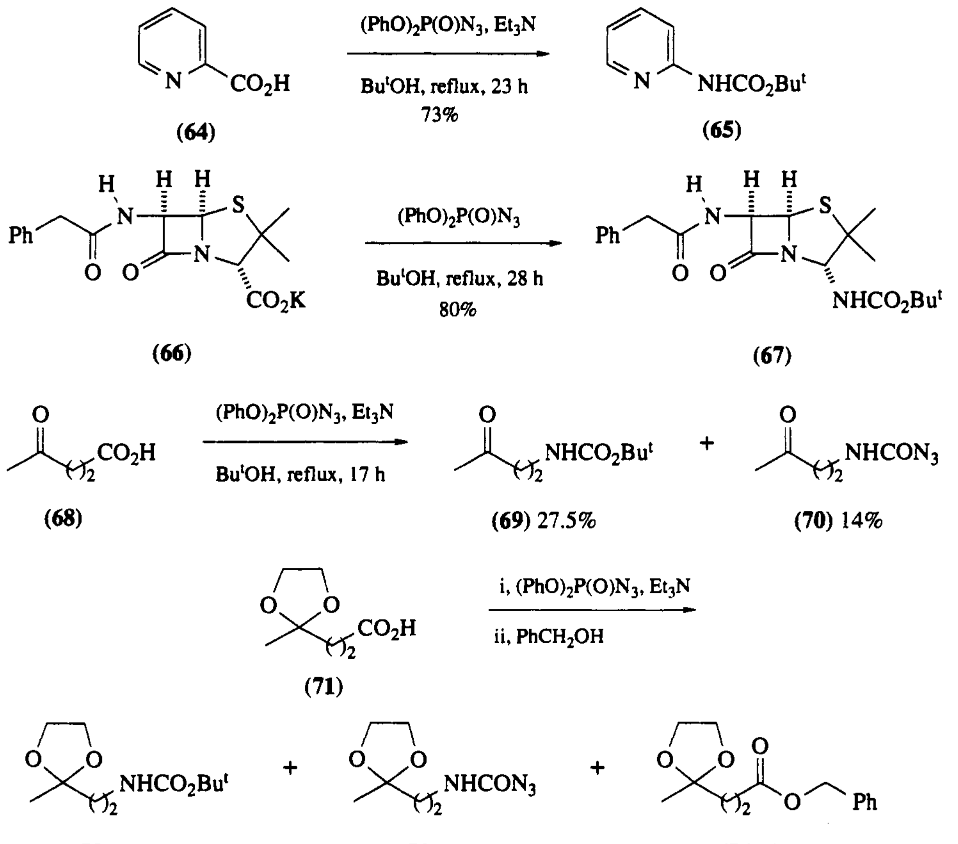


(**62**)



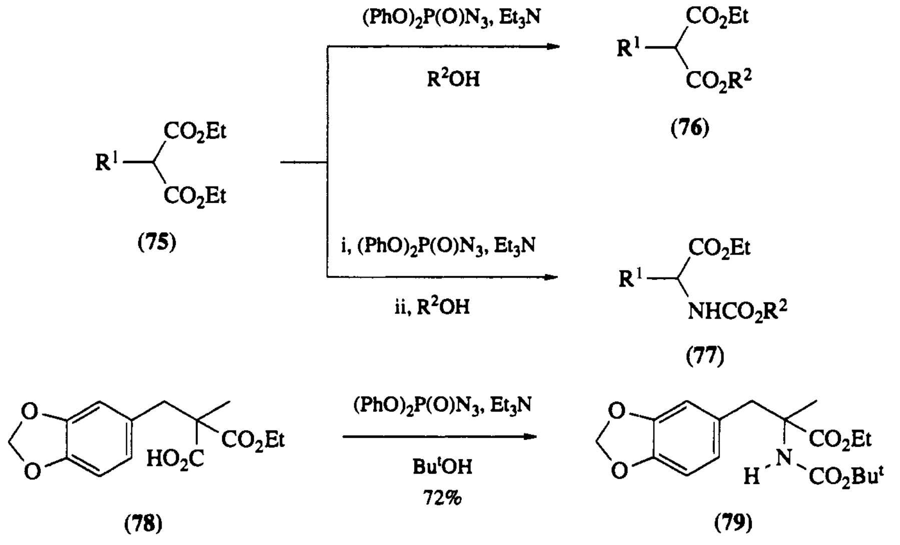
(**63**)

Pyridine-2-carboxylic acid (**64**), which is known to fail in the Schmidt reaction, smoothly undergoes the reaction with DPPA to give the *t*-butylurethane (**65**).[18] The potassium salt of penicillin G (**66**) also gives the *t*-butylurethane (**67**) in a single operation. Although levulinic acid (**68**) gives the *t*-butylurethane (**69**) together with the carbamoyl azide (**70**) in unsatisfactory yields, the corresponding acetal derivative (**71**) smoothly undergoes the rearrangement to give the urethane (**72**) in good yield, together with small amounts of the carbamoyl azide (**73**) and the benzyl ester (**74**; Scheme 18).[18]



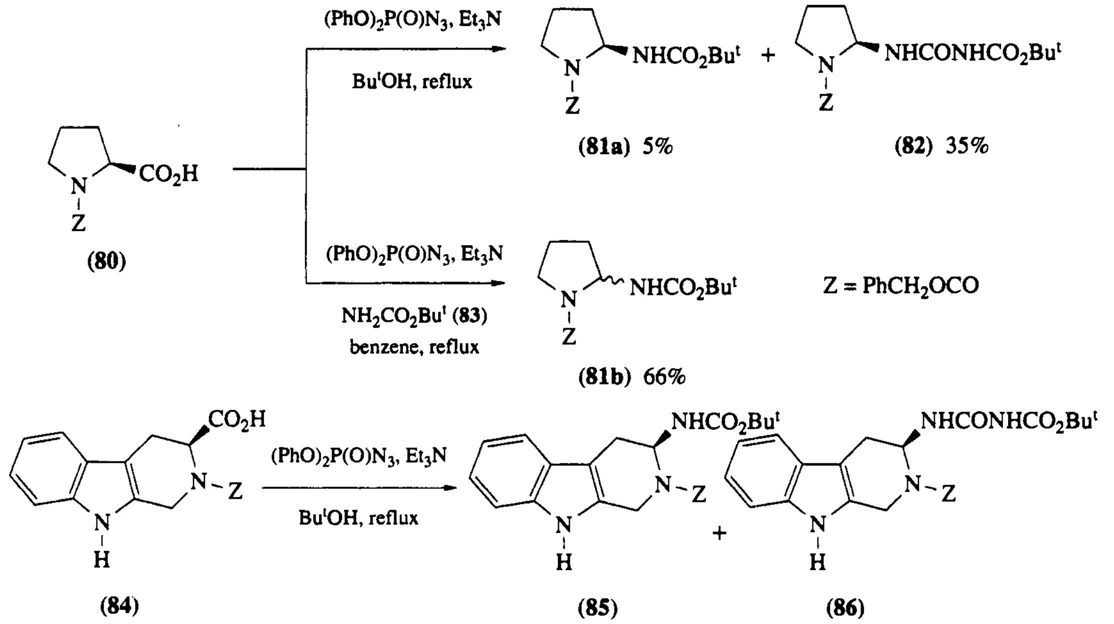
Scheme 18

Reaction procedures affect the products when malonic acid half-esters (**75**) with an acidic hydrogen at the α-position are subjected to the modified Curtius reaction.[82,83] The usual one-pot procedure, in which alcohols are present from the beginning, affords esters (**76**), whereas the two-in-one procedure, in which alcohols are added after the formation of isocyanates, conveniently produces urethanes (**77**; Scheme 19). Formation of esters can be explained by the generation of ketene intermediates in equilibrium with acyl azides. The former irreversibly react with alcohols to give esters.[83] Malonic acid half-esters with no acidic hydrogen, *e.g.* (**78**), do not undergo the esterification but give the rearranged products, *e.g.* (**79**), even in the one-pot procedure since no ketene intermediates can be formed (Scheme 19).



Scheme 19

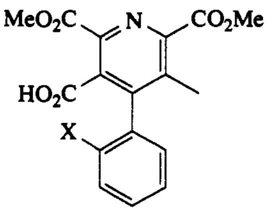
The one-step modified Curtius reaction of *N*-benzyloxycarbonyl-L-proline (**80**) gives the allophanate (**82**) as the major product in addition to the expected urethane (**81a**).[84] However, the use of *t*-butyl carbamate (**83**) as an additive changes the reaction course and the desired carbamate (**81b**), though accompanied by racemization, is obtained in good yield. Similarly, the β-carboline derivative (**84**) also affords a mixture of the urethane (**85**) and the allophanate (**86**), with the latter as the major product, by a one-step procedure.[85] The two-step procedure, however, produces more of the urethane (**85**; Scheme 20).



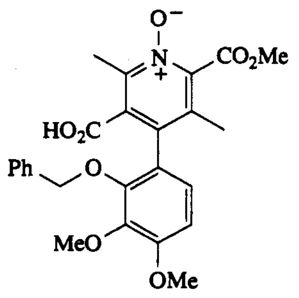
	(85)	(86)
one-step procedure	10%	32%
two-step procedure	22%	–

Scheme 20

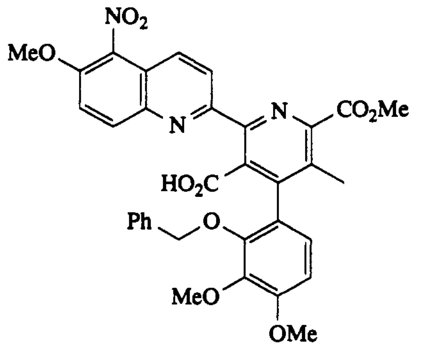
Within the total synthesis of the antitumor antibiotics streptonigrin and lavendamycin, sterically hindered polyfunctional pyridinecarboxylic acids (**87–89**) have been conveniently converted to their corresponding amines by treatment with DPPA–triethylamine in refluxing benzene for 1–25 h, followed by a brief reflux after addition of water.[86-90]



(**87a**) X = H, 60% (ref. 86)
(**87b**) X = Br, 71% (ref. 87)

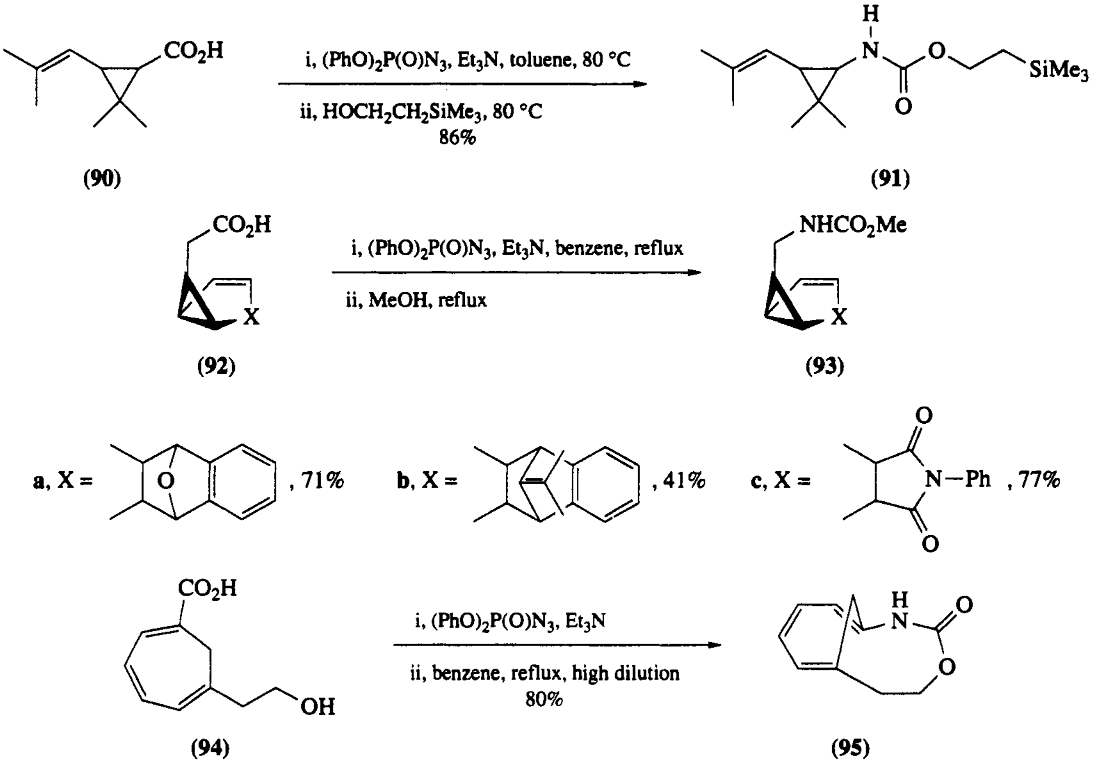


(**88**) 83% (ref. 88)



(**89**) 43% (refs. 89, 90)

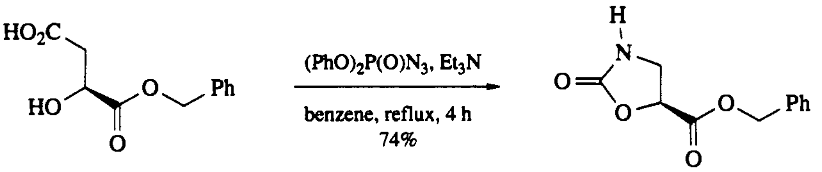
Sensitive molecules such as (**90**),[91] (**92**),[92] and (**94**)[93] smoothly undergo the modified Curtius reaction with DPPA to give the corresponding carbamates (**91**), (**93**) and (**95**), as shown in Scheme 21.



Scheme 21

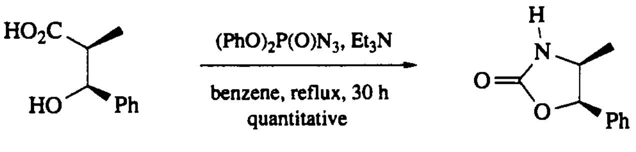
Analogously, the Curtius rearrangement followed by an intramolecular cyclization easily occurs by the reaction of DPPA with hydroxycarboxylic acids (**96**) and (**98**), giving cyclic carbamates (**97**)[94] and (**99**; equations 40 and 41).[95]

Rearrangement of β-alanine and succinic acid derivatives (**100** and **102**) gives 1-acyl-2-imidazolidinones (**101**) and β-alanine derivatives (**103**) respectively (Scheme 22).[96] However, the *N*-methylcarbox-



(96) **(97)**

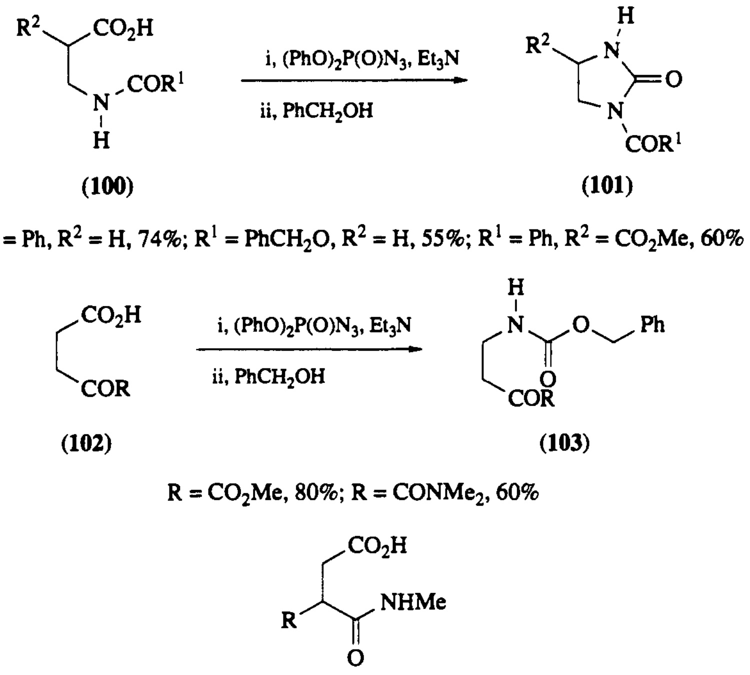
(40)



(98) **(99)**

(41)

amide function has been found to have a deleterious effect and the compounds (**104a**) and (**104b**) afford a complex mixture of products.



(100) **(101)**

R^1 = Ph, R^2 = H, 74%; R^1 = $PhCH_2O$, R^2 = H, 55%; R^1 = Ph, R^2 = CO_2Me, 60%

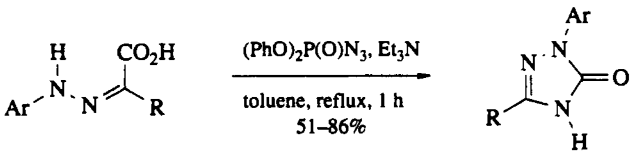
(102) **(103)**

R = CO_2Me, 80%; R = $CONMe_2$, 60%

(**104a**) R = H
(**104b**) R = PhCONH

Scheme 22

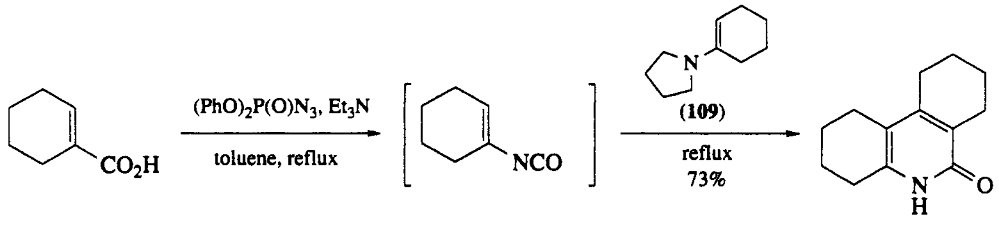
1-Aryl-1,2,4-triazolin-5-ones (**106**) are conveniently prepared from arylhydrazones of α-keto acids (**105**) by the Curtius rearrangement with DPPA, followed by an intramolecular cyclization (equation 42).[97]



(105) **(106)**

(42)

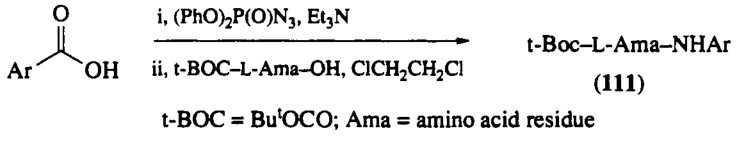
1-Cyclohexenyl isocyanate (**108**), produced from 1-cyclohexenecarboxylic acid (**107**) and DPPA *in situ*, reacts with 1-(*N*-pyrrolidinyl)cyclohexene (**109**) to give the pyridone derivative (**110**; equation 43).[98] The similar vinyl isocyanate–enamine cyclocondensation presents a general method for the preparation of various pyridone derivatives.



(43)

(107) **(108)** **(110)**

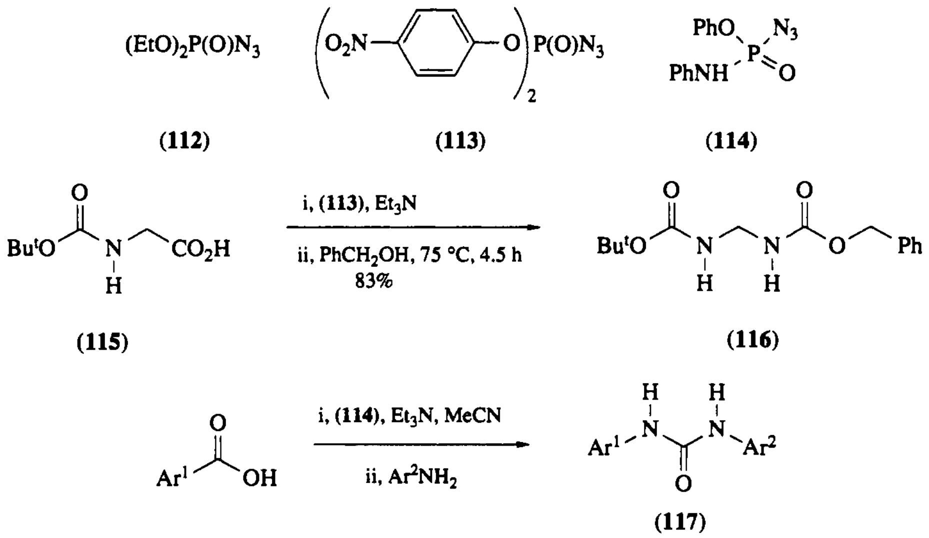
Preparation of α-amino acid amides of aromatic amines (**111**) is easily conducted as a one-pot procedure by the modified Curtius reaction of aromatic carboxylic acids with DPPA, followed by reaction with *N*-protected α-amino acids (equation 44).[99] By this method, *N*-*t*-butoxycarbonyl-L-leucine *p*-nitroanilide, which serves as a substrate for leucine aminopeptidase after deblocking of its *t*-butoxycarbonyl group, has been efficiently prepared from *p*-nitrobenzoic acid and *N*-*t*-butoxycarbonyl-L-leucine.



(111) (44)

t-BOC = Bu^{t}OCO; Ama = amino acid residue

Analogs of DPPA such as diethyl phosphorazidate (**112**),[18] di-*p*-nitrophenyl phosphorazidate (**113**)[100] and phenyl *N*-phenylphosphoramidoazidate (**114**)[101] can also be used for the Curtius reaction. Di-*p*-nitrophenyl phosphorazidate (**113**) has been proposed as a reagent for the determination of the carboxy terminal residue of peptides.[100] A simple protected form of diaminomethane (**116**), an interesting building block for peptide mimetics, has been prepared from *t*-butoxycarbonylglycine (**115**) using di-*p*-nitrophenyl phosphorazidate (**113**; Scheme 23).[102] Phenyl *N*-phenylphosphoramidoazidate (**114**) has been utilized for the preparation of *N*,*N*′-diarylureas (**117**) from aromatic carboxylic acids and aromatic primary amines.[101]



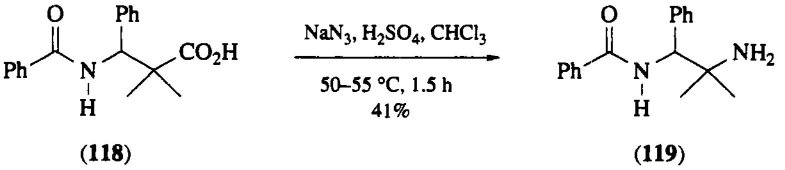
Scheme 23

4.4.4 THE SCHMIDT REACTION

4.4.4.1 With Carboxylic Acids

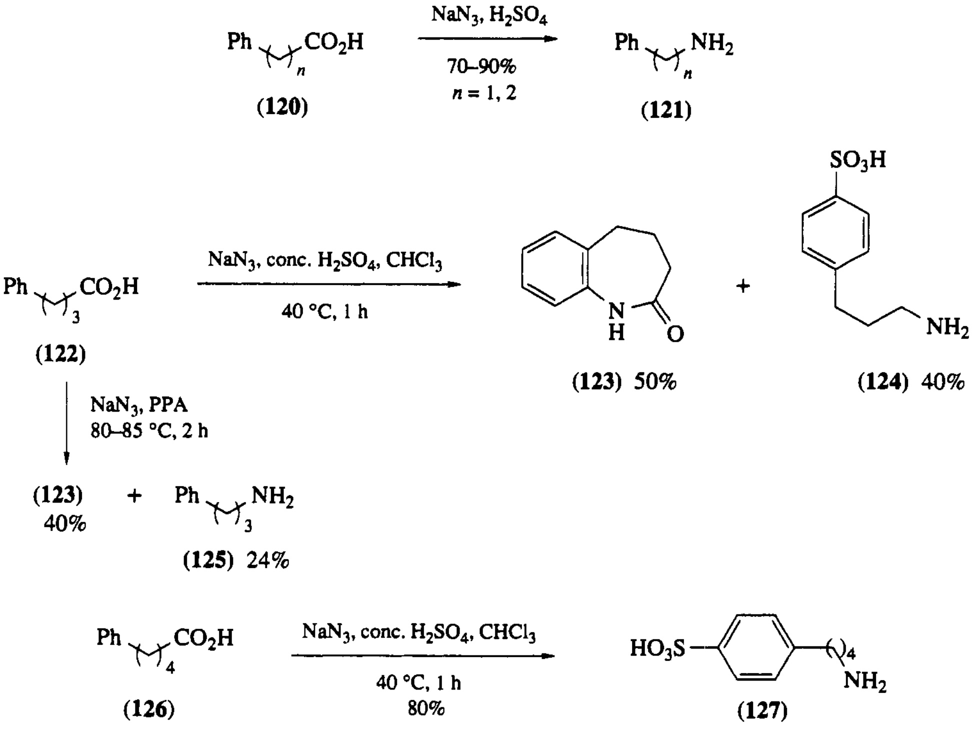
The Schmidt reaction[10–13] is usually carried out using a mixture of sodium azide and sulfuric acid, which generates hydrazoic acid. Free hydrazoic acid together with sulfuric acid may also be used. Although the Schmidt reaction of carboxylic acids is quite useful for the preparation of amines with one less carbon unit, it is less flexible than the other rearrangements since it requires hazardous hydrazoic acid and strongly acidic conditions. Since hydrazoic acid is very poisonous and potentially explosive, the reaction should be conducted under an efficient hood and precautions should be taken against explosion, especially in a large-scale preparation. In place of sulfuric acid, polyphosphoric acid and trifluoroacetic acid–trifluoroacetic anhydride may be used. Usual solvents are chloroform, 1,2-dichloroethane and benzene.

Aliphatic carboxylic acids, even in the case of a sterically hindered carboxylic acid such as (**118**), are usually converted to the corresponding amines, *e.g.* (**119**), by the Schmidt reaction (equation 45).[103]



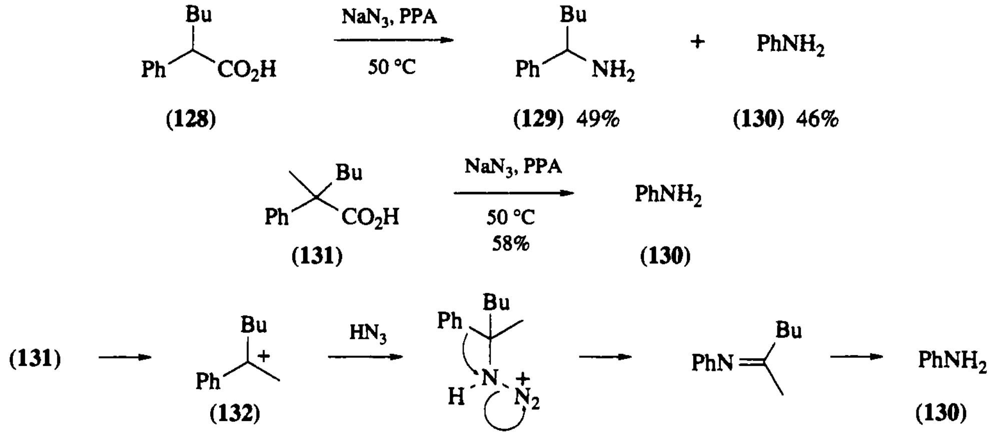
(45)

Both phenylacetic and 3-phenylpropionic acids (**120**) easily undergo the Schmidt reaction under the standard conditions using sulfuric acid, giving the corresponding amines (**121**).[104] 4-Phenylbutyric acid (**122**), however, produces the cyclic lactam (**123**), in addition to the sulfonated amine (**124**). Replacement of sulfuric acid with polyphosphoric acid again affords the lactam (**123**) mainly, together with 3-phenylpropylamine (**125**) as a minor product. In the rearrangement of 5-phenylpentanoic acid (**126**), only the sulfonated amine (**127**) is obtained, as shown in Scheme 24.



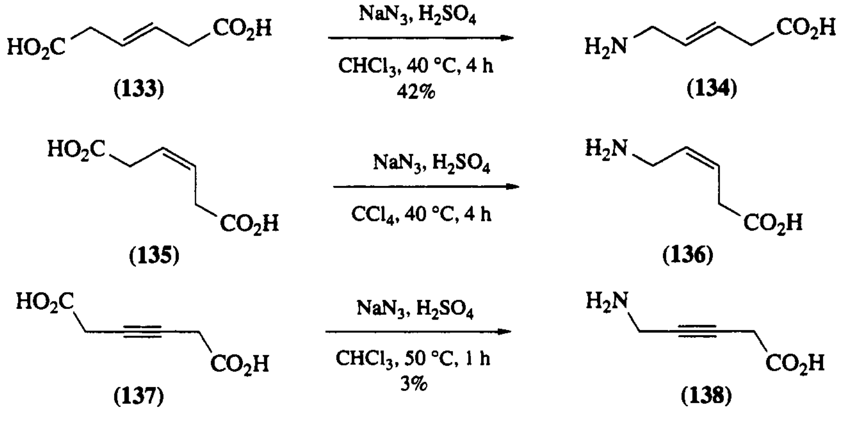
Scheme 24

Treatment of 2-phenylhexanoic acid (**128**) with sodium azide in polyphosphoric acid furnishes the expected amine (**129**) together with aniline (**130**) in a nearly equal ratio, as shown in Scheme 25.[105] 2-Phenyl-2-methylhexanoic acid (**131**) gives aniline (**130**) only and no Schmidt product is obtained. Similar treatment of diphenylacetic, 2,2-diphenylpropionic and triphenylacetic acids mainly gives the unchanged starting materials. Except in the case of triphenylacetic acid, a small amount of aniline (**130**) is formed. The above anomalous formation of aniline can be explained by the decarboxylation at the initial step to form a benzyl-type cation (**132**), which reacts with hydrazoic acid, followed by rearrangement with concomitant expulsion of nitrogen and then hydrolysis.



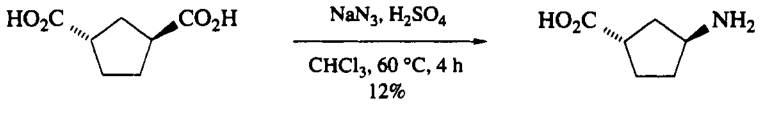
Scheme 25

(*E*)-Hex-3-ene-1,6-dioic acid (**133**) undergoes the Schmidt reaction with 1 equiv. of sodium azide to give (*E*)-5-aminopent-3-enoic acid (**134**) in moderate yield, shown in Scheme 26. The Schmidt reaction of the corresponding (*Z*)-isomer (**135**) analogously proceeds to give the (*Z*)-amino acid (**136**) though with much lower efficiency.[106] Furthermore, hex-3-yne-1,6-dioic acid (**137**) gives the Schmidt product (**138**) in very low yield, presumably because of competing additions of hydrazoic acid to the triple bond.



Scheme 26

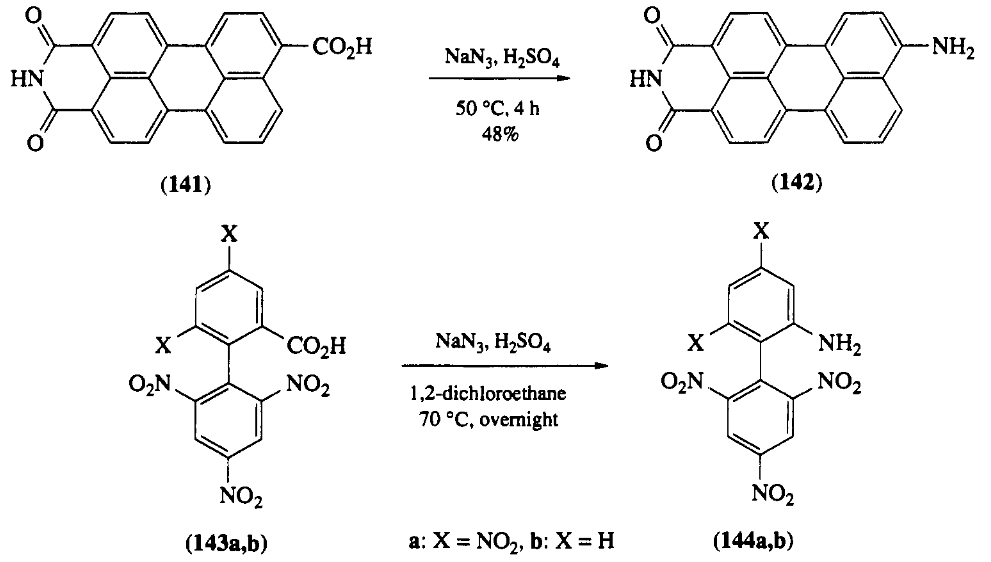
The absolute configuration of (+)-*trans*-cyclopentane-1,3-dicarboxylic acid (**139**) has been determined to be (1*S*, 3*S*) by the correlation with *trans*-(1*S*, 3*S*)-3-aminocyclopentanecarboxylic acid (**140**) through the Schmidt reaction (equation 46).[107]



(46)

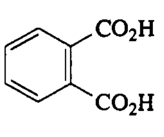
(**139**) (**140**)

Aromatic carboxylic acids, *e.g.* **(141)**,[108] also undergo the Schmidt reaction to give amines, *e.g.* **(142)**, in a single operation. Although the Schmidt reaction of 2′,4,4′,6,6′-pentanitrobiphenyl-2-carboxylic acid **(143a)** proceeds to give the amine **(144a)** in 49% yield, the corresponding 2′,4′,6′-trinitro analog **(143b)** affords only unchanged starting material (Scheme 27).[109] In the latter case, however, conversion to the amine **(144b)** has been achieved by the Curtius reaction *via* the acyl chloride.

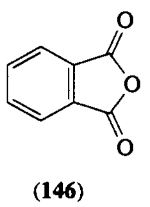


Scheme 27

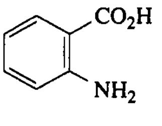
Treatment of phthalic acid **(145)** with sodium azide under acidic conditions has been reported[110] to give various products: anthranilic acid **(147)** and a trace of *o*-phenylenediamine **(148)** in concentrated sulfuric acid; and anthranilazide **(149)** and benzimidazol-2-one **(150)** in 90% sulfuric acid. Analogously, phthalic anhydride **(146)** gives the following products: anthranilic acid **(147)**, benzimidazol-2-one **(150)** and some 3,1-benzoxazine-2,4(1*H*)-dione (isatoic anhydride) **(151)** in sulfuric acid; and benzimidazol-2-one **(150)** in acetic acid. A recent report[110] has revealed that the Schmidt reaction of phthalic acid **(145)** in 90–98% sulfuric acid gives anthranilic acid **(147)** and anthranilazide **(149)** (major products) by a process thought to involve 3,1-benzoxazine-2,4(1*H*)-dione **(151)** as an intermediate. Benzimidazol-2-one **(150)** is produced in this reaction by a secondary process from anthranilazide **(149)**. Photolysis of **(149)** also produces **(150)**.



(145)



(146)



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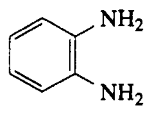
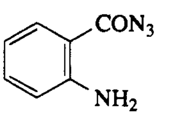
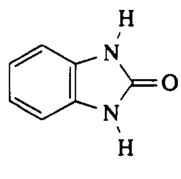


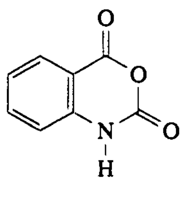
(148)



(149)



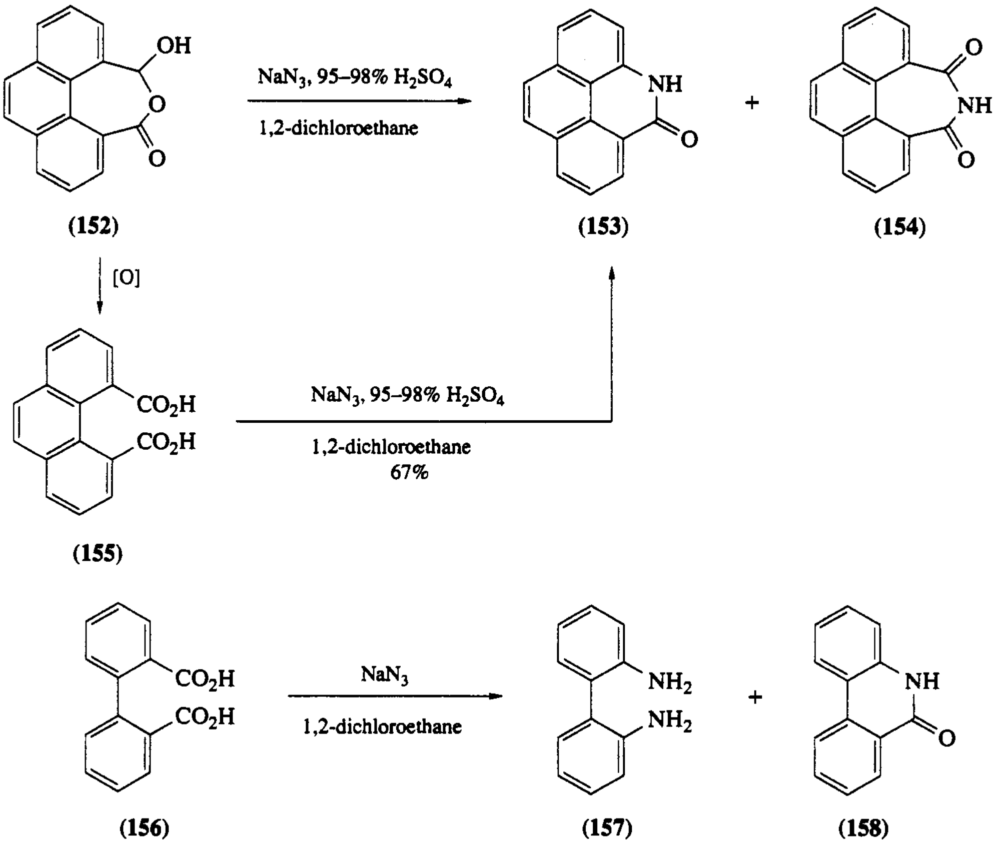
(150)



(151)

Under the Schmidt reaction conditions, the lactol **(152)** of 4-formyl-5-phenanthroic acid gives 1-azapyren-2(1*H*)-one **(153)** and phenathrene-4,5-dicarboximide **(154)**.[110] The compound **(153)** may be formed by attack of hydrazoic acid at the latent aldehyde site in preference to the carboxy site (see Section 4.4.4.2). Phenanthrene-4,5-dicarboxylic acid **(155)**, obtained by oxidation of **(152)**, similarly affords

(**153**) as the major product. Diphenic acid (**156**) also undergoes the Schmidt reaction to give 2,2′-diaminobiphenyl (**157**) and phenanthridone (**158**) in proportions dependent on the sulfuric acid concentration, as shown in Scheme 28.



	(157)	(158)
95–98% H_2SO_4 :	43%	6%
90% H_2SO_4 :	5%	56%

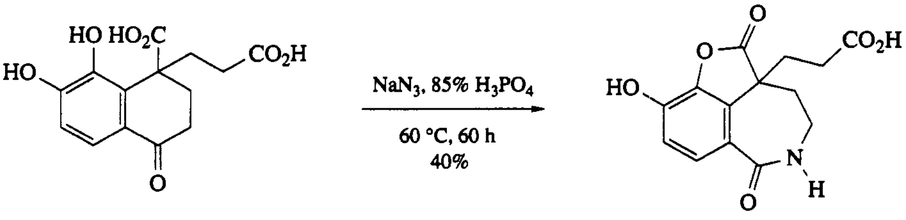
Scheme 28

4.4.4.2 With Ketones

In addition to carboxylic acids, hydrazoic acid reacts with ketones, aldehydes, alcohols and alkenes under strongly acidic conditions. Among them, the Schmidt reaction of ketones[10–12] has been most studied because of its synthetic possibilities as well as its similarity to the Beckmann rearrangement (Section 4.3.1). A drawback of the Schmidt reaction of unsymmetrical ketones is that which one of its substituents will migrate depends on the structures and reaction conditions (see equation 4 in Section 4.4.1.1). Regioselective migration, however, has been observed in many cases. Although the Schmidt reaction with ketones does not strictly belong with the degradation reactions reviewed in this chapter, it will be discussed here briefly since it is often used and its reaction procedure and mechanism are very similar to those of the Schmidt reaction with carboxylic acids.

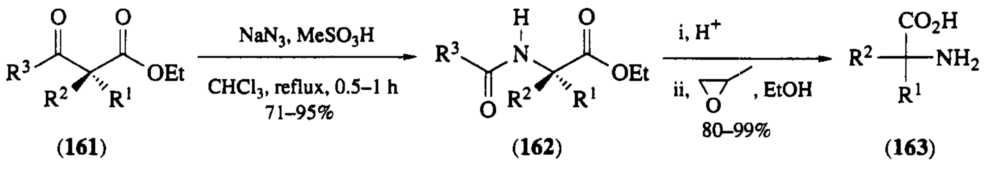
In general, ketones are preferentially attacked by hydrazoic acid when both ketonic and carboxylic groups are present in the same molecule (*cf.* conversion of **152** to **153** in Scheme 28). Thus, treatment of the ketophenolic acid (**159**) with sodium azide in phosphoric acid chemo- and regio-selectively gives the lactam–lactone (**160**) as the sole product (equation 47).[111]

The Schmidt rearrangement of optically active α,α-bisalkylated β-keto esters (**161**) regioselectively proceeds to give *N*-acyl α-alkylated α-amino acid esters (**162**) with retention of configuration and little or no racemization.[112] Acid hydrolysis of (**162**), followed by treatment with propylene oxide, affords α-alkylated α-amino acids (**163**) in high yield and optical purity (equation 48).



(159) **(160)**

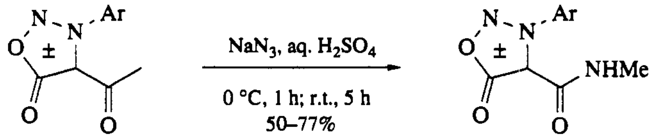
(47)



(161) **(162)** **(163)**

(48)

4-Acetyl-3-arylsydnones (**164**) undergo the regioselective Schmidt reaction to give 3-arylsydnone-4-*N*-methylcarboxamides (**165**) in good yields without formation of 4-acetamidosydnones (equation 49).[113] In contrast to this, the Beckmann rearrangement of the oxime of (**164**, Ar = phenyl) does not proceed at all.



(164) **(165)**

(49)

An interesting version of the Schmidt or Beckmann rearrangement utilizes thioketals (**166**), which generate thionium ions (**167**) as carbonyl substitutes, giving amides (**169**) or imino sulfides (**170**) *via* α-azido sulfides (**168**), as shown in Scheme 29.[114] Thus, amides or lactams can be obtained in good yields by treatment of thioketals (**166**) with iodine azide (IN_3), followed by the rearrangement of the resulting α-azido sulfides (**168**) with trifluoroacetic acid. This method may be superior to the normal Schmidt or Beckmann rearrangement. For example, the rearrangement of the oxime (**171**) leads to the lactam (**174**) in very poor yield under Beckmann conditions but the yield is greatly increased by starting with the thioketal (**172**) and going *via* the α-azido sulfide (**173**). The thioketal (**175**) is also smoothly converted to *N*-*t*-butylacetamide (**177**) *via* the α-azido sulfide (**176**), while the Schmidt reaction of pinacolone exclusively affords fragmentation products.[114]

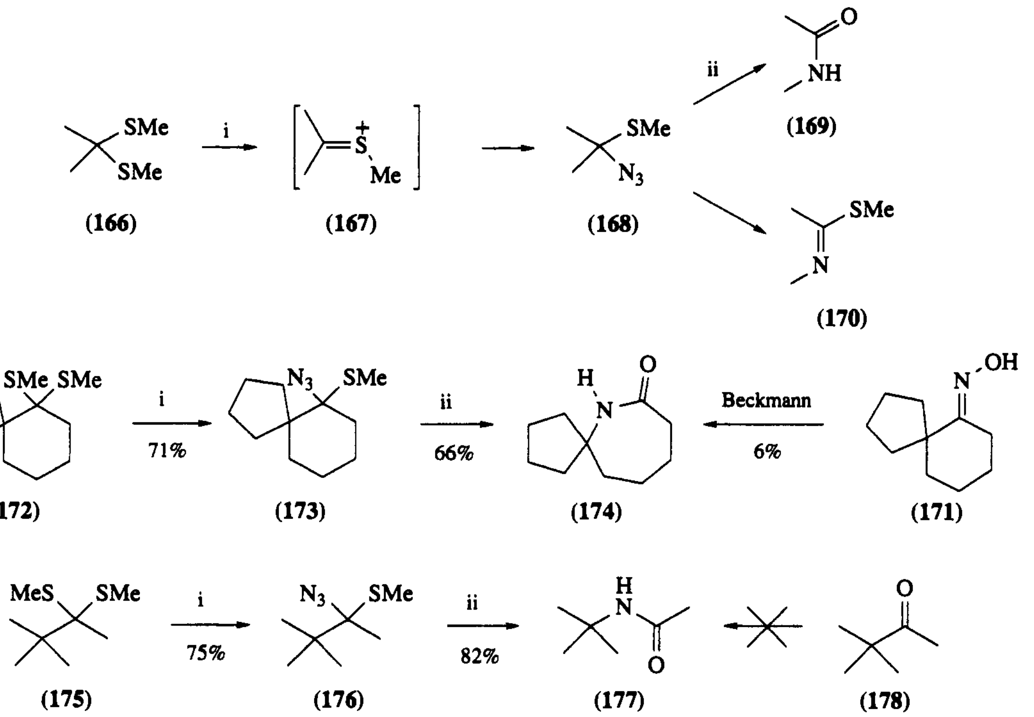
Imino sulfides (*e.g.* **180**), regarded as an activated form of amides, can be prepared in a single step from thioketals (*e.g.* **179**) by the action of sodium or trimethylsilyl azide, tin(IV) chloride and a trace of iodine (equation 50).[114]

Another version of the Schmidt-type rearrangement starts from silyl enol ethers (**181**) prepared from acylbenzenes and does not need any acid catalysts.[115] The silyl enol ethers (**181**) react with *N*-chlorosuccinimide (NCS) in the presence of sodium azide and benzyltriethylammonium chloride to give chloro azido derivatives (**182**) *via* siloxycarbinyl cations. Subsequent thermal rearrangement of the azido products (**182**) leads to anilide derivatives (**183**; equation 51).

4.4.5 THE LOSSEN REACTION

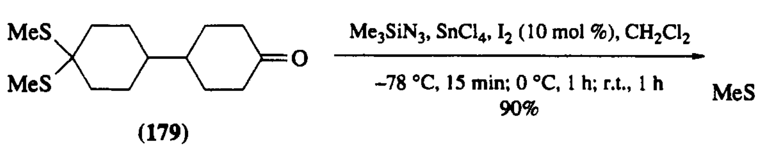
4.4.5.1 Under Basic Conditions

The Lossen reaction[14,15] is the rearrangement of hydroxamic acids, which are prepared from acids, acyl chlorides and esters. It is usually conducted under alkaline conditions. Initial attachment of electron-withdrawing groups to the oxygen atom of the hydroxamic acids is essential to conduct the reaction; the

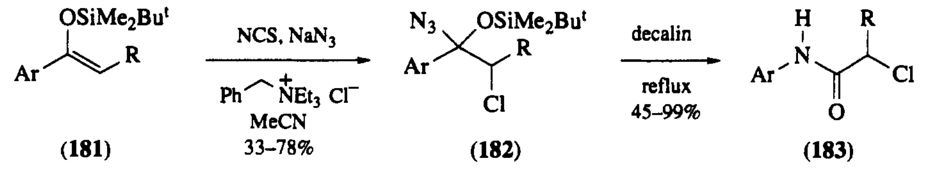


i, IN_3, CH_2Cl_2–MeCN, –78 °C, 2 h; ii, CF_3CO_2H, $CHCl_3$

Scheme 29



(50)

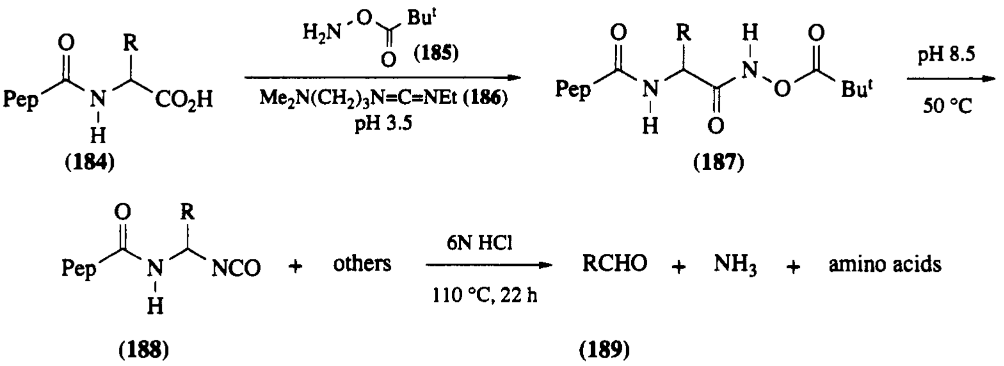


(51)

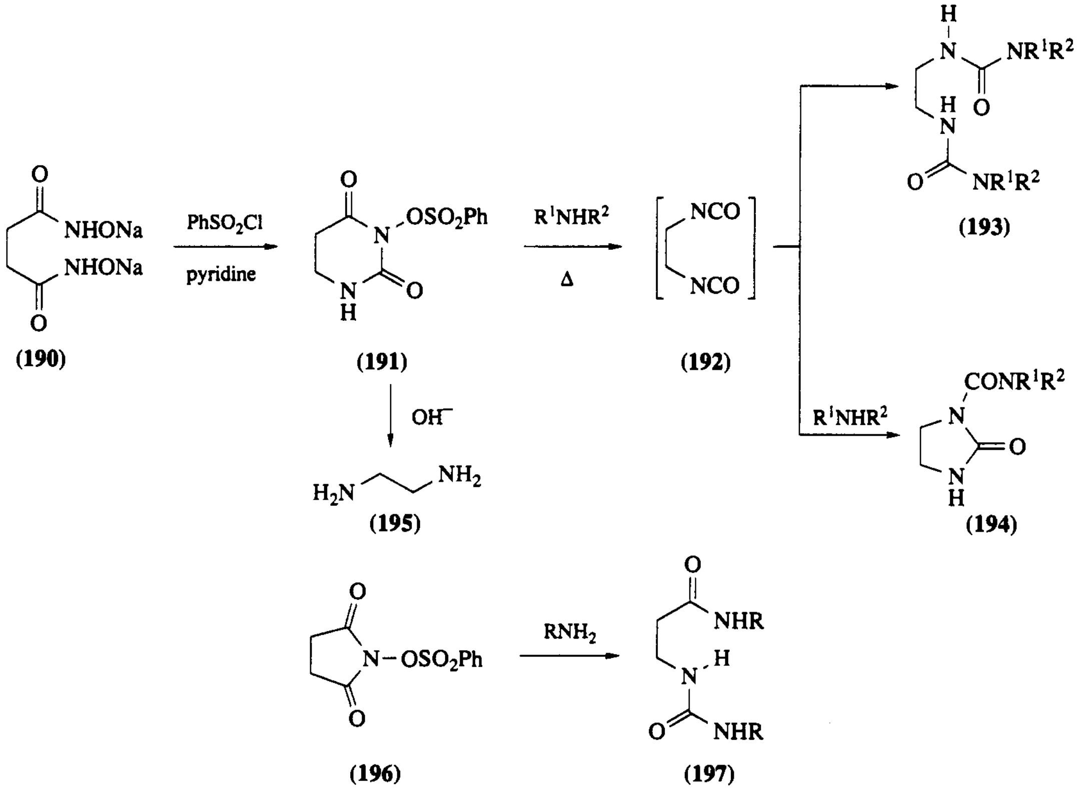
rate of the Lossen rearrangement is directly proportional to the acidity of these groups, which act as leaving groups, or their conjugate acids, where the leaving groups are basic anions.[116] *O*-Acylhydroxamic acids are most often used, though *O*-sulfonyl or *O*-phosphoryl derivatives may also be employed.

The Lossen reaction of peptide carboxylic acids has been investigated in order to determine the carboxy terminal amino acid residue of peptides.[117] The procedure first involves the formation of *O*-pivaloylhydroxamic acids (**187**) by condensation of peptide carboxylic acids (**184**) with *O*-pivaloylhydroxylamine (**185**) using a water soluble carbodimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (**186**). The Lossen rearrangement of (**187**) occurs at pH 8.5 and 50 °C to give a mixture of isocyanates (**188**) and their reaction products, which, on acidic hydrolysis, afford the aldehydes (**189**), ammonia and amino acids, as shown in Scheme 30.[117] Identification of aldehydes determines the C-terminal amino acids of the original peptides.

The bishydroxamate (**190**) prepared from ethyl succinate partially undergoes the Lossen rearrangement with benzenesulfonyl chloride in pyridine to give the uracil derivative (**191**).[118] Treatment of (**191**) with ammonia or various amines yields a mixture of 1,2-bis(ureido)ethanes (**193**) and 1-carboxamido-2-imidazolidones (**194**) *via* the Lossen product, while a hydroxide ion initiated Lossen rearrangement of (**191**) leads to ethylenediamine (**195**), as shown in Scheme 31. *N*-Benzenesulfonyloxysuccinimide (**196**) also undergoes the Lossen reaction with amines to give β-ureidopropionamides (**197**).[118]

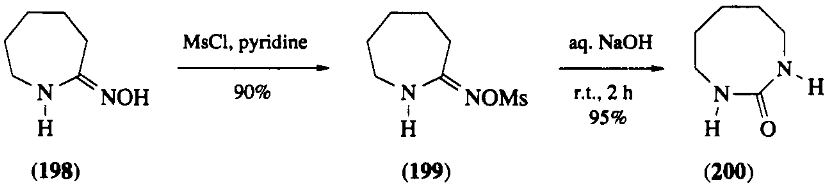


Scheme 30



Scheme 31

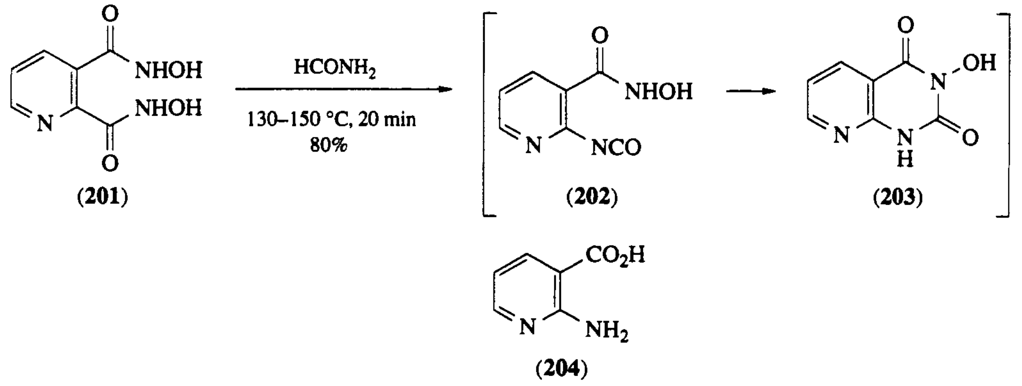
Although the Lossen reaction of *O*-acylated derivatives of the amide oxime (**198**) has failed, its mesylate (**199**) easily gives the Lossen product (**200**) under alkaline conditions (equation 52).[119]



(52)

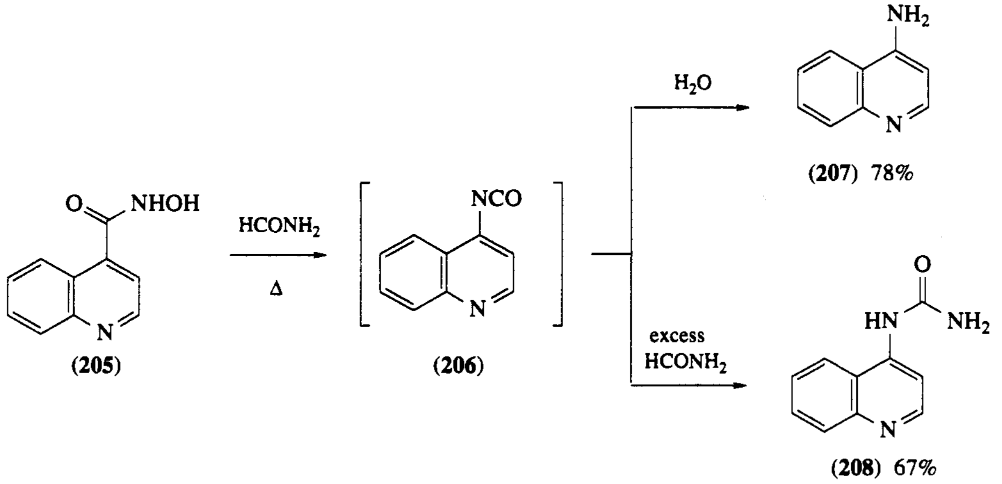
4.4.5.2 Under Neutral Conditions

A useful variant of the Lossen reaction proceeds under neutral conditions without any prior treatment of the hydroxamic acids. This 'amide modification' of the Lossen rearrangement involves a short heating of the hydroxamic acid in formamide to give amines.[120–122] Anthranilohydroxamic acid[120] and pyridinecarbohydroxamic acids[121] undergo the rearrangement to produce benzimidazol-2-one and aminopyridines respectively. The Lossen rearrangement of the hydroxamic acid (**201**) derived from quinolinic acid regioselectively occurs to give 2-aminonicotinic acid (**204**) in good yield *via* the isocyanate (**202**) and then the Leuchs anhydride-type intermediate (**203**; equation 53).[121] The latter intermediate (**203**) is also obtained when the disodium salt of (**201**) is heated with benzenesulfonyl chloride.



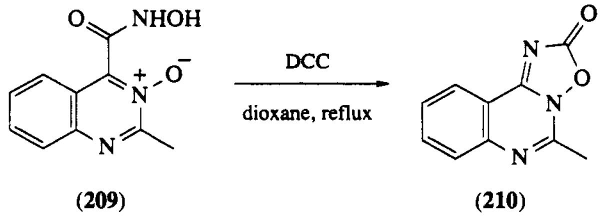
(53)

Short heating of 4-quinolinecarbohydroxamic acid (**205**) with formamide affords 4-aminoquinoline (**207**) *via* the isocyanate (**206**), while use of a large excess of formamide and increasing the temperature slowly give *N*-(4-quinolyl)urea (**208**) exclusively, as shown in Scheme 32.[122] Intermediacy of *O*-formates or equivalents has been suggested in the above modification of the Lossen reaction.[121]



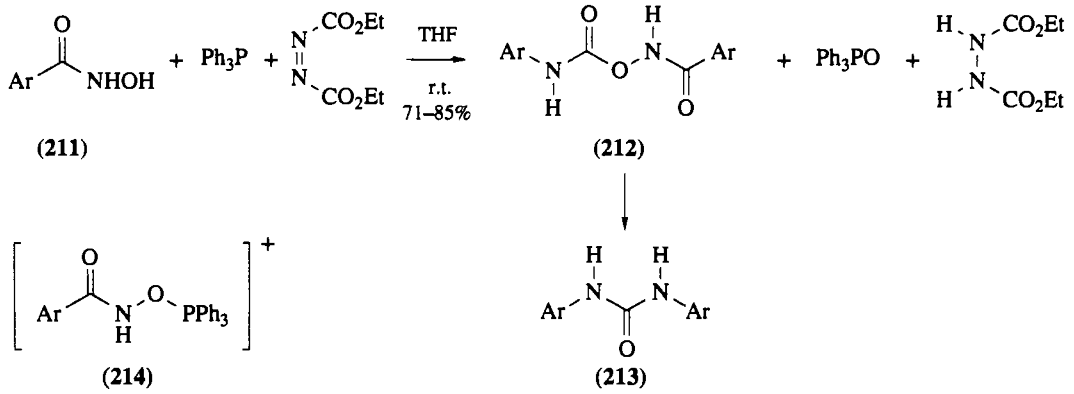
Scheme 32

N,*N*′-Dicyclohexylcarbodiimide (DCC) also mediates the Lossen reaction of hydroxamic acids under neutral conditions.[123,124] In the conversion of the hydroxamic acid (**209**) to the tricyclic compound (**210**), the Lossen rearrangement is accompanied by an intramolecular cycloaddition (equation 54).[123]



(54)

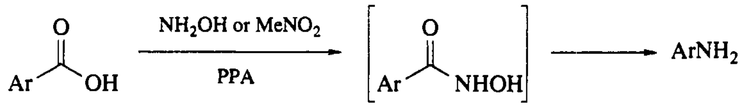
A combination of triphenylphosphine and diethyl azodicarboxylate (the Mitsunobu reagent)[125] is useful for the rapid conversion of aromatic hydroxamic acids (**211**) to *O*-(*N*-arylcarbamyl)hydroxamates (**212**), products of the Lossen rearrangement.[126] In some cases, a spontaneous second Lossen rearrangement occurs to give diarylureas (**213**), as shown in Scheme 33. The yields of (**212**) and (**213**) are 70–85%. The intermediacy of the phosphonium salts (**214**) has been suggested.



Scheme 33

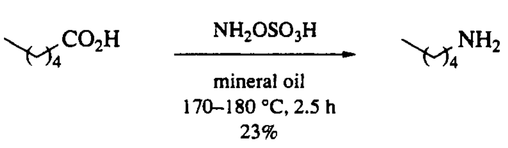
4.4.5.3 Under Acidic Conditions

Aromatic carboxylic acids can be converted to aromatic amines in a single operation by the action of polyphosphoric acid and hydroxylamine[127] or nitromethane.[128] The intermediates are hydroxamic acids which are activated by phosphorylation with polyphosphoric acid and undergo the rearrangement (equation 55). When nitromethane is used, hydroxylamine is first formed by the action of polyphosphoric acid. This one-step Lossen reaction works well with aromatic acids containing electron-donating substituents, but fails or gives poor yield with aliphatic acids and with aromatic acids containing electron-withdrawing groups.



(55)

Hydroxylamine-*O*-sulfonic acid can be also used for the Lossen rearrangement. Heating acids with hydroxylamine-*O*-sulfonic acid in hot mineral oil[128] or polyphosphoric acid[129] affords amines, though the reaction conditions for this transformation still need to be optimized (equations 56 and 57).



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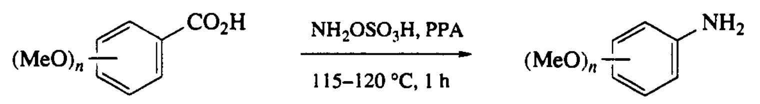

(57)

4-methoxy, 35%; 2,4-dimethoxy, 25%

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4.5
Functional Group Transformations *via* Allyl Rearrangement

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4.5.1 INTRODUCTION

Functionalized allylic systems are not only often part of target molecules but also have potential as versatile synthetic intermediates. They can frequently be used to generate multifunctional compounds by further elaboration of the C═C bond, namely by reduction (*e.g.* hydrogenation)[1] or oxidation (*e.g.* to alcohols, diols, oxiranes, aldehydes or ketones)[2] or by diverse addition reactions.[3] As such reactions can very often be performed with remarkable stereocontrol by means of the allylic functionality, especially in intramolecular reactions, the potential of functionalized allylic systems is immense.

Another fascinating, unique property of allylic systems is their propensity for allylic rearrangement with transfer of functionality from one end of the allylic system to the other and concomitant double bond shift with or without transformation of functional groups. In the latter case (X = Y; equation 1) a reaction is synthetically useful only in unsymmetrical cases for a 1,3-transposition of the functional group.

(1)

Such reactivity is likewise known for propargylic systems leading to allenic systems (equation 2).[4]

(2)

The usefulness of these allylic or propargylic rearrangements in synthesis is obvious as they allow 1,3-transposition of functionality, permitting allylic functional group transformation. There are quite a number of functional group transformations *via* allyl rearrangements known, proceeding either by intermolecular or by intramolecular reactions, and by different reaction mechanisms. Desirable features for a valuable synthetic procedure are the following: (i) the reaction should be regiospecific, leading only in one direction; (ii) the stereochemistry of the double bond should be controllable in a predictable manner; (iii) high optical yields should be possible with chiral systems. Intramolecular reactions are the more likely to comply with these requirements as they proceed very often by a concerted mechanism *via* rigid, cyclic, five- or six-membered transition states, leading to high stereocontrol. Prominent examples are 2,3- and 3,3-sigmatropic rearrangements such as the Wittig or the Claisen rearrangements. In intermolecular reactions, especially when a reactive intermediate, *e.g.* a more or less free allylic anion, carbenium ion or radical is involved, the regioselectivity is already a problem as the reactive intermediate can be captured at either end of the allylic system and the proportion of the attack will be mainly influenced by steric factors. In nucleophilic and electrophilic substitutions this notorious problem refers to the competition of S_N and S_N' or S_E and S_E' reactivity; in the reaction of allyl metal compounds with electrophiles it reflects the α- *versus* γ-reactivity of the allylic 'carbanionic' species.

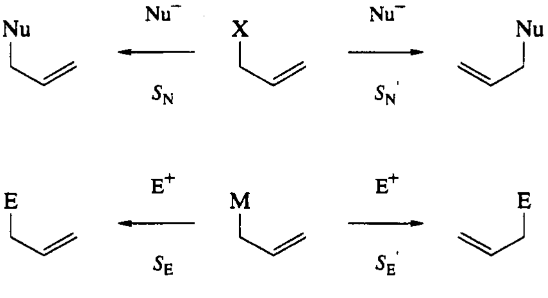
A general discussion of such inherent problems and the principles of allylic rearrangements will be presented first, followed by specific examples of functional group transformations, which will be systematically surveyed regardless of the mechanism involved.

Such a systematic review is especially useful since a knowledge of the functional group transformation is essential in retrosynthetic analysis.[5] In the so-called 'transform'-based strategy 'functional group interchanges' (or 'interconversions'; FGI) or 'functional group transpositions' (FGT) are applied to simplify a target molecule and one has to look for synthetic reactions which allow these transformations to perform.

4.5.1.1 Intermolecular Reactions with Allylic Rearrangement

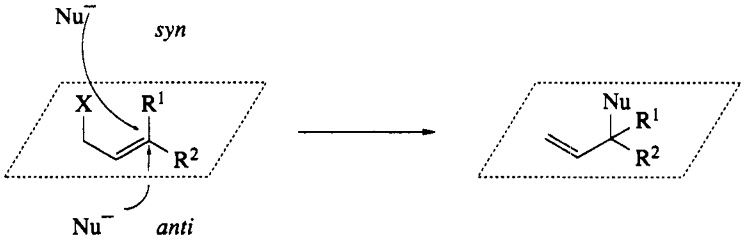
4.5.1.1.1 Substitution reactions with double bond shift

Substitution reactions with allylic rearrangement are known in nucleophilic S_N as well as in electrophilic S_E reactions (Scheme 1).[6]



Scheme 1

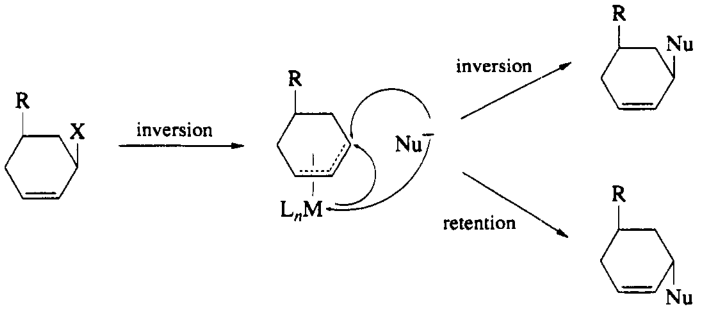
The exchange of an allylic functional group with double bond shift by a nucleophilic substitution generally presents problems because the competing direct substitution is very often the dominating reaction. The proportion of S_N to S_N' reaction is mainly determined by steric effects, the attack of the nucleophile being preferred at the least hindered site. Under equilibrating conditions the thermodynamic stabilities of the products will be decisive. So the substitution pattern of the allylic substrate plays the most important role for regiochemical control. Whereas with systems with the leaving group in a primary or secondary position one normally gets a mixture of products, substitution of a leaving group at a tertiary position will proceed with allylic rearrangement. With regard to stereochemistry, reaction conditions which favor a bimolecular reaction mechanism are to be preferred because in the case of an allylic carbenium ion the stereochemical integrity will be lost. Although there is still a dispute about the preferred mode of an S_N2' reaction,[7] there seems to be a preference for *syn* attack of the nucleophile not only in cyclic but also in acyclic cases (Scheme 2).



Scheme 2

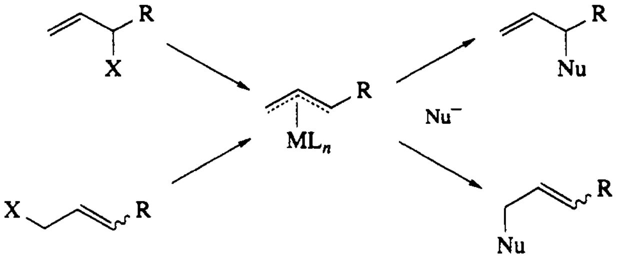
Valuable preparative applications are rare and especially in ring-forming reactions other stereochemical factors such as ring strain and conformational effects will determine the stereochemistry. However the use of metal compounds to influence regio- and stereo-selectivity continues to excite interest.[8] For C—C bond formation the coupling of allylic acetates with organocuprates offers broad synthetic potential as it generally seems to proceed with double bond shift.[9]

In recent years there has been an impressive development in transition metal promoted substitution reactions which can also be utilized for transforming allylic functionalities. An especially useful process, already extensively used in organic synthesis, is the the Pd^0-catalyzed nucleophilic substitution of allylic substrates.[10,11] The stereochemical outcome of the reaction can be explained by a widely accepted model which involves a two-step sequence: (i) formation of a π-allyl intermediate with inversion of configuration; and (ii) the attack of the incoming nucleophile either directly on the allyl ligand, especially with soft nucleophiles, again with inversion of configuration thereby leading to an overall retention of stereochemistry, or, with hard nucleophiles, primarily on the metal center followed by an internal transfer to the allyl system with retention effecting a net inversion of stereochemistry (Scheme 3).



Scheme 3

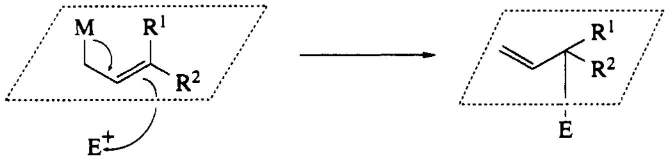
A wide range of allylic leaving groups, including acetates and other esters, ethers, alcohols, amines, sulfinates, epoxide and nitro groups, can be substituted by a variety of heteroatom and carbon nucleophiles most commonly by stabilized carbanions and amines. However control of regioselectivity still remains one of the most difficult and challenging problems: although reaction of the less substituted end of the allyl system usually predominates, a number of variables influence the regioselectivity and it is difficult to draw any general conclusion. In the context discussed here it is especially necessary to point out that the regioisomeric nature of the product is not directly influenced by the regiochemistry of the starting material as a common π-allyl intermediate is formed from regioisomers, independent of the geometry of the double bond. Other factors will determine whether a formal S_N2 or S_N2' reaction occurs (Scheme 4).



Scheme 4

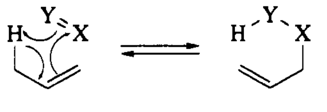
Beside the fascinating aspect that the reactions can be brought about catalytically with the possibility of asymmetric induction by optically active catalysts,[10] the mildness of the reaction conditions, allowing many functional groups to be tolerated, will increase the number of applications in the future.

Electrophilic substitutions can also be used for functional group transformation with allyl rearrangement. In some respects electrophilic substitutions are even better than nucleophilic substitutions as the normal mode of electrophilic substitution is by a formal S_E2' mechanism with double bond shift. Allylsilanes[12] and allylstannanes[13] especially can be employed for such reactions with electrophiles. As these compounds can be generated stereospecifically (in contrast to allylic Grignard reagents which would be equilibrated to the different geometrical isomers) and react with a wide variety of electrophiles they constitute a valuable tool for synthetic purposes, being 'stable' equivalents of allyl anions, the reactivity decreasing from allyltin to allylsilicon compounds. Regarding stereochemistry, it is almost generally found that the S_E' reactions take place with *anti* stereochemistry (Scheme 5).



Scheme 5

Lastly it should be mentioned that appropriate allylic substrates can also be substituted in a radical S_H' reaction with rearrangement, but the synthetic applications are rather limited.[14] Quite a different intermolecular reaction, where an allylic shift occurs, is the ene reaction, in which an allylic hydrogen is substituted in a concerted process *via* a six-membered transition state (equation 3).

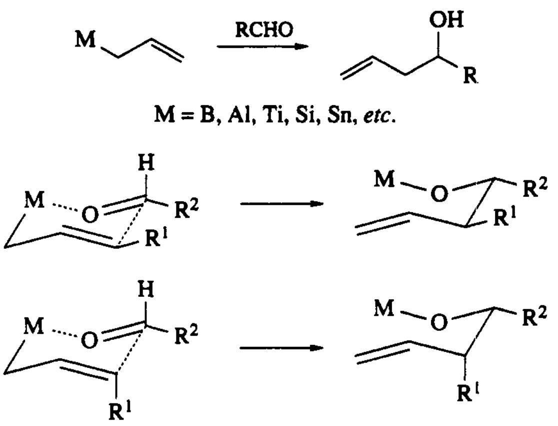


(3)

In recent years this reaction has frequently been utilized for allylic functionalization and there are some interesting applications in synthesis.[15] In connection with the topic of this chapter only the retro-ene reaction has to be taken into consideration here.

4.5.1.1.2 Reactions of allylmetal compounds with electrophiles

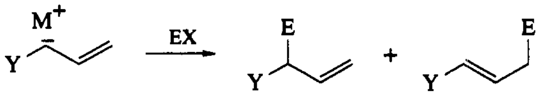
Rearrangement of an allylic (or propargylic or allenic) system is effected if the derived anion, either in form of an organometallic compound[16] or a heteroatom-stabilized 'carbanion',[17] is attacked by electrophiles at the γ-position. However, competing α-reactivity is most often observed as well, and a lot of experimental material exists with respect to this problem,[18] but generalizations are difficult to make.[19] The regioselectivity depends on different factors, not least on the nature of the electrophile, so that it can dramatically change from one electrophile to the other. Regioselectivity is more of a problem in alkylation than in the reaction with a carbonyl group, but by change of the 'counterion', transforming an allyllithium into a copper or a titanium compound, one can often direct alkylation to occur at the γ-position. Some allylic compounds, namely boron, aluminum, titanium, silicon and tin derivatives, exhibit mainly γ-selectivity in addition reactions to a carbonyl group,[20] apparently because of a tight, highly organized chair transition state with distinct Lewis acid–carbonyl interaction (Scheme 6).



M = B, Al, Ti, Si, Sn, *etc.*

Scheme 6

In accordance with this model one finds diastereoselectively *anti* products on reaction of aldehydes with (*E*)-allyl compounds, whereas allyl systems with the (*Z*)-configuration give mainly *syn* products and it is even possible to effect asymmetric induction. As the double bond of the product can be oxidatively cleaved to a C═O group, the reaction can be regarded as a stereoselective aldol reaction, an aspect which explains the widespread interest in this type of reaction. With heterosubstituted allylic anions it is sometimes possible to effect predominantly γ-attack with different electrophiles by the choice of the heteroatom.[21] For instance it is well known that with sulfur substituents like —SR, —SOR or —SO_2R the α-attack dominates, but doubly lithiated allenethiol possesses high γ-reactivity and can be used as a homoenolate anion equivalent in reaction with electrophiles such as alkyl halides (Scheme 7).[22]



M = Li, Na, K, Mg, Ti, *etc.*
Y = OR, SR, SOR, SO_2R, NR_2, SiR_3, POR_2, *etc.*

Scheme 7

On the other hand the inherent α-selectivity of allylsulfur carbanions can sometimes be transformed to a γ-reactivity by a sigmatropic rearrangement, earning in addition the stereoselectivity typical for such reactions (see Section 4.5.2.3). Due to their significance in synthesis a lot of work has been done on reactions of heteroatom-substituted allyl anions with special emphasis on their use as homoenolate anion equivalents.[23,24] The more recent developments, with the possibility of introducing diastereoselectivity, will be discussed later in Section 4.5.3.2.1.

4.5.1.2 Intramolecular Allylic Rearrangements

A versatile and very powerful strategy for functional group transformation *via* allyl rearrangement involves intramolecular reactions of the 2,3-[25] and 3,3-sigmatropic[26] type, as exemplified in generalized form in Scheme 8.

Scheme 8

The outstanding significance of these reactions in synthesis originates from the high stereochemical control and the possibility of transferring chirality associated with the internal migration of an allyl group due to the highly ordered cyclic transition states of such processes.[27,28] In contrast to the 3,3-sigmatropic rearrangement, the diastereoselectivity with regard to newly formed adjacent stereogenic centers is normally lower in 2,3-sigmatropic processes, because the ratio of diastereomers is not controlled by the significant energy difference between a chair and a boat conformation of the six-membered transition state, but by the much lower energy difference between *endo* and *exo* five-membered envelope transition states.

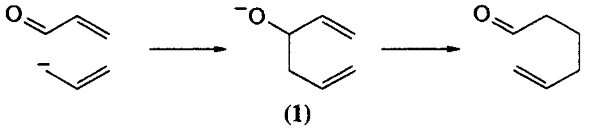
Besides the high stereochemical control of 2,3- and 3,3-sigmatropic rearrangements it is their obvious generality with respect to hetereoatom variation which has led to numerous synthetically useful applications. Even though not all possibilities have been examined yet, an impressive number of combinations of heteroatoms X and Y in the 2,3- and X, Y and Z in the 3,3-sigmatropic reactions have been realized.

4.5.1.2.1 2,3-Sigmatropic rearrangements

Quite a number of synthetically useful transformations in allylic systems belong to this class of reactions, namely the Wittig–ether rearrangement,[29,30] the Stevens–Sommelet rearrangement of ammonium ylides,[31] the Meisenheimer rearrangement of amine oxides,[32] the Büchi rearrangement[33] and the Mislow allyl sulfoxide–allyl sulfenate rearrangement.[34] Some of them are relevant to the subject of this review for heteroatom to heteroatom or heteroatom to carbon transformation and will be systematically presented with examples in the appropriate section. A thorough general discussion of 2,3-sigmatropic reactions is given in Chapter 4.6, Volume 6.[25]

4.5.1.2.2 3,3-Sigmatropic rearrangements

This category encompasses the Cope (X = Y = Z = C),[26] the Claisen (X = O, Y = Z = C)[26,35] and other hetero-Cope rearrangements.[36] Even though a concerted mechanism is not always certain, especially not with multiheteroatom systems and in some catalyzed versions,[37] a high degree of stereoselectivity in the formation of double bonds and stereogenic centers is normally found which allows very useful synthetic applications in the hetero-Cope cases. In the all-carbon case only the oxy-Cope rearrangement is of synthetic relevance (equation 4).[38,39]



(1)

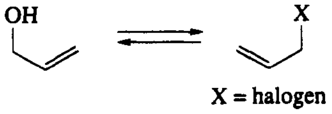
(4)

Considering that the system (1) is generated by the 1,2-addition of an allyl anion to an α,β-unsaturated carbonyl system, the rearrangement allows an indirect clean 1,4-addition to the α,β-unsaturated carbonyl system.

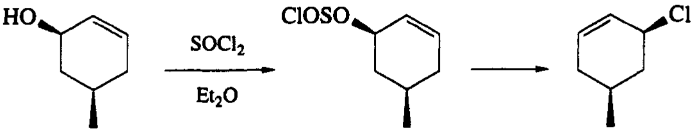
4.5.2 1,3-HETEROATOM TRANSPOSITIONS

4.5.2.1 Oxygen–Halogen Transpositions

The transformation of an allylic alcohol to an allylic halide (equation 5) or the reverse reaction normally leads to a mixture of isomers of direct and allylic substitution products. Only when tertiary allylic alcohols are employed or a rearrangement leads to extended conjugation of double bonds does a transposition of functionality occur predominantly.[40] While a number of procedures have been developed for the conversion of allylic alcohols to halides without rearrangement,[41] there seems to be only one reaction where a cleanly rearranged product is obtainable in a substitution of a primary or secondary allylic (and propargylic) hydroxy group to a chloride, that is by thionyl chloride in ether, probably by a cyclic S_Ni process. The regioselectivity is worse in other solvents and is lost in the presence of a base. In accordance with the mechanism it is a *syn* facial substitution, as has been demonstrated in cyclic cases (equation 6)[42] or with optically active propargyl alcohols, which give rise to optically active chloroallenes (equation 7).[43]



(5)



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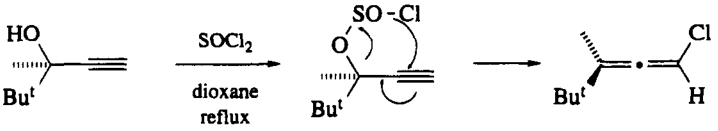
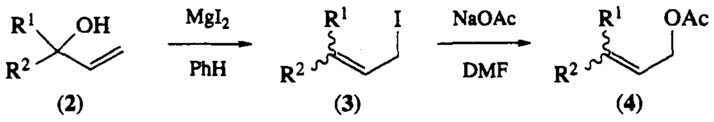


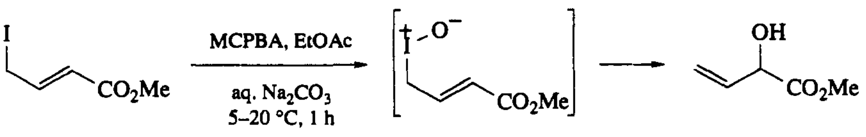
(7)

Recently a remarkable sequence of substitution reactions was published providing the first general method for the generation of primary allyl acetates from primary, secondary and tertiary alcohols.[44] Interestingly, the first reaction of the transformation of allyl alcohols (**2**) with anhydrous magnesium iodide in benzene gives regiospecifically the rearranged primary allylic iodides (**3**) from which the corresponding primary allylic acetates (**4**) can be obtained without rearrangement with anhydrous sodium acetate in dimethylformamide (equation 8).



(8)

A substitution of an allylic halide by an oxygen function is a problem with regard to regioselectivity too. Clean allylic rearrangements can be observed with tertiary halides and in intramolecular substitutions. In the latter case steric requirements seem to dictate the stereochemistry and examples with *syn*[45] and *anti* S_N'[46] substitutions are known. A unique regiospecific method for the transformation of allylic iodides to rearranged allylic alcohols, which may be rather general, uses an intramolecular rearrangement of a derived allylic iodoso compound (equation 9).[47]



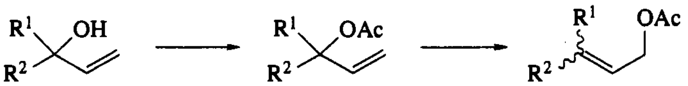
(9)

4.5.2.2 Oxygen–Oxygen Transpositions

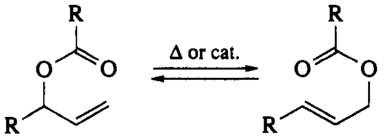
The best known example of this kind is the rearrangement of allyl acetates, a synthetically very useful reaction, especially in the case of tertiary systems (equation 10). These undergo isomerization sometimes even under the conditions of acetylation.[48] Otherwise, Lewis acid catalysis, preferably with $PdCl_2(MeCN)_2$, will bring about the isomerization smoothly (equation 11).[49]

The analogous reactions of acetates of primary and secondary allyl alcohols normally lead to equilibrium mixtures only slightly favoring primary allyl acetates. The equilibration of allyl alcohols by the Pd-catalyzed equilibration of derived esters or carbamates has some advantages in comparison with the

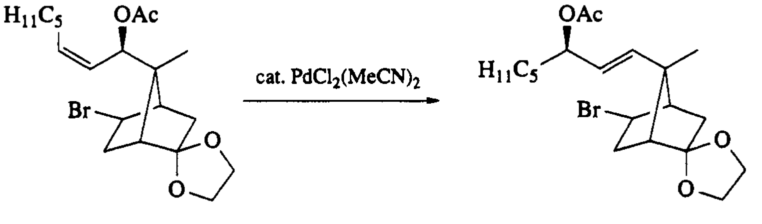
(10)


(11)

classical acid-catalyzed isomerization of allyl alcohols, which proceeds *via* allyl cations giving: high yield; no complication by dehydration, cyclization or skeletal rearrangement; and as a consequence of its 3,3-sigmatropic character clean suprafacial stereoselection (equation 12).[49]


(12)

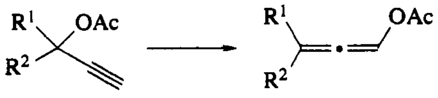
In an interesting example where steric effects seem to drive the reaction in the required direction the reaction proceeds by complete transfer of chirality (equation 13).[50]


(13)

Other examples where secondary allyl esters are rearranged in one direction are found in the carbohydrate field with glycals.[51] In the case of propargylic oxygen functionalities a 1,3-shift is also possible. With propargylic alcohols this is the classical Meyer–Schuster reaction,[52] which has been extensively used for the preparation of α,β-unsaturated carbonyl compounds. Besides acid catalysts such as sulfuric, hydrochloric or acetic acid, which may give rise to unselective rearrangements and side reactions, oxo derivatives of vanadium, molybdenum or tungsten have been used.[53] Recently titanium/copper-based catalysts have been recommended for the reaction (equation 14).[54]

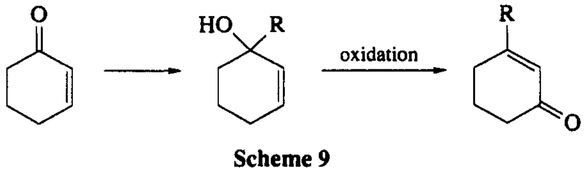

(14)

The isomerization of propargylic alcohols to α,β-unsaturated carbonyl compounds can also be effected by means of the rearrangement of derived propargylic esters (**5**) *via* allenic esters (**6**; equation 15).[55]


(15)

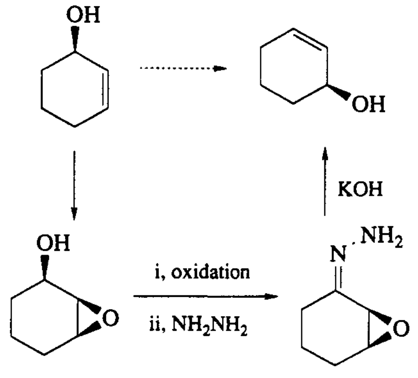
(5) **(6)**

The rearrangement can be catalytically brought about with silver and copper salts[56] or more recently with Pd^{II} compounds.[57] α,β-Unsaturated carbonyl compounds are also often formed under rearrangement on oxidation of allylic alcohols, especially when they are tertiary. This process can serve to perform a 1,3-transposition of carbonyl groups in α,β-unsaturated ketones (Scheme 9).[58]



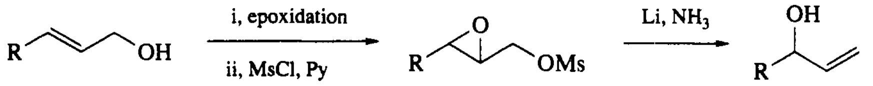
Scheme 9

There are some other methods for 1,3-oxygen–oxygen transposition of allylic alcohols which are not based on intra- or inter-molecular substitutions but on epoxidation of the allylic alcohol followed by a reductive rearrangement, so that the problem of regioselectivity can be avoided. One example is the so-called Wharton procedure[59] which seems to be very generally usable and is depicted in Scheme 10 for cyclohexenol. As the epoxidation of such cyclic allyl alcohols with peracids exhibits high diastereoselectivity the sequence permits a *syn* facial 1,3-migration of the hydroxy group with synthetically valuable chirality transfer (Scheme 10).



Scheme 10

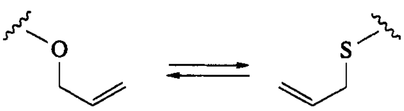
Another method, where a different reduction methodology is employed, can be used to generate secondary and tertiary allylic alcohols from primary ones,[60] and when this method is used in combination with Sharpless asymmetric epoxidation enantioselectivity may even be achieved (Scheme 11).[61]



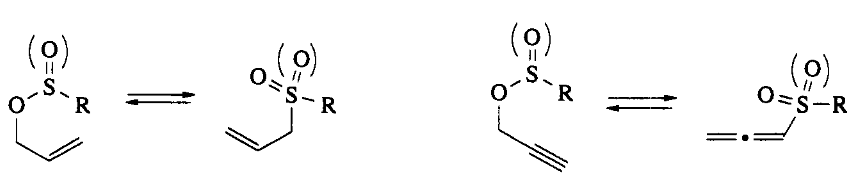
Scheme 11

4.5.2.3 Oxygen–Sulfur Transpositions

The synthetically most useful oxygen–sulfur transpositions (equation 16) are the allyl sulfenate–allyl sulfoxide and the propargyl sulfenate–allene sulfoxide rearrangements, the driving force of both being the formation of the strong S=O bond at the cost of the weak O—S bond (Scheme 12).[62]



(16)

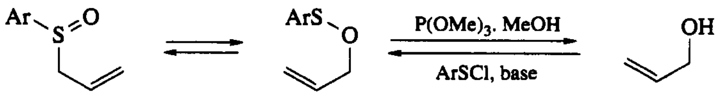


Scheme 12

The rearrangements take place most often spontaneously below room temperature with allyl and propargyl sulfenates. The corresponding sulfinates require much higher temperatures to be rearranged to the sulfones and the reaction is no longer reversible.[63]

As a consequence of the 2,3-sigmatropic nature of the rearrangements they are accompanied by high stereoselectivity allowing 1,3-chirality transfer and efficient control of the double bond configuration, giving predominantly *trans* geometry. Furthermore in the sulfenate–sulfoxide case the opportunity for chirality transfer from carbon to sulfur and *vice versa* exists, but its applicability in synthesis is limited since racemization is possible due to the reversibility of the allyl sulfenate–sulfoxide rearrangement.

On the other hand the reversible nature of the allyl sulfenate–sulfoxide rearrangement can be used very efficiently for the facile interconversion of allylic sulfoxides and alcohols *via* their sulfenate esters (Scheme 13).

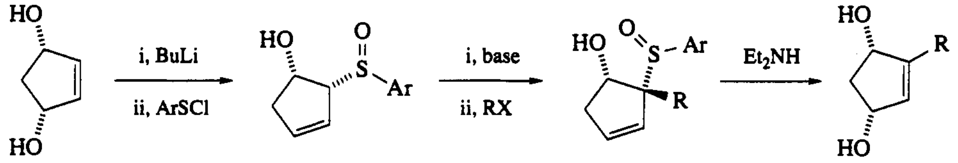


Scheme 13

Even though the sulfenate ester is usually in low equilibrium concentration with the isomeric sulfoxide, it can be trapped by thiophiles like trimethyl phosphite, leading eventually to complete formation of the alcohol.

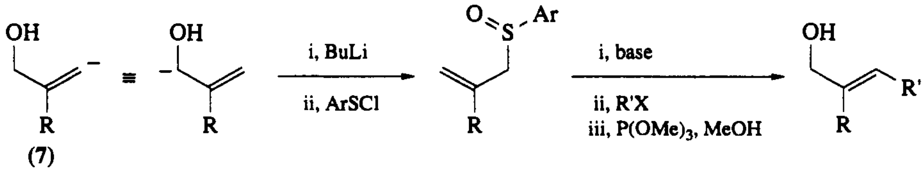
The synthetic potential of these transformations was first fully recognized by Evans[64] and they have been utilized since in various versions in numerous applications, some of which are discussed here.

Evans' rather general route to γ-substituted allyl alcohols is depicted in a specific example, which demonstrates the stereochemical outcome of the suprafacial rearrangements in cyclic systems (Scheme 14).[65]



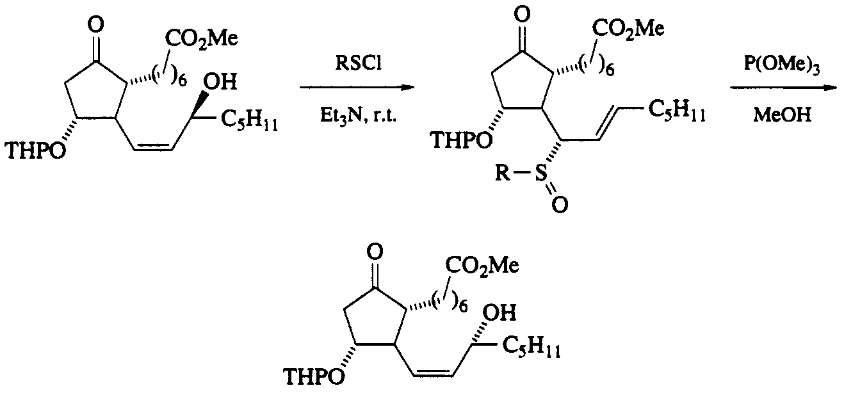
Scheme 14

The methodology of using allyl alcohols as d^3-synthons of type (7) has proven to be a very general one, providing an easy and highly stereoselective route to allylic alcohols with exclusive formation of (*E*)-double bonds in acyclic systems, even in the case of trisubstituted alkenes (Scheme 15).[66]



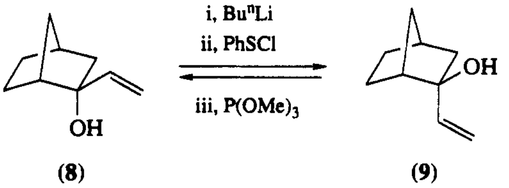
Scheme 15

In an acyclic situation the transformations can also lead to complete 1,3-chirality transfer, as exemplified by remarkable studies in the prostaglandin field (Scheme 16).[67]



Scheme 16

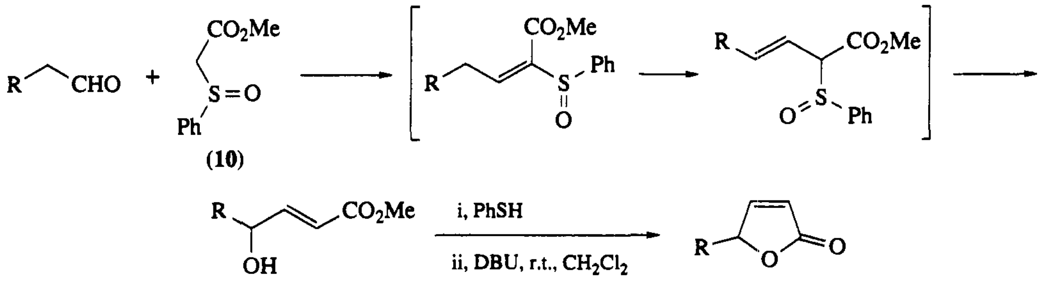
Other examples of directed epimerization of allyl alcohols by such processes are known, *e.g.* in the case of the bicyclic system (**8**) an *exo* to *endo* ratio of 8 to 1 was obtained starting from the more accessible *endo*-alcohol (**8**; equation 17).[68]



(**8**) (**9**)

(17)

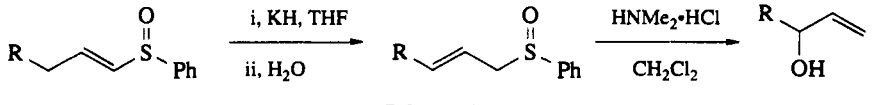
Allyl sulfoxide systems appropriate for a transformation to allylic alcohols can also be generated by other preparative methods, *e.g.* by isomerization of aryl vinyl sulfoxides. Such an isomerization occurs in connection with a Knoevenagel reaction of (**10**) with aldehydes leading finally to γ-hydroxy-α,β-unsaturated systems (**11**), which can easily be transformed into α,β-unsaturated γ-lactones (**12**; Scheme 17).[69]



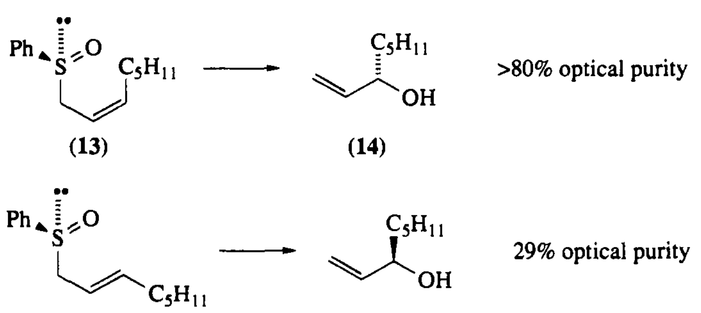
(**10**) (**11**) (**12**)

Scheme 17

Hoffmann has used an isomerization of readily available aryl vinyl sulfoxides, which can be obtained in optically active form, to study the possibility of generating optically active allyl alcohols by employing chirality transfer from sulfur to carbon.[70] While this synthetic route (Scheme 18) to allylic alcohols generally works well and gives good yields, the optical yields which could be obtained are only satisfactory in some cases, *e.g.* (*R*)-(*Z*)-sulfoxide (**13**) gave the (*S*)-(+)-octenol (**14**) with greater than 80% optical purity, whereas the (*R*)-(*E*)-isomer (**15**) yielded only 29% of the (*R*)-(–)-enantiomer (**16**; Scheme 19).



Scheme 18

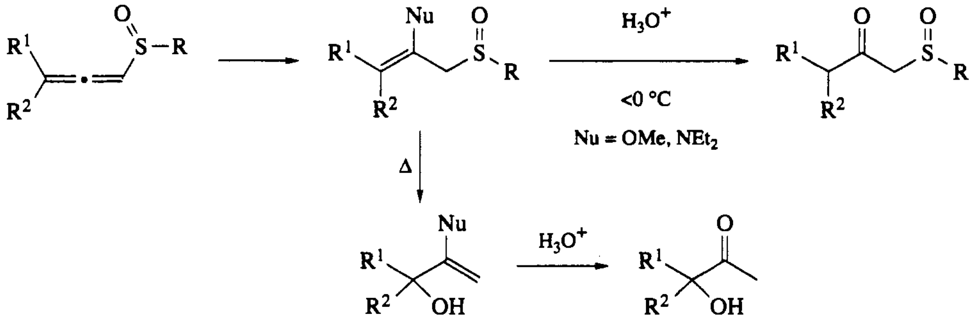


(**13**) (**14**) (**15**) (**16**)

Scheme 19

Besides the low optical yields of the reaction the known hazard of racemization and (*E*)/(*Z*)-isomerization of optically active allylic sulfoxides, which can only be avoided below 0 °C, limits the synthetic utility of such a process.

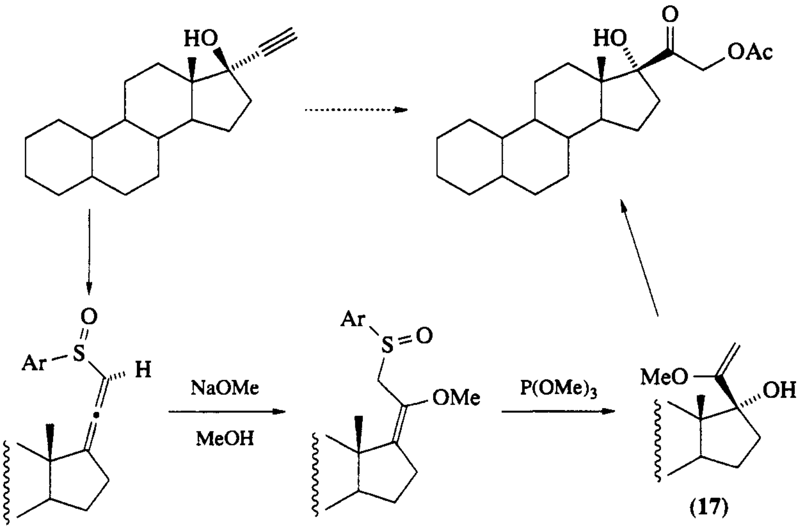
Clean conjugate addition of appropriate nucleophiles to allenic sulfoxides has been used to produce allylic sulfoxide systems. Horner has described the formation of functionalized allylic alcohols when adding nucleophiles like amines, alcohols or thiols to allenic sulfoxides in excess.[71] If the addition is performed with equimolar amounts at lower temperature, so that the 2,3-sigmatropic rearrangement is avoided, the intermediate addition products (enamines or enol ethers) can be hydrolyzed to the synthetically valuable β-keto sulfoxides (Scheme 20).[72]



Scheme 20

The overall process, considering that the propargylic alcohols are generated from carbonyl compounds, constitutes a reductive nucleophilic substitution with additional introduction of the synthetically valuable sulfoxide functionality.

An impressive application, where the stereochemical consequences of unsaturated sulfoxide–sulfenate rearrangements are convincingly utilized, provides an efficient and stereoselective method for the corticosteroid side chain formation, starting from 17-keto steroids (Scheme 21).[73]

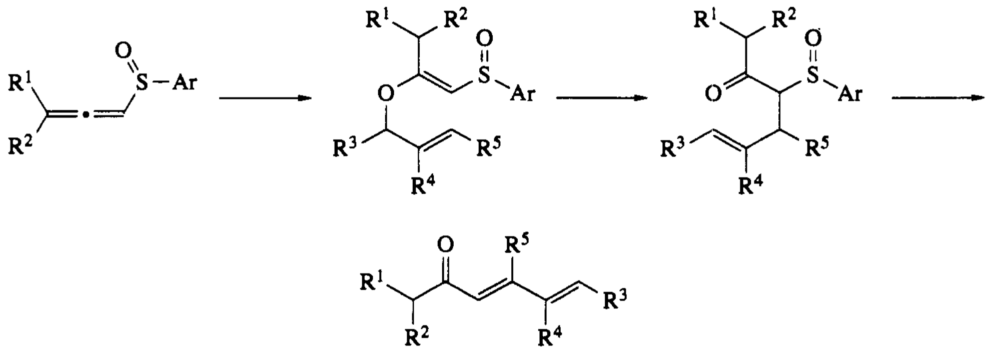


(17)

Scheme 21

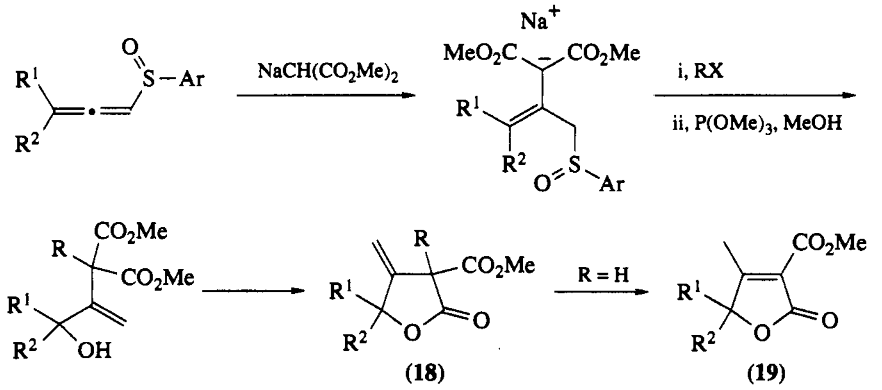
Under the influence of the angular methyl group the addition of acetylene occurs from the α-side, giving the opposite configuration at C-17 to that required for the corticosteroids, but the rearrangement of the diastereomeric methanol adducts of the derived allenic sulfoxide is also forced to proceed at the α-side, leading finally to the correct configuration. The elaboration of the required side chain in (17) can easily be accomplished.

The addition of allylic alcohols to electrophilic allenes leads to another interesting possibility for their use in synthesis. The addition products respresent Claisen systems and can be forced to rearrange. More valuable applications of this principle will be discussed in Section 4.5.3.1.3. In the case of allenic sulfoxides the rearrangement is followed by elimination of sulfinic acid, giving easy access to conjugated dienones (Scheme 22).[74]



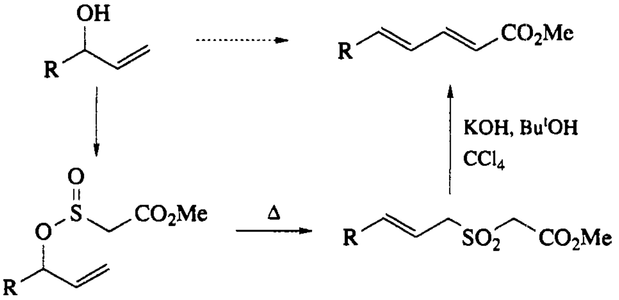
Scheme 22

When adding malonic ester anion to an allenic sulfoxide, rearrangement of the derived addition product leads to an allylic alcohol which cyclizes to (**18**) and isomerizes to the isolated product (**19**). If one alkylates the intermediate carbanion one gets an entry to a β-methylenelactone system (**18**; Scheme 23).[75]



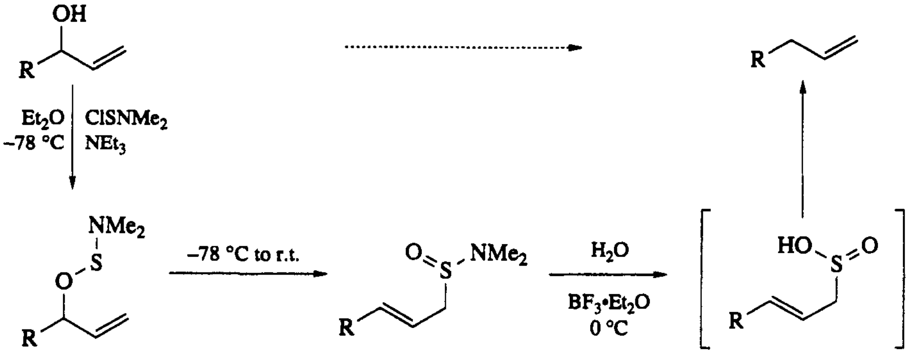
Scheme 23

In all the examples discussed, unsaturated aryl-substituted sulfur compounds were used. But one is not restricted to this substitution if synthetic purposes require otherwise. One example is depicted in Scheme 24. Combining the rearrangement in turn with a Ramberg–Bäcklund extrusion of SO_2 leads to a relatively facile synthesis of conjugated dienoic acids.[76]



Scheme 24

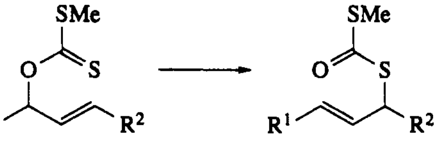
Unsaturated sulfinamides can also be obtained by a 2,3-sigmatropic rearrangement, again very easily affording the product with (*E*)-double bond geometry in most cases (Scheme 25).[77]



Scheme 25

When the allylic sulfinamides are hydrolyzed under special conditions (classical methods like alkali- or acid-catalyzed hydrolysis did not work properly) the obtained allylic sulfinic acids are unstable and will fragment smoothly again with allylic rearrangement into terminal alkenes.

There is one other synthetically interesting O → S transformation based on a hetero-Cope reaction, which is worth mentioning here. This rearrangement (equation 18) is so easy that on attempting to prepare allylic xanthates (**20**) one isolates instead the rearranged (*E*)-thiocarbonates (**21**),[78] which can be used in synthesis, *e.g.* as protected thiol derivatives[79] or as precursors for allylic radicals.[80]



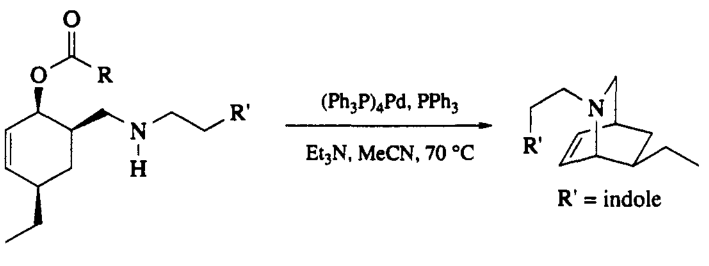
(20) **(21)**

(18)

4.5.2.4 Oxygen–Nitrogen Transpositions

A direct *N*-substitution of an allylic substrate with an oxygen leaving group (equation 19) lacks generality and the problem of regio- and stereo-selectivity also arises in Pd-catalyzed reactions. Such a substitution *via* π-allyl–palladium intermediates may be useful in cases where the steric situation allows only one mode of attack, as exemplified in the key step of an ibegamine synthesis by Trost, where the intramolecular reaction leads to clean allylic *syn* substitution (equation 20).[81]

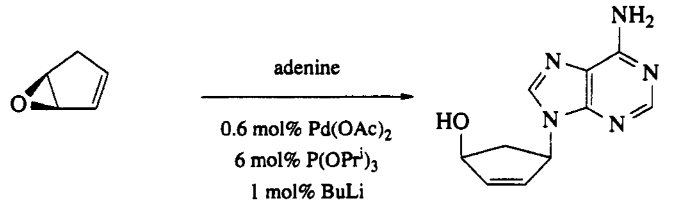
(19)



(20)

An intermolecular reaction, again with overall *syn* S_N' substitution, was successfully applied in a synthesis of the carbocyclic nucleoside analog aristeromycin to introduce the nitrogen base stereoselectively (equation 21),[82] although with heteronucleophiles, unlike the case of carbon nucleophiles, a lower propensity for attack distal to oxygen to give the 1,4-product with vinyloxiranes exists.

Recently even asymmetric allylic substitution reactions using optically active Pd catalysts have become known.[83,84] An example of an intramolecular allylic substitution with nitrogen is seen in equation (22).



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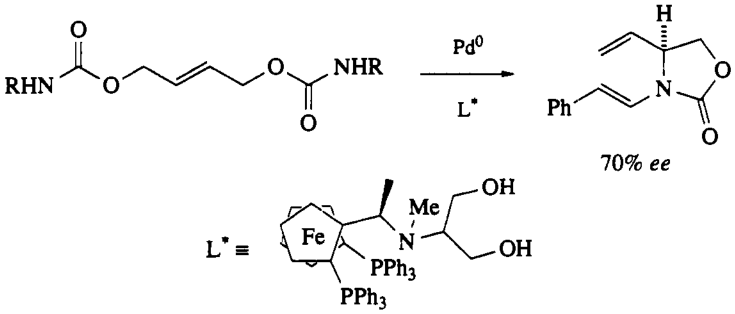
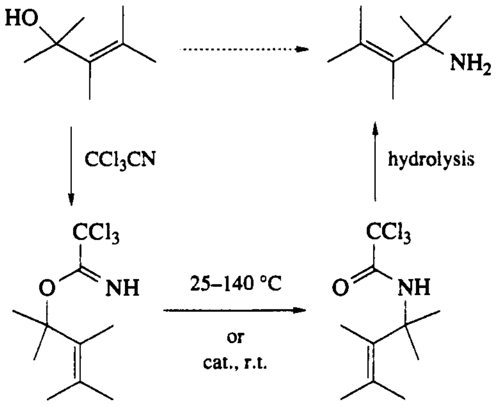


(22)

The most reliable methods for allylic O → N conversions are based on intramolecular rearrangements. For example, the rearrangements of allylic *N*-phenylimidates have long been known, but the required temperature of 200 °C limits synthetic applications. With trichloromethylacetimidates, which are easily prepared and rearrange at much lower temperatures, Overman has introduced a very useful method for the allylic transformation of a hydroxy group into an amino function (Scheme 26),[85] leading to a general synthesis of allylic amines with the stereochemical features expected from a 3,3-sigmatropic rearrangement.[86,87] Catalysis with Pd^{II} or Hg^{II} salts has proven to be effective in some cases.[88]



Scheme 26

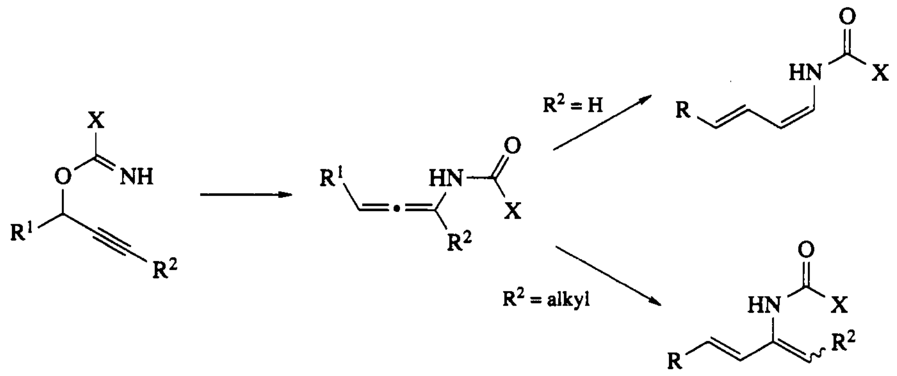
Thermal rearrangement of imidate esters of propargylic alcohols leads *via* *N*-acylaminoallenes to *N*-acyl-1-amino-1,3-dienes or *N*-acyl-2-amino-1,3-dienes, depending upon the substitution of the propargylic alcohol (Scheme 27).[85]

It is interesting to note that in the case of *N*-acyl-1-amino-1,3-dienes the (1*Z*,3*E*)-isomer is probably formed because a 1,5-sigmatropic hydrogen migration is involved in the tautomerization. If X is not the CCl_3 group but a potential leaving group such as the pyrrolidine function, the intermediate diene will react further by elimination of HX to a (1*Z*,3*E*)-diene isocyanate (**22**), which undergoes electrocyclic ring closure to yield ultimately a substituted 2-pyridone system (Scheme 28).

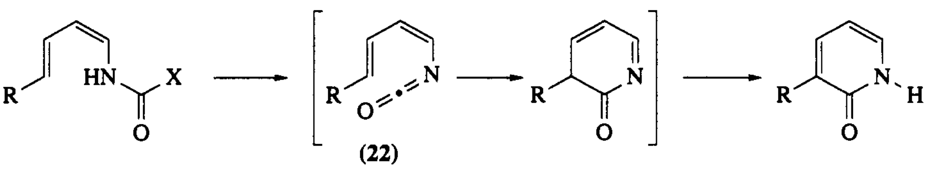
With another hetero-Cope reaction one is able to introduce an aryl-substituted amino group (Scheme 29).[89]

Not a 3,3-sigmatropic but an S_Ni-like reaction is involved in an oxygen–nitrogen transposition which allows the introduction of a secondary amine function (Scheme 30).[90]

There are not many examples of the direct transformation of an allylic amino to a rearranged oxygen functionality. One example is found in the Meisenheimer rearrangement of amine oxides, which occurs with almost complete chirality transfer, as seen in equation (23).[91]

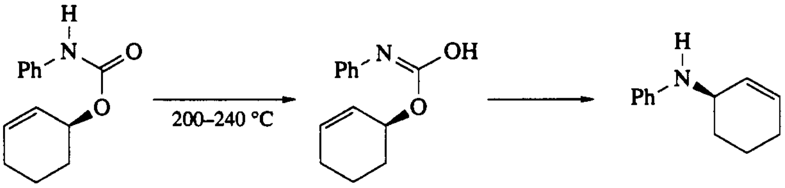


Scheme 27

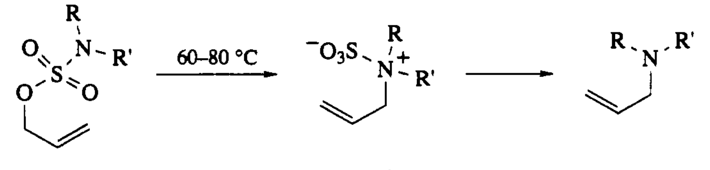


(22)

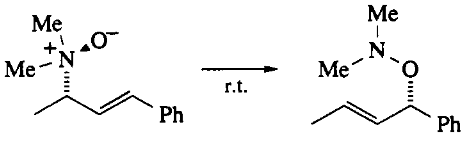
Scheme 28



Scheme 29



Scheme 30



(23)

4.5.2.5 Oxygen–Phosphorus Transpositions

In an analogous reaction to that of sulfenates, unsaturated esters of $\mathrm{P^{III}}$ compounds rearrange easily (equation 24) to corresponding allyl- and allenyl-phosphoryl compounds because the strong heteroatom–oxygen double bond is formed (Scheme 31).[92]

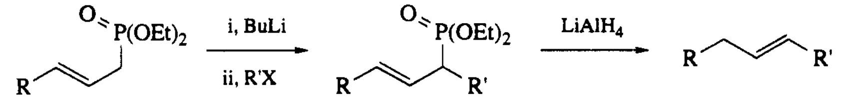
This reaction presents a very efficient way of preparing many kinds of unsaturated phosphoryl systems, *e.g.* phosphonic acid chlorides (X = Cl) phosphonates (X = OR) or phosphine oxides (X = alkyl, aryl), tolerating almost all types of substitution at the carbon chain.[92,93] The chemistry of allylic phospho-

(24)

Scheme 31

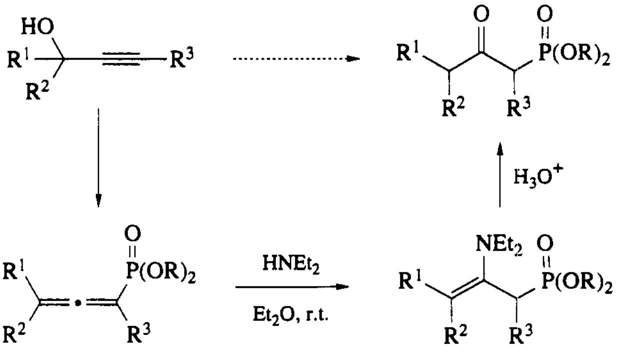
ryl compounds is not as rich as that of allylic sulfoxides, as in contrast to an S=O group the P=O group is difficult to remove from an organic compound except by an alkenation reaction[94] and in some cases, from an allylic position, by reduction with $LiAlH_4$ accompanied by an allylic shift.[95]

This reactivity has been used preparatively in combination with the known tendency of allylic phosphonates to be alkylated in the α-position (Scheme 32).[95]



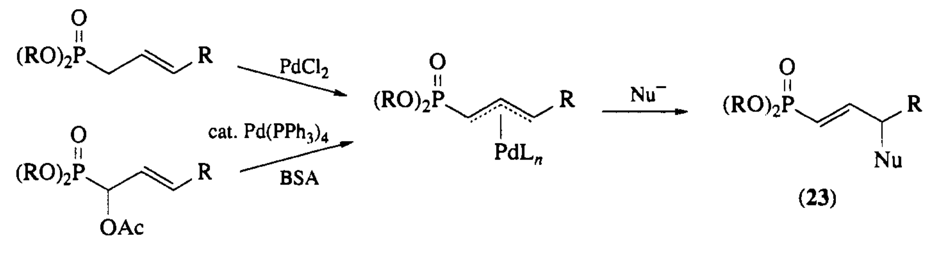
Scheme 32

Interestingly, an alkenation reaction can even be brought about with an allenic phosphonate leading to cumulatrienes.[96] A very useful application of allenic phosphoryl compounds is due to their electrophilic properties, which allow easy addition of nucleophiles like alcohols or amines. The adducts can be hydrolyzed to β-keto phosphonates. The reaction sequence starting from propargylic alcohols can even be performed as a 'one-pot reaction', thus constituting a convenient and very general synthetic route to this important class of organophosphorus compounds (Scheme 33).[97,98]



Scheme 33

Recently an allylic phosphonate has been shown to react as an allylic phosphonate cation by transformation to a π-allyl–palladium complex, susceptible to attack by nucleophiles such as stabilized carbanions (Scheme 34).[99]



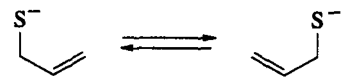
(23)

Scheme 34

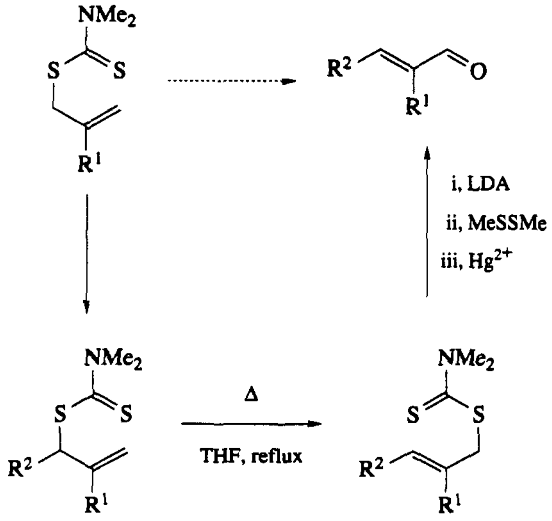
Starting from the readily available α-acetoxyallyl phosphonates, reaction to the γ-substituted systems (**23**) takes place under Pd catalysis.

4.5.2.6 Sulfur–Sulfur Transpositions

The only synthetic application of an allylic S → S transposition (equation 25) seems to be in the synthesis of (*E*)-α,β-unsaturated aldehydes *via* a 3,3-sigmatropic rearrangement of allylic dithiocarbamates (Scheme 35).[100]



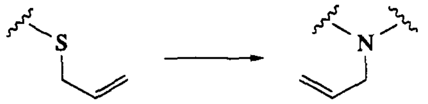
(25)



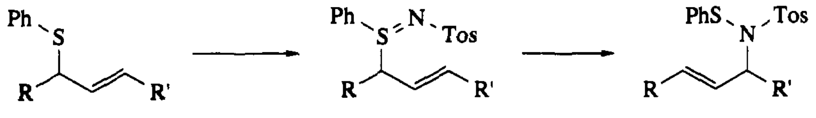
Scheme 35

4.5.2.7 Sulfur–Nitrogen Transpositions

Allylic sulfides can be transformed by a 2,3-sigmatropic rearrangement into allylic nitrogen derivatives (equation 26) *via* a sulfimide intermediate (Scheme 36).[101,102]



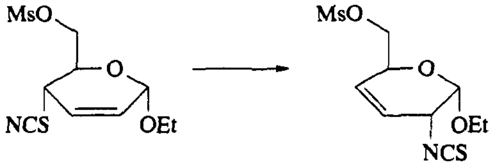
(26)



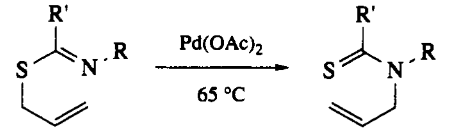
Scheme 36

The reaction is analogous to the allyl sulfenate–allyl sulfoxide rearrangement and is also known in the selenium case.[103] As sulfur and selenium functionalities are common activating groups in organic synthesis, this highly stereocontrolled transformation can sometimes be very useful.

3,3-Sigmatropic rearrangements have also found use in allylic S → N transposition. The rearrangement of allyl thiocyanates to allyl isothiocyanates (equation 27)[104] belongs to this class as does the rearrangement of *S*-allyl thioimidates (equation 28).[105]



(27)

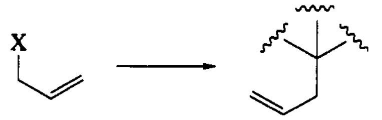


(28)

In the latter case the S → N allyl group migration is only efficient when Pd^{II} catalysis is employed, otherwise, at much higher temperatures, a double bond isomerization occurs first and is then followed by an S → C allyl shift by means of a thio-Claisen rearrangement. As the appropriate *S*-allyl thioimidates are easily prepared by alkylation of thioamides with allyl halides, the overall process is an S_N' substitution of an allylic halide by an amine, a reaction which is difficult to achieve directly.

4.5.3 1,3-HETEROATOM TO CARBON TRANSPOSITIONS

1,3-Heteroatom to carbon transposition is represented in equation (29).



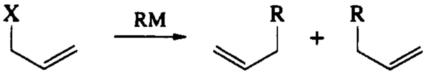
(29)

4.5.3.1 C—C Bond Formation by Nucleophilic Attack on the Allylic System

When there is the intention of effecting an allylic rearrangement in the C—C bond formation step, it is obvious that intramolecular processes are principally better than intermolecular ones as there always exists the competition of S_N *versus* S_N' reactions with intermolecular processes, although there have been a number of improvements regarding this problem in recent years. Because of the huge amount of literature only selected examples, which demonstrate the general trends, can be presented here.

4.5.3.1.1 Allylic substitution with carbon nucleophiles

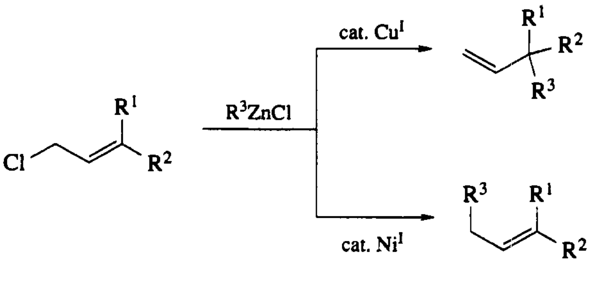
Allylation of an organometallic reagent is an important carbon–carbon bond forming reaction (equation 30).



(30)

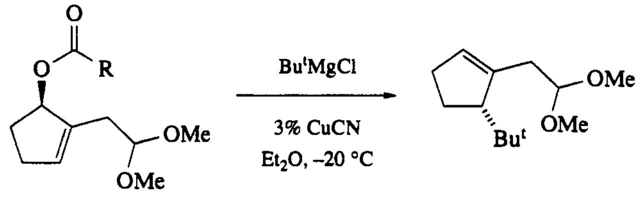
Besides ordinary halides and sulfonic acid esters, the development of transition metal catalyzed processes has enabled allylic alcohols, acetates, carbonates, vinyl epoxides and vinyllactones also to be successfully employed as allylic substrates.

With alkyl-lithium and -magnesium compounds (the most common organometallic reagents) the regioselectivity of the reaction with an allylic electrophile is the primary problem. Normally a mixture of S_N and S_N' products is obtained. The readily available organozinc reagents (prepared *in situ* from RLi and $ZnCl_2$ in THF) undergo highly regio- and chemo-selective allylation reactions under mild conditions, where the regioselection can be completely changed from S_N to S_N' simply by changing the catalyst from a nickel-based to a copper-based one (Scheme 37).[106]

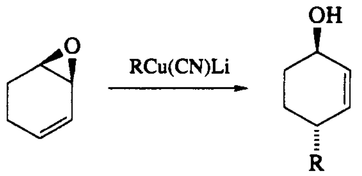


Scheme 37

The observed regioselectivity (92–98%) compares favorably with that of the more elaborate stoichiometric reagent RCu·BF$_3$, which was used previously,[107] even for the reaction in which a sterically congested quaternary center is created. Generally Cu organic compounds are known to prefer γ-attack on allylic substrates, especially with allylic acetates and vinyloxiranes, in most cases with *anti* stereoselectivity.[108] Two examples are shown in equations (31)[109] and (32).[8]



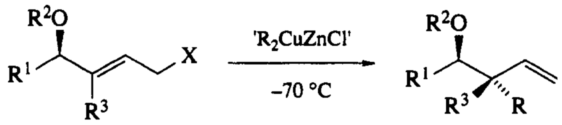
(31)



(32)

The S_N2' addition of organocopper reagents to vinyloxiranes is now a well-established synthetic route to allylic alcohols, often giving remarkable stereocontrol.[8]

Recently an example of a virtually complete diastereofacial selectivity in the S_N' allylation of organocopper/zinc reagents was reported.[110] The best results were achieved with a new 'zinc cuprate' reagent, the structure of which has not yet been elucidated (equation 33). This reagent was developed as a catalytic system for zinc alkyl reagents.



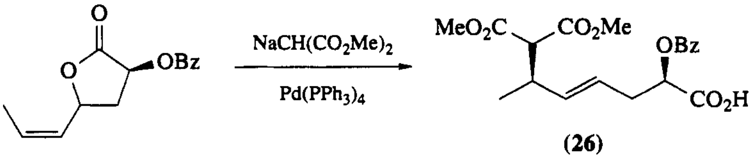
(24)

(33)

A single diastereomer was formed by *anti* attack on (**24**; equation 33) with 98% regioselectivity, regardless of the nature of the substituent R^1 on the stereogenic center, the R^2-protecting group on oxygen or the nature of the leaving group. The reaction of the *cis* isomers of (**24**) was also *anti* selective.

Another fascinating development in the field of allylic alkylation is the Pd^0-catalyzed nucleophilic substitution of allylic compounds.[10,11] Allylic acetates are by far the most often used allylic substrates, but many others are possible, and vinyloxiranes and vinyllactones especially offer many useful synthetic opportunities. Stabilized carbanions are mainly employed as nucleophiles for allylic alkylations, although other nucleophiles, *e.g.* simple zinc or boron enolates can be employed.[111] As a consequence of the reaction mechanism, with the formation of a π-allyl intermediate, the regioselectivity is not determined by the position of the leaving group but by other factors, mainly steric ones. The stereoselectivity, however, is normally very high, resulting usually in retention of configuration due to a double inversion during the reaction. Therefore a high degree of 1,3-chirality transfer may occur if the substitution reaction proceeds with double bond shift.

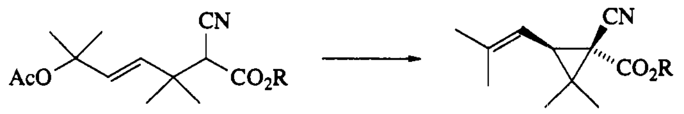
The optically active allylic lactone (**25**; equation 34), for example, reacted with sodium malonate in the presence of Pd(PPh$_3$)$_4$ to give stereospecifically the acid (**26**), which was utilized for the generation of the side chain of vitamin K.[112]



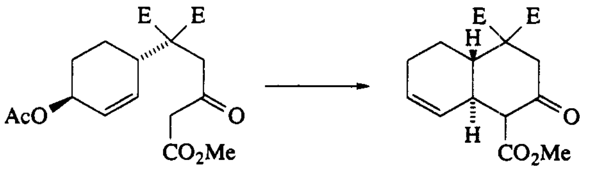
(25) **(26)**

(34)

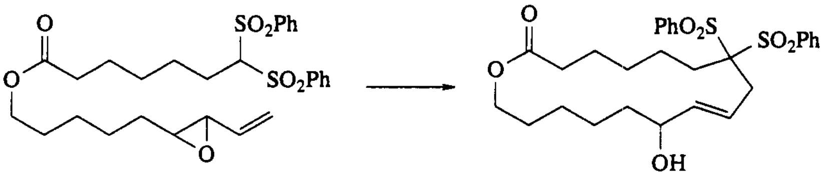
However, Pd-catalyzed allylic alkylations have found more applications in intra- rather than in intermolecular substitution reactions. Many of these alkylations are highly regio- and stereo-selective and occur with allylic rearrangement and are applied to construct various carbo- and hetero-cyclic systems.[113,114] Some illustrative examples are shown in equations (35)–(37).[115–118]



(35)

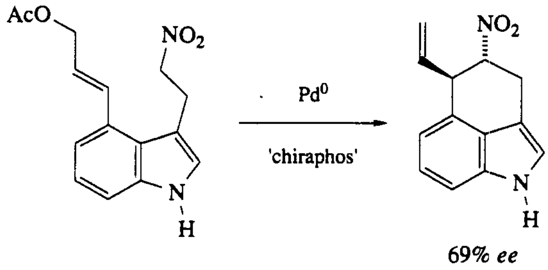


(36)



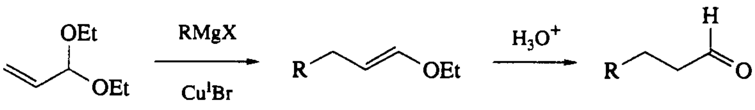
(37)

A most spectacular stereochemical aspect of the Pd-catalyzed reactions is the possibility of creating new stereogenic centers in the allylic substrate or in the nucleophile when chiral phosphine–palladium complexes are employed. Although the full potential of these reactions has still to be exploited, the results thus far are promising and the first successful applications have become known (*e.g.* equation 38).[119]



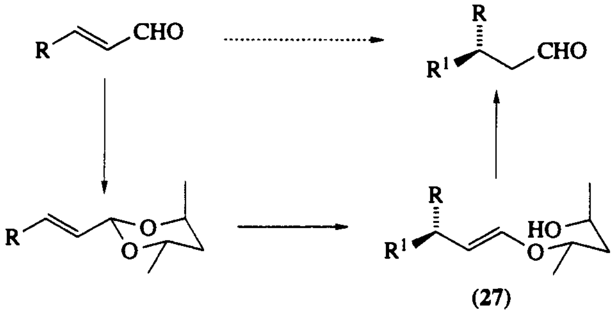
(38)

Yet another development which is worth mentioning in this context is the S_N' substitution of acetals of unsaturated carbonyl compounds. The phenomenon that the reaction of an allylic acetal with a Grignard reagent in the presence of CuBr may occur as a vinylogous substitution with double bond shift has been long known.[120] The reaction can be utilized in an efficient synthesis of 3-substituted propionaldehydes using the acrolein acetal as a homoenolate cation equivalent (Scheme 38).[121]



Scheme 38

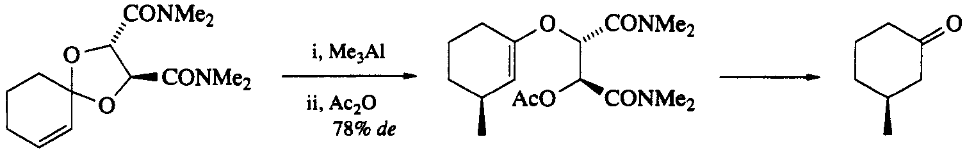
This type of reaction attracted broad interest when it was discovered that high regioselectivity can also be effected with organoaluminum compounds and other nucleophiles in the presence of Lewis acids and that by employing chiral cyclic acetals (from optically active 1,2- or 1,3-diols) diastereoselective transformations can be realized.[122,123] Such reactions are synthetically very valuable when considering that the overall process represents an enantioselective Michael addition, where the chiral auxiliary can be recycled (Scheme 39).[124]



(27)

Scheme 39

The stereochemical outcome of the reaction is in most cases consistent with an *anti* S_N2' substitution in a transoid transition, leading to the (*E*)-enol ethers (**27**). Whereas acetals of α,β-unsaturated aldehydes react regioselectively only with 'soft' alkenyl- and aryl-copper reagents, the reaction of α,β-unsaturated ketals always affords the S_N'-product, also with aliphatic copper compounds. With cyclic enones, like cyclohexenone ketals, however, the diastereoselectivity is poor (only up to 26% *de*). In contrast organoaluminum compounds seem to give generally better regio- and diastereo-selectivity. In this case another advantage is that inexpensive tartaric acid derived acetals can be employed successfully, affording diastereoselectivities of up to 78%, even with a cyclohexenone system (Scheme 40).[125]

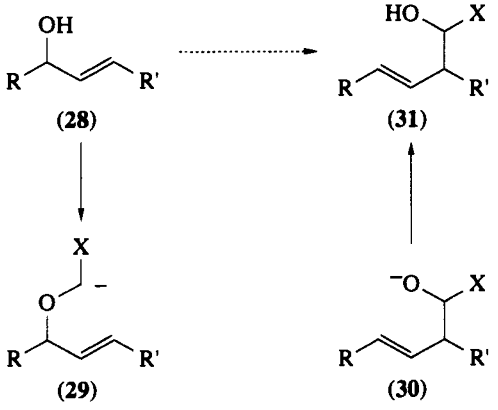


Scheme 40

Even though the regio- and diastereo-selectivities of these reactions are not yet satisfactory in many cases, the potential of this type of conjugate addition is obvious.[126]

4.5.3.1.2 Transformation of allyl alcohols to rearranged homoallyl alcohols or β,γ-unsaturated carbonyl compounds

A synthetically very useful method for regiospecific carbon–carbon bond formation by an allylic transposition is provided by the 2,3-Wittig rearrangement of α-allyloxy carbanions (**29**; Scheme 41).[29,30]

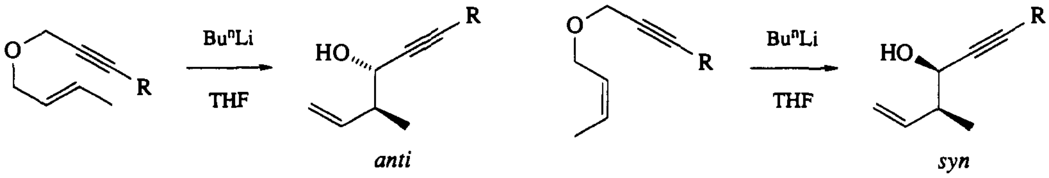


(28) (31) (29) (30)

Scheme 41

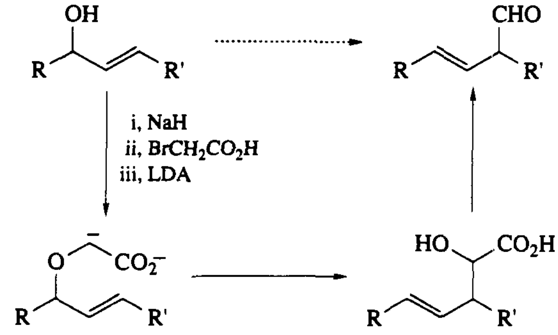
Since the appropriate allylic ethers, as starting material, are generated normally from allyl alcohols, the 2,3-Wittig rearrangement permits easy construction of homoallyl alcohol systems (**31**) from allyl alcohols (**28**). Due to its sigmatropic nature the rearrangement possesses several stereochemical features which make it an increasingly important tool for the stereorational synthesis of highly functionalized acyclic and macrocyclic systems: (i) generation of specific alkene geometries with preferential formation of an (*E*)-double bond; (ii) diastereoselective creation of vicinal chiral centers; and (iii) potential 1,3- and 1,4-transfer of chirality.

The required allyloxy carbanion may be generated either by direct deprotonation with a strong base, by transmetalation of Sn-substituted systems[127] or, most recently, by reductive lithiation.[128] In the former case substituents X, which facilitate carbanion formation, are helpful for a clean reaction by establishing regioselective deprotonation at temperatures low enough to avoid competing 1,2-shifts. Typical synthetically useful substituents include phenyl, vinyl, alkynic or alkoxycarbonyl groups. The propargylic variants possess particular advantages: one gets an unusually high level of either diastereoselection by proper choice of the geometry of the allyl system and the rearrangement product contains unique multifunctionality for further synthetic transformations (Scheme 42).[129]



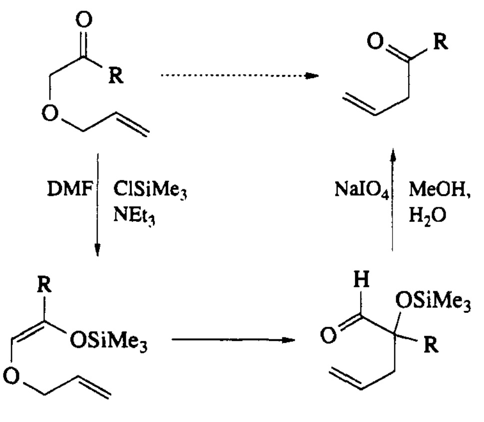
Scheme 42

In the case of $X = CO_2H$ (Scheme 41) the product of the rearrangement is an unsaturated α-hydroxycarboxylic acid which may be converted to an aldehyde by oxidation, thus allowing a stereoselective synthesis of β,γ-unsaturated aldehydes (Scheme 43).[130]



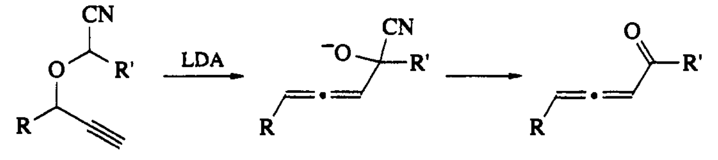
Scheme 43

With a ketone function as an activating group ($X = RC{=}O$) a Wittig rearrangement is induced on silylation with TMS-Cl and triethylamine in DMF; interestingly no competing Claisen rearrangement is observed.[131] The rearranged product can be cleaved to a β,γ-unsaturated ketone (Scheme 44).



Scheme 44

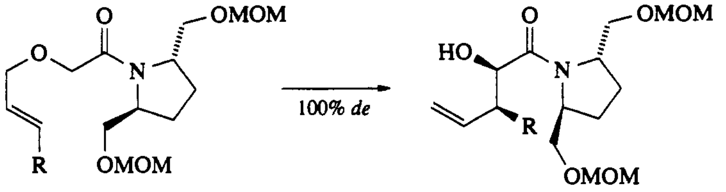
If X in Scheme 41 represents a cyanide group (X = CN) the rearrangement of the anion leads to a cyanohydrin anion as the product, which can yield a carbonyl function directly.[132] The reaction is not only known for allylic ethers but also for propargylic ethers, giving access to allenic carbonyl compounds in the latter case (equation 39).[133]



(39)

With a phenylsulfonyl group as X (Scheme 41) the intermediate, after rearrangement, will decompose directly to an aldehyde function, which reacts with excess alkyllithium to form an unsaturated alcohol.[134] The often efficient transfer of chirality from C-1 of an optically active allylic alcohol to the newly created stereogenic centers at C-3 and/or C-4 is another valuable aspect of the 2,3-Wittig rearrangement which has already found extensive use in natural product synthesis.[30]

With regard to asymmetric synthesis, the possibility that a stereogenic center outside the sigmatropic framework can direct the stereochemical outcome of the electrocyclic process has been intensively exploited recently.[30] One method for asymmetric induction has been realized with X representing a chiral carboxylic acid derivative. From the various chiral auxiliaries studied, the C_2 symmetrical amide (**32**) seems to be the most effective,[135] giving (*via* its zirconium enolate) essentially 100% diastereoselectivity and *erythro* selection, thus permitting ready access to optically active α-hydroxycarboxylic acids (equation 40).

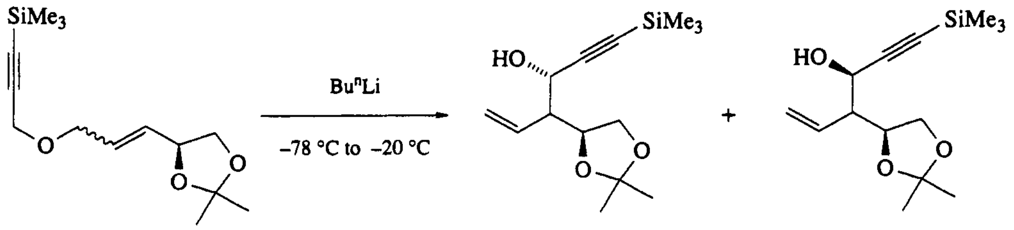


(**32**)

(40)

Another system which affords rearrangement products of high optical purity uses the diastereofacial selection of an 8-phenylmenthol-derived ester.[136]

Interestingly an asymmetric induction can also be caused by an external stereocenter in the allylic moiety of the anionic Wittig system, as has been demonstrated recently (Scheme 45).[137]



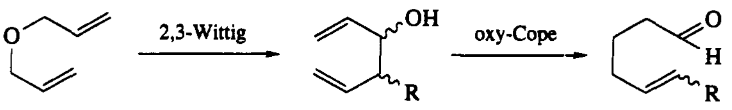
(*Z*) 0 : 100

(*E*) 83 : 17

Scheme 45

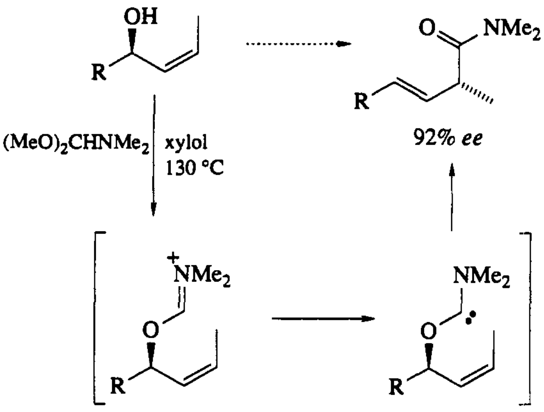
Lastly it should be mentioned that a 2,3-Wittig rearrangement can be coupled with other sigmatropic processes in synthetically valuable 'tandem' sequences. An illustrative example is a 'tandem' 2,3-Wittig–oxy-Cope rearrangement, which provides a versatile route to δ,ε-unsaturated carbonyl compounds (Scheme 46).[138]

It is remarkable that the (*E*)/(*Z*)-stereochemistry of the oxy-Cope product is not dependent on the *erythro*/*threo* ratio of the 2,3-Wittig rearrangement but on the specific rearrangement procedures used: thermal rearrangement exhibits higher (*E*)-selectivity (92–95%) than the anionic oxy-Cope and siloxy-Cope variants.



Scheme 46

A reaction which transforms allylic alcohols to homologous β,γ-unsaturated amides by means of a 2,3-sigmatropic process was first described by Büchi.[33] When an allyl alcohol is heated with *N,N*-dimethylformamide acetal, a rearrangement occurs apparently involving a nucleophilic carbene as an intermediate, leading to a product with 95–100% (*E*)-geometry of the double bond (Scheme 47).



Scheme 47

The Büchi rearrangement has found synthetic use, *e.g.* for the synthesis of chiral isoprenoid building blocks, as it also allows effective 1,3-transfer of chirality.[139]

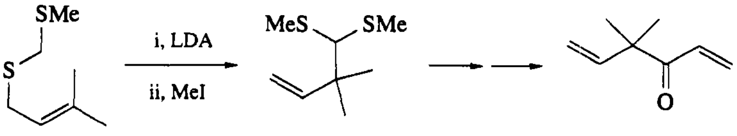
4.5.3.1.3 Transformation of allyl hetero- to homoallyl hetero-systems

One possibility of transforming allyl hetero- to homoallyl hetero-systems is by 2,3-sigmatropic rearrangements analogous to the 2,3-Wittig reaction, namely its *thio* and *aza* counterparts, where an allyl group migrates from a sulfur or nitrogen instead of an oxygen atom to an adjacent carbanionic center (Scheme 48).[30] In these cases the corresponding nitrogen or sulfur ylides are also able to rearrange in the same manner. In all cases an electron-withdrawing group Y is normally present to facilitate and direct carbanion formation.

X = S, NR; Y = electron-withdrawing group

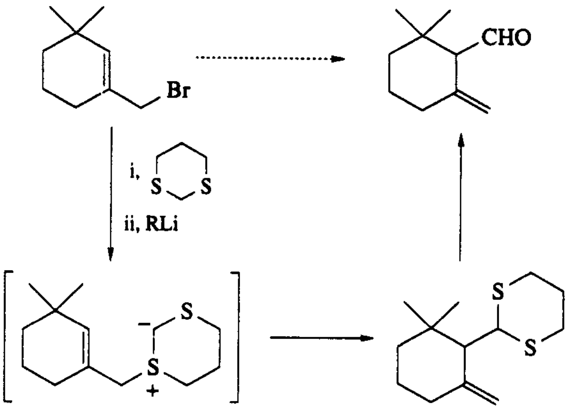
Scheme 48

Whereas the thio-2,3-Wittig reaction is well recognized and used, particularly in terpene synthesis (*e.g.* Scheme 49),[140] the amino counterpart is less studied.

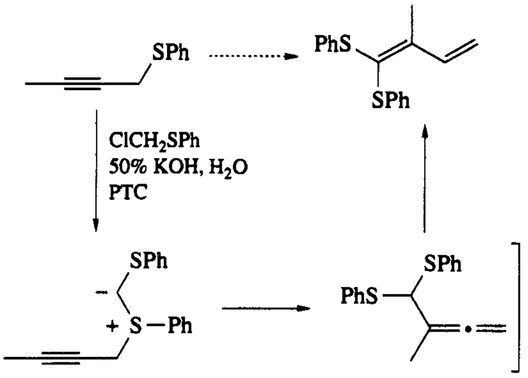


Scheme 49

The variants with allylic ammonium[31] and sulfonium ylides[141] are well known and correspond to the Sommelet–Hauser and the Stevens rearrangement.[31] Two representative examples are shown in Schemes 50 and 51.

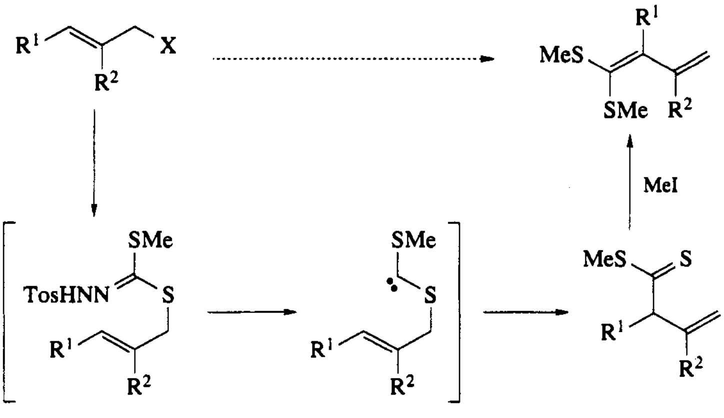


Scheme 50



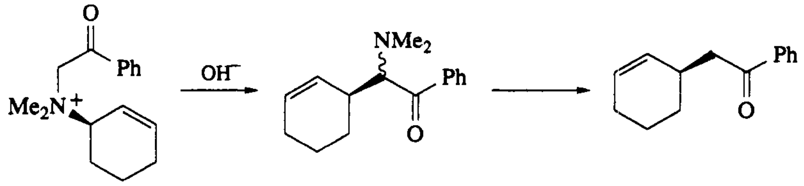
Scheme 51

In Scheme 50 it can be seen that the reaction can be used for the conversion of an allylic halide to an allylically shifted formyl group.[142] A 1,1-dithio-1,3-butadiene system, synthesized *via* rearrangement of the ylide,[143] is also accessible by a different kind of 2,3-sigmatropic rearrangement involving a nucleophilic carbene intermediate (Scheme 52).[144] The same type of rearrangement has found synthetic application in a bakkenolid A synthesis.[145]



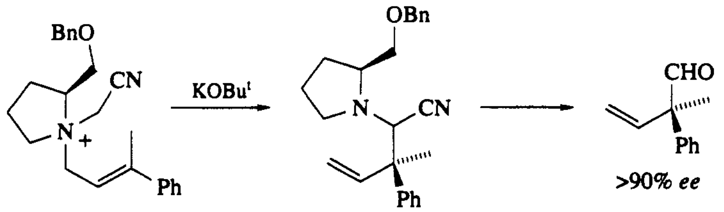
Scheme 52

With the aid of a nitrogen ylide rearrangement, it is possible to transform an allylic secondary amine to an unsaturated carbonyl system, in certain circumstances with transfer of chirality (Scheme 53).[27]



Scheme 53

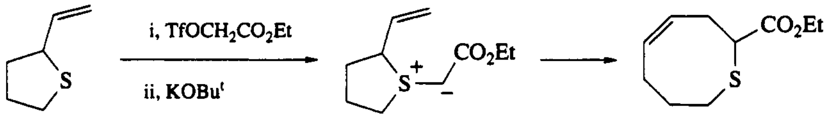
Especially interesting is the possibility for asymmetric synthesis by employing amino acid derived ylide systems (*e.g.* 33; Scheme 54), which allows the synthesis of optically active β,γ-unsaturated aldehydes.[146]



(33)

Scheme 54

2,3-Sigmatropic rearrangements of cyclic sulfonium and ammonium ylides have been extensively used in ring contraction and ring enlargement methods.[147] An example is shown in Scheme 55.



Scheme 55

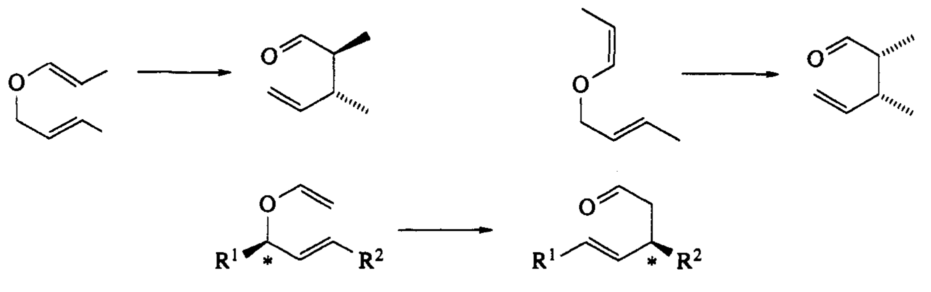
4.5.3.1.4 Transformation of allyl alcohols and allylamines to γ,δ-unsaturated carbonyl compounds

One of the most versatile and useful allylic rearrangements is the aliphatic Claisen rearrangement with its different variants, which allows an easy, very general access to γ,δ-unsaturated carbonyl compounds (Scheme 56).[35,36]

$X = H, OR, NR_2, O^-, CH_2^-$

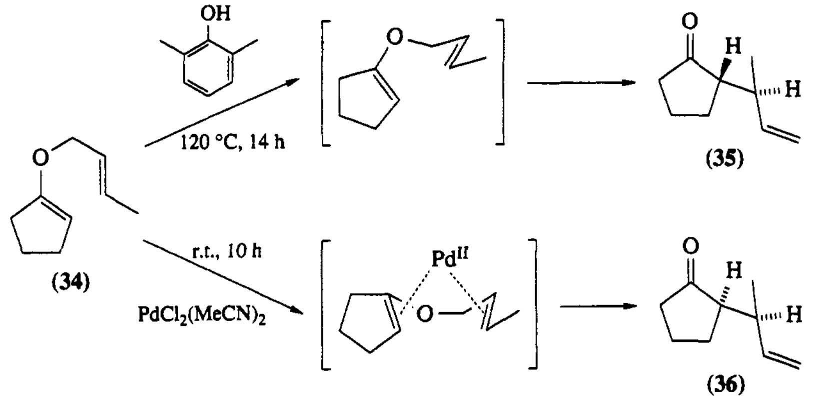
Scheme 56

This 3,3-sigmatropic rearrangement's extraordinary role in synthesis results from several characteristic features: (i) a wide range of carbonyl derivatives is available with variation of X in Scheme 56 (aldehydes, ketones, acids, esters, lactones, thioesters and amides); (ii) more functionalized derivatives may be employed; and (iii) high stereoselectivity in the formation of double bonds and new stereocenters is usually observed. Therefore the Claisen rearrangement has found extensive use particularly for the stereocontrolled construction of acyclic systems.[148] Of special significance is the stereoselective generation of vicinal centers from terminal monosubstituted double bonds, depending upon their configuration, and the possibility of transferring chirality along the allyl system (Scheme 57).



Scheme 57

It is now well established that the rearrangement proceeds more easily the more electron-donating the substituent X is. With an anionic X-group the reaction may take place below room temperature. In the case of X = O the ester enolate Claisen variant is represented, with X = C it is the 'carbanion-accelerated' version of the Claisen rearrangement that takes place. Another possibility to moderate the rather drastic conditions for the classical type of the Claisen rearrangement, is to catalyze the reaction,[37] a development which bears high potential, particularly with regard to control of stereochemistry.[149–151] Nakai has described the diastereocontrolled rearrangement of cyclic enol ethers, which is dependent upon the catalyst employed.[151] Starting from (**34**) in the presence of 2,6-dimethylphenol the *anti* product (**35**; Scheme 58) results, which is also the main product in the thermal reaction without a catalyst; under catalysis with a Pd complex at room temperature the *syn* product (**36**) is formed. This striking result is explained by a change in the transition state comformation: in the phenol-catalyzed reaction a usual chair conformation is involved, whereas a complexation of the 1,5-diene with the Pd catalyst leads to a boat transition state (Scheme 58).

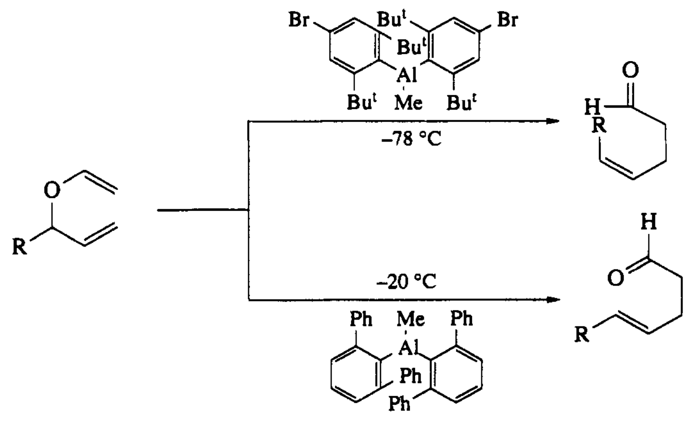


Scheme 58

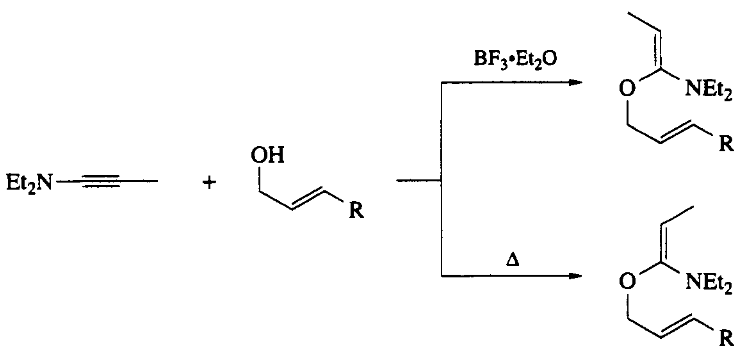
Another unprecedented stereochemical control in a Claisen rearrangement was reported recently by Yamamoto using organoaluminum reagents (Scheme 59).[152] Sometimes (*e.g.* with R = $Cu_2CH{=}CH{-}C_5H_{11}$) complete reversal of double bond geometry could be achieved simply by modifying the bulky aluminum catalyst.

To exploit the whole capacity of the Claisen rearrangement, appropriate methods for the preparation of the allyl vinyl ethers starting from allyl alcohols are necessary. The classical approach involves vinylation with simple vinyl ethers or acetals. Unfortunately these methods fail with more complex systems and do not allow, except in the case of cyclic enol ethers, control of the stereochemistry of the substituted enol ether double bond. Until recently it was only possible to generate such substituted systems with appreciable stereocontrol *via* ketene *N,O*-acetals.[153,154] Their preparation by addition of allyl alcohols to substituted ynamines can lead to adducts of either (*E*)- or (Z)-geometry, depending upon the conditions used (Scheme 60).

The principally practicable route to allyl vinyl ethers by alkenation of allyl formates, has not yet been exploited in this context.[155] In another approach, the nucleophilic addition of allylic alcohols to alkynic esters, one observes the exclusive formation of *trans*-enol ethers;[156,157] the stereochemical information is lost, however, after the rearrangement, due to enolization of the formed formylacetic acid derivatives. On the other hand the nucleophilic addition of allyl alcohols to acceptor-substituted allenes like allenic sulfones or phosphonates offers a novel route with fascinating potential.[158–160] Such systems that are readily

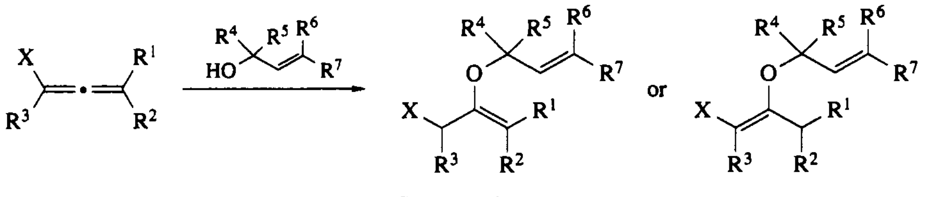


Scheme 59



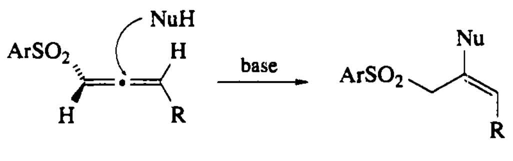
Scheme 60

accessible *via* a 2,3-sigmatropic rearrangement, allow the easy synthesis of α,β- or β,γ-unsaturated adducts, depending upon the substitution pattern of the allene and the reaction conditions (Scheme 61).



Scheme 61

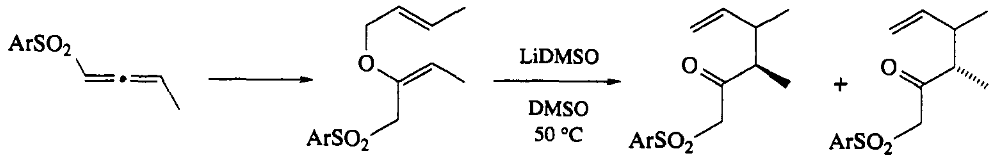
In an extensive study Denmark could elaborate conditions to control the formation of the conjugated or the (in most cases thermodynamically more stable) deconjugated system.[159] With terminal monofunctionalized allenic sulfones one observes predominantly attack from the sterically less hindered face of the allene leading to *trans* adducts (equation 41).



(41)

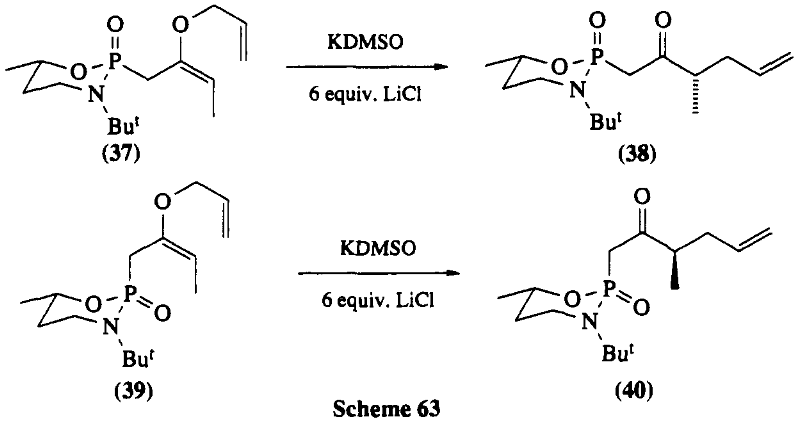
The adducts of the reaction of allyl alcohols with allenic sulfones are especially interesting as they allow the carbanion-accelerated Claisen rearrangement to take place. By deprotonation, or directly by addition of an allyl alcoholate anion, a system is generated, which rearranges much more easily than the uncharged system and with high diastereoselectivity (Scheme 62).

Even highly functionalized systems with vicinal quaternary centers can be prepared very readily.



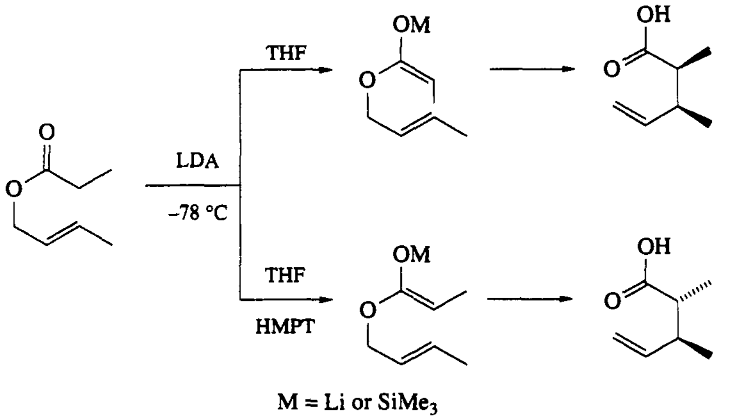
Scheme 62

A new perspective was opened up recently when Denmark demonstrated that with chirally modified phosphoryl-activated allenes an asymmetric induction could be effected.[160] From easily generated allenyl phosphoramidates containing an optically active amino alcohol, the diastereomeric adducts (37) and (39) could be obtained by addition of allyl alcohol. When the separated adducts were employed in the carbanionic Claisen rearrangement, a remarkable asymmetric induction (90:10) could be achieved with preferential formation of the diastereomers (38) or (40) respectively, whereas in a thermal reaction no stereoselection was observed (Scheme 63). Another example of an asymmetric induction in Claisen rearrangements is reported by Welch.[161]



Scheme 63

From the different variants of the Claisen rearrangement the reaction of allyl ester enolates or the derived silylated ketene acetals has found the most widespread application. The apparent reason for this popularity is that the starting material is generated by a simple esterification and the rearrangement takes place under very mild conditions so that even difficult C—C bond formations can be effected after having joined two readily accessible partners together. The method proved the more attractive after Ireland had developed conditions to influence the geometry of the enolates, formed by a strong, non-nucleophilic base like LDA, by appropriate choice of the solvent so that a diastereoselective control of the rearrangement is possible: in THF the (*E*)-enolate is formed predominantly, whereas on adding HMPT the ratio of the isomers is practically reversed (Scheme 64).[162]

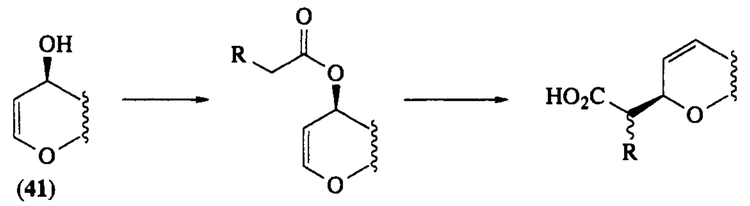


M = Li or SiMe$_3$

Scheme 64

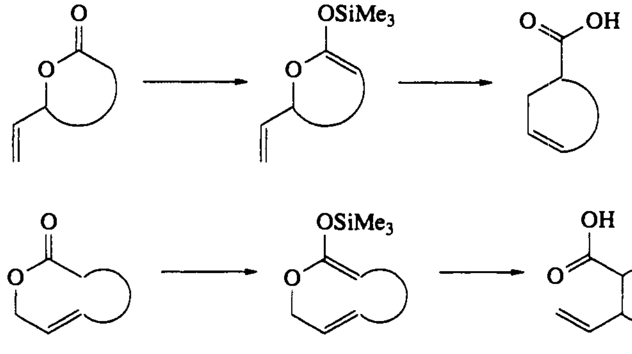
To avoid complications with the reactive enolates and to preserve the stereochemistry it has proven practical to employ the derived silyl enol ethers, formed by trapping the enolates with chlorotrialkylsilane instead of the enolates themselves. The rearrangement of the silyl enol ethers takes place under mild conditions, too, often at room temperature, and exhibits all the characteristics of 3,3-sigmatropic rearrangements, namely high stereoselectivity in the formation of double bonds and stereocenters.

The potential of the ester enolate Claisen rearrangement for the stereocontrolled synthesis of highly functionalized, complex systems has been demonstrated in numerous applications in natural product synthesis. Utilizing the 1,3-chirality transfer Ireland has synthesized oxygen heterocycles with chiral side chains, such as are found as units in polyether antibiotics and macrolides, starting from enantiomerically pure furanoid or pyranoid glycal systems of type (**41**), which are easily accessible from carbohydrates (Scheme 65).[163–168]



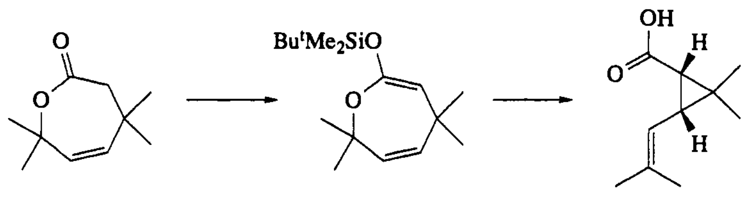
Scheme 65

Interesting possibilities arise when unsaturated lactones are employed in the enolate-Claisen rearrangement: either ring enlargements[169] or ring contractions[170] can be promoted (Scheme 66).



Scheme 66

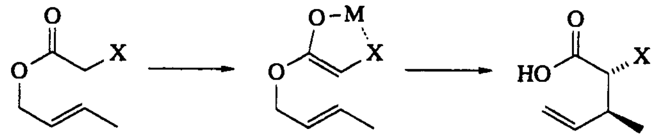
Versatile procedures have been developped particularly for the latter sequence;[171,172] one illustrative example, leading to a simple synthesis of *cis*-chrysanthemum acid, is shown in Scheme 67.[173]



Scheme 67

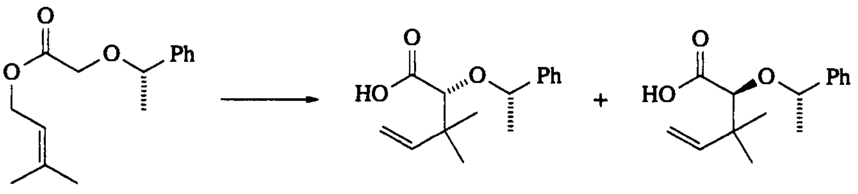
The deliberate control of stereochemistry is the most fascinating aspect of the Ireland–Claisen rearrangement. Another possibility for influencing the geometry when forming the enolate emerges with allylic acetic acid esters containing substituents in the α-position, which are capable of chelating. A selective entry to the diastereomeric series becomes possible due to intramolecular coordination of the corresponding lithium enolates (Scheme 68).[174]

New prospects are opened up with glycolate ester derivatives having an incorporated stereogenic center outside the Claisen system which may cause asymmetric induction during the rearrangement, as can be seen in a recent example (Scheme 69).[175]



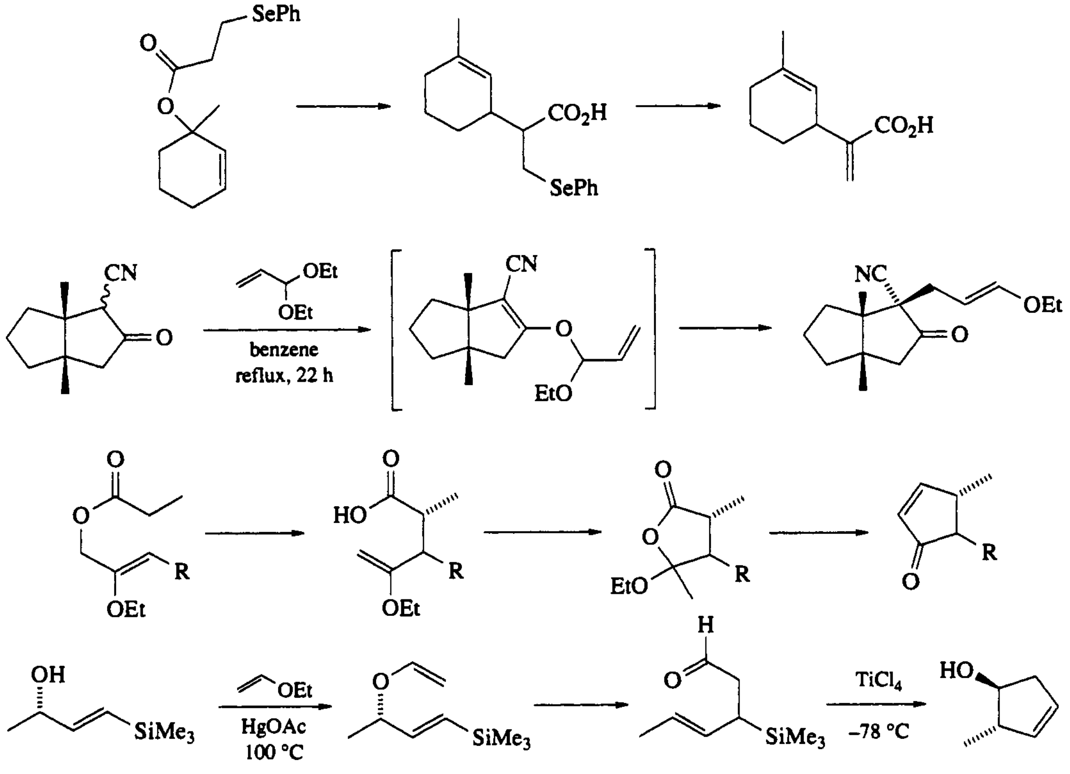
$X = O^-, OR, NR_2, CH_2C(O^-)HR$

Scheme 68



Scheme 69

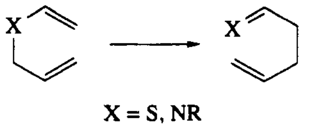
Finally some selected examples will further demonstrate the synthetic versatility of the Claisen rearrangement when different functionalities in either the allyl or the vinyl part of the system are present (Scheme 70).[176-178] By appropriate choice of substituents in strategically important positions, systems can be built up which are suitable for further elaboration in a synthetic scheme.



Scheme 70

Besides alkoxy groups in positions which allow the generation of 1,5- or 1,4-dicarbonyl compounds respectively, silicon substituents also offer many opportunities.[179]

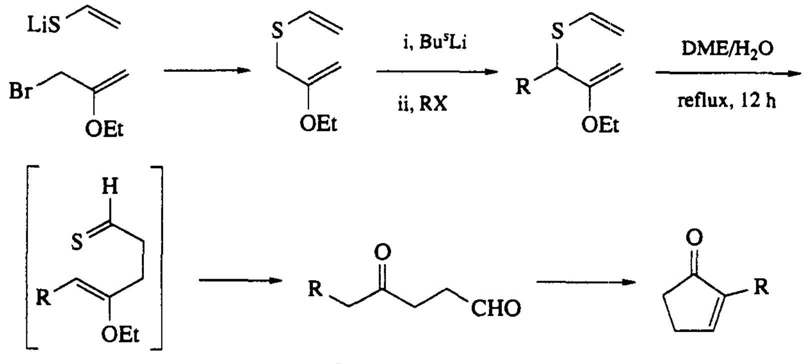
A further aspect of the generality of Claisen-type rearrangements is that the oxygen atom can be replaced by nitrogen or sulfur, leading to the amino- or thio-Claisen[180] variants. They can also be viewed as hetero-Cope rearrangements, so that the amino-Claisen is also known as a 3-aza-Cope rearrangement (Scheme 71).



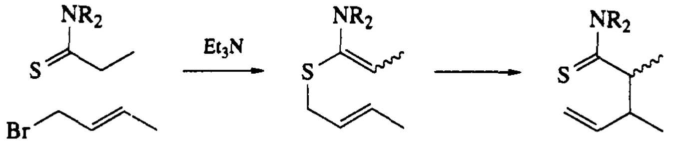
Scheme 71

The aza-Cope rearrangement generally requires higher temperatures than the corresponding oxa analog, but quaternization or catalysis may allow milder conditions to be used.

The thio-Claisen rearrangement has its special value when the specific reactivity of a sulfur function, *e.g.* its carbanion-stabilizing effect or the high nucleophilicity of S, can be utilized, as in syntheses of γ-keto aldehydes (Scheme 72)[181] or thioamides (Scheme 73).[182]

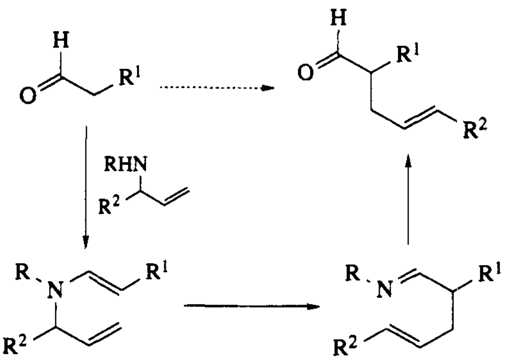


Scheme 72



Scheme 73

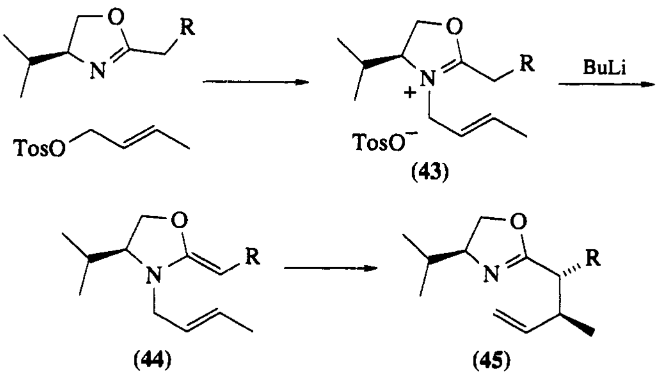
Beside the simple allylic N → C transformation, which allows an allylation in the α-position of aldehydes avoiding completely the problem of *O*- *versus C*-alkylation (Scheme 74),[183] the amino-Claisen rearrangement seems especially suited for effecting asymmetric induction by employing optically active amine systems.[184,185]



(42)

Scheme 74

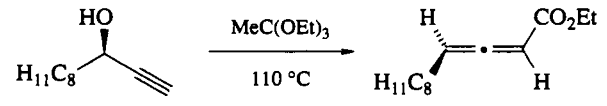
With a chiral auxiliary in (**42**) such as 1-phenylethylamine (R = CHMePh), the diastereomeric excess in the reaction is low (*de* < 30%) and only improves somewhat when $TiCl_4$ catalysis is used to lower the temperature and simultaneous 1,4- and 1,5-asymmetric induction is attempted.[184] A more promising approach was found in the amino-Claisen rearrangement of *N*-allylketene *N,O*-acetals (**44**), which are easily derived from optically active oxazolines (**43**) by alkylation with tosylated allyl alcohols and subsequent deprotonation (Scheme 75).[185]



Scheme 75

Four diastereomeric rearranged oxazolines were obtained with (**45**) as the main product. Obviously, the relative diastereoselection, influenced by the stereogenic center, is acceptable, but the internal diastereoselection, which is controlled by the ketene *N,O*-acetal double bond in (**44**), could be better.

Finally it should be mentioned that most Claisen rearrangements are also possible with propargylvinyl systems leading to allenic derivatives, and very often providing efficient syntheses of functionalized allenes. From a stereochemical point of view such an approach is of special interest as it offers the opportunity of transferring chirality from a centrodissymmetric compound to an axial dissymmetric one. A rare application in synthesis is depicted in equation (42).[186]



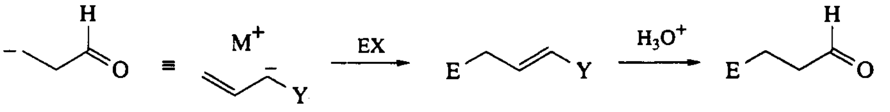
(42)

4.5.3.2 C—C Bond Formation with the Allyl System as the Nucleophile

There are two main synthetic applications where the reaction of an allyl system with electrophiles is accompanied by an allylic rearrangement. One consists of the use of heteroatom-substituted allylic anions as homoenolate anion equivalents and the other represents a synthetically valuable alternative to the aldol reaction by addition of allyl metal compounds to aldehydes.

4.5.3.2.1 Heteroatom-substituted allylic anions as homoenolate anion equivalents

Heteroatom-substituted allylic anions can serve as homoenolate anion equivalents in reaction with electrophiles, when γ-attack can be realized and the formed vinyl heterocompound can be hydrolyzed to an aldehyde (Scheme 76).[23,24]

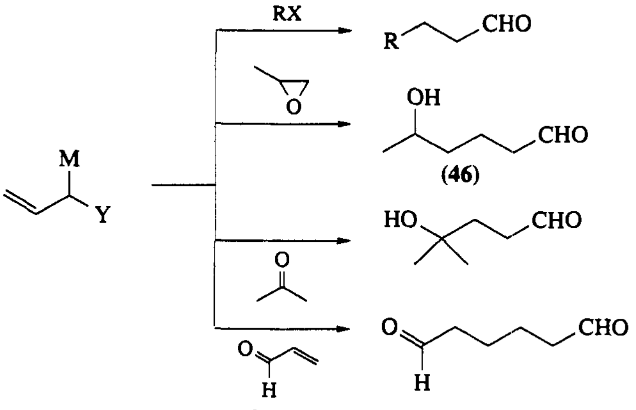


$Y = NR_2, OR, SR, SiR_3,$ *etc.*

Scheme 76

The potential of homoenolate anions on reaction with different electrophiles (Scheme 77) is evident and explains why a great deal of effort has been expended to get high γ-selectivity in reactions of such allyl metal compounds.

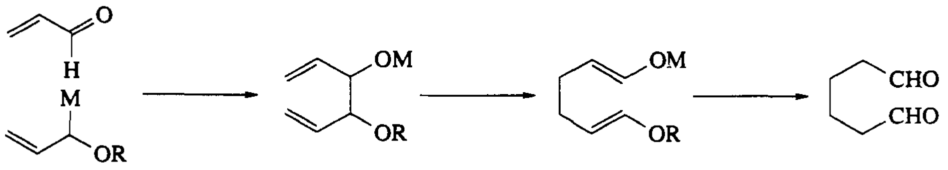
Whereas with most alkylating agents the α,γ-selectivity is still a problem and one has often to rely on the more pronounced γ-selectivity of Cu and Ti derivatives, γ-selective addition is, however, normally observed with oxiranes, leading to 1,5-oxygen-substituted systems (**46**). A 1,4-relationship of oxygen



(46)

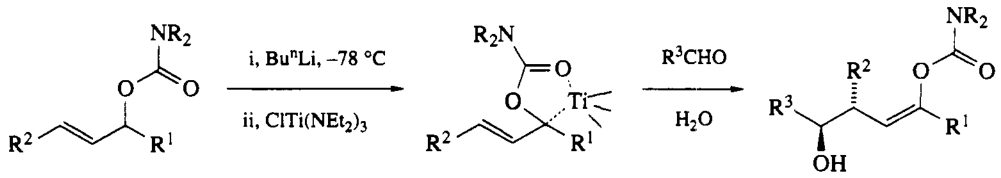
Scheme 77

functions is obtained on γ-selective addition to a carbonyl group, whereas conjugate addition to an α,β-unsaturated carbonyl compound leads to a 1,6-relationship. Conceptually it is interesting that the last arrangement also results when an α-selective 1,2-addition to an α,β-unsaturated carbonyl compound can be accomplished, since the product can be induced to undergo an oxy-Cope rearrangement. The idea has been realized by Evans who could bring about the addition of oxygen-substituted anions to acyclic and cyclic α,β-enones γ-regioselectively after their conversion to organo-zinc or -cadmium reagents (Scheme 78).



Scheme 78

The addition of heteroatom-substituted allylic anions to aldehydes has found particular interest as it represents a homoaldol reaction. Metalated allyl carbamates seem to be the most valuable reagents developed for this purpose as they are prepared easily and exhibit high γ-selectivity and diastereoselectivity, at best in their titanated form (Scheme 79).[187]



(47)

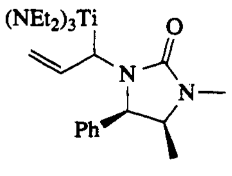
97% *de*

Scheme 79

It is especially remarkable that optically active homoaldol adducts can be obtained when enantiomerically pure 2-alkenyl carbamates (**47**; R^1 = alkyl) are employed.[188] Apparently the deprotonation occurs with retention of configuration and leads to configurationally stable lithium derivatives, which, after metal exchange with $Ti(OPr^i)_4$, again with retention, add to aldehydes with efficient 1,3-chirality transfer coupled with enantiofacial differentiation at the carbonyl group, indicating a rigid six-membered transition state. Recently even an asymmetric homoaldol reaction by enantioselective lithiation of prochiral primary alkenyl carbamates in the presence of (–)-sparteine was reported.[189]

Several other chiral homoenolate anion equivalents have been successfully exploited for asymmetric homoaldol reactions, *e.g.* (**48**) and (**49**),[190,191] but their preparation seems more laborious than that of the carbamates (**47**).

The 1,4-addition reaction of stabilized allylic carbanions with conjugated enones is normally complicated by the ambident reactivity of the carbanion. Clean γ-selective conjugate addition to cyclic enones, however, has been observed with lithiated allylic sulfoxides, phosphine oxides and phosphonates



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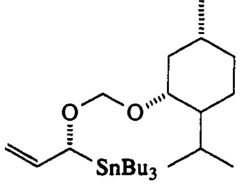
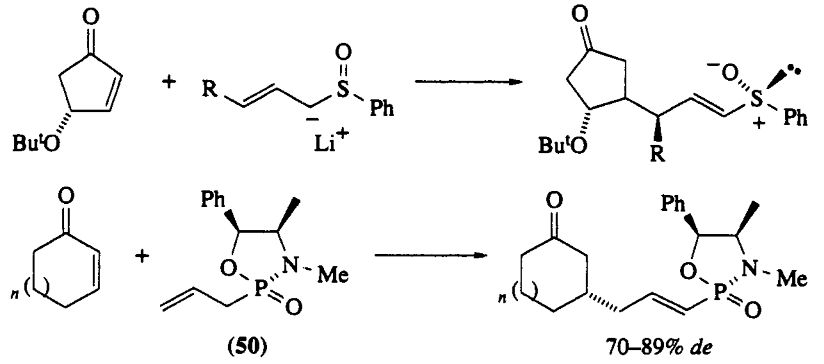


(49)

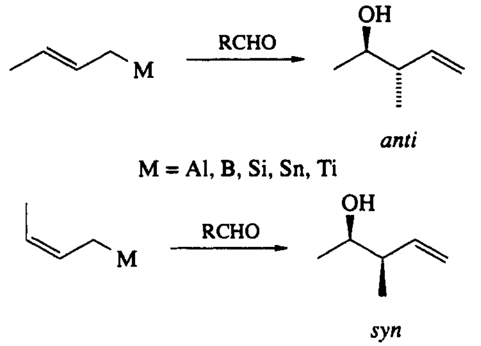
(Scheme 80).[192] The reactions exhibit high diastereoselectivity, probably due to a 10-membered *trans*-decalyl-like transition state, and with chiral allyl phosphonyl anions of type (**50**) even good asymmetric induction could be accomplished.[193]



Scheme 80

4.5.3.2.2 Addition of allylmetal compounds to aldehydes: synthesis of homoallylic alcohols

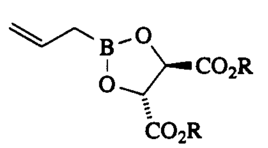
The allylation of aldehydes plays an important role in stereoselective synthesis since in one step several stereogenic centers can be generated and the resulting homoallylic alcohols can be oxidized to β-hydroxycarbonyl compounds, so that the overall process represents an indirect aldol reaction. By employing allyl metal compounds with M = Al, B, Si, Sn, Ti the addition occurs generally with allylic rearrangement under high diastereocontrol, leading to *anti* or *syn* products, respectively, depending upon the geometry of the double bond in the educt (Scheme 81).[194]



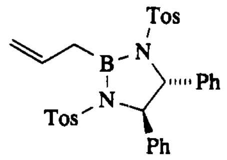
Scheme 81

With allyltin derivatives a change of the relative configurations at the newly formed stereogenic centers is observed when the reaction, which is rather slow without a catalyst, is performed in the presence of BF_3, apparently as a consequence of the now open transition state with BF_3 activation of the carbonyl group and the reaction not going *via* a cyclic, six-membered transition state as is usual.[13]

Allylboronates,[195,196] however, have attracted most interest, as they are easily prepared, stand out because of their high degree of chemoselectivity and, as it has turned out in several investigations, can be chirally modified to generate systems (**51**)–(**53**),[197–199] which allow highly enantioselective formation of homoallyl alcohols.



(51)



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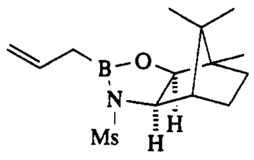
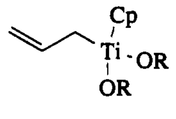
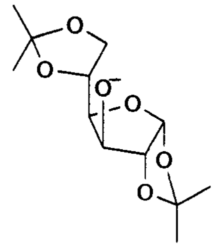


(53)

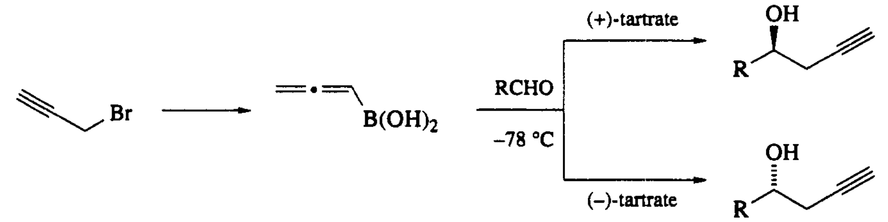


(54)

OR =



Allenylboronic acid, readily accessible from propargylic halides, on esterification with tartaric acid esters can also be induced to add to aldehydes with high enantioselectivity to give homopropargylic alcohols (Scheme 82).[200]



Scheme 82

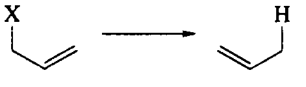
Another promising asymmetric allylation of aldehydes, mediated by a D-glucose-derived titanium reagent (**54**), has recently been described.[201]

4.5.4 1,3-HETEROATOM–HYDROGEN TRANSPOSITIONS

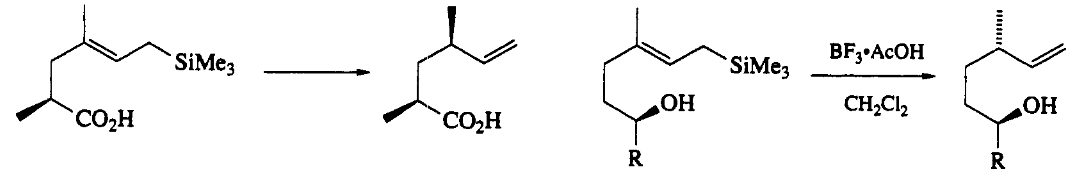
1,3-Heteroatom to hydrogen transpositions in allylic systems (equation 43) can be observed in different reactions, namely the protonation of allyl metal compounds, in reductions of allyl heterocompounds and in retro-ene reactions. Except for the last reaction, which proceeds by a cyclic transition state, the problem of regioselectivity restricts the synthetic value of such reactions and it is only in specific cases that this can be overcome.

Allylic or propargylic metal compounds are often intermediates in isomerization reactions of unsaturated systems (see Section 4.5.5); the product distribution on protonation depends very much on the substitution and the conditions of hydrolysis and most often mixtures of isomers are obtained. In contrast double bond shift generally occurs on protodesilylation of allylic silanes by acids, a reaction which takes place stereospecifically *anti*.[12] Only when intramolecular delivery of the proton in a chair-like transition state is possible may a different kind of stereoselectivity be effective and good 1,3- or 1,4-induction in hydrogen transfer be observed (Scheme 83).[202]

Reductive removal of an allylic heteroatom functionality is a synthetically very useful operation if it can be effected in a regioselective manner. It seems generally easier to find conditions for reduction without a double bond shift than with clean allylic rearrangement. An exception is found in the reduction of allylic phosphonates with $LiAlH_4$,[95] most likely because of a preceding complexation of the reducing agent with the phosphoryl group and then an internal hydride transfer. Such a reactivity, where the hydride reagent is directed by a functionality in the molecule, is probably the rationale for most of the re-

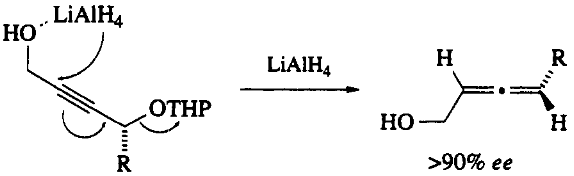


(43)



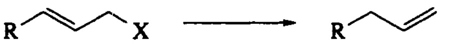
Scheme 83

ductions which proceed with allylic rearrangement. An example where an interesting chirality transfer results is seen in equation (44).[203]



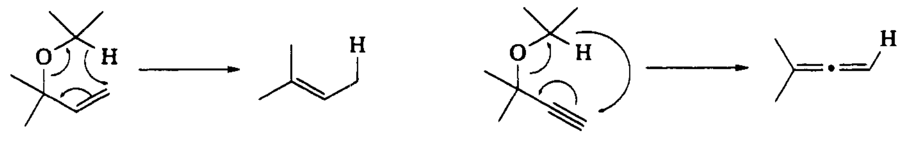
(44)

While in propargylic systems a vinylogous reduction is the normal reactivity, in allylic systems a double bond shift on reduction is realized more generally only when terminal alkenes are produced. Especially interesting in this respect is the Pd-catalyzed hydrogenolysis of allylic acetates (X = OAc) with ammonium formate (equation 45).[204]

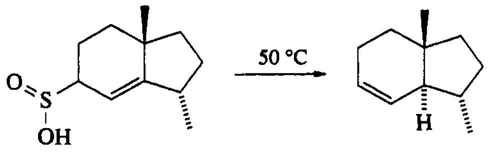


(45)

The removal of an allylic functionality is always accompanied by an allylic rearrangement when it proceeds by a retro-ene reaction. In most cases such a reaction requires high temperatures as in the thermolysis of allylic or, preparatively more useful, propargylic ethers (Scheme 84),[205] but allylic sulfinic acids undergo fragmentation slightly above room temperature[77,206] with the potential of high stereocontrol, as the example demonstrates (equation 46).[206]



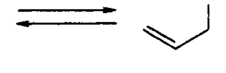
Scheme 84



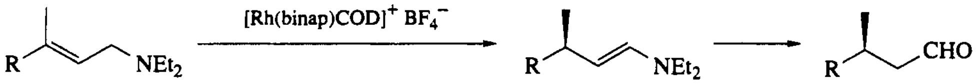
(46)

4.5.5 1,3-HYDROGEN–HYDROGEN TRANSPOSITIONS: ISOMERIZATION OF ALLYL AND PROPARGYL SYSTEMS

Prototopic rearrangements of allylic (equation 47) and propargylic systems sometimes provide useful synthetic transformations of unsaturated compounds; in such cases the regioselectivity presents no difficulties. Due to the easy and clean isomerization of allyl ethers to vinyl ethers with $(Ph_3P)_3RhCl$ or $KOBu^t$/DMSO an allyl ether can serve as a protecting group for a hydroxy function.[207] With chiral rhodium complexes such a migration of the double bond can even be brought about in an asymmetric manner, giving rise to chiral enamines (**56**) from allylamines (**55**; Scheme 85).[208]



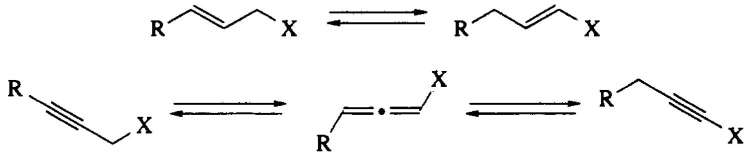
(47)



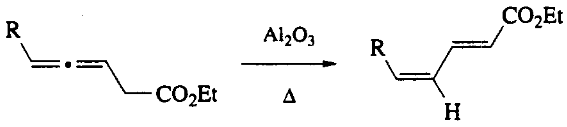
(55) **(56)** up to 99% *ee*

Scheme 85

The base-catalyzed isomerization of propargylic systems can in some cases be used for easy access to heterosubstituted allenes, *e.g.* for alkoxy-substituted allenes starting from the ether of a propargylic alcohol. The problem is that in many other systems an equilibrium exists where the isomerization does not stop at the allenic stage but also leads to the alkynic isomer (Scheme 86). There are relatively few examples where a 1,3-sigmatropic hydrogen shift leads to a synthetically useful isomerization. One example has been found in the thermal rearrangement of β-allenic esters to (2*E*,4*Z*)-dienoic esters over an alumina catalyst, in high yield, with 90–100% stereospecificity (equation 48).[209]



Scheme 86



(48)

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4.6

2,3-Sigmatropic Rearrangements

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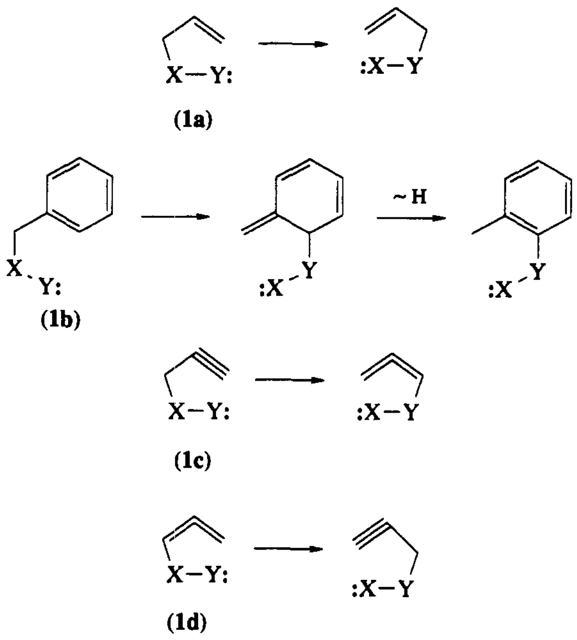
4.6.1 INTRODUCTION

'2,3-Sigmatropic rearrangement' is termed the 1,3-shift of an allylic atom pair —X—Y with a concomitant 1,2-shift of an electron pair from Y to X (Scheme 1). It is symmetry allowed as a concerted suprafacial process.

The substrate of a 2,3-sigmatropic rearrangement contains an allylic (**1a**), benzylic (**1b**), propargylic (**1c**) or allenylic (**1d**) C—X bond. It can be anionic ($Y = CR_2^-$) or neutral (*inter alia* **1** = ylide or carbene). The X-part of the migrating —X—Y atom pair must be a heteroatom since part of the driving force of a 2,3-sigmatropic rearrangement is provided by the better stabilization of the migrating electron pair on X *vs.* Y. This driving force is big enough to make 2,3-sigmatropic rearrangements irreversible, a noteworthy exception being the sulfoxide–sulfenate rearrangement —X—Y pairs which were rearranged successfully in this fashion are summarized elsewhere.[1–3]

2,3-Sigmatropic rearrangement is a method for the synthesis of functionalized alkenes, aromatics, allenes or alkynes. The C—X bond of the starting material (**1**) serves to introduce the C—Y bond into the molecular framework regioselectively and often stereoselectively. The newly formed C—X bond can be carbon–carbon or carbon–heteroatom. In the following, 2,3-rearrangements will be discussed in this order.

2,3-Rearrangements were reviewed with particular emphasis on their stereochemistry by Hoffmann[3] and Hill.[4] Individual treatments are available for the sulfoxide–sulfenate rearrangement,[5] sulfonium ylide rearrangement[6] and 2,3-Wittig rearrangement.[7] Some aspects of 2,3-shifts in selenium containing compounds are covered in ref. 8. A substrate-oriented discussion of the 2,3-Wittig rearrangement is Marshall's contribution in Volume 3, Chapter 3.11. Supplementary material on ylide rearrangements and allene synthesis *via* 2,3-sigmatropic rearrangements is contained in refs. 9 and 10, respectively.

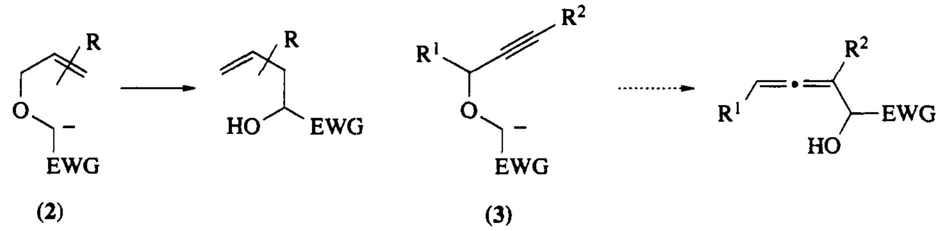


Scheme 1 2,3-Sigmatropic rearrangements

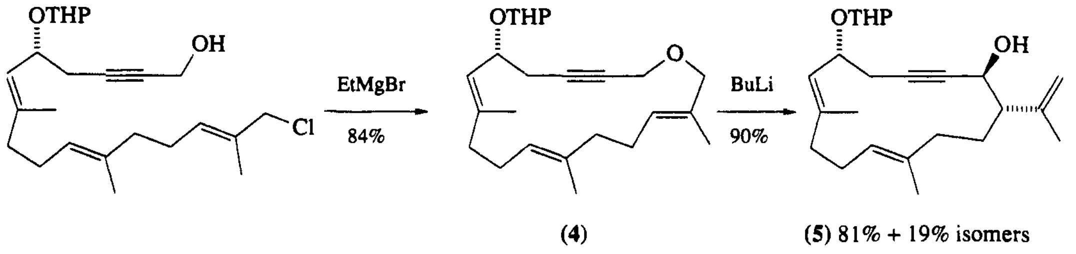
4.6.2 FORMATION OF CARBON–CARBON BONDS

4.6.2.1 Rearrangement of Ethers

2,3-Sigmatropic rearrangements of ethers are usually performed as Wittig rearrangements of metalated ethers. Usually, the substrate is allylic (**2**). Only a few examples are known for propargylic ethers (**3**; equation 1). The 2,3-Wittig rearrangement of allylic ethers is increasingly used in synthetic work. A remarkable application is Marshall's synthesis of the cerembrolide precursor (**5**; equation 2).[11,12]

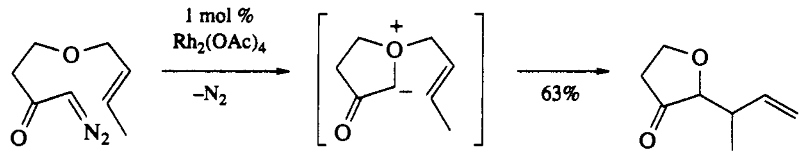


(1)



(2)

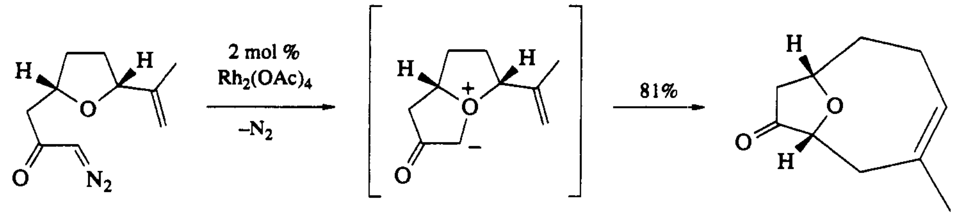
Rearrangements *via* oxonium ylides are scarce.[9c,13,14] Nonetheless, interesting structures were prepared from ylides like (**6**; equation 3)[15] or (**7**; equation 4).[16] The potential of ylide rearrangement methodology in the context of total synthesis is unexplored, but interesting target molecules are already identified.[16]



(3)

(6)

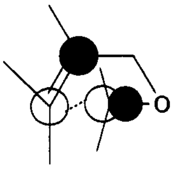
1 isomer



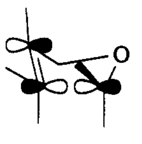
(4)

(7)

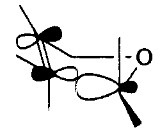
The transition state of the 2,3-Wittig rearrangement is visualized as envelope (**8**) by Nakai[7] or envelope (**9**) by Midland.[17] Small sets of experimental results were interpreted successfully with these pictures. However, (**8**) and (**9**) fail to accommodate the whole set of data. A modified transition state (**10**) is therefore suggested. In (**10**), the lone pair attacks the C═C bond from the rear. This direction of approach circumvents an antibonding interaction with the orbital on the nonattacked *sp*^{2}-center. A second modification concerns the geometry of the carbanion moiety of the rearranging species; unless it is integrated in an enolate or an azaenolate (where planarity is assumed; *vide infra*), it should be pyramidal as shown. Finally, pyramidalization of the double bond is expected in the transition state due to the beginning rehybridization from *sp*^{2} to *sp*^{3}. Indeed, a transition state structure very similar to (**10**) was found by means of MM2/STO-3G calculations starting from lithio allyl methyl ether;[18] computationally, however, the ensuing reaction was not a 2,3-shift.



(**8**) Nakai



(**9**) Midland

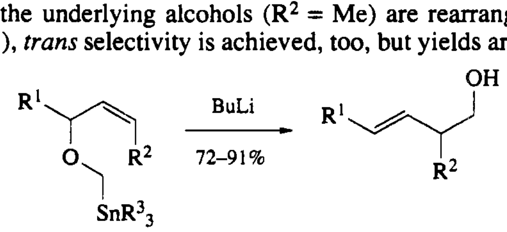


(**10**) Modified

4.6.2.1.1 (E)/(Z)-Selectivity

Disubstituted alkenes with a *trans* double bond can be generated routinely from Wittig rearrangements; in the case of ester enolate Wittig rearrangements, *cis* selectivity can be achieved. For trisubstituted alkenes, (*E*)- and (*Z*)-selective syntheses are known.

The Still–Wittig rearrangement of stannylated *cis*-ethers (**11**) gives *trans* homoallylic alcohols (**12**) selectively (equation 5).[19] If the underlying alcohols (R^2 = Me) are rearranged under Büchi's conditions (DMF acetal, xylene, reflux), *trans* selectivity is achieved, too, but yields are lower (41–49%).[23]

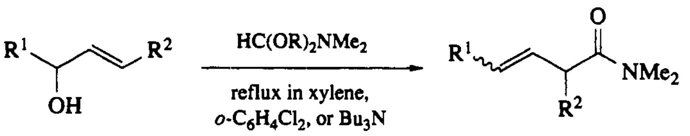


(5)

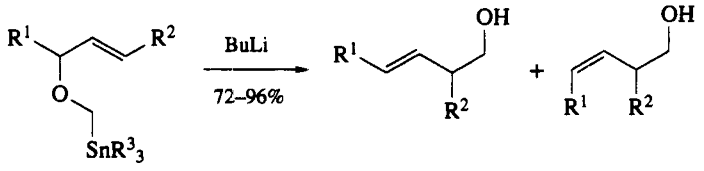
(**11**) (**12**)

The Büchi rearrangement is stereochemically superior to the Still–Wittig rearrangement when one elaborates secondary allylic alcohols (**13**) with or without a *trans* alkenic substituent. In these cases, the Büchi rearrangement gives preponderantly or exclusively *trans* product (equation 6).[23,24] The corresponding Still–Wittig rearrangements of (**14**; R^2 = H, Me) give alcohols as *cis*/*trans* mixtures (equation

7).[19,21] Alkenic stereoselection in the Still–Wittig rearrangement results presumably from conformational control in a very early transition state (Scheme 2).[19] There, the substituent R^{α} prefers equatorial (**15**) over axial (**16**) orientation, if the 1,2-allylic strain is smaller than the 1,3-allylic strain, and *vice versa*.[25] This implies *trans* products in the former (*vide supra*) and (*Z*)-products in the latter case (*vide infra*).



(**13**) 87–100% *trans* (6)

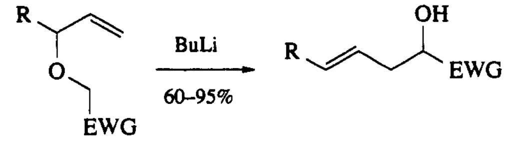


(**14**) 35–53% : 65–47% (7)

(**15**) no 1,3 allyl strain (**16**) no 1,2 allyl strain

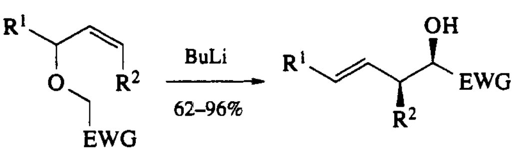
Scheme 2 *Cis*/*trans* selectivity of the Still–Wittig rearrangement

Secondary anions amenable to 2,3-Wittig rearrangements contain a stabilizing electron-withdrawing group (EWG). The EWG can be 'hydrocarbon' (vinyl, alkynyl, aryl) or 'acyl' (acid, ester, amide, imido ester). Ethers (**17**) with EWG = hydrocarbon furnish homoallylic alcohols (**18**) containing one new stereocenter with 93–100% *trans* selectivity (equation 8).[26–30] If similar homoallylic alcohols with two new stereocenters are required, *trans* selective access along with 91–99% *syn* diastereoselection is straightforward starting from *cis* ethers (**19**; equation 9).[17,31–35]



(**17**) (**18**) 93–100% *trans* (8)

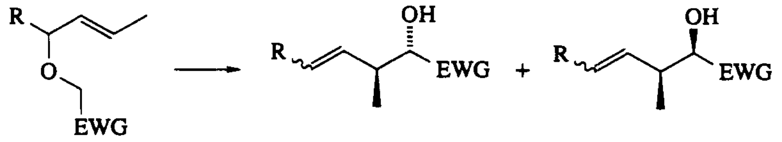
EWG = $H_2C{=}CH$, $H_2C{=}CMe$, Ph, 9-fluorenyl, $HC{\equiv}C$, $MeC{\equiv}C$, $Me_3SiC{\equiv}C$



cis-(**19**) 91–99% *syn*
>98% *trans* (9)

EWG = $H_2C{=}CH$, $H_2C{=}CMe$, Ph, $HC{\equiv}C$, $MeC{\equiv}C$, $Me_3SiC{\equiv}C$

Trans configuration in the homoallylic alcohol with concomitant *anti* diastereoselectivity is observed starting from the *trans* ethers (**20**; equation 10) (Table 1). The comparatively low simple diastereoselectivity of these reactions (60–91%) reflects the general difficulty in obtaining *anti* products from 2,3-Wittig rearrangements (*cf.* Section 4.6.2.1.2).



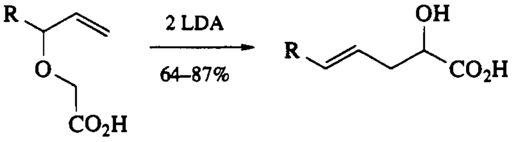
(20) *trans* **(21)** *anti* **(22)** *syn* (10)

Table 1 *Trans* Selective Formation of Homoallylic Alcohols With *Anti* Configuration[a]

EWG	*R*	*Yield (%)*	*Trans (%)*	*Anti (%)*	*Ref.*
$H_2C{=}CH$—	Pr^i	75	100	60	17
Ph—	Pr^i	95	82	76	17
HC≡C—	Me/Pr^i	62/63	100/92	91/89	31/17

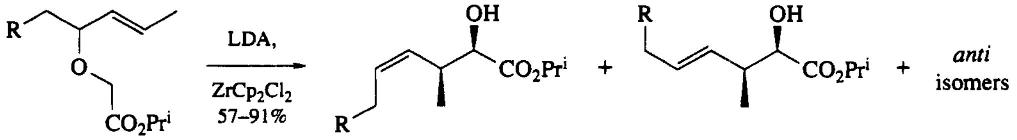
[a] See equation (10).

Acids (**23**) give unsaturated hydroxy acids (**24**) with more than 95% *trans* selectivity *via* their dianions (equation 11).[36] Under Nakai's oxonium ylide rearrangement conditions,[14] acid (**23**; R = Me) preferred the *cis* product although only slightly (57:43 ratio). The methyl ester derived from the same acid showed little, albeit complementary, *cis:trans* selectivity when rearranged *via* its tetrabutylammonium enolate[37] (22:78) and an oxonium ylide[14] (69:31). It is unknown, how this ester rearranges as a lithium enolate, but the stereorandom reaction of an isopropyl ester upon treatment with LDA discourages the expectation of selectivity.[38] However, by adding complexes MCp_2Cl_2 of tetravalent transition metals (Ti, Zr, Hf) to the lithio enolates of isopropyl esters (**25**) at −100 °C and warming up subsequently, Katsuki attained an astonishing level of 93–99% *cis* selectivity (equation 12).[38,39] In addition, these reactions are highly *syn* selective.



(23) **(24)** >95% *trans* (11)

R = Me, $n\text{-}C_5H_{11}$, $n\text{-}C_7H_{15}$



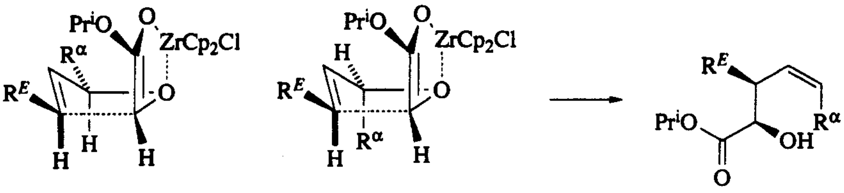
(25) **(26)** *syn, cis* **(27)** **(28)** (12)

93–99 : 0–4 : 0–3

R = H, $n\text{-}C_7H_{15}$, $BnOCH_2$, $BnOCH_2CH_2$, PhS

Ti, Zr and Hf enolates do not react *via* a transition state (**29**) akin to the (**70**) proposed later for enolates with lithium as a small counterion. With its large counterion, (**29**) would exhibit a destabilizing interaction between the voluminous cyclopentadienyl ligands and the substituent R^α. No such interaction occurs in the preferred transition state (**30**). (**30**) precedes *cis*-alkenes (**31**) with *syn* configuration (Scheme 3).

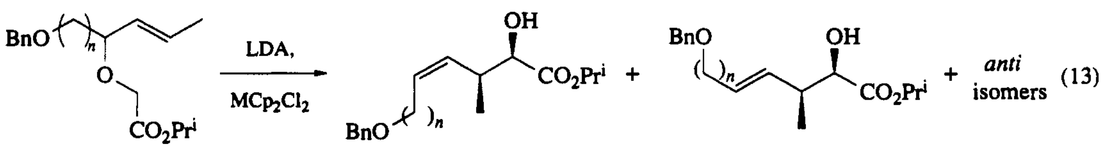
The side chain of Katsuki's esters (**25**) turned out less innocent in these rearrangements than its location 'outside of the cyclic transition state' suggests. In fact, an appropriately placed oxygen atom in the side chain of such esters (**32**; equation 13) can steer the double bond geometry of the reaction product. Compare, for example, the stereochemically complementary results reported for ester (**25**; side chain = *n*-heptyl)[38] and (**32a**; side chain = $BnOCH_2$).[39] With $ZrCp_2Cl_2$ as additive, the first reaction is 99% *cis*



(29) **(30)** **(31)** *cis, syn*

Scheme 3 Transition states rationalizing *cis* and *syn* selectivity of Wittig rearrangements with EWG = acyl (large counterion)

selective, while the second furnished a 3:2 mixture of *trans* and *cis* isomers. For all of the oxygenated esters (**32**), the geometry of the newly formed double bond could be varied from preferentially *cis* to preferentially *trans* (Table 2).[39] Notice that part of the stereocontrol stems from tuning the size and the acidity of the metal core in the added MCp_2Cl_2 (Ti → Zr → Hf).



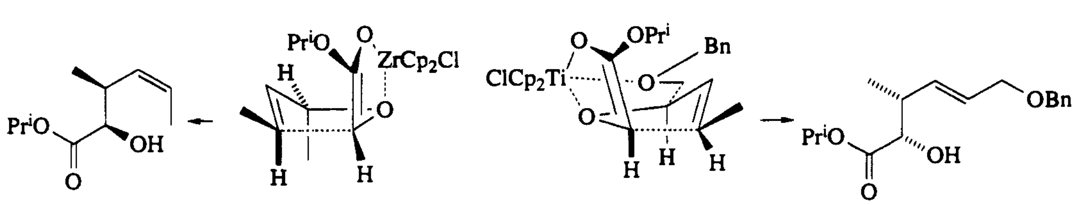
(32) **(33)** *syn, cis* **(34)** *syn, trans* **(35)**

Table 2 Counterion Effects on the *cis*/*trans* Selectivity of Ester Enolate Wittig Rearrangements[a]

(32)	*n*	*M*	*Yield (%)*	*(33):(34):(35)*
(a)	1	Ti	72	2:96:2
		Zr	53	40:60:0
(b)	2	Ti	31	16:65:19
		Zr	62	96:2:2
(c)	3	Ti	37	21:43:36
		Zr	57	94:4:2

[a] See equation (13).

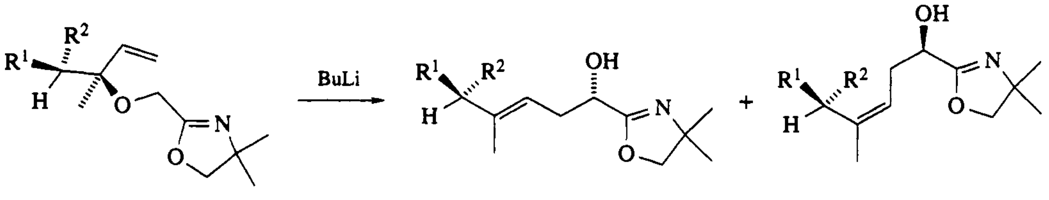
The Zr enolate of ester (**25**; R = H) should rearrange *via* transition state (**37**) where methyl as the side chain points downward. This follows from the discussion of Scheme 3 (*vide supra*). In contrast, the side chain $BnOCH_2$ of ester (**32a**) is located on the upper face of transition state (**38**). There, its oxygen atom is complexed by the metal. One stereochemical consequence is the *trans* configuration in the rearrangement product. The other consequence is opposite absolute configurations at the newly formed stereocenters in *trans*-(**39**) *vs*. *cis*-(**36**). This aspect will be emphasized later (*vide infra*).



(36) *cis*, (2*R*) **(37)** **(38)** **(39)** *trans*, (2*S*)

Scheme 4 Transition states rationalizing the *cis* and *trans* dichotomy of Katsuki's Wittig rearrangements

Another example of remote control of *cis*/*trans* selectivity was provided by Kallmerten.[40] He studied Wittig rearrangements of the tertiary oxazolinyl ethers (**40**; equation 14) (Table 3).[40] By changing (off the pericyclic transition state) a methyl group into MOMO the previous 72:28 (*Z*)-selectivity was completely inverted into >100:1 (*E*)-selectivity. Remarkably, the MOMO effect depends heavily on which of the diastereomers is used: (**41b**) gave a nearly balanced ratio of (*E*)- and (*Z*)-isomers (64:36), which falls far behind the perfect (*E*)-selectivity displayed by the epimer (**41c**).



(14)

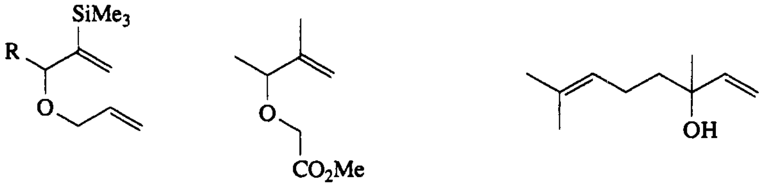
(40) **(41)** *(E)* **(42)** *(Z)*

Table 3 Remote Control of the (*E*)/(*Z*) Selectivity in the 2,3-Wittig Rearrangements of Oxazolinyl Anions[a]

(40)	*R*^{1}	*R*^{2}	*Yield (%)*	*(E):(Z)*
(a)	Me	Me	—	28:72
(b)	Me	MOMO	95	64:36
(c)	MOMO	Me	82	>100:<1

[a] See equation (14).

Wittig rearrangements other than those just mentioned or Büchi rearrangements do not necessarily lead to stereochemically pure triply substituted alkenes (Scheme 5). However, with appropriate substrates, (*E*)- and (*Z*)-selectivity can be realized. The most noteworthy among these stereoselective transformations is the (*Z*)-selective Still–Wittig rearrangement.[19] The homoallylic alcohol (**46**), for example, gave (**47**) as a 96.5:3.5 mixture of (*Z*)- and (*E*)-isomers (equation 15).[42] Conveniently, the formation of the Bu_3SnCH_2 ether and the subsequent rearrangement can be performed in a one-pot operation;[19] for similar applications see ref. 43.



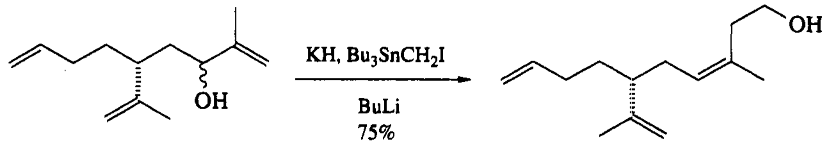
(**43**) → *(E):(Z)*

R = Me, 36:64
R = n-C_5H_{11}, 33:67

(**44**) → *(E):(Z)* = 31:69

(**45**) → isomeric ratio = 58:42

Scheme 5 Substrates of nonstereoselective Wittig (**43**[41,27] and **44**[14]) or Buchi (**45**)[24] rearrangements

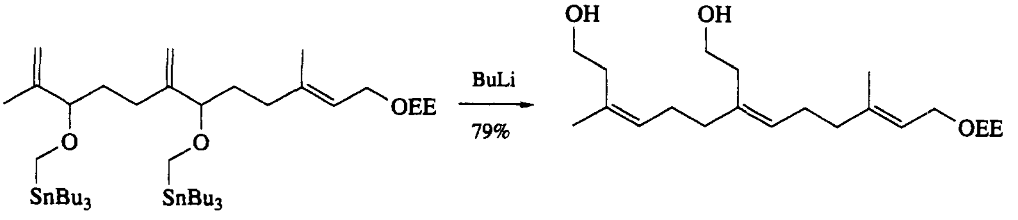


(15)

(46) **(47)** *(Z):(E)* = 96.5:3.5

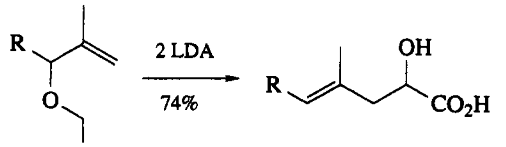
Unequalled in elegance is the double Still–Wittig rearrangement of (**48**), which gave the bis-(*Z*,*Z*)-homoallylic alcohol (**49**) in 95% isomeric purity (equation 16).[44] (*Z*)-Selectivity has also been noted for the Wittig rearrangement of an acid dianion (equation 17).[36]

The transformation (**50**) → (**51**) includes a 2,3-rearrangement (Scheme 6).[45] It exhibits (*E*)-selectivity and allows incorporation of a nucleophile *in situ*. The nucleophile can be adjusted to the synthetic demands. Upon reduction of the aldehyde intermediate (**53**), a primary homoallylic alcohol (**54**) should be formed. This would constitute the (*E*)-selective complement of Still's (*Z*)-selective synthesis[24] (*vide supra*).



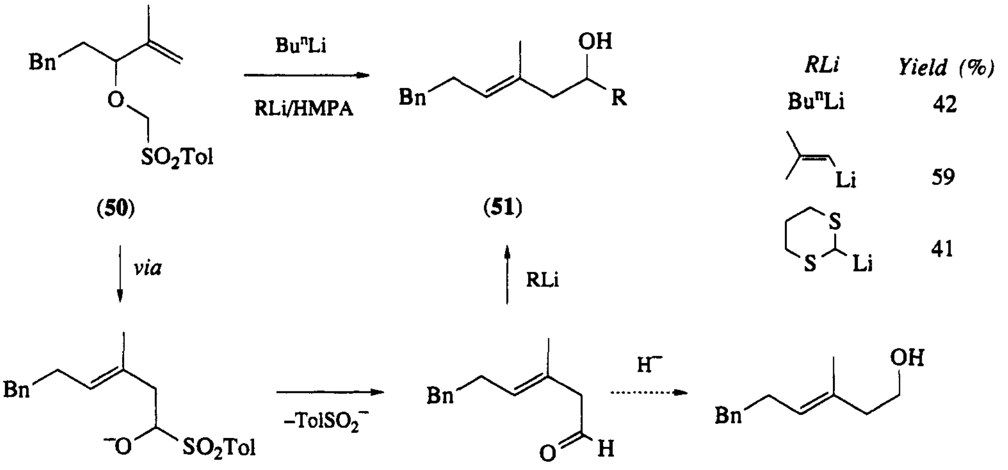
(16)

(48) **(49)** >95% *(Z, Z, E)*



(17)

$R = n\text{-}C_5H_{11}$, >95% *(E)*



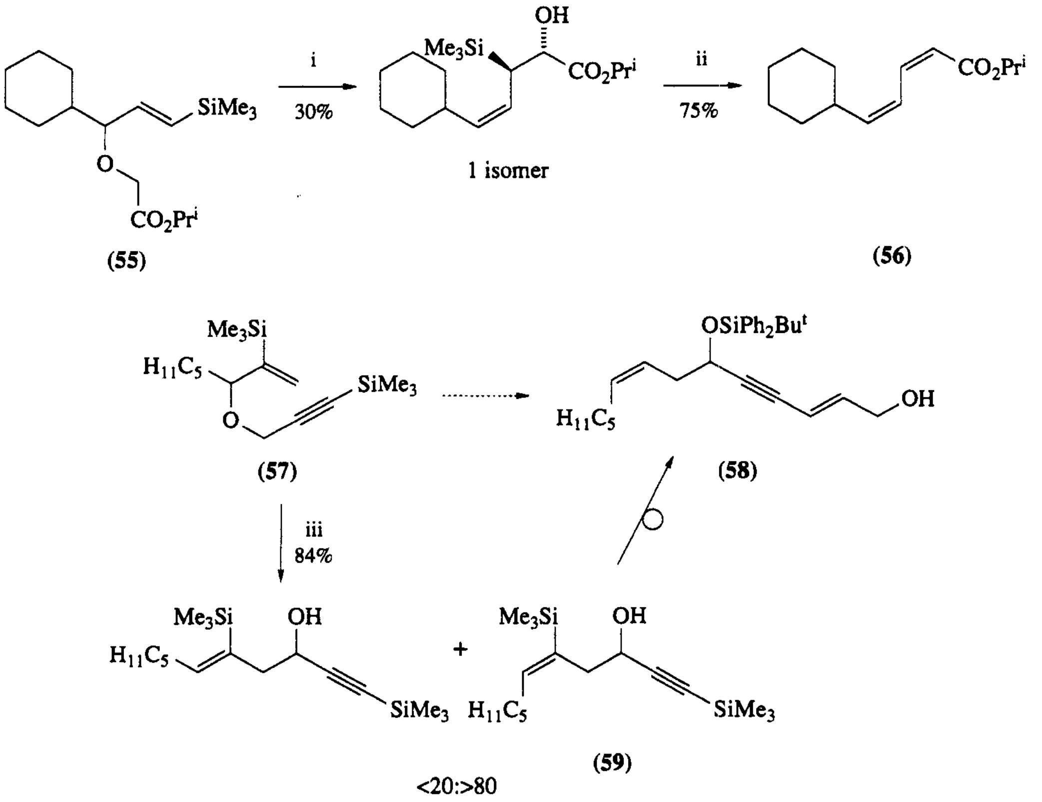
(50) **(51)** **(52)** **(53)** **(54)**

Scheme 6

Silicon-containing substrates acquired some merit in the stereoselective synthesis of alkenes *via* 2,3-rearrangements (Scheme 7). Starting from the terminally silylated ether (**55**), one (*Z*)-bond is generated by the Wittig rearrangement; a second (*Z*)-bond is introduced by an ensuing Peterson elimination.[46] Pattenden presented a potentially generally applicable concept: by desilylation, he 'translated' the (*E*)-selective rearrangement of the internally silylated ether (**57**) into the (*Z*)-configuration of (**58**).[27]

4.6.2.1.2 Diastereocontrol

Nakai, Midland, Katsuki and others have studied *syn/anti* selective 2,3-Wittig rearrangements extensively. It is not yet possible to unambiguously explain all results, but a number of stereochemically useful transformations have emerged. The simple diastereoselectivity of 2,3-Wittig rearrangements of ethers (Scheme 8) with EWG = hydrocarbon (Table 4) can be summarized as follows: (i) *cis/trans* isomeric ethers give epimeric products; (ii) *cis*-ethers react more selectively than their *trans* isomers; (iii) *cis*-derived diastereoselectivities are hardly affected by structural variation of the starting material, while they are affected profoundly in the *trans* series; (iv) *cis*-ethers give homoallylic alcohols with *syn* configuration and, if possible, a *trans* C═C bond. Products are at least 90%, often 95% and occasionally 100% isomerically pure (exception: 72% *syn* in entry 5); and (v) *trans*-ethers lead usually to the *anti* diastereomer (exceptions: entries 6, 13 and 15). 90% selectivity is rare (entries 9 and 11) and if occasionally



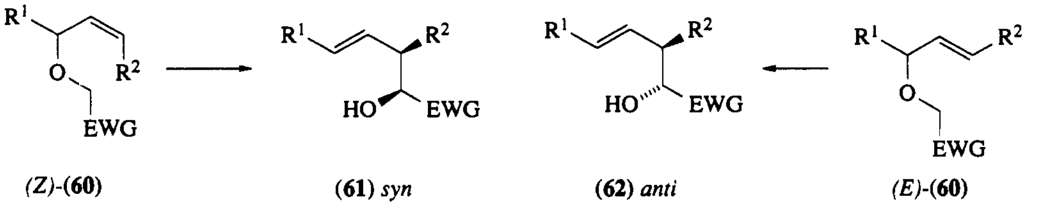
i, LDA, $ZrCp_2Cl_2$ (method: equation 12); ii, $BF_3{\bullet}OEt_2$; iii, BuLi (*cf.* **43**; Scheme 5)

Scheme 7 Silicon assistance in stereoselective alkene synthesis *via* 2,3-Wittig rearrangements

encountered (EWG = substituted alkynyl) not so in general: compare the 1:99 *syn:anti* ratio of entry 11 with the reversed 73:27 ratio of entry 13.

These diastereoselectivities can be rationalized by transition state (**64**; Scheme 9). A pyramidal configuration of the anionic center is assumed (*cf.* nonplanarity of a benzylic[50] or an allylic anion[51]). This leaves more space for an equatorial substituent EWG (**64**) than for an axial EWG (**65**). The resulting product structure (**63**) agrees well with the general trends of Table 4. The finer issue — why (**64**) is preferred over (**65**) in the case of (*Z*) *vs.* (*E*)-alkenes — remains unexplained.

Syn/*anti* selectivities of 2,3-Wittig rearrangements of ethers (Scheme 10) with EWG = acyl are compiled in Table 5. Oxonium ylide rearrangements are included (entries 2 and 7). The following observations can be made: (i) (*Z*)-ethers give useless *syn*/*anti* mixtures (exception: entry 4); (ii) (*E*)-ethers give *syn* products with selectivities between close to 90% and 100%; and (iii) branching of the vinylic substituent was probed in entry 4 (EWG = CO_2R). When compared to the ester enolate rearrangements of entries 3 and 5 with linear alkyl groups as vinylic substituents, the proportion of *anti* product is dramatically increased. In fact, the rearrangement product obtained from the (*Z*)-ether is exclusively *anti*. To branch the vinylic substituent might be a worthwhile consideration in other cases, too, when a homoallylic alcohol with *anti* stereochemistry is required.



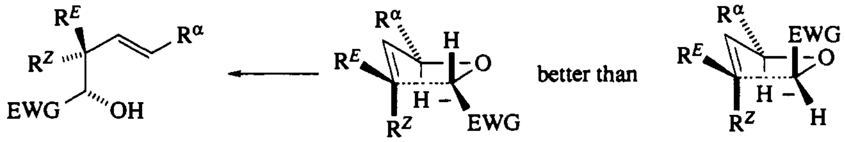
(*Z*)-(**60**) (**61**) *syn* (**62**) *anti* (*E*)-(**60**)

Scheme 8

Table 4 Wittig Rearrangements of (*E*)/(*Z*) Isomeric Ethers with EWG = Hydrocarbon[a,b]

Entry	*EWG*	R^1	R^2	*From (Z)-(60)* *Yield (%)*	*From (Z)-(60)* *Syn (%)*	*From (E)-(60)* *Yield (%)*	*From (E)-(60)* *Anti (%)*	*Ref.*
1	$H_2C{=}CH$—	H	Me	88	92	81	84	26
2		Pr^i	Me	84	92	75	60	17
3	$H_2C{=}CMe$—	H	Me	71	95	70	72	26
4		Pr^i	Me	93	93	89	56[c]	17
5	PhCH=CH—	H	Me	70–98	72	70–98	76	47
6	Ph	H	Me	70–98	95	70–98	39	47
7		Pr^i	Me	89	93	95	76[d]	17
8	$MeOC_6H_4$—	H	Me	70–98	100	70–98	60	47
9	$HC{\equiv}C$—	H	Me	56	90	72	99	31
10		Pr^i	Me	89	91	63	89[e]	17
11	$MeC{\equiv}C$—	H	Me	55	100	65	99	31
12		H	f	62	98	73	77	48
13	$Me_3SiC{\equiv}C$—	H	Me	74	100	72	27	31
14		H	f	77–87	100	84–86	85–87	48,49
15		H	g	77	99	93	41	48
16		Pr^i	h	>85	>98	—	—	33

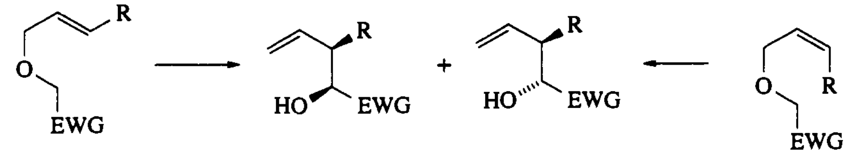
[a] See Scheme 8. [b] In this and the following tables, *syn*/*anti* ratios are given for starting materials of 100% geometrical purity wherever possible; these ratios are either experimental or calculated from data referring to less than 100% sterically pure allylic ethers.[c–e] In addition, 11, 22 and 9 rel-% of (*Z*)-isomer(s) with unassigned configuration(s) were found.[f] R^2 = 2,2-Dimethyl-1,3-dioxolan-4-yl.[g] R^2 = TBDMSO—CHMe—.[h] R^2 = TBDMSO—CH_2—.



(63) **(64)** **(65)**

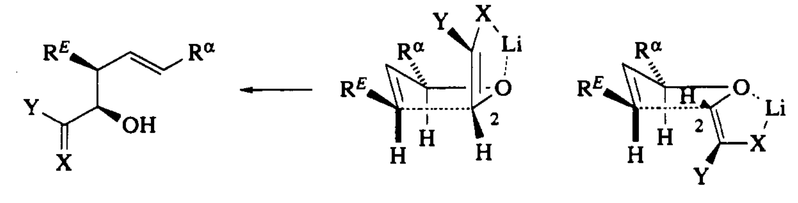
Scheme 9 Transition states rationalizing *syn*/*anti* selectivities of Wittig rearrangements with EWG = hydrocarbon

The 'metalated ethers' with EWG = acyl are simply enolates and azaenolates. These allow for intramolecular bridging *via* the Li^+ cation (Scheme 11). Agreement with the experiments would be attained if such bridging was favored on the *endo* face of the five-membered transition state (**70**). Indeed, the atom H-2 in the enolate is less sterically hindered in *endo*-(**70**) *vs*. *exo*-(**71**). In (**70**), the H-2 is directed towards a small hydrogen atom, while it would be confronted with the larger alkyl group R^E in (**71**).



(E)-(**66**) (**67**) *syn* (**68**) *anti* *(Z)*-(**66**)

Scheme 10

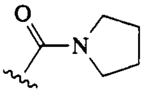
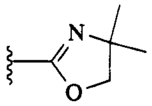
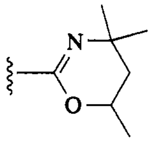


(**69**) *trans, syn* (**70**) (**71**)

Scheme 11 Transition states rationalizing the diastereoselectivity of Wittig rearrangements with EWG = acyl

Nakai's oxonium ylide rearrangement (Table 5, entry 7) is believed to proceed *via* (**76**) to give *syn*-(**77**) and *anti*-(**78**; Scheme 12), respectively.[14] These diastereoselectivities are difficult to understand in view of the strikingly deviating selectivities reported for the related ylide (**73**).[13] Presumably, one deals with different reactive species. Speculatively, ylide (**76**) cyclizes to (**80**), a zwitterionic isomer of a ketene Si-acetal (Scheme 13). (**80**) would resemble sterically the transition state (**70**) of ester enolate Wittig rearrangements (Scheme 11). Accordingly, the *syn*/*anti* selectivities resulting from (**80**) are similar to those explained *via* (**70**). (**73**), on the other hand, can hardly react other than *via* transition state (**79**). (**79**) resembles the transition state (**64**) of Wittig rearrangements with EWG = hydrocarbon and shows equal *syn*:*anti* ratios.

Table 5 2,3-Rearrangements of (*E*)/(*Z*) Isomeric Ethers with EWG = Acyl[a,b]

			*From (E)-(**66**)*		*From (Z)-(**66**)*		
Entry	*EWG*	*R*	*Yield (%)*	*Syn (%)*	*Yield (%)*	*Syn:anti*	*Ref.*
1	CO_2H	Me	60	32	73	77:23	36
2		Me[c]	92	88	—	—	14
3	CO_2—menthyl	Me, Bu[n]	75–88	92–93	—	—	52
4	CO_2R	d	40–75	*ca.* 32–80	40–79	0:100	53
5	CO_2Pr^i	Me	14	82	20	67:33	38
6		Me[e]	47	98	15	88:12	38
7	CO_2Me	Me[c]	83	95	86	50:50	14
8		Me	98	96	—	—	54
9		Me	80	89	80	18–24:82–76[f]	55
10		Me	92	100	82	64:36	55

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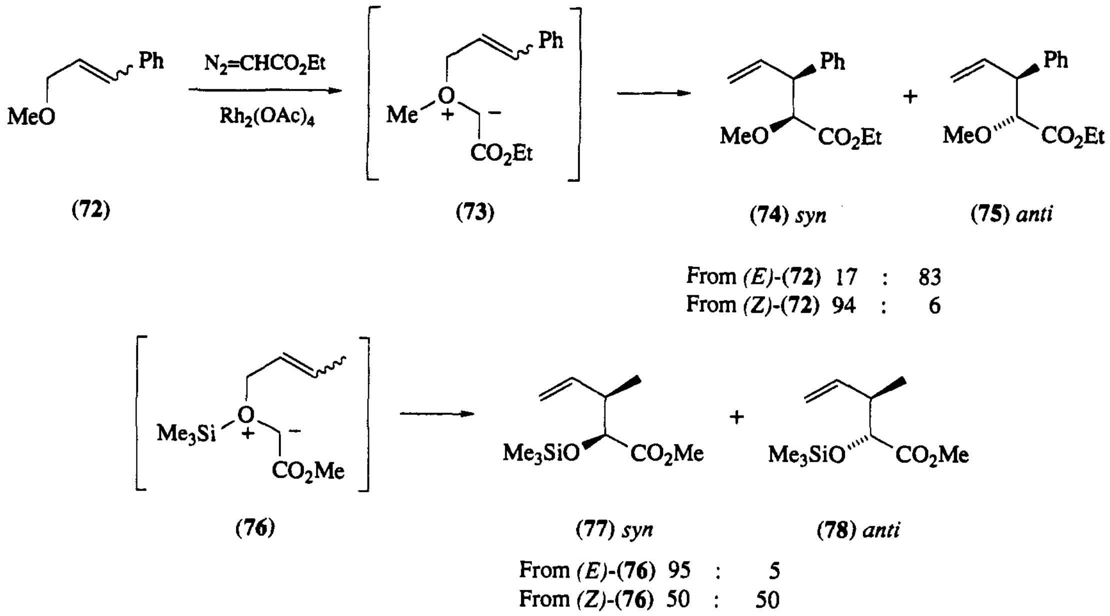
[a] See Scheme 10. [b] See footnote b of Table 4. [c] With Me_3SiOTf/NEt_3. [d] R = 2,2-Dimethyl-1,3-dioxolan-4-yl. [e] In the presence of $ZrCp_2Cl_2$. [f] Ref. 55 is ambiguous with 28:78 given for the (*E*):(*Z*) mixture ($\Sigma \neq 100\%$).

Taking the product-oriented view, homoallylic alcohols (**82**; equation 18) with *syn* configuration can be prepared from (*E*)- or (*Z*)-alkenes in 95% isomeric purity (Table 6). Less numerous and less selective — but again including the choice of (*E*)- or (*Z*)-ethers as starting materials — are the syntheses of the *anti* epimers (**84**; equation 19) (Table 7).

Perfect *anti* selectivities may also result where they would not have been predicted on the basis of much less satisfactory model studies (*cf.* Table 5, entries 1 and 9). Pertinent examples are the Wittig rearrangements of the sterically demanding acid (**85**; equation 20)[57,58] or of the oxazoline (**87**; equation 21).[40] The highly *syn,cis* selective synthesis of homoallylic alcohols (**26**) from isopropyl esters was discussed earlier in a different context (equation 12, Scheme 3).[38,39]

Axial *vs.* equatorial selectivities of Wittig rearrangements were studied with the *t*-butylcyclohexane derivatives (**89**; equation 22) (Table 8). The lithio dianion of acid (**89a**) prefers equatorial attack. The Bu^tO_2C (**89b**) and $Me_3SiC{\equiv}C$ substituted ethers (**89c**) undergo nonstereoselective rearrangements. The Still–Wittig reaction of (**89d**) is the only one among all known 2,3-sigmatropic shifts on this skeleton that prefers axial attack (67:33).

The conversion of the cyclopentenyl alcohol (**92**) into the homoallylic alcohol (**93**) occurs by a diastereoselective Still–Wittig rearrangement on the less hindered face of the molecule (equation 23).[60]



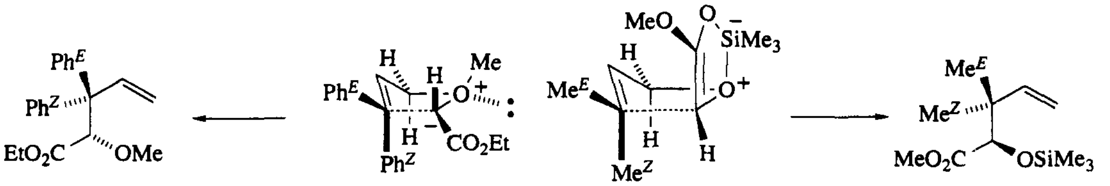
(72) **(73)** **(74)** *syn* **(75)** *anti*

From (*E*)-(**72**) 17 : 83
From (*Z*)-(**72**) 94 : 6

(76) **(77)** *syn* **(78)** *anti*

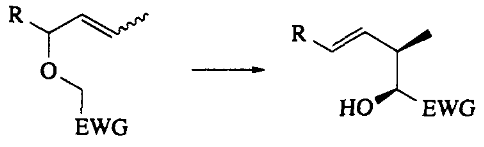
From (*E*)-(**76**) 95 : 5
From (*Z*)-(**76**) 50 : 50

Scheme 12 Oxonium ylide rearrangements



(74/75) **(79)** **(80)** **(77/78)**

Scheme 13 Transition states of oxonium ylide rearrangements



(18)

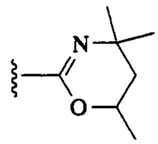
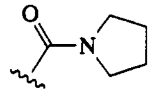
(81) **(82)** *syn*

4.6.2.1.3 *Control of the absolute configuration of the rearrangement product*

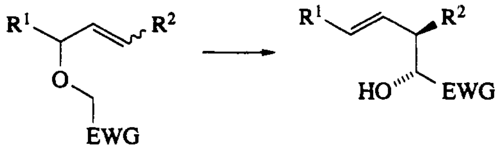
The absolute configuration of Wittig rearrangement products can be controlled starting from chiral ethers (**94**; Scheme 14). In the formation of (**95a**) configurational control stems from chirality transfer. Product types (**95b**)–(**95d**) are configurationally enriched through the influence of asymmetric induction. In the metalated ether (**94a**) the chiral center is a part of the five-atom backbone involved in the sigmatropic process. In the anions (**94b**)–(**94d**), the chiral center is only attached to the backbone in question. No matter where the location of the chiral center is in (**94b**)–(**94d**), it induces the formation of products with defined absolute configurations.

Complete chirality transfer from *cis*-ethers (**96**; equation 24) to homoallylic alcohols (**97**) was the cornerstone for numerous applications of the Wittig rearrangement in natural product synthesis (Table 9). The predictability of the absolute configuration of the rearranged product on the basis of a suprafacial bond shift and the ready availability of optically active starting materials make these reactions attractive.

Table 6 Synthesis of *Syn* Homoallylic Alcohols^{a,b}

(81)	*EWG*	*R*	*Yield (%)*	*Syn (%)*	*Ref.*	*Ref. for similar results*
(*E*)		H	92	100	55	
		H	98	96	54	56
	CO_2Pr^i	H	47	98	38^c	
	CO_2Me	H	83	97	14^d	
(*Z*)	$Me_3SiC{\equiv}C$—	Pr^i	62	>98	48	31, 48, 49
	$MeC{\equiv}C$—	H	55	100	31	48
	$MeOC_6H_4$—	H	70–98	100	47	47
	$H_2C{=}CMe$—	Pr^i	93	97	35	26, 34

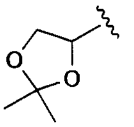
[a] See equation (18). [b] See footnote b of Table 4. [c] LDA, $ZrCp_2Cl_2$. [d] Me_3SiOTf mediated rearrangement of the isolated ketene Si-acetal.



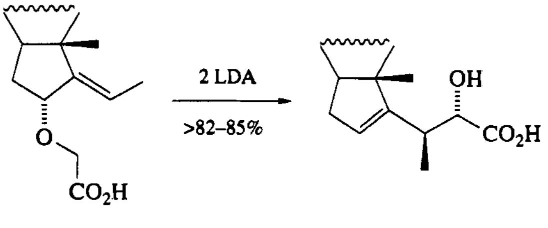
(19)

(83) **(84)** *anti*

Table 7 Synthesis of *Anti* Homoallylic Alcohols^{a,b}

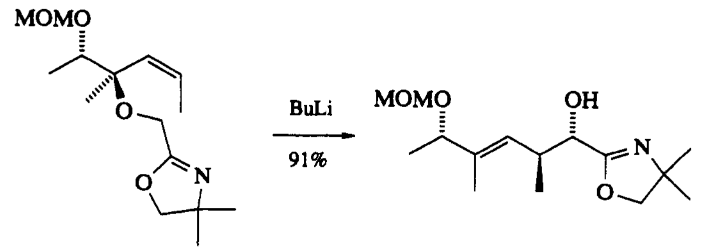
(83)	*EWG*	*R^1*	*R^2*	*Yield (%)*	*Anti (%)*	*Ref.*
(*E*)	$MeC{\equiv}C$—	H	Me	65	99	31
(*E*)	$HC{\equiv}C$—	H	Me	72	99	31
		Pr^i	Me	63	89^c	17
(*Z*)	CO_2R	H		40–79	100	53

[a] See equation (19). [b] See footnote b of Table 4. [c] Together with 9 rel-% of (*Z*)-isomer(s) with unassigned configuration(s).



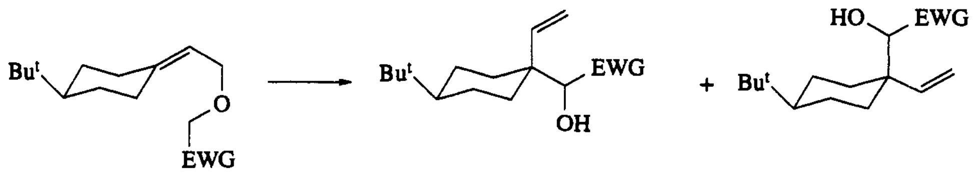
(20)

(85) **(86)** >98:<2



(87) (88) >100:1

(21)



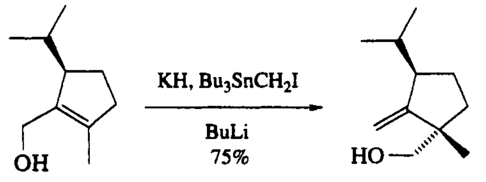
(89) (90) equatorial attack (91) axial attack

(22)

Table 8 Wittig Rearrangements in Conformationally Fixed Cyclohexanes[a]

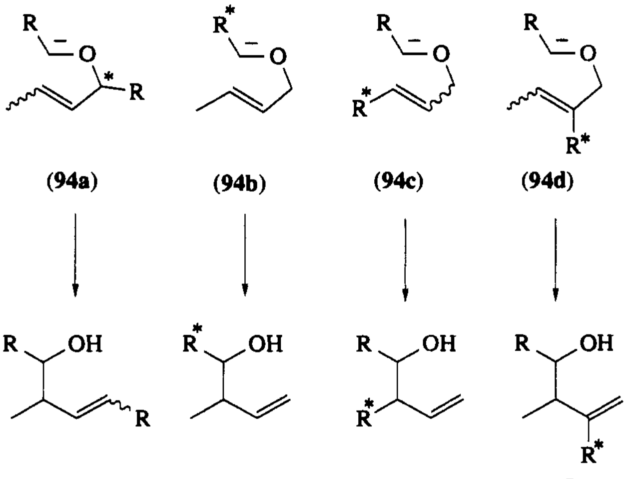
(89)	*EWG*	*Yield (%)*	*(90):(91)*	*Ref.*
(a)	CO_2H	63	*ca.* 100:*ca.* 0	36
(b)	CO_2Bu^t	51	71:29	59
(c)	$Me_3SiC{\equiv}C$—	74	55:45	59
(d)	Bu_3Sn^b	86	34:66	59

[a] See equation (22). [b] EWG = H in (90) and (91).



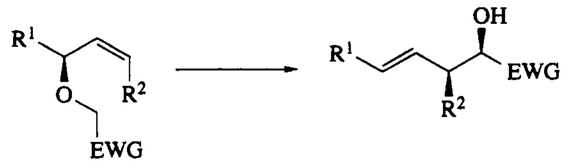
(92) (93)

(23)



(95a) (95b) (95c) (95d)

Scheme 14



(24)

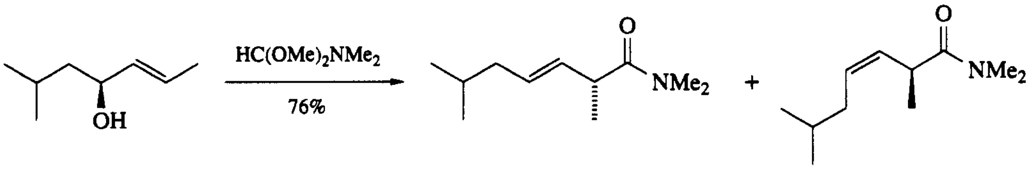
(96) **(97)** *syn*, 1 enantiomer

Table 9 Chirality Transfer in 2,3-Wittig rearrangements[a]

EWG	*R^1*	*R^2*	*Yield (%)*	*Ref.*	*Synthesis use*
Me_3Sn[b]	R^n	Me	80	20	Steroid side chain
	R^s	—$CMe_2OTBDMS$	82–84	22	Steroid side chain
$H_2C{=}CMe$—	Pr^i	Me	93	35	Prelog–Djerassi lactone
$Me_3SiC{\equiv}C$—	Me	Me	>64	61	Pheromone
	Me	Bu^n	96	32	Blastmycinone
	Pr^i	—$CH_2OTBDMS$	>85	33	Talaromycin

[a]See equation (24).[b]EWG = H in (**97**)

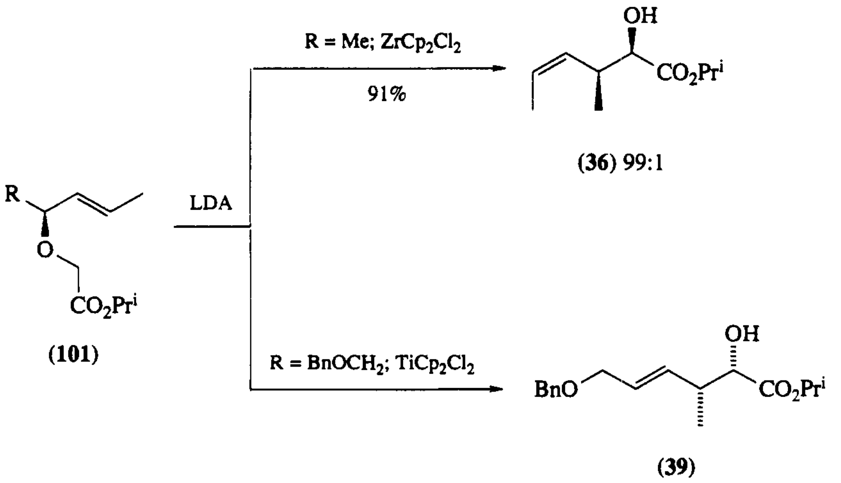
Allylic alcohols with a *trans* double bond give product mixtures in the Still–Wittig rearrangement (*cf.* equation 7[21]). Advantageously, such substrates (*e.g.* **98**) can be converted to homoallylic alcohols with 100% chirality transfer by the Büchi rearrangement (equation 25).[23]



(25)

(98) **(99)** 87:13 **(100)**

Proper variation of a 'remote' substituent allowed selective conversion of different alcohols (**101**) of identical stereostructure into hydroxy acids (**36**)[38] and (**39**)[39] of opposite absolute configurations (Scheme 15). The underlying reason was already presented *en passant* in Scheme 4.



(36) 99:1

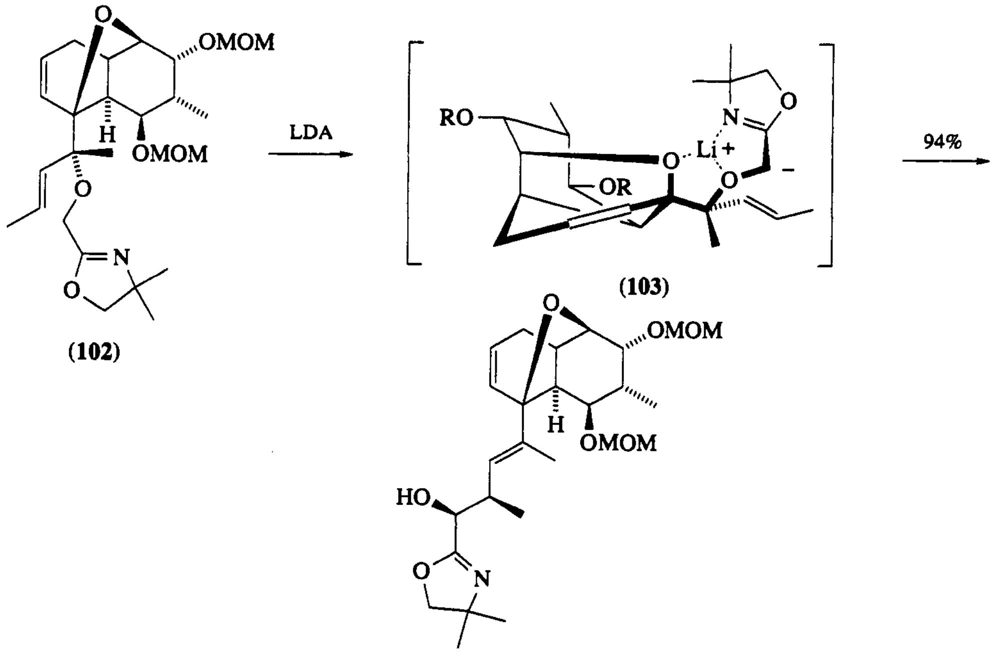
(101)

(39)

Scheme 15

Skilful use of chelation by the oxygen bridge was made in the elaboration of oxazoline (**102**) to the rearranged (**104**). Only one out of eight possible stereoisomers was formed (equation 26).[62] Highly efficient chirality transfer from similar substrates with the Still–Wittig rearrangement is also known.[63]

Chirality transfer out of a cycle was used repeatedly in steroid side chain synthesis (equation 27;[64] *cf.* equation 20[57,58]). The rigidity of the substrate grants high stereocontrol. The advantage of an unequivocal



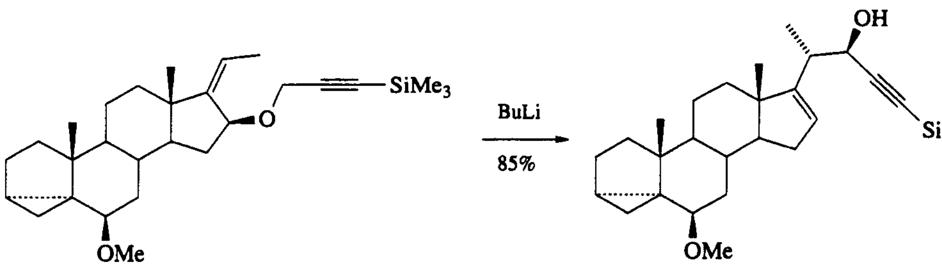
(102)

(103)

(104)

(26)

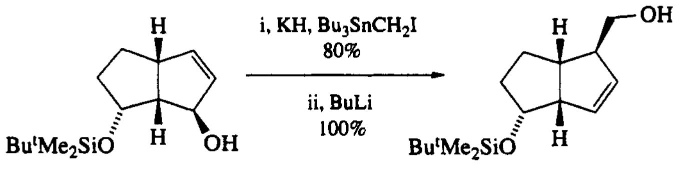
orientation of the rearranging moiety with respect to the attacked C=C bond is shared by chirality transfer within cycles. The one-pot two-step conversion of alcohol (**107**) into its homolog (**108**) illustrates how a hydroxy group serves to direct a hydroxymethyl group to a given face of a molecule (equation 28).[65] For successful chirality transfer, dissociative 1,2- or 2,3-pathways must not interfere; this was, however, reported occasionally starting from substituted 2-cyclohexenols under Wittig[19,7] or Büchi rearrangement conditions.[23]



(27)

(105)

(106)

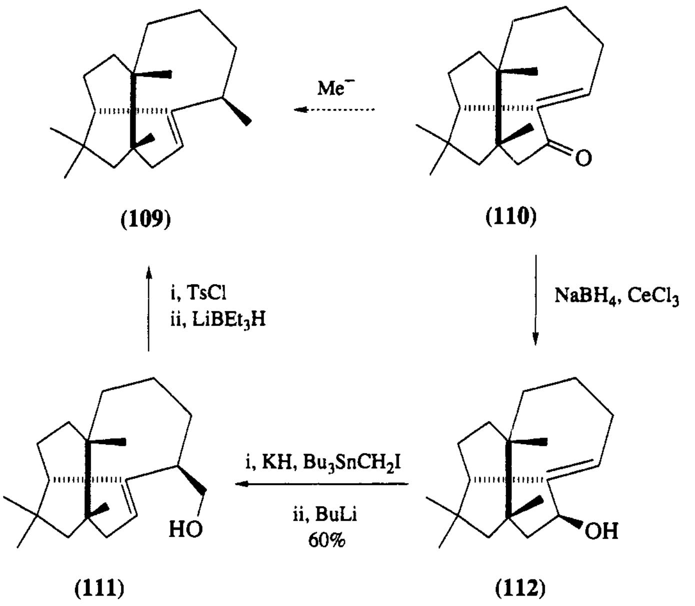


(28)

(107)

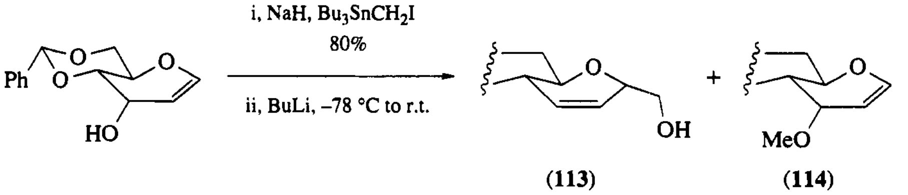
(108)

How a CH_2OH group can be guided into a molecule by means of a hydroxy group which is carried through a Still–Wittig rearrangement, is nicely demonstrated in the total synthesis of laurenene (**109**; Scheme 16).[66] Since Me_2CuLi introduced the missing methyl group into (**110**) from the wrong, *i.e.* bottom, face, recourse was made to a rearrangement *via* alcohol (**112**). It delivered the CH_2OH entity from the desired, *i.e.* top, face into (**111**). Finally, it was unmasked to the methyl group of the target molecule.



Scheme 16

Chirality transfer through a Still–Wittig reaction provided the *C*-glycoside (**113**) from the enol ether (equation 29).[67] The low yield (25%) was mainly due to protonation of the intervening oxyanion to the methyl ether (**114**) prior to rearrangement. Presumably, this side reaction could have been suppressed with HMPA as cosolvent.[68]



(29)

Asymmetric induction by a chiral substituent in the anion moiety provides efficient access to homoallylic alcohols with (*S*)- (Scheme 17) or (*R*)-configuration (Scheme 18), respectively. Optically active alcohols with defined absolute and concomitant *anti* configuration have not yet been prepared with satisfactory selectivity.

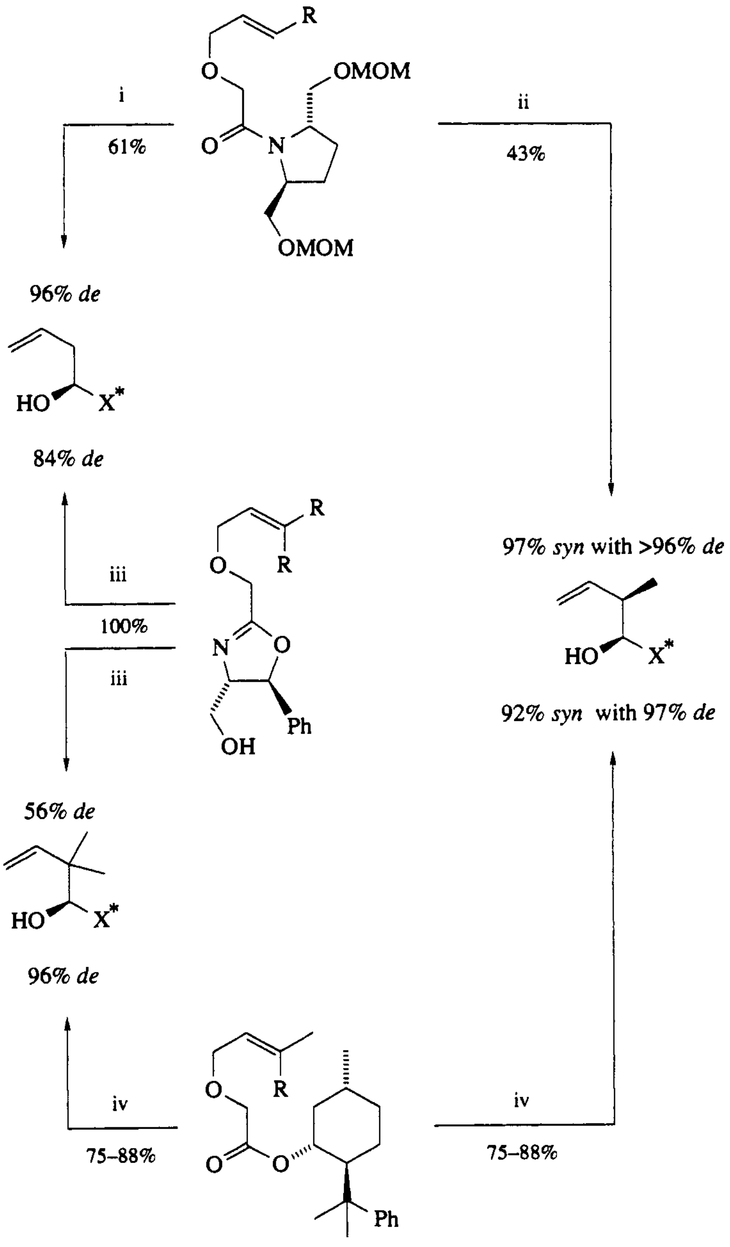
A chiral anion moiety dictates the stereochemistry of the macrocyclic ring contraction (**4**) → (**5**) of a lithiated allylic propargylic ether (equation 2); scope and utility of such reactions are detailed in Volume 3, Chapter 3.11. Chiral allyl moieties also effect stereocontrol in the Wittig rearrangement of ethers (**116**). There, the chirality resides in an allylic C—O bond. Depending on the size of the neighboring R group, the epimers (**117**)/(**118**; equation 30) result in ratios ranging from 96:4–45:55 (Table 10).[68]

The main product is thought to arise from transition state (**119**; Scheme 19).[68] (**119**) is stabilized through the antiperiplanar alignment of the allylic *C—O orbital with respect to the approaching carbanion.[71] This geometry entails the formation of the *syn* product (**117**). The diastereomeric transition state (**120**) is caused by the alkyl substituent striving for the least hindered orientation with respect to the pericyclic transition state. (**120**) competes with the electronically favored (**119**) only if R is sterically demanding.

MOM and MEM protecting groups induce *syn* selectivity in this type of rearrangement more efficiently than benzyl groups; (**122**) is the only detectable isomer obtained from MEM ether (**121**; equation 31).[68] The mode of action of these auxiliaries can be understood by secondary orbital interactions in transition state (**123**). The amino group of allylamine (**124**) acts as a similar inducer of asymmetry. This compound, again, led to a single rearrangement product (**125**; equation 32).[72] Carbamate (**126**), likewise, gave only one rearranged alcohol in 88% yield.[72]

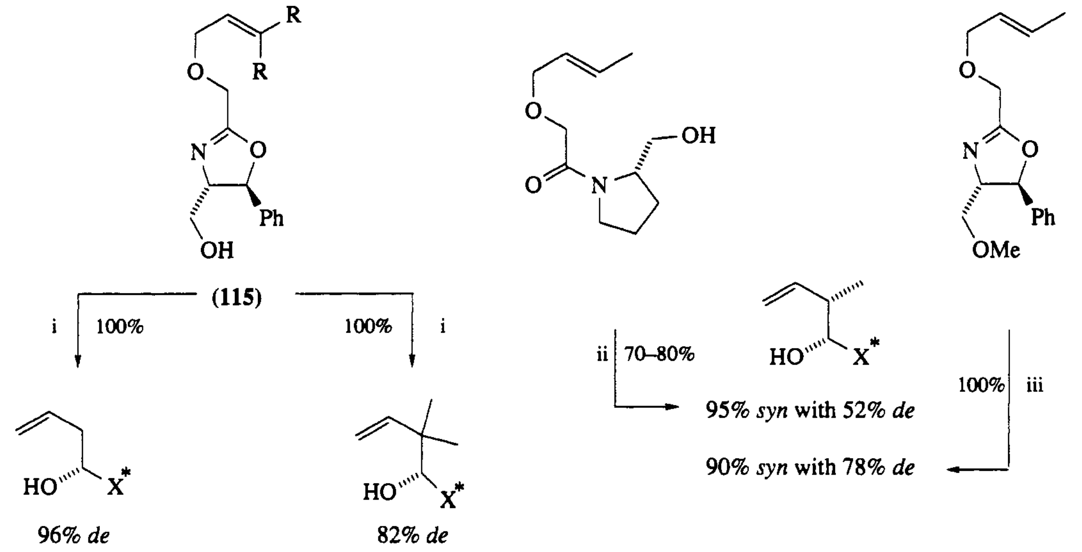
Asymmetric induction plus simple diastereoselectivity is observed in the Wittig rearrangements of ester (**127**; equation 33)[53] or silyl ether (**130**; equation 34).[48,49] The configuration of the allylic carbon is identical in the two reactions and analogous to that of the foregoing examples. Interestingly, the accompanying *syn*/*anti* preferences are complementary: the C—OH bond is oriented downward in (**128**) and upward in (**131**). How the C—OH bond is arranged with respect to the vinyl group depends on the size of the carbanionic substituent. The alkynyl group of transition state (**132**) protrudes unhindered over the heterocycle, whereas the voluminous ester moiety of transition state (**129**) is pushed away from the dioxolane.

Asymmetric induction of the same kind controls the configuration at the allylic methine carbon in compound (**134**); (**134**) results from a chain-elongating Wittig rearrangement (mechanism: Scheme 6) of sulfone (**133**; equation 35).[73] Surprisingly, the sense of the asymmetric induction in the rearrangement of silyl ether (**135**; equation 36)[48] is opposite to that of more than a dozen other (*E*)-ethers.[49,53,68,72]



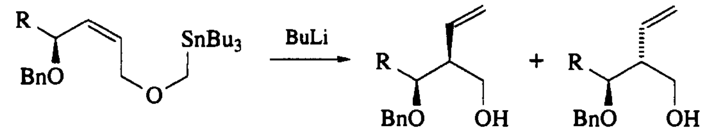
i, BuLi;[56] ii BuLi, $ZrCp_2Cl_2$;[56] iii,KH;[69] iv, LDA[52]

Scheme 17 Synthesis of masked hydroxy acids with (2*S*) configuration



i, KH, 18-crown-6;[69] ii, LDA;[54] iii, BuLi[70]

Scheme 18 Synthesis of masked hydroxy acids with (2*R*) configuration

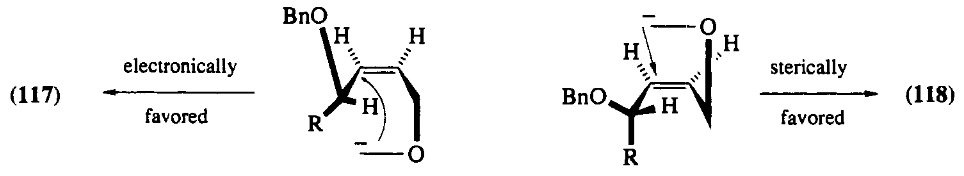


(116) (117) (118) (30)

Table 10 Asymmetric Induction in Wittig Rearrangements of Allylic Ethers[a]

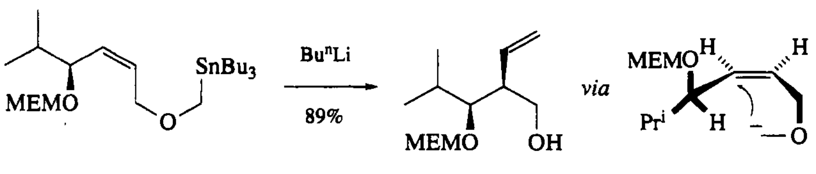
R	*Yield (%)*	*(117):(118)*
BnCH2—	81	96:4
Pr^i	78	93:7
Ph	71	89:11
Bu^t	67	45:55

[a] See equation (30).

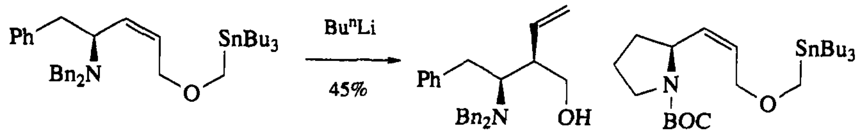


(119) (120)

Scheme 19 Transition states of Wittig rearrangements under the influence of asymmetric induction

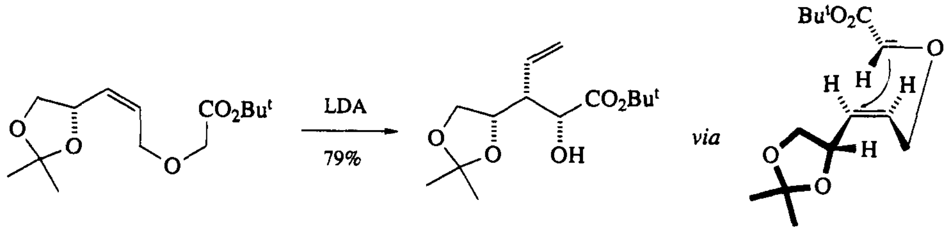


(121) (122) (123) (31)



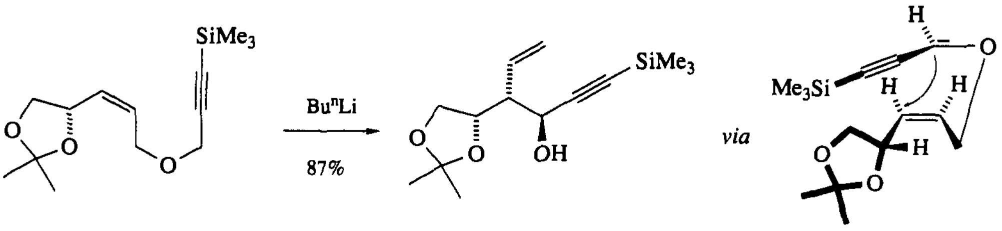
(124) (125) (126)

(32)



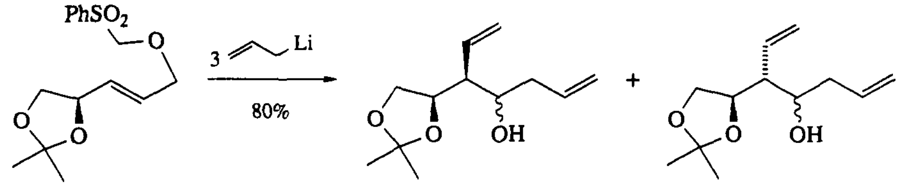
(127) (128) (129)

(33)



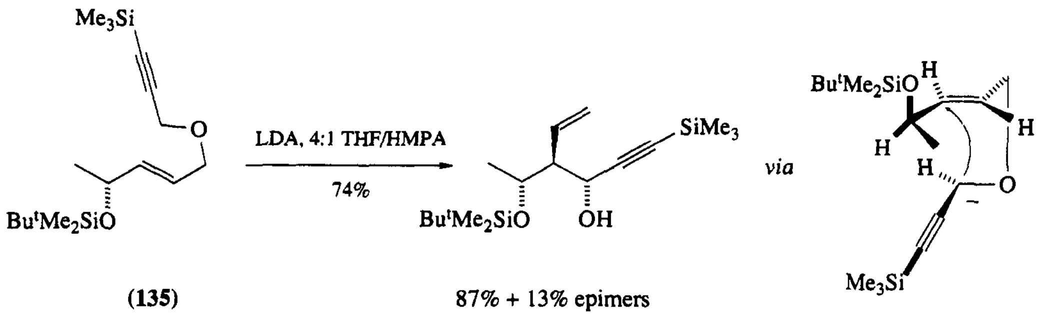
(130) (131) (132)

(34)



(133) (134) 93:7

(35)



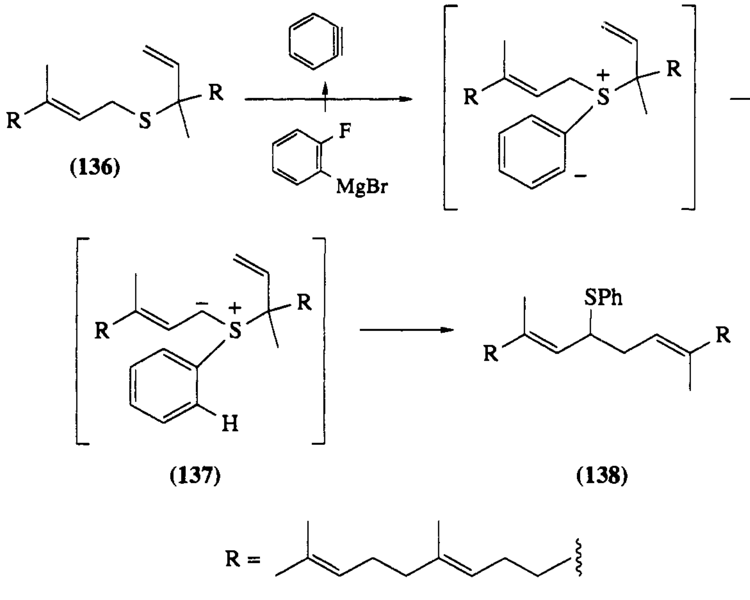
(135) 87% + 13% epimers

(36)

4.6.2.2 Rearrangement of Sulfides and Amines

2,3-Sigmatropic rearrangements of allylic nitrogen or sulfur compounds are usually performed with ylides. Of the corresponding anionic 2,3-rearrangements, thia-Wittig rearrangements are known, their aza counterparts virtually not. Even the thia-Wittig rearrangements have been rarely used apart from early model studies. Multistep syntheses of some of the starting materials,[74] suspected noncompatibility of other functionality with the strongly basic thio anion and the attractiveness of the sulfonium ylide rearrangement as a methodological alternative played their role in discouraging from applications.

Onium salt precursors for ylide rearrangements are easily obtained from amines or sulfides by alkylation. The direct transformation of sulfides into sulfonium ylides is possible, too. To this end, sulfides are reacted with carbenoids like $CH_2I_2/ZnEt_2$,[75] $(MeO_2C)_2C{=}N_2/CuSO_4$,[76] $(EtO_2C)_2C{=}N_2/Rh_2(OAc)_4$[77] or $LiC{\equiv}CCMe_2Cl$.[78] In a related approach, the reaction with benzyne was used to transform a sulfide (**136**) to a sulfonium ylide (**137**) in a single operation. (**137**) rearranged under the reaction conditions and gave one major product (**138**) in high yield (Scheme 20).[79]



Scheme 20

Sulfonium methylides can also be prepared from sulfides by treatment with Me_3SiCH_2OTf followed by desilylation with CsF.[80] This method allows the regioselective generation of sulfonium ylides (*i.e.* **140**),[81] which would not form under equilibrium deprotonation conditions (*cf.* **139** → **141**; Scheme 21).[82] Neither the (*Z*)-selective (90:10) formation of a trisubstituted alkene[76] nor enantioselective versions[83,84] have become essentials of ylide rearrangement methodology. Far more important are aspects of regio- and diastereo-control.

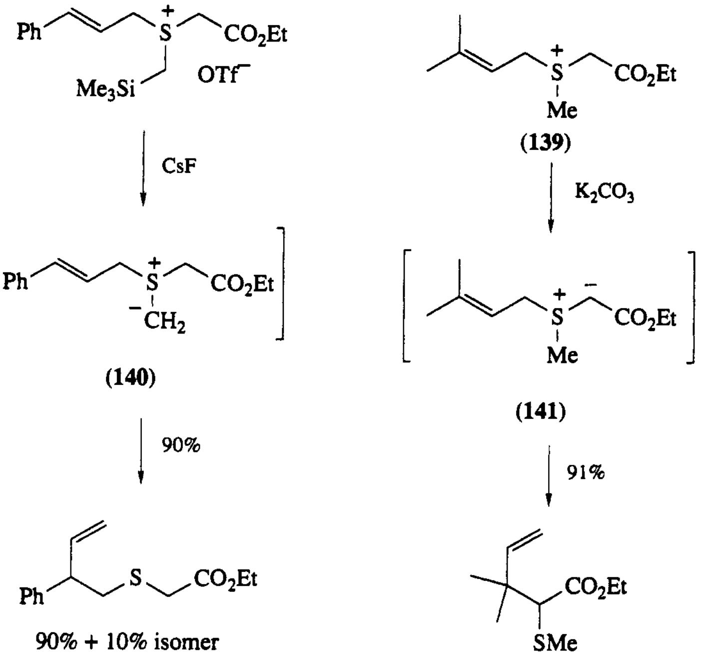
4.6.2.2.1 Regioselectivity

The base-induced 2,3-shift in a benzyltrialkylammonium halide (Sommelet–Hauser synthesis) effects an *ortho*-selective aminomethylation of aromatics. A variation (*ortho*-selective formylation) is shown in equation (37).[85] Unfortunately, the 1,2-Stevens rearrangement (→ 10% **143**) of the intervening ylide competes with the 2,3-pathway (→ **142**). A reliable tool to circumvent this very general difficulty is still unknown.[86] Nonetheless, 2,3-rearrangement pathways can be very efficient as demonstrated by the synthesis of the cyclic amine (**144**; equation 38).[87]

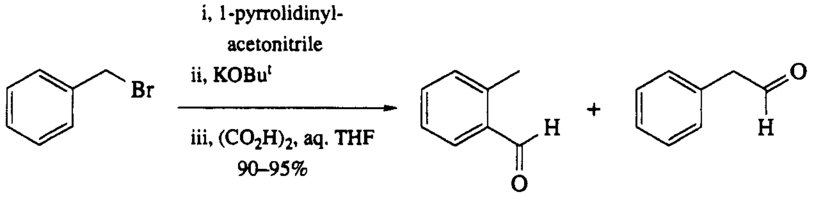
Sulfur ylides are also apt to introduce carbon atoms regioselectively into aromatic frameworks (equation 39).[88]

4.6.2.2.2 Diastereoselectivity

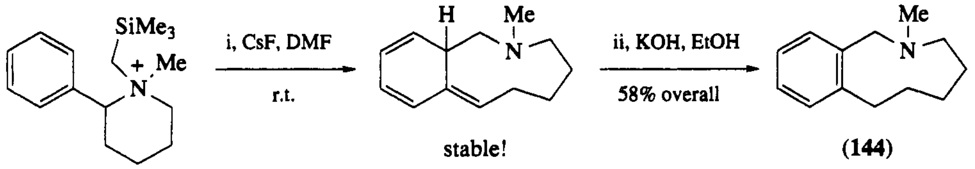
If opportunity is given, a (thiolated) carbon atom can be transferred from a sulfur ylide to a double bond with diastereocontrol. The carbon remains on that side of the molecule which contained the sulfur initially (*e.g.* equation 40).[75] By similar chirality transfer, the β-oriented phenylthio group of octalin (**147**) determines the β-orientation of the transposed $PhSCH_2$ unit in the reaction product (**148**; equation 41).[89] The efficient formation of a quaternary center from (**147**) is all the more remarkable since an



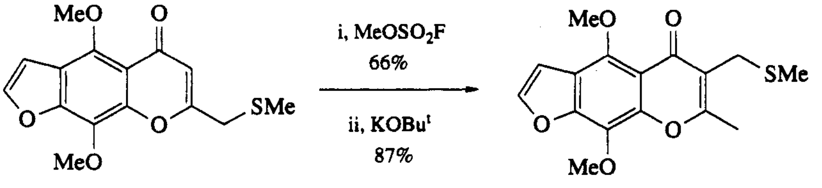
Scheme 21



(142) 90:10 (143) (37)



stable! (144) (38)

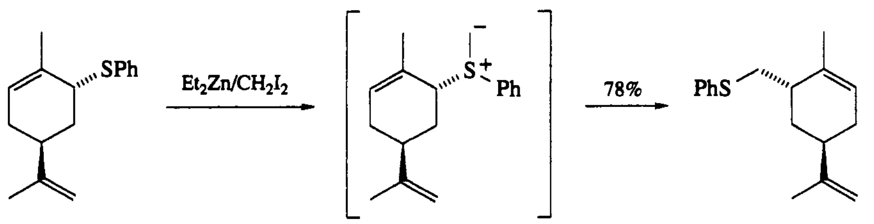


(145) (146) (39)

electron rich C═C bond is attacked. Attempted 2,3-Wittig rearrangements of the structurally related stannyl ether (**149**) were sluggish and accompanied by decomposition and 1,2-rearrangement.[19]

Chirality transfer in acyclic substrates has received little attention so far. However, the complete stereoselectivity of the rearrangement (**150**) → (**151**; equation 42) indicates a potential not yet fully appreciated.[90]

Ylides may attack preponderantly one of the two diastereotopic faces of a C═C bond in the course of a 2,3-sigmatropic shift. Facial selectivity with respect to exocyclic C═C bonds will be considered first.



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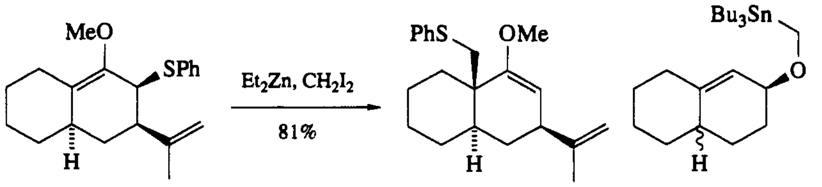
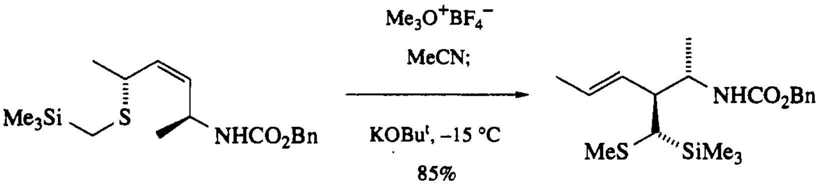


(147) **(148)** **(149)**

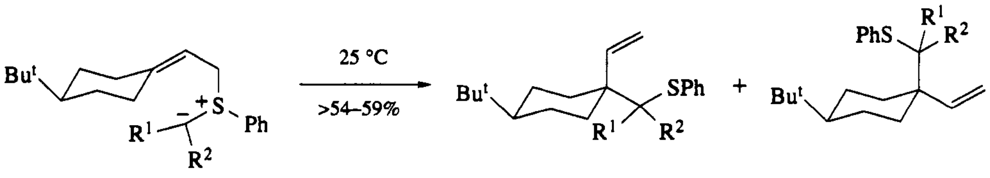
(41)



(150) **(151)**

(42)

Equatorial attack was reported for the rearrangements of sulfonium and nitrogen ylides in the conformationally fixed Bu^t-substituted cyclohexanes (**152**; equation 43)[1] and (**153**; equation 44),[91] respectively.

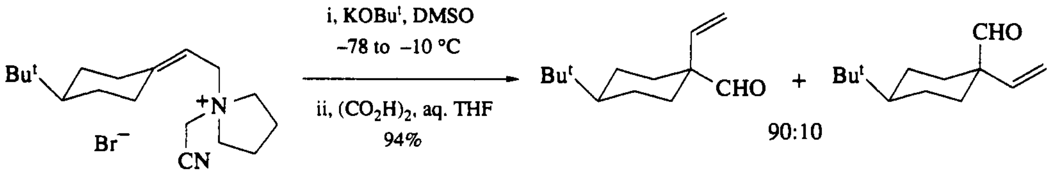


(152)

(43)

R^1	*R^2*	*Equatorial attack*	:	*Axial attack*
Cl	Cl^a	97		3
H	CO_2Et	91		9

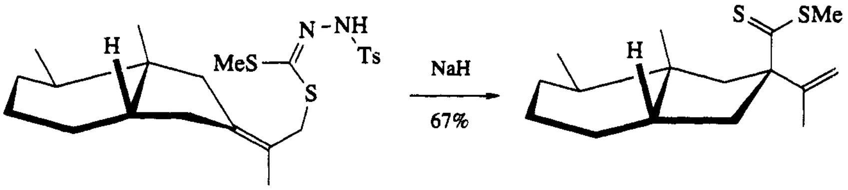
[a] Product: R^1,R^2 = C=O



(44)

(153) equatorial attack axial attack

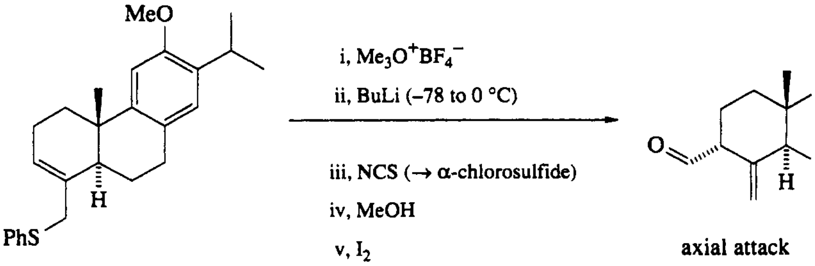
A thia-Wittig rearrangement in the methylenecyclopentane (**154**) proceeded to (**155**) without formation of the epimer (equation 45).[1] Obviously, the reaction proceeds on the less hindered (convex) face of the bicyclic framework. Equally high diastereoselectivity — unassigned, but presumably also on the less hindered (*exo*) face — is recorded for the 2,3-rearrangement of a methylenecyclopentane-derived sulfur ylide.[75]



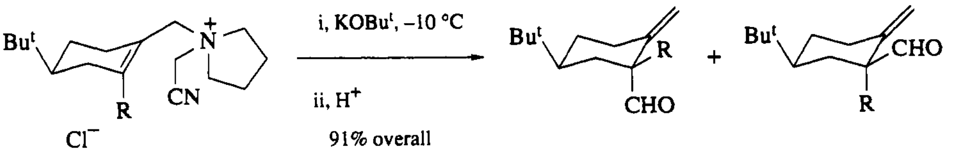
(154) (155) (45)

Surprisingly, a methylenecyclohexane-derived carbazate akin to (**154**) gave negligibly more equatorial (55%) than axial attack when treated under the same conditions. When the rearrangement was initiated with 10 mol % Cu(acac)$_2$, equatorial attack amounted to 65%.[74] The first observation is clearly inconsistent with Evans' reaction (**154**) → (**155**). The copper catalysis of the second process suggests the existence of a synthetically unexplored second rearrangement mechanism through a carbenoid.

The conformationally fixed six-membered ring (**156**) contains an endocyclic C=C bond. (**156**) displays axial selectivity in the 2,3-sigmatropic shift of the corresponding sulfur ylide (equation 46).[92] Unselective, on the other hand, is the seemingly related rearrangement (**157a**) → (**158a/159a**) of a nitrogen ylide (equation 47).[91] In this system, axial attack is in part (80%) restored upon replacing the alkenic hydrogen of (**157a**) by a methyl group in (**157b**).[91]



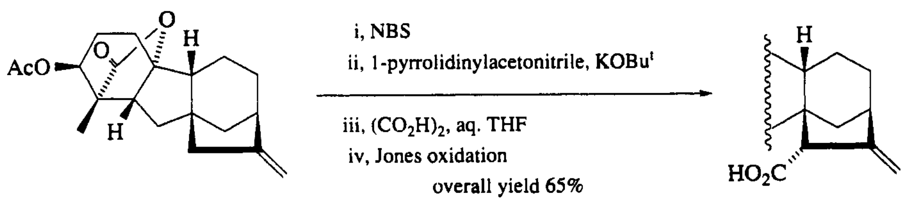
(156) (46)



(157) (47)

	R	(158) Axial attack	:	(159) Equatorial attack
(a)	H	57	:	43
(b)	Me	80	:	20

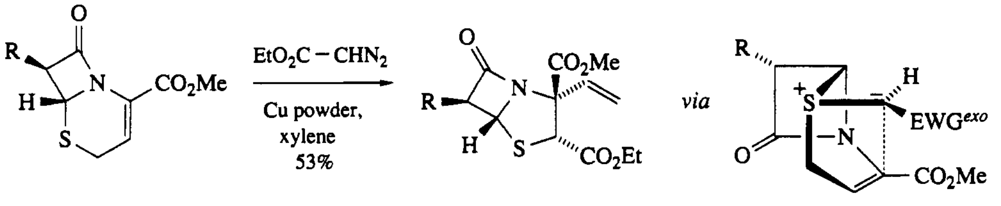
That isomerization of the β,γ-unsaturated aldehyde to the conjugated isomer during hydrolysis is negligible as in the case of (**158a/159a**; equation 47) is no standard feature of this reaction.[93] Presumably, smaller strain of the deconjugated isomer contributes to leaving certain of these aldehydes unaltered. Mostly due to this hindrance of isomerization, the carboxylation (**160**) → (**161**) could be accomplished with excellent stereocontrol (equation 48).[94]



(48)

(160) (161)

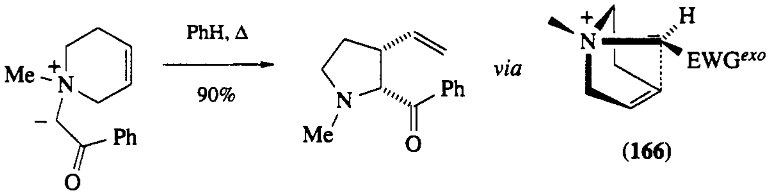
Ylides with substituted carbanions can form vicinal stereocenters upon 2,3-rearrangement. In acyclic compounds, little stereocontrol[9b,95] is documented more often than good control.[96] Cyclic ylides, on the other hand, exhibit high stereoselectivities for ring contractions *via* 2,3-sigmatropic shifts. The oldest and still the most impressive among such reactions is Yoshimoto's transformation of the cephalosporin (**162**) into the penicillin skeleton (**163**). Diastereoselectivity follows from an *exo* preference of the ester group in transition state (**164**; equation 49).[97]



(49)

(**162**) R = NHCOBn (**163**) (**164**)

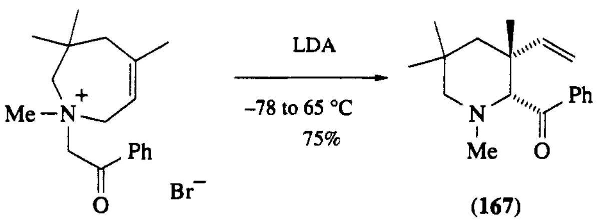
Turning to ammonium ylides, the *cis* selective ring contraction of the ylide (**165**) is noteworthy (equation 50).[98] From the product structure, again an *exo* preference is deduced for the electron-withdrawing group (here: benzoyl) in the corresponding transition state (**166**). Notice the similarity of transition states (**166**; nitrogen ylide) and (**164**; sulfur ylide). The (*Z*)-configuration of the rearranged piperidine (**167**) follows from similar considerations (equation 51).[99] The yield of this reaction, in the course of which a quaternary stereocenter is created, is remarkably good (75%).



(50)

(**166**)

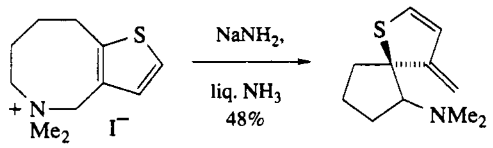
(**165**)



(51)

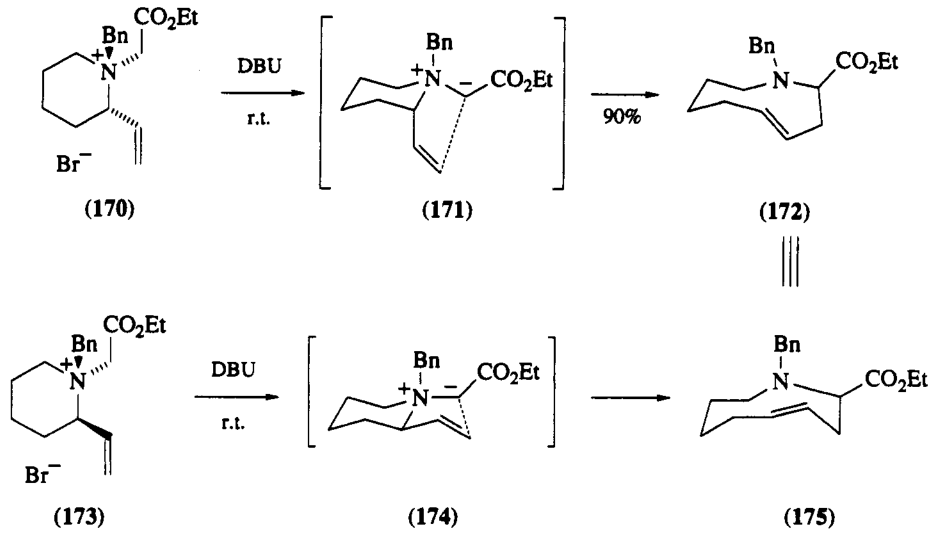
(**167**)

An interesting ring contraction of the eight-membered heterocycle (**168**) furnished the spirocycle (**169**) in which the aromaticity is lost (equation 52).[100] Unfortunately, the stereochemical integrity of the rearrangement product was not commented upon. Ylides are used for ring expansion reactions likewise. The *cis* and *trans* isomeric ylides (**170**) and (**173**) lead to the same rearrangement product (**172** ≡ **175**) with a *trans* double bond (Scheme 22).[101] This result can be rationalized on the assumption that in each of the transition states (**171**/**174**) the ester enolate is equatorial.



(52)

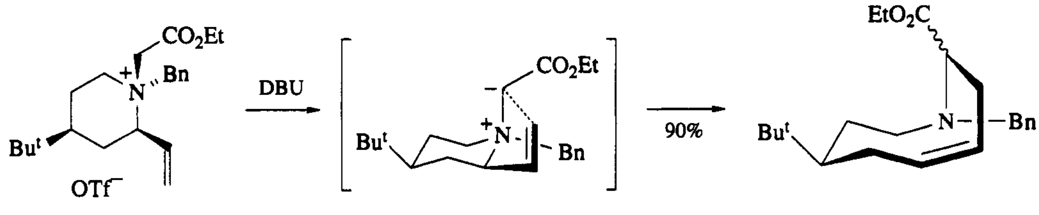
(**168**) (**169**)



(170) **(171)** **(172)** **(173)** **(174)** **(175)**

Scheme 22

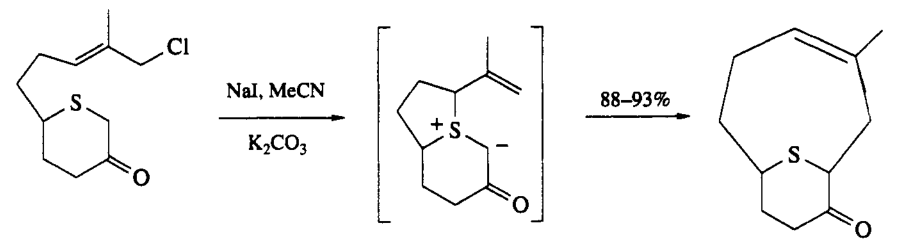
In an interesting variation of these rearrangements, a Bu^t group was introduced into ylide (**171**) to lock the enolate side chain axially and the vinyl group equatorially (*e.g.* **176**). This turns the geometry of the rearrangement product *cis* (equation 53).[102]



(53)

(176)

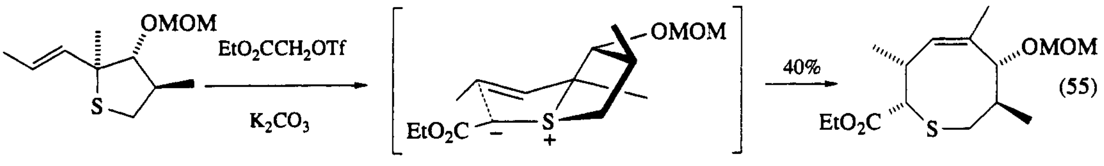
Comparable *cis/trans* selectivities and similar conformational effects on them were studied in ring enlargements of cyclic sulfonium ylides.[103] Rearrangements of sulfur ylides performed in repetition were used for stepwise ring expansion 5- → 8- → 11- → 14- → 17-membered.[104] Synthesis applications of sulfonium ylide mediated ring expansions are mostly due to Vedejs.[6] For example, the key step of his total synthesis of zygosporin[105] was an intramolecular allylation of type (**177**) → (**178**; equation 54).[106] An ylide (**178**) is formed initially in which the sulfur brings the previously separated termini of the molecule close to each other. This sets the stage for an ensuing efficient (93% yield) sigmatropic bond shift.



(54)

(177) **(178)**

The 2,3-rearrangement (**179**) → (**180**) indicates the possibility of obtaining ring-expanded products with high diastereocontrol. Only one (**180**) of four possible stereoisomers was formed (equation 55).[107a] Subsequently, the ester group of the first rearrangement product (**180**) was transformed into another C=C bond. Thus, a second ring expansion *via* a sulfonium ylide could be performed carrying the material further towards methinolide.[107b]



(55)

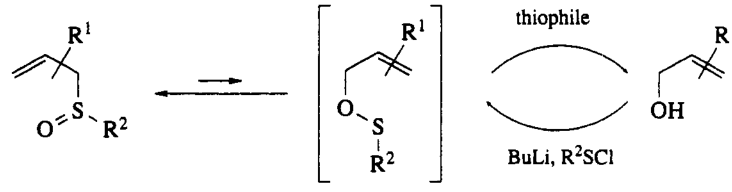
(179) **(180)**

4.6.3 FORMATION OF CARBON-HETEROATOM BONDS

4.6.3.1 Sulfoxide–Sulfenate Rearrangement

The interconversion of C—O and C—S bonds is realized by the 2,3-sigmatropic shift of β,γ-unsaturated sulfoxides/sulfenates. In a higher oxidation state a sulfone–sulfinate 2,3-rearrangement is known; this is of little importance in synthetic chemistry as it is associated with a stepwise rearrangement mechanism which interferes even in slightly hindered substrates.[108]

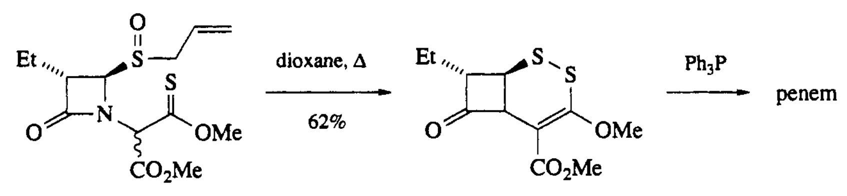
Allylic sulfoxides (**181**) and sulfenates (**182**) are related by a reversible reaction (equation 56). The equilibrium is shifted towards the sulfoxide. Due to the low barrier associated with this 2,3-shift optically active allylic sulfoxides can racemize at room temperature.[109] Accordingly, the reaction of an alcohol (**183**) with PhSCl *via* sulfenate (**182**) continues through the 2,3-rearrangement to the sulfoxide. Allylic sulfenates are very seldom isolable.[110] When, conversely, an allylic sulfoxide (**181**) is heated in the presence of a thiophile ($P(OMe)_3$, R_2NH, NaSR), the sulfenate (**182**) is removed from the equilibrium mixture by O—S bond cleavage. The ultimate reaction product obtained from an allylic sulfoxide, therefore, is an allylic alcohol (equation 56).



(56)

(181) **(182)** **(183)**

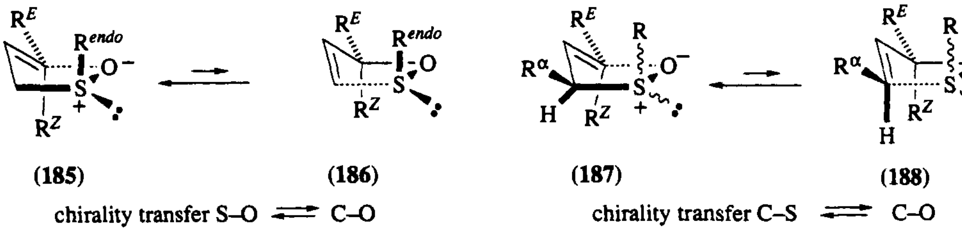
In such desulfurizing 2,3-rearrangements, the alcohol is usually sought and the thiophile–SR molecule undesired. One of the few instances where the thio compound was desired, is the conversion of sulfoxide (**184**) into a penem (equation 57).[111]



(57)

(184)

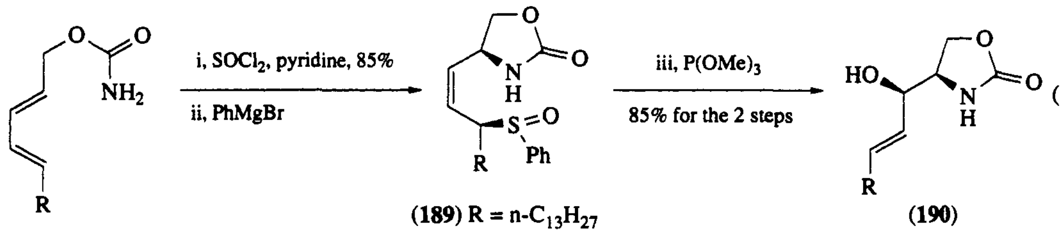
The stereochemical course of sulfoxide–sulfenate rearrangements was reviewed by Hoffmann in detail.[3] The results can be summarized as follows: (i) chirality transfer from the stereocenter on sulfur to carbon is only observed for sulfoxides without α-substituents (left-hand part of Scheme 23). Then, the (*Z*)-isomers react preferentially *via* the *endo* transition state (**185**) with up to 90% chirality transfer. (*E*)-Sulfoxides are less selective and therefore worthless as precursors for optically active rearrangement products. (ii) Any substituent R^α of the sulfoxide overrides stereocontrol originating in the stereocenter on sulfur (right hand part of Scheme 23). How chirality is transmitted is here determined exclusively by the desire of R^α to be quasi-equatorial in the transition state (**187**). At the same time, this orientation of R^α is tantamount to a *trans* configuration in the rearranged alcohol.



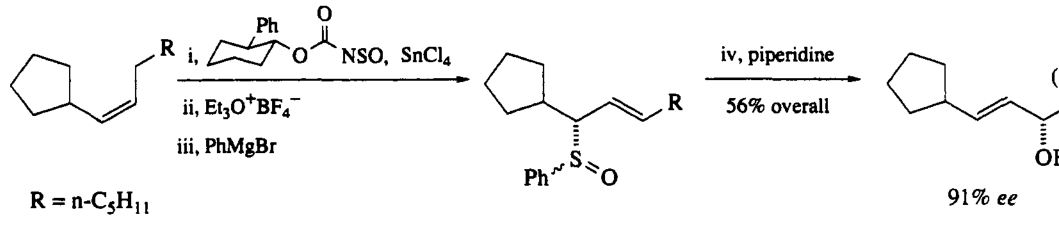
Scheme 23

4.6.3.1.1 *Chirality transfer and diastereoselectivity*

Chirality transfer from the C—S bond of sulfoxide (**189**) to the C—O bond of the sphingosine derivative (**190**) gave a single isomer (equation 58).[112] This type of chirality transfer will become more popular due to Whitesell's synthesis of suitable homochiral sulfoxides (equation 59).[113]



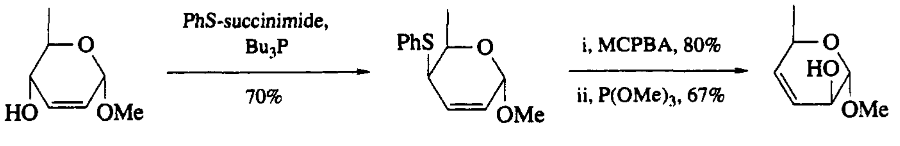
(58)



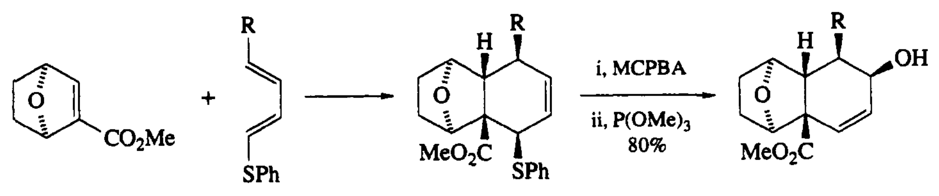
(59)

Chirality transfer in cycloalkenes is a more common practice. Equations (60)–(62) illustrate stereoselective syntheses of cyclohexenols.[110,114,115] Similar functionalizations of medium-sized rings are also known (10-membered[116] and 14-membered[117]). The many different ways to access allylic sulfoxides make their rearrangements a particularly versatile tool.

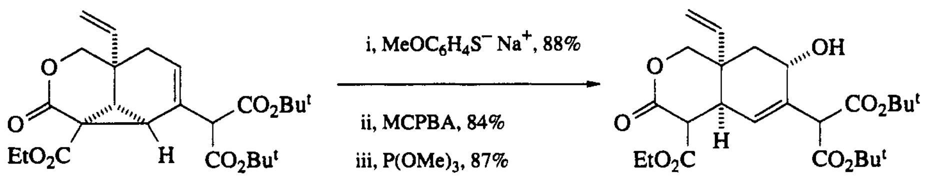
Unlike the foregoing rearrangements, that of sulfoxides (**191**) and (**193**) was accomplished with only one of the epimers (equation 63).[118] The reactive epimer was believed to be (**191**) because of its similarity with the favorable transition state (**185**) from Scheme 23. Going from the sulfenate (**194**) to sulfoxide (**195**; equation 64),[119] the phenyl group prefers the opposite orientation compared with the



(60)

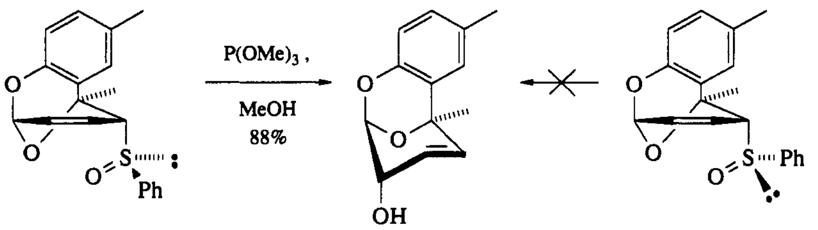


(61)



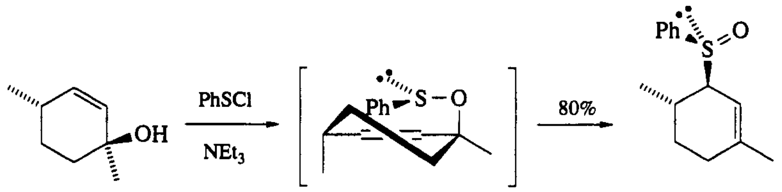
(62)

rearrangement (**191**) → (**192**). Obviously, the stereochemistry of equations (62) and (63) warrants a reconsideration.[120]



(63)

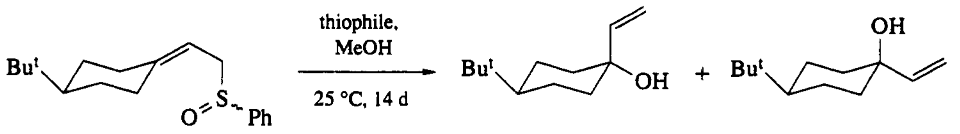
(191) **(192)** **(193)**



(64)

(194) **(195)**

In the *exo*-methylenecyclohexane (**196**) two diastereotopic faces of a C═C bond are available for the sulfoxide rearrangement. Under various desulfurization conditions the less hindered equatorial attack predominates (equation 65).[121] The greatest equatorial selectivity (92:8) was observed with the strongest thiophiles, *i.e.* $P(OMe)_3$ or $P(NEt_2)_3$. Piperidine gave less equatorial alcohol (66:34). Presumably, $P(OMe)_3$ captures the kinetically formed mixture of sulfenates, while partial equilibration of the isomers precedes the S—O bond cleavage with piperidine.



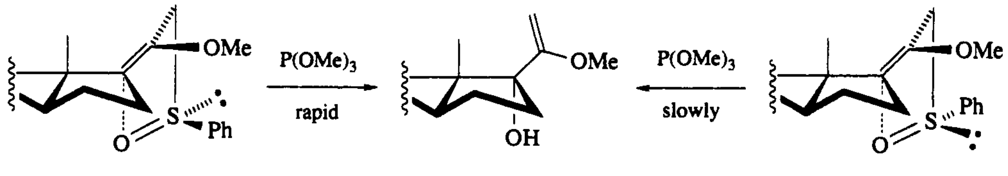
(65)

(196)

Thiophile	*Yield (%)*	*Equatorial attack*	:	*Axial attack*
$LiBH_3CN$	24	58	:	42
Piperidine	90	66	:	34
PhS^-	99	88	:	12
$P(OMe)_3$, $P(NEt_2)_3$	99	92	:	8

The *exo*-methylenecyclopentane (**197**) is also functionalized on the less hindered side upon rearrangement (Scheme 24).[122] The isomeric sulfoxide *epi*-(**197**) gave the same product (**198**) but more slowly. The retarding effect is due to the enforced *exo* orientation of the phenyl group in the transition state while *endo* is preferred (*cf.* Scheme 23).

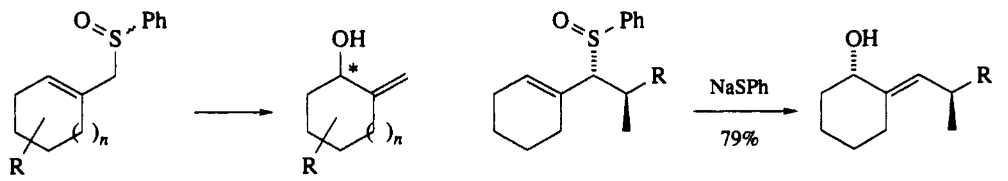
Selective attack on one of the two diastereotopic faces of an endocyclic alkene (**199**) is encountered occasionally.[123] However, in the absence of an α-substituent, the chiral center on the sulfur of (**199**) exerts stereochemical control itself (*cf.* **185** in Scheme 23). Hence, selectivities caused by the ring factors



(197) **(198)** *epi*-**(197)**

Scheme 24

may be compensated for in part.[124,125] In case of lack of diastereofacial selectivity in the 2,3-rearrangement of sulfoxide (**199**), stereocontrol can be restored in a secondary sulfoxide (**200**; Scheme 25).[126] The propensity of the side chain to become a *trans* alkenic substituent (*cf.* Scheme 23) provides the key control element.

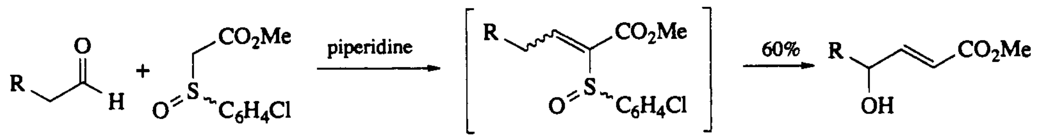


(199) **(200)**

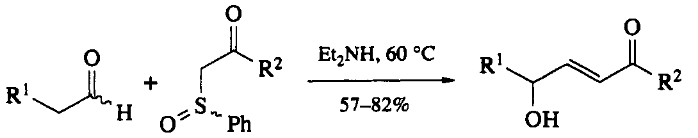
Scheme 25

4.6.3.1.2 Miscellaneous applications

A useful extension of sulfoxide–sulfenate rearrangements exploits the greater stability of allylic *vs.* vinylic sulfoxides.[127] For example, the Knoevenagel product (**202**) is deconjugated under the conditions of its formation. This sets the stage for a 2,3-rearrangement in the same pot (equation 66).[128] Optically active condensation products give hydroxy esters (**201**) with 64–72% *ee*.[129] 50–80% *ee* were reported for the analogous synthesis of the corresponding hydroxy nitriles.[130] The reaction of β-keto sulfoxides with aldehydes follows the same course of events (equation 67).[131]

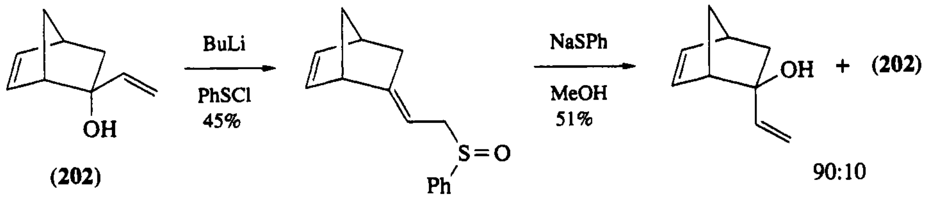


(201) (66)



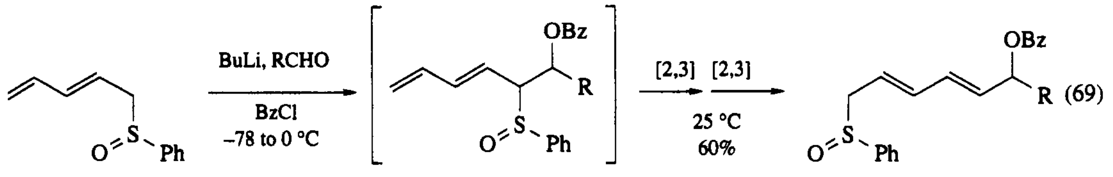
(67)

Sulfenate → sulfoxide and sulfoxide → sulfenate rearrangements were combined in the inversion of secondary[132] or tertiary allylic alcohols (equation 68).[133]



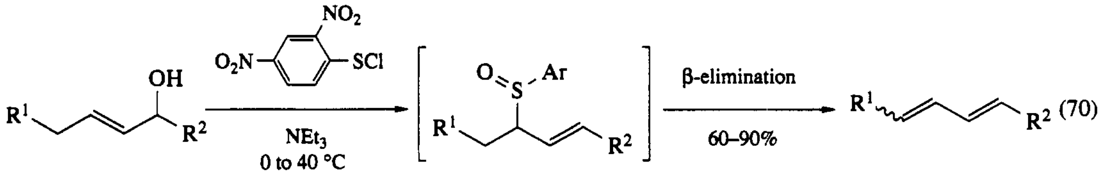
(68)

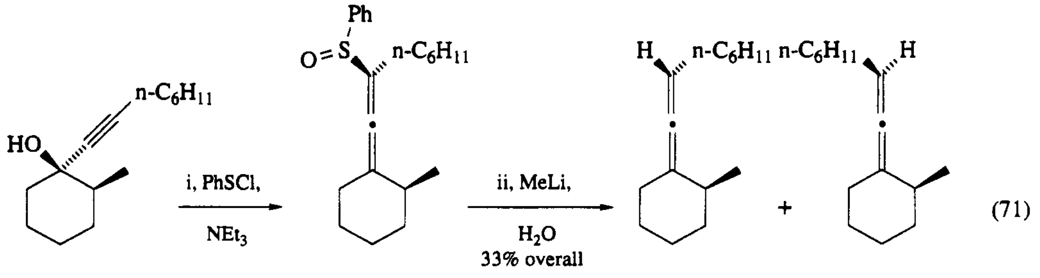
A beautiful application of two consecutive 2,3-sigmatropic shifts was provided by Corey (equation 69).[134] In a one-pot operation he elaborated sulfoxide (**203**) into sulfoxide (**204**), which gave an α,β,γ,δ-unsaturated aldehyde by a Pummerer rearrangement (for a similar application see ref. 135).



(**203**) (**204**)

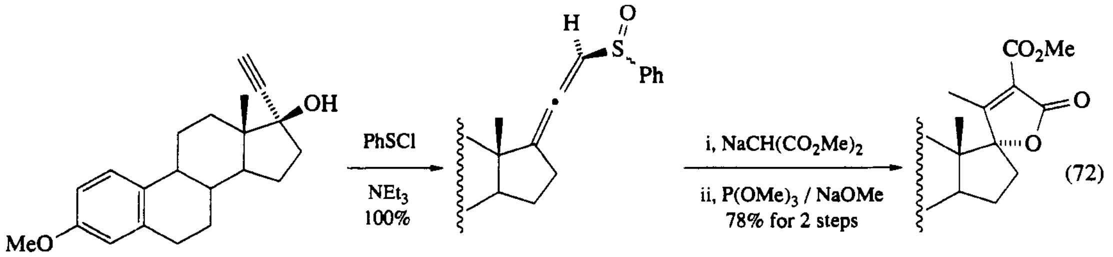
The role of allylic sulfoxides as homoaldol equivalents in the synthesis of (*E*)-allylic alcohols was summarized earlier.[5] A more recent finding is that allylic sulfoxides are precursors for conjugated dienes (equation 70).[136] The elimination is regioselective but stereorandom. The 2,3-rearrangement of propargylic sulfenates gives allenyl sulfoxides. Allenyl sulfoxides are valuable synthetic intermediates. They can be converted into stereochemically homogeneous allenes, *e.g.* (**205**; equation 71).[137]



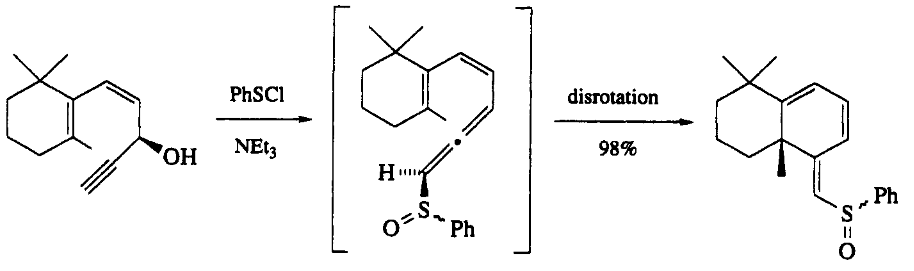


(**205**) 96:4

Altenbach used the Michael addition of sodium methyl malonate to allene (**206**) for a diastereoselective spiroannulation to a steroid (equation 72).[138] Or, in imaginative work by Okamura, allenyl sulfoxides were transformed into enantiomerically pure hydrocarbons by pericyclic reactions like electrocyclic ring closure (equation 73)[139] or intramolecular cycloaddition (equation 74).[140] Note that the starting materials (propargylic alcohols) are readily accessible as single enantiomers.



(**206**)



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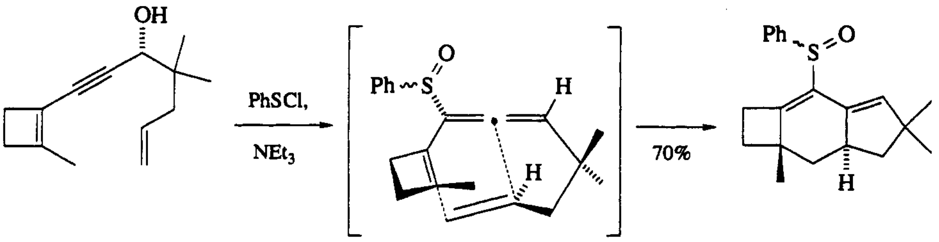
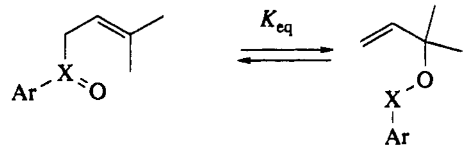


(74)

4.6.3.2 Selenoxide–Selenate Rearrangement

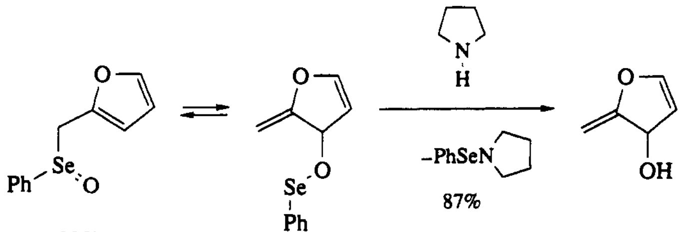
According to Reich, selenoxides (**207b**) rearrange to selenates (**208b**) extremely fast compared with the reaction rate going from sulfoxide (**207a**) to sulfenate (**208a**; equation 75).[141] In addition, the more stable in a pair of isomers is structurally different, *i.e.* sulfoxide and selenate, respectively. Probably, this relationship reflects the smaller overlap in Se═O *vs.* S═O double bonds. From the equilibrium constant K_{eq}, one obtains 11 kcal mol^{-1} (1 cal = 4.18 J) driving force for the conversion of a selenoxide into a selenate. This amount is sufficient to overcome the aromaticity of furan (**209**; equation 76).[141]



(207) Ar = 4-$O_2NC_6H_4$ **(208)**

	X	K_{eq}	$\Delta G^{\ddagger}$ (207) → (208) (kcal mol^{-1})
(a)	S	0.042	19.8 (−30 °C)
(b)	Se	10^{12}	13.5 (−80 °C)

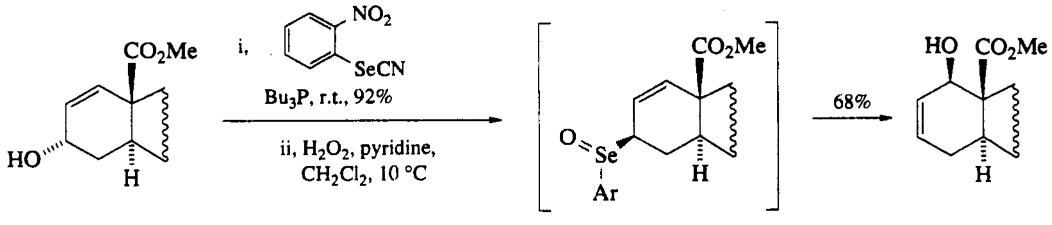
(75)



(209)

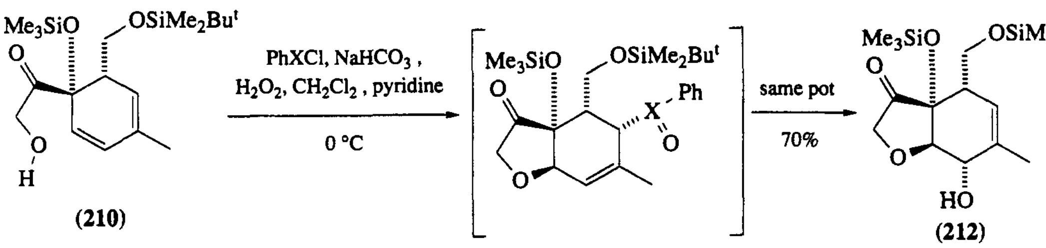
(76)

In fact, allylic selenoxides (**207b**) are so unstable with respect to their rearrangement products that they are never (**209** is an exception) isolated. The oxidation of an allylic selenide leads, after hydrolysis, directly to the rearranged alcohol. Equation (77) demonstrates how such a rearrangement can be incorporated in the diastereoselective 1,3-transposition of an allylic alcohol.[142]



(77)

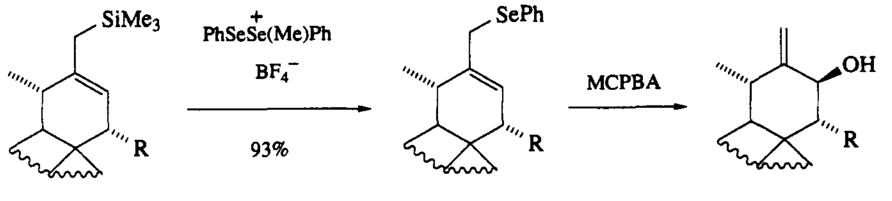
Sulfide and selenide precursors for 2,3-rearrangements can be obtained stereochemically pure by chalcogeno-etherifications (equation 78).[143] From these precursors thio-(**211**) and seleno-(**211**) were prepared by oxidation. While the sulfoxide refused to rearrange to alcohol (**212**) under various conditions, the selenoxide did so even at 0 °C. Here, the extra driving force of selenoxide *vs.* sulfoxide rearrangements was an essential; it pushed the selenoxide through a transition state obviously too sterically hindered for the less reactive sulfur analog.



(**210**) (**212**) (78)

X = Se: seleno-(**211**)
X = S: thio-(**211**)

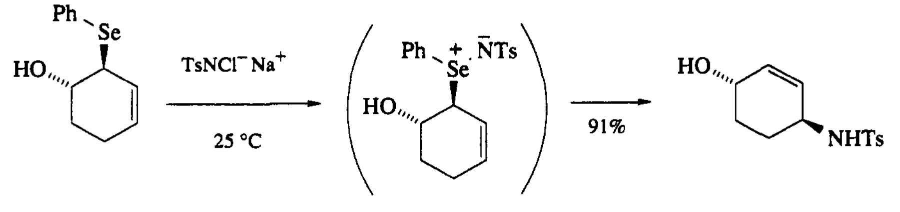
To use a selenate instead of a sulfoxide rearrangement for the preparation of allylic alcohols can be advantageous if silicon is present in the starting material. Vedejs found that the allylsilane (**213**) could be selenylated to give (**214**; equation 79);[144] this reaction includes a rapid 1,3-shift of the initially formed selenide. Oxidation and 2,3-rearrangement to the alcohol (**215**) followed uneventfully.



(**213**) (**214**) (**215**) (79)

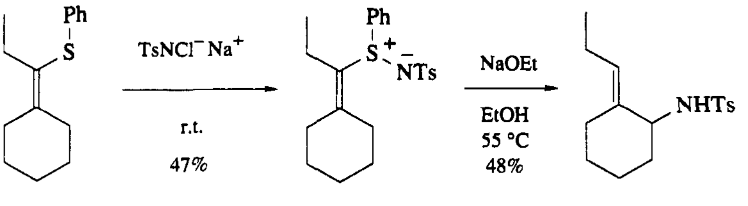
4.6.3.3 Introduction of Allylic Nitrogen

Primary and secondary allylic amines can be prepared from allylic selenides.[145] Chirality transfer from the C—Se to the C—N bond may be included for stereocontrol (equation 80).



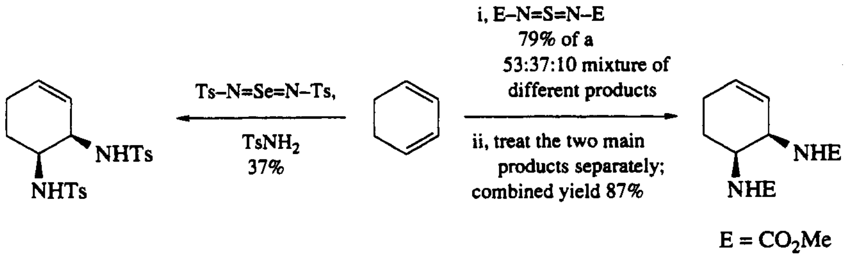
(80)

A similar amination is known in the sulfur series (equation 81).[146] Here, the reactive species is generated *in situ* from (**216**). Deprotonation and reprotonation isomerize the vinylsulfimide (**216**) to an allylsulfimide which gives the amino compound (**217**). (**217**) exhibits the expected (*cf.* Scheme 25) (*E*)-configuration of the C=C bond.



(**216**) (**217**) (81)

[4 + 2] cycloadditions and 2,3-rearrangements are involved in *cis* vicinal bisaminations of certain 1,3-dienes (Scheme 26).[147,148] In these reactions, chirality is transferred from C—Se or C—S bonds to C—N bonds.



Scheme 26

4.6.4 REFERENCES

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4.7

Polonovski- and Pummerer-type Reactions and the Nef Reaction

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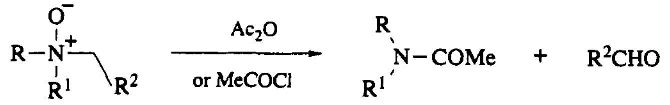
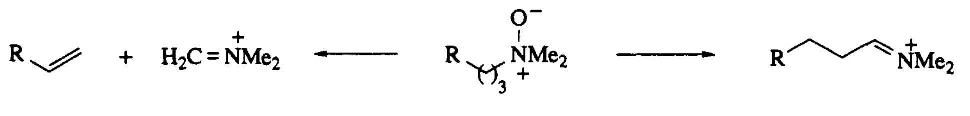
4.7.1 INTRODUCTION

In 1927 the Polonovskis reported their discovery that treatment of a tertiary amine *N*-oxide with acetic anhydride or acetyl chloride results in a rearrangement in which one of the alkyl groups attached to nitrogen is cleaved and the *N*-acetyl derivative of the corresponding secondary amine and aldehyde are obtained (equation 1).[1,2] Although originally considered to be a mild method for *N*-demethylation of tertiary amines, it is now recognized that the Polonovski reaction provides ready access to iminium ions, enamines, tertiary amides and/or secondary amines and aldehydes.[3–6]



(1)

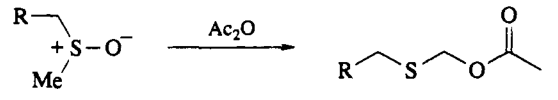
The central feature of this reaction is the transformation of an *N*-oxide to an iminium ion intermediate. Depending upon the *N*-oxide structure and the acid anhydride or other activating reagent employed, this can occur through loss of an α-hydrogen or through fragmentation of a C_α–carbon bond (equation 2).



(2)

In principle, any reagent capable of activating the *N*-oxide oxygen can promote the Polonovski reaction. However, acid anhydrides, and in particular trifluoroacetic anhydride (the modified Polonovski reaction), are usually employed. The discussion in this chapter will therefore be limited mainly to the use of acid anhydrides. Brief mention is made in Sections 4.7.2.5 and 4.7.2.6 of the use of iron salts, sulfur dioxide and organo-silicon and -selenium derivatives as activating agents.

Also discovered near the beginning of the century,[7] the Pummerer reaction can be broadly defined as a reaction in which a sulfoxide bearing at least one α-hydrogen can readily be transformed to α-substituted sulfides upon treatment with electrophilic reagents.[8–11] The net result is a redox reaction in which the sulfoxide group is reduced to the sulfide and the α-carbon is oxidized. When acetic or trifluoroacetic anhydride is used as the activating reagent, acyloxy sulfides are formed (equation 3). These labile products are readily hydrolyzed in aqueous media to the corresponding thiol, formaldehyde and either acetic or trifluoroacetic acid.



(3)

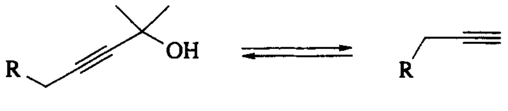
In many respects the Pummerer reaction can be regarded as the sulfur version of the Polonovski reaction (and *vice versa*), and by analogy to the Polonovski reaction the central intermediate is a sulfur-stabilized carbocation (thionium ion). Although the existence of this species is only transient, it reacts to give a number of different products, *e.g*. α-acetoxy sulfides, vinyl sulfides, cationic cyclization products, *etc*., depending upon the sulfoxide structure and reaction conditions. Other reaction pathways are specific to the Pummerer reaction as a result of sulfur's ability to expand its valence shell (additive Pummerer reactions). A moderate degree of asymmetric induction is also observed in certain Pummerer reactions, where optically pure sulfoxides are substrates.

Although the emphasis in this chapter is placed on the use of acid anhydrides in the Pummerer reaction, a number of other activating reagents, *e.g*. acids, in particular *p*-toluenesulfonic acid, and trialkylsilyl halides, have been employed. Mention of these reagents is made in cases where their use leads to an improvement in yields or selectivity, or to a transformation which is not possible using an acid anhydride. Acetyl chloride is usually not employed in the Pummerer reaction because of the simultaneous presence of acetate ion and chloride ion in the reaction medium. The product of these reactions is predominantly the thioacetal derived from spontaneous decomposition of the initially formed α-acetoxy sulfide.

The reaction of sulfides bearing α-methylene hydrogens with halogenating agents, to form α-halo sulfides, can be classified as a Pummerer reaction of halosulfonium salts.[8] With chlorine and bromine it is sometimes difficult to limit the reaction to monosubstitution. However, monosubstituted products are produced in high yields using *N*-halosuccinimides, sulfuryl and thionyl chloride and cyclic phosphorus chlorides. The α-halo sulfides obtained in these reactions react in an identical fashion to the α-acyloxy sulfides obtained in the classical Pummerer reaction of a sulfoxide.

The Nef reaction, discovered in 1894, involves the transformation of a carbon bearing a primary or a secondary nitro group to the corresponding aldehyde or ketone (equation 4).[12] The addition of acetylides to aldehydes or ketones is also sometimes referred to as the Nef reaction, since the first example was also reported by Nef.[13] The resultant alcohol may be looked upon as a protected form of the alkynic group, which is easily regenerated according to a 'retro-Nef reaction' (equation 5).[14]

(4)



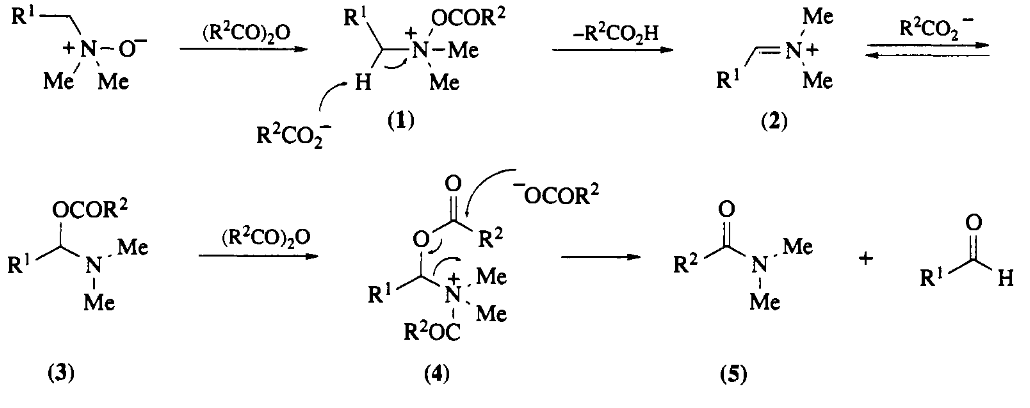
(5)

In this chapter the Nef reaction refers to the reaction of nitroalkanes. As nitro compounds are readily available and can be involved in a variety of reactions, the Nef reaction often represents the key transformation in a reaction sequence. A review of this topic appeared in 1990[15] and an article has been published on the chemistry of nitroaliphatic compounds, including the Nef reaction.[16]

4.7.2 THE POLONOVSKI REACTION

4.7.2.1 Mechanism

The first step in the Polonovski reaction of an amine *N*-oxide with an acid anhydride, acyl chloride or chloroformate ester is the formation of the *O*-acylimonium salt (**1**; Scheme 1). Such species are highly unstable. However, they can be detected *in situ* (^{1}H NMR), and in certain cases actually isolated, if prepared using powerful acylating agents such as acetyl perchlorate.[17]



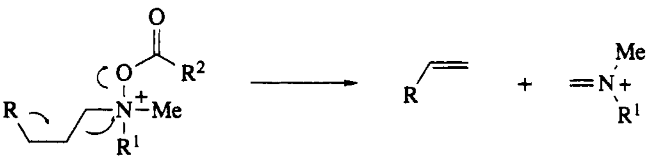
Scheme 1

The conversion of (**1**) to the iminium ion (**2**) occurs by an ionic *E*2-type elimination mechanism.[17-19] In support of this mechanism, the Polonovski reaction is accelerated by the addition of acetate ion or amine bases, and markedly decelerated when carried out in acidic media. These observations point to the involvement of the counterion $R^2CO_2^-$ in the removal of the proton from the α-carbon. Further support comes from studies which demonstrate that there is a pronounced preference in nonbiased systems for loss of the hydrogen which is antiperiplanar to the N—O bond.

The subsequent position of the equilibrium reaction between the iminium ions (**2**) and their addition products (**3**) is a function of both the nucleophilicity of the counterion $R^2CO_2^-$ and the acidity of the reaction medium. When $R^2CO_2^-$ is an acetate anion, this equilibrium is displaced entirely toward intermediates (**3**). Such α-acetoxymethylamines are very labile entities; however, under special conditions they can be isolated.[20] In the presence of trifluoroacetic acid, intermediate (3) reverts back to the iminium ion. This reversibility and the low nucleophilicity of the trifluoroacetate anion explain why the modified Polonovski reaction using trifluoroacetic anhydride does not proceed beyond the iminium ion stage. This characteristic of the modified Polonovski reaction has considerable synthetic potential, as discussed in the following sections.

The elaboration of the acetoxymethylamines (3) to the corresponding tertiary amides (5) can occur during aqueous work-up and *in situ* under nonhydrolytic conditions by reaction with a further molecule of acetic anhydride, followed by acetate ion promoted fragmentation of intermediates (4).

The alternative Polonovski reaction mode, in which C_α—C bond cleavage is observed, can occur if two conditions are met (equation 6): (i) the C_α—C bond to be broken is activated towards cleavage by an adjacent electron-donating center (double bond, aromatic ring or heteroatom); and (ii) the C_α—C and N—O bonds are antiperiplanar.



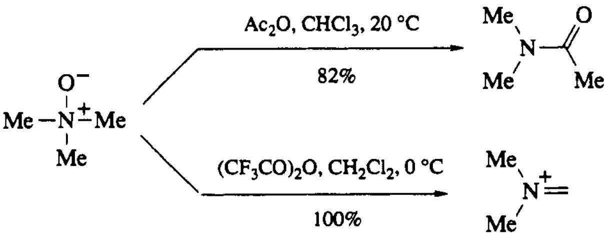
(6) (7) (8)

(6)

The reaction by which (6) is transformed to (7) and the iminium ion (8) is, in fact, a manifestation of the Grob fragmentation,[21] and is of considerable interest because extensive modification of the tertiary amine structure is achieved in a single operation.

4.7.2.2 Carbon–Hydrogen Elimination Reactions

As mentioned above, the capacity of the intermediate iminium ion (2) to condense with its counterion is a crucial product-determining step. This is illustrated by the reaction of trimethylamine *N*-oxide with acetic and trifluoroacetic anhydride (Scheme 2). With acetic anhydride the *N*-demethylated product dimethylacetamide is formed in high yield,[18] whereas with trifluoroacetic anhydride under similar conditions the iminium ion (9), a synthetically useful Mannich reagent, is generated in nearly quantitative yield.[22]



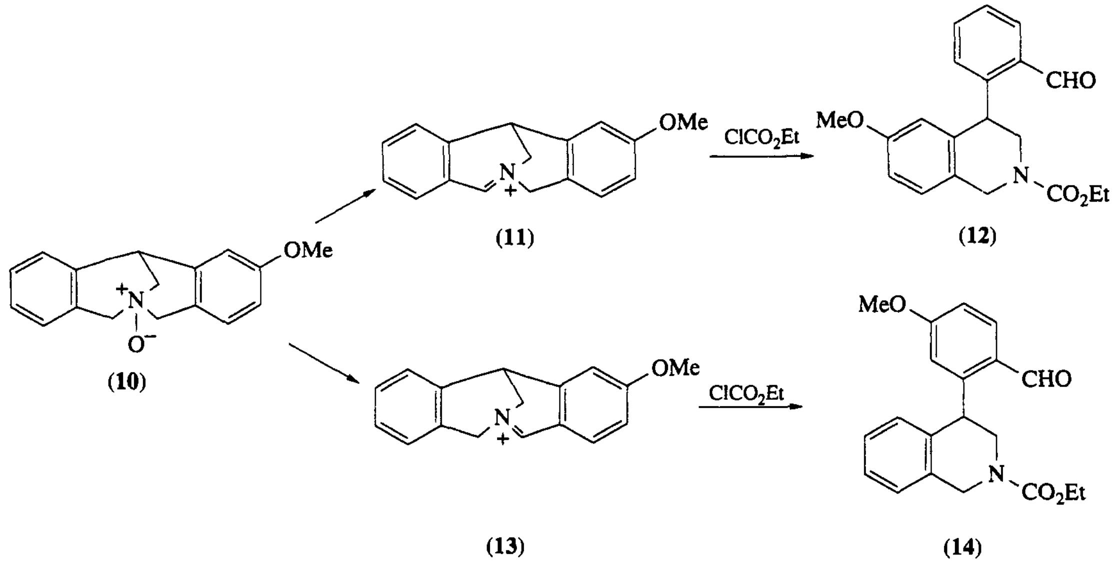
(9)

Scheme 2

4.7.2.2.1 *Regio- and stereo-chemistry*

For an unsymmetrical *N*-oxide the regiochemistry of the Polonovski reaction is determined by a preference for loss of a proton from either of the carbon centers α to the nitrogen in the step which forms the iminium ion, as illustrated in Scheme 1. The anhydride plays a fundamental role in the orientation of this *E*2 elimination reaction, since both the base and the leaving group on the nitrogen are derived from it. As a rule it is found that the thermodynamically more stable iminium ion is produced when trifluoroacetic anhydride is employed, while with acetic anhydride the product obtained generally depends upon the kinetic acidity of the α-hydrogens. These results reflect the fact that with trifluoroacetic anhydride an excellent leaving group is generated along with a weak base, whereas with acetic anhydride a comparatively poor leaving group and a much stronger base are produced.

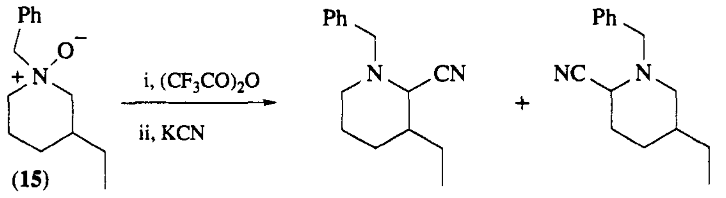
These arguments are evoked to explain the results obtained in the reaction of *N*-oxide (**10**) with different acid anhydrides (Scheme 3).[23] Thus with stronger bases ($Et_3N > MeCO_2^- > Cl^-$) the *E*1cB character of the transition state is considered to be enhanced, favoring the formation of (**12**) *via* the less stable iminium ion intermediate (**11**). Opposed to this is the trend with better leaving groups ($CF_3SO_3^- > CF_3CO_2^- > MeCO_2^-$) towards formation of compound (**14**) *via* the more stable iminium ion (**13**).



	(12):(14)	*Yield (%)*		*(12):(14)*	*Yield (%)*
Ac_2O, 12 h	2:1	75	$(CF_3CO)_2O$	1:1	95
Ac_2O, Et_3N, 30 min	3:1	71	$(CF_3SO_2)_2O$	1:5	89
MeCOCl	1:1	92	CF_3SO_2Cl	1:2	25

Scheme 3

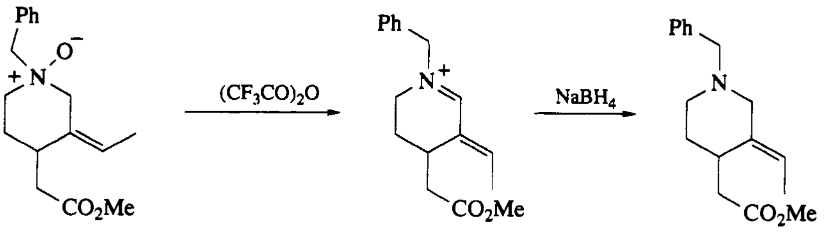
As might be expected, when the acidity of an α-hydrogen is increased by the presence of an adjacent electron-withdrawing group, double bond or aromatic ring, the Polonovski reaction occurs predominantly, if not exclusively, in the direction of the activated center. However, the influence of such a group is overcome if the *N*-oxide is incorporated into a piperidine ring as in (**15**; equation 7). The greater stability of the intermediate endocyclic iminium ions is responsible for this effect.



(7)

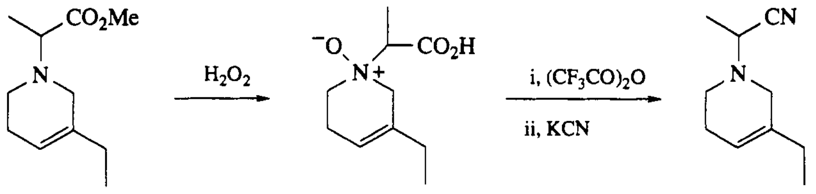
Unfortunately, in 3-alkyl-substituted piperidine *N*-oxides there is generally little discrimination between the ring α-carbon centers, and mixtures of regioisomeric products are obtained. When a $\Delta^{3,4}$ double bond is present in the starting *N*-oxide, however, this functionality will direct the Polonovski reaction towards elimination of one of the allylic hydrogens. Thus, the (*Z*)-ethylidene product (**18**) is obtained from (**16**) after reduction of the conjugated iminium ion intermediate (**17**; equation 8).[24]

Formation of exocyclic iminium ions can be achieved under special circumstances where a functionality other than hydrogen is lost during the elimination step. One version of this technique takes advantage of the fact that carboxylic acid esters are readily hydrolyzed to the parent acids during *N*-oxide formation with hydrogen peroxide. Thus, on sequential treatment of the *N*-oxide (**19**) with hydrogen peroxide, trifluoroacetic acid and potassium cyanide the exocyclic, rather than the endocyclic, aminonitrile (**20**) is produced in 48% yield (equation 9).[25]



(8)

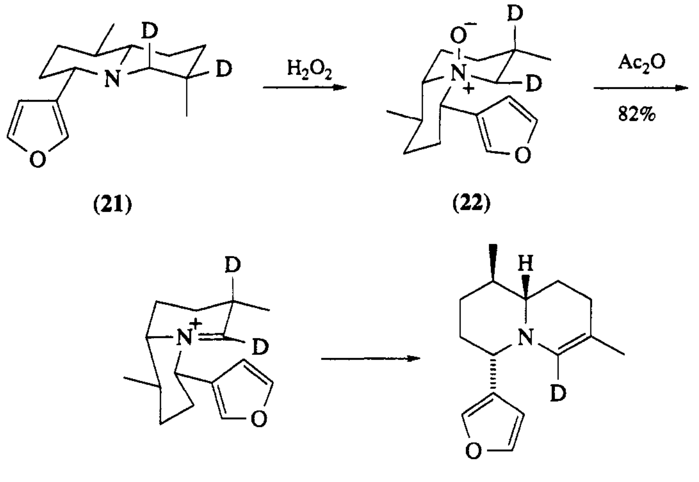
(16) (17) (18)



(9)

(19) (20)

Studies of the Polonovski reaction in conformationally rigid polycyclic systems reveal the stereochemical requirements for the elimination step. For example, the 6β,7β-dideutero derivative (**22**) of nupharidine is converted on reaction with acetic anhydride into Δ^6-dehydrodeoxynupharidine (**24**) containing a single deuterium atom at $C\alpha$ (Scheme 4).[26]



(21) (22)

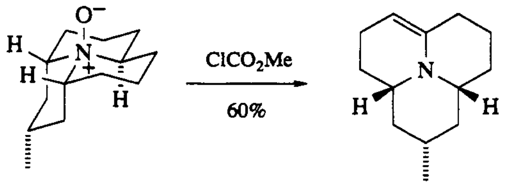
(23) (24)

Scheme 4

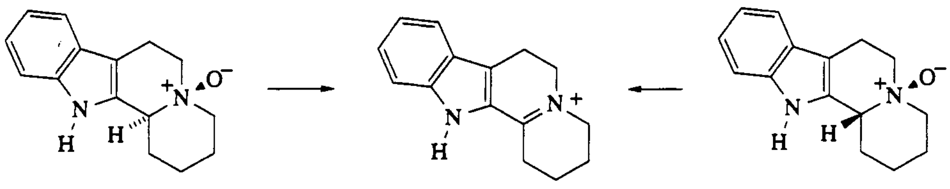
The formation of the intermediate iminium ion (**23**) in the reaction thus involves loss of the 6α-H which is *trans* diaxial, *i.e.* antiperiplanar, to the N—O bond of (**22**). Although the *N*-oxide (**22**) could conceivably undergo the Polonovski reaction *via* its alternative *cis*-decalin conformer, this is highly improbable because in this conformation the three ring substituents would be axially oriented. Accordingly, the structure of an *N*-oxide cannot always be correlated with that of the free base because of the possibility of nitrogen inversion (compare **21** with **22**).

A similar high degree of stereoselectivity is observed in the Polonovski reaction of coccinelline (**25**; equation 10), which produces enamine (**26**) through loss of the *trans* diaxial hydrogen.[27]

The situation is more complicated in cyclic systems such as the indoloquinolizidine *N*-oxide (**27a,b**), where one of the α-carbon centers is activated by the presence of an aromatic (indole) substituent, as compound (**28**) is obtained from both the *cis* and *trans* isomers of (**27**; Scheme 5).[28] Since the relative rates and yields of the two reactions are comparable, it appears that *anti* elimination is not an absolute requirement for this and related Polonovski reactions.



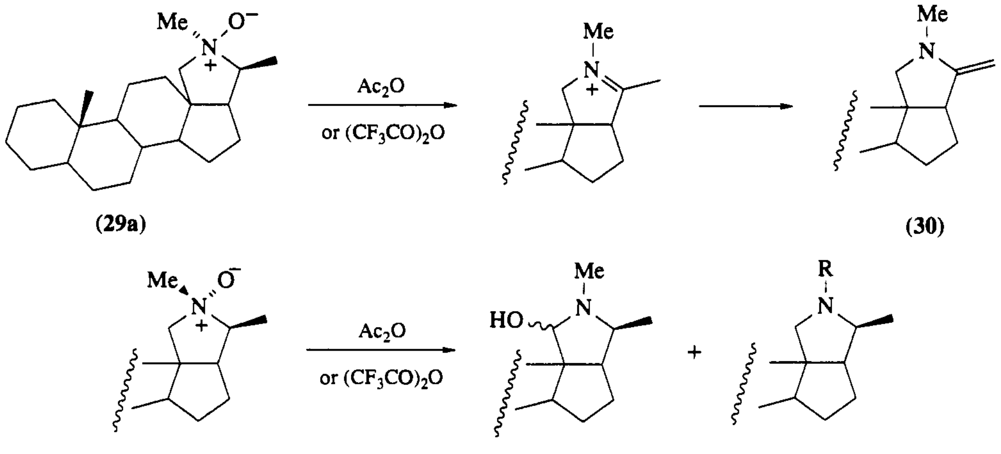
(25) **(26)** (10)



(27a) **(28)** **(27b)**

Scheme 5

For pyrrolidine *N*-oxides, one might *a priori* anticipate iminium ion formation to occur by a *syn* elimination process, since the N—O and adjacent C$_\alpha$—H bonds cannot become antiperiplanar to each other. However, the *N*-oxide (**29a**) of the steroid alkaloid conanine reacts with acetic and trifluoroacetic anhydride exclusively by the *anti* pathway to give the exocyclic enamine (**30**; Scheme 6).[29] Release of steric strain between the C-16 methylene and the ring methyl substituent is undoubtedly a major driving force in this reaction. More revealing is the reaction of *N*-oxide (**29b**), which would give the same enamine product if a *syn* pathway is favored. The observed formation of compounds (**31**) and (**32**) argues in favor of the *anti* elimination.



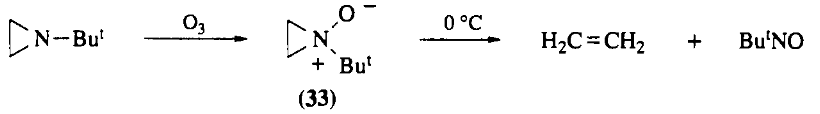
(29a) **(30)**

(29b) **(31)** 1:4 **(32)**

R = COMe (from Ac$_2$O);
R = H (from (CF$_3$CO)$_2$O)

Scheme 6

To date no reports of the Polonovski reaction of *N*-oxides of four- or seven- and higher-membered cyclic tertiary amines have appeared. Aziridine *N*-oxides can be prepared by ozonolysis of *N*-*t*-butylaziridine; however, these compounds are unstable above 0 °C.[30] At higher temperatures compound (**33**) undergoes first-order decomposition to ethylene and 2-methyl-2-nitrosopropane (equation 11).

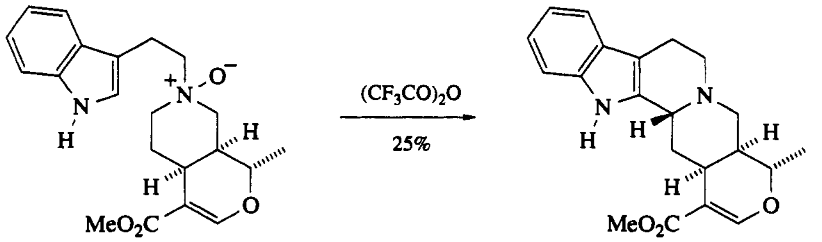


$$\text{N-Bu}^t \xrightarrow{O_3} \overset{O^-}{\underset{+\ \text{Bu}^t}{\text{N}}} \xrightarrow{0\ ^\circ\text{C}} \text{H}_2\text{C}{=}\text{CH}_2 + \text{Bu}^t\text{NO} \qquad (11)$$

(33)

4.7.2.2.2 Iminium ion cyclizations

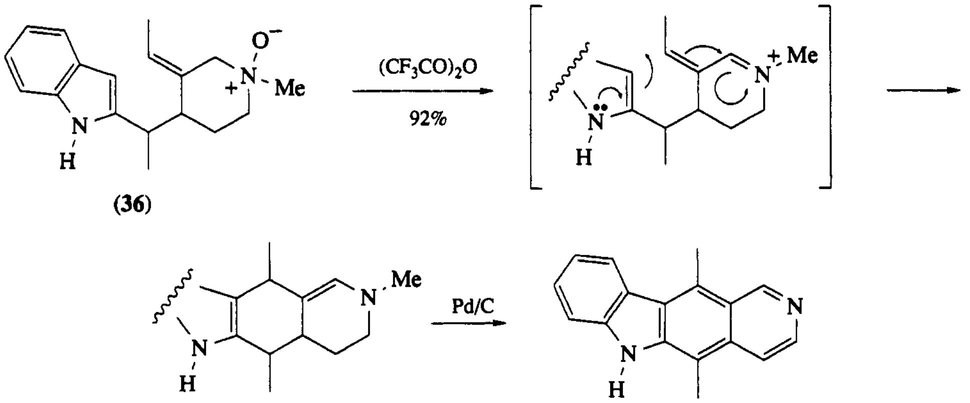
Iminium ion cyclizations such as the Pictet–Spengler reaction have been widely used in alkaloid chemistry to create a carbon–carbon bond between the carbon α to the basic nitrogen and an aromatic ring. The requisite iminium ions in these reactions are often readily available *via* the modified Polonovski reaction. Although two steps, *N*-oxide formation and reaction with trifluoroacetic anhydride, are involved, this approach is often preferable to the reaction of a tertiary amine with mercury(II) acetate, in which it is necessary to destroy the amine–mercury complex at the end of the reaction. In this way the secoheteroyohimbinoid *N*-oxide (**34**) was cyclized selectively to akuammigine (**35**; equation 12).[31] Using mercury(II) acetate a nearly equal mixture of (**35**) and its C-3 β-H epimer tetrahydroalstonine is obtained.



(12)

(34) **(35)**

Carbon–carbon bond formation by intramolecular cyclization of conjugated iminium ions is also possible, as illustrated by the transformation of amine oxide (**36**) to (**37**), a key intermediate in the synthesis of the pyridocarbazole alkaloid ellipticine (**38**; Scheme 7).[32]



(36)

(37) **(38)**

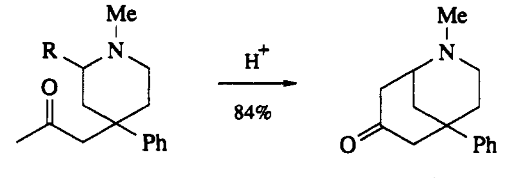
Scheme 7

With few exceptions the activation of a methyl group in an iminium ion cyclization is not efficient under modified Polonovski conditions. However, the yields of such reactions are significantly improved by using iron salts or sulfur dioxide as the activator (see Section 4.7.2.5).

4.7.2.2.3 Formation of α-cyanoamines and related iminium ion reactions

In a number of instances the iminium ion intermediates formed under Polonovski conditions are too reactive or labile to be employed as such in projected syntheses. The acidity of the Polonovski reaction medium is sometimes a further problem when considering *in situ* reactions with organometallic reagents and other carbon nucleophiles. One technique that can circumvent this problem is to convert these labile iminium ion intermediates into their more stable α-cyanoamine derivatives. There are two advantages to this approach. First, the reaction of cyanide ion with iminium salts generally gives high yields, and secondly, the resultant α-cyanoamines react efficiently as 'iminium ion equivalents' with a wide range of nucleophilic reagents. An additional gain is the possibility of effecting an 'umpolung' of the normal reactivity of iminium ions *via* the reaction of α-cyanoamine anions with electrophiles. The dual reactivity of these cyanide adducts thus broadens considerably the scope of application of iminium ions in synthetic chemistry.

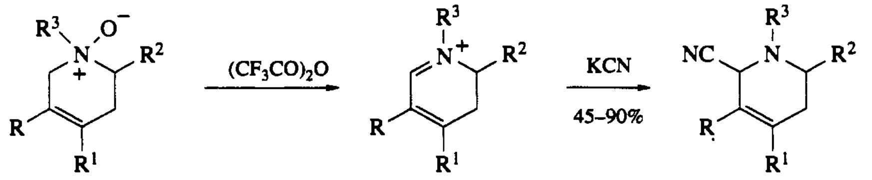
The use of α-cyanoamines in place of their less stable iminium ion precursors often results in high product yields in the Pictet–Spengler and other ring closure reactions. Thus, the Polonovski-derived α-cyanoamine (**39a**) cyclized to (**40**) in 84% yield, whereas reaction of the tertiary amine (**39b**) with mercury(II) acetate was unsuccessful (equation 13).[33] The conversion of unstable 5,6-dihydropyridinium salts (**41**), obtained by reaction of tetrahydropyridine *N*-oxides with trifluoroacetic anhydride, into the stable, synthetically versatile tetrahydropyridine-2-carbonitrile (**42**) is another area in which use of this methodology has met with particular success (equation 14).[34]



(**39a**) R = CN
(**39b**) R = H

(**40**)

(13)

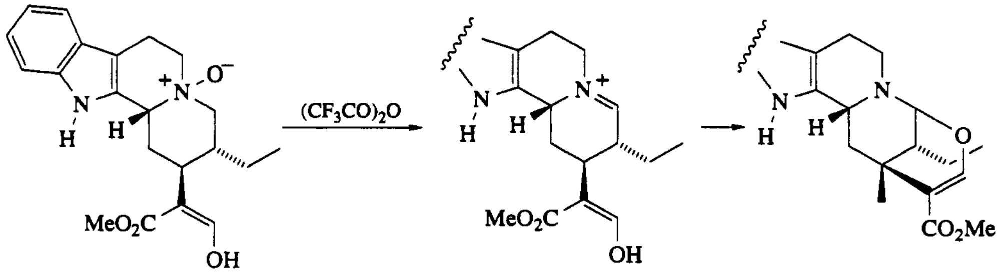


(**41**)

(**42**)

(14)

The intramolecular reaction of an iminium ion with an oxygen nucleophile is the key step in the synthesis of dihydromancunine (**43**; equation 15).[35]



(**43**)

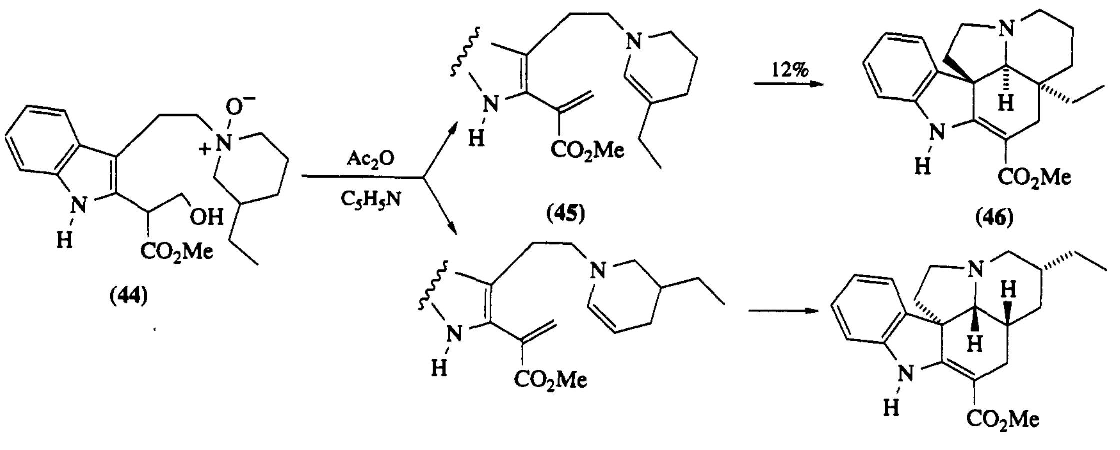
(15)

4.7.2.2.4 Enamines

Enamines can be obtained as the products of the Polonovski reaction of amine oxides and, in particular, by reaction of piperidine *N*-oxides with acetic anhydride. This is primarily due to the fact that when acetate is the counterion the intermediate iminium ions are labile and readily tautomerize. The formation of enamines during the Polonovski reaction is also favored by the presence of a base. In fact, enamines are often obtained in high yield from the reaction of an *N*-oxide with trifluoroacetic anhydride in the presence of triethylamine or pyridine. Conversion of intermediate iminium ions, generated under modified Polonovski conditions, to enamine products can also occur during hydrolytic work-up.

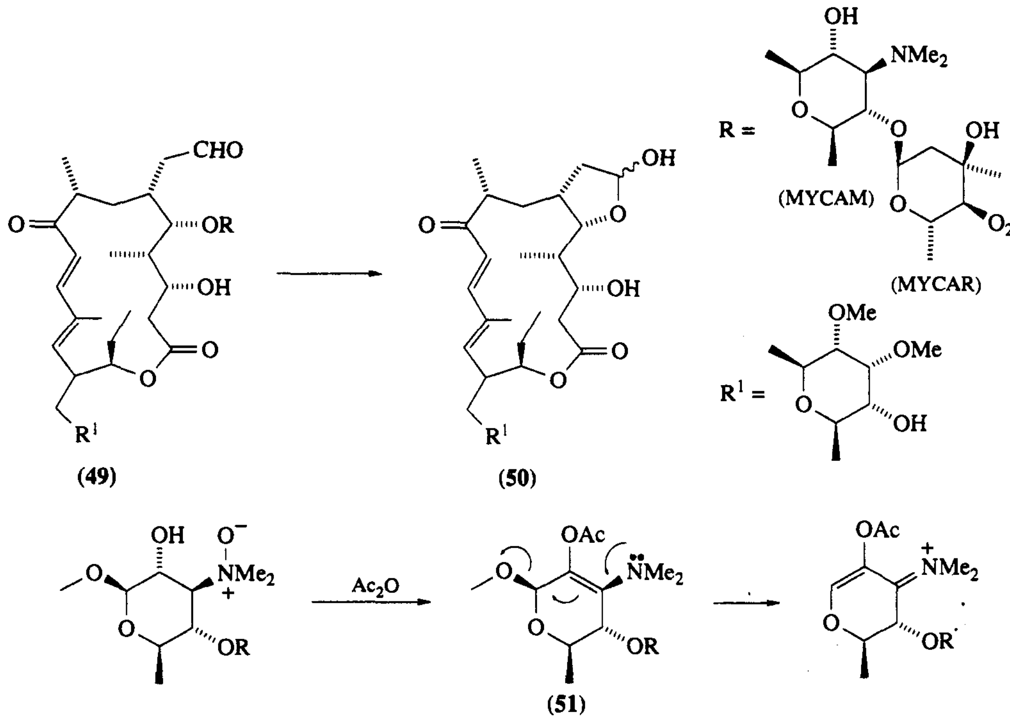
Reaction of the *N*-oxide (**44**) with acetic anhydride–pyridine provides a direct means for the *in situ* generation of the highly reactive dehydrosecodine intermediate (**45**).[36] This species undergoes spontaneous cyclization to give vincadifformine (**46**; 12%) *via* an intramolecular Michael reaction followed by B/C ring closure (Scheme 8). ψ-Vincadifformine (**48**) is also produced in this reaction *via* the enamine

(47), since a simple ethyl side chain in the starting *N*-oxide has no 'directing effect' on the iminium ion forming step.



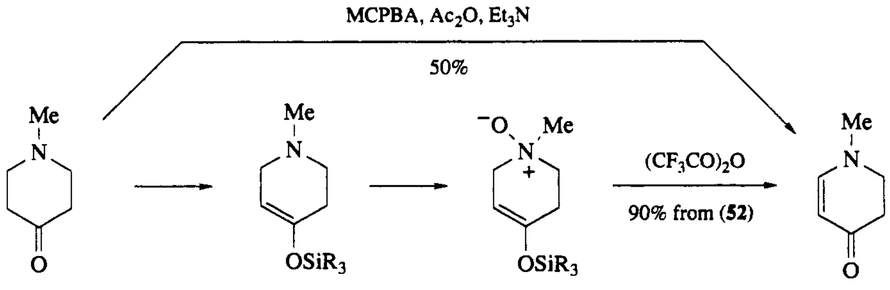
Scheme 8

The Polonovski reaction also provides a solution to the difficult problem of cleaving the glycoside bond linking an amino sugar to the aglycone in tysolin (**49**) and related 16-macrolide antibiotics. The idea is to generate an endocyclic enamine (**51**) so that the lone pair of electrons on nitrogen can assist in breaking the glycoside bond through a vinylogous β-elimination reaction (Scheme 9). Using acetic anhydride, the yield of the desired hemiacetal (**50**) is only 10%.[37] However, as might be expected under modified Polonovski conditions (trifluoroacetic anhydride–pyridine), the yield of (**50**) is significantly increased (65%).[38]



Scheme 9

The enamino ketone (**54**) can also be prepared by a Polonovski approach, involving either sequential addition of *m*-chloroperbenzoic acid, acetic anhydride and triethylamine to a cooled solution of (**52**) in methylene chloride[39] or reaction of the *N*-oxide (**53**) with trifluoroacetic anhydride (Scheme 10).[40] Although the latter approach involves three distinct steps, the overall yield of (**54**) is higher.

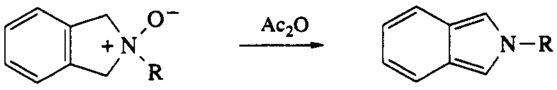


(**52**) (**53**) (**54**)

Scheme 10

4.7.2.2.5 Pyrrole ring formation and other reactions of five-membered rings

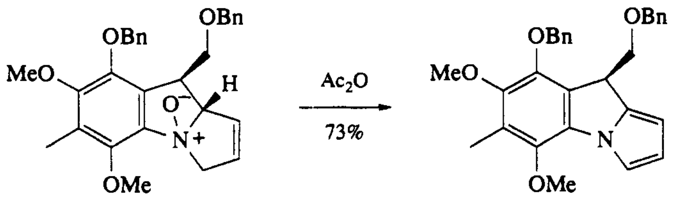
Although in cyclic systems studied to date the *N*-oxide function has been for the most part incorporated into a six-membered ring system, there are several examples where pyrrolidine or dihydropyrrole *N*-oxides are the substrates. For instance, the reaction of amine oxide (**55**) with acetic anhydride at 0 °C provides a convenient route to the *N*-alkylisoindole (**56**; equation 16).[41]



(16)

(**55**) (**56**)

The mitosane *N*-oxide derivative (**57**) is similarly converted into the pyrroloindole derivative (**58**) in high yield upon reaction with acetic anhydride in chloroform (equation 17).[42] The corresponding reaction of the 1,2-diacetoxy derivative (**59**) is more complex, however, as there is no directing functionality to orient the reaction (Scheme 11). One of the reaction products (**62**) is viewed as being formed *via* intermediates (**60**) and (**61**). If this mechanistic rationale is correct then the transformation of (**59**) to (**62**) represents a new manifestation of the Polonovski reaction.

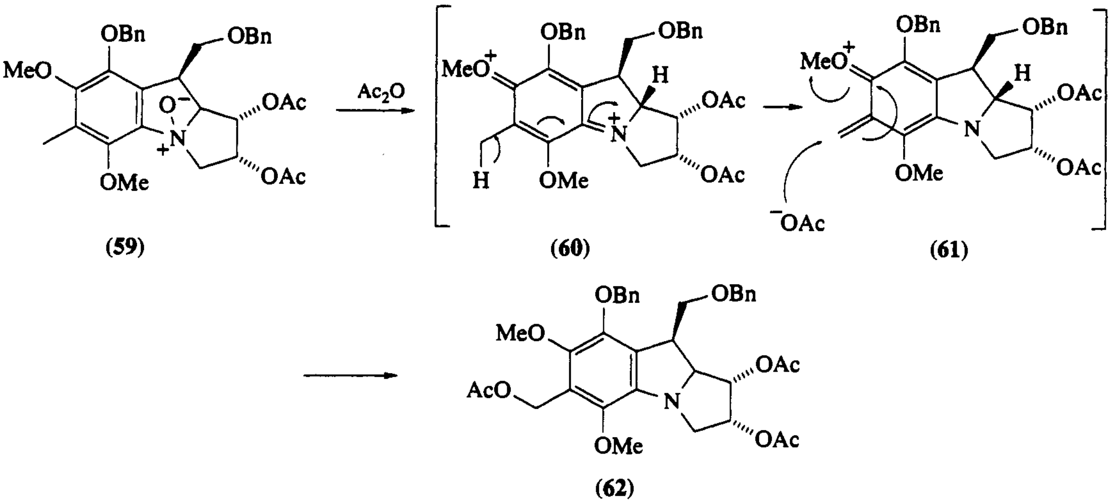


(17)

(**57**) (**58**)

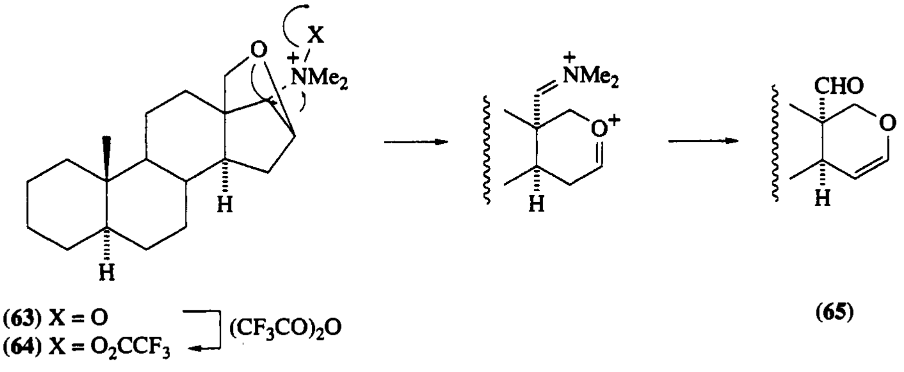
4.7.2.3 Carbon–Carbon Fragmentation Reactions

As outlined in the section on mechanism, Polonovski reactions in which intermediate iminium ions are produced by fragmentation of the C_α–carbon bond are of considerable interest in synthesis since extensive modification in structure is achieved in a single operation. However, not every *N*-oxide substrate can react in this manner. In fact, for this reaction mode to become operative, the C_α–carbon bond to be broken must be both activated toward cleavage by an adjacent electron-donating center (double bond, aromatic ring or heteroatom) and be oriented antiperiplanar to the N—O bond.



Scheme 11

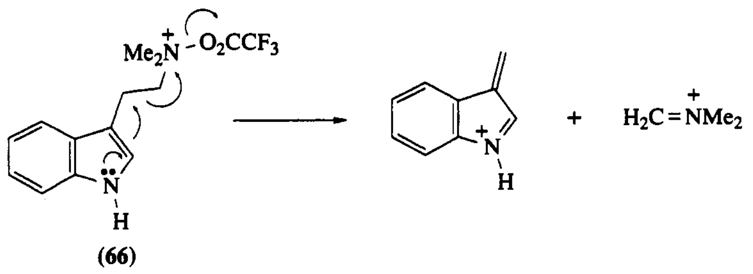
The first example of this fragmentation reaction to be described is the conversion of the *N*-oxide (**63**) to the 17-oxa-D-homoandrostane derivative (**65**; Scheme 12).[43] The crucial step in this transformation involves the participation of the lone pair of electrons on oxygen in the departure of trifluoroacetate ion from the *O*-acylimonium salt intermediate (**64**).



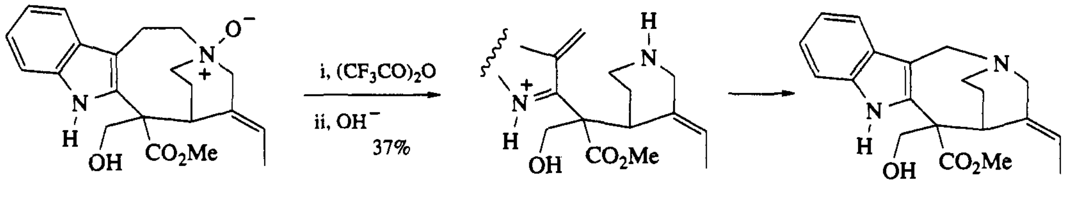
Scheme 12

Phenethylamine-type *N*-oxides also undergo carbon–carbon bond fragmentation under modified Polonovski conditions, as illustrated by the reaction of *N*,*N*-dimethyltryptamine *N*-oxide (**66**), wherein cleavage of the side chain is facilitated through participation of the electrons on the indole nitrogen (equation 18).[44] The ease with which *N*-oxide (**66**) undergoes fragmentation implies that the *in vivo* equivalent of this reaction is important in the biosynthesis of certain indole alkaloids, such as ellipticine (**38**)[45] and vallesamine (**67**; Scheme 13),[46] whose derivation from tryptophan is not immediately obvious.

Without doubt the most relevant and spectacular application of the Polonovski reaction is the development of the first successful method of preparation of the indole antitumor agent vinblastine (**68**). This



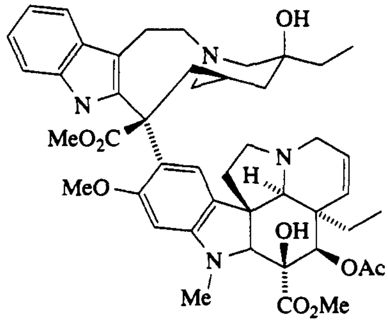
(18)



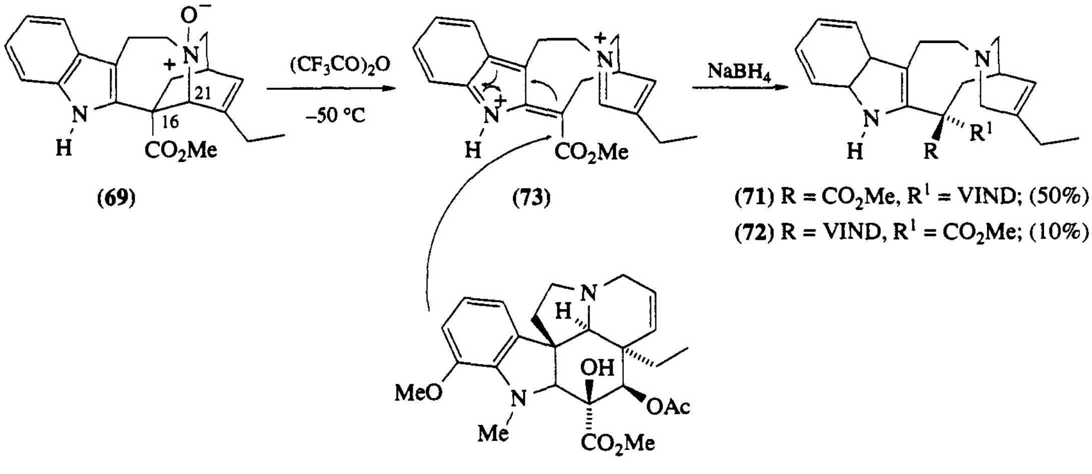
(67)

Scheme 13

difficult problem was resolved by reacting catharanthine *N*-oxide (**69**) with trifluoroacetic anhydride at > –50 °C in the presence of vindoline (**70**), followed by treatment with sodium borohydride (Scheme 14).[47,48] In this way the natural configuration dimer (**71**) is obtained in 50% yield along with only minor amounts of (**72**).



(68)



(69)

(73)

(**71**) R = CO_2Me, R^1 = VIND; (50%)

(**72**) R = VIND, R^1 = CO_2Me; (10%)

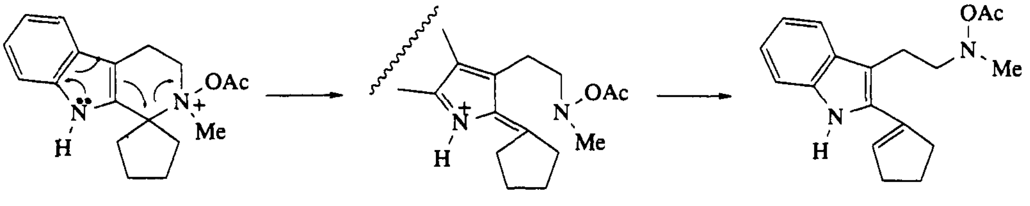
(**70**) VIND

Scheme 14

Although the precise mechanism of the coupling reaction is not thoroughly established, one can visualize the formation of (**71**) as arising from initial fragmentation of the C(16)—C(21) bond of (**69**), followed by condensation of vindoline with the more accessible α face of the iminium ion (**73**). The impact of the Polonovski approach in this area is emphasized by the fact that all other attempts to couple vindoline with 16,21-seco derivatives of catharanthine lead invariably to formation of the unnatural dimer. A Polonovski reaction was also a key step in the subsequent elaboration of anhydrovinblastine (**71**) to (**68**).[49]

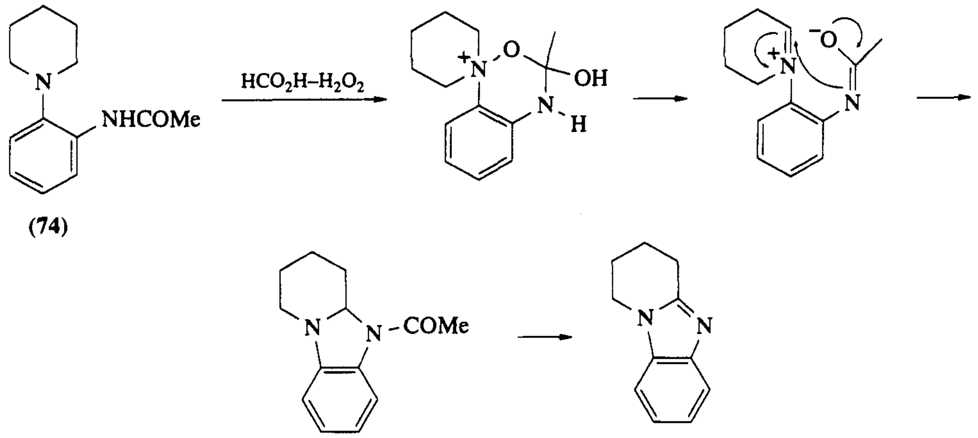
4.7.2.4 Other Reactions

In several instances reaction of an amine oxide with an acid anhydride triggers a process in which the amine oxide nitrogen is converted into a leaving group and the C_α—N bond is cleaved (Scheme 15).[50] Interestingly, these reactions occur to the exclusion of the Polonovski pathways, *i.e.* elimination of the benzylic α-hydrogen or fragmentation of the phenethylamine chain.



Scheme 15

In a number of reactions the Polonovski products are obtained directly on reaction of a tertiary amine with peroxy acids. This can happen when the peroxy acid is present in excess, in which case it acts as both the oxidizing and activating agent, or when an appropriately positioned acid or amide group, which can act as an internal activator, is present in the *N*-oxide. The latter situation is illustrated by the efficient conversion of compound (**74**) to the benzimidazole (**75**; Scheme 16).[51]

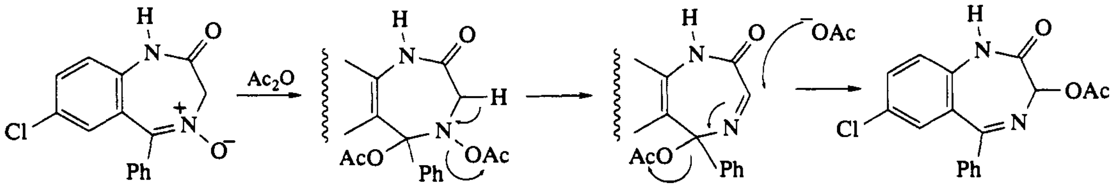


(**74**)

(**75**)

Scheme 16

There is one special example involving the reaction of 1,4-diazepine *N*-oxides such as (**76**), a trisubstituted nitrone, with acetic anhydride which has repeatedly been referred to as a Polonovski reaction, because the acetate group is introduced at the saturated C-3 position in the product (**77**).[52] However, an alternative mechanism proposed for this reaction appears more likely (Scheme 17) as it conserves all the aspects of the chemistry of nitrones with the slight variation that the elements of acetic acid are eliminated through loss of the C-3 proton.[53]



(**76**)

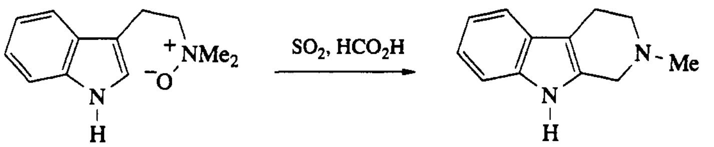
(**77**)

Scheme 17

4.7.2.5 Iron Salts and Sulfur Dioxide as Activators in the Polonovski Reaction

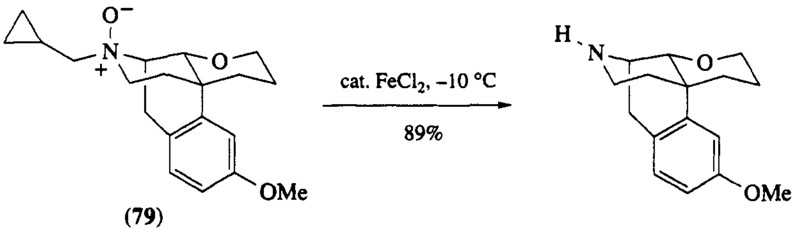
Iron(II) salts and sulfur dioxide activate *N*-oxides in the Polonovski reaction. The mechanism by which iminium ions are generated is different in both cases. In the iron reaction an Fe^{II}/Fe^{III} redox process occurs involving two one-electron transfer steps,[54,55] whereas in the sulfur dioxide reaction an intramolecular ionic mechanism is evoked.[56] A major distinguishing feature between these Polonovski reaction variants and the classical reaction using acid anhydrides is that they exhibit a marked preference for oxidation at the methyl carbon center of *N*-methyl-substituted amine oxides. The yields of these reactions are generally moderate, however, as reduction of the *N*-oxide to the tertiary amine is a competing side reaction. In fact, both iron salts and sulfur dioxide (at elevated temperatures) have been employed as reagents to deoxygenate amine oxides selectively. Attention must, therefore, be paid to experimental conditions (temperature, solvent, pH, concentration of reactants, *etc.*) in order to optimize the formation of the desired Polonovski products.

The Pictet–Spengler cyclization of *N*,*N*-dimethyltryptamine *N*-oxide (**66**) to the tetrahydrocarboline (**78**) using sulfur dioxide in anhydrous formic acid[57] and the selective *N*-dealkylation of the morphinan *N*-oxide (**79**) using catalytic quantities of iron(II) chloride[58] (equations 19 and 20) illustrate the advantages of using these activating reagents in the Polonovski reaction.



(66) **(78)**

(19)



(79)

(20)

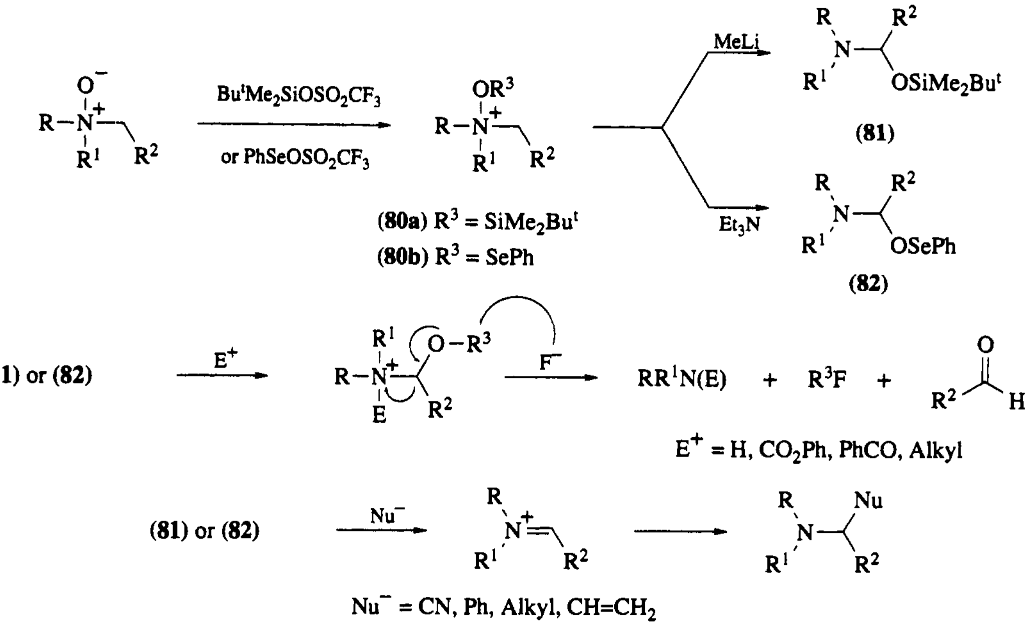
Finally, mention should be made of the use of iron porphyrins as catalysts in the Polonovski reaction. An added feature of this approach is that the *N*-oxide can act as an oxygen source for other synthetically useful, iron porphyrin catalyzed transformations.

4.7.2.6 Silicon and Selenium Polonovski Reactions

t-Butyldimethylsilyl triflate promotes the rearrangement of *N*-oxides to α-silyloxyamines (**81**) *via* the *O*-silylimonium salts (**80a**; Scheme 18).[59] The intermediate (**80a**) is remarkably stable, however, and strong bases such as methyl- or butyl-lithium are required to promote the transformation to (**81**). At present it has not been determined whether this reaction occurs by an elimination–addition mechanism, as in the conventional Polonovski reaction (Scheme 1), or by formation of an anion at the α-carbon center followed by migration of the silyloxy groups in a manner analogous to the Stevens rearrangement.

In a second variation, benzenselenyl triflate is employed as the activator and α-selenyloxyamines (**82**) are obtained.[60] The interesting feature of this reaction is that the *O*-selenylimonium salts (**81b**) are labile, and quantitative rearrangement to (**82**) is observed using weaker bases, such as triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

The α-silyl- and α-selenyl-oxyamines obtained are reactive towards both electrophiles and nucleophiles, the typical procedure involving addition of the appropriate reagent to a solution of (**80a**) or (**80b**) in THF generated *in situ* (Scheme 18).



Scheme 18

4.7.3 THE PUMMERER REACTION

4.7.3.1 Mechanism, Regio- and Stereo-chemistry

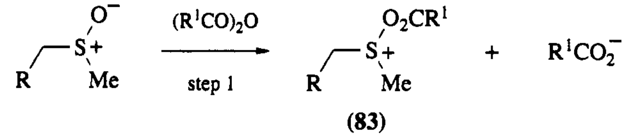
The mechanism of the Pummerer reaction can essentially be broken down into four steps (equations 21–24).[8–11] The initial step involves acylation of the sulfoxide oxygen to form an acyloxysulfonium salt (**83**). In the following step, removal of a proton from the α-carbon of (**83**) produces an acylsulfonium ylide (**84**). This ylide subsequently undergoes concurrent electron reorganization and S—O bond cleavage to give the ion pair (**85**). In the final step, condensation of acetate ion with the sulfur-stabilized carbocation gives the α-acyloxy sulfide product (**86**).

The acyloxysulfonium salts (**83**) are markedly more stable than the corresponding *N*-acyloxyimonium salts generated in the Polonovski reaction (Scheme 1). In contrast, although there is substantial kinetic isotope ^{18}O labeling and Hammett correlation data in favor of the formation of ylide (**84**) and carbocation (ion pair) (**85**), neither of these intermediates has been identified or characterized spectroscopically. The high reactivity of thionium ions is reflected by the fact that they react with weakly nucleophilic trifluoroacetate ion to give α-trifluoroacetoxy sulfides as products. Iminium ions generated in the modified Polonovski reaction are stable in the presence of $CF_3CO_2^-$.

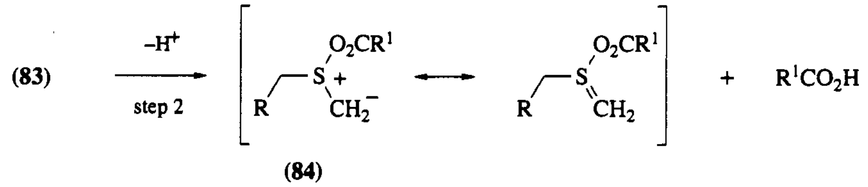
Variations on the mechanism presented in equations (21) and (22) occur since, depending upon the sulfoxide structure and the acid anhydride employed, any one of the steps 1 to 3 can be rate determining. The mode by which migration of the acyloxy group to the α-carbon center in step 4 occurs is also dependent upon these factors. Generally, this involves an intermolecular process. However, a growing number of cases exist in which this step occurs intramolecularly *via* a tight ion pair. Intramolecular acyloxy migration is one prerequisite for asymmetric induction in the Pummerer reaction.

The most extensively investigated class of Pummerer reactions involves the reaction of aryl alkyl sulfoxides, acyclic dialkyl sulfoxides or cyclic sulfoxides with acid anhydrides. In these reactions proton removal is rate determining and the product regiochemistry is determined by the kinetic acidities of the α-protons, *i.e.* $CH_2COR > CH_2CN > PhCH_2 > CH_3 >$ *n*-alkyl > *s*-alkyl. These reactions are highly succeptible to steric effects, however, as suggested by the formation of nearly equal amounts of compounds (**88**) and (**89**) in the reaction of benzyl methyl sulfoxide (**87**) with acetic anhydride (equation 25).[8,61]

The elimination of acetic acid from the initially formed acylsulfonium salt in the reaction of sulfoxides (**87**) and (**90a,b**; Scheme 19) is considered to involve a concerted nonsynchronous *E*2-type mechanism, rather than the stepwise process depicted in equations (22) and (23).[62,63] In the latter study, retention of



(21)



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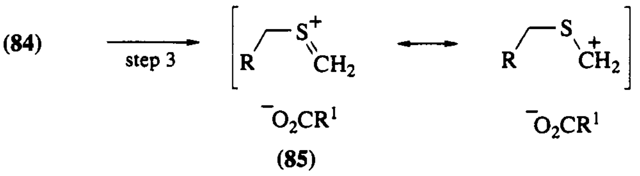

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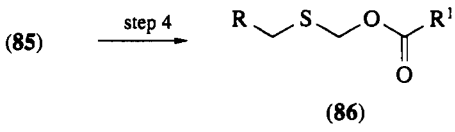

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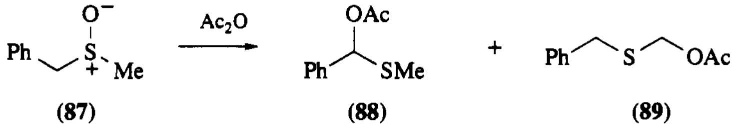
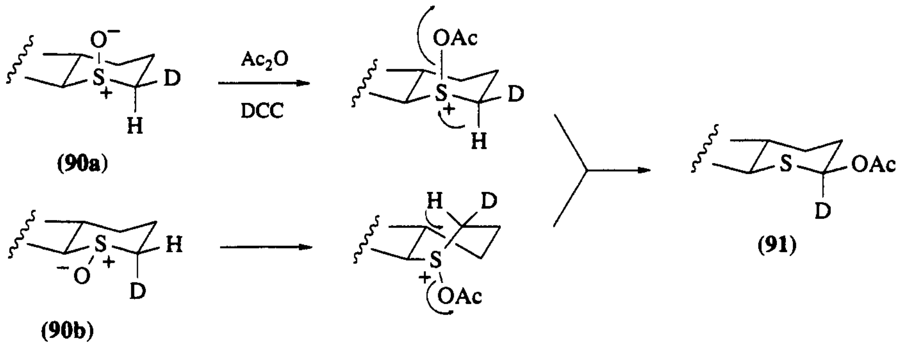


(25)

the deuterium label in the product (**91**) from both reactions strongly suggests that formation of a thionium ion intermediate involves a stereospecific *anti* elimination.

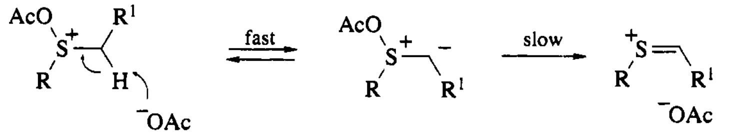


Scheme 19

In this class of Pummerer reactions subsequent formation of the α-acyloxy sulfide involves, in the majority of instances, an intermolecular acyloxy migration. The reaction of *p*-tolyl benzyl sulfoxide with acetic anhydride is an exception. However, even in this case no asymmetric induction is observed.[64]

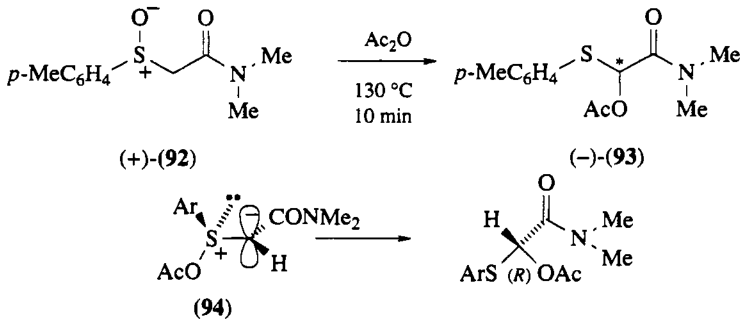
The third step in the Pummerer reaction is rate determining in reactions in which proton removal is fast and reversible and S—O bond cleavage is slow. These '*E*1cB' Pummerer reactions are observed when R′ (equation 26) is an electron-withdrawing group such as cyano, carbonyl, alkynyl or cyclopropyl. The presence of these groups facilitates proton removal while at the same time retarding departure of the leaving group due to strong inductive effects.

An important feature of these reactions is that acyloxy migration occurs intramolecularly. Moderate (30–70% *ee*) induction of asymmetry at the α-carbon is observed. In fact, Pummerer reactions in which chiral transfer occurs are almost exclusively restricted to this category. The very tight nature of the α-thiocarbenium–acetate ion pair and very rapid recombination (ion pair return) are considered to be two



(26)

important factors in this process. Another aspect of equal importance is the preference for one ylide conformer in the transition state leading to the ion pair. In the absence of such a bias racemic products are obtained. In the reaction of (–)-*N*,*N*-dimethyl-*p*-tolylsulfinylacetamide (**92**) with acetic anhydride (Scheme 20), correlation of the absolute stereochemistry of the starting material with the reaction product (**93**) provided evidence suggesting that the sterically less-hindered conformer (**94**) is preferred in the ylide to ion pair transition state.[65]



Scheme 20

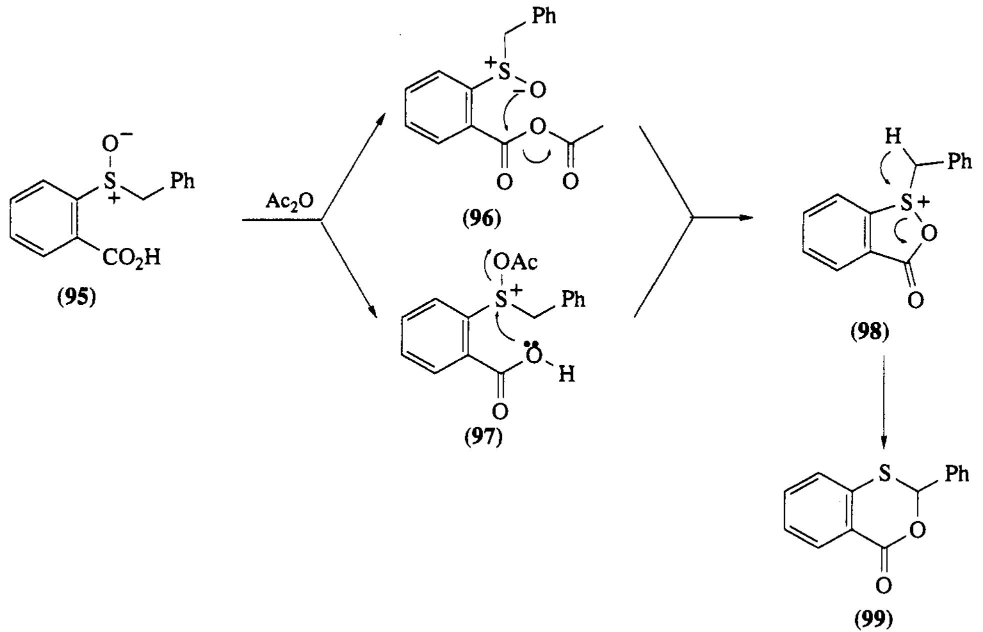
Several factors contribute to the fact that the extent of chiral transfer in the Pummerer is only moderate. These include the acidity of the reaction medium, oxygen exchange and the lifetimes of the ylide and ion pair intermediates. Although the Pummerer reaction is accelerated by the presence or addition of acid, its presence also influences the tightness of the ion pair. Oxygen exchange, through which the starting chiral sulfoxide is racemized, is a problem in all Pummerer reactions. This process is particularly rapid when trifluoroacetic anhydride is employed. Naturally, for any asymmetric induction to be possible the lifetime of the ion pair must be very short. The longer the existence of this species, the greater is the chance that acyloxy migration will occur intermolecularly and/or that rotation about the S—C bond will occur.

Pummerer reactions in which acylation of the sulfoxide oxygen is rate determining are rare, having been demonstrated for the reaction of DMSO with acid anhydrides and for the reaction of *O*-carboxyphenyl sulfoxides such as (**95**). This latter reaction (Scheme 21) is particularly interesting in that formation of the acyloxysulfonium intermediate (**98**) occurs by two competing intramolecular pathways, involving either reaction of the sulfoxide oxygen with the activated *O*-carboxy group in (**96**) or displacement of acetate ion from (**97**).[66] The two pathways are not equivalent, as the former, which predominates when DCC is used as the activating agent, involves retention of configuration, whereas the latter, which predominates under acetic anhydride conditions, occurs with inversion. In agreement with this picture (+)-(**95**) reacts with DCC to give (–)-(**99**) (29.9% optical purity) and with acetic anhydride to give (+)-(**99**) (11% optical purity).

4.7.3.2 Preparation and Elaboration of α-Acyloxy Sulfides

When acetic anhydride is employed in the Pummerer reaction, reflux temperatures are generally required. However, at elevated temperatures α-acetoxy sulfides are labile and if a β-hydrogen is present elimination of acetic acid and formation of a vinyl sulfide becomes a competing reaction (*cf.* Section 4.7.3.5). This problem is reduced by addition of sodium acetate to the reaction medium[67] or by using trifluoroacetic anhydride.[68,69] With this more reactive activating agent, high yield conversion of sulfoxides to α-trifluoroacetoxy sulfides is achieved under much milder conditions (0–20 °C). These reactions can be further accelerated by addition of a hindered base. However, once again, if a β-hydrogen is present in the sulfoxide substrate, vinyl sulfide formation may be favored.

α-Acyloxy sulfides undergo a variety of synthetically useful transformations. Of particular interest is the fact that these *O*,*S*-acetals are readily hydrolyzed to aldehydes. α-Trifluoroacetoxy sulfides are very



Scheme 21

prone to reaction under acid and base hydrolysis conditions, and often simple treatment of these Pummerer products with aqueous sodium hydrogen carbonate is sufficient to liberate the aldehyde.[68,70] Aldehydes are also obtained by partial reduction of the ester carbonyl of α-acetoxy sulfides using diisobutylaluminum hydride at –78 °C.[71] The Pummerer reaction thus provides a direct means for the conversion of a sulfoxide to an aldehyde, the versatility of this transformation in synthesis being augmented by the fact that sulfoxides are accessible by a number of different routes.

These two points are illustrated by the approach for the synthesis of deoxyleukotriene D (**105**; Scheme 22).[72] The required sulfoxide (**102**) for the Pummerer reaction step was obtained by reaction of the conjugate base of another sulfoxide (**100**) (a 4-formyl-*trans*,*trans*-buta-1,3-dienyl anion equivalent) with methyl 5-formylpentanoate. On warming, the resultant product (**101**) undergoes a spontaneous 3,2 double sigmatropic rearrangement giving (**102**). Pummerer reaction of (**102**) followed by hydrolysis of the intermediate acetoxy sulfide (**103**) furnished aldehyde (**104**). Compound (**104**) was subsequently converted to leukotriene (**105**) using Wittig chemistry.

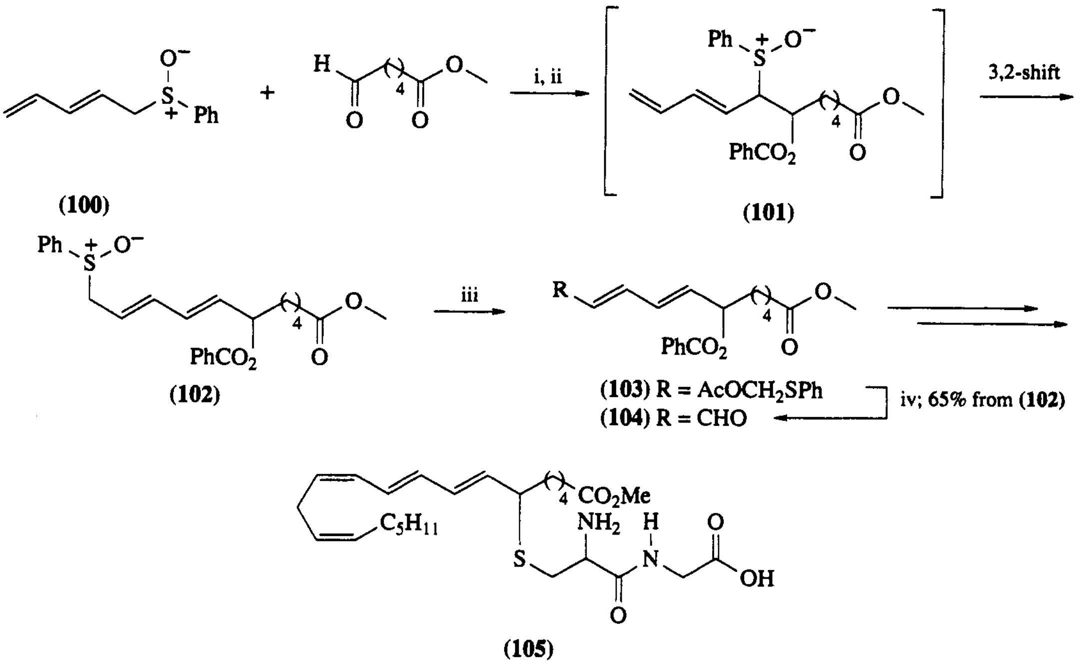
Several methods have been developed which permit the direct conversion of α-acyloxy sulfides to acetals. This can be achieved by treatment with mercury(II) acetate and *p*-toluenesulfonic acid in methanol, or even more directly by effecting the Pummerer reaction with iodine in methanol.[73,74] α-Keto acetals are similarly obtained in high yields from the reaction of β-keto sulfoxides in refluxing methanol containing iodine.[74]

Interestingly, the α-acetoxy sulfides (**106**) obtained from the reaction of β-keto sulfoxides with acetic anhydride containing sodium acetate undergo *in situ* oxidation–reduction and acyl transfer, giving α-acetoxy thiol esters (**107**) as products (Scheme 23).[75] Yields in this process are generally high.

Selective transformation of α-acetoxy sulfides to primary alcohols is achieved using $LiAlH_4$, diisobutylaluminum hydride at 0 °C and sodium borohydride in ethanol at room temperature.[76–78] Selective reduction of the Pummerer product (**108**) to the primary alcohol (**109**) is a key step in the elegant approach developed for the synthesis of monosaccharides (Scheme 24).[76]

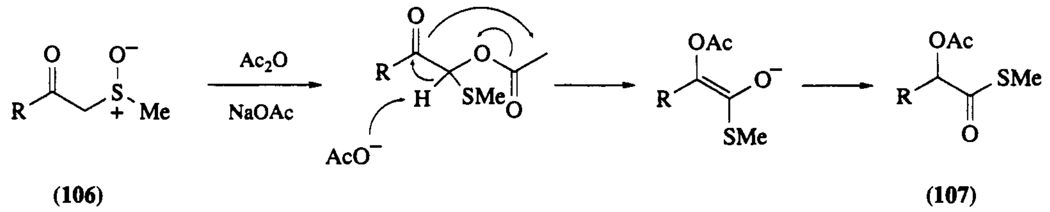
4.7.3.3 Inter- and Intra-molecular Reactions of α-Acyloxy Sulfides or their Thionium Ion Precursors with Nucleophiles

As α-acyloxy sulfides are relatively labile entities, inter- and intra-molecular displacement of the acyloxy group by a nucleophile is possible. For example, reaction of 1-*O*-acetyl-4-thiotetroses such as (**110**) with pyrimidine and purine bases in acidic media provides a convenient route to biologically interesting thionucleosides (**111**; equation 27).[79] The reaction with internal nucleophiles is illustrated by the conversion of sulfoxide (**112**) to the 2,6-epithio-3-benzazocine (**114**; Scheme 25).[80] Heating sulfoxide (**112**) in acetic anhydride for 24 hours leads to a mixture of compounds (**113**; 34%), (**114**; 18%) and the *N*-acetyl

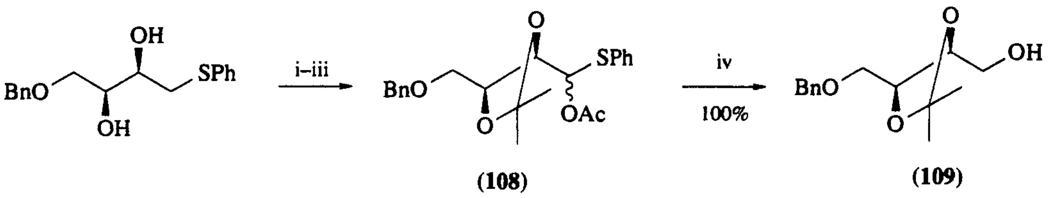


i, Bu^nLi, THF, –78 to –40 °C; ii, PhCOCl, THF, –40 to 0 °C;
iii, TFAA–Ac_2O, NaOAc, AcOH, 2,6-lutidine, 0 to 25 °C; iv, $CaCO_3$, $HgCl_2$, MeCN–H_2O

Scheme 22



Scheme 23



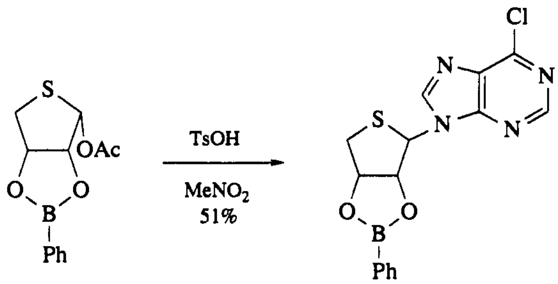
i, $MeC(OMe)_2Me$, H^+; ii, MCPBA, CH_2Cl_2, –20 °C; iii, Ac_2O, NaOAc, heat; iv, $LiAlH_4$, ether, 0 °C

Scheme 24

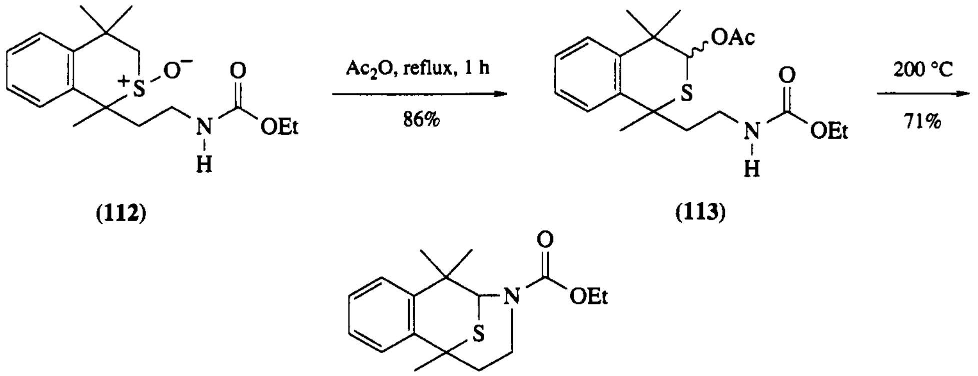
derivative of (**113**; 45%). The overall yield of product (**114**) is considerably increased, however, by the two-step procedure in which (**113**) is formed selectively by brief treatment of sulfoxide (**112**) with acetic anhydride, followed by subsequent intramolecular capture by nitrogen of the thionium ion generated from (**113**) under thermal conditions.

A biomimetic synthesis of β-lactams is similarly achieved by treatment of optically pure sulfoxide (**115**; R = H) with trimethylsilyl triflate and diisopropylethylamine (DIPEA; Scheme 26).[81,82]

Compound (**116**) is obtained in 41% chemical yield and 67% *ee*, one of the highest reported cases of asymmetric induction in the Pummerer reaction. The use of a silicon activating reagent in this reaction is crucial as the reaction of sulfoxide (**115**; R = Me) with trifluoroacetic anhydride gave compound (**119**), presumably *via* intermediates (**117**) and (**118**). This latter result points to the possibility that this and

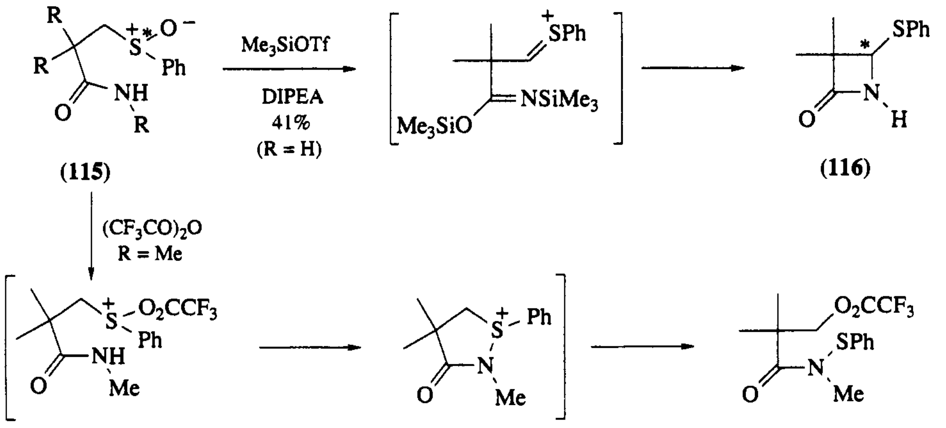


(110) **(111)** (27)



(112) **(113)** **(114)**

Scheme 25



(115) **(116)** **(117)** **(118)** **(119)**

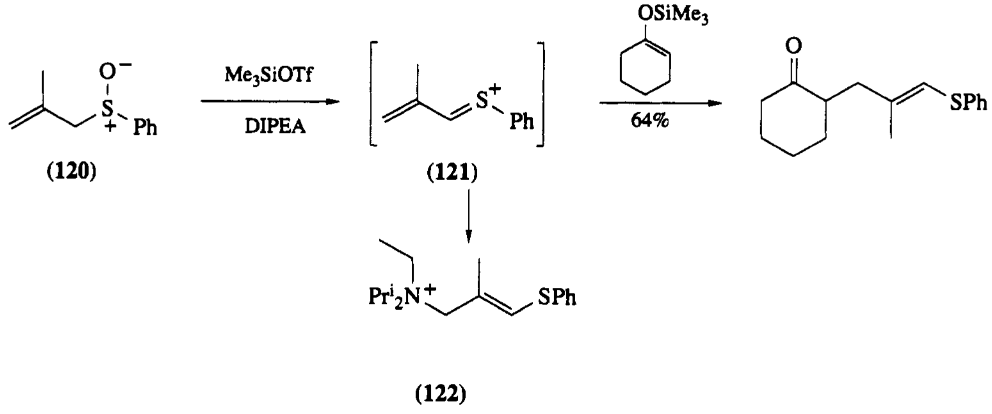
Scheme 26

other intramolecular Pummerer reactions may occur by an additive Pummerer mechanism (*cf.* Scheme 21 and Section 4.3.3.6).

Conjugate addition to vinylthionium ions is observed in the reaction of allylic sulfoxide (**120**) with enol silyl ethers in the presence of trimethylsilyl triflate and diisopropylethylamine (Scheme 27).[83] However, in certain cases moderate yields were obtained. This has been traced to a competing reaction of the intermediate (**121**) with the tertiary amine base to give the quaternary ammonium salt (**122**).

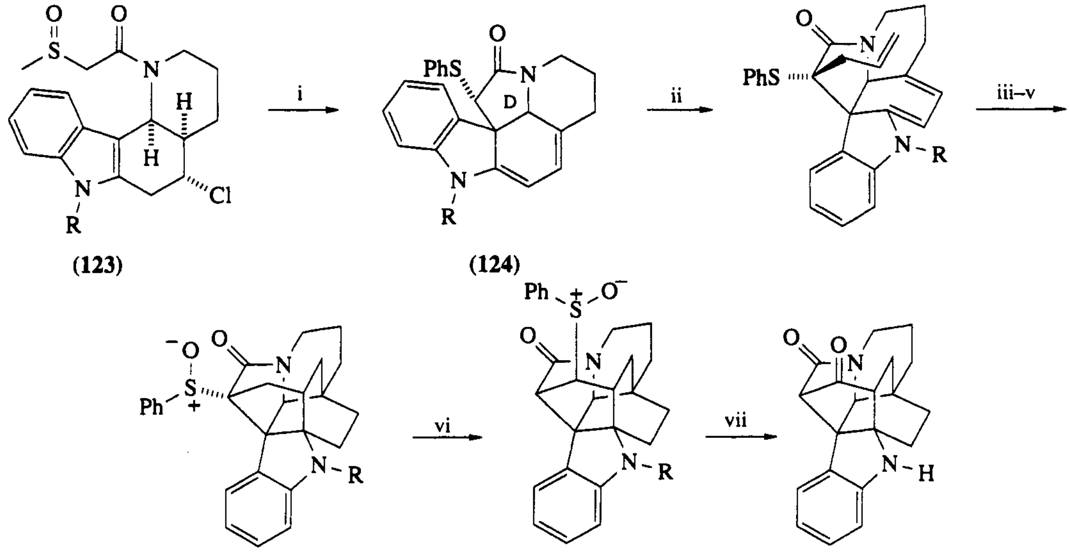
4.7.3.4 Reactions of α-Acyl Sulfides with π-Systems

α-Acylthionium ions generated from α-acyl sulfoxides under Pummerer conditions are powerful electrophiles, reacting efficiently in inter- and intra-molecular reactions with aromatic and heteroaromatic



Scheme 27

systems as well as carbon–carbon double bonds. Pioneered by Yonemitsu and coworkers,[84] the key step in a number of elegant alkaloid syntheses involves intramolecular reaction of α-acylthionium ions with aromatic rings. The synthesis of the *Aspidosperma* indole alkaloid kopsanone (**125**) by Magnus and Gallagher[85] is a particularly good illustration of this approach (Scheme 28), as it not only demonstrates how the Pummerer reaction of α-acyl sulfoxides can be used to construct the alkaloid D-ring (**123** → **124**), but also shows in subsequent steps how the same sulfur atom can be used to introduce other functionality into the molecule.

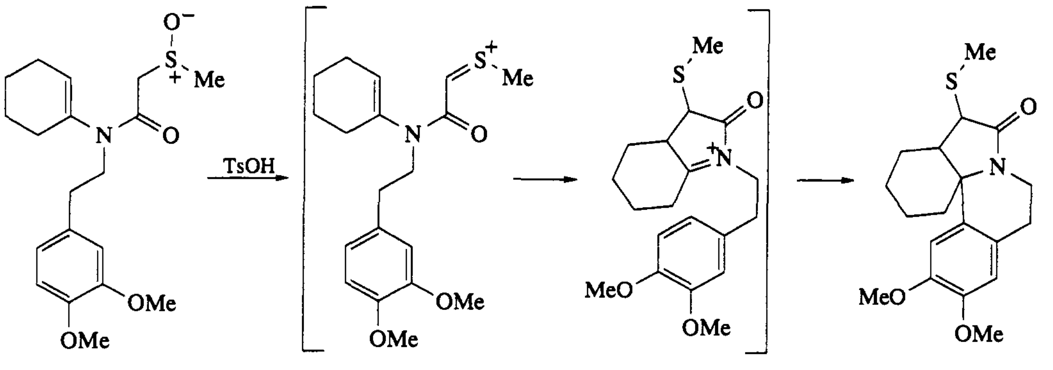


i, TFAA, CH_2Cl_2, 0 °C then 130 °C, PhCl; ii, $KN(SiMe_3)_2$, THF, 0 °C, allyl bromide; iii, 100 °C; iv, $TsNHNH_2$, NaOAc, EtOH; v, MCPBA; vi, AcOH, 230 °C; vii, TFAA, CH_2Cl_2, 0 °C, then PhCl, TFA, 130 °C

Scheme 28

Non-nucleophilic activating agents, such as *p*-toluenesulfonic acid, are generally used to generate the intermediate thionium ions. The use of trifluoroacetic anhydride in the Pummerer step of the kopsanone synthesis is feasible, since at elevated temperatures an equilibrium is established between the thionium ion and trifluoroacetoxy sulfide intermediates. Trifluoroacetic anhydride in combination with a Lewis acid can also be used. Under these latter conditions efficient intermolecular reactions of acylthionium ions with aromatic systems are observed.[86]

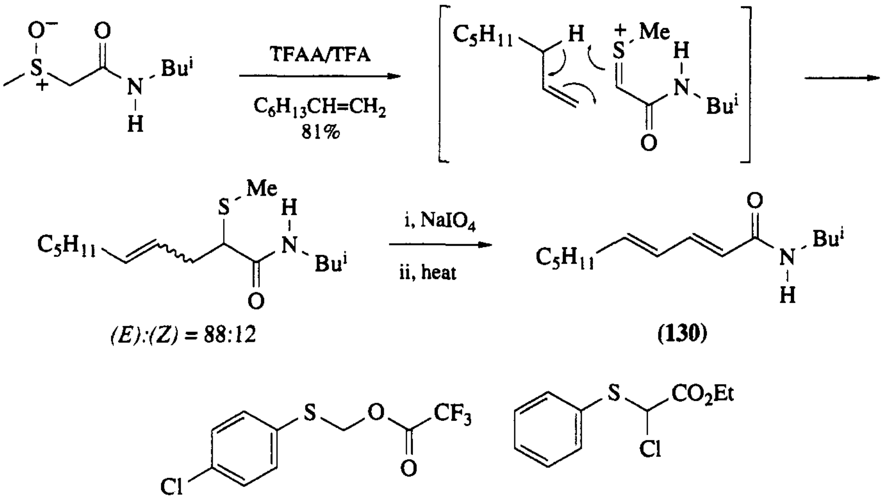
A detailed study of the Pummerer reaction of a series of *N*-alkenyl-α-sulfinylacetamides has shown that, depending upon the number and position of methyl groups on the double bond, five- or six-membered ring lactams are obtained.[87] This reaction has been applied to a concise synthesis of the erythrinane alkaloid derivative (**129**; Scheme 29).[88] On reaction of sulfoxide (**126**) with *p*-toluenesulfonic acid in dichloroethane an α-acylthionium ion (**127**) is produced, which undergoes cationic alkene cyclization generating the iminium ion intermediate (**128**), which in turn condenses with the aromatic ring giving (**129**).



(**126**) (**127**) (**128**) (**129**)

Scheme 29

α-Acylthionium ions also undergo intermolecular cationic alkene cyclizations or 'ene'-type reactions with alkenes bearing at least one allylic hydrogen, as illustrated in Scheme 30 for the synthesis of pellitorine (**130**).[89] 4-Chlorophenylthiomethyl trifluoroacetate (**131**) and the chlorosulfide (**132**) are also good initiators of these 'ene'-type reactions.[90,91]



(E):*(Z)* = 88:12

(**130**)

(**131**) (**132**)

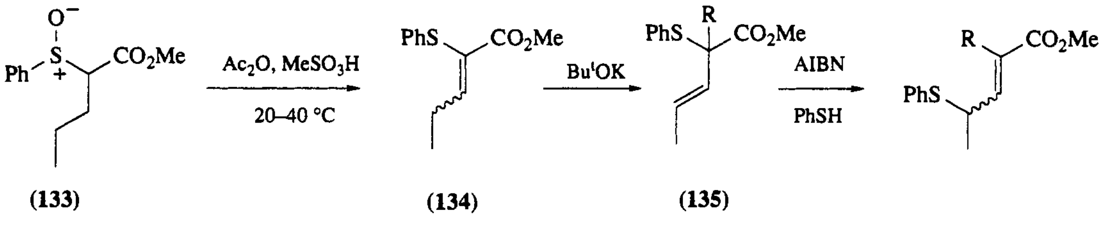
Scheme 30

4.7.3.5 Vinyl Sulfides

Vinyl sulfides and the corresponding sulfoxides are versatile reagents which react as Michael acceptors, Diels–Alder dienophiles, annelating agents and carbonyl equivalents. They are also interesting substrates for extended enolate chemistry.

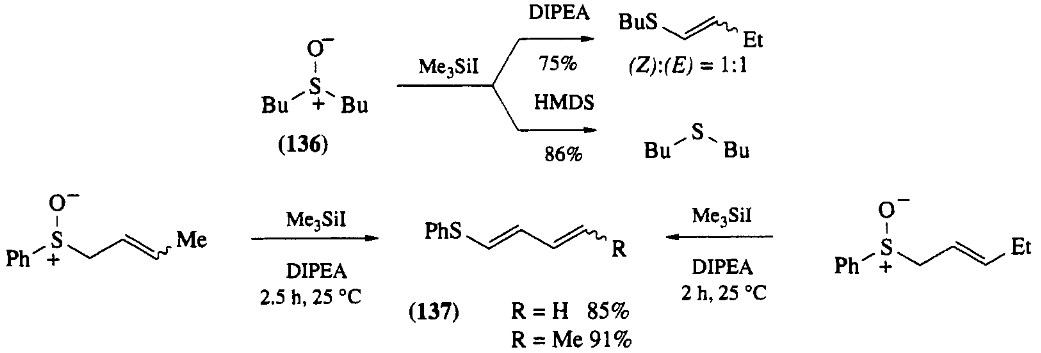
Vinyl sulfides are prepared from sulfoxides under a variety of conditions. These include reaction with acetic anhydride at reflux, with trifluoroacetic anhydride in the presence of an amine base[92] and with acetic anhydride in the presence of an acid catalyst.[93] In fact, precautions must be taken in certain Pummerer reactions discussed in the preceding sections to avoid competing vinyl sulfide formation.

Reaction of 2-phenylsulfinyl esters such as (**133**) with acetic anhydride is slow at room temperature, but when a catalytic amount of methanesulfonic acid is present in the reaction medium, conversion to the vinyl sulfide (**134**) is complete after a few hours at 20–40 °C (Scheme 31).[94,95] Mixtures of (*E*)/(*Z*) isomers are usually obtained, with the (*Z*)-isomer generally being the more stable. These isomers are interconverted on heating, a process which occurs slowly on standing, even in the dark. The discovery that photochemical or free radical induced 1,3-shift of the PhS group in (**135**) to the γ-position can be effected offers an additional opportunity to modulate the α/γ selectivity in the extended enolate chemistry of α,β-unsaturated carbonyl systems.



Scheme 31

Trimethylsilyl iodide (TMS-I) can be used as an activating agent in the conversion of sulfoxides to vinyl sulfides providing a sufficiently reactive hindered base, *i.e.* DIPEA, is employed (Scheme 32).[96] When dibutyl sulfoxide (**136**) is treated with TMS-I in the presence of HMDS rapid formation of dibutyl sulfide and iodine is observed, indicating that HMDS is too weak a base to effect deprotonation at a rate competitive with iodide ion displacement. Note also that this procedure can be used to prepare 1-thiophenyl-1,3-butadienes (**137**) and that either allylic or vinyl sulfoxides can be used as the precursors to these synthetically useful dienes.



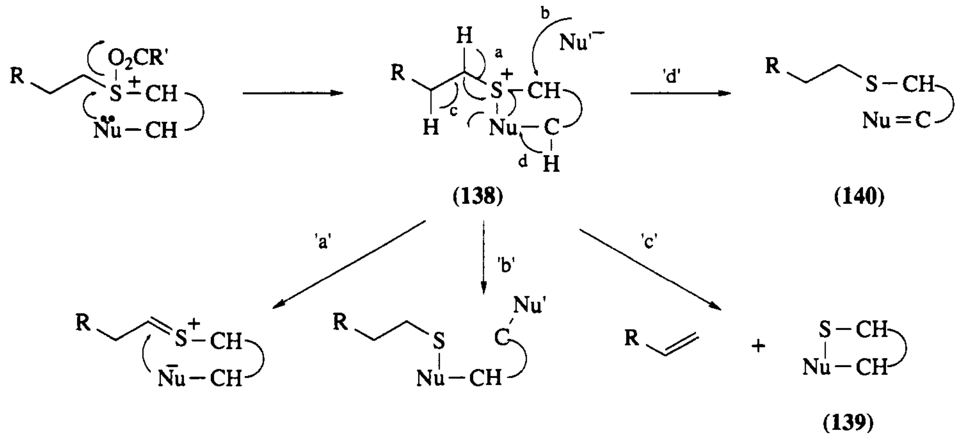
Scheme 32

4.7.3.6 Additive and Vinylogous Additive Pummerer Reactions

The additive Pummerer reaction is a reaction in which displacement of the acyloxy group in the initially formed acyloxysulfonium salt by an internal nucleophile occurs to give a new positively charged sulfur species (Scheme 33). A number of pathways are open for the subsequent reaction of intermediate (**138**), including elimination of the proton α to the sulfur to give a thionium ion (pathway a), displacement of the sulfur from the α′-carbon by an external nucleophile (pathway b), elimination of a β-proton with formation of an alkene and (**139**) (pathway c) and loss of a proton from the carbon atom α to 'Nu' with formation of (**140**; pathway d).

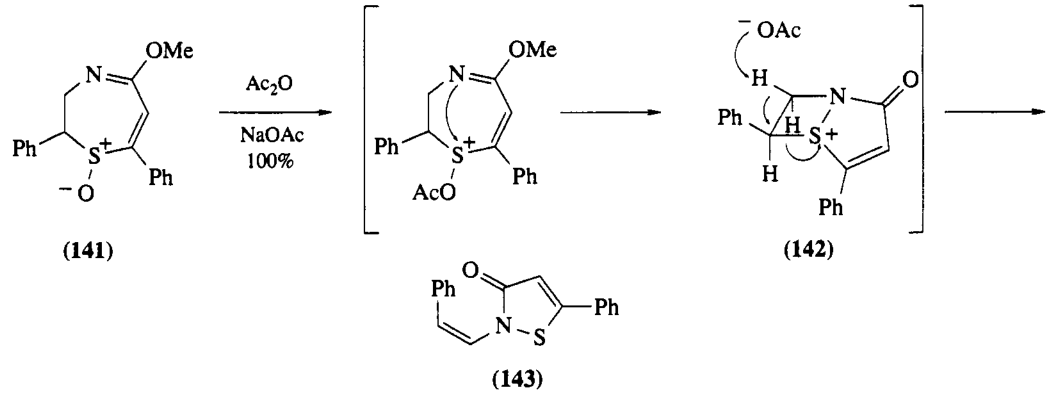
The reactions of *O*-carboxyphenyl sulfoxides (**95**) and sulfoxide (**115**) encountered earlier (Schemes 21 and 26) are examples of the additive Pummerer reaction in which pathways a and b are operative.

A Pummerer reaction which proceeds *via* pathway c is observed when the tetrahydrothiazepine *N*-oxide (**141**) is treated with acetic anhydride and sodium acetate (Scheme 34).[97] In this reaction highly efficient rearrangement to the isothiazoline derivative (**143**) occurs *via* formation and stereoselective eliminative ring opening of the bicyclic intermediate (**142**). Interestingly, the sulfoxide obtained when

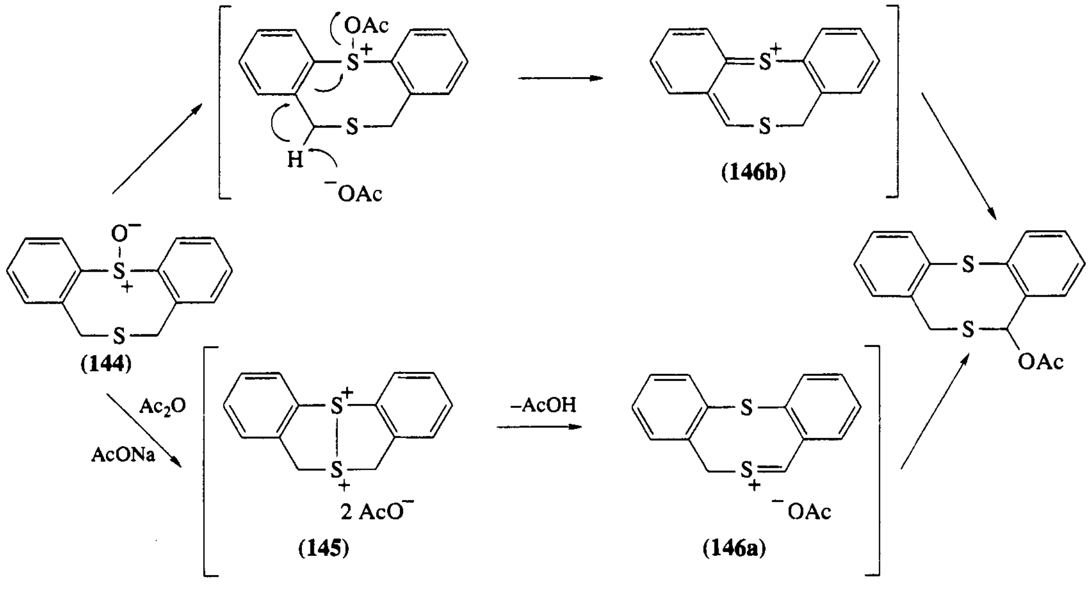


Scheme 33

the two phenyl substituents in (**141**) are replaced by *t*-butyl groups undergoes a normal Pummerer reaction.



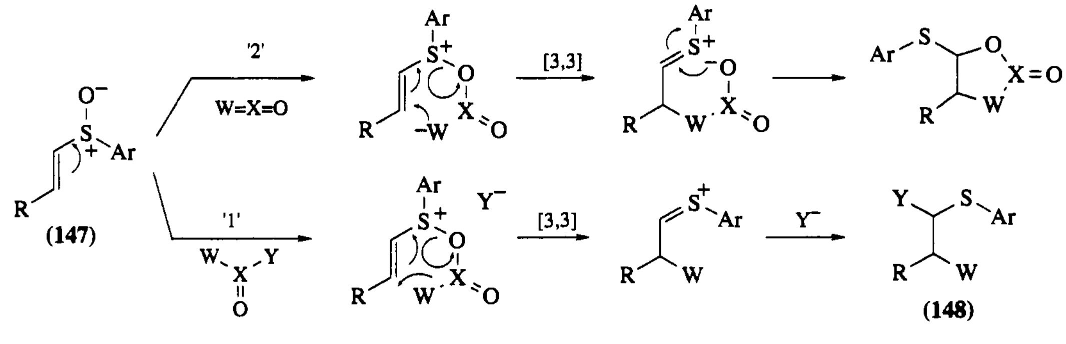
Scheme 34



Scheme 35

In the reaction of sulfoxide (**144**) with acetic anhydride the available evidence points to the formation of the disulfide dication intermediate (**145**) and subsequent rate-determining loss of a benzylic proton to give (**146a**; pathway d; Scheme 35).[98] On the basis of experiments conducted on related substrates the alternative mechanism involving the formation of the quinidomethide intermediate (**146b**) was ruled out.

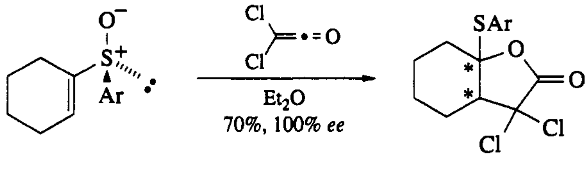
Vinyl sulfoxides also partake in additive Pummerer reactions. Of particular interest in this category are cases where the sulfoxide activating agent also provides the internal nucleophile. Two general pathways for such vinylogous additive Pummerer reactions are presented in Scheme 36.[99]



(147) **(148)**

Scheme 36

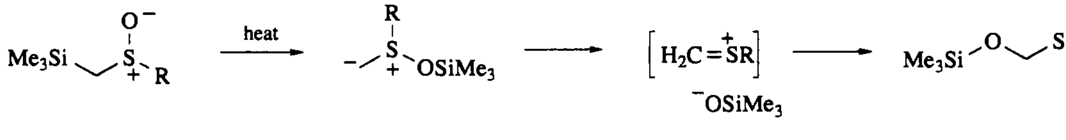
The reaction of sulfoxide (**147**) with thionyl chloride, which produces α,β-dichlorosulfides (**148**; Y = W = Cl) in 85–95% yields, is an example of pathway 1.[99] Illustrating pathway 2 is the remarkable enantiospecific formation of lactone (**150**) from the reaction of dichloroketene with the chiral sulfoxide (**149**; equation 28).[100]



(149) **(150)** (28)

4.7.3.7 Sila-Pummerer Reactions: Preparation of Trimethylsilyloxy Sulfides

In the sila-Pummerer reaction, aryl or alkyl trimethylsilyl sulfides (**151**) rearrange to the corresponding trimethylsiloxy sulfides (**153**) *via* a mechanism in which the key step is a stereocontrolled 1,3-shift of the silyl group in (**151**) from carbon to oxygen, producing ylide (**152**; Scheme 37).[101] Gentle heating is generally all that is required to induce this Pummerer reaction. In fact, the reaction often occurs spontaneously during preparation of the sulfoxide.

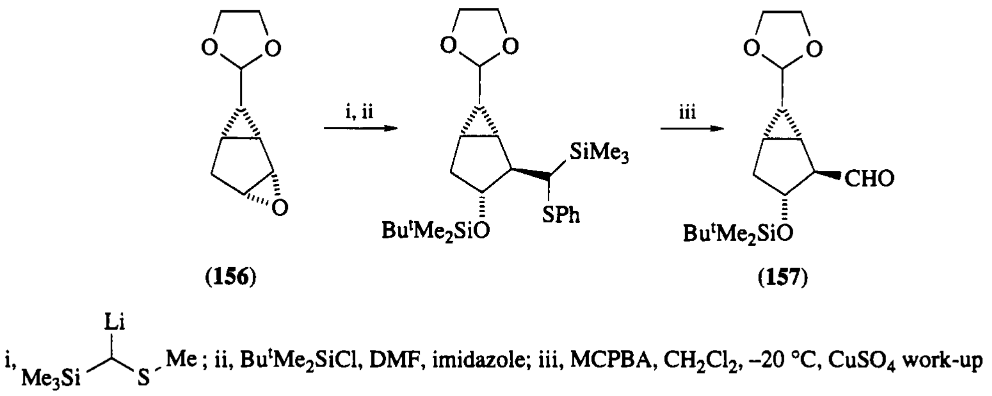


(151) **(152)** **(153)**

Scheme 37

The sila-Pummerer reaction is of considerable synthetic use as the *O,S*-acetal products can be hydrolyzed to give aldehydes under particularly mild conditions (*cf.* Section 4.7.3). Of added interest is the possibility of contracting the starting trialkylsilyl sulfides using reagents such as the conjugate base of Me_3SiCH_2SR (**154**) and Me_3SiCH_2SH (**155**).

In the synthesis of the novel prostacyclin analog (**157**) an aldehyde group was introduced at the 2-position by regiospecific ring opening of the epoxide (**156**) with the lithium anion of (**154**) and subsequent sila-Pummerer reaction (Scheme 38).[102] The aldehyde derivative (**157**) was obtained directly from the Pummerer reaction after work-up with aqueous CuSO4 solution.

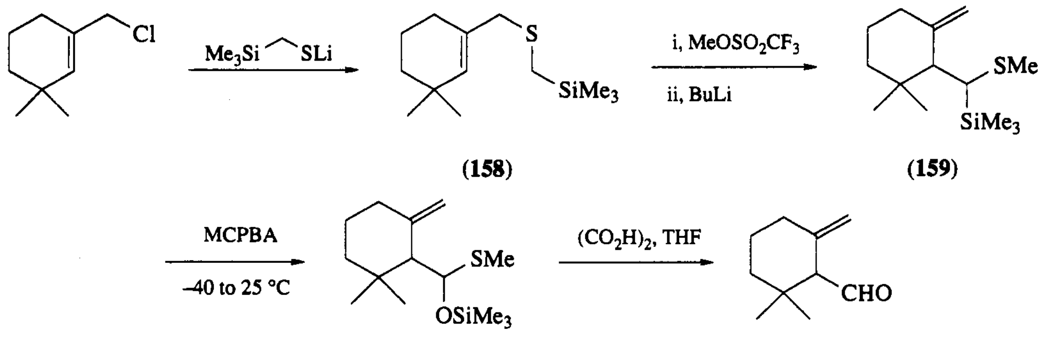


(156) **(157)**

i, ; ii, Bu^tMe_2SiCl, DMF, imidazole; iii, MCPBA, CH_2Cl_2, –20 °C, $CuSO_4$ work-up

Scheme 38

The synthesis of α-cyclocitral (**161**) in Scheme 39 illustrates further how trimethylsilyl sulfides can be synthesized and readily converted to aldehydes by the sila-Pummerer reaction.[103] Compound (**159**) was prepared by a route involving a 2,3-sigmatropic rearrangement of the ylide derived from intermediate (**158**). The sila-Pummerer rearrangement of the sulfoxide derived from (**158**) occurred below room temperature. Unfortunately, however, the enhanced rate of the rearrangement to (**160**) conferred by the methyl substituent on the intermediate sulfoxide was accompanied by greater than normal difficulty in the *O,S*-acetal hydrolysis step.

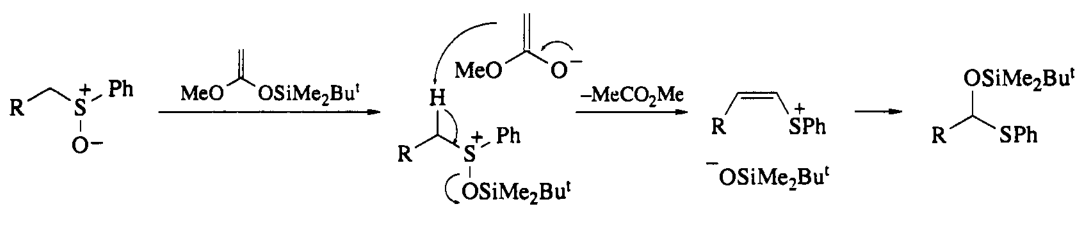


(158) **(159)**

(160) **(161)**

Scheme 39

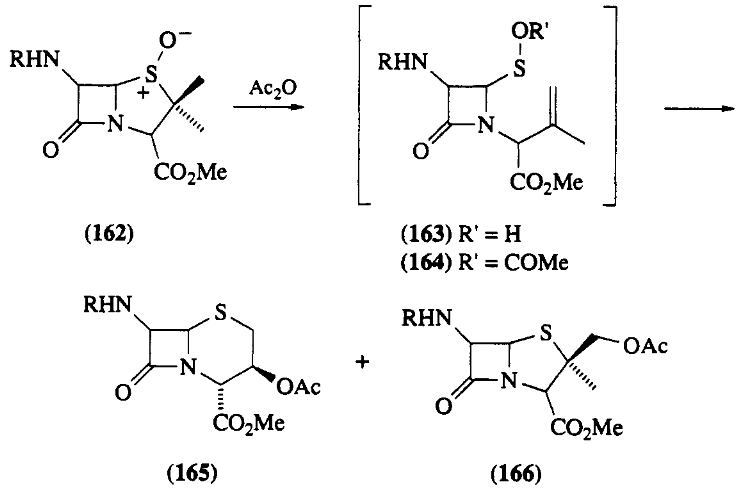
A recent study demonstrates that trimethylsiloxy sulfides can also be prepared by the reaction of sulfoxides with *O*-silylated ketene acetals (Scheme 40).[104] Although by definition this transformation is not a sila-Pummerer reaction, it provides the first set of conditions by which compounds (**153**) are prepared using a silicon activating reagent.



Scheme 40

4.7.3.8 The Abnormal Pummerer Reaction

Morin *et al.* showed that the reaction of penicillin sulfoxides (**162**) with refluxing acetic anhydride leads to formation of the ring-expanded cepham derivatives (**165**) and compound (**166**; Scheme 41).[105] Although this transformation was effected under Pummerer conditions, it occurs by a different mechanism, hence the term 'Abnormal Pummerer reaction'.



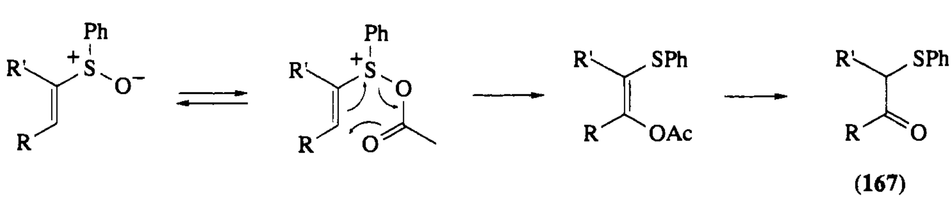
Scheme 41

Rearrangements of this type are generally observed when there are no α-hydrogens in the sulfoxide substrate and many examples of the reaction are now known. The mechanism by which they occur is dependent upon the sulfoxide structure.[106] In the reaction of sulfoxide (**162**) the sulfenic acid (**163**) or its *O*-acetyl derivative are presumed to be intermediates. The former would arise from a 2,3-sigmatropic shift of the hydrogen of the C-2 alkyl group and the latter from an eliminative ring opening in which positive sulfur is the leaving group.

4.7.3.9 Other Activating Reagents

Acid anhydrides and/or acids are employed in the majority of synthetic applications of the Pummerer reaction. However, there are a number of other reagents which activate the sulfoxide oxygen in the Pummerer reaction. The use of organosilicon reagents is discussed in Sections 4.7.3.3, 4.7.3.5 and 4.7.3.7 in connection with the preparation of trimethylsiloxy sulfides and vinyl sulfides. Recently it was shown that the trimethylsilyl ester of polyphosphoric acid also promotes the Pummerer rearrangement.[107]

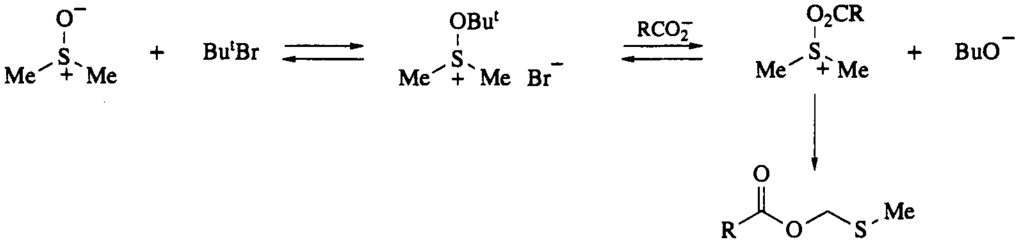
Isopropenyl acetate acts as an acetyl transfer reagent in vinylogous additive Pummerer reactions, providing an efficient means for the conversion of vinyl sulfoxides to α-acyl sulfides (**167**; equation 29).[108]



(29)

Interestingly, carboxylic acids can be converted into the corresponding methylthiomethyl derivatives (**169**) in high yield by the addition of a solution of DMSO and *t*-butyl bromide to a suspension of the carboxylic acid in DMSO containing a weak base (Scheme 42).[109] This transformation is believed to involve activation of the sulfoxide through formation of (**168**), followed by displacement of the *t*-butoxide anion by the carboxylic acid and a normal Pummerer reaction.

α-Fluoro sulfides are conveniently prepared by the Pummerer-type reaction of sulfoxides with (diethylamino)sulfur trifluoride (DAST).[110] Thallium(III) nitrate[111] and phenyl iodosylbis(trifluoroacetate)[112] have also been employed as activating agents in Pummerer-type reactions.



(169)

Scheme 42

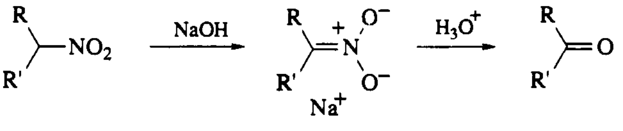
4.7.4 THE NEF REACTION

4.7.4.1 Mechanism

In most cases the Nef reaction is characterized by treatment of nitro compounds with a mineral or organic base to give a nitronate salt, which is subsequently hydrolyzed, oxidized or reduced to afford a carbonyl derivative.

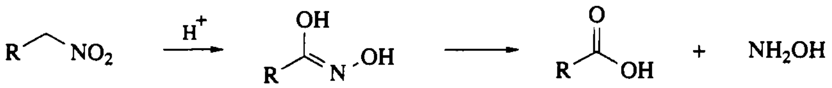
4.7.4.1.1 Hydrolysis of salts of nitroalkanes

The original procedure for the Nef reaction involved the aqueous sulfuric acid hydrolysis of the salts (**170**) obtained by the treatment of primary and secondary nitroalkanes with sodium hydroxide (equation 30).[15] In contrast, if a neutral primary nitro derivative is treated in hot concentrated mineral acid, the corresponding carboxylic acid (**172**) is formed *via* the hydroxamic acid (**171**; equation 31). This reaction is known as the Meyer reaction and was first described in 1873.[113] Protonation of salts of nitroalkanes occurs preferentially at the oxygen atom to give the *aci* form (**173**; equation 32).



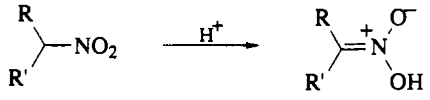
(170)

(30)



(171) (172)

(31)



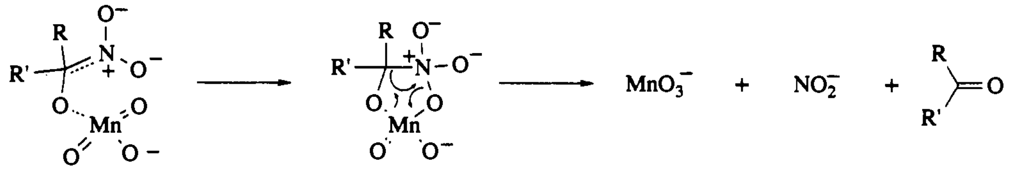
(173)

(32)

A kinetic study of the effect of water on the hydrolysis of (**173**) established the existence of two reaction pathways leading to the carbonyl derivatives, depending on water concentration.[114] The unsatisfactory results observed in many instances led to modifications of the hydrolysis conditions. The supposed limitation of the Nef reaction due to steric hindrance is probably a result of the low solubility of nitroalkanes in aqueous alkali, as demonstrated by the success of the reaction if THF–H_2O,[115] alcoholic sodium hydroxide[116] or alkoxide[117] is used. Silica gel[118–120] as a reaction medium is of great advantage when the use of organic solvents is undesirable. A two-layer method represents an improvement for the conversion of aromatic nitroalkanes.[121]

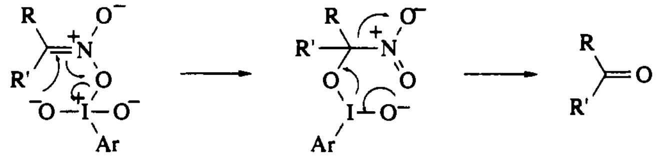
4.7.4.1.2 Oxidation reactions

The oxidizing agents usually employed for cleavage of double bonds are able to transform nitronate anions into carbonyl derivatives. The permanganate ion oxidation has been well studied.[122] The stepwise formation of the activated complex (**174**) as the slow step is a possibility but the formation of (**175**) *via* a concerted *cis* cycloaddition could also be the rate-limiting step (equation 33). Although the yield is generally high, oxidizable functions such as double bonds and hydroxy groups do not survive or at least result in decreased yields. Among modifications of methods using $KMnO_4$ as an oxidant, two interesting improvements have been described.[123–125] The electronic similarity of nitronates and enols led to the use of epoxidizing agents on nitronates[126–128] or their trialkylsilyl derivatives.[129] An α-hydroxy nitro compound is thought to be the intermediate leading to the carbonyl derivative. *m*-Iodylbenzoic acid, a reagent for cleaving glycols, also oxidized secondary nitronates to ketones (equation 34).[130]



(33)

(174) **(175)**



(34)

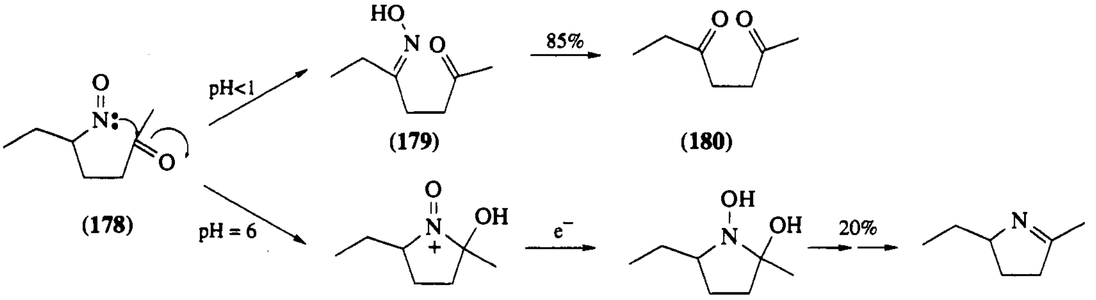
(176) **(177)**

4.7.4.1.3 Reduction reactions

Reagents such as $TiCl_3$,[131,132] VCl_2[133] and $CrCl_2$[134,135] are able to reduce nitro compounds to oximes and/or imines, which in turn are rapidly hydrolyzed to carbonyl derivatives. These reactions are usually performed in an acidic medium; however, to improve the yield a variety of pH conditions have been studied.

Reactions of titanium(III) chloride, one of the most useful reducing agents, can be carried out on free nitro compounds or on nitronate anions. The mechanisms of these two cases are thought to proceed by different pathways.

Since oximes are reduced to imines with buffered aqueous $TiCl_3$, one can assume that reduction of nitronate anions might progress through a similar mechanism. With regard to the reduction of nitro compounds themselves, there is some evidence for the intermediacy of a nitroso compound (**178**; Scheme 43). Indeed, at low pH tautomerization of (**178**) to oxime (**179**) would be rapid, whereas with $TiCl_3$–NH_4OAc at pH 6 the nitro group is trapped to give only pyrroline (**183**), due to slow tautomerism.



(178) **(179)** **(180)** **(181)** **(182)** **(183)**

Scheme 43

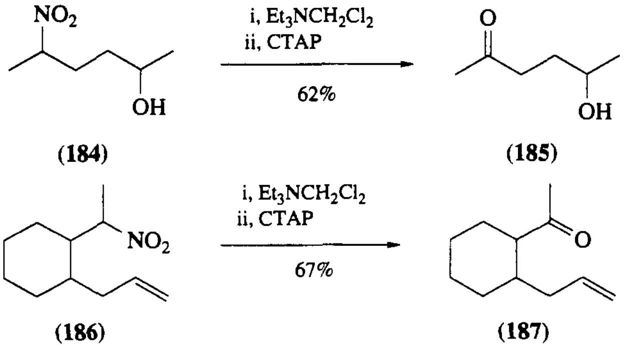
4.7.4.2 Scope and Limitations

The Nef reaction often represents the key transformation in a reaction sequence in which it is involved. The synthesis of simple aliphatic ketones or aldehydes is probably not the most useful application of the Nef reaction. More important is the access to dicarbonyl compounds for intramolecular cyclization reactions leading to a large variety of carbocycles or heterocycles. However, the method can be capricious and success depends on the structure of the substrate. In order to overcome synthetic drawbacks, several roundabout methods have been devised for application to peculiar polyfunctionalized molecules. The number of modifications of the Nef reaction which can be carried out under a wide variety of conditions clearly reveals that no procedure is of general application. The scope and limitations of the different modifications will be discussed considering the structure of desired carbonyl derivative.

4.7.4.2.1 Simple aldehydes and ketones

Most of the methods allow preparation of simple alphatic and aromatic aldehydes and ketones. With some oxidants competitive transformation of aldehydes to carboxylic acids is observed. For high molecular weight compounds the yield drops under hydrolytic conditions because of poor aqueous solubility of these derivatives; in contrast this inconvenience does not exist in alcoholic media.[117] Some methods require apparatus which is not always available or compatible with large-scale reactions, *e.g.* electrolysis,[136–138] ozonolysis[139,140] or singlet oxygen reactions.[141] $TiCl_3$ reduction exhibits some general character but yields are dependent on pH conditions (see above) if other functional groups are present in the molecule. Ozone[139,140] reacts with monosubstituted alkenes which are inert to singlet oxygen[141] and $TiCl_3$.

Cetyltrimethylammonium permanganate (CTAP),[123] a stable quaternary ammonium salt, provides a valuable modification of the original permanganate procedure for selective conversion of substrates containing alkenic and hydroxy groups. Yields are good to excellent (Scheme 44) and large quantities of substrate can be transformed.



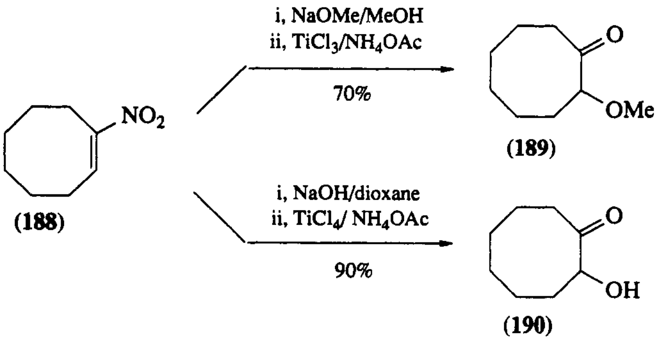
Scheme 44

α,β-Unsaturated nitroalkenes give 1,4-addition with reducing agents. Thus lithium tri-*s*-butylborohydride[142] and chromium(II) chloride[135] give the corresponding nitroalkanes, which are subsequently transformed into the saturated ketones. The same mechanism is followed when 1-nitrocyclooctene (**188**) is treated in a one-pot reaction with base (NaOH or NaOMe) then reduced by $TiCl_3$; the α-hydroxy or α-methoxy ketones are formed in excellent yields (Scheme 45).

The ester function is in general unaffected by most of the Nef reaction conditions. Of particular interest are those reactions using methanol or ethanol as the solvent for hydrolysis.[116,117] It is worth noting that treatment of a nitronate salt by sulfuric acid in absolute methanol at −10 °C yields dimethyl acetal, *i.e.* a protected form of the aldehyde.[143] For solid phase hydrolysis, silica gel[118–120] or potassium permanganate supported on silica gel[144–146] are remarkably efficient reagents, especially for small scale reactions.

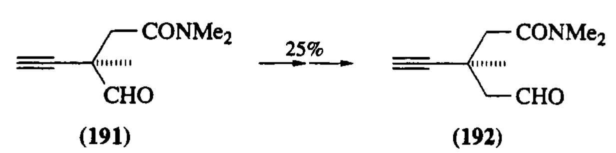
(i) Elongation reactions

The base-catalyzed addition of nitromethane to an aldehyde according to the Henry reaction, followed by the Nef reaction, is a classical method for elongation of the carbon chain in carbohydrate chemistry[4,147] Facile β-elimination of the hydroxy group allows the synthesis of α,β-unsaturated aldehydes or



Scheme 45

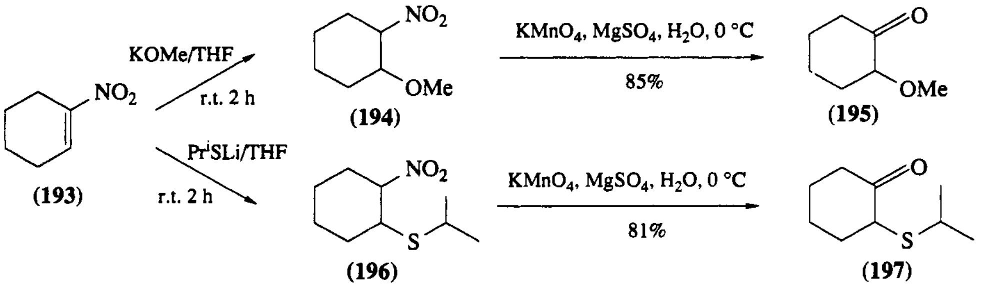
deoxy sugars after hydrogenation of the double bond.[147] Homologation of an aldehyde in a polyfunctional synthetic intermediate (**191**) is accomplished efficiently (equation 35).[117]



(35)

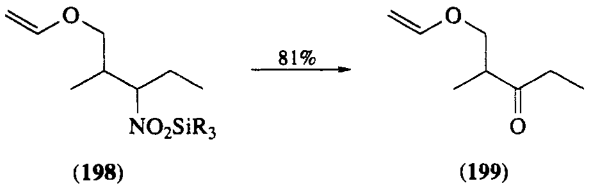
4.7.4.2.2 α-Substituted ketones

α-Alkoxycarbonyl compounds are part of macrolide antibiotics and polyether ionophores. In contrast to aldehydes, α-substituted ketones are difficult to synthesize by known methods. A straightforward manner of solving this problem is the one-pot 1,4-addition of alkoxides to nitroalkenes, followed by a Nef reaction, a process suitable for both cyclic or alicyclic ketones (*e.g.* **193**, **195**; Scheme 46).[129] The combination of these two reactions also provides a valuable route to α-sulfenylated ketones (**197**; Scheme 46).[125]



Scheme 46

Very mild conditions, which do not affect enol ethers, involve treatment of trialkylsilyl nitronates with MCPBA (equation 36)[129]. Nitro derivatives themselves do not react with MCPBA.



(36)

Preparation of α-fluoro ketones or aldehydes can also be achieved by cerium ammonium nitrate[148] oxidation of the corresponding silyl nitronates. *C*-acylation compounds derived from nitroalkanes can be transformed into α-diketones or keto esters. This procedure, while theoretically interesting, has not been extensively explored because acylation of the nitronate anion often occurs at oxygen.

4.7.4.2.3 1,3-Dicarbonyl compounds

1,3-Dinitroalkanes, obtained by condensation of nitroalkane Mannich base with other nitroalkanes or by Michael addition of nitroalkanes to nitroalkenes give 1,3-diones only when a secondary amine is used as base;[149] however, yields are moderate (~ 40%).

Interestingly, hydrazines react with 1,3-dinitroalkanes to afford pyrazoles, in most cases in high yields (equation 37).[150]

(37)

(200) **(201)**

4.7.4.2.4 1,4-Dicarbonyl compounds

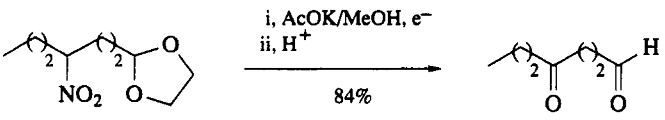
1,4-Dicarbonyl compounds are valuable intermediates in the preparation of natural products and related compounds containing pyrrole, thiophene, furan or cyclopentenone ring systems.

Reaction of nitroalkanes with Michael acceptors, followed by the Nef reaction, represents a versatile synthetic route for the preparation of 4-oxoalkanals,[138] 1,4-diketones[146] and 4-oxo esters.[143]

(i) 4-Oxoalkanals

The sensitivity of 4-oxoalkanals requires that special care be taken in their preparation.

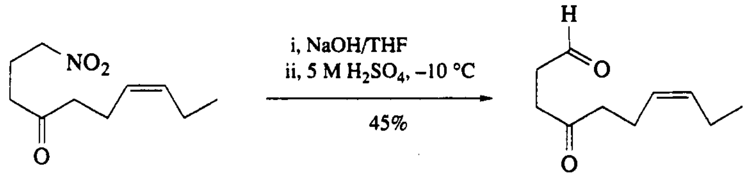
The Michael reaction of nitroalkanes with acrolein, catalyzed by tributylphosphine, followed by acetalization of the resultant adduct, led to 1,1-ethanediyldioxy-4-nitroalkane (**202**), which is oxidized by an electrolytic procedure[138] to 4-oxoalkanal 1-acetal, the protected form of the expected 4-oxoalkanal (**203**; Scheme 47).



(202) **(203)**

Scheme 47

Aqueous acid hydrolysis of the primary nitro derivative (**204**) gives the desired keto aldehyde (**205**) in moderate yield (Scheme 48).[115]

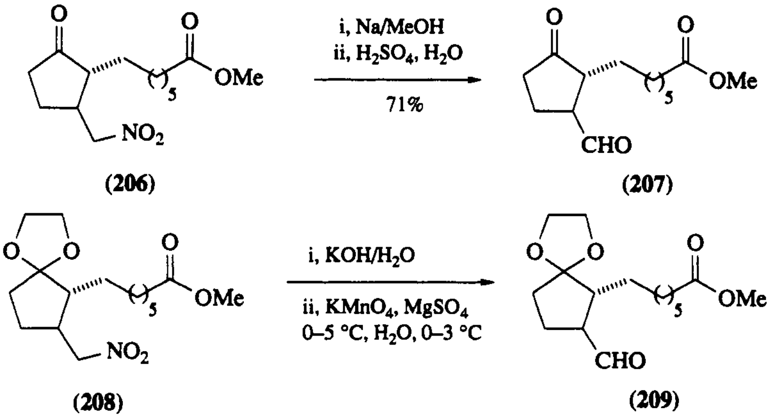


(204) **(205)**

Scheme 48

The utility of the Nef reaction in the synthesis of prostanoic acids is illustrated by the preparation of the key cyclopentanecarbaldehydes (**207**)[151] and (**209**)[152] (Scheme 49).

Selectively protected keto aldehyde (**209**) is prepared by $KMnO_4$ oxidation of (**208**).



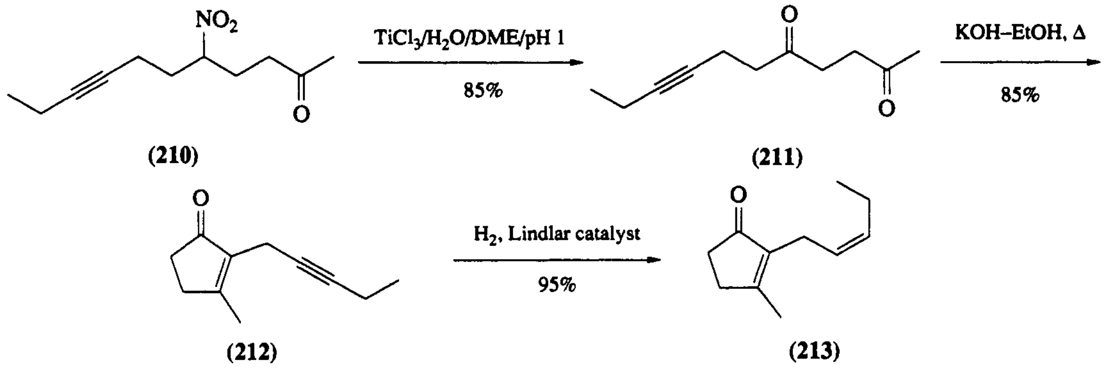
Scheme 49

(ii) 1,4-Diketones

Efforts have been devoted to the synthesis of 1,4-diketones as key intermediates for the synthesis of the cyclopentenone ring found in jasmone and its derivatives.

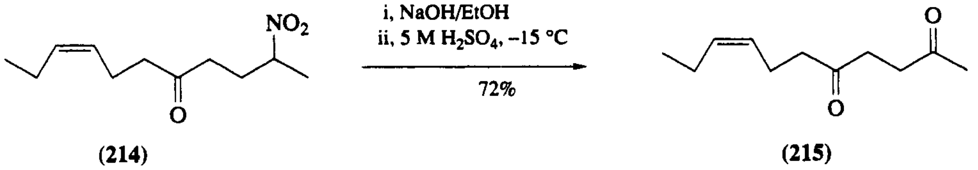
Many reaction conditions can be efficiently utilized for the Nef reaction leading to robust 1,4-diketones.[116,118,120,123,128,136,139,141,146]

Mild procedures are required for the preparation of 1,4-diketones which incorporate unsaturations. The most straightforward route to (*Z*)-jasmone (**213**) illustrates the efficiency of $TiCl_3$ reduction of (**210**) to give the diketone (**211**) in 85% yield (Scheme 50).[153]



Scheme 50

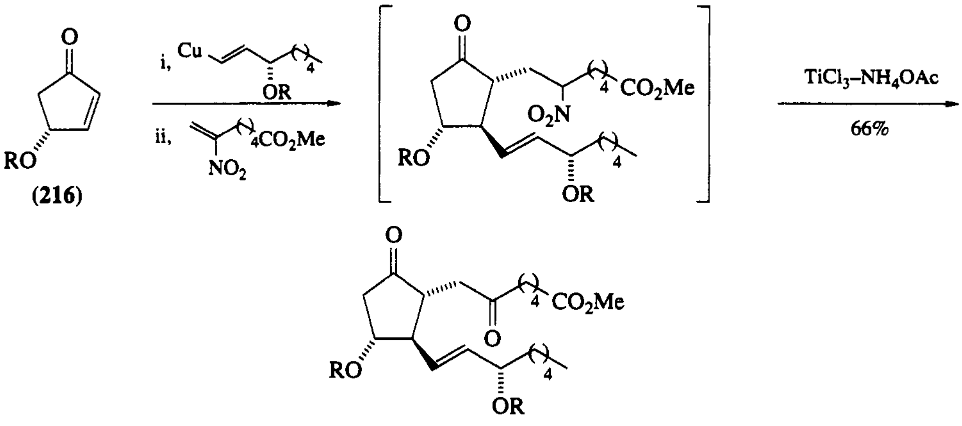
Acid hydrolysis of the ethylenic nitro derivative (**214**) gave (**215**; Scheme 51) in good yields when the reaction temperature was kept at −15 °C to avoid isomerization of the double bond.



Scheme 51

The $TiCl_3$ conditions are the most appropriate for the one-pot synthesis of the 6-oxo-PGE_1 derivative (**217**; Scheme 52).[154]

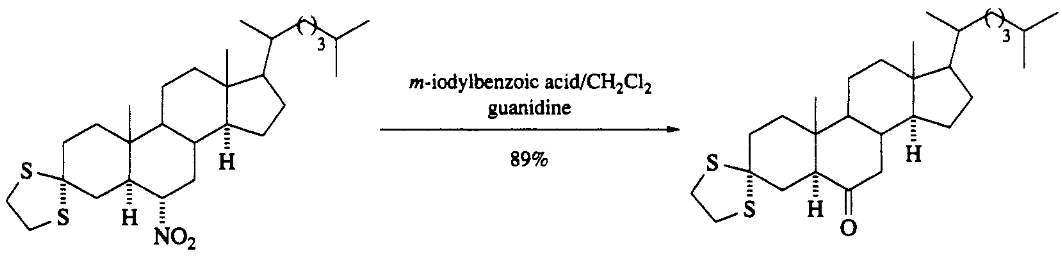
The use of supported $KMnO_4$ is disavantaged by the removal of the dicarbonyl compound from the surface of the silica gel and the yields are not convenient for large scale experiments.[144,146] *m*-Iodylbenzoic acid[130] is a mild oxidative reagent which does not affect the dithiolane moiety of the monoprotected 1,4-diketone (**219**; Scheme 53).



(216)

(217)

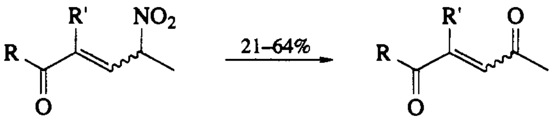
Scheme 52



(218) **(219)**

Scheme 53

2,3-Unsaturated 1,4-diketones are available from the corresponding nitro ketones by adsorption on silica gel,[118] oxidation with peroxodisulfate[155] or reduction with ascorbic acid (equation 38).

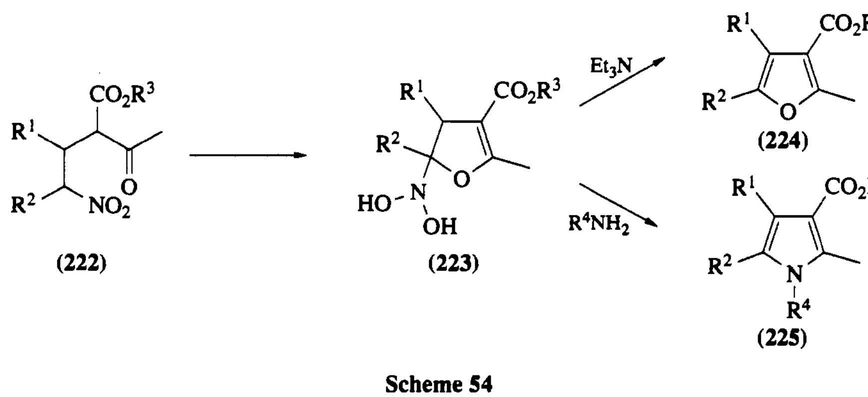


(38)

(220) **(221)**

(iii) Formation of heterocycles

Intramolecular reactions of nitronic acids, obtained from nitroalkenes and acetoacetate, lead to furans or *N*-substituted pyrroles, depending on the organic base which is used (Scheme 54).[156,157]



(222) **(223)** **(224)** **(225)**

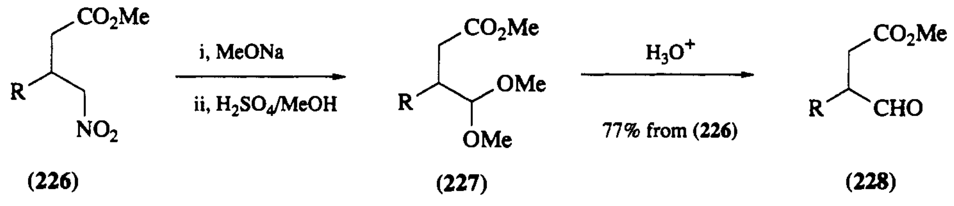
Scheme 54

Primary amines or tertiary amines afford respectively only furans (**224**) or *N*-substituted pyrroles (**225**).

The reaction in the presence of secondary amines gives a mixture of pyrrole and furan.

(iv) 4-Oxo Esters

Amongst numerous methods available, the Nef reaction appears to be the most flexible procedure for the synthesis of 4-oxo-3-alkylbutanoates (**228**); (Scheme 55), intermediates in the preparation of dienes used for cycloaddition reactions.

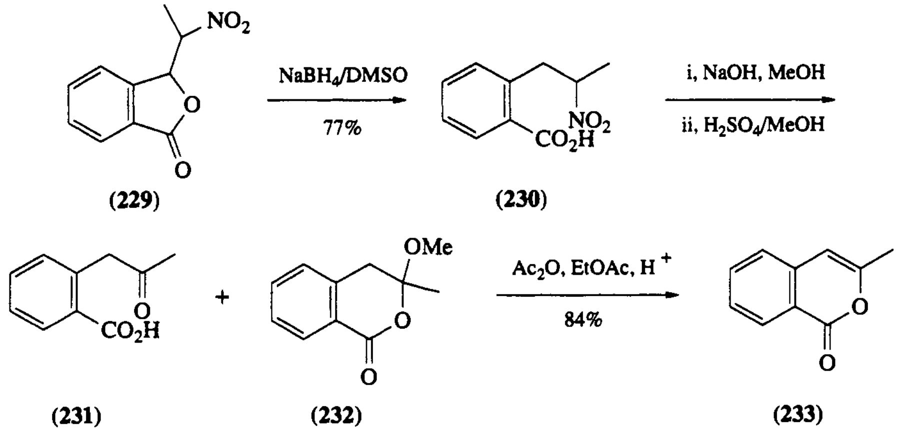


Scheme 55

4.7.4.2.5 1,5-Dicarbonyl compounds

A general route for the regiospecific synthesis of 3-alkylbenzopyran-1-ones,[158] which occur in natural products, is based upon the formation of nitroalkyl-susbtituted isobenzofuranones from Henry condensation of nitroalkanes with phthalaldehydic acids.

Amongst several Nef conditions,[127,128,131,132,154] utilization of hydrolysis in methanolic phase gave the best yields of the carboxy acetal (**232**) mixed with the keto acid (**231**), which led to the desired compound (**233**) after dehydration (Scheme 56).



Scheme 56

4.7.5 REFERENCES

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5.1

Eliminations to Form Alkenes, Allenes and Alkynes and Related Reactions

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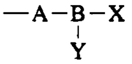
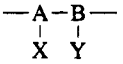
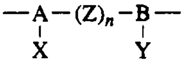
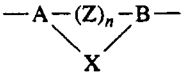
5.1.1 INTRODUCTION

If a molecule loses two atoms or groups, which will not be replaced by other atoms or groups, this reaction is called an elimination reaction. These reactions may be catalyzed by base, acid, iodine, metals or application of heat. Table 1 gives a survey of the possible elimination reactions and their products.

Table 1 Possible Elimination Reactions

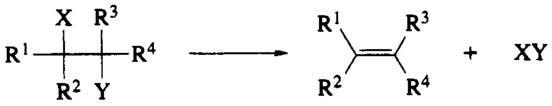
Substrate[a]	*Name*	*Products*
 $-\text{A}-\underset{\text{Y}}{\underset{\vert}{\text{B}}}-\text{X}$	1,1- or α-elimination	Carbenes, nitrenes
 $-\underset{\text{X}}{\underset{\vert}{\text{A}}}-\underset{\text{Y}}{\underset{\vert}{\text{B}}}-$	1,2- or β-elimination	Alkenes, alkynes, allenes
 $-\underset{\text{X}}{\underset{\vert}{\text{A}}}-(\text{Z})_n-\underset{\text{Y}}{\underset{\vert}{\text{B}}}-$ $n = 1, 2$	1,(n + 2)-elimination	Cumulenes, conjugated dienes, ring systems
 $-\text{A}-(\text{Z})_n-\text{B}-$ bridged by X $n = 0, 1, 2$	Extrusions	Alkenes, alkynes, aromatic systems

[a] X and Y represent leaving groups.

This article concentrates on the most important type of elimination reaction from the preparative point of view: β-elimination in solution.

5.1.2 MECHANISMS

A β-elimination is characterized as shown in Scheme 1.



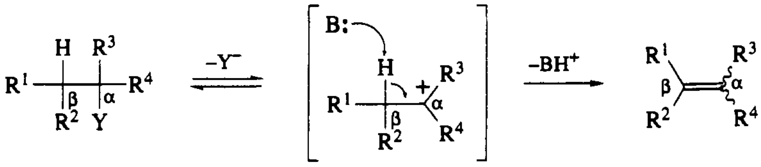
Scheme 1

Depending upon the sequence of C—X and C—Y cleavage, a distinction is made between three possible mechanisms, described in the following sections, but one should always bear in mind that all three mechanisms are idealized extremes and that borderline cases exist.

5.1.2.1 The *E*1 Mechanism (Elimination, Monomolecular)[1]

In the case of an *E*1 reaction (*e.g.* HY elimination) a two-step process is involved (see Scheme 2). In the first step (slow, rate-determining) the leaving group Y departs from the substrate as an anion and a carbocation is formed. Since the latter is also the intermediate of an S_N1 reaction, the S_N1 substitution may be a competing reaction. In the second step (fast) the positively charged substrate molecule will lose a proton from C-β to a base (*e.g.* the solvent).

Characteristic features of this mechanism are that: (i) the rate of the reaction does not depend on the concentration of the base and the kinetics are first order (in substrate); (ii) the reaction may not be stereospecific; (iii) the elimination/substitution ratio is mostly independent of the leaving group (but in solvents of low ionization energy ion pairs are formed and then the ratio depends upon the leaving group); (iv) by-products are formed *via* rearrangements; (v) the reaction is reversible; (vi) generally the most stable alkene is formed (Zaitsev orientation; see Section 5.1.2.5)

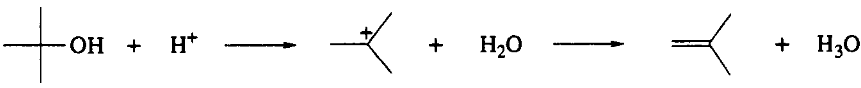


Scheme 2

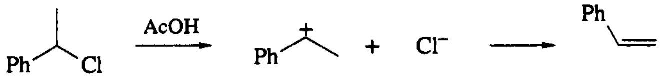
Because the characteristics (ii)–(v) are generally undesirable for preparative work, *E*1 conditions should be avoided if complications can arise.

*E*1 reactions are favored by: (i) substitution of substrate in the α-position with alkyl or aryl groups, because they stabilize carbocations (for this reason primary alkyl halides generally do not react *via* an *E*1 mechanism); (ii) polar protic solvents (*e.g.* H_2O, ROH, HCO_2H); (iii) substitution of the substrate in the β-position with alkyl substituents, because of the less-hindered transition state of the *E*1 reaction (change from *sp*^{3} to *sp*^{2}) compared to S_N1 and *E*2 reactions; (iv) a good leaving group Y (*e.g.* OH_2^+).

These points may be illustrated by two examples: acid-catalyzed dehydration of tertiary alcohols (Scheme 3),[2] and solvolytic dehydrohalogenation of secondary alkyl halides (Scheme 4).[3]



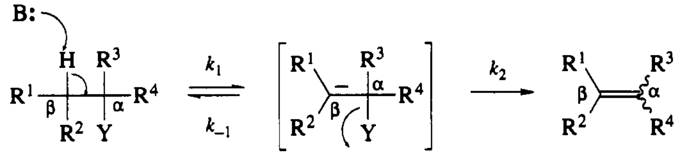
Scheme 3



Scheme 4

5.1.2.2 The *E*1c*B* Mechanism (Elimination, Monomolecular, Conjugate Base)

Like the *E*1 reaction, the *E*1c*B* reaction takes place by a two-step process (Scheme 5). However, the substrate molecule now loses a proton to the attacking base in a fast and reversible step, and a carbanion is formed at C-β. The second step (slow, rate-determining) is the departure of the leaving group Y.



Scheme 5

This mechanism is characteristic of substrates having a poor leaving group, such as fluorine, but a very acidic proton at the β-position. Depending on the conditions of the reaction, four limiting cases can be considered: (i) $k_1 > k_2$, $k_{-1} >> k_2$ (*E*1c*B*$_R$; R = reversible), *i.e.* a reversible reaction with specific base catalysis; (ii) *E*1c*B*$_{IP}$ (IP = ion pair), where there is no free carbanion, the protonated base stays close to the substrate and there is no H/D isotope effect, because the proton abstraction is not rate determining; (iii) $k_2 >> k_{-1}$ (*E*1c*B*$_{IRR}$; IRR = irreversible), where Y is a very good leaving group and the proton abstraction is rate determining, so the reaction is irreversible and exhibits general base catalysis; (iv) $k_1 >> k_2$ (*E*1$_{anion}$), where a stable carbanion is formed, which is slowly converted to the product.

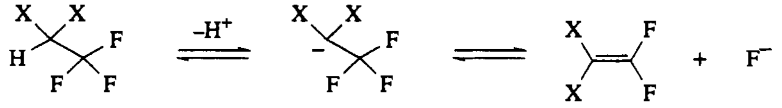
These four cases are illustrated in Table 2.[4]

An example of the *E*1c*B* elimination, the dehydrofluorination of $X_2CH—CF_3$ (X = Hal), is shown in Scheme 6 (F = poor leaving group; acidic proton at C-β).[5]

Table 2 Kinetic Predictions for Base-induced β-Eliminations

Mechanism	*Kinetic order*[a]	*β-Hydrogen exchange faster than elimination*	*General or specific base catalysis*	k_H/k_D	*Electron withdrawal at C-β*[d]	*Electron release at C-α*[d]	*Leaving group isotope effect or element effect*
$E1_{\text{anion}}$	1	Yes	General[c]	1.0	Rate decrease	Rate increase	Substantial
$E1cB_{\text{R}}$	2	Yes	Specific	1.0	Small rate increase	Small rate increase	Substantial
$E1cB_{\text{IP}}$	2	No	General[e]	1.0–1.2	Small rate increase	Small rate increase	Substantial
$E1cB_{\text{IRR}}$	2	No	General	2–8	Rate increase	Little effect	Small to negligible
$E2$[b]	2	No	General	2–8	Rate increase	Small rate increase	Small

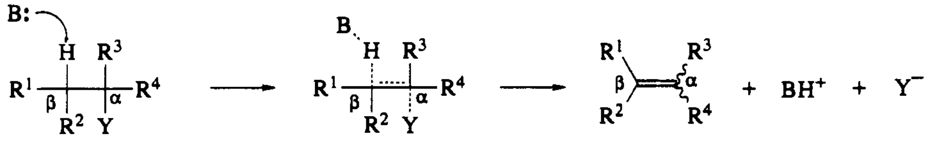
[a] All mechanisms exhibit first-order kinetics in substrate. [b] Only transition states with considerable carbanion character are considered in this table. [c] Specific base catalysis predicted if extent of substrate ionization reduced from almost complete. [d] Effect on rate assuming no change in mechanism is caused, as steric factors upon substitution at C-α and C-β have not been considered. The rate predictions are geared to substituent effects such as these giving rise to Hammett reaction constants on β- and α-aryl substitution. [e] Depends on whether ion pair assists in removal of leaving group.



Scheme 6

5.1.2.3 The *E*2 Mechanism (Elimination, Bimolecular)

In contrast to the mechanisms mentioned before, *E*2 elimination takes place in a concerted, but not necessarily synchronous, manner. While the attacking base is abstracting a proton from C-β, cleavage of the C(α)—Y bond is progressing. In the transition state all five atoms or groups are coplanar and a double bond is subsequently formed between C-α and C-β (Scheme 7).



Scheme 7

The characteristics of this mechanism are that: (i) the attacking base and the substrate both take part in the rate-determining step, which has second-order kinetics overall (first-order in base and first-order in substrate); (ii) a large primary isotope effect is usually observed; (iii) since the mechanisms of *S*N2 and *E*2 differ much more than those of *S*N1 and *E*1 reactions, the substitution/elimination ratio can be controlled in most cases by choosing appropriate conditions; (iv) no rearrangement reactions are observed; (v) the rate of elimination depends upon the strength of the base; (vi) the stereospecificity of an *E*2 reaction depends on the conditions (see Section 5.1.2.4).

These characteristics are excellent for preparative work, so synthetic chemists usually try to run elimination reactions under *E*2 conditions. To pull an elimination into the favorable *E*2 region, the following conditions have to be observed: (i) the leaving group Y should have a poor tendency to leave the substrate and low electron-withdrawing power (*e.g.* NR_3^+, PR_3^+, SR_2^+); (ii) use of a strong base in high concentration; (iii) the C-α atom should be sterically hindered by branching, so that the substitution reaction is rendered more difficult, if this is possible in view of the synthetic target; (iv) the attacking center of the base should be sterically hindered in order that only the proton at C-β, and not C-α, can be reached; (v) the solvent must be polar aprotic (*e.g.* DMF, DMSO).

The *E*1 and *E*1c*B* mechanisms are regarded as the two extreme cases[6] and the *E*2 mechanism lies somewhere between them. Whether the transition state of an elimination is more *E*1-like, more *E*1c*B*-like or exactly *E*2 depends upon the substrate, the leaving group, the attacking base and the medium of the reaction.

For example, if the substrate has a poor leaving group, the attacking base will abstract the proton at C-β a little earlier than the bond between C-α and Y is cleaved. This leads to a transition state with more

*E*1*cB* character. On the other hand, if the substrate has an electron-releasing group at C-α, the acidity of the proton at C-β will be reduced and now the leaving group is able to leave the substrate a little earlier. This gives a transition state with more *E*1 character.[7]

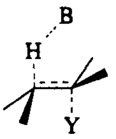
5.1.2.4 Stereoselectivity

Stereoselectivity means the specific formation of either (*E*)- or (*Z*)-alkenes. Unlike the *E*1-reaction, which has only poor stereoselectivity because of the intermediate formation of a planar carbocation, the stereoselectivity of the *E*2 reaction is very high. In the transition state all five groups or atoms involved must be coplanar. This implies a dihedral angle between C(β)—H and C(α)—Y of either 0° (ecliptic arrangement, synperiplanar) or 180° (staggered arrangement, antiperiplanar).

Because the ecliptic arrangement is energetically unfavorable, *E*2 reactions prefer *anti* elimination. This is also shown by frontier orbital arguments.[8]

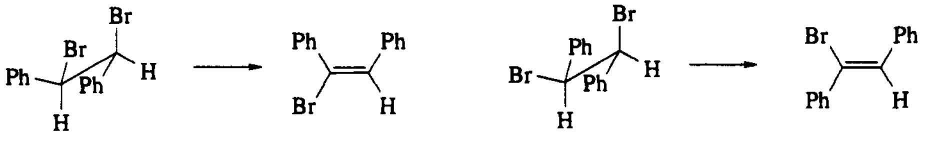
Usually this antiperiplanar conformation is easy to reach for acyclic compounds, because of the low energy barrier between the conformations.

There may also exist an interaction between the base and C-α, especially for weak attacking bases, which has already nucleophilic quality. It is to be supposed that such eliminations will proceed *via* the transition state shown in Scheme 8.[9]



Scheme 8

The dehydrobromination of 1,2-dibromo-1,2-diphenylethane is an example of *anti* elimination. The reaction of the *meso* isomer (**4**) results in the formation of (*E*)-bromostilbene (**5**). The same reaction with the (±)-isomer (**6**) gives (*Z*)-bromostilbene (**7**; Scheme 9).[10]



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

Scheme 9

The preference for *anti* elimination is especially evident in reactions with systems of fixed configuration such as vinylic haloalkenes. Usually those reactions use the *E*1*cB* pathway, because of the relatively high acidity of the vinylic proton. However, if this proton is not especially activated by electron-withdrawing groups at C-β and if the attacking base is not too strong, the reaction is shifted into the *E*2 region. The reaction of the *cis*-alkene (**10**) leads to the allene (**11**) rather than to the alkyne (**9**; Scheme 10).[11] If the substrate does not have this choice, the reaction will proceed *via* a *syn* elimination and the rate is strongly decreased.[12]

(**8**) (**9**) (**10**) (**11**)

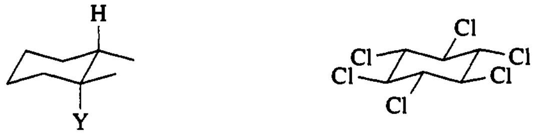
Scheme 10

Another case is the elimination reaction in cyclic systems. In such systems the conformation is determined by the flexibility or rigidity of the ring. The following correlation between ring size and degree of selectivity is observed (Table 3).[13]

Table 3 The Effect of Ring Size on the Percentage of *Syn* Elimination Product

Ring size	*Syn elimination (%)*	*Ring size*	*Syn elimination (%)*
Cyclobutyl	90	Cyclohexyl	4
Cyclopentyl	46	Cycloheptyl	37

The table shows that *E*2 eliminations, particularly in five- and seven-membered ring systems, are not completely stereospecific, but four- and six-membered rings exhibit strong preferences. Six-membered rings in particular show distinct *anti* selectivity, because it is very easy for such systems to reach the *trans*-diaxial conformation (**12**) (Scheme 11; Barton's rule).[14] This *anti* selectivity can be seen very clearly in the elimination reaction with the isomers of 1,2,3,4,5,6-hexachlorocyclohexane. The isomer (**13**), which has no Cl *trans* to an H, loses HCl about 7000 times more slowly than the slowest of the other isomers.[15]



(12) **(13)**

Scheme 11

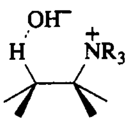
Syn elimination in *E*2 reactions will be observed if: (i) it is impossible for H and Y to reach antiperiplanar conformation (see Scheme 12);[16] (ii) one *syn*-H (H^1 in **15**) is more acidic than all the others (H^2 and H^3 in **15**; Scheme 13);[17] (iii) *syn* elimination is sterically privileged (and furthermore the attacking base, *e.g.* OH^-, may operate as a complexing reagent; Scheme 14);[18] or (iv) the counterion of the attacking base is able to form an ion pair with the substrate, although if the reaction is performed in the presence of crown ethers the relative rate of *syn* elimination is rapidly decreased (Scheme 15).[19]

(14)

Scheme 12

(15)

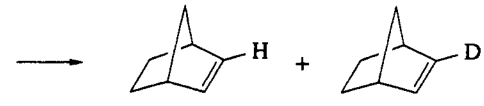
Scheme 13



(16)

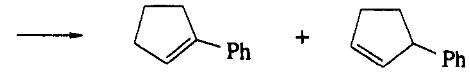
Scheme 14

(14)



No crown ether	98%	0%
With crown ether	70%	27.2%

(15)

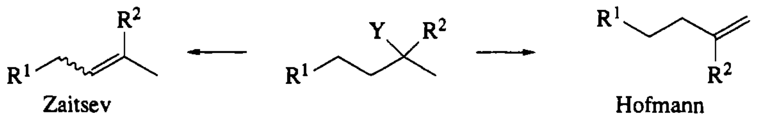


Crown ether (mol. equiv.)		
0.00	89.2%	10.8%
0.31	46.5%	53.5%
1.0	30.1%	69.9%
2.2	30.8%	69.2%

Scheme 15

5.1.2.5 Orientation

If a substrate molecule has more than one β-H atom, the elimination reaction may lead to more than one alkene. The orientation is called Zaitsev orientation[20] if the resulting double bond has the largest numbers of substituents possible; this means that the proton is abstracted from the most highly substituted carbon. If the elimination reaction runs the other way, the orientation is called Hofmann orientation.[21] In general, the Zaitsev product is thermodynamically more stable than the Hofmann product, due to hyperconjugation (Scheme 16).



Scheme 16

The orientation also depends on other factors. If there is a choice between the formation of a conjugated or unconjugated double bond, usually the conjugated system is formed. Furthermore, a double bond will never be formed to a bridgehead carbon atom if the ring size is not large enough (Bredt's rule).[22]

In addition the orientation depends upon the following factors: (i) the acidity of the β-H atom; (ii) the reactivity and character of the leaving group; (iii) the strength of the attacking base; (iv) the sizes of the attacking base and the substrate.

These points are illustrated by the following examples.

A fluoroalkane reacts with a strong base in an *E*1c*B* reaction because it has a poor leaving group and an acidic proton in the β-position. If there are several β-protons, the one leading to the most stable carbanion will be abstracted, thus a Hofmann product is formed. If there is a better leaving group, the reaction is moved into the *E*1 region. Now all factors which stabilize carbocations are important, *e.g.* high substitution at C-β; this means that the Zaitsev product is formed (Table 4).[23]

*E*2 reactions have their own rules: (i) if the leaving group is uncharged (*i.e.* negatively charged after cleavage) Zaitsev orientation is preferred; (ii) if the leaving group is charged (*i.e.* uncharged after the reaction) Hofmann orientation is preferred in acyclic systems and Zaitsev orientation in six-membered rings.

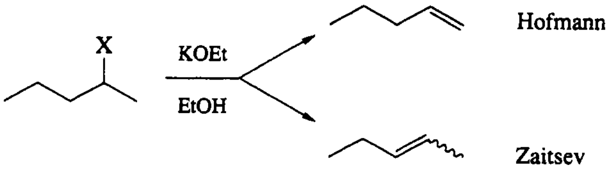
The effect of base strength is illustrated by the reaction shown in Scheme 17.

With the poor base potassium benzoate only 7.2% Hofmann product (**22**) could be obtained; with the strong base potassium *t*-butoxide the yield is raised to 20%.[24]

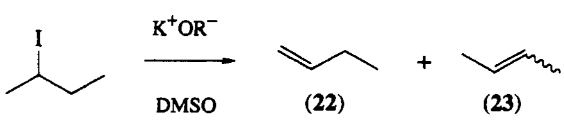
Table 5 demonstrates the effect of steric hindrance of the base.[25]

The larger the attacking base, the smaller is the proportion of Zaitsev product. Every kind of steric hindrance (in the substrate as well as in the leaving group or the attacking base) will make the transition

Table 4 The Effect of the Leaving Group on Orientation

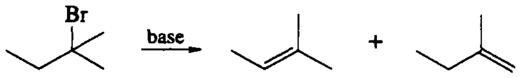


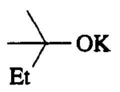
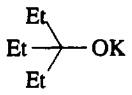
X =	*F*	*Cl*	*Br*	*I*
Zaitsev product (%)	17	64	75	80
Hofmann product (%)	83	36	25	20



Scheme 17

Table 5 The Effect of the Bulkiness of the Attacking Base on Orientation



Base	*1-Alkene (%)*	*Base*	*1-Alkene (%)*
EtOK	38		78
Bu^tOK	73		89

state which leads to the Zaitsev product energetically more unfavorable, so that the formation of the Hofmann product is preferred.

If steric hindrance is not significant, electronic effects will predominate. Finally, it should be noted that there is a statistical factor in favor of the Hofmann elimination, because there are usually more protons that can be eliminated on the Hofmann side.

5.1.2.6 *E1 versus E2 versus E1cB*

5.1.2.6.1 The effect of substituents

The *E*1 mechanism is preferred if α-alkyl and α-aryl groups are in the substrate, because they stabilize carbocations. This mechanism is also supported by β-alkyl groups, because they decrease the acidity of β-protons. On the other hand, β-aryl groups favor the *E*1c*B* mechanism, as they stabilize carbanions by conjugative effects. Electron-withdrawing groups (*e.g.* NO_2, SO_2Ar) move the reaction towards *E*1c*B*, especially in connection with poor leaving groups.

5.1.2.6.2 The attacking base

In *E*1 reactions the solvent usually operates as the attacking base. If a base is added, the mechanism can be pushed into the *E*2 region. Preparatively useful examples use OH^-, OR^- or NH_2^-, with their conjugate acids as solvents. A highly concentrated strong base moves the mechanism towards *E*1*cB* and a weak base in a polar aprotic solvent promotes an *E*2 mechanism.

5.1.2.6.3 The leaving group

A good leaving group favors *E*1 and *E*2 mechanisms, whereas a poor leaving group, especially if it is positively charged, favors *E*1*cB*, bacause of the increasing acidity of the β-H atom. Very good leaving groups shift the mechanism towards the *E*1 end of the spectrum.

5.1.2.6.4 The medium

A more polar medium favors the more ionic mechanisms, *i.e.* *E*1 or *E*1*cB*. Addition of crown ethers can move a reaction from *E*1 to the *E*2 mechanism.

5.1.2.7 The Elimination/Substitution Ratio

5.1.2.7.1 The effect of substituents

In general, elimination is increased by nearly all electron-withdrawing groups (*e.g.* CF_3, NO_2, SO_2Ar, CN, C=O, CO_2Et, *etc.*) because they (i) increase the acidity of β-H atoms; (ii) stabilize carbanions; and (iii) stabilize double bonds by conjugative effects. Because of (i) and (ii), the effect of electron-withdrawing substituents in the β-position is more pronounced than in the α-position.

If the reaction has second-order kinetics, elimination is preferred if the substrate has α-branching (*e.g.* *t*-butyl) groups. One reason for this is the statistical factor: there are more protons which can be eliminated. Secondly, there is a steric factor: the nucleophilic attack on the α-C is hindered. Thirdly, branching at α-C accelerates elimination, due to greater hyperconjugative stabilization of the double bond being formed.

If the reaction obeys first-order kinetics, the same factors promote elimination. A branching at the β-position promotes *E*2, and for steric reasons *E*1 is also promoted. But if the leaving group is charged, the *E*2 proportion is decreased; electron-withdrawing groups promote elimination and move the mechanism toward *E*1*cB*.

In general, therefore, overcrowded substrates prefer elimination, because the product is less hindered than the substitution product.

5.1.2.7.2 The attacking base

Strong bases favor elimination rather than substitution and the *E*2 mechanism rather than *E*1, particularly if they are highly concentrated. Reaction with low concentrations of base or no base in ionizing solvents promotes S_N1 rather than *E*1. Strong nucleophiles or weak bases favor substitution, unless the solvent is polar aprotic, in which case an *E*2 reaction is preferred.

5.1.2.7.3 The leaving group

If first-order kinetics apply, the elimination/substitution ratio is independent of the leaving group as long as there is no formation of ion pairs. With second-order kinetics only iodine (of the halogens) affects the ratio; it favors elimination. If the leaving group is OTs, substitution is preferred. On the other hand elimination is promoted if the leaving group is positively charged. The following sequence is observed:[26] $OTs < Br < {}^+SMe_2 < {}^+NMe_3$.

5.1.2.7.4 The medium

(i) Solvent

The more polar the solvent, the more substitution product will be produced, *e.g.* alcoholic KOH favors elimination and aqueous KOH favors substitution. In most solvents the S_N1 reaction predominates over the *E*1 reaction. An *E*1 reaction is best carried out in a weakly nucleophilic polar solvent.

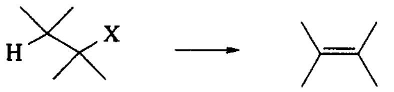
(ii) Temperature

Raising the temperature promotes elimination, since the activation energy is higher for elimination than for substitution. There are more bond changes in elimination reactions, so the entropic factor becomes important. This means that the factor $T\Delta S^*$ will be the determining factor at higher temperatures in the Gibbs–Helmholtz equation $\Delta G^* = \Delta H^* - T\Delta S^*$ and will more than compensate for an unfavorable enthalpy of activation.

5.1.3 ALKENES

5.1.3.1 Dehydrohalogenation of Alkyl Halides

The general reaction for the dehydrohalogenation of alkyl halides is shown in Scheme 18.



Scheme 18

This is a very useful reaction, which can be carried out with iodides, bromides, chlorides and fluorides.[27] The main problems are competing substitution reactions, orientation of the double bond (Zaitsev *versus* Hofmann) and the diastereoselectivity (*E versus Z*). By selecting the proper conditions it is possible in most cases to obtain the desired compound. The rate of elimination depends strongly on the leaving group (iodides usually eliminate much more quickly than bromides and chlorides), the structure of the substrate, the solvent and the base. The bases most frequently used are alkali metal hydroxides in alcohols or dipolar aprotic solvents, alkoxides in the corresponding alcohol or in DMSO, and alkali metal amides in NH_3 or inert solvents. Hydroxide ion has also been used for elimination in phase transfer catalysis.[28] Tertiary amines, *e.g.* pyridine, quinoline and dimethylaniline, are usually applied at higher temperatures; sterically hindered amines, *e.g.* ethyldicyclohexylamine (Hünig bases) or the bicyclic amidines 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU)[29] are used when substitution reactions are competing. The ratio of elimination to substitution product can also be increased by raising the reaction temperature.

The regiochemistry of the elimination, if the basic structure is given, can be influenced by the choice of the leaving group and the base. Fluorides yield the Hofmann product preferentially, while iodides afford the Zaitsev product. Strong bulky bases, *e.g.* $KOBu^t$ in Bu^tOH, increase the proportion of Hofmann product. The advantage of the bulky base is lost in DMSO.[30]

Table 6 shows the results of treating acyclic chloro- or bromo-alkanes with certain bases.

In eliminations from alkyl halides, an increase in the proportion of the 1-alkene (Hofmann product) is often accompanied by a decrease in the (*E*)/(*Z*) 2-alkene ratio as the base/solvent system is changed from EtOK/EtOH to Bu^tOK/Bu^tOH (see Table 7).[30]

In the first three eliminations in Table 7 the associated base is the main reacting species, whereas in the last three eliminations it is the dissociated base.

However, with β-phenyl-substituted compounds the effects of base association on double bond orientation are opposite to those shown in Table 7. Here the (*E*)/(*Z*) ratios are larger with the associated than with the dissociated base.[33]

Alkali metal organometallics, when used as bases in elimination reactions, often afford many by-products; however, with triphenylmethylpotassium good results were obtained.[34] On the other hand, some weak bases, such as alkali halides, sometimes in the presence of the corresponding carbonates, in DMF or HMPA have been used successfully for eliminations.[31,35] In some cases, dehydrohalogenation has

Table 6 Results of Base Treatment of an Acyclic Chloro- or Bromo-alkane[31]

Base		*Elimination*				
	Primary	*Secondary*	*Tertiary*	*BZ*[a]	*Orientation*[e]	*(E)/(Z) ratio*[f]
NaOMe/MeOH	–[d]	(+)[c]	+[b]	–	70% Z[g]	4.0
KOBu^t/Bu^{t}OH	–	+	+	+	85% H[h]	1.5
KOBu^t/DMSO	+	+	+	+	55% H	4.5
Quinoline	(+)	(+)	+	+	85% Z	2.5
Triethylamine	–	(+)	+	–	Z	
Hünig bases	+	+	+	+	75% Z	
Amidines	–	+	+	(+)	80% Z	
Alkali metal amides	(+)	+	+	–	Z	
Alkali metal halides	–	(+)	+	–	Z	
Solvolysis	–	–	(+)	(+)	Z	
Pyrolysis	+	+	+	+	60% Z	2.5

[a] BZ, benzyl. [b] +, clean elimination without concomitant substitution. [c] (+), some substitution competing. [d] –, unsatisfactory for preparative purposes. [e] Standard deviation +/– 5%. [f] Standard deviation +/– 0.5. [g] Z, Zaitsev. [h] H, Hofmann.

Table 7 Orientation and Diastereoselectivity in Some Eliminations from 2-Iodobutane at 50 °C[32]

Base/solvent	*1-Butene (%)*	*(E)/(Z) ratio for 2-butene*
EtOK/EtOH	11.7	3.25
Bu^{t}OK/Bu^{t}OH	34	2.17
Et_3COK/Et_3COH	49.3	1.50
Bu^{t}OK/DMSO	20.7	2.99
Et_3COK/DMSO	20.9	3.13
EtONa/DMSO	17.1	3.32

been accomplished by heating in DMF[36] or HMPA[37] without the addition of any other reagent; however, if the resulting HX is not removed from the reaction mixture immediately, rearrangement products *via* carbenium ion intermediates will be formed.

5.1.3.2 Dehalogenation of 1,2-Dihalides

The general reaction for the dehalogenation of 1,2-dihalides is shown in Scheme 19.

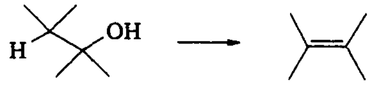
Scheme 19

Dehalogenation can be effected with many metals, *e.g.* zinc,[38,39] magnesium,[39] lithium[39] and sodium in ammonia.[40] Other reagents are sodium naphthalenide,[41] phenyllithium, lithium aluminum hydride,[42] chromium(II) chloride,[43] sodium iodide,[44] sodium sulfide[45] and sodium selenide.[46] Usually good yields are obtained in these reactions; however, since the best route to the starting material is halogen addition to an alkene, the preparative value is limited. An advantage over dehydrohalogenation is the fixed position of the formed double bond. The mechanisms of the dehalogenations are complex and depend on the particular conditions.[47] The reactions are sometimes stereospecifically *anti*, but in other cases no stereospecificity has been observed.[48]

5.1.3.3 Dehydration of Alcohols

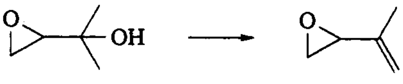
The general reaction for the dehydration of alcohols is shown in Scheme 20.

Since OH is a poor leaving group, catalysts which convert the OH group to a better leaving group, or high temperatures have to be used for this type of elimination. However, with strong acids, *e.g.* H_2SO_4, H_3PO_4, TsOH, rearrangements and ether formation can be observed, because then a carbenium ion intermediate may be formed (*E*1 conditions).



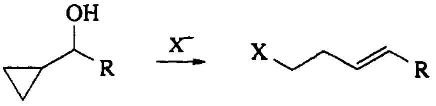
Scheme 20

For volatile alcohols, up to 1-dodecanol, vapor phase eliminations over Al_2O_3[49] or ThO_2[50] are excellent methods, since no significant side reactions occur. Another way of avoiding competing side reactions is the formation of appropriate esters and their subsequent pyrolysis or treatment with base. For the pyrolysis acetates and xanthogenates[51] and for base-catalyzed eliminations tosylates,[52] mesylates or triflates are usually used. The use of bis(tetra-*n*-butylammonium) oxalate is recommended to induce elimination rather than substitution in tosylates.[53] Heating of arenesulfonates in polar aprotic solvents, such as DMSO[54] or HMPA,[55] gives the corresponding alkenes in high yields. For some problematic eliminations, $Ph_2S[OC(CF_3)_2Ph]_2$[56] or $MeO_2CNSO_2NEt_3$[57] have been used with excellent results for secondary and tertiary alcohols (Scheme 21).



Scheme 21

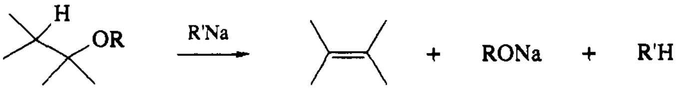
Another interesting alkene synthesis starts from a cyclopropyl-substituted alcohol, which, on reaction with magnesium halides,[58] is converted to a haloalkene; Me_3SiX has also been used in this type of reaction (Scheme 22).[59]



Scheme 22

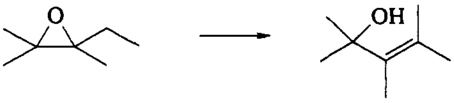
5.1.3.4 Alkenes from Ethers

With some very strong bases, such as alkyl-sodium or -lithium compounds or sodium amide, ethers can be converted to alkenes (Scheme 23).[60] The reaction is supported by electron-withdrawing groups in the β-position; thus, $EtOCH_2CH(CO_2R)_2$ can be converted to $H_2C{=}C(CO_2R)_2$ (retro-Michael-type reaction).



Scheme 23

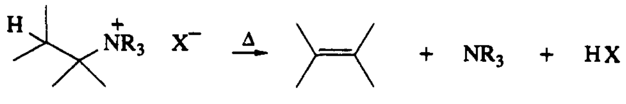
The conversion of epoxides to allylic alcohols (Scheme 24) can also be considered here. A variety of reagents, including lithium diethylamide,[61] *t*-butyldimethylsilyl iodide,[62] a dialkylboryl triflate[63] and an ethylaluminum dialkylamide[64] have been used successfully.



Scheme 24

5.1.3.5 Alkenes from Quaternary Ammonium Salts

The general reaction for obtaining alkenes from quaternary ammonium salts is shown in Scheme 25.



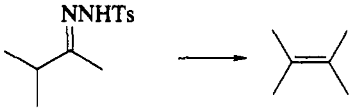
Scheme 25

In this reaction two different procedures have been used. The first is the classical Hofmann degradation, which prepares the alkene by thermal decomposition of the quaternary ammonium hydroxide.[65] Hofmann orientation is generally observed in acyclic and Zaitsev orientation in cyclohexyl substrates. The second is the treatment of quaternary ammonium halides with very strong bases, *e.g.* PhLi, KNH_2 in liquid NH_3.[65,66] The formation of the alkene proceeds *via* an *E*1 mechanism, which means a *syn* elimination in contrast to the *anti* elimination which is observed in most of the classical Hofmann degradations. In some cases this type of elimination can also be accomplished by heating the salt with KOH in polyethylene glycol monomethyl ether.[67]

Sulfonium compounds yield alkenes in reactions which are analogous to the ammonium compounds.

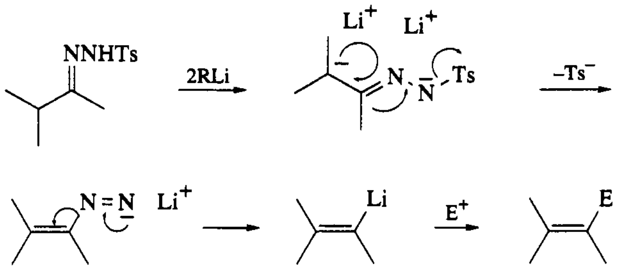
5.1.3.6 Alkenes from *p*-Toluenesulfonylhydrazones

Scheme 26 illustrates the general reaction for the generation of alkenes from *p*-toluenesulfonylhydrazones (tosylhydrazones).



Scheme 26

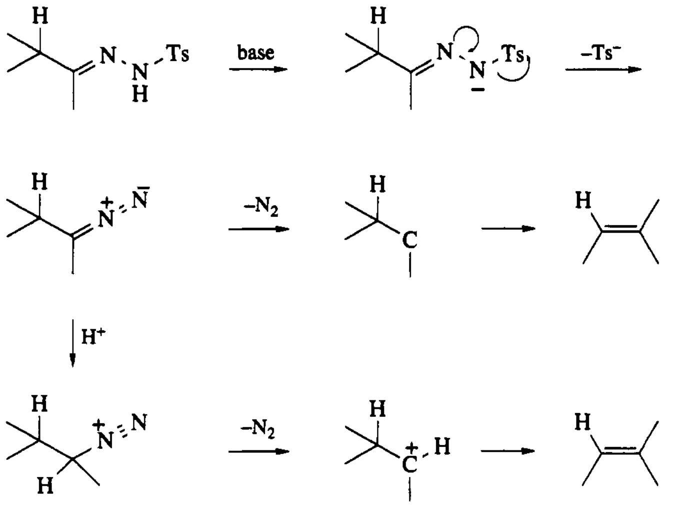
The reaction of a tosylhydrazone with at least 2 equiv. of an alkyllithium reagent in ether or hexane generates the dianion (Shapiro reaction); this gives, after loss of Ts^- and N_2, the vinyllithium compound, which can be trapped by a variety of electrophiles, *e.g.* H^+, CO_2, DMF (Scheme 27).[68] The less-substituted alkene is formed predominantly under these conditions.



Scheme 27

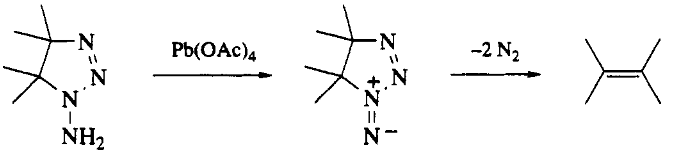
The reaction of tosylhydrazones with sodium in ethylene glycol to give alkenes had been observed before (Bamford–Stevens reaction);[69] other bases, *e.g.* NaOMe,[70] alkali metal hydrides[71] and $NaNH_2$[72] were also used. However, in these cases side reactions occur and, in contrast to the Shapiro reaction, the more highly substituted alkene is predominantly formed. Two mechanisms are discussed for these reactions: a mechanism *via* a carbenium ion, which usually takes place in protic solvents, and a carbene mechanism in aprotic solvents (Scheme 28). In both cases diazo compounds are intermediates, which can sometimes be isolated.[73]

In the absence of protons, the carbene is formed after loss of nitrogen and subsequent or concerted migration of hydrogen affords the alkene; insertion reactions or migration of other groups can lead to side products. In the presence of protic solvents, a carbenium ion is formed *via* a diazonium ion; this carbenium ion may then lose a proton to give the alkene or may give other reactions typical of carbenium ions.



Scheme 28

In the oxidative decomposition of 1-*N*-aminotriazolines, two molecules of nitrogen are lost from the nitrene intermediate. The oxidation of an aminotriazoline with lead tetraacetate was used for the synthesis of a strongly pyramidalized alkene (Scheme 29).[74]



Scheme 29

5.1.4 ALKYNES

The methods for the synthesis of alkynes have been extensively reviewed in the past 20 years;[75] two books, which deal particularly with the preparative aspects of alkyne chemistry, have been published.[76]

Except for the syntheses of acetylene and propyne, which are prepared in technical processes from carbides, from methane by oxidation, or by electric arc processes, all carbon–carbon triple bonds must be generated by an elimination reaction. Again, as in the synthesis of alkenes, the most important is the dehydrohalogenation.

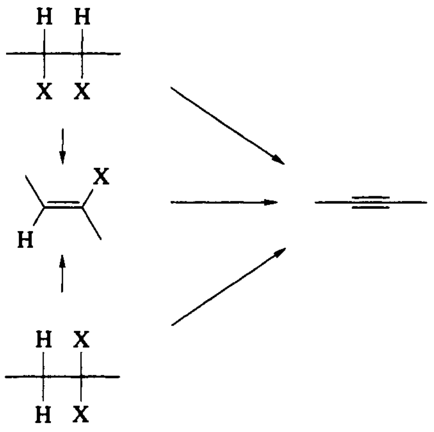
5.1.4.1 Dehydrohalogenation of 1,2- or 1,1-Dihaloalkanes

Scheme 30 illustrates the general reaction for the dehydrohalogenation of 1,2- and 1,1-dihaloalkanes.

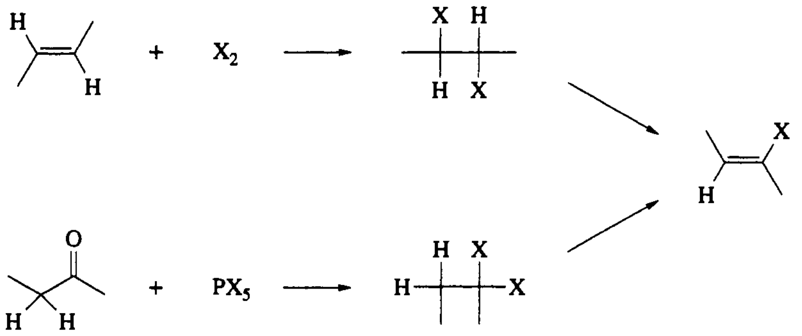
In most cases, bromo or chloro derivatives are used as starting materials. The 1,2-dihaloalkanes are usually prepared from the alkenes by halogen addition, the 1,1-dihaloalkanes from the corresponding carbonyl compounds with PCl_5 or other acid chlorides (Scheme 31). Some 1,1-dichloroalkanes can be prepared from vinyl chloride by addition of a secondary or tertiary alkyl chloride (Scheme 32). The 1-haloalkenes can be prepared from either the 1,2- or the 1,1-dihaloalkanes by elimination of 1 mol of hydrogen halide or by a Wittig reaction (Scheme 33).

Bromo compounds generally eliminate faster than the corresponding chloro compounds. Electron-withdrawing substituents in the substrate facilitate the elimination.

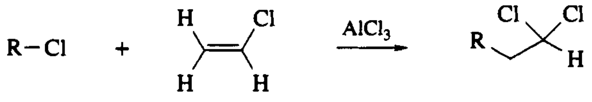
To accomplish the elimination, the substrate must be treated with a base. Whereas elimination of 1 mol HX from chloro- or bromo-alkanes can be effected with a weaker base, *e.g.* tertiary amines or K_2CO_3, the elimination of the second mole of HX requires stronger bases, *e.g.* $NaNH_2$, $LiNPr^i_2$ or RLi. Thus,



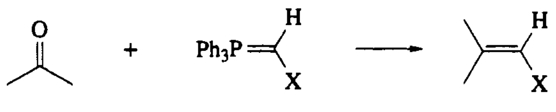
Scheme 30



Scheme 31

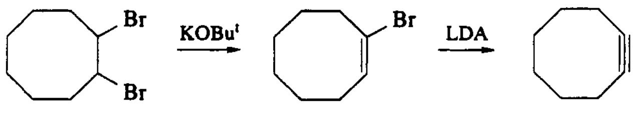


Scheme 32



Scheme 33

treatment of 1,2-dibromocyclooctane with KOBu^t yields 1-bromocyclooctene, which can be converted to cyclooctyne with LDA (Scheme 34).[77]

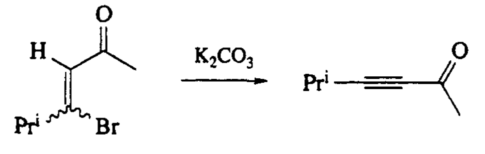


Scheme 34

The formation of the allene, sometimes a serious complication in alkyne synthesis, is not a problem in this case, because 1,2-cyclooctadiene, once formed, dimerizes readily and can therefore be easily removed from cyclooctyne by distillation.

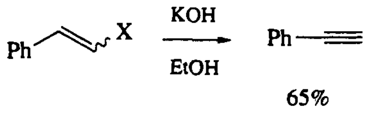
The oxygen bases, alkali metal carbonates, alkali metal hydroxides and alkoxides are used to a large extent. The solvents are alcohols, ether, THF, dioxane, glycol or glycol ethers (for higher temperatures), DMSO, HMPA or crown ethers. The latter three increase basicity by generating 'naked' anions, because the cations are strongly solvated.

Alkali metal carbonates, being weak bases, can only eliminate to the alkyne if a strongly electron-withdrawing group facilitates elimination. Thus, the bromovinyl ketones (both *cis* and *trans*) can be converted to the alkynic ketone with K_2CO_3 (Scheme 35); the elimination from the educt having H and Br in a *trans* configuration is about 10 times faster.[78]

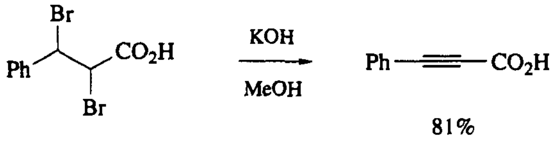


Scheme 35

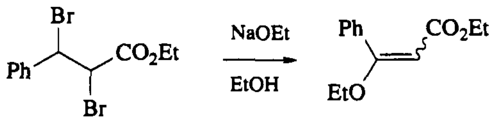
The use of KOH in alcohols is a convenient method for preparing acetylenes (Schemes 36[79] and 37[80]). However, when the corresponding ester is treated with sodium ethoxide in ethanol, the major product is the vinyl ether, which is formed by a nucleophilic addition of ethoxide to the activated triple bond (Scheme 38).[81]



Scheme 36



Scheme 37

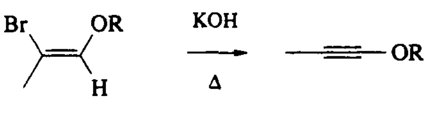


Scheme 38

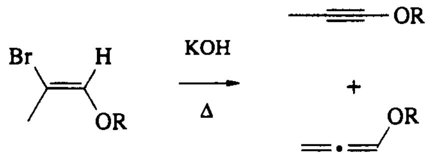
As mentioned before, allenes can be formed by prototropic rearrangement of alkynes or, if an appropriate hydrogen is present in the allylic position, by direct elimination. The bromovinyl ether yields, in a *trans* elimination, the alkyne ether (Scheme 39), but the other isomer, where *trans* elimination is not possible, gives both the alkynyl ether and the allenyl ether (Scheme 40).[82] This corresponds to the problem of Hofmann and Zaitsev orientation in alkene synthesis.

Use of KOH without a solvent prevents the alcohol addition to the alkyne formed; usually the alkynes are directly distilled from the mixture of their halogenated precursors and KOH (Schemes 41[83] and 42[84]).

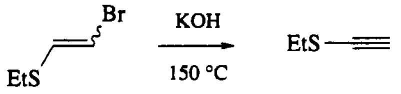
The alkali metal amides are stronger bases than the alkoxides. Therefore, in many reactions milder conditions can be applied; sodium amide in liquid NH_3 is most widely used. In contrast to the oxygen



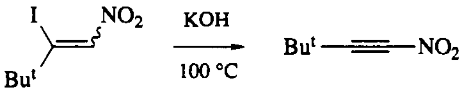
Scheme 39



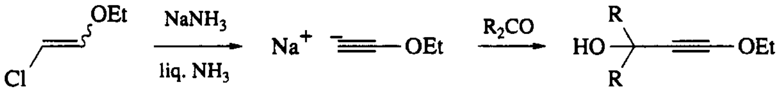
Scheme 40



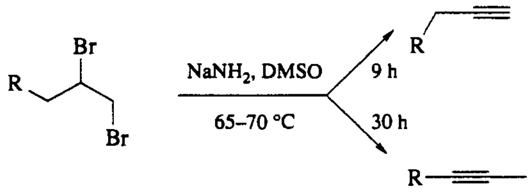
Scheme 41



Scheme 42



Scheme 43

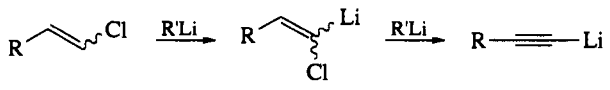


R = n-C_8H_{17}, n-$C_{11}H_{23}$ to n-$C_{14}H_{29}$

Scheme 44

bases, both *cis*- and *trans*-haloalkenes are converted to the alkyne; in the preparation of terminal alkynes no isomeric allenes or alkynes are formed, since the sodium salt of the terminal alkyne precipitates. This sodium alkynide can be used immediately for further reactions, *e.g.* with ketones (Scheme 43).[85] In DMSO the sodium alkynides are soluble and the terminal alkynes can, under equilibrium conditions, isomerize to the more stable internal alkynes (Scheme 44).[86] Lithium dialkylamides have been used successfully in the preparation of aryl- and alkyl-alkynes[77,87] and in the synthesis of ynamines, where elimination and concurrent substitution took place.[88]

Butyllithium is an excellent reagent for the dehydrohalogenation of 1-chloroalkenes or 1,1-dichloroalkanes to terminal alkynes;[89] the organolithium compound must be added dropwise to avoid alkylation of the intermediate carbenoids, leading to alkenes. Three equivalents of alkyllithium are necessary to convert the 1,1-dichloroalkane to the alkyne (two equivalents from 1-chloroalkenes; Scheme 45).

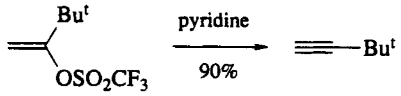


Scheme 45

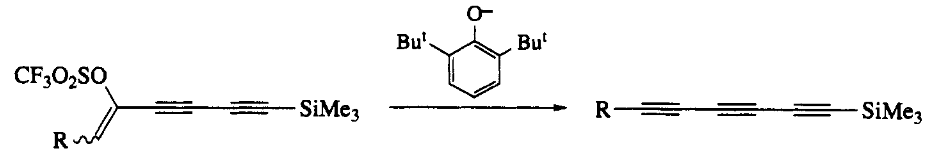
Sodium hydride can be used as a dehydrohalogenating agent in dipolar aprotic solvents, such as DMSO or HMPA. Halostilbenes have been converted to the corresponding diarylalkynes in this way.[90]

5.1.4.2 Elimination of 'Acids' Other Than Hydrogen Halides

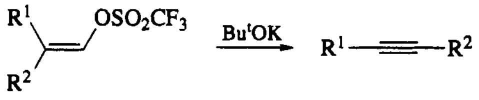
If the anions of these acids are good leaving groups, elimination from their enol esters can be effected by the bases used for elimination of hydrogen halides. Enol triflates, on treatment with pyridine (Scheme 46),[91] 2,6-di-*t*-butyl phenoxide (Scheme 47)[92] or potassium *t*-butoxide (Scheme 48)[93] yield the corresponding alkynes.



Scheme 46



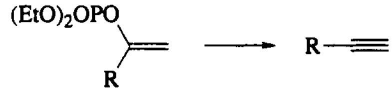
Scheme 47



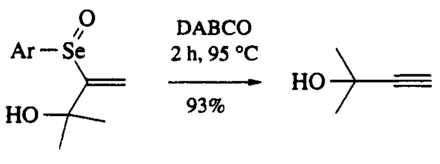
R^1, R^2 = H, Pr^n; Ph, Ph; Ph, Me

Scheme 48

Enol phosphates treated with $NaNH_2$ in liquid ammonia[94] or with lithium dialkylamides[95] give the alkynes in good yields (Scheme 49).[96] Vinyl selenoxides can also be used as a starting material for the preparation of alkynes. Thermolysis at 85–95 °C takes place in the presence of DABCO if a *syn* elimination to the alkyne is possible (Scheme 50). If a *syn* elimination to an alkyne is blocked by a substituent, allene formation can occur.[97]

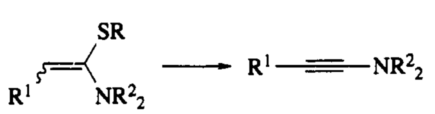


Scheme 49



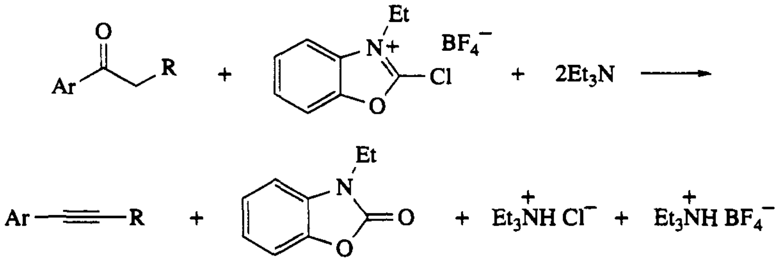
Scheme 50

Ynamines have been prepared from ketene *S,N*-acetals on treatment with lithium dialkylamides or $NaNH_2$ (Scheme 51).[98]



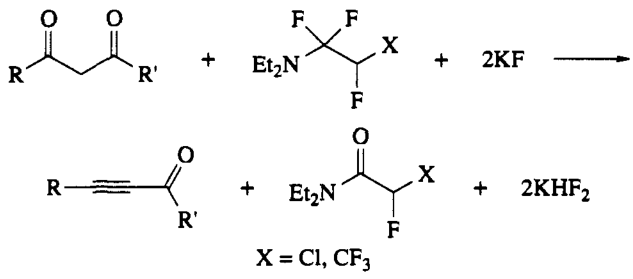
Scheme 51

A one-step dehydration of ketones to alkynes is possible in some cases. Aryl ketones can be converted to arylalkynes by treatment with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate in the presence of triethylamine at room temperature (Scheme 52).[99]



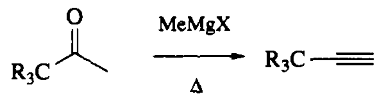
Scheme 52

Alkynic ketones can be prepared in good yields from β-diketones using α,α-difluoroalkylamines and KF (Scheme 53).[100]



Scheme 53

Some 17β-alkynic steroids were formed from hindered 20-oxo compounds *via* thermolysis of Grignard-derived enolates (Scheme 54).[101]



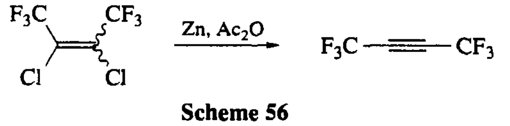
Scheme 54

5.1.4.3 Dehalogenation of 1,1- or 1,2-Dihaloalkenes and Other Eliminations of Two Vicinal Leaving Groups

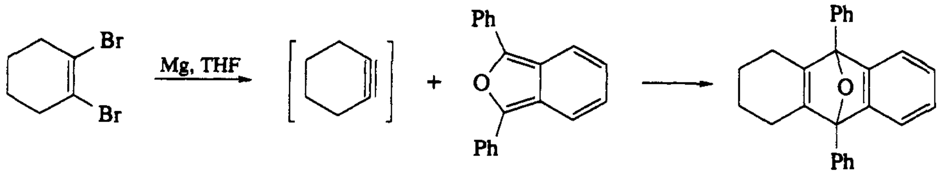
The general reaction for the dehalogenation of 1,1- and 1,2-dihaloalkenes is shown in Scheme 55.

Scheme 55

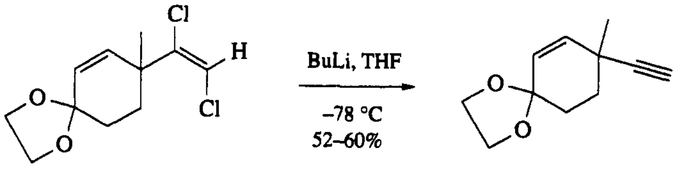
As in the preparation of alkenes, dehalogenation leading to alkynes has been effected mainly by zinc (Scheme 56),[102] magnesium (Scheme 57)[103] and organolithium (Scheme 58)[104] compounds. Since in most cases the best route to 1,2-dihaloalkenes is halogen addition to alkynes, this method is of limited preparative value. Advantages over dehydrohalogenation are the fixed position of the resulting triple bond and the exclusion of allene formation.



Scheme 56

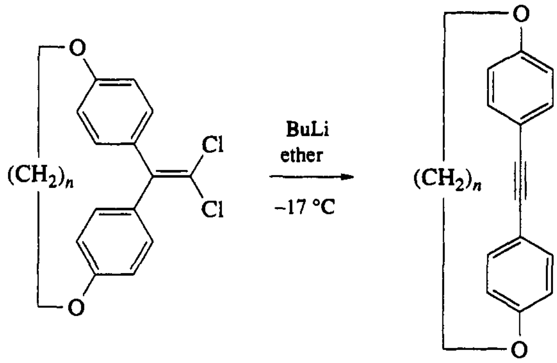


Scheme 57



Scheme 58

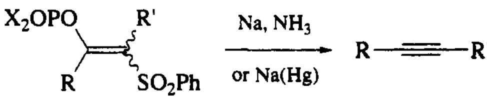
Organolithium compounds can also induce the rearrangement of 1,1-diaryl vinyl dichlorides and dibromides (Fritsch–Buttenberg–Wiechell rearrangement) to diarylalkynes;[105] *p,p′*-bridged cyclic diarylalkynes[106] can be prepared *via* this route (Scheme 59).



n = 11, 23%; *n* = 12, 47%; *n* = 13, 75%;
n = 14, 90%; *n* = 18, 75%

Scheme 59

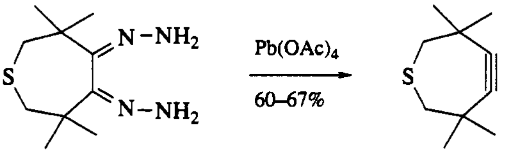
Elimination of two unlike leaving groups with a metal is realized in the synthesis of alkynes from 1-sulfonylenol-2-phosphates with sodium in liquid ammonia or sodium amalgam in THF (Scheme 60).[107]



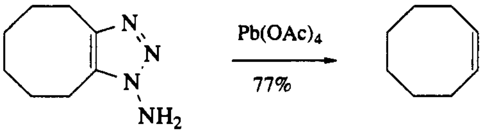
Scheme 60

5.1.4.4 Oxidative Decomposition of 1,2-Dihydrazones and 1-Amino-1,2,3-triazoles

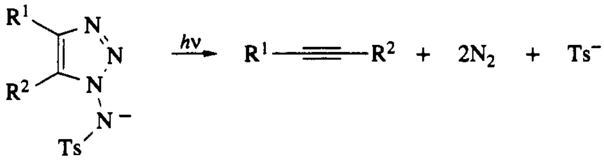
1,2-Dihydrazones can be oxidized to alkynes with O_2 (CuCl as a catalyst),[108] HgO,[109–111] F_3CCO_2Ag[112,113] and $Pb(OAc)_4$ (Scheme 61).[114] 1-Amino-1,2,3-triazoles, which are sometimes observed as by-products in the HgO oxidation of 1,2-dihydrazones, can be oxidized with $Pb(OAc)_4$ to give alkynes. Cyclooctyne[115] has been prepared and cycloheptyne and cyclohexyne[116] have been generated by this method (Scheme 62). The 1-tosylamino-1,2,3-triazoles can also be used as educts for alkyne synthesis; the anions are decomposed to yield the corresponding alkyne, N_2 and toluenesulfinate (Scheme 63).[117]



Scheme 61



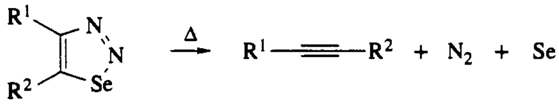
Scheme 62



Scheme 63

5.1.4.5 Elimination from 1,2,3-Selenadiazoles

Many 1,2,3-selenadiazoles, which are prepared from semicarbazones and SeO_2, give alkynes on pyrolysis (Scheme 64). R^1 and R^2 can be H, alkyl and aryl, and R^1 can also be CN and CO_2Et.[118]



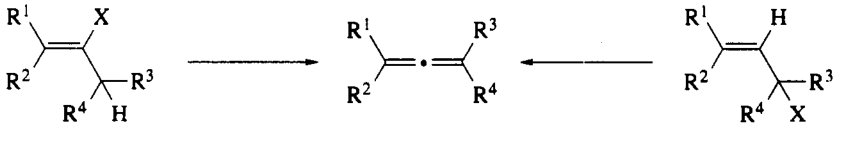
Scheme 64

5.1.5 ALLENES

In general, allenes are prepared by the same types of reactions which lead to alkenes: elimination of hydrogen halides, halogens and water from adjacent carbon atoms. However, some methods are characteristic of allene synthesis, *e.g.* the dehalogenation of *gem*-dihalocyclopropanes, rearrangement of alkynes and the 1,4-addition to vinylalkynes.

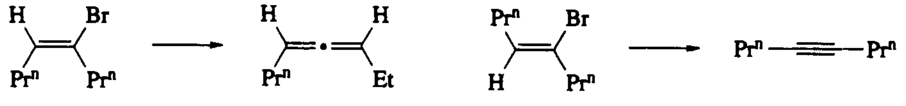
5.1.5.1 Dehydrohalogenation of Vinylic or Allylic Halides

The general reaction for the dehydrohalogenation of vinylic and allylic halides is shown in Scheme 65.



Scheme 65

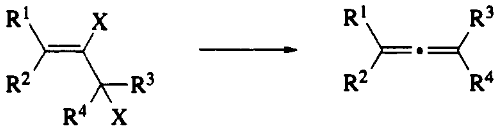
The base-induced dehydrohalogenation of vinyl halides and allyl halides often gives low yields of allenes because of the competing reaction to alkynes; alkynes can either be formed by direct elimination from vinyl halides or by isomerization of the allene first formed to the isomeric alkyne. Since it has been established that *anti* elimination of hydrogen halide from vinyl halides to yield alkynes is much faster than *syn* elimination, the proper choice of the starting material is often important for a successful allene synthesis. When (*E*)-4-bromo-4-octene was treated with NaOMe, the sole product was 3,4-octadiene, whereas the corresponding Z-educt yielded 4-octyne (Scheme 66).[119]



Scheme 66

5.1.5.2 Dehalogenation of 2,3-Dihalopropenes

The general reaction for dehalogenation of 2,3-dihalopropenes is shown in Scheme 67.

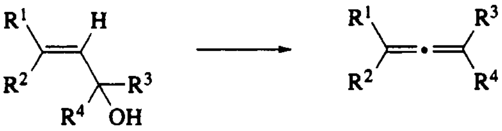


Scheme 67

The dehalogenation of 2,3-dihalopropenes with zinc dust gives allenes in high yields. Ethanol has often been used as a solvent, but sometimes alkenic impurities were observed in the allene. This can be avoided by the use of butyl or isopentyl acetate as a solvent.[120]

5.1.5.3 Dehydration of Allylic Alcohols

The general reaction for the dehydration of allylic alcohols is shown in Scheme 68.



Scheme 68

Dehydration of allylic alcohols with strong acid leads to allenes if an isomerization to an alkyne is not possible. This method has been used for the synthesis of tetraarylallenes[121] and tetra-*t*-butylallene.[122] This method was also used for the first synthesis of an optically active allene by an enantioselective dehydration using (+)-camphorsulfonic acid.[123]

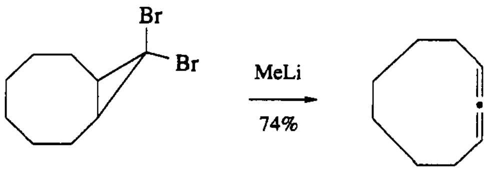
5.1.5.4 Dehalogenation of *gem*-Dibromocyclopropanes

The general reaction for the dehalogenation of *gem*-dibromocyclopropanes is shown in Scheme 69.

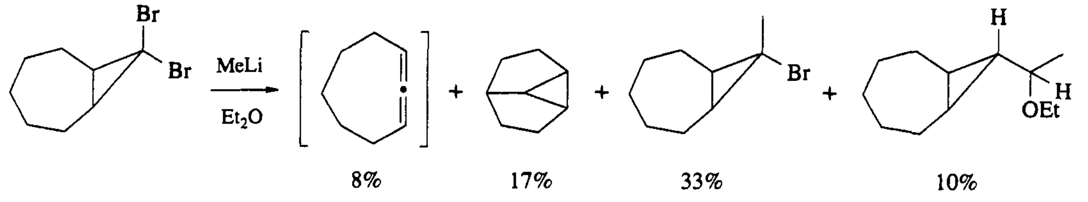
Scheme 69

The dehalogenation of *gem*-dibromocyclopropanes is a general route to a great variety of allenes. For the dehalogenation magnesium and sodium[124] were first used; later methyllithium[125] was successfully applied. 1,2-Cyclononadiene was prepared in this way;[126] by using optically active *trans*-cyclooctene as an educt, optically active 1,2-cyclononadiene was obtained (Scheme 70).

Attempts to isolate unsubstituted cyclic allenes with less than nine carbons were not successful. The highly strained 1,2-cyclooctadiene was generated as a short-lived intermediate; it dimerized to give a 1,2-dimethylenecyclobutane.[127] In addition several by-products were obtained (Scheme 71).

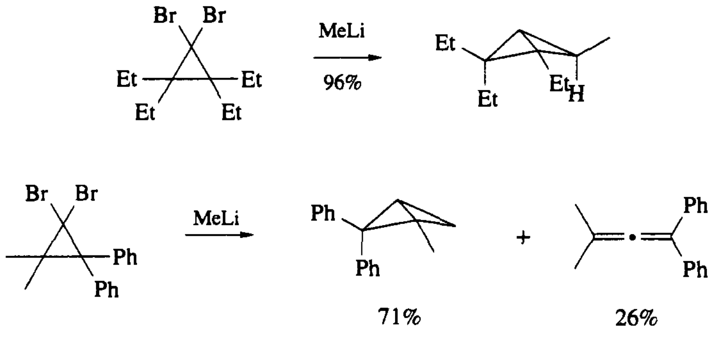


Scheme 70



Scheme 71

Another limitation of this procedure occurs in the case of tetraalkyl-substituted dibromocyclopropanes; they do not yield allenes, but rather bicyclobutanes (Scheme 72).[128,129] However, tetrasubstituted dibromocyclopropanes with two aryl substituents do give allenes, at least as a by-product.[129]



Scheme 72

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5.2

Reductive Elimination, Vicinal Deoxygenation and Vicinal Desilylation

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5.2.1 INTRODUCTION

In this chapter we deal with the regio- and stereo-controlled synthesis of alkenes by reductive elimination of 1,2-disubstituted alkanes. Where appropriate the related 1,4-elimination reactions leading to conjugated dienes will also be considered. The principal criterion for inclusion here is synthetic utility, and reactions such as the Julia alkenation are given prominence because they incorporate a reductive elimination as a key step in a sequence which is connective. Consequently such reductive eliminations should not be considered in isolation, but as an integral part of a sequence which achieves regio- and stereo-controlled synthesis of an alkene but, more importantly, also achieves the union of two fragments or the creation of a ring.

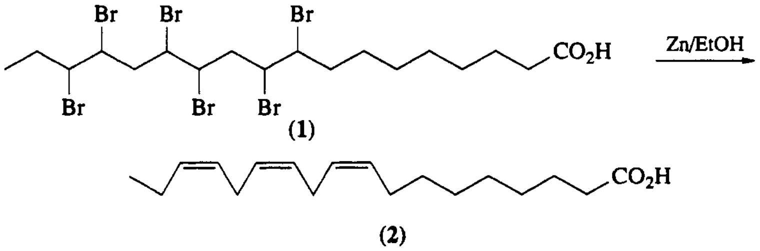
In the narrower context of simple functional group manipulation, reductive eliminations have proved valuable in the vicinal deoxygenation of cheap and readily available natural products such as carbohydrates to give synthetically useful fragments. However, comparatively few of the vast array of reductive eliminations recently reported were deemed worthy of inclusion because the reagents required were esoteric, expensive or obnoxious, or because the 1,2-disubstituted alkanes were themselves prepared from alkenes. Unless there are very pressing reasons, one cannot advocate the synthesis of alkenes from alkenes: to travel in circles is the domain of astronomers not chemists!

At the end of the chapter we briefly consider some reactions such as the fluoride-induced elimination of β-silyl sulfones, which are not reductive eliminations but which have been included because of their relation to the Julia alkenation.

5.2.2 REDUCTIVE ELIMINATION OF VICINAL HALOGEN DERIVATIVES

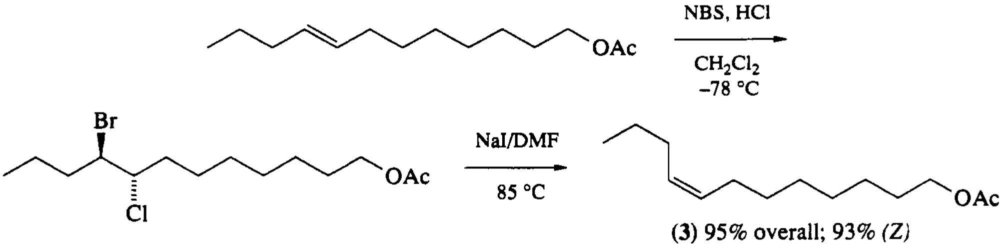
5.2.2.1 1,2- and 1,4-Dihalides

The reductive elimination of vicinal dihalides has been extensively investigated and early work up to 1971 has been reviewed by Schlosser.[1] The reaction is generally *anti* stereoselective with *vic*-dibromides and can be achieved by a wide range of reagents under mild conditions.[2–4] Since the *vic*-dihalide substrates are usually prepared stereoselectively by *anti* addition of halogens to alkenes, the reaction is of only limited synthetic value. Equation (1) illustrates a practical use of reductive elimination in the isolation of a natural product. Saponification of raw linseed oil followed by treatment with bromine gives a crystalline hexabromostearic acid (**1**), which undergoes efficient stereoselective reductive elimination to give the highly air sensitive linolenic acid (**2**) in 25% overall yield.[5]



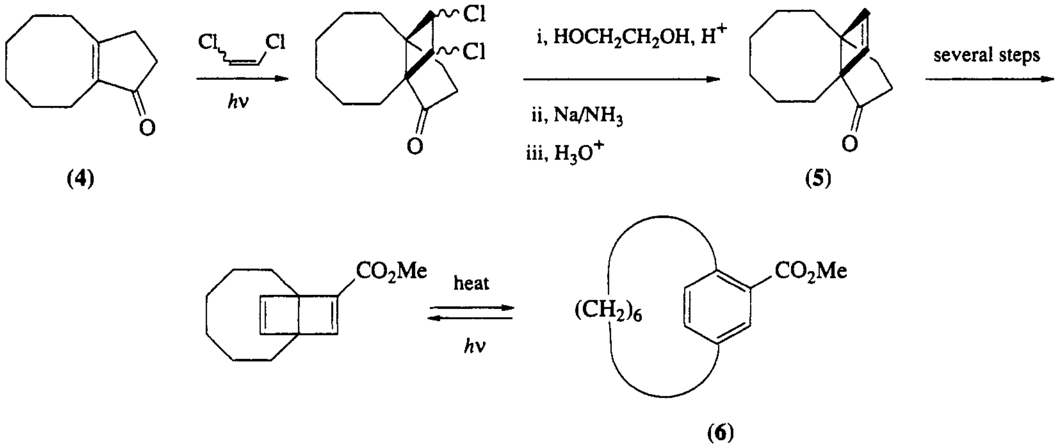
(1)

The reductive elimination of *vic*-bromochlorides and *vic*-dichlorides with metals such as zinc is much less stereoselective than the corresponding *vic*-dibromides. However, with NaI in DMF the reductions are highly stereoselective and proceed with a net *syn* elimination. These observations have been used to effect an alkene inversion as shown in Scheme 1 for the preparation of the sex pheromone (**3**) of the oriental fruit moth.[6,7] Treatment of *vic*-dichlorides with sodium phenylselenolate also results in a *syn* elimination.[8]



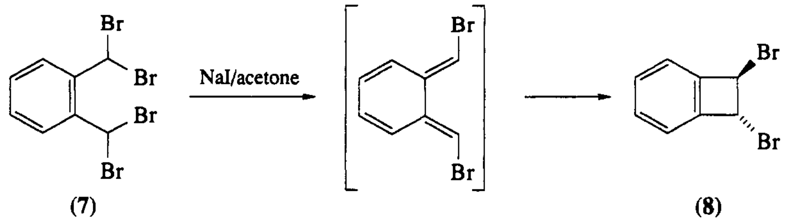
Scheme 1

A combination of a photochemical [2 + 2] cycloaddition of dichloroethylene to enone (**4**), followed by a reductive elimination, was used to prepare the tricyclic cyclobutene (**5**), which served as a precursor to the highly strained 8-carboxy[6]paracyclophane (**6**; Scheme 2).[9] A similar strategy has been used to prepare other strained propellanes.[10]

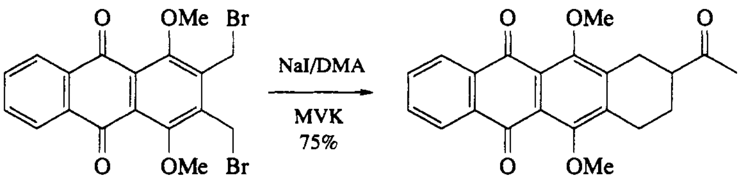


Scheme 2

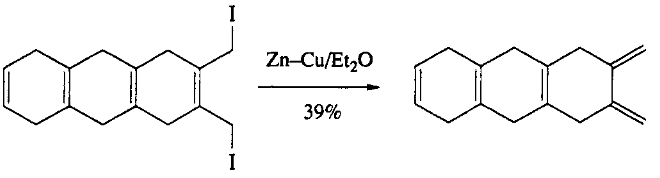
o-Quinodimethanes are highly reactive dienes, which have been trapped both intramolecularly and intermolecularly with dienophiles and used as valuable intermediates in the synthesis of natural products.[11] These intermediates were first generated unwittingly by Finkelstein[12] in 1910, who treated the tetrabromide (**7**) with NaI to give the dibromobenzocyclobutene (**8**; equation 2) but it was not until 1957 that Cava and Napier[13] first proposed the generation of the *o*-quinodimethane system by a reductive 1,4-elimination. A recent synthesis of 4-demethoxydaunorubicin (equation 3) illustrates the generation and trapping of an *o*-quinodimethane using the Finkelstein method.[14] Recently a wide range of reducing agents have been employed to generate *o*-quinodimethanes, including Zn in association with ultrasonic irradiation,[15] $CrCl_2$[16] and a variety of metals.[17] Similar conditions can be used[18] to effect 1,4-elimination of diiodides for the generation of 1,3-dienes (equation 4).



(2)



(3)

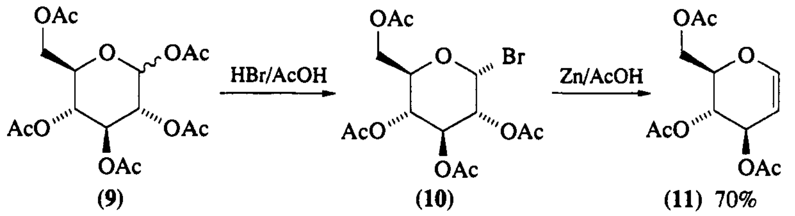


(4)

5.2.2.2 Halohydrins

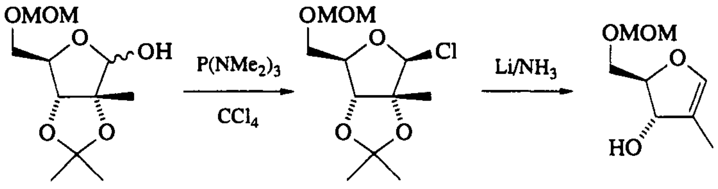
Many of the same reagents that reduce *vic*-dihalides also reduce halohydrins with similar regiochemical and stereochemical advantages. However, halohydrins are more useful alkene precursors because they can be prepared by a greater variety of methods. The Fischer–Zach synthesis of 3,4,6-tri-*O*-acetyl-D-glucal (**11**; Scheme 3) reported in 1913 is one of the first synthetically useful applications of reductive elimination reactions to the manipulation of natural products and the method is still widely used today.[19]

In the key step, the glycosyl bromide (**10**) was treated with Zn in acetic acid in conditions typical of those of dissolving metal reduction, and this has led to the speculation that the elimination occurs by addition of two electrons from the metal to the C-1 carbonium ion formed by ionization of the halide, followed by elimination of the adjacent acetoxy group. Alternatively, organozinc intermediates could be involved. Protic solvents are necessary for the reaction and acetic acid can be replaced by ethanol or 1-propanol but if still milder conditions are required, the elimination can be effected with trimethyl phosphite.[20]



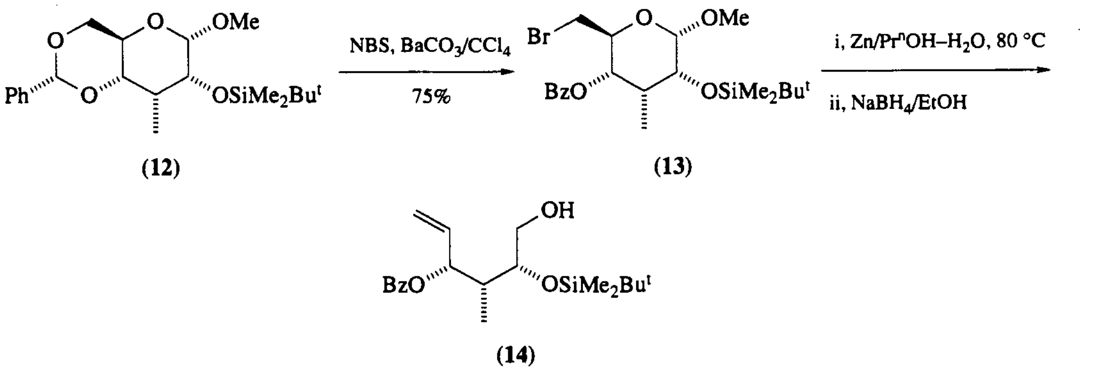
Scheme 3

Furanoid glycals are not stable to the acidic conditions used to prepare the pyranoid congeners. Scheme 4 illustrates a very mild method for preparing furanosyl chlorides, which undergo efficient reductive elimination on treatment with lithium in liquid ammonia.[21] Alternatively, a Zn–Ag couple adsorbed on graphite will reduce furanosyl bromides[22] and the corresponding chlorides react with the radical anion prepared from naphthalene and sodium.[23]

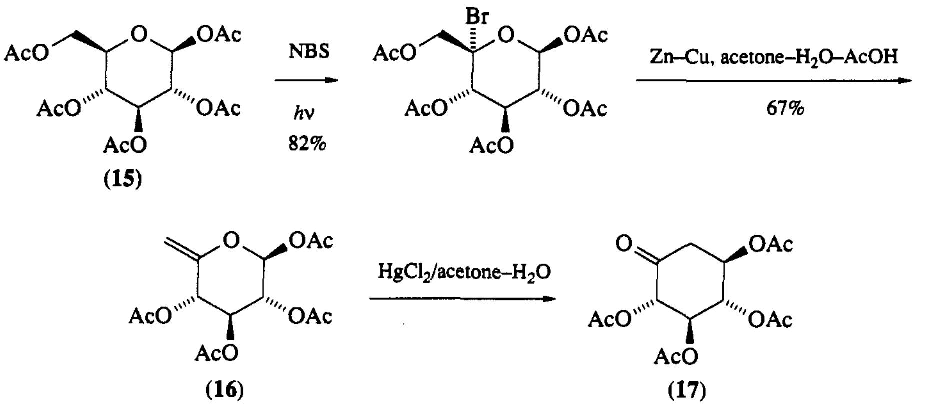


Scheme 4

Reductive elimination reactions have provided a rich mine of methodology for the modification of carbohydrate precursors into useful chiral building blocks. The two examples included here come from a synthesis of the antibiotic pseudomonic acid (Scheme 5)[24] and the Ferrier synthesis of 6-deoxyinonose triesters from pyranose acetates (Scheme 6).[25] An efficient and highly regioselective synthesis of the 6-bromoglycoside (**13**) by oxidative cleavage of the 4,6-benzylidene acetal (**12**) with *N*-bromosuccinimide, followed by reductive cleavage of the ring, gave an aldehyde, which was further reduced to the fragment (**14**) having three contiguous chiral centres. In the 6-deoxyinonose synthesis the requisite halogen atom was introduced stereo- and regio-selectively by a photochemically induced bromination of β-D-glucose pentaacetate (**15**). Reductive elimination then afforded the exocyclic 6-deoxy-5-enose sugar (**16**), which rearranged on treatment with $Hg(OAc)_2$ to the carbocyclic 6-deoxyinosose (**17**).

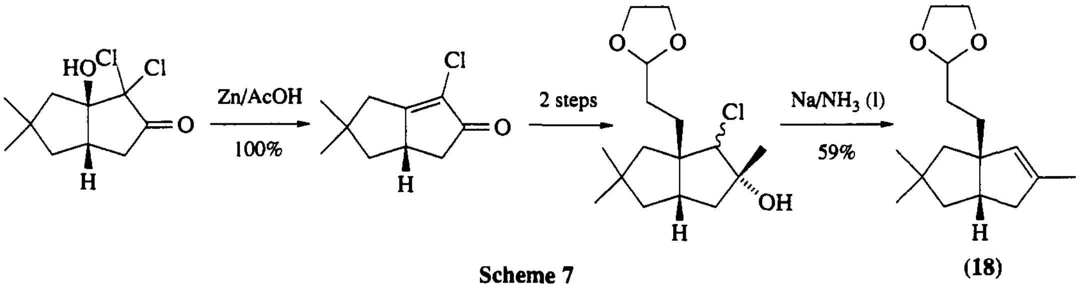


Scheme 5

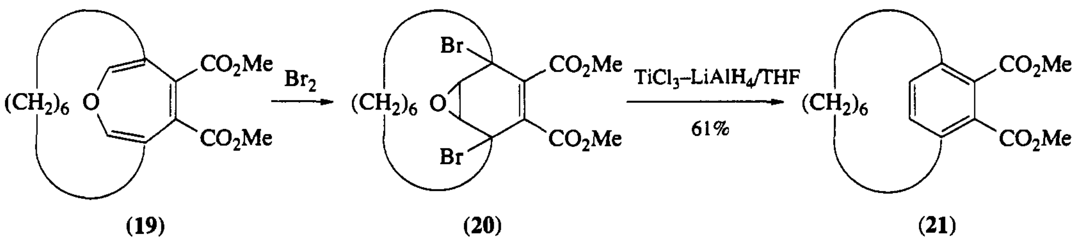


Scheme 6

A pair of reductive eliminations on chlorohydrin intermediates was used to achieve regioselective introduction of alkene functionality in a synthesis of (**18**), a precursor of the sesquiterpenoid pentalenene (Scheme 7).[26] Key steps in Tochtermann's synthesis of [6]-paracyclophane derivative (**21**; Scheme 8)[27] were bromination of the bridged oxepine (**19**) followed by reductive elimination of the resultant dibromooxirane (**20**).

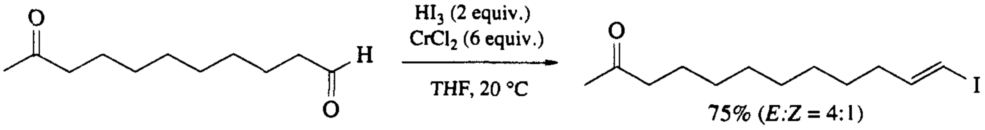


Scheme 7



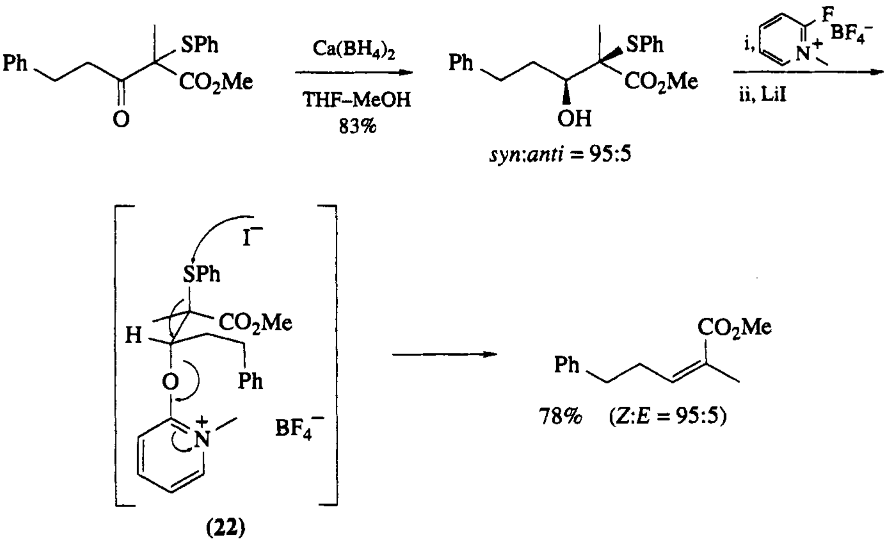
Scheme 8

Reductive eliminations of halohydrin derivatives can also be used to prepare functionalized alkenes. Trihalomethanes react chemoselectively with aldehydes in the presence of ketones[28] in a reaction initiated by $CrCl_2$. The (*E*)-isomer of the alkenyl iodide was formed stereoselectively in the example in equation (5).

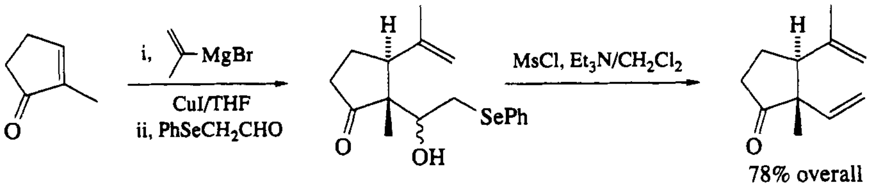


(5)

A stereoselective synthesis of the (*Z*)-isomer of α,β-unsaturated esters (Scheme 9) from α-phenylthio-β-keto esters results from an iodide-induced *anti* elimination of the pyridinium salt (**22**).[29] An analogous reaction based on a β-phenylseleno alcohol derivative (Scheme 10) was exploited in a synthesis of the sesquiterpenoid confertin.[30] A notable feature of this sequence is the use of phenylselenoacetaldehyde as a vinyl cation equivalent.[31]



Scheme 9



Scheme 10

5.2.3 REDUCTIVE ELIMINATION OF OXIRANES AND THIIRANES

The earliest general method for the reductive deoxygenation of oxiranes to alkenes involved multistep procedures in which halohydrins were intermediates. Cornforth,[32] for example, used an oxirane deoxygenation in an early synthesis of squalene (Scheme 11). Diastereoselective double addition of homogeranyllithium (**23**) to the dichloro diketone (**24**) gave the bis(chlorohydrin) (**25**), which was first converted to the diepoxide (**26**). Subsequent treatment with NaI and Zn in HOAc buffered with NaOAc gave squalene (**27**).

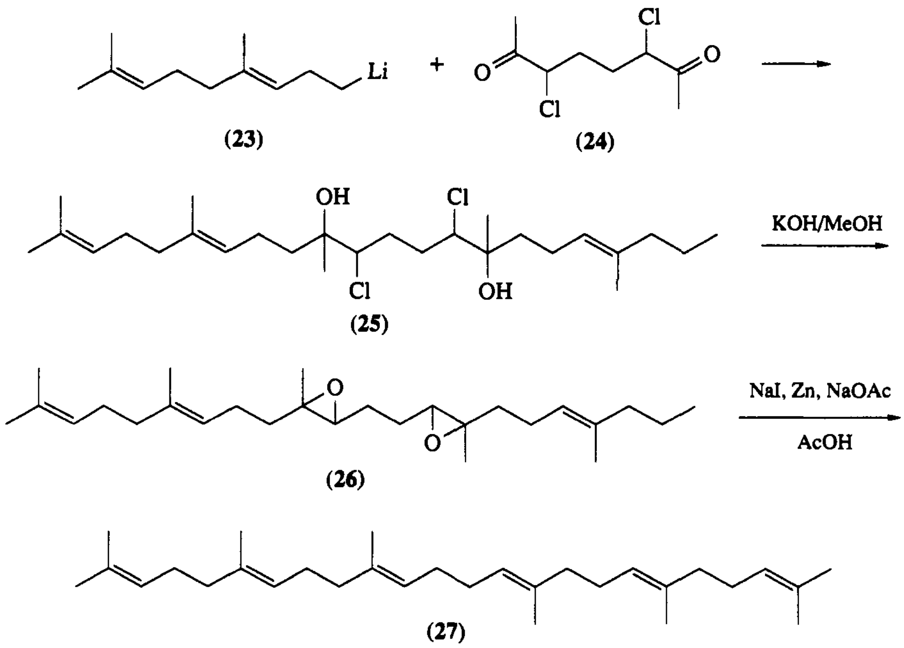
By using $POCl_3$ in pyridine in the reductive elimination of an iodohydrin intermediate (Scheme 12), the acid sensitive α,β-unsaturated acetal (**28**) was prepared.[33]

The stereoselective reductive deoxygenation of aliphatic *cis*-oxiranes to the corresponding *cis*-alkenes *via* iodohydrin intermediates has been accomplished by convenient one-pot procedures (equations 6 and 7).[34,35]

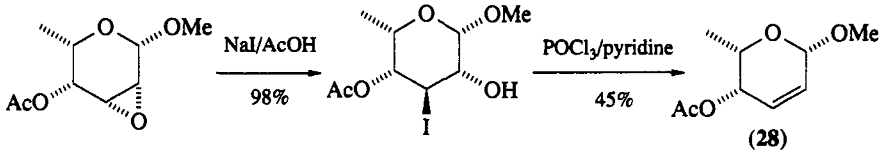
For the one-step conversion of oxiranes to alkenes a variety of reducing metals have been used, including Li,[36] Ti^0,[37] low-valent Nb,[38] Cr^{II},[39] and Sm^{II}.[40] In the latter case, HMPA and *N,N*-dimethylaminoethanol facilitate the reaction.[41] Reaction of 2 equiv. of Bu^nLi with WCl_6 produces a reagent which effects efficient deoxygenation of oxiranes, as exemplified in equation (8).[42] This reagent is particularly valuable for the deoxygenation of tri- and tetra-substituted oxiranes and is compatible with ethers and esters, although aldehydes and ketones reductively couple with it.

A synthesis of *trans*-γ-irone (**29**; Scheme 13) achieved the introduction of an exocyclic methylene adjacent to a hindered centre *via* reductive deoxygenation of an oxirane with a low-valent Ti reagent.[43]

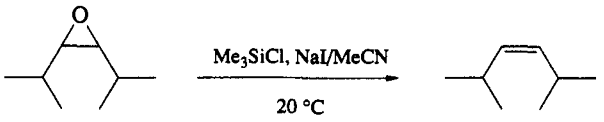
The reductive desulfurization of thiiranes has been accomplished with Raney nickel, Li in $EtNH_2$, Zn in HOAc, Bu_3SnH, and P_2I_4 in DMF but the reaction has seldom been applied to organic synthesis.[44] A noteworthy procedure for preparing moderately hindered tetrasubstituted alkenes, which proceeds *via* a thiirane intermediate, was developed independently by Barton[45] and Kellogg.[46] The procedure, illustrated in Scheme 14 for the preparation of (**34**), involved reaction of thiocamphor (**30**) with diazoalkane



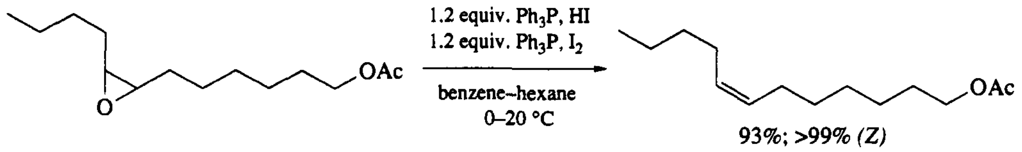
Scheme 11



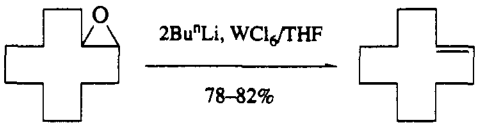
Scheme 12



(6)

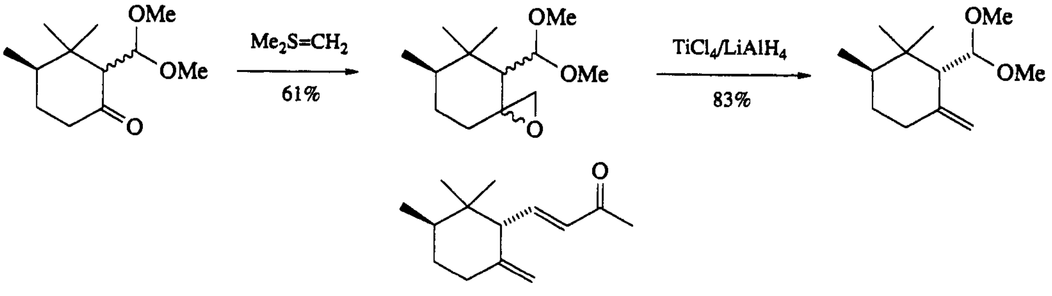


(7)



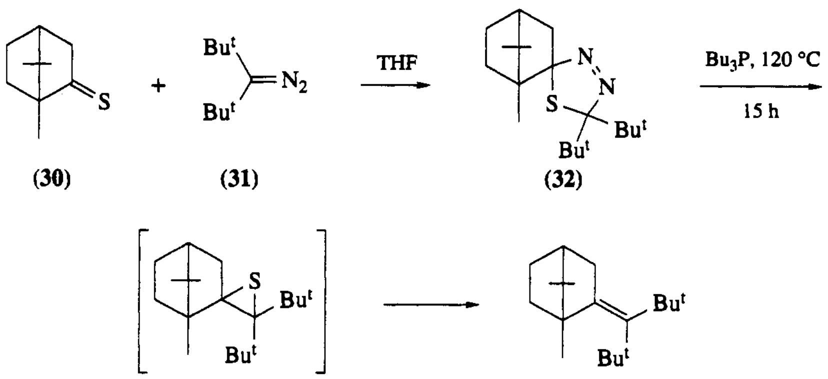
(8)

(**31**) to give the 1,3,4-thiadiazole (**32**), which, on heating with Bu_3P, extruded N_2 to afford thiirane (**33**). However, under the reaction conditions, (**33**) underwent reductive desulfurization to the alkene (**34**) with concomitant formation of $Bu_3P{=}S$. An alternative method involving the generation of the analogous 1,3,4-selenadiazoles, followed by thermal extrusion of N_2 and Se metal, can be applied to even more hindered alkenes.[47]



(29)

Scheme 13



(30) **(31)** **(32)**

(33) **(34)** 64% overall

Scheme 14

5.2.4 DEOXYGENATION OF *VIC*-DIOLS

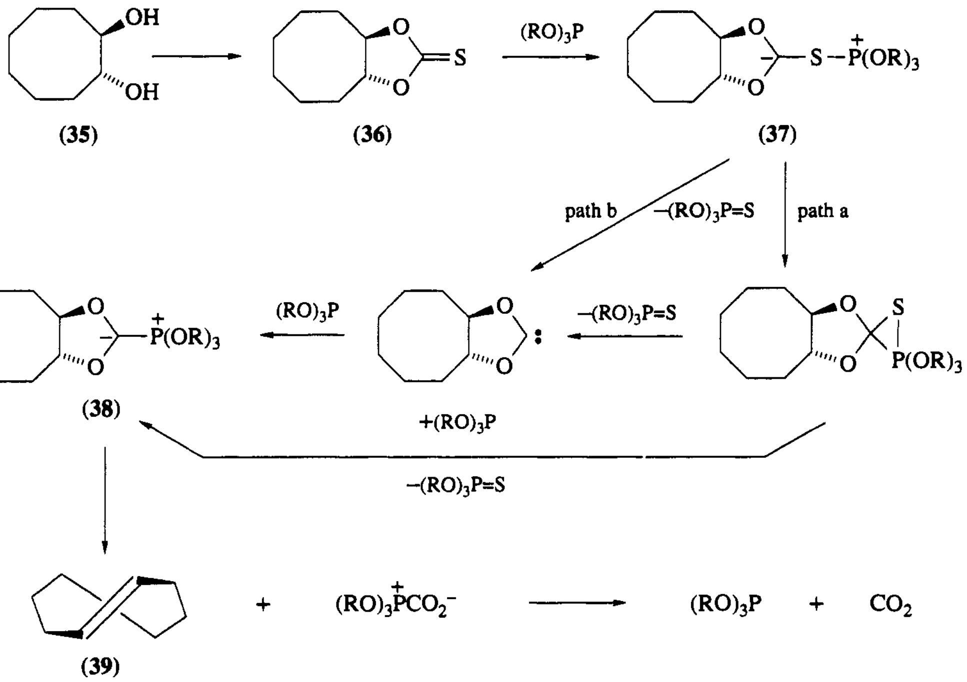
5.2.4.1 Fragmentation of Thioxocarbonates

The regio- and stereo-selective deoxygenation of *vic*-diols to alkenes based on the *syn* elimination of cyclic derivatives provides an especially valuable method for the modification of carbohydrates and the synthesis of strained or twisted alkenes.[48] The first generally useful method reported in 1963 by Corey and Winter[49] involves a two-step procedure involving conversion of the *vic*-diol to a cyclic thionocarbonate (1,3-dioxolane-2-thione) followed by stereospecific fragmentation on heating with trivalent phosphorus compounds. The procedure and mechanism of the reaction are illustrated in Scheme 15 for the synthesis of optically active *trans*-cyclooctene (**39**).[50] Resolution of *trans*-cyclooctane-1,2-diol *via* the monophthalate ester gave the enantiomer (**35**), which was converted to the thioxocarbonate (**36**) by refluxing with thiocarbonyldiimidazole (TCDI) in toluene. The resultant thioxocarbonate was then heated with triisooctyl phosphite at 135 °C for 17 h, during which time the product was removed from the reaction mixture in a stream of N_2. Optically active *trans*-cyclooctene was thus obtained in 84% yield in >99% isomeric purity.

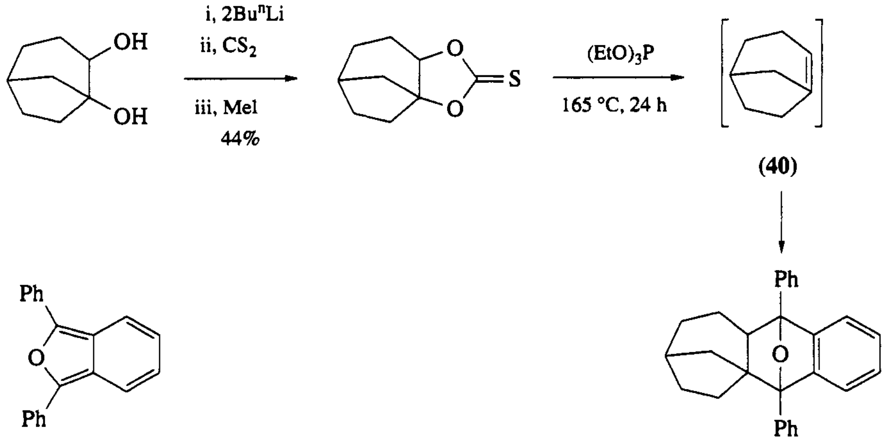
The mechanism of the reaction involves nucleophilic attack by the phosphite on the sulfur atom of (**36**) to give the 1,3-dipole (**37**), which is converted to ylide (**38**) either by cyclization–desulfurization (path a) or α-elimination–carbene capture (path b). Concerted 1,3-dipolar cycloreversion of the ylide then gives the product. Alternatively, direct stereospecific 1,3-dipolar cycloreversion of zwitterion (**37**) may account for the product.

If the alkene is too unstable to permit isolation, it may be trapped *in situ* with a suitable reagent. The highly strained bridgehead alkene (**40**; Scheme 16) was prepared and trapped in this way as a Diels–Alder adduct with 1,3-diphenylisobenzofuran (**41**).[51]

The high temperatures and protracted reaction times required for the Corey–Winter reaction can lead to detrimental side reactions. Much lower reaction temperatures can be achieved by using 1,3-dimethyl-

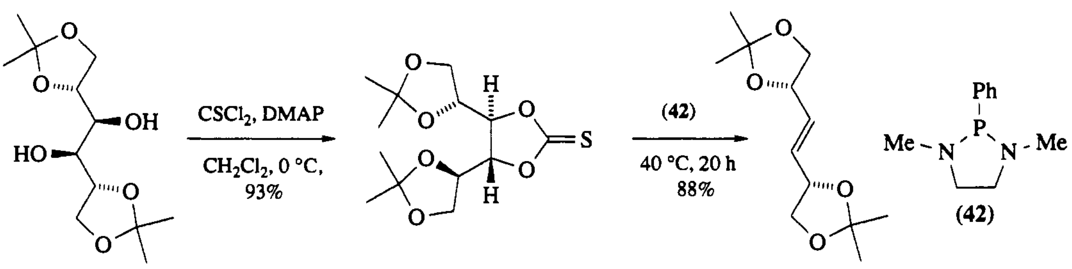


Scheme 15



Scheme 16

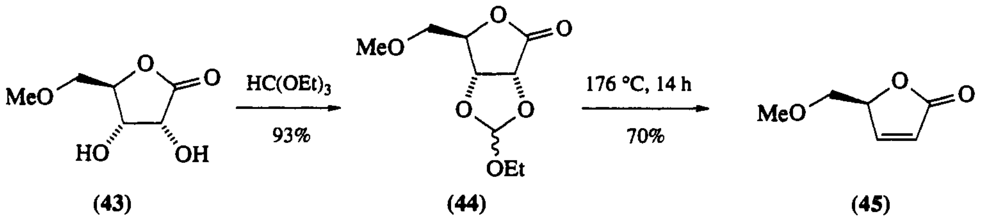
2-phenyl-1,3,2-diazaphospholidine (**42**) as the thiophile, as shown in Scheme 17.[52] The reagent (**42**) is prepared in one step (70% yield) from *sym*-dimethylethylenediamine and dichlorophenylphosphine.



Scheme 17

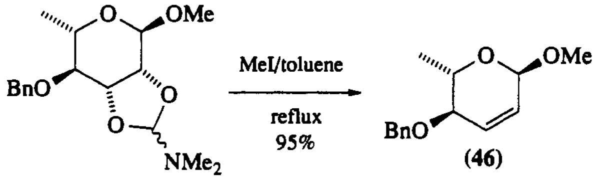
5.2.4.2 Fragmentation of 2-Methoxy-, 2-Acetoxy- and 2-Dimethylamino-1,3-dioxolanes

Eastwood[53] has devised an alternative one-pot deoxygenation of *vic*-diols which, like the Corey–Winter reaction, depends upon the fragmentation of a 1,3-dioxolane intermediate. The reagents required are cheaper and less obnoxious than the Corey–Winter sequence and the procedure is amenable to large scale operation. For example (+)-5-*O*-methyl-D-ribonolactone (**43**) was converted to the 2-methoxy-1,3-dioxolane (**44**) on heating with excess triethyl orthoformate (Scheme 18); subsequent heating at 176 °C gave CO_2, EtOH and the butenolide (**45**).[54] A trace of HOAc is frequently used to catalyze the fragmentation. The mechanism of the reaction has been examined in some detail.[48]



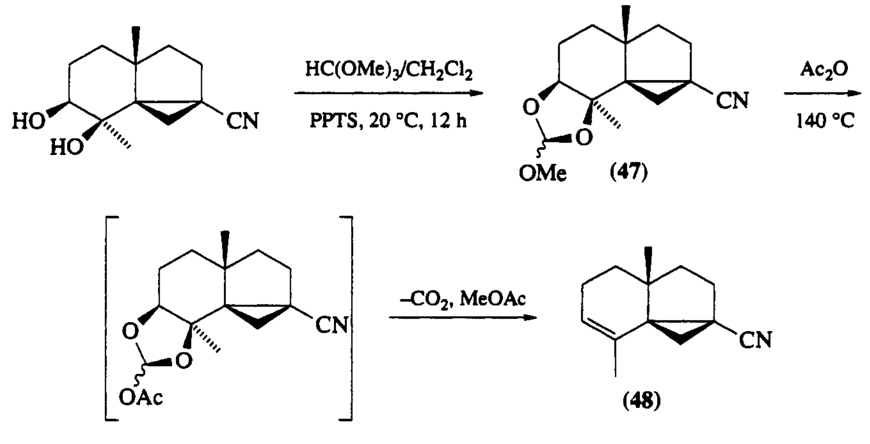
Scheme 18

2-Dimethylamino-1,3-dioxolanes, prepared by the reaction of the diol with dimethylformamide dimethylacetal, react *in situ* with MeI to give quaternary ammonium salts, which typically fragment at lower temperature (110–130 °C) to give the alkene, CO_2 and Me_3NHI.[55] For acid sensitive compounds such as the unsaturated acetal (**46**; equation 9), these conditions are superior to the original Eastwood procedure. Fragmentation of the 2-dimethylamino-1,3-dioxolane can also be effected by Ac_2O[56] and in some cases this modification is preferred, since the weakly nucleophilic acetate by-product causes fewer serious side reactions than iodide.[57,58]



(9)

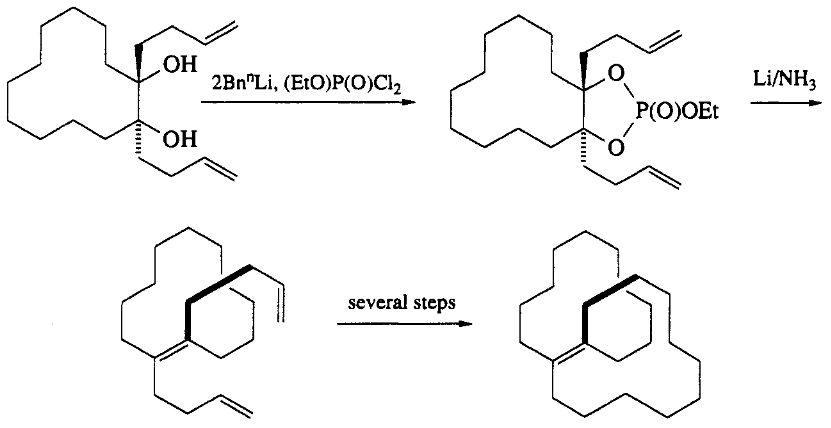
Stereospecific conversion of *vic*-diols into alkenes can also be achieved at moderate temperatures *via* 2-acetoxy-1,3-dioxolanes. These are generated as intermediates by heating a 2-methoxy-1,3-dioxolane with Ac_2O. The acid sensitive trisubstituted alkene (**48**) was efficiently prepared by this method as shown in Scheme 19.[59]



Scheme 19

5.2.4.3 Reductive Elimination of Cyclic Phosphates

The cyclic phosphate and phosphoramidate derivatives of *vic*-diols undergo a two-step reductive elimination on treatment with Li/NH_3, Na–naphthalene, $TiCl_4$–Mg(Hg) or $TiCl_4$–K.[60] In acyclic systems the reaction is only moderately stereoselective.[60] The reaction has particular value in the synthesis of tetrasubstituted alkenes from highly hindered *vic*-diols. Scheme 20 illustrates its use in the synthesis of [10,10]-betweenanene (**49**).[61]



(**49**)

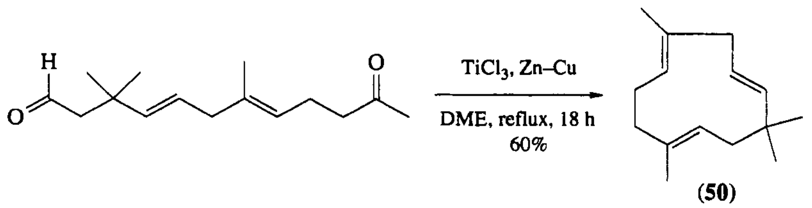
Scheme 20

5.2.4.4 Transition Metal Mediated Deoxygenation of *vic*-Diols

The McMurry reaction[62] is a powerful and versatile method for synthesizing a wide variety of alkenes. The intramolecular variant of the reaction is especially useful for preparing medium ring cycloalkenes, as illustrated in equation (10) for the synthesis of humulene (**50**).[63] Two distinct stages are involved: (i) reductive coupling of a dicarbonyl to produce a *vic*-diolate (**51**), bound to Ti^I embedded in a Ti^0 matrix; and (ii) stepwise fragmentation to the alkene and Ti^{II} oxide (Scheme 21). It is only the second stage of the process, the fragmentation of the *vic*-diolate intermediate, that will be discussed here; for a fuller discussion of the McMurry reaction see Volume 1, Chapter 3.1.

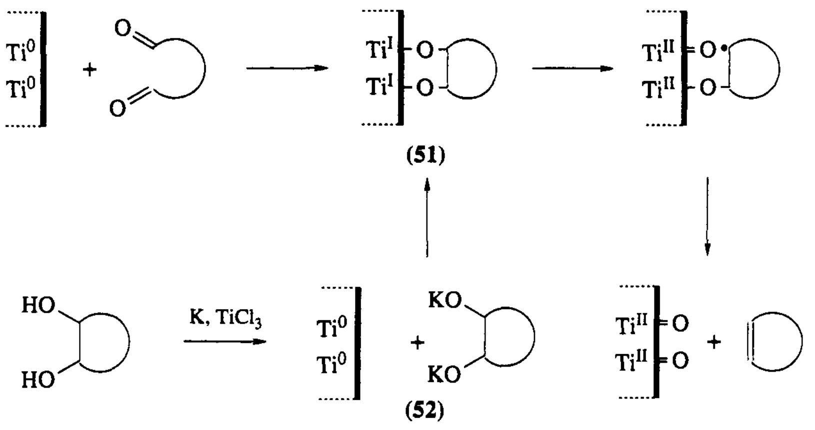
A Ti^0 reagent, prepared by the reaction of $TiCl_3$ with K metal, provides a one-step procedure for the deoxygenation of *vic*-diols. The reaction is run in refluxing THF in the presence of excess K metal to convert the diol to the diolate (**52**), which then reacts with Ti^0 to form the same intermediate (**51**) implicated in the McMurry coupling. Acyclic systems reduce with little stereoselectivity (equation 11) and *trans*-diols deoxygenate as readily as the corresponding *cis* isomers (equation 12). These results are in accord with the mechanism outlined in Scheme 21 in which the reaction takes place on the surface of a Ti^0 particle and the loss of stereochemistry is explained by the stepwise fragmentation of the bound diolate.[64] The utility of the reaction is limited by the incompatibility of many functional groups to the powerful reducing conditions. Thus ketones, thioketones, acyloins, bromohydrins, oxiranes, cyanohydrins and allylic or benzylic alcohols are some of the functional groups which are affected by the reagent. Related deoxygenations of *vic*-diols can be achieved using potassium hexachlorotungstate.[65]

Allylic 1,4-diols also deoxygenate to give conjugated dienes using a Ti^0 catalyst prepared from $TiCl_4$ and LAH[66] or $TiCl_3$ and LAH. The latter reagent mixture has been exploited in a synthesis of vitamin A (**53**; equation 13).[67]

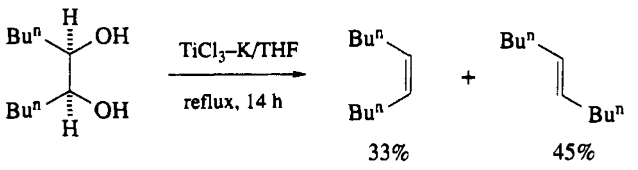


(**50**)

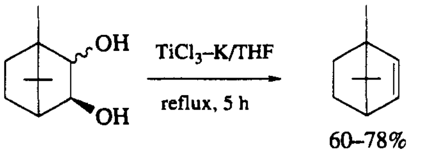
(10)



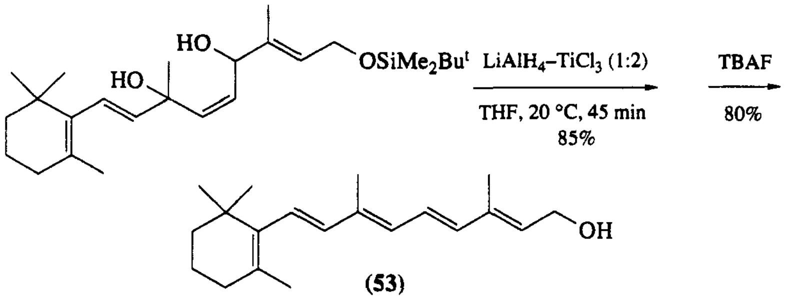
Scheme 21



(11)



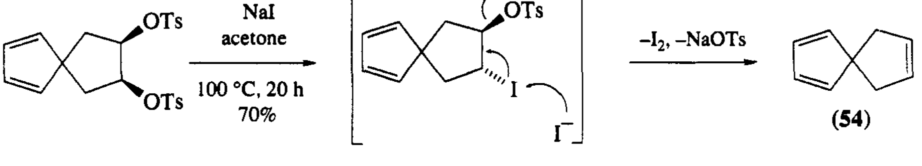
(12)



(13)

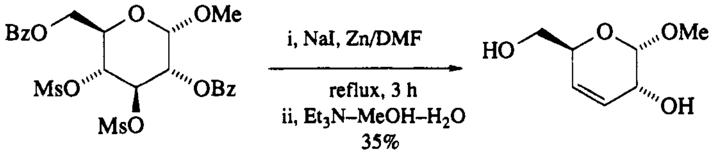
5.2.4.5 Reductive Elimination of Acyclic *vic*-Diester Derivatives

The generation of an alkene by the reaction of a *vic*-disulfonate ester with iodide (the Tipson–Cohen reaction) has been known since 1943 and in some cases it has proved useful where other methods have failed, as in the preparation of the spirocyclic triene (54; Scheme 22).[68] The mechanism probably involves an initial nucleophilic displacement to give an iodohydrin sulfonate, which then undergoes iodide-induced elimination to the alkene. Methanesulfonates can be used as well as arenesulfonates.

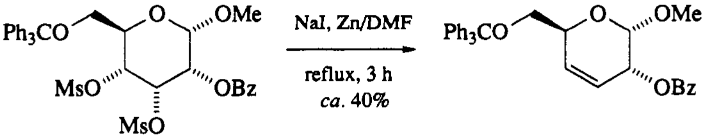


Scheme 22

The reaction has been most often applied to the synthesis of cycloalkenes, since the acyclic version shows low stereoselectivity. A modification of the original Tipson–Cohen conditions has been developed by Fraser-Reid and coworkers[69] for the elaboration of carbohydrate derivatives, in which sodium iodide in conjunction with Zn or Zn–Cu couple in refluxing DMF is used to effect the elimination. As can be seen from the examples shown in equations (14) and (15), the reaction proceeds with equal ease for both *cis* and *trans* isomers.

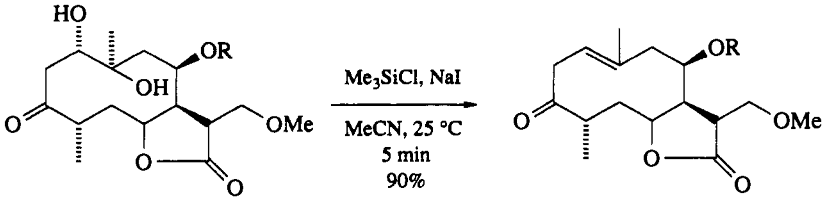


(14)



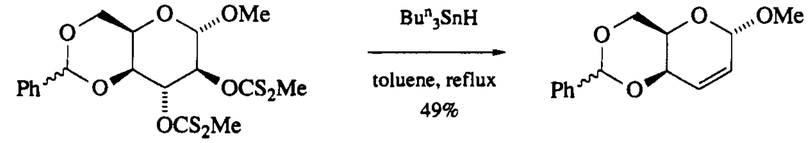
(15)

A one-pot conversion of *vic*-diols to alkenes can be achieved at room temperature using TMS-I generated *in situ* (equation 16).[70]



(16)

Barton and coworkers developed a very useful procedure for the deoxygenation of alcohols, which involves conversion of the alcohol to the corresponding xanthate derivative followed by reaction with Bu_3SnH.[71] When applied to the bis(xanthates) derived from *vic*-diols the reaction gives alkenes, as illustrated in equation (17).[72] Once again alkene formation is independent of the stereochemistry of the starting diols.



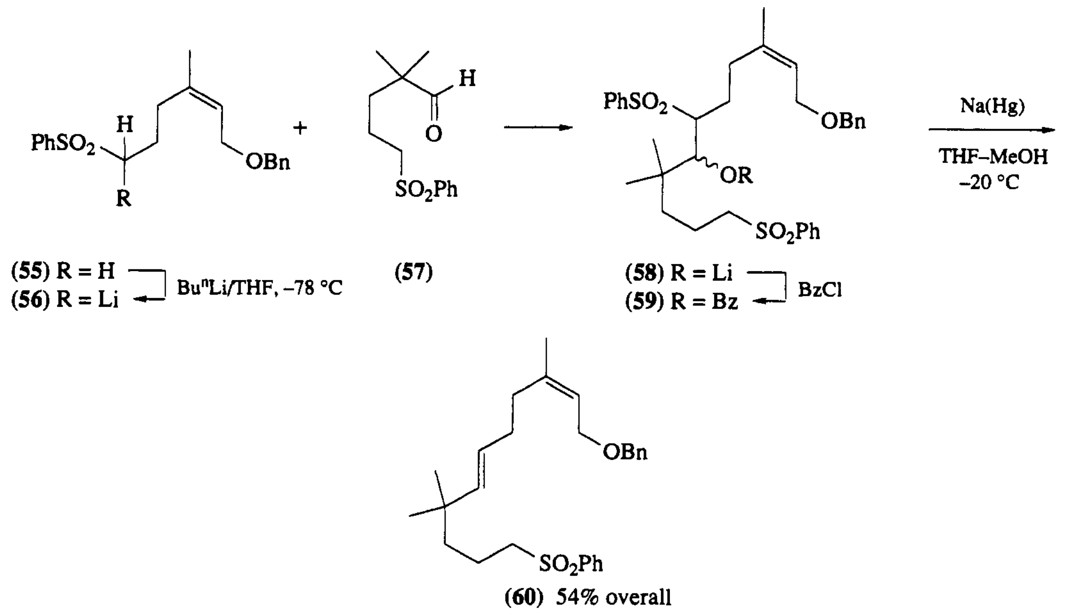
(17)

5.2.5 CONNECTIVE ALKENE SYNTHESES *VIA* REDUCTIVE ELIMINATION

5.2.5.1 The Julia Alkenation

In 1973 Julia and Paris[73] reported a new alkene synthesis which, like the Horner–Wittig reaction, is connective and regiospecific. A subsequent study of its scope and stereochemistry led to improved reaction conditions, which have since been widely adopted.[74] The Julia alkenation consists of four distinct stages, as exemplified in Scheme 23 by the synthesis of the fragment (**60**) of moenocinol.[75] These are: (i) metalation of the aryl alkyl sulfone (**55**); (ii) condensation of the α-metalated sulfone (**56**) with the aldehyde (**57**) to give a β-arylsulfonyl alkoxide adduct (**58**); (iii) functionalization of the adduct to give the β-benzoyloxy sulfone (**59**); and (iv) reductive elimination of the β-benzoyloxy sulfone using Na-Hg to generate the diene (**60**).

The first three stages can be performed in a single reaction vessel, although the overall yield of the sequence can be improved by isolating the β-hydroxy sulfone at the second stage and functionalizing the hydroxy group in a separate step. Purification of intermediates is not normally required.



Scheme 23

By comparison with the Horner–Wittig reaction, the Julia alkenation has two principal assets. First, as the nucleophilic partner in the connective step (stage 2), sulfones are used, which are often more readily available and more easily purified than the corresponding phosphonium salts. Secondly, the 1,2-disubstituted alkenes produced in the key reductive elimination step have predominantly (*E*)-stereochemistry. One detraction of the Julia alkenation is its length — it can be foiled at any one of the four stages. In practice, stage 2, the condensation of the metalated sulfone with the carbonyl, is usually the most problematic but in certain circumstances all of the stages have their pitfalls. These will be examined individually below.

5.2.5.1.1 Scope and limitations

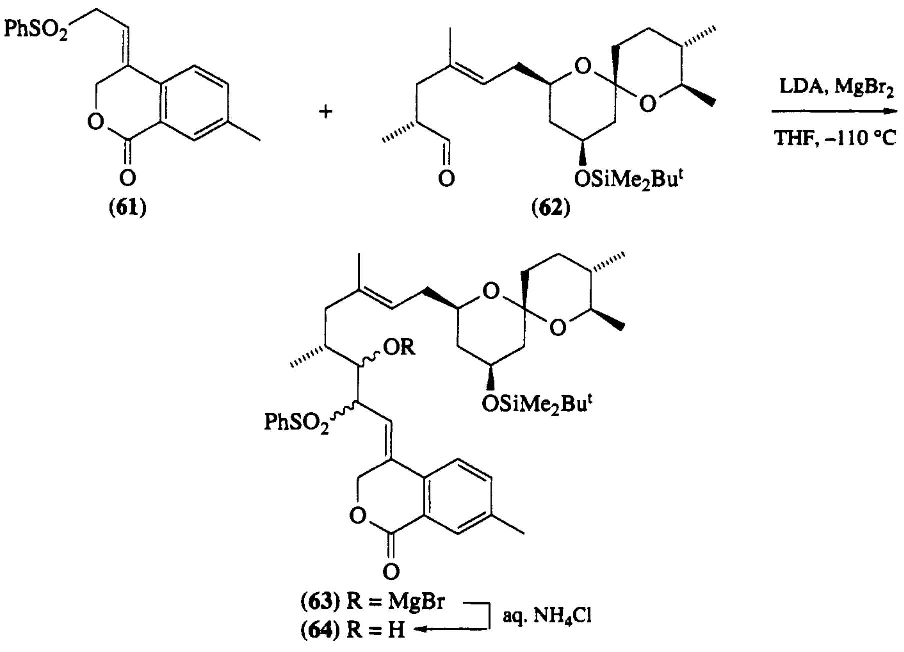
(i) Sulfone metalation

Aryl alkyl sulfones are about as acidic as esters. They react rapidly with Bu^{n}Li or LDA in THF at –78 °C to give homogeneous solutions of α-lithiated sulfones, which are bright yellow in the case of simple aryl alkyl sulfones to red-orange in the case of aryl allyl sulfones. The corresponding magnesio derivatives can be prepared by addition of EtMgBr to a solution of the sulfone in THF followed by a brief period at reflux or, more conveniently, by transmetalation of the lithio derivative with anhydrous $MgBr_2$, prepared by reacting Mg with 1,2-dibromoethane in THF. The magnesio derivatives are only faintly colored.

Problems have been encountered in the metalation of phenyl alkyl sulfones with Bu^{n}Li when the α-protons are hindered. In such cases, competitive abstraction of the protons *ortho* to the sulfone group on the aryl ring may take place but this can be avoided by using LDA as the base.

(ii) Condensation of metalated sulfones with carbonyls

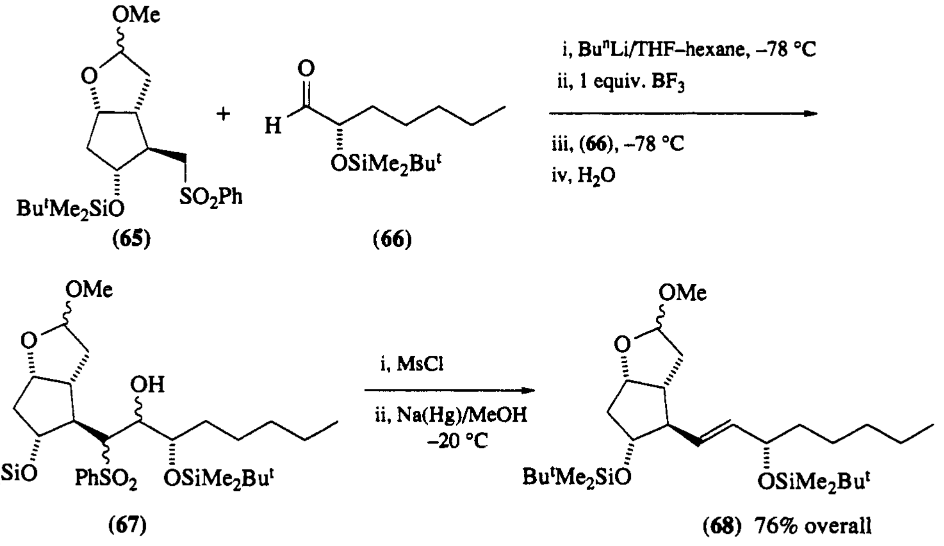
The addition of metalated sulfones to aldehydes or ketones is a reversible reaction and the principal cause of failure in the Julia alkenation results from an unfavorable equilibrium at this stage. The reverse reaction is favored when the β-alkoxy sulfone adduct is sterically encumbered. Adducts derived from ketones are more vulnerable than those derived from aldehydes. Stabilization of the sulfone anion by conjugation with an aromatic ring or chelation with a proximate heteroatom are also important contributors to favoring the reverse reaction. However, by varying the metal counterion, the position of equilibrium can be adjusted. For example, the lithio derivative of the sulfone (**61**; Scheme 24) failed to condense with the aldehyde (**62**) but the desired adduct (**64**) could be obtained in 81% yield from the corresponding magnesio derivative.[76] Successful addition was only achieved by adding a solution of LDA to a mixture of the sulfone, the aldehyde and excess $MgBr_2$ in THF at −110 °C. These unusual conditions were determined by the instability of the metalated derivatives of the sulfone. The beneficial effect of magnesium has been exploited by others.[77-80]



81% overall

Scheme 24

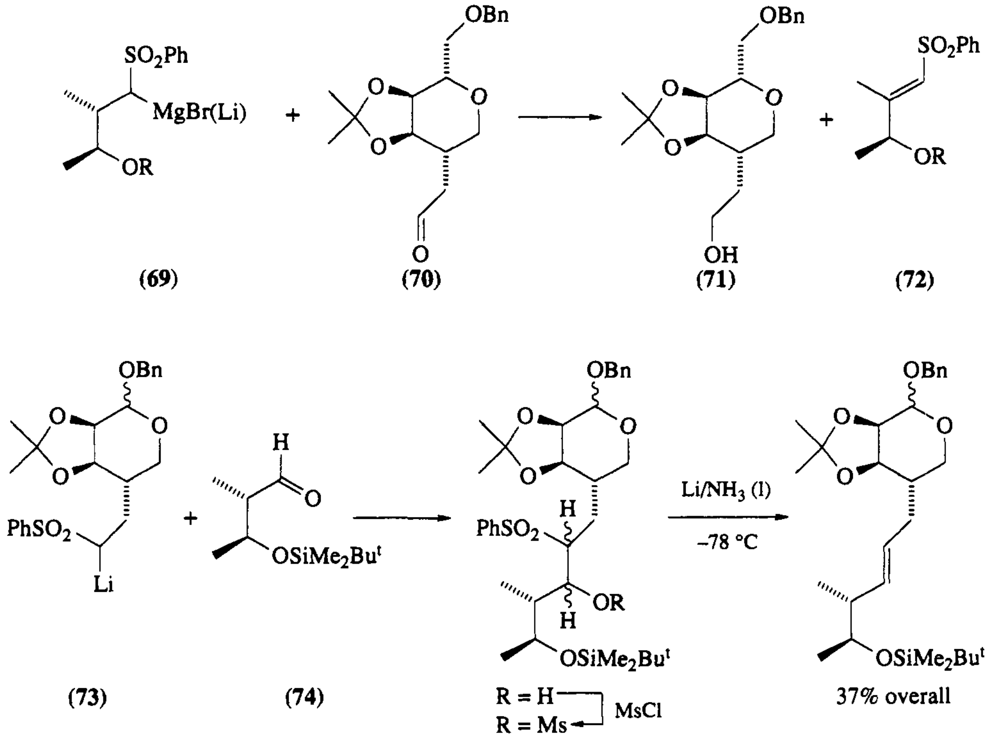
Neither the lithio nor the magnesio derivatives of the sulfone (**65**) reacted with the aldehyde (**66**). However, the 'ate' complex derived from the lithio derivative and BF_3 gave a 90% yield of the desired adduct (**67**), which was transformed to the alkene (**68**) in the usual way (Scheme 25).[81]



Scheme 25

An interesting divergence in behavior between the lithio and magnesio derivatives of the sulfone (**69**) has emerged from studies on the synthesis of the antibiotic pseudomonic acid C. The lithio derivative of

(**69**; Scheme 26) formed a stable chelate with the proximate oxygen, which prevented addition to the aldehyde (**70**). The magnesio derivative, on the other hand, acted as a reducing agent, giving (**71**) and (**72**) as the main products.[74] However, by reversing the functionality, the lithio derivative of sulfone (**73**) successfully condensed with the aldehyde (**74**).[82]



Scheme 26

Metalated sulfones with β leaving groups can be generated at low temperature and trapped with electrophiles. For example the α-lithio sulfone (**76**; Scheme 27) was prepared by metalation with LDA at −90 °C in 9:1 THF–HMPA and condensed with aldehyde (**75**). Acetylation of the adduct followed by reductive elimination gave an intermediate in the synthesis of the antibiotic ingramycin.[83]

The unfavorable equilibrium in the condensation of metalated sulfones with carbonyls can be surmounted in other ways. For example, β-keto sulfones, which are prepared by condensation of metalated sulfones with esters, are efficiently reduced to β-hydroxy sulfones with $NaBH_4$. These reactions were deployed in the preparation of the (*E*)-alkene in the side chain of the intermediate (**77**; Scheme 28) on the way to brefeldin A.[84]

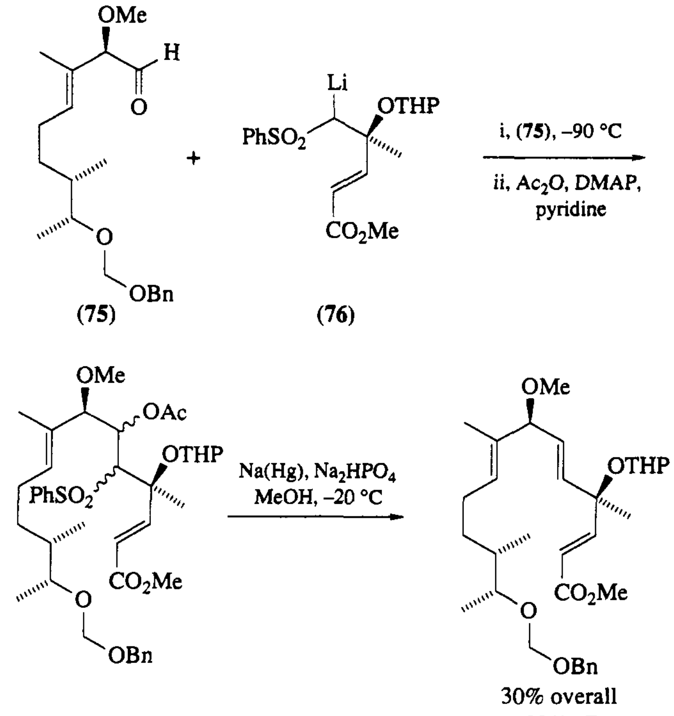
Another method for securing union of the sulfone and carbonyl fragments involves trapping the intermediate alkoxide by an intramolecular alkylation. This procedure was used in the synthesis of the diumycinol intermediate (**78**; Scheme 29).[85]

(iii) Preparation of the β-acyloxy sulfone

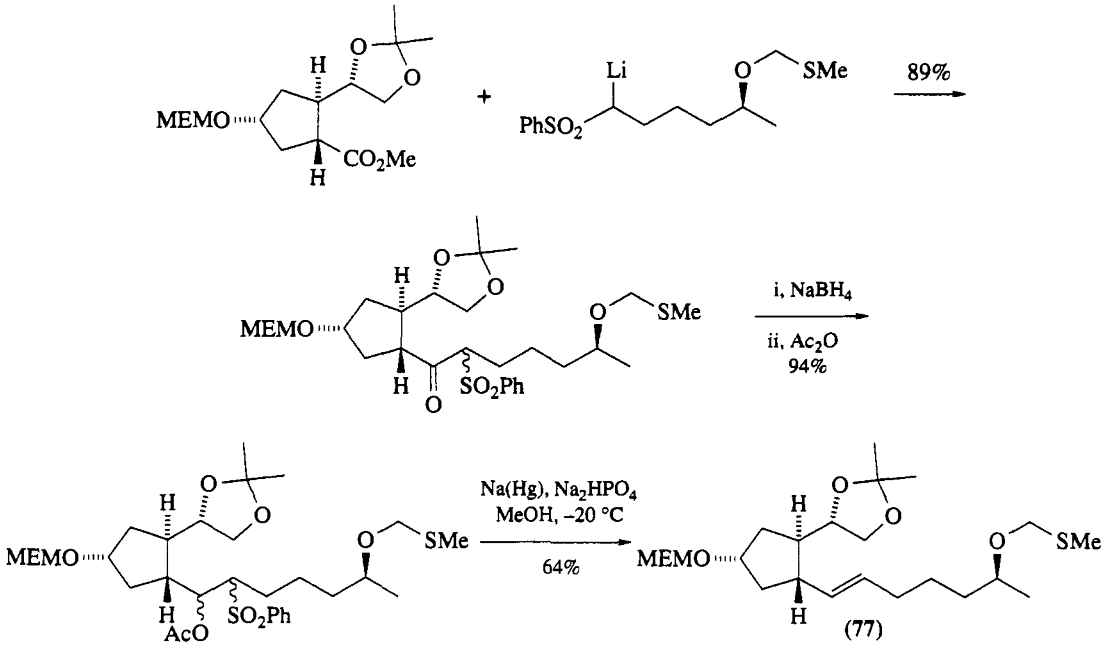
In many cases functionalization of the adduct (stage 3) is superfluous since β-hydroxy sulfones undergo reductive elimination under the usual Julia alkenation conditions. However, the yields are usually lower than the corresponding reductive elimination with the more reactive β-acetoxy, β-benzoyloxy or β-methanesulfonyloxy sulfones owing to competing retroaldolization under the basic conditions of the reaction. A further complication is reductive desulfonylation, as shown in equation (18).[86]

(iv) Reductive elimination

The reductive elimination step is effected by adding an excess of 5.65% Na(Hg) (2.5 mg atom of Na g^{-1}) to an efficiently stirred solution of the sulfone in 3:1 THF–MeOH at −20 °C. A protic solvent is essential for the reaction and a detailed study[77] revealed that MeOH was superior to EtOH or Pr^iOH at low



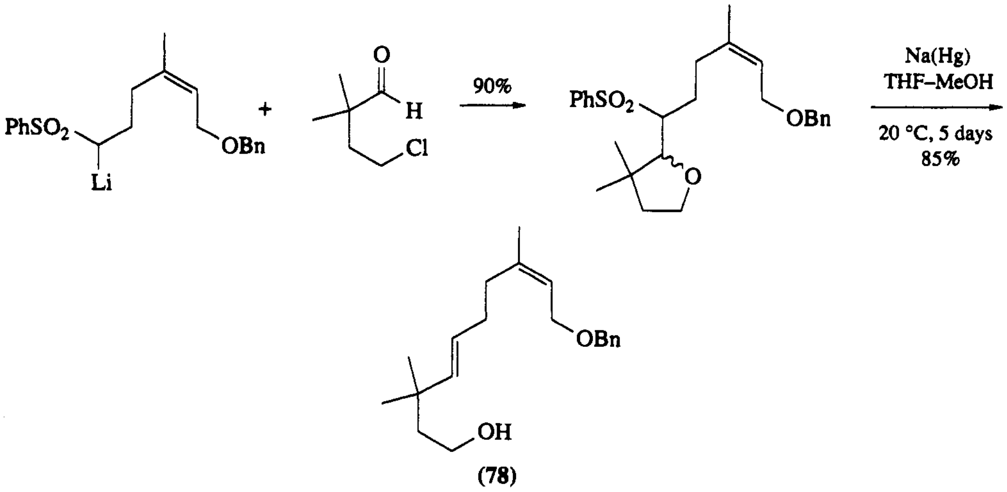
Scheme 27



Scheme 28

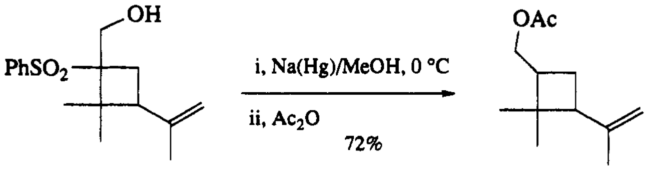
temperature. The THF or other cosolvents are needed to improve solubility of the organic substrates and diminish the rate of reaction of the Na(Hg) with the MeOH. The formation of NaOMe — an agent of serious side reactions — is slow at –20 °C and its effects can be ameliorated but not altogether suppressed by the addition of Na_2HPO_4 as a heterogeneous base scavenger.[87]

Electrochemical methods,[88] Li/NH_3 (l)[82] and modified Beauvault–Blanc reduction conditions[86,89] have also been used to effect reductive elimination. An example of the latter reaction is illustrated in equation (19).

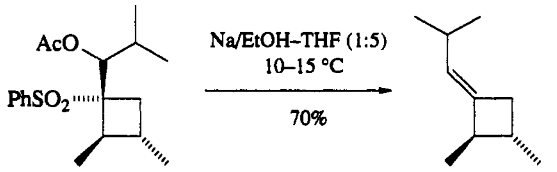


(78)

Scheme 29

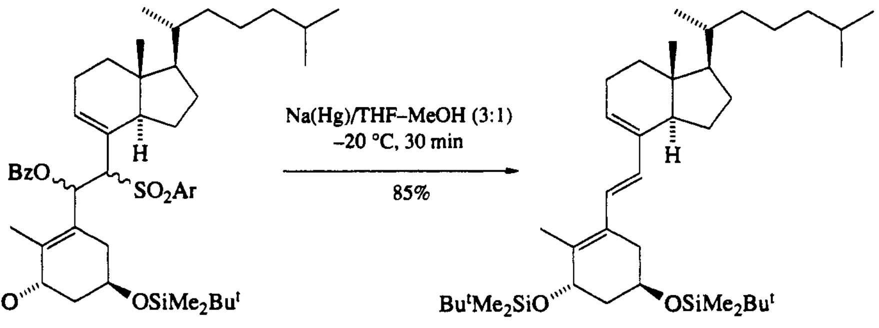


(18)



(19)

The rate of reductive elimination can vary considerably depending on the β-substituent and the structure of the product. Formation of conjugated dienes and trienes is fast (*ca.* 15–30 min) — especially when the sulfone occupies an allylic position; simple alkenes require 1–5 h. Although methanesulfonates, benzoates and acetates react at roughly similar rates, reductive elimination of β-alkoxy sulfones requires higher temperatures and longer reaction times. The large rate difference depending on leaving group and product structure is illustrated by comparing the reductive elimination in Scheme 29 (ether oxygen leaving group, 5 d at room temperature) with the formation of the conjugated triene in the tachysterol derivative (**79**) (30 min, –20 °C) shown in equation (20).[90] The reductive elimination shown in Scheme 27 gives further testimony to the importance of leaving group structure on the course of the reaction. In this case elimination can take place in either of two directions. Nevertheless the reaction was regioselective in the direction of the better leaving group (acetate), even though the alternative mode of elimination would have generated a conjugated diene ester containing a trisubstituted double bond.

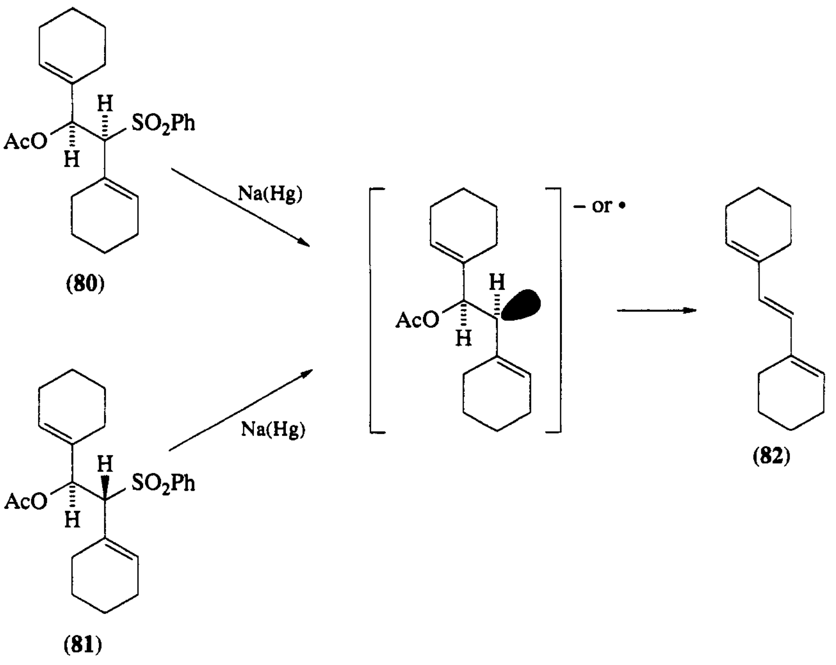


(79)

(20)

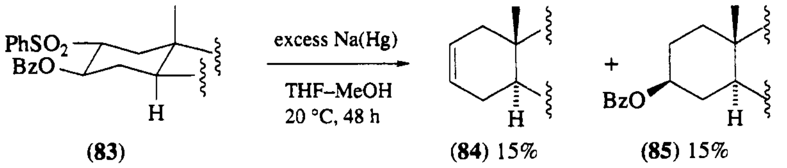
5.2.5.1.2 Stereochemistry

The stereochemistry of the alkene is independent of the stereochemistry of the β-acyloxy sulfone precursor.[77,91] Thus reductive elimination of the pure diastereomeric β-acetoxy sulfones (**80**) and (**81**) gave the triene (**82**; Scheme 30). Similar results have been reported for β-hydroxy sulfones.[78] These results can be interpreted in terms of an intermediate carbanion (or radical) derived from electron transfer from the metal to the sulfone group, followed by elimination of benzenesulfinate anion (or radical) in which the *p*-orbital is *trans* coplanar to the acetoxy group and the substituents as far apart as possible. According to this view the overall stereochemistry is governed by steric interactions of the substituents and assumes that the intermediate anion or radical has sufficient lifetime to equilibrate. There are two further implications: firstly, the alkenes obtained should represent the thermodynamic mixture and secondly, increased branching, especially on those carbons adjacent to the carbons bearing the arylsulfonyl and the acyloxy groups, should increase stereoselectivity.[92] As can be seen from Table 1 this is the case. Furthermore, it can be seen from entries 2 and 3 that interchanging the position of the sulfone and the acyloxy groups has no effect on the stereochemical outcome of the reaction.



Scheme 30

Adverse conformational effects can affect the reductive elimination. For example, in the cholestane derivative (**83**; equation 21), the *trans* diequatorial substituents cannot achieve a *trans* coplanar relation demanded by the mechanism suggested in Scheme 30 unless the ring undergoes an unfavorable conformational change to a boat. Consequently only a 15% yield of cholest-2-ene (**84**) was obtained, along with 15% of the benzoate (**85**) derived from protonation of the carbanion before elimination could occur. It is noteworthy that the reductive elimination of (**83**) is unusually slow at –20 °C and could only be effected with a large excess of Na(Hg) at room temperature. This suggests that there may be a stereoelectronic advantage in the reductive elimination in a coplanar relation between the arylsulfonyl and the acyloxy leaving groups. The rate advantage in a *trans* coplanar relation between leaving groups in other reductive eliminations is well known.[93,94]



(21)

Table 1 Scope and Stereochemistry of Alkenes from Reductive Elimination of β-Substituted Sulfones

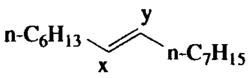
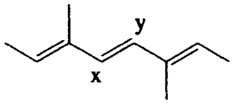
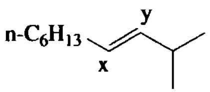
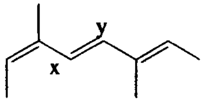
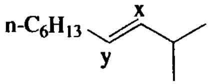
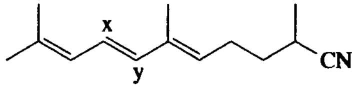
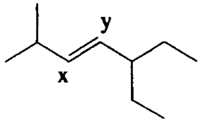
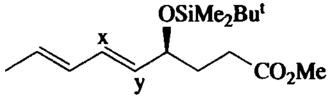
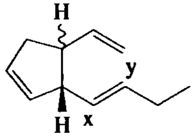
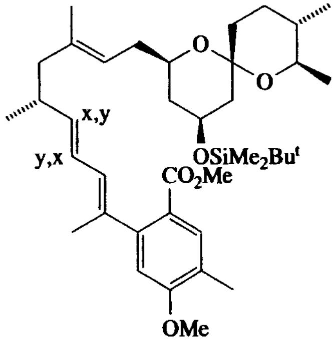
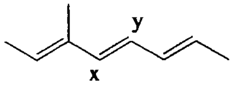
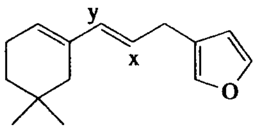
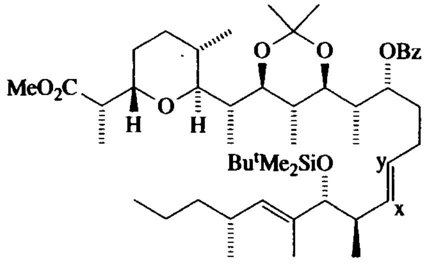
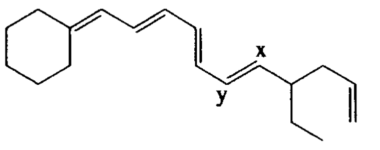
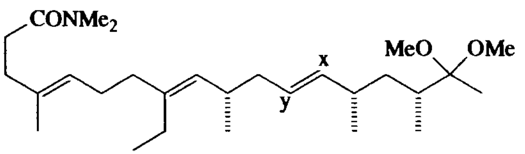
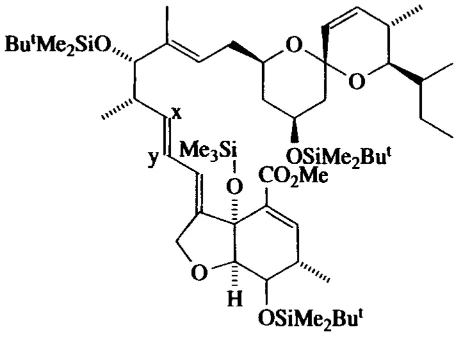
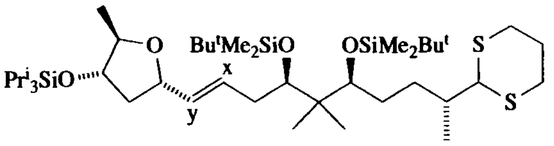
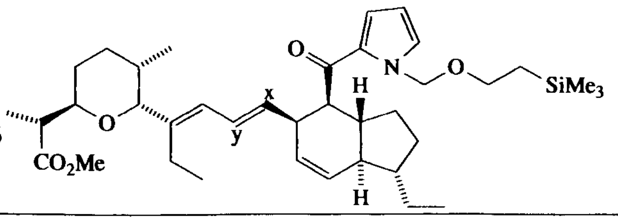
Entry	*Alkene* [a]	*Yield (%)*	*[E:Z] ratio*	*Ref.*	*Entry*	*Alkene* [a]	*Yield (%)*	*[E:Z] ratio*	*Ref.*
1		53	4:1	92	7		61	98:2	92
2		63	9:1	92	8		75	98:2	92
3		68	9:1	92	9		47	12:1	96
4		71	100:1	92	10		81	—	97
5		33	6:1	95	11		70	100:0	98
6		68	97:3	92					

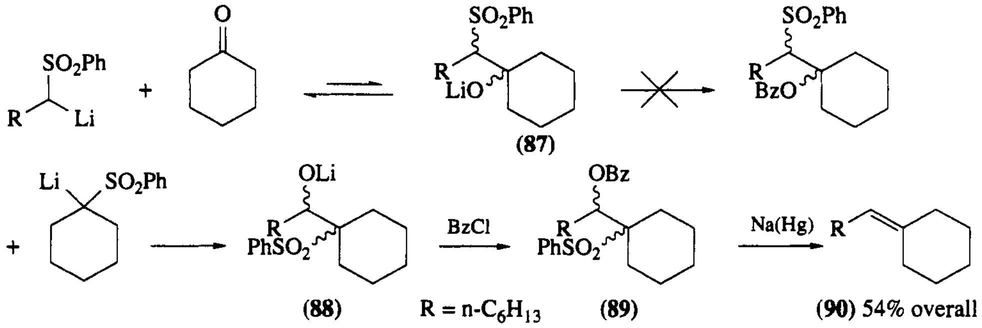
Table 1 *(continued)*

Entry	*Alkene* [a]	*Yield (%)*	*[E:Z] ratio*	*Ref.*	*Entry*	*Alkene* [a]	*Yield (%)*	*[E:Z] ratio*	*Ref.*
12		65	6:1	99	17		50	8:1	80
13		49	10:1	100					
14		68	4:1	101	18		47	100:0	104
15		46	100:0	102					
16		53	100:0	103					

[a] x and y represent the site of the aryl sulfonyl and β-substituent respectively in the β-substituted precursor. y = OH, OMs, OBz or OAc.

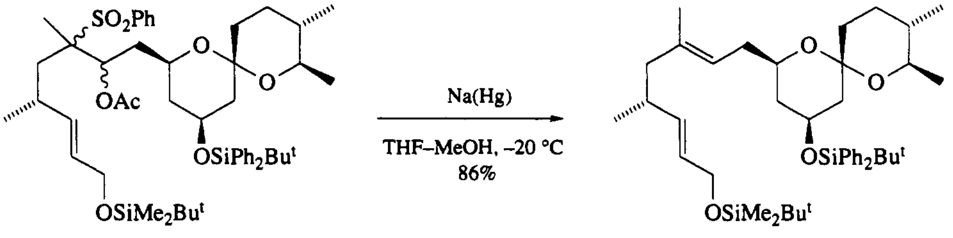
5.2.5.1.3 Trisubstituted alkene synthesis

A serious obstacle to the use of the Julia alkenation for the synthesis of trisubstituted alkenes is illustrated in Scheme 31. Addition of cyclohexanone to the lithiated sulfone (**86**) gave intermediate (**87**), which could not be acylated under the reaction conditions because of the sterically hindered tertiary alkoxide. Owing to an unfavorable equilibrium, (**87**) reverted back to starting materials. However, by reversing the functionality of the fragments a stable adduct (**88**) was formed in which the less hindered secondary alkoxide was acylated and the resultant β-benzoyloxy sulfone (**89**) reductively eliminated to the alkene (**90**) in 54% overall yield. Trisubstituted alkenes have been generated by reductive elimination of β-hydroxy sulfones[105,106] but, in general, retroaldol reactions compete.



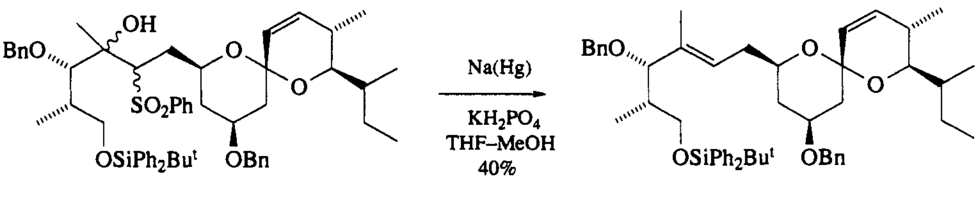
Scheme 31

Little is known about the stereochemistry of trisubstituted alkene formation in the Julia alkenation. In a synthesis of milbemycin β_3 Barrett and coworkers[107] generated intermediate (**91**; equation 22) as a mixture of isomers (E:Z = 5:3) by reductive elimination of a β-acetoxy sulfone; however, a similar reductive elimination on the β-hydroxy sulfone shown in equation (23) gave a single isomer.[104] The marked difference in the yield of these two transformations reflects the advantage of suppressing the retroaldolization reaction by acylation.



(**91**) E:Z = 5:3

(22)

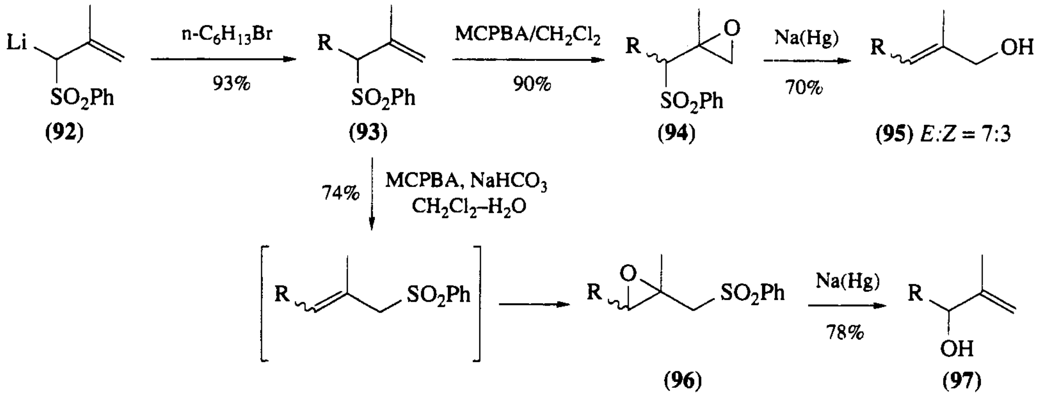


(23)

5.2.5.1.4 Variations

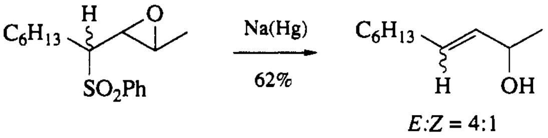
(i) Reductive elimination of 2,3-epoxy sulfones

A three-stage synthesis of allylic alcohols has been devised (Scheme 32),[108] which consists of: (i) alkylation of a sulfone-stabilized allylic carbanion; (ii) peroxy acid oxidation of the allylic sulfone to give a 2,3-epoxy sulfone; and (iii) reductive elimination of the 2,3-epoxy sulfone to give the allylic alcohol. The overall strategy is similar to that of the Evans–Mislow allylic alcohol synthesis based on the 2,3-sigmatropic rearrangement of allylic sulfoxides.[109] However, there are regiochemical advantages to the sulfone-based method exemplified by comparing the alkylation of (**92**) (*n*-hexyl bromide, 96% yield, exclusive α-alkylation) with the corresponding sulfoxide (*n*-hexyl iodide, 42% yield, α:γ = 2:5).[110]

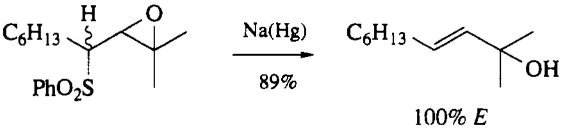


Scheme 32

A disadvantage of this procedure is that reductive cleavage of the epoxy sulfones leading to trisubstituted alkenes, *e.g.* (**95**), is not stereoselective. However, formation of disubsituted alkenes follows the trends found in the standard Julia alkenation in that *trans*-alkenes are favored (equation 24) and proximate branching increases the stereoselectivity (equation 25). Unlike the standard Julia alkenation, the stereochemistry of the epoxy sulfone reductive elimination depends on the stereochemistry of the precursor.[111]



(24)

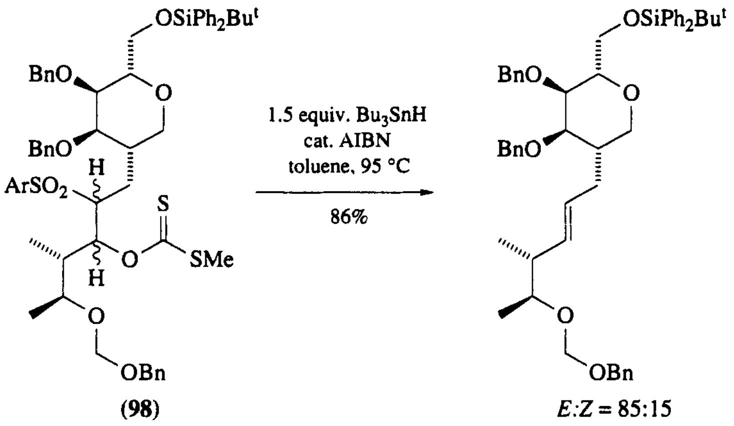


(25)

The scope of the sulfone-based allylic alcohol synthesis is enhanced by the discovery that certain allylic sulfones undergo a 1,3-rearrangement, caused by *m*-chloroperbenzoic acid and $NaHCO_3$ in aqueous dichloromethane. Under these conditions epoxidation of the allylic sulfone (**93**; Scheme 32) gave the rearranged epoxy sulfone (**96**) in 79% yield. Subsequent reductive elimination of (**96**) gave the regioisomeric allylic alcohol (**97**). A radical chain mechanism has been proposed for the rearrangement, which is restricted to those allylic sulfones in which the arylsulfonyl group can migrate from a more- to a less-substituted carbon.

(ii) Radical-mediated reductive elimination

The greatest drawback to the Julia alkenation is the inherent limitation in scale imposed by the use of Na(Hg) as the reducing agent and the inconvenient temperature used in the reductive elimination step. A potential solution to the problem of scale has been provided by Lythgoe and Waterhouse,[112] who reported that thiocarbonyl derivatives of β-hydroxy sulfones undergo reductive elimination at elevated temperature on treatment with Bu_3SnH. The reductive elimination of the xanthate derivative (**98**; equation 26) illustrates the value of the reaction in the elaboration of the side chain of pseudomonic acid[113] — a problem which has resisted efficient solution using standard Wittig or Julia methodology. The principal impediment to the use of the reaction in the synthesis of conjugated alkenes is the ease with which allylic xanthates undergo 3,3-sigmatropic rearrangement to dithiocarbonates.[114,115]



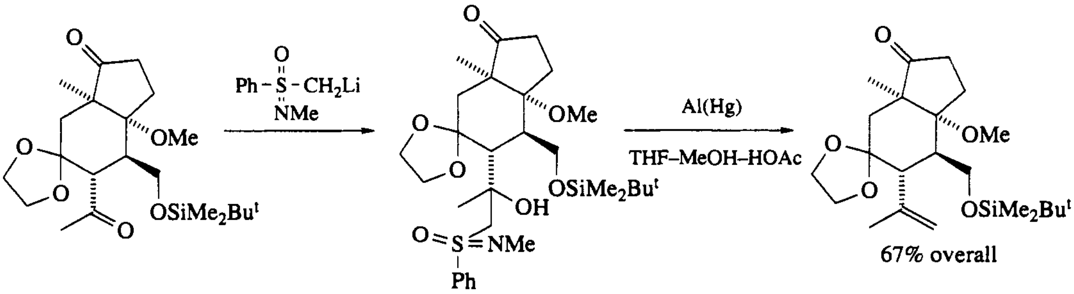
(98)

E:Z = 85:15

(26)

(iii) Reductive elimination of β-hydroxy sulfoximines

Sulfoximines are N-analogs of sulfones and their β-hydroxy derivatives, which are less prone to retro-aldolization, undergo reductive elimination on treatment with Al(Hg) in aqueous THF containing some acetic acid. The reaction takes place at room temperature or below. Despite these marked advantages, the sulfoximine modification of the Julia alkenation has not found wide acceptance, primarily because the sulfoximines are less readily available and less robust than the corresponding sulfones. Furthermore, the reductive eliminations of β-hydroxysulfoximines tend to be less *trans* stereoselective than the sulfone-based reactions and the stereochemistry of the product is influenced by the stereochemistry of the starting β-hydroxysulfoximine.[116] However, in certain instances the reaction has provided a useful alternative method for introducing a methylene in sterically demanding environments, as illustrated in the transformations depicted in Scheme 33, which were used in a synthesis of the alkaloids picrotoxinin and coriamyrtin.[117] Similar transformations were used in a synthesis of a thromboxane A2 agonist.[118] The chromatographic resolution of optically active β-hydroxysulfoximines has resulted in methodology which leads to ketone methylenation and resolution.[116]

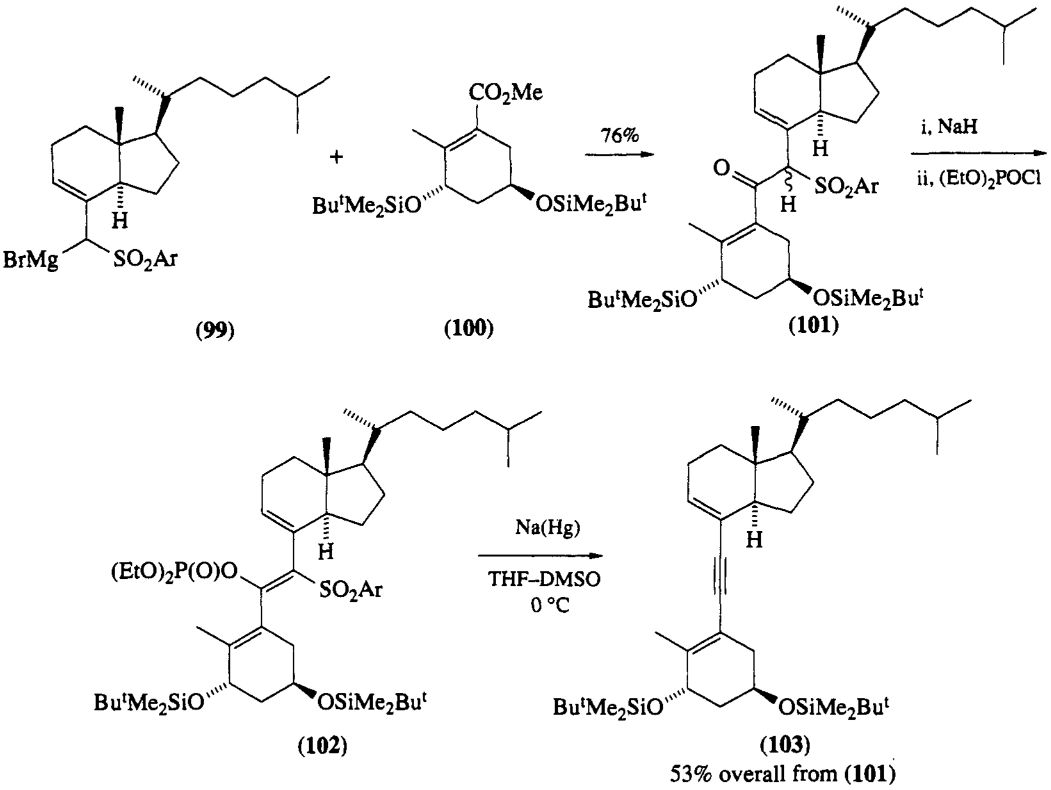


Scheme 33

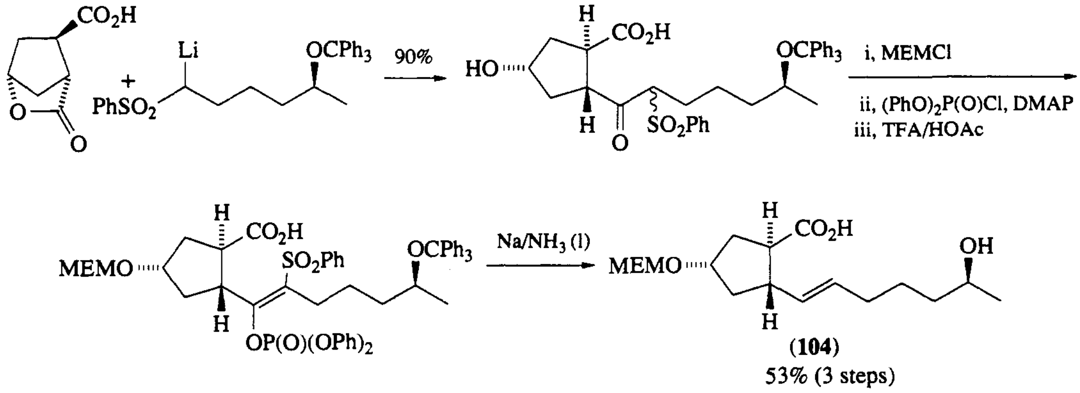
(iv) Reductive elimination of β-arylsulfonyl enol esters

A connective synthesis of alkynes inspired by the Julia alkenation was developed by Lythgoe and coworkers for the synthesis of 1α-hydroxyvitamin D3,[90,119] as shown in Scheme 34. The β-keto sulfone (**101**) derived by condensation of the the metalated sulfone (**99**) with the ester (**100**) was converted to the enol phosphate (**102**), which on reductive elimination gave the enynene (**103**).

The precise conditions for the reductive elimination are important. Use of Na(Hg) in THF–MeOH[95] or THF alone gives messy reactions, owing to substantial cleavage of the P—O bond of the enol phosphate but this can be avoided with Na(Hg) in THF–DMSO. Alternatively, Na in liquid ammonia can be used to effect the reductive elimination but the reaction must be very carefully controlled in order to avoid reduction of the alkyne to a *trans*-alkene.[120] A deliberate over-reduction of the initial alkyne product to an alkene was used in a synthesis of the intermediate (**104**) in a synthesis of brefeldin (Scheme 35).[121]



Scheme 34

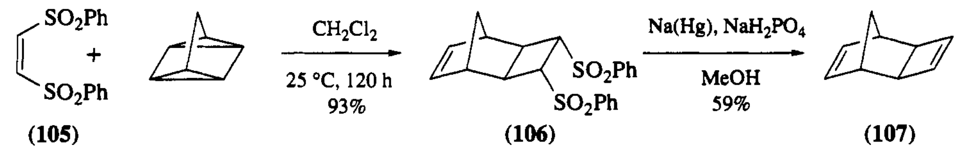


Scheme 35

(v) Reductive elimination of 1,2-disulfones

A new method for introducing an ethylenic bridge *via* a cycloaddition reaction makes use of either (*Z*)-1,2-di(phenylsulfonyl)ethylene (**105**) or the less reactive (*E*)-isomer as synthetic equivalents of acetylene.[122] The high activation due to the two sulfonyl groups promotes cycloaddition even to very unreactive dienes. The removal of the two sulfonyl groups for the required formation of the carbon–carbon double bond is achieved by reduction at room temperature with Na(Hg) in methanol buffered with NaH_2PO_4[123] or Mg in MeOH at 50 °C.[124] These properties, associated with the stability of the reagents and the ease of performance of the reactions, make this method a very useful synthetic tool for the preparation of polycyclic dienes and a valid alternative to the commonly available reagents that largely depend upon oxidative methods.

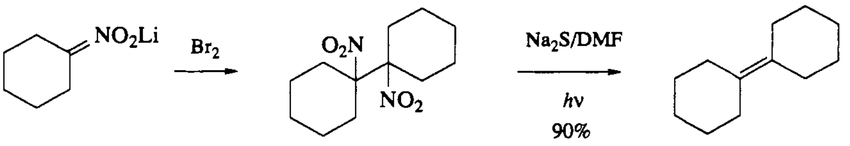
The synthesis of the diene (**107**) from the quadricyclane cycloadduct (**106**) reflects the value of the method (Scheme 36).



Scheme 36

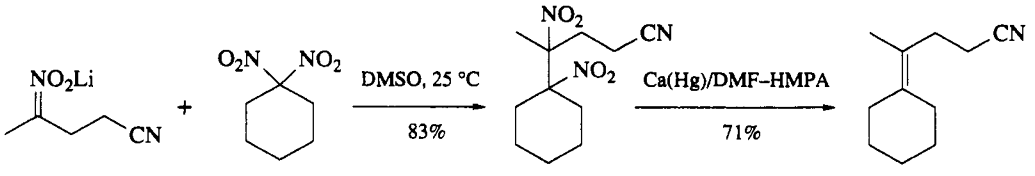
5.2.5.2 Reductive Elimination of β-Substituted Nitroalkanes

The anions of nitroalkanes (nitronates) can be used as precursors in a connective and regiospecific synthesis of tetrasubstituted alkenes. They are easily formed on reaction with LiOMe and undergo oxidative dimerization in the presence of bromine.[125] The resultant 1,2-dinitroalkanes (Scheme 37) participate in a reductive elimination involving an $E_{\mathrm{RC}}1$ radical chain mechanism when irradiated in the presence of Na_2S, PhSNa or the lithium nitronate derived from 2-nitropropane.



Scheme 37

An alternative procedure (Scheme 38) affords a connective synthesis of unsymmetrical tetrasubstituted alkenes.[126] In this case the lithium nitronate reacted with a 1,1-dinitroalkane to give the 1,2-dinitroalkane intermediate. Reductive elimination was effected by Ca(Hg) in DMF–HMPA.



Scheme 38

The power of the nitroalkane coupling procedure was exploited by Vasella and coworkers[127] in order to fuse two furanose derivatives to form the unique enediol ether (**111**). Coupling of the lithiated nitrofuranose (**108**) with the 1-nitrofuranosyl bromide (**109**) took place on irradiation to afford the dinitrododecadiulose derivative (**110**), which then underwent reductive elimination on treatment with Na_2S.

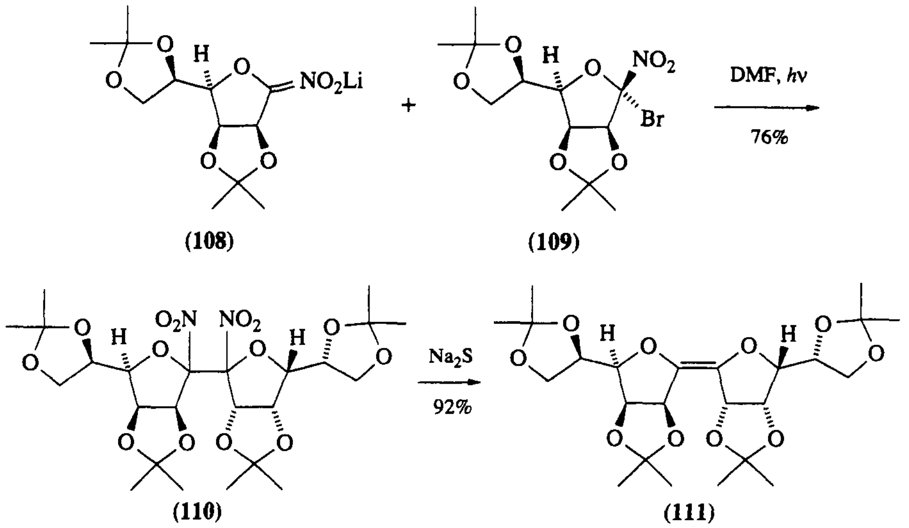
A major drawback to the 1,2-dinitroalkane approach to tetrasubstituted alkenes is its poor stereoselectivity. Thus treatment of the *erythro-* and *threo-*1,2-dinitroalkanes (**112** and **113**; Scheme 40) respectively with Bu_3SnH in refluxing benzene gave the alkene as a 1:1 mixture of isomers.[128] By contrast, the reductive elimination of certain β-nitro sulfones is stereospecific because the elimination of the radical intermediate is faster than bond rotation. For example, treatment of the β-nitro sulfones (**114**) and (**116**) with Bu_3SnH gave the alkenes (**115**) and (**117**) with high efficiency and stereoselectivity (equations 27 and 28).

The synthesis of the requisite β-nitro sulfones is accomplished by reacting a carbanion stabilized with a cyano and arylsulfonyl group with a 1-bromonitroalkane, as shown in equation (29).[129] Carbanions stabilized by one arylsulfonyl group or by an arylsulfonyl and nitro group do not react.

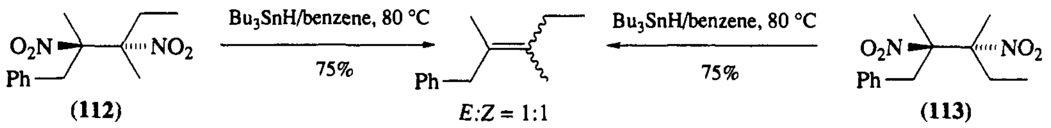
β-Phenylsulfonylnitroethylene (**118**) has been used as an alkyne equivalent in cycloaddition reactions because the cycloadducts undergo reductive elimination to the alkene (Scheme 41).[130]

5.2.6 VICINAL DESILYLATION

The formation of an Si—F bond (142 kcal mol^{-1}; 1 cal = 4.18 J) is a highly exothermic process, which provides the driving force for a number of synthetically useful reactions. Fluoride initially attacks an empty 3*d*-orbital of silicon to form a pentacoordinate siliconate species. In molecules containing a leav-

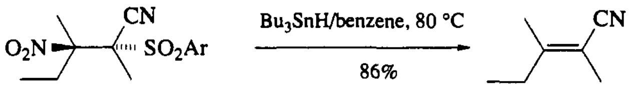


Scheme 39

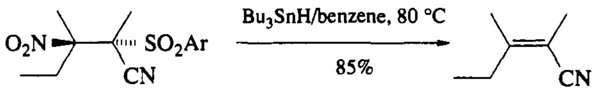


E:*Z* = 1:1

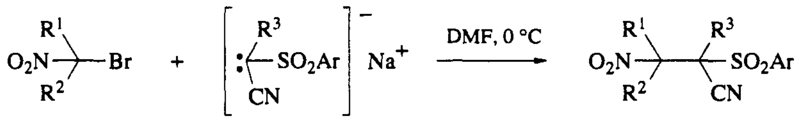
Scheme 40



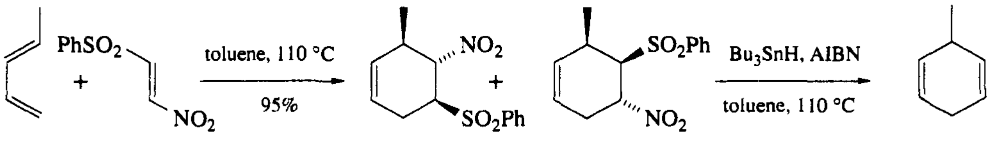
(115) *E*:*Z* = 98:2 (27)



(117) *E*:*Z* = 3:97 (28)



(29)



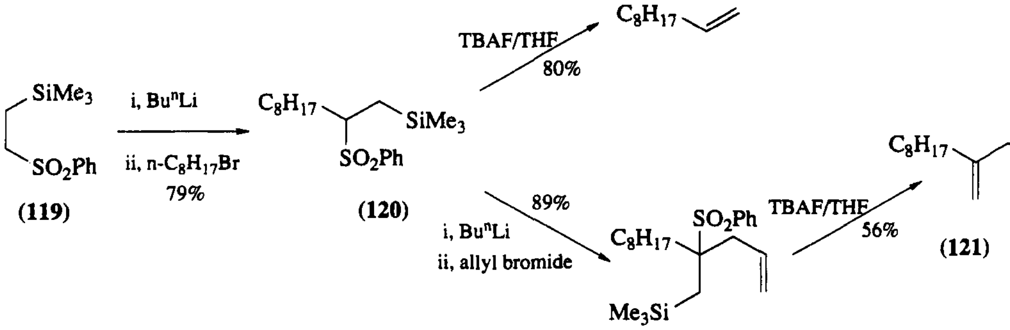
2:3

Scheme 41

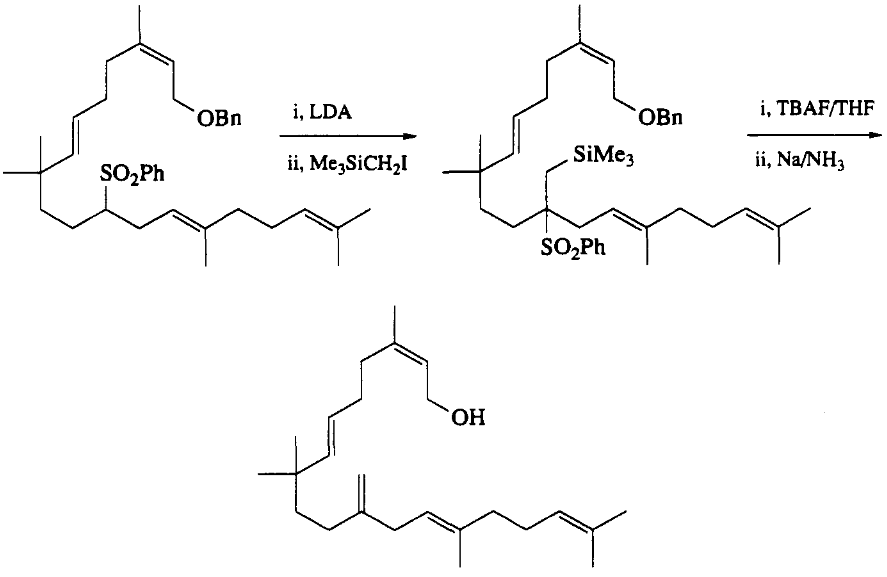
ing group β to the siliconate, elimination takes place to generate an alkene. Among the leaving groups which have proved effective are arylsulfonyl, halide, ester, trialkylammonium and ether groups. A brief review of the fluoride-induced 1,2-, 1,4- and 1,6-elimination of silanes has appeared.[131]

5.2.6.1 β-Silyl Sulfones

The fluoride-induced elimination of β-trimethylsilyl sulfones to give terminal alkenes was first reported in 1979.[132] The β-silyl sulfone (**120**; Scheme 42), prepared by the alkylation of the readily available crystalline sulfone (**119**), undergoes elimination on warming with TBAF in THF to give 1-decene in 80% yield. A second alkylation–elimination sequence can then be performed to give a 1,1-dialkylethylene derivative (**121**). Thus, the sulfone (**119**) may serve as a synthon for $CH_2{=}CH^-$ or $CH_2{=}C^{2-}$ in which the alkene is liberated under specific and mild conditions. Scheme 43 illustrates an application of the β-silyl sulfone elimination to the introduction of the C-11 methylene of moenocinol (**122**).[77]



Scheme 42

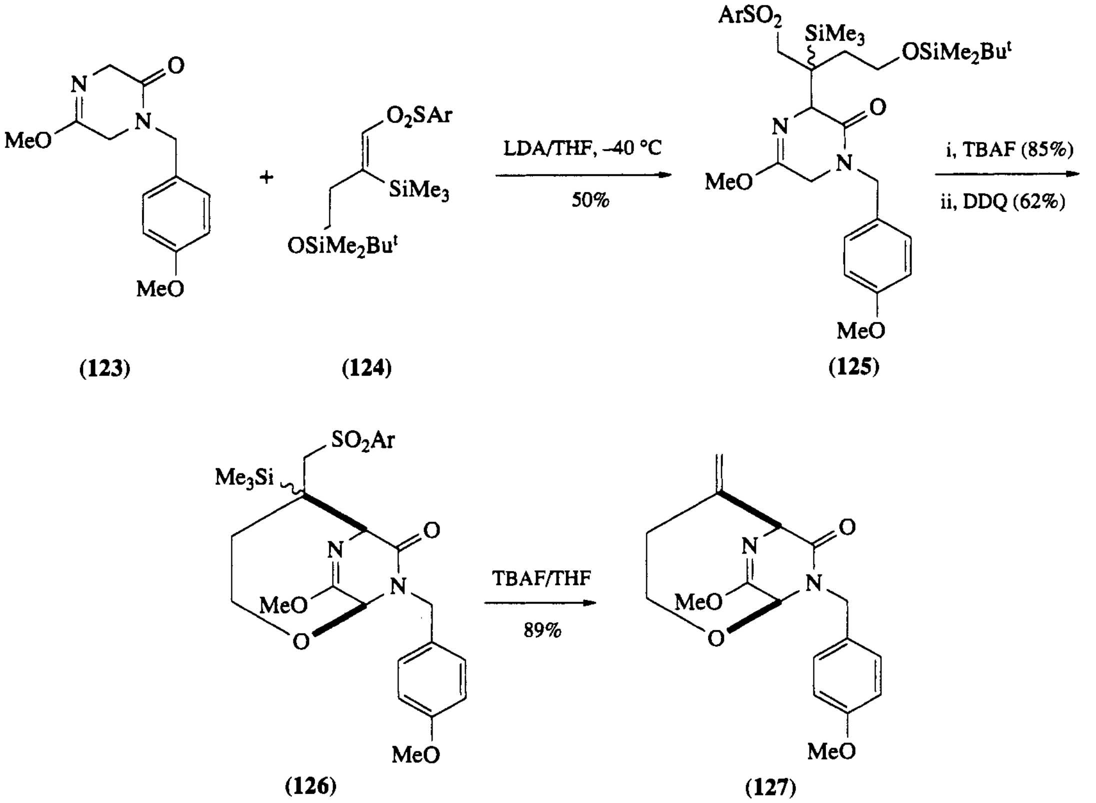


(**122**) 40% overall

Scheme 43

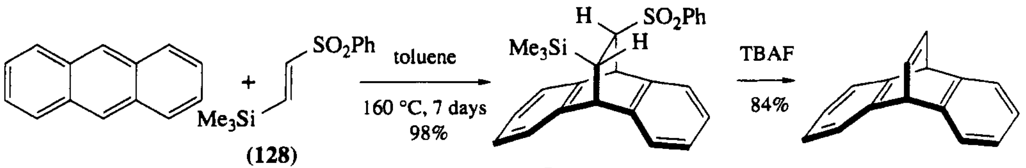
A major detraction to the β-silyl sulfone route to alkenes is its narrow scope, owing to the paucity of methods for preparing the requisite β-silyl sulfones. The method has so far been largely restricted to monosubstituted and 1,1-disubstituted ethylene derivatives because the β-silyl sulfones have usually been most conveniently and economically prepared by the alkylation of a sulfone anion with iodomethyltrimethylsilane. Unfortunately higher haloalkylsilanes are difficult to prepare and their alkylation chemistry remains unexplored.

Sammes and coworkers[133] devised a promising solution to the synthesis of substituted β-silyl sulfones, which has been exploited in a new approach to the antibiotic bicyclomycin (Scheme 44). In their approach the β-silyl sulfone (**125**) was prepared by conjugate addition of the lithium enolate of the monoimino ether derivative (**123**) of a dioxopiperazine to the unsaturated β-silyl sulfone (**124**). After oxidative cyclization to the bicyclic system (**126**), the latent alkene functionality was unleashed in 89% yield on treatment with TBAF in THF at room temperature to give the basic skeleton of bicyclomycin.



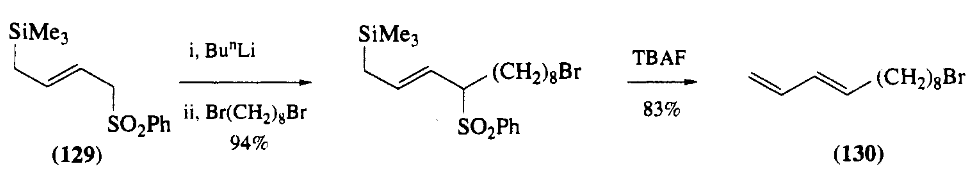
Scheme 44

(*E*)-1-Trimethylsilyl-2-phenylsulfonylethylene (**128**) has been exploited as an alkyne equivalent since it undergoes Diels–Alder cycloadditions with relatively reactive dienes to give β-silyl sulfones, which can then be eliminated to the alkene (Scheme 45).[134] However, (**128**) is a poorer dienophile than the 1,2-disulfone (**105**) but it has the advantage that the α-position of the sulfone in the cycloadduct can be alkylated prior to fluoride-induced elimination.



Scheme 45

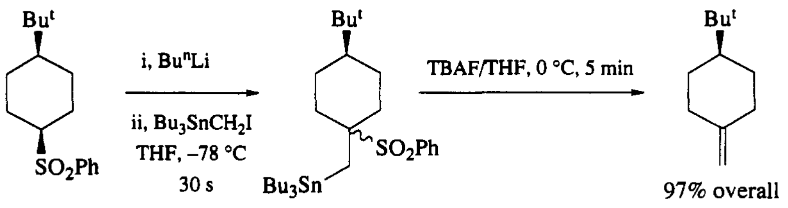
A fluoride-induced 1,4-elimination reaction illustrates the use of 1-trimethylsilyl-4-phenylsulfonyl-2-butene (**129**) as a synthon for a butadiene anion (Scheme 46).[135] The elimination is stereoselective, giving the (*E*)-diene (**130**) exclusively.



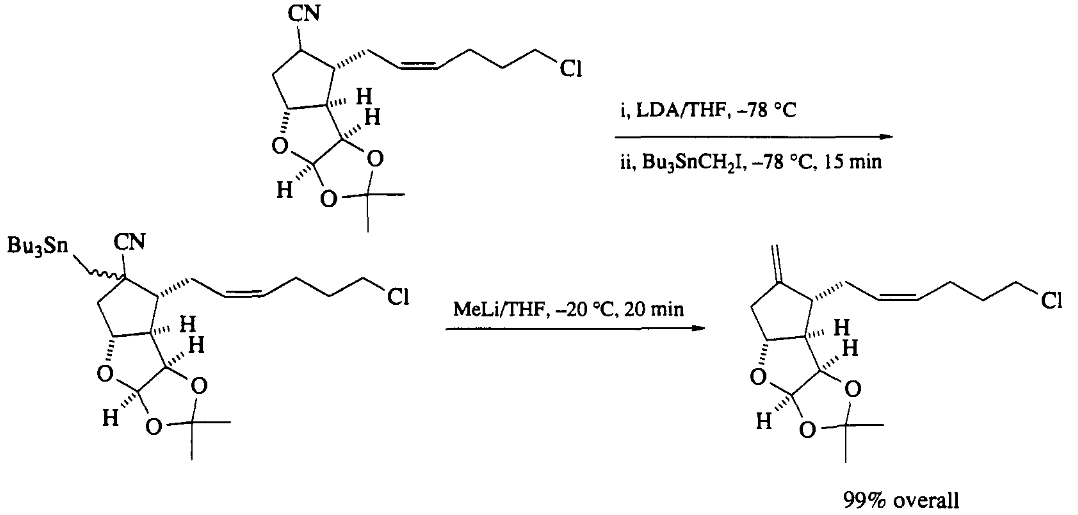
Scheme 46

Fluoride also has a high affinity for tin and the analogous β-stannyl sulfone elimination is an efficient and fast reaction.[136] The requisite β-stannyl sulfones are prepared by alkylation of the sulfone anions as in the silicon case; however, the iodoalkylstannanes react faster [relative rate order Me_3SiCH_2I (1),

Bu_3SnCH_2I (600), Me_3SnCH_2I and Bu^nI (10 000). Fluoride-induced elimination takes place at 0 °C in less than 5 minutes (Scheme 47). Nitrile anions alkylate even faster than sulfones with Bu_3SnCH_2I, but the subsequent elimination requires MeLi. Both reactions proceed in good yield (Scheme 48).[137] Silica gel is also effective in causing elimination of β-trialkylstannyl sulfones to alkenes.[138]



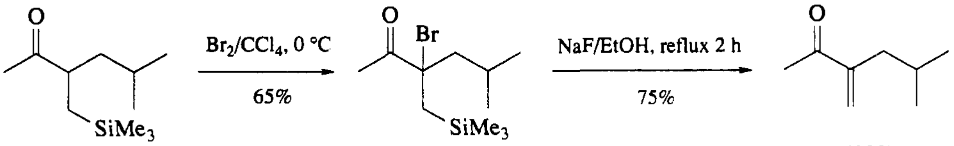
Scheme 47



Scheme 48

5.2.6.2 β-Silylhaloalkanes

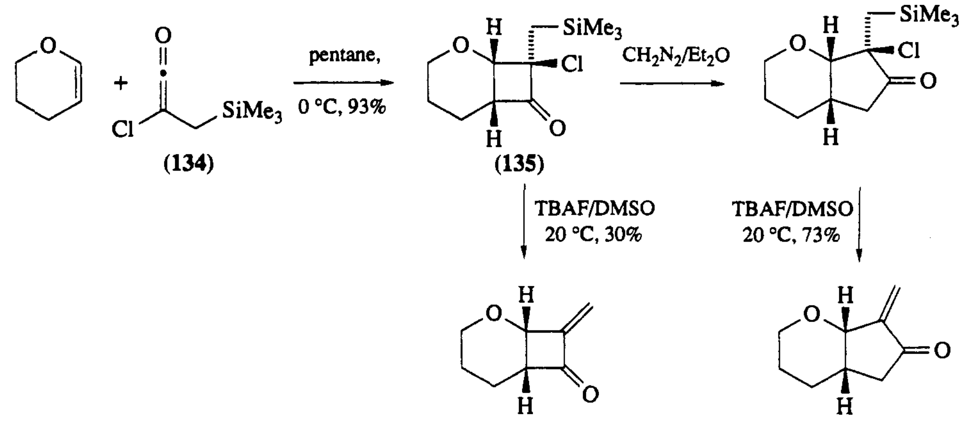
The fluoride-induced fragmentation of β-silylhaloalkanes is a clean and efficient reaction which has been limited by the relative inaccessibility of the starting material. Fleming and Goldhill[139] have exploited the easy introduction of a bromine atom α to a ketone as a means for introducing unsaturation adjacent to a ketone function in a regiocontrolled fashion. Scheme 49 shows how the β-silylketone (**131**) serves as a masked version of the enone (**133**). The regioselectivity of the kinetically controlled bromination reaction is noteworthy. In all the examples studied there is a bias in favor of the side of the ketone on which the silyl group is placed, regardless of the level of substitution at that site. Thus bromination of (**131**) gave a 65% yield of the desired bromo ketone (**132**) along with a further 15% of the regioisomer. This is surprising since a trimethylsilyl group is both bulky and a π-electron-donating substituent, and would on both counts be expected to deter enolization towards itself, yet the opposite is actually the case. The desilylbromination can be achieved with NaF in aqueous ethanol, as illustrated, or with benzyltrimethylammonium fluoride (BTAF) in THF. These transformations can also be adapted to the synthesis of α-methylenelactones.



(**131**) (**132**) (**133**)

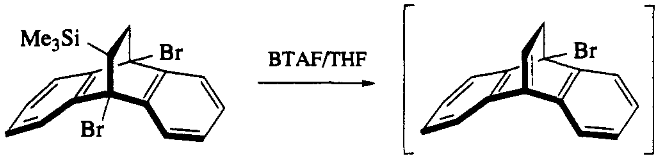
Scheme 49

A fluoride-induced desilylchlorination of α-chloro-β-silyl ketones has been used to prepare α-methylenecyclobutanones and α-methylenecyclopentanones (Scheme 50).[140] In this case, the requisite α-chloro-β-silylcyclobutanone precursor (**135**) was prepared by an efficient [2 + 2] cycloaddition of chloro[(trimethylsilyl)methyl]ketene (**134**) with 3,4-dihydro-2*H*-pyran.

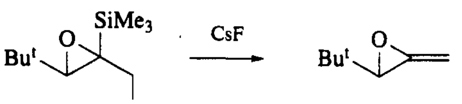


Scheme 50

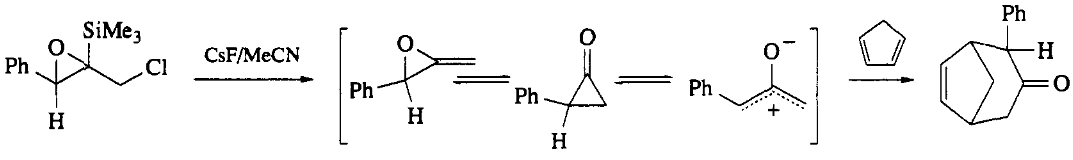
The desilylhalogenation reaction has been used to good effect in the preparation of highly reactive alkenes since the alkali metal or tetraalkylammonium fluorides used to induce the reaction and the fluorosilane by-products are largely inert. For example, the bridgehead alkene (**137**) was generated as a reactive intermediate from the desilylbromination of the β-silyl bromide (**136**) using BTAF in THF (equation 30).[141] Similarly, the highly reactive allene oxide (**139**) was generated from the β-silyl chloride (**138**; equation 31) on treatment with CsF and the product isolated by blowing a stream of N_2 through the reaction mixture.[142] Other allene oxides with less bulky substituents are too reactive to be isolated but they have been generated as transient intermediates by the same procedure. Heterolysis of the allene oxide moiety leads to an oxyallyl 1,3-dipole which can be trapped by 1,3-dipolar cycloaddition (Scheme 51)[143] or, in special cases, rearrange to an isolable cyclopropanone.



(**136**) (**137**) (30)



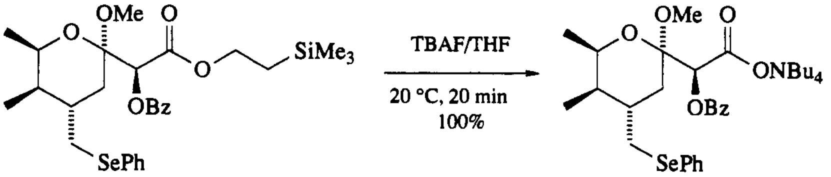
(**138**) (**139**) (31)



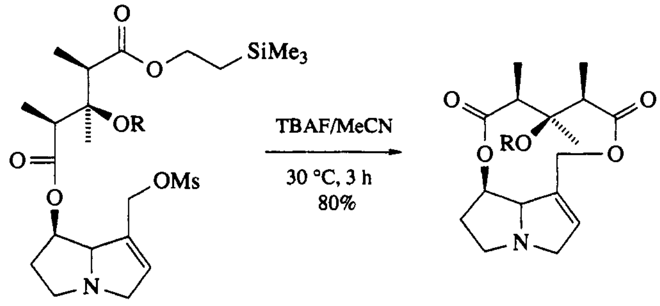
Scheme 51

5.2.6.3 β-Silyl Esters and Ethers

The efficiency and specificity of the fragmentation of β-silyl-substituted derivatives have great value in the design of new protecting groups[144] — a subject treated in greater detail in part 3 of this volume. Carboxylic acids, for example, are easily protected as their 2-(trimethylsilyl)ethyl esters, which are about as stable as ethyl esters under most reaction conditions. However, on treatment with TBAF they fragment to give Me_3SiF, ethylene and the tetrabutylammonium salt of the acid. The conditions for the deprotection are sufficiently mild for amino acids to be liberated without racemization. Equation (32) gives an example of the generation of a highly unstable carboxylic acid salt using this method[145] and equation (33) illustrates the chemospecific liberation and subsequent reaction of a carboxylic acid intermediate in the presence of an ester function.[146]



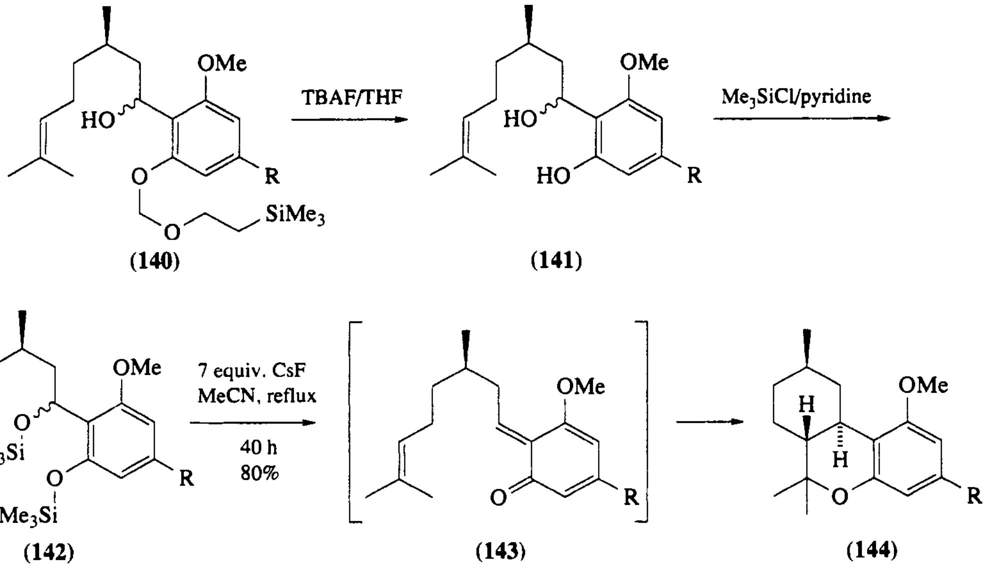
(32)



(33)

Primary, secondary and tertiary alcohols can be protected in good yield as their 2-(trimethylsilyl)ethoxymethyl ethers (abbreviated SEM ethers) by reaction with 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) in dichloromethane in the presence of Pr^i_2NEt.[147] The resultant ethers are stable to the conditions used to remove THP and TMS ethers (3:1:1 THF:HOAc:H_2O). Deprotection takes place on treatment with TBAF in THF at 45 °C.

Fluoride-induced fragmentation reactions were used in two stages of a synthesis of hexahydrocannabinol methyl ether (**144**; Scheme 52).[148] One of the phenolic hydroxy functions in the resorcinol derivative (**140**) was selectively liberated from the SEM ether to give the diol (**141**), which was converted to the *bis* (trimethylsilyl) ether (**142**). Subsequent treatment with CsF resulted in a 1,4-elimination to the *o*-quinone methide (**143**) intermediate, which underwent an intramolecular [4 + 2] cycloaddition to give the product in good yield.

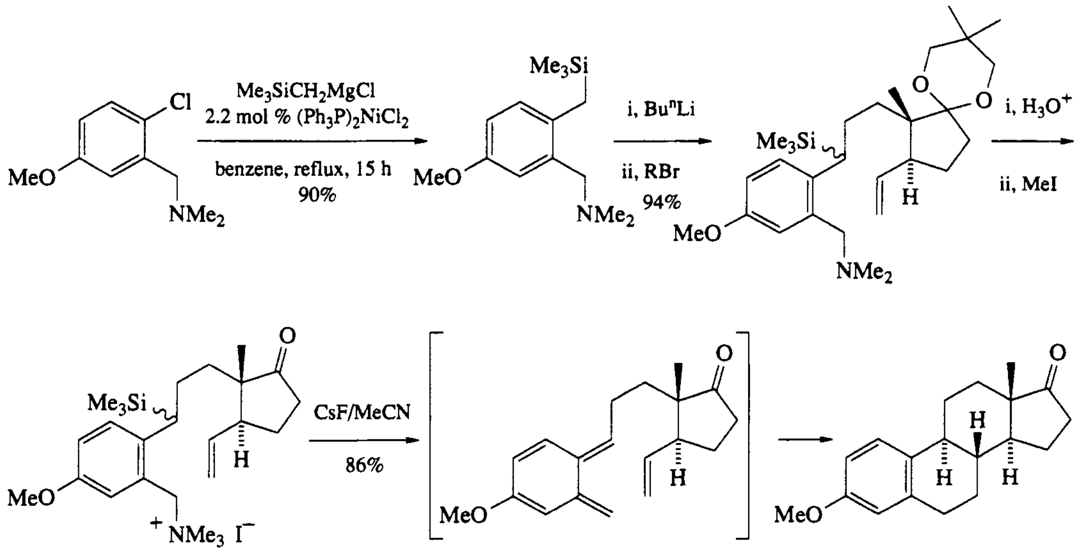


Scheme 52

5.2.6.4 *o*-Quinodimethanes *via* 1,4-Fragmentation

This last section deals with the generation of *o*-quinodimethanes using fluoride-induced fragmentation reactions. Strictly speaking these are not vicinal desilylations but they bear a close affinity to the reactions discussed above.

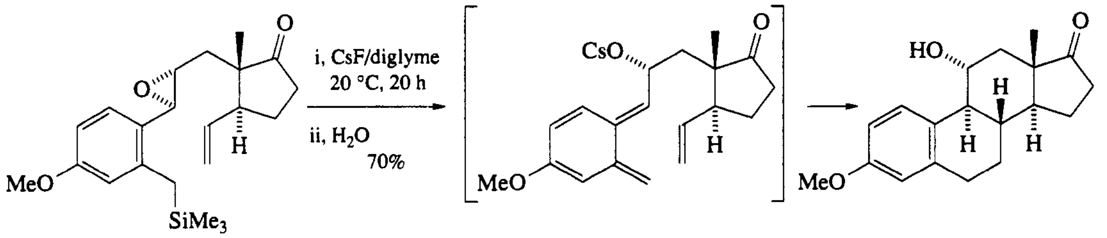
Ito and coworkers[149] developed a mild and efficient procedure for generating *o*-quinodimethanes[11] as reactive intermediates in [4 + 2] cycloadditions. The key step in the sequence, illustrated here by the synthesis of Estrone methyl ether (**146**; Scheme 53) involves a fluoride-induced fragmentation of the *o*-[α-(trimethylsilyl)alkyl]benzyltrimethylammonium iodide (**144**) to give the *o*-quinodimethane (**145**), which underwent stereoselective intramolecular [4 + 2] cycloaddition to give the desired tetracyclic framework in (**146**). The entire process was conducted at room temperature. The annulation reaction is not limited to intramolecular cycloadditions; intermolecular versions of the reaction proceed equally well.



(144) **(145)** **(146)**

Scheme 53

Contemporaneous with the work of Ito was a synthesis of 11-α-hydroxyestrone methyl ether (**148**) by Magnus and coworkers (Scheme 54)[150] in which the requisite *o*-quinodimethane intermediate was generated by the fragmentation of the *o*-[(trimethylsilyl)methyl]aryl oxirane derivative (**147**) using CsF.



(147) **(148)**

Scheme 54

The synthesis of *O*-quinodimethanes has recently been reviewed.[151]

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5.3

The Cope Elimination, Sulfoxide Elimination and Related Thermal Reactions

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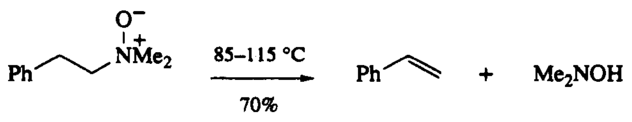
5.3.1 INTRODUCTION

This chapter is concerned with a group of thermally induced elimination reactions widely used for the introduction of carbon–carbon double bonds into complex molecules. These reactions form a discrete group of elimination reactions in that they proceed with *syn* stereochemistry *via* concerted cyclic transition states.[1,2] Related *syn* elimination processes are believed to be involved in other elimination reactions, *e.g.* alcohol dehydration using the Burgess reagent,[3] but are not discussed here. One of the advantages of the *syn* elimination reactions discussed in this chapter is that they do not require the use of strongly acidic or basic reagents; they are simply carried out by heating the substrate to the required temperature.

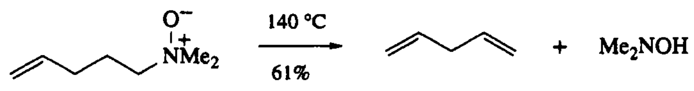
5.3.2 COPE ELIMINATION

5.3.2.1 Introduction

Tertiary amine oxides fragment on heating to give an alkene and an *N*,*N*-dialkylhydroxylamine (*e.g.* equations 1 and 2). This reaction was studied extensively by Cope, and is commonly referred to as the 'Cope elimination'.[4]

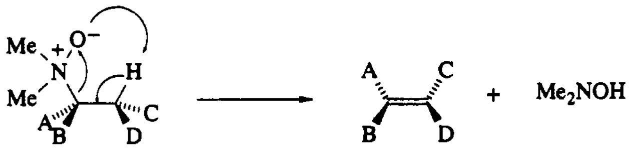


(1)

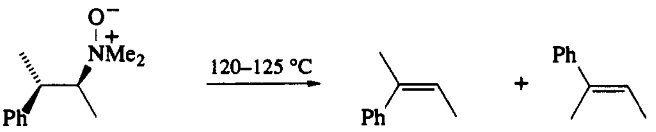


(2)

Early stereochemical evidence supported the *syn* elimination mechanism outlined in equation (3). Pyrolysis of the *erythro*-2-amino-3-phenylbutane (**1**) gave mainly the (*Z*)-alkene (**2**; equation 4), whereas the *threo* isomer (**4**) gave more of the (*E*)-alkene (**3**; equation 5).[5,6] This stereochemistry has since been confirmed by deuterium labeling, the *trans*-labeled cyclooctyldimethylamine oxide (**5**) giving *cis*-cyclooctene with no loss of label, and the *cis*-labeled isomer (**6**) giving partially labeled product (78% d_1, 22% d_0) consistent with an isotope effect of about 3.[7]

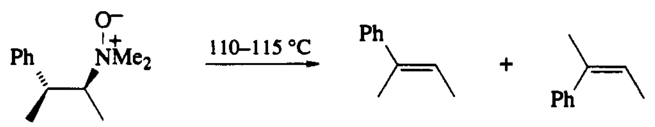


(3)



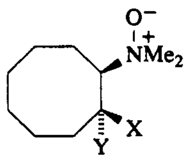
(1) (2) 95:5 (3)

(4)



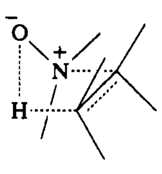
(4) (3) 99.7:0.3 (2)

(5)

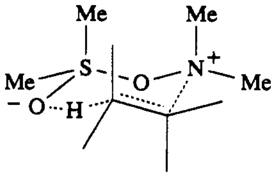


(**5**) X = H, Y =D
(**6**) X = D, Y = H

Kinetic isotope effects have been used to probe the Cope elimination mechanism in more detail. In diglyme the β-deuterium isotope effect was found to be temperature independent, consistent with a nonlinear hydrogen transfer *via* a bent cyclic transition state (**7**).[8] In contrast, a substantial temperature dependence of the β-deuterium isotope effect was found in DMSO, suggesting that a linear hydrogen transfer was involved, possibly *via* the transition state (**8**), involving a molecule of DMSO.[8,9]

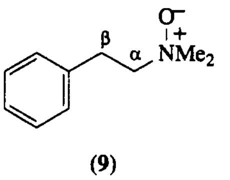


(**7**)

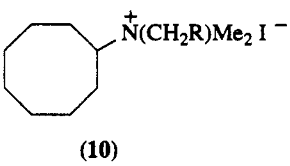


(**8**)

The observation of large ^{14}C isotope effects in thermal decomposition of both α- and β-(^{14}C)-labeled (2-phenylethyl)dimethylamine oxide (**9**), together with linear free energy data, has been interpreted in terms of a transition state for elimination in which there is considerable cleavage of both the C(α)—N and C(β)—H bonds, significant carbanionic character on the β-carbon and little carbon–carbon double bond development.[10] However, the development of significant double bond character in the transition state was postulated to explain the exclusive formation of *cis*-cyclooctene from cyclooctyldimethylamine oxide.[7] This contrasts with the formation of mixtures of *cis*- and *trans*-cyclooctenes from fragmentation of the ylide generated from the quaternary ammonium salt (**10**) using strong base.[11]



(**9**)



(**10**)

The Cope elimination has been used less widely than the Hofmann elimination of quaternary ammonium hydroxides, but in some cases has advantages in terms of the ease of manipulation and lack of product isomerization, *e.g.* nonconjugated alkenes can be obtained without double bond migration, as in equation (2).[4]

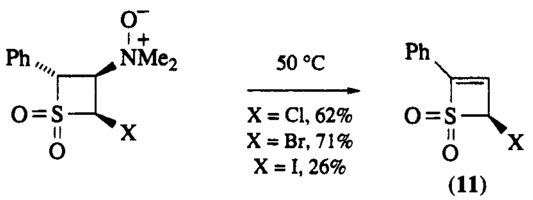
Tertiary amines can be converted into amine oxides using a variety of oxidizing agents, including aqueous hydrogen peroxide, peroxy acids and ozone. Often the amine oxides are not purified. Instead any excess of the oxidant is destroyed, and the amine oxide solution concentrated to leave a crude material, which is then pyrolyzed under reduced pressure with the alkene removed as it is formed.[4] Alternatively the elimination can be carried out in solution with significant rate enhancements being observed in DMSO.[6] This was originally explained in terms of increased basicity of the amine oxide in the dipolar aprotic solvent, but may be due to a change of mechanism as indicated above.[9]

5.3.2.2 Stereo- and Regio-chemistry

The Cope elimination has been used to synthesize a variety of acyclic alkenes. 1,2-Disubstituted acyclic alkenes are usually obtained with the (*E*)-stereochemistry because of steric hindrance to (*Z*)-alkene formation. The stereochemistry of trisubstituted alkenes is determined by the configuration of the starting amine oxide and is not usually affected by subsequent isomerization.[4]

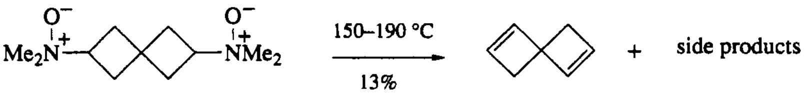
Cyclic alkenes synthesized by the Cope elimination include small ring cycloalkenes, *e.g.* cyclobutene[12] and the thiete 1,1-dioxide (**11**; equation 6).[13] However, the Cope elimination route to the spirodiene (**12**; equation 7) was less efficient than the analogous Hofmann procedure.[14] The stereochemistry of cyclic alkenes prepared by the Cope elimination depends upon the ring size with *cis*-cycloalkenes being obtained for eight-membered and smaller rings, and *trans*-cycloalkenes being obtained for larger rings.[15]

For acyclic compounds the regioselectivity depends upon statistical factors and the relative acidities of the different β-hydrogens, the elimination preferring to take place towards the most acidic hydrogen. This can also influence the regioselectivity of elimination from alicyclic compounds, *e.g.* the α,β-unsaturated carbonyl compound (**14**) was obtained from the β-aminocarbonyl compound (**13**),[16] and the allylic alcohol (**16**) was the major product obtained on oxidation and pyrolysis of the hydroxyamine (**15**).[17]



(11)

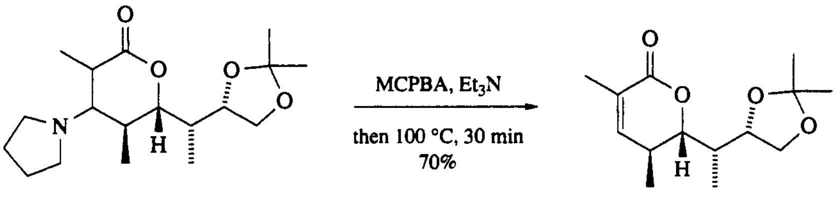
(6)



(12)

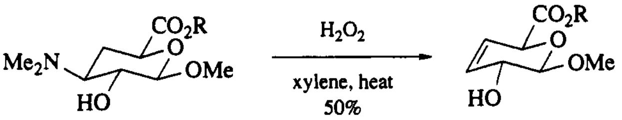
(7)

However, for alicyclic compounds the product composition can also be controlled by the necessity of achieving a cyclic transition state. Thus whereas the dimethylmenthylamine oxide (**17**) gave a mixture of 2- and 3-menthenes (**19**) and (**20**), only the 2-isomer (**19**) was obtained from neomenthylamine oxide (**18**).[18] High regioselectivities have also been obtained from some steroidal tertiary amine oxides.[19]



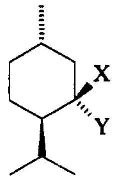
(13) (14)

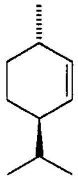
(8)

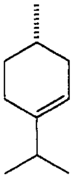


(15) (16)

(9)



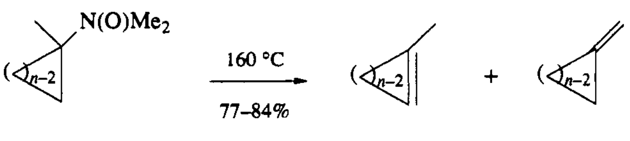




(17) X = H, Y = N(O)Me$_2$ (19) (20)

(18) X = N(O)Me$_2$, Y = H

The preference for endo- or exo-cyclic elimination depends on the ring size. The cyclopentyl- and cycloheptyl-dimethylamine oxides (**21**; *n* = 5, 7) give more of the endocyclic alkene (**22**; *n* = 5, 7) whereas the cyclohexylamine oxide (**21**; *n* = 6) gives predominantly the exocyclic alkene (**23**; *n* = 6) because the six-membered ring has to adopt an unfavorable boat conformation in the transition state for endocyclic elimination (equation 10).[20]



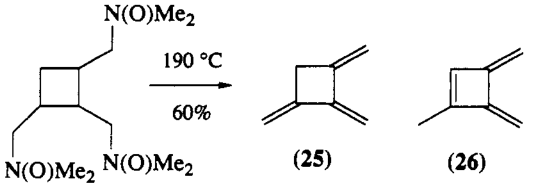
(21) (22) (23)

(10)

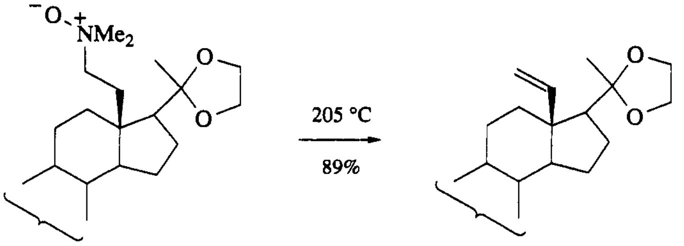
Table 1 Endo- *vs.* Exo-cyclic Elimination from Amine Oxide Pyrolysis

Amine oxide (**21**) *n*	*Endo* (**22**) (%)	*Exo* (**23**) (%)
5	97.5	2.5
6	2.8	97.2
7	84.8	15.2

Exocyclic alkenes can also be prepared using dimethylaminomethylcycloalkanes,[21] *e.g.* pyrolysis of the trisamine oxide (**24**) gave trimethylenecyclobutane (**25**; equation 11). In this case the analogous Hofmann elimination was accompanied by double bond migration and gave dimethylene-1-methylcyclobutene (**26**).[22] Terminal double bonds can also be introduced using Cope eliminations. An example is found in the synthesis of the vinyl steroid (**27**; equation 12).[23]

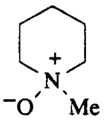


(24) **(25)** **(26)** (11)



(27) (12)

The success of ring-opening Cope eliminations of heterocyclic amine oxides depends upon the accessibility of the five-membered ring transition state. *N*-Methylpiperidine oxide (**28**) does not undergo ring opening even at 240 °C in a sealed tube, although the analogous seven- and eight-membered ring amines fragment at 165 °C. The α-methylamine oxide (**29**) fragments cleanly at 160–165 °C, whereas its epimer (**30**) gives no identifiable products on pyrolysis (equation 13).[24]



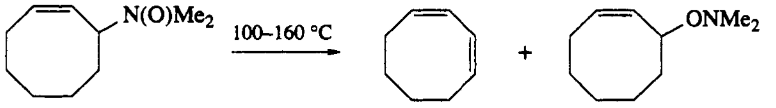
(28)

(**29**) R = Me, R' = H
(**30**) R = H, R' = Me

72% (38% after redistillation) (13)

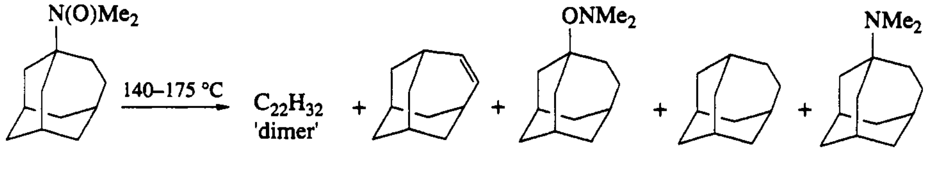
5.3.2.3 Side Reactions

The Cope elimination for alkyldimethylamine oxides is generally reliable providing the cyclic transition state can be attained. However, allylic and benzylic amine oxides undergo a competing rearrangement, the Meisenheimer rearrangement, which gives rise to *O*-substituted hydroxylamines as well as the desired alkene, *e.g.* thermolysis of the cyclooctenyldimethylamine oxide (**31**; equation 14) gives a mixture of *cis,cis*-cycloocta-1,3-diene (**32**) and the *O*-cyclooctenyl-*N*,*N*-dimethylhydroxylamine (**33**).[25] The Meisenheimer rearrangement of allylic amine oxides is believed to involve a concerted 2,3-shift,[26] whereas radical pair intermediates are involved in the rearrangement of benzylic amine oxides.[27]

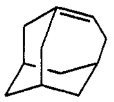


(**31**) (**32**) 50% (**33**) 19% (14)

The Meisenheimer rearrangement can compete with the formation of highly strained alkenes. The pyrolysis of the homoadamantylamine oxide (**34**; equation 15) gave a mixture of products, including hydrocarbons believed to have been formed by dimerization of 3-homoadamantene (**36**), which was trapped by 1,3-diphenylisobenzofuran, and the Meisenheimer product (**35**).[28]

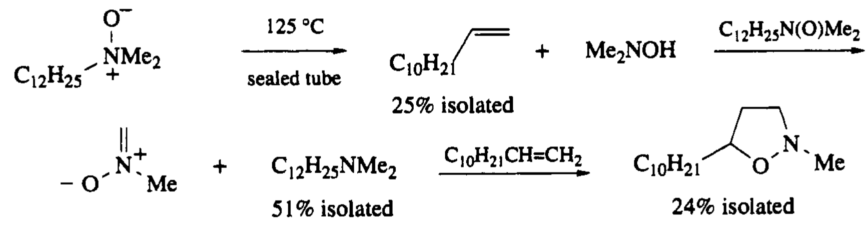


(**34**) 9% 5% (**35**) 25% 29% 12% (15)



(**36**)

Normally the Cope elimination is carried out by thermolysis of the amine oxide under reduced pressure with removal of the alkene as it is formed. However, if carried out in a closed system, secondary products can be formed by oxidation of the *N*,*N*-dialkylhydroxylamine by unchanged amine oxide to form a nitrone, which then adds to the alkene (Scheme 1).[29]

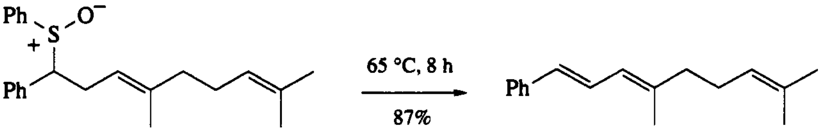


Scheme 1

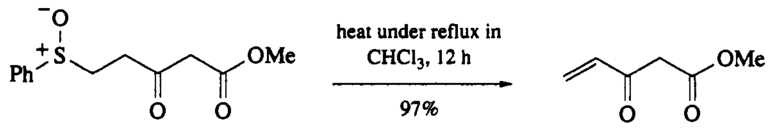
5.3.3 SULFOXIDE ELIMINATION

5.3.3.1 Introduction

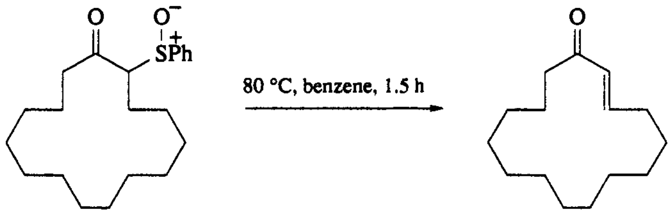
Sulfoxides fragment on heating to form alkenes and sulfenic acids. This reaction, known for over a century, has been developed into a useful alkene synthesis,[30,31] particularly for the synthesis of α,β-unsaturated carbonyl compounds as illustrated in equations (16)–(18).[32–35]



(16)

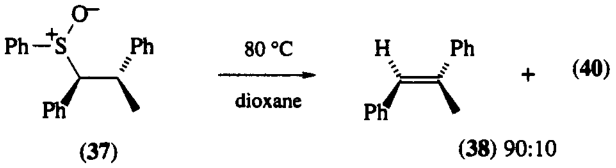


(17)

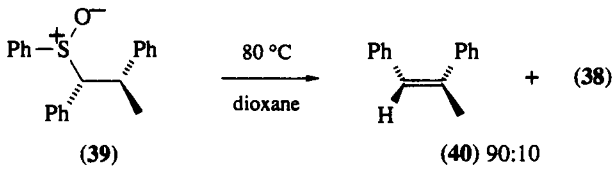


(18)

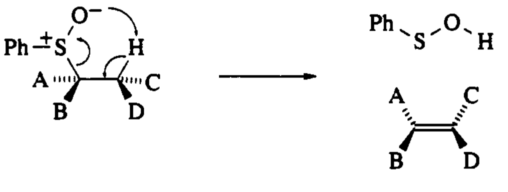
The stereochemistry of trisubstituted alkene formation was demonstrated by Kingsbury and Cram who found that the *erythro*-sulfoxide (**37**) gave mainly the (*E*)-alkene (**38**; equation 19) with the (*Z*)-alkene (**40**; equation 20) being the major product from thermolysis of the *threo*-sulfoxide (**39**). The rate and stereochemistry of elimination was found to be independent of solvent, and so the concerted *syn* elimination mechanism outlined in equation (21) was proposed.[36] The variation of the β-deuterium isotope effect with temperature is consistent with a linear hydrogen transfer,[8] and the elimination has been found to be reversible, with sulfenic acids being trapped both inter- and intra-molecularly by addition to alkenes to give sulfoxides (Schemes 2 and 3).[37,38]



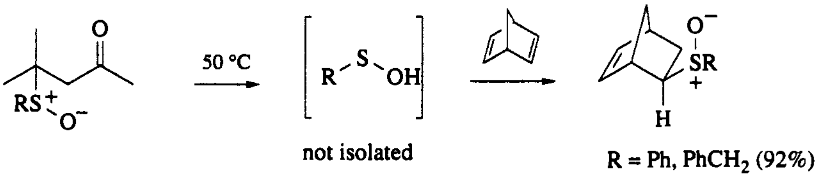
(19)



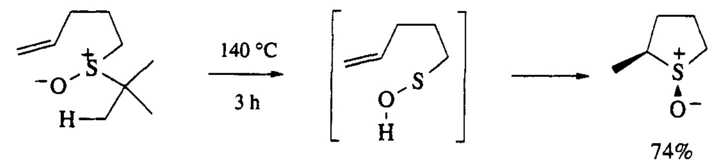
(20)



(21)



Scheme 2

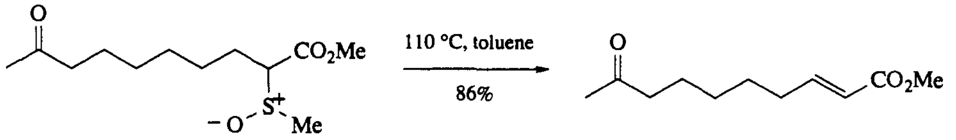


Scheme 3

The temperatures required for sulfoxide elimination depend upon the stability of the alkene being formed, with temperatures in the range 50–110 °C commonly used for conjugated alkenes. Phenyl sulfoxides fragment faster than the analogous methyl sulfoxides.[32] The reaction has also been used for the generation of sulfenic acids and this will be briefly discussed in Section 5.3.3.3.3.

5.3.3.2 Stereo- and Regio-chemistry

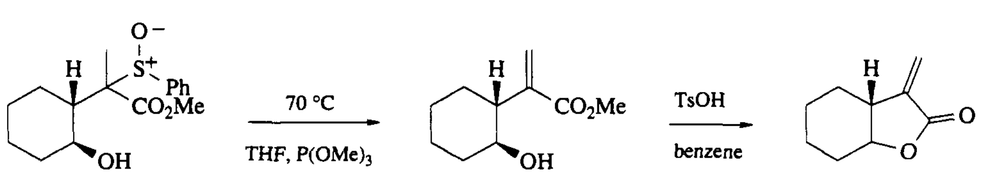
Acyclic 1,2-disubstituted alkenes from sulfoxide pyrolyses are obtained with the *trans* geometry because of increased torsional interaction in the transition state leading to the *cis* isomer (*e.g.* equation 22).[39] The stereochemistry of tri- and tetra-substituted alkenes is determined by the stereochemistry of the precursor sulfoxides and is predictable on the basis of the *syn* elimination mechanism. In practice the stereospecific synthesis of such alkenes is limited by the availability of isomerically pure starting materials.



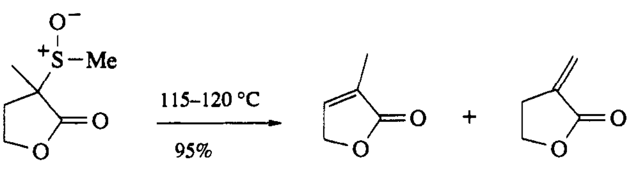
(22)

Sulfoxide fragmentation for acyclic sulfoxides takes place towards the most acidic β-hydrogen with the following order being observed in acyclic systems: $C{=}CCH_2 \approx C{\equiv}CCH_2 > ArCH_2 \approx CH_3 > CH_2 >> CH$.[32] For example, elimination of sulfoxide (**41**) takes place towards the more acidic methyl group to give the α-methylenelactone (**42**; Scheme 4) after cyclization.[40] In contrast, fragmentation of cyclic sulfoxides shows a preference for endocyclic elimination, *e.g.* thermolyses of the lactone sulfoxides (**43**)[39] and (**45**)[41] give more of the endocyclic alkenes (**44**; equation 23) and (**46**; equation 24), respectively, perhaps reflecting the increased stability of the endocyclic alkenes.

For sulfoxides with β-silyl substituents there is some preference for elimination to take place towards the silyl group. On protodesilylation both the allyl- and vinyl-silanes formed give the same alkene, so providing a regioselective and high yielding alkene synthesis (Scheme 5).[42] If there is no β-hydrogen,

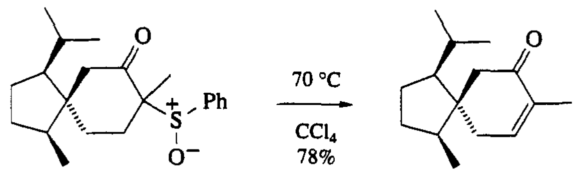


(**41**) Scheme 4 (**42**)



(23)

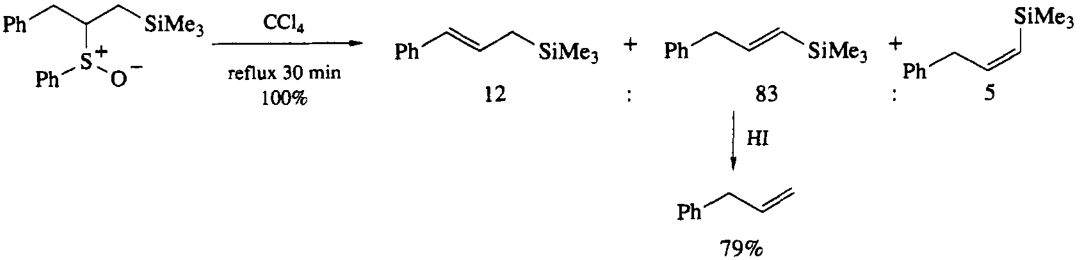
(**43**) (**44**) 87:13



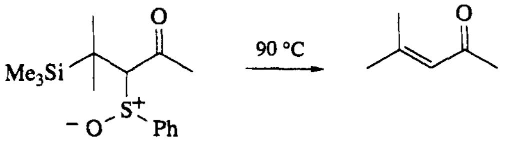
(45) **(46)**

(24)

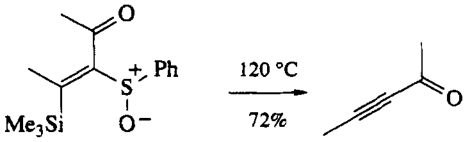
β-silyl sulfoxides undergo a *syn* elimination of the silylsulfenate (equation 25), which can also be used for the synthesis of alkynes providing the silyl and sulfoxide substituents are *cis* disposed (equation 26).[43]



Scheme 5

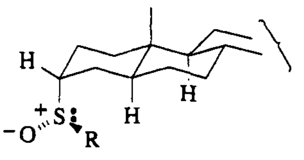


(25)



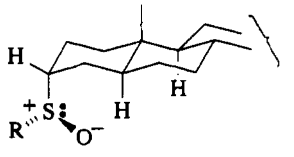
(26)

Most of the sulfoxides discussed above were generated by oxidation of the corresponding sulfide. This would have given mixtures of diastereoisomers due to the chirality of the sulfoxide group, but the isomers were not separated. However, the influence of the configuration at sulfur on the regioselectivity of sulfoxide elimination has been examined for a series of steroidal sulfoxides.[44] For 3α-alkylsulfinyl-5α-cholestanes the regioselectivity depends upon the configuration at sulfur and the bulk of the alkyl group. Thermolysis of the (*S*)-sulfoxide (**47**) gave a mixture of the 2- and 3-cholestenes (**51**) and (**52**), ratio 70:30, respectively, whereas the (*R*)-sulfoxide (**49**) gave more of the 3-cholestene (**52**); ratio (**51**):(**52**) = 30:70 in this case.[44] When the 3-(1-adamantyl)sulfinylcholestanes (**48**) and (**50**) were pyrolyzed at 110 °C the eliminations were completely regioselective, the (*S*)-isomer (**48**) giving only the 2-cholestene (**51**), and the (*R*)-isomer giving only the 3-cholestene (**52**).[45] These regioselectivities were explained in terms of steric interactions in the transition states for elimination. For the (*S*)-isomers (**47**) and (**48**) the conformation (**53**) leading to the 2-cholestene is less hindered than conformation (**54**). From these results it would appear that the sulfoxide configuration can influence the regioselectivity of elimination, at least in sterically hindered systems where the acidities of the β-hydrogens are similar.



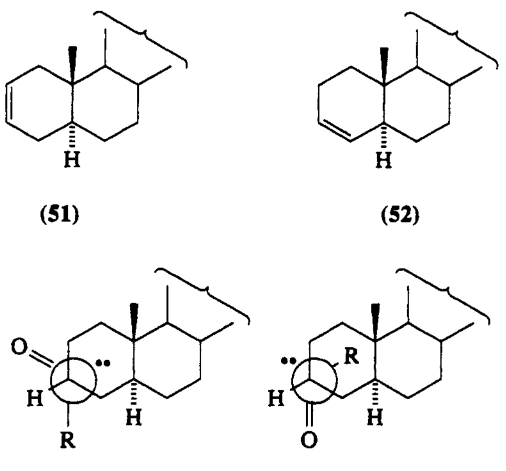
(**47**) R = Bu^t

(**48**) R = 1-adamantyl



(**49**) R = Bu^t

(**50**) R = 1-adamantyl

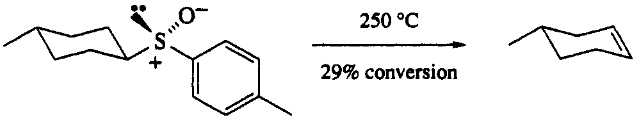


(51) **(52)**

(53) **(54)**

Figure 1

The use of optically active sulfoxides for the synthesis of optically active alkenes has been reported,[46] *e.g.* the (*S*)-sulfoxide (**55**) gave the (*S*)-alkene (**56**) on heating at 250 °C (equation 27). However, the observed enantiomeric excesses were only modest and the reactions were only carried out to low conversions.



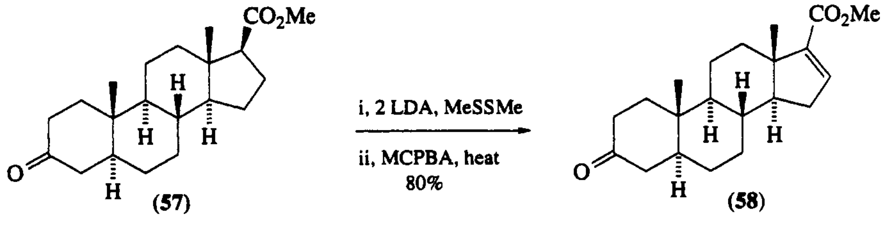
(27)

(55) **(56)** 47% *ee*

5.3.3.3 Applications of Sulfoxide Elimination in Synthesis

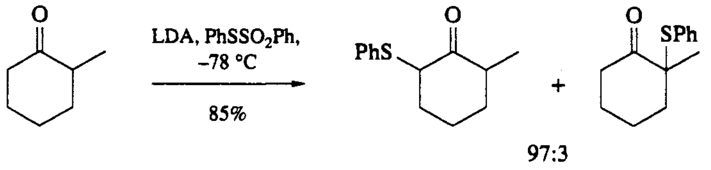
5.3.3.3.1 Alkene synthesis

α-Sulfinyl carbonyl compounds fragment on thermolysis under mild conditions to give α,β-unsaturated carbonyl compounds.[30-32] The preparation of these compounds by α-sulfenylation of esters and ketones followed by oxidation has been developed by Trost and coworkers.[47] Treatment of an ester or ketone with a strong base, often LDA, followed by quenching the enolate anion with dimethyl or diphenyl disulfide, provides the α-sulfenylated carbonyl compound, which can be oxidized by a suitable oxidant, *e.g.* MCPBA or $NaIO_4$. Ketone enolates tend to be less reactive than ester enolates towards disulfides, the more reactive diphenyl disulfide being the preferred reagent for such cases. Indeed, the dilithiated keto ester (**57**) can be sulfenylated regioselectively α to the ester using dimethyl disulfide to give the α,β-unsaturated ester (**58**; equation 28) after oxidative elimination.[39] Unsymmetric ketones can be sulfenylated regioselectively using diphenyl disulfide, but the more reactive phenylbenzenethiosulfonate gives improved regioselectivity (*e.g.* equation 29).[32,47] The phenylsulfenylation and oxidative elimination of β-dicarbonyl compounds has also been used for the synthesis of 1,1-dicarbonyl-substituted alkenes, *e.g.* butenolides (**59**) and (**60**; R = Me, Pr^i, Bu^t).[48]

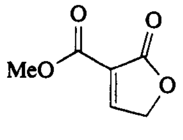


(28)

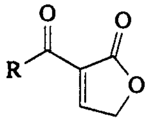
(57) **(58)**



(29)



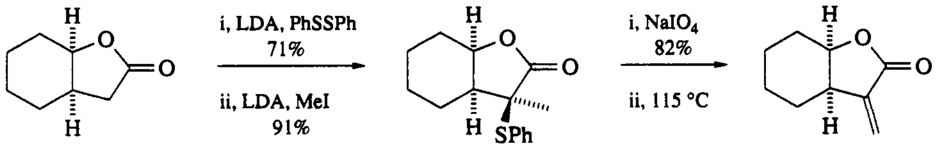
(59)



(60)

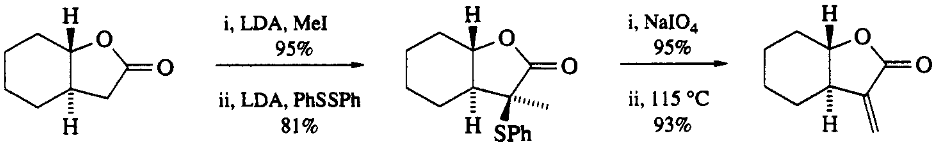
The intermediate α-sulfenyl carbonyl compounds may be alkylated prior to oxidative elimination. Phenylsulfenylation of the *cis*-fused butyrolactone (**61**), followed by methylation and oxidative elimination, gave the α-methylenebutyrolactone (**62**) because endocyclic elimination is sterically inhibited (Scheme 6). For the *trans*-fused butyrolactone (**63**), the alkylation was carried out first to ensure exocyclic elimination (Scheme 7).[49] The intermediate α-sulfinylcarbonyl compounds may also be modified before elimination, the alkylation of keto sulfoxides (**64**) providing a useful synthesis of α,β-unsaturated γ-keto esters (**65**; Scheme 8).[50–52] In some cases the use of an excess of strong base provides a dimetallated species which can be alkylated at the more reactive site before elimination, *e.g.* an approach to α′-alkylated vinyl ketones (Scheme 9).[53]

An alternative synthesis of α-methylene ketones and esters is provided by enolate alkylation using benzyl bromomethyl sulfide followed by oxidative elimination (Scheme 10).[54] The addition of sodium thiophenoxide to α-methylenebutyrolactones has been recommended for protection of the sensitive double bond, which can be regenerated by oxidative elimination.[55]



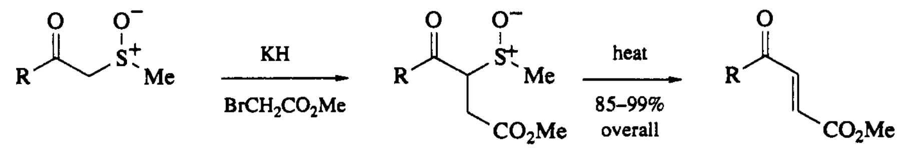
(61) **(62)**

Scheme 6



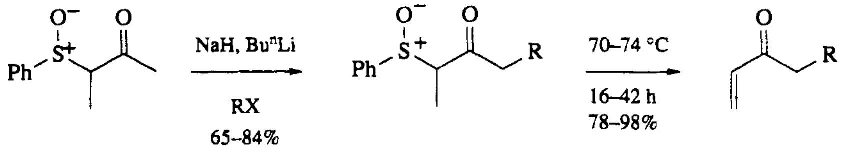
(63)

Scheme 7



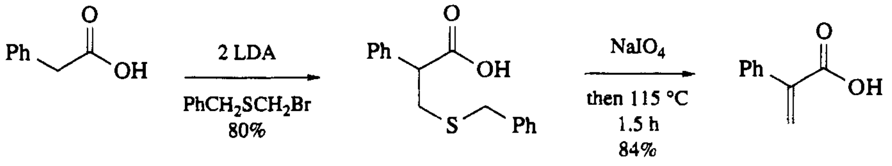
(64) **(65)**

Scheme 8

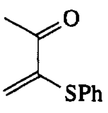


Scheme 9

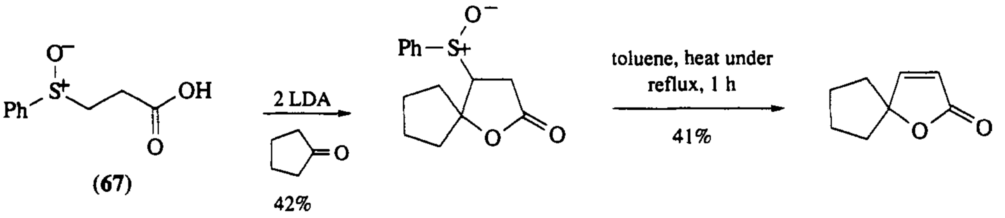
α-Phenylsulfenylvinyl ketones, *e.g.* (**66**), are good Michael acceptors.[56] The intramolecular alkylation of sulfides has provided a route to large-ring compounds,[57] and aldol condensations of the β-phenylsulfinylcarboxylic acid have been used to prepare 5-substituted butenolides (Scheme 11).[58] α,β-Unsaturated lactones have also been prepared by intramolecular acylation of sulfoxides.[59]



Scheme 10



(**66**)

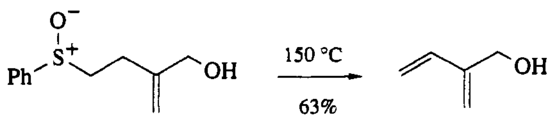


(**67**)

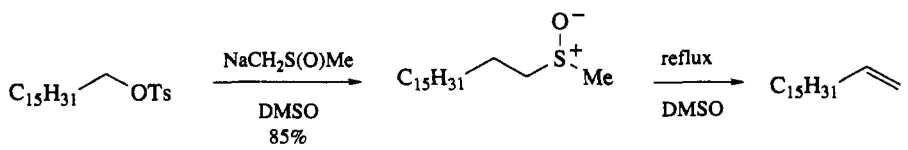
Scheme 11

From these examples it can be seen that sulfoxide pyrolysis has been widely used for the synthesis of α,β-unsaturated carbonyl compounds. Sulfoxide pyrolysis has also been used for the synthesis of other types of alkene although the temperatures required are usually higher, *e.g.* equation (30).[33,60,61] The alkylation of dimsyl sodium followed by pyrolysis has been used as an alternative to the Wittig reaction for the synthesis of terminal alkenes (Scheme 12),[62] and Michael addition to phenyl vinyl sulfoxide followed by pyrolysis was used in a novel approach to α-vinylcarbonyl compounds in which the vinyl sulfoxide is being used as the synthetic equivalent of the vinyl cation (Scheme 13).[63] For β-hydroxy sulfoxides the elimination takes place away from the hydroxy group to give allylic alcohols, but higher temperatures are required than for elimination from the corresponding hydroxy selenoxides, which are readily available by epoxide opening and which also give allylic alcohols (Section 5.3.4.2.2).[64] Ketones are formed if the elimination can only take place towards the hydroxy substituent (equation 31)[65] and vinyl chlorides can be obtained from α-chloro sulfoxides.[66]

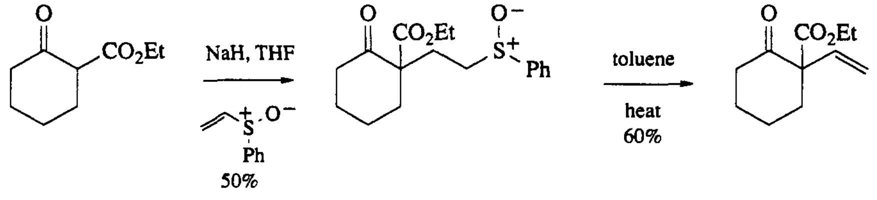
Allylic sulfoxides are known to equilibrate with their isomeric sulfenates *via* a 2,3-sigmatropic shift, which has been developed into a useful allylic alcohol synthesis when the unstable sulfenate is trapped (Scheme 14).[67] However, this rearrangement is reversible and so need not necessarily interfere with pyrolytic elimination of the sulfoxide, *e.g.* the long-chain hydroxydiene (**69**) was obtained on pyrolysis of the sulfoxide (**68**; equation 32).[68] A study of substitution effects on the relative rates of rearrangement



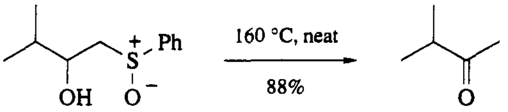
(30)



Scheme 12

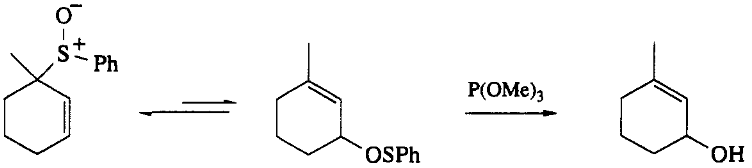


Scheme 13

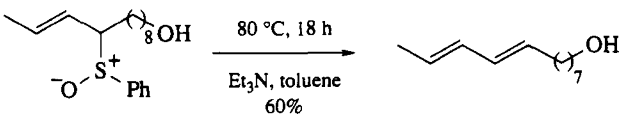


(31)

and elimination of alkyl aryl sulfoxides has shown that the elimination is favoured by electron-withdrawing substituents in the aryl ring.[69] Analogous 1,4-eliminations have also been studied.[70]



Scheme 14



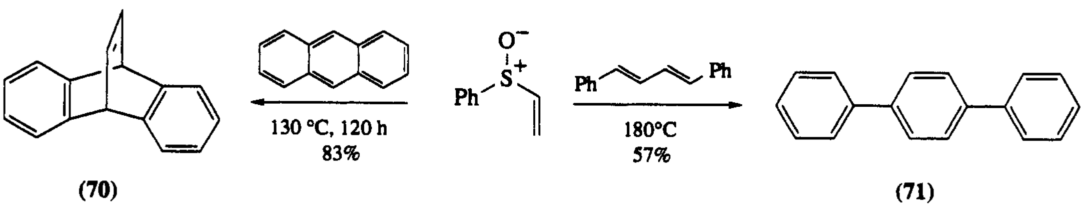
(68) **(69)** (32)

5.3.3.3.2 *Vinyl sulfoxides as dienophiles*

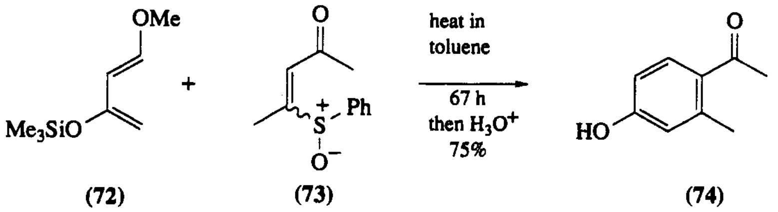
Vinyl sulfoxides are useful Diels–Alder dienophiles. Thermolysis of the adducts gives rise to alkenes *via* sulfoxide elimination and so over the two steps the vinyl sulfoxides are the synthetic equivalents of alkynes, *e.g.* phenyl vinyl sulfoxide reacts with anthracene and 1,4-diphenylbuta-1,3-diene with concomitant sulfoxide elimination under the Diels–Alder conditions to give adducts (**70**) and (**71**; Scheme 15).[71] β-Phenylsulfinyl-α,β-unsaturated-carbonyl compounds have also been used as Diels–Alder dienophiles in chemistry developed for a synthesis of disodium prephenate and epiprephenate.[72,73] With the electron rich diene (**72**), vinyl sulfoxides (**73**) and (**75**) gave rise to products (**74**; equation 33) and (**76**; equation 34) after hydrolysis.[72] For the prephenate synthesis the phenylsulfinylmethylenelactone (**77**) was used, giving cyclohexadienone (**78**; Scheme 16) after sulfoxide elimination and hydrolysis.[73]

5.3.3.3.3 *Sulfoxide elimination for sulfenic acid generation*

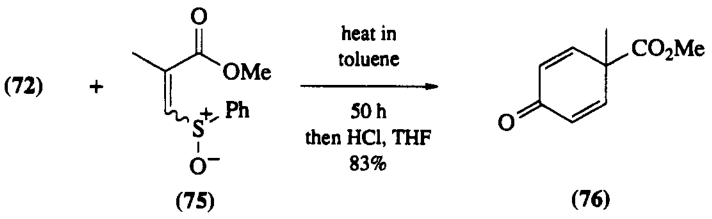
So far in this chapter sulfoxide pyrolysis has been discussed in connection with alkene synthesis. However, the other products of these reactions, the sulfenic acids, are also of interest, and have been generated for study by several methods including sulfoxide pyrolysis. Thermolysis of di-*t*-butyl sulfoxide (**79**;



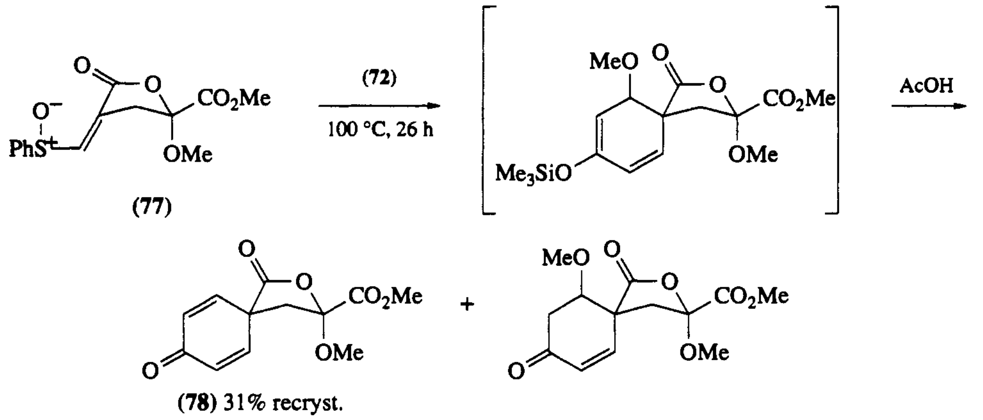
Scheme 15



(33)



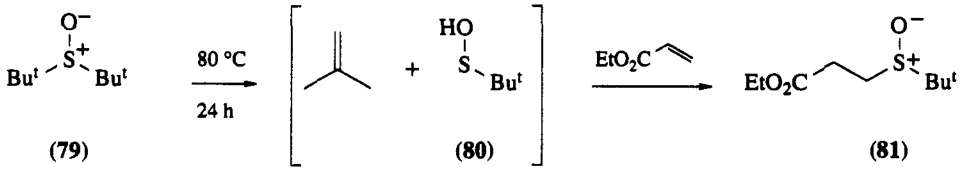
(34)



Scheme 16

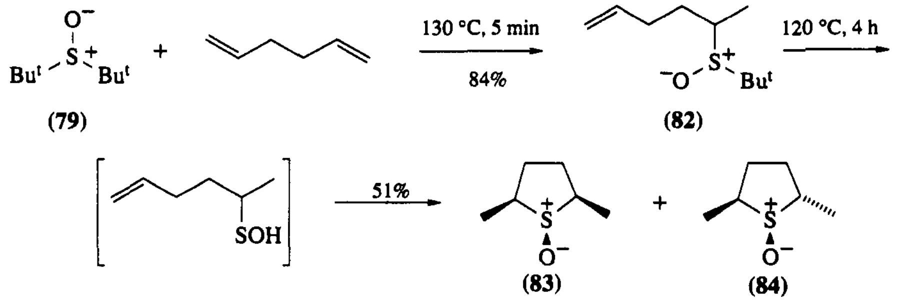
Scheme 17) at 80 °C generates 2-methylpropanesulfenic acid (**80**), which was trapped by ethyl acrylate to give the sulfoxide (**81**), formation of sulfoxide (**81**) corresponding to the reverse of sulfoxide elimination.[74] 2-Methylpropanesulfenic acid (**80**), generated by elimination from di-*t*-butyl sulfoxide, has also been trapped by addition to dienes to give (*t*-butylsulfinyl)alkenes; these eliminate 2-methylpropene to release the alkenesulfenic acids, which then cyclize. For example, di-*t*-butyl sulfoxide (**79**; Scheme 18) and hexa-1,5-diene gave the alkenyl sulfoxide (**82**) after heating at 130 °C for 5 min. Further heating of this sulfoxide eliminated 2-methylpropene and released the alkenesulfenic acid, which cyclized to give the *cis*- and *trans*-dimethylthiolane 1-oxides (**83**) and (**84**).[38,75] This intramolecular addition of sulfenic acids to alkenes has been used for the synthesis of thietanoprostanoids (Scheme 19).[76]

Sulfenic acids also react with alkynes,[74] and (*t*-butylsulfinyl)alkynes (**85**) eliminate 2-methylpropene on thermolysis to give the (*E*)-alkenyl sulfoxides (**87**) stereoselectively *via* cyclization of the intermediate sulfenic acids (**86**; Scheme 20).[77] The stereochemistry of the adduct (**87**) is established by the mechanism of sulfenic acid addition. For the intermolecular trapping of sulfenic acids by alkynes, generation of the sulfenic acids by thermolysis of the corresponding β-sulfinylpropionitrile (**88**; equation 35) is the preferred route.[77] Sterically hindered sulfenic acids have also been generated by flash vacuum pyrolysis of sulfoxides and trapped intermolecularly by alkynes.[78]



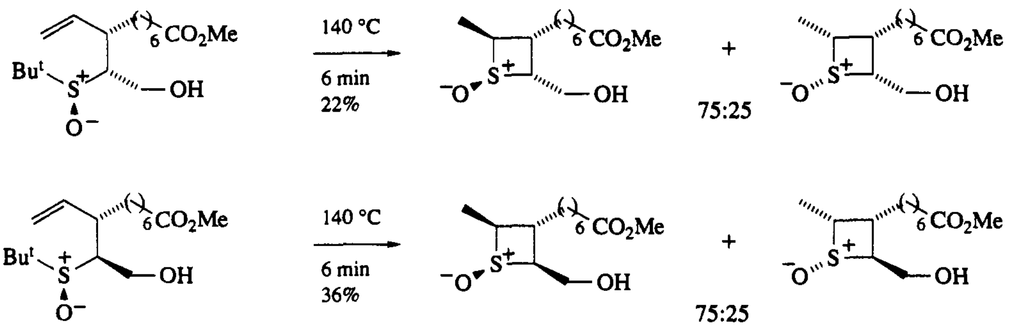
(79) (80) (81)

Scheme 17

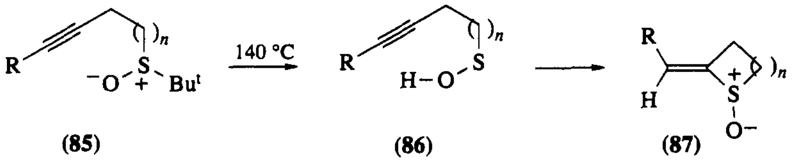


(79) (82) (83) (84)

Scheme 18

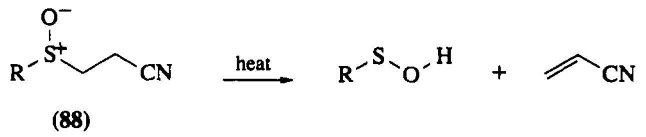


Scheme 19



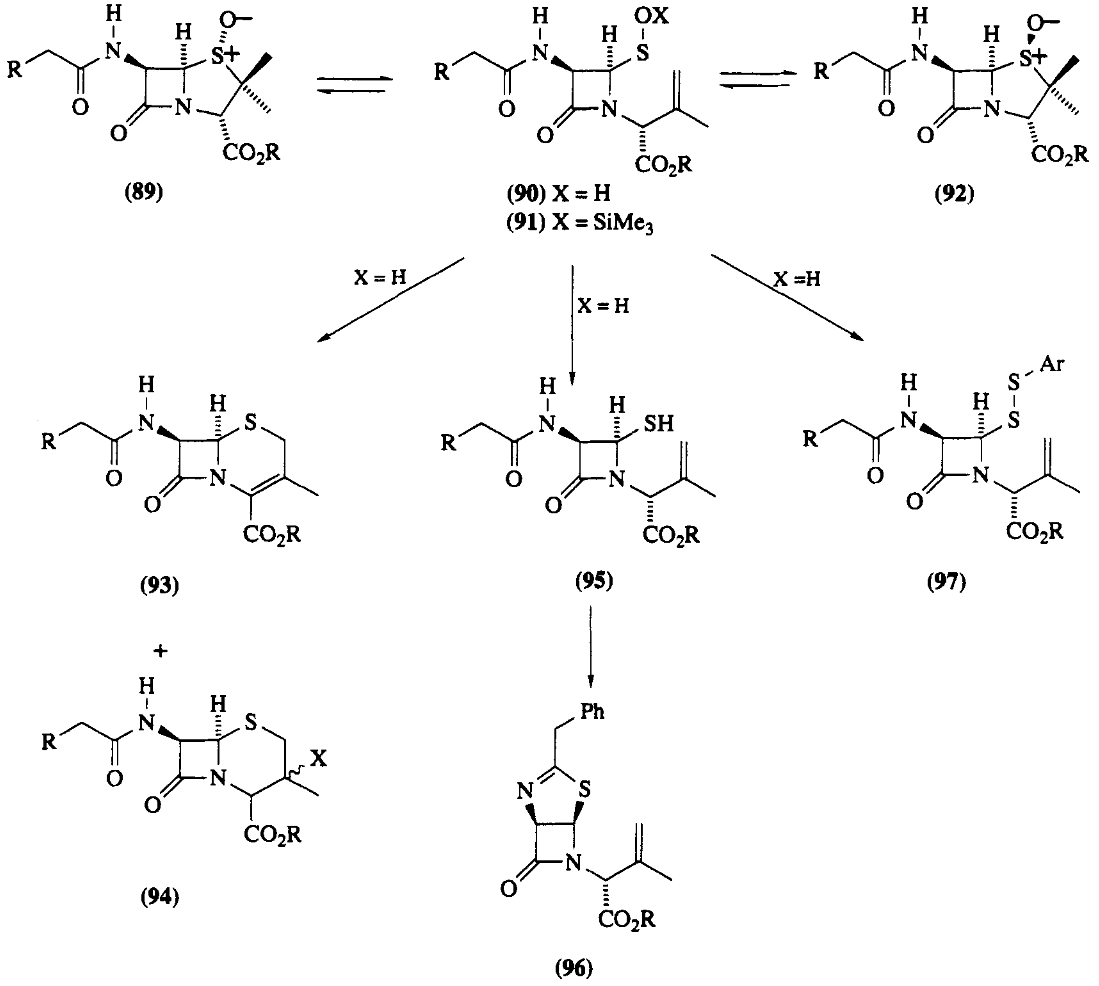
(85) (86) (87)

Scheme 20



(88) (35)

Unsaturated sulfenic acids have been generated by thermolysis of cyclic sulfoxides.[79] This has proved to be particularly important for the conversion of penicillins into cephalosporins, and the chemistry of penicillin sulfoxides has been widely studied in this respect.[80] Thus thermolysis of penicillin sulfoxides (**89**) and (**92**) generates the corresponding sulfenic acid (**90**; Scheme 21), which in the presence of acid catalysts undergoes electrophilic intramolecular alkene addition to give mixtures of cephems (**93**) and cephams (**94**) with the ratio of products being dependent upon the reaction conditions used. The intermediate sulfenic acids (**90**) have also been trapped as their silyl ethers (**91**), from which the parent sulfenic acids can be regenerated, reduced to thiols (**95**), which cyclize to form thiazolines (**96**), and used to prepare mixed disulfides (**97**). This elegant chemistry has been thoroughly reviewed,[80] and may find applications in other areas of organic synthesis.



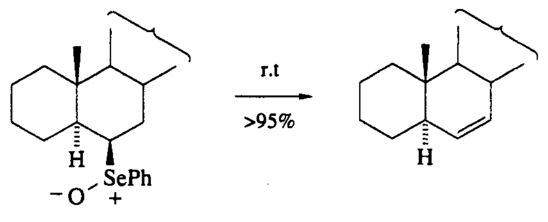
Scheme 21

5.3.4 SELENOXIDE ELIMINATION

5.3.4.1 Introduction: Stereo- and Regio-chemistry

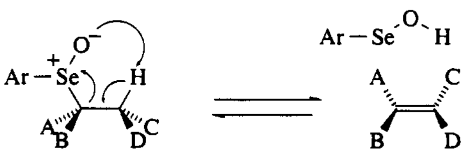
The instability of alkyl selenoxides had been known for many years but it was not until the early 1970s that the *syn* elimination of selenoxides was recognized and developed into a useful synthesis of alkenes.[81] In 1970, the two 5β-cholestane selenoxides (**98**; equation 36), epimeric at selenium, were separated, and shown to fragment readily, albeit at different rates, to give cholest-6-ene (**99**) regioselectively.[82] The *syn* elimination mechanism outlined in equation (37) was proposed to account for the regioselectivity of these eliminations. The more labile epimer was assigned the (*S*)-configuration at selenium by analogy with the corresponding sulfoxide since it would be expected to encounter less steric hindrance than the other isomer in the conformation required for fragmentation.[82] The *syn* stereochemistry of selenoxide elimination has since been confirmed (Scheme 22).[83]

Selenoxide elimination is now widely used for the synthesis of α,β-unsaturated carbonyl compounds,[84] allyl alcohols[85–87] and terminal alkenes[88] since it proceeds under milder conditions than those required for sulfoxide or any of the other eliminations discussed in this chapter. The selenoxides are usually generated by oxidation of the parent selenide using hydrogen peroxide, sodium periodide, a peroxy acid or ozone, and are not usually isolated, the selenoxide fragmenting *in situ*. The other product of the elimination, the selenenic acid, needs to be removed from the reaction mixture as efficiently as possible. It can disproportionate with any remaining selenoxide to form the corresponding selenide and seleninic acid, or undergo electrophilic addition to the alkene to form a β-hydroxy selenide, as shown in

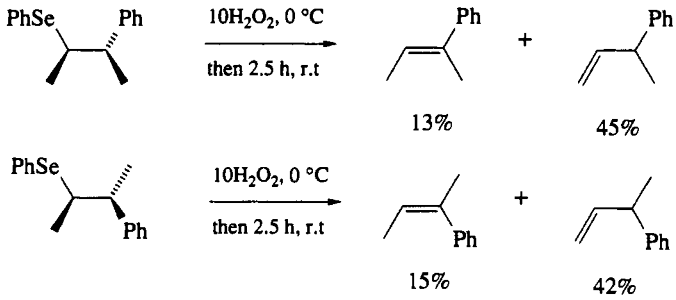


(98) **(99)**

(36)

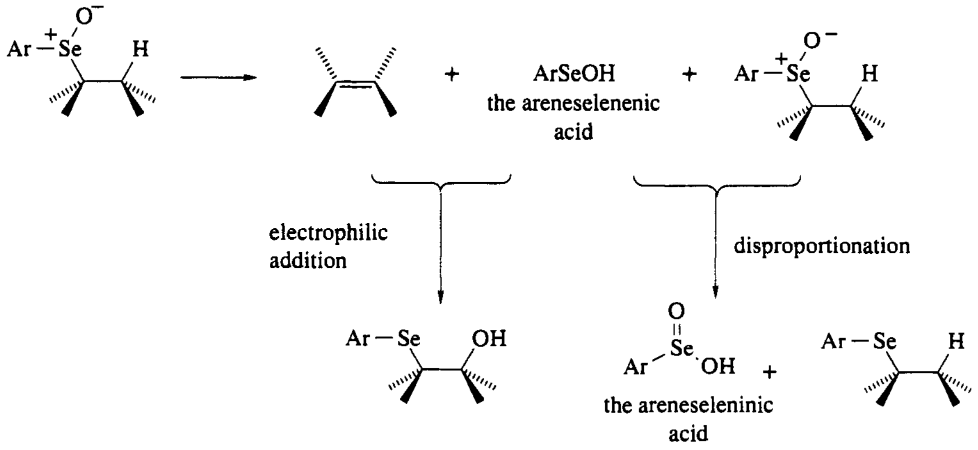


(37)



Scheme 22

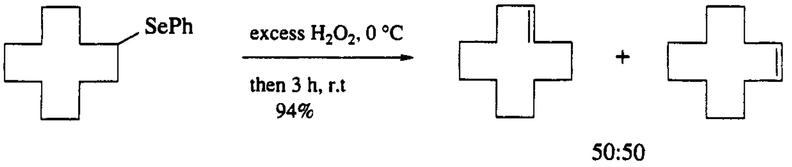
Scheme 23.[87–90] To avoid these side reactions an excess of oxidant is frequently used to oxidize the selenenic acid as quickly as it is formed to the corresponding seleninic acid. Alternatively an amine can be added to convert the selenenic acid into the selenenamide.[81]



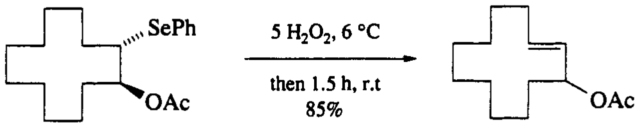
Scheme 23

As with amine oxides and sulfoxides, acyclic 1,2-disubstituted alkenes are usually obtained with the (*E*)-stereochemistry, although the formation of α,β-unsaturated nitriles is reported to give a mixture of (*E*)- and (*Z*)-isomers.[91] For cyclic alkenes, the stereochemistry of double bond formation depends upon ring size. However, it can be affected by conformational factors, *e.g.* cyclododecyl phenyl selenide gives a mixture of *cis*- and *trans*-cyclododecenes on oxidative elimination (equation 38)[83] but only the (*E*)-isomer (**101**) was obtained from the acetoxycyclododecyl selenide (**100**; equation 39).[92]

The regioselectivity of selenoxide elimination is similar to that observed for sulfoxides in that it takes place preferentially towards allylic, propargylic and benzylic hydrogens to form conjugated alkenes with $CH_3 > CH_2 \gg CH$, *e.g.* the conjugated diene (**103**) was obtained from selenoxide (**102**; equation 40).[93]



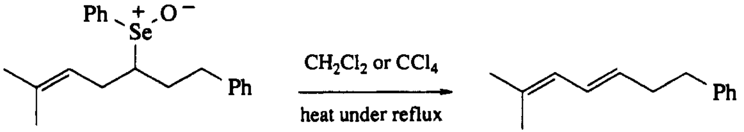
(38)



(100) **(101)**

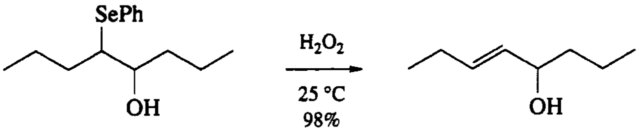
(39)

However, the regioselectivity is also affected by statistical factors and if these two effects are in opposition, then the regioselectivity may not be very great, *e.g.* Scheme 22.[83] However, one extremely useful aspect of the regioselectivity of selenoxide elimination is the marked preference for elimination to take place away from an electronegative atom. β-Oxygen substituents in particular are very effective at directing the elimination away from themselves, as indicated in equations (41) and (42), and this forms the basis of a very useful allylic alcohol synthesis (Section 5.3.4.2.2).[85,94]

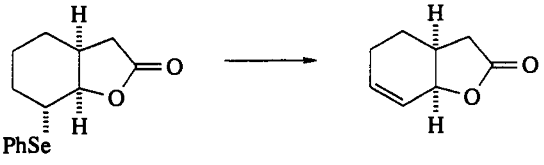


(102) **(103)**

(40)

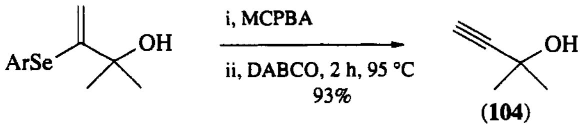


(41)



(42)

Unlike sulfoxide elimination, selenoxide elimination can be used to prepare alkynes, providing the *syn* elimination process is sterically feasible, and has been used for the preparation of terminal alkynes (*e.g.* **104**; equation 43).[95,96]



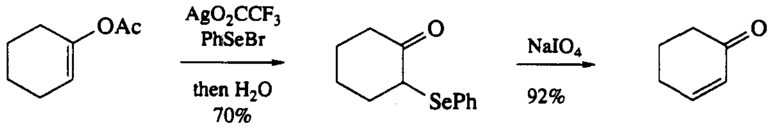
(104)

(43)

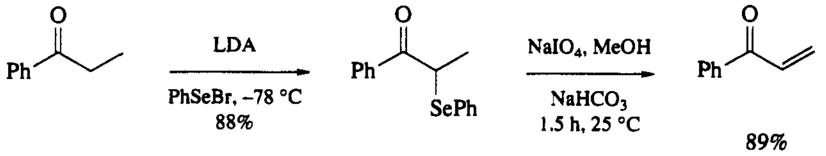
5.3.4.2 Applications of Selenoxide Elimination

5.3.4.2.1 Synthesis of α,β-unsaturated carbonyl compounds

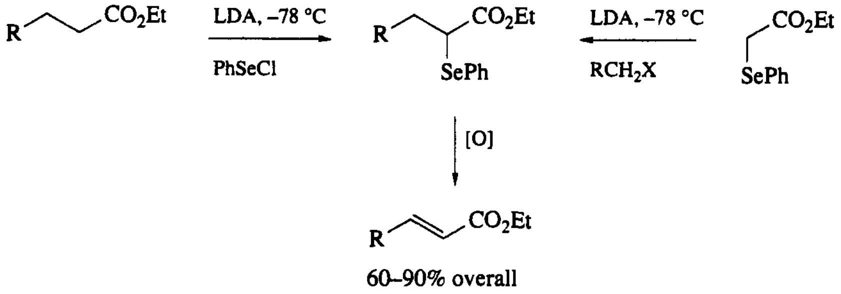
Several procedures have been developed for the preparation of α-arylselenocarbonyl compounds including phenylselenenylation of enol acetates,[97] enol ethers[98] and lithium and copper enolates.[99,100] Oxidative elimination then provides the α,β-unsaturated carbonyl compound (Schemes 24–26). Alternatively the α-phenylseleno compound can be alkylated prior to oxidative elimination (Scheme 26).[101]



Scheme 24

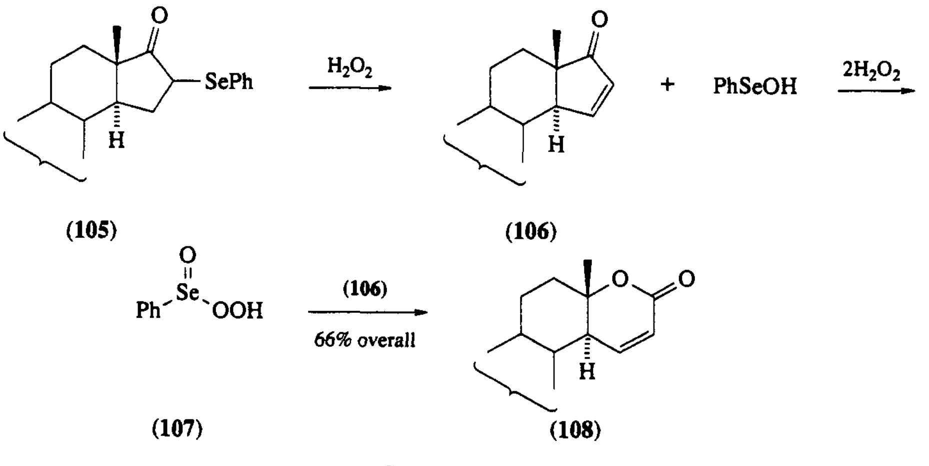


Scheme 25



Scheme 26

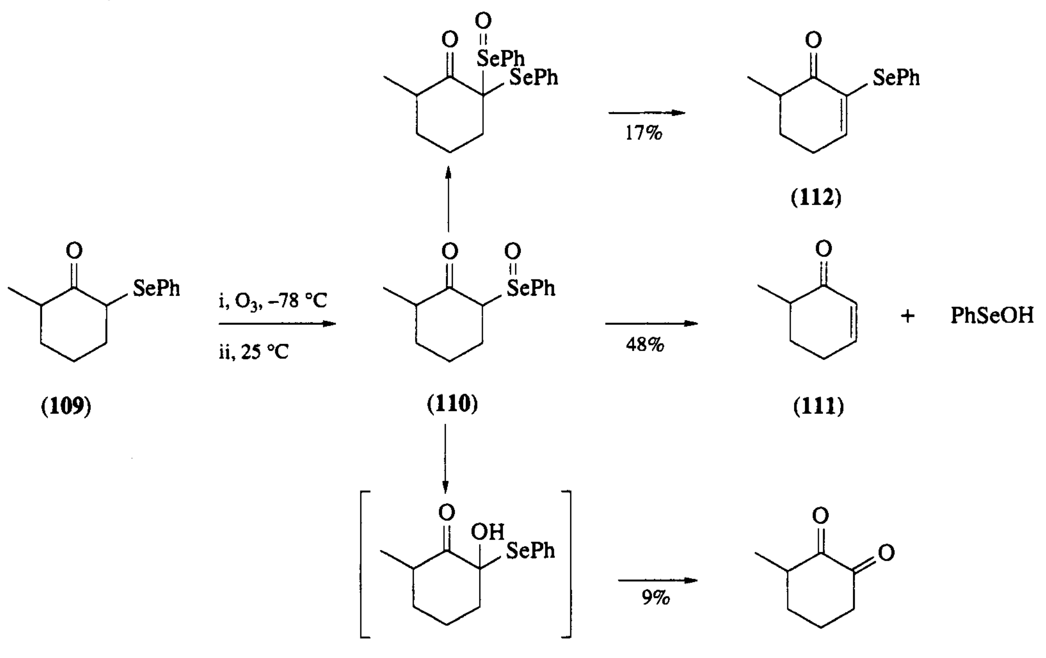
Although the selenoxide elimination when forming an α,β-unsaturated carbonyl compound is generally fast and efficient, the choice of conditions can be important if side reactions are to be avoided, especially if there is steric hindrance to the formation of the *syn* elimination transition state.[81,82] For example, an excess of oxidant is frequently used to remove the areneselenenic acid as it is formed in order to prevent the side reactions outlined in Scheme 23. However, in some cases the excess of oxidant can cause further oxidation. When the steroidal phenylseleno ketone (**105**) was oxidized using an excess of hydrogen peroxide, the major product was the unsaturated lactone (**108**). It appeared that the benzeneselenenic acid released during the elimination to form the unsaturated ketone (**106**) was being oxidized to benzene peroxyseleninic acid (**107**), which then effected a Baeyer–Villiger oxidation of the ketone (Scheme 27).[102,103] Moreover, Pummerer and other side reactions can interfere with the efficient oxidative elimination of α-phenylseleno ketones if the *syn* elimination is slow, because of the increased acidity



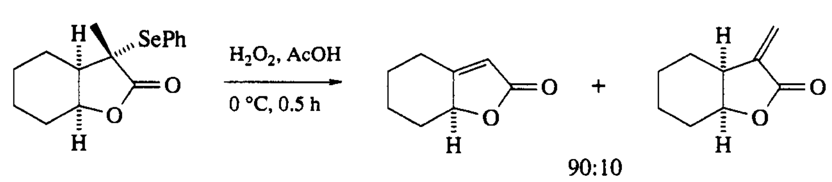
Scheme 27

of the α-hydrogen due to stabilization of the corresponding enolate anion by both the carbonyl and selenoxide groups. Oxidation of 6-methyl-2-phenylselenocyclohexanone (**109**) gave 6-methylcyclohex-2-enone (**111**), together with the phenylselenocyclohexenone (**112**) and diketone (**113**) formed by phenylselenenylation and Pummerer rearrangement of the intermediate selenoxide (**110**), respectively, as outlined in Scheme 28.[84,100] Low yields of enone were also obtained from 2-phenylselenocyclo-heptanone and -octanone due to competing Pummerer rearrangements.[100] The addition of a secondary amine to keep the reaction mixture basic has been recommended to prevent the Pummerer reaction, which is catalyzed by acids. Alternatively the ketone can be protected as a ketal prior to the oxidative elimination since this reduces the acidity of the α-hydrogens.[84] Recently better yields of the desired oxidative elimination product were obtained using 2-pyridinylseleno ketones.[104] However, notwithstanding these side reactions, the oxidative elimination of α-phenylselenocarbonyl compounds has been widely used in synthesis and generally gives very good results.[81]

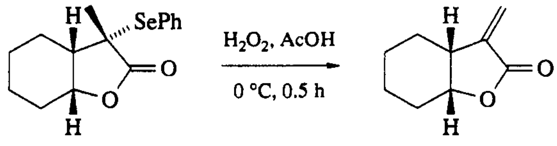
With α-phenylselenolactones, endocyclic elimination is preferred if the *syn* elimination is possible (equation 44), perhaps because the conformation leading to the exocyclic product involves greater dipole–dipole interaction between the selenoxide and the carbonyl group. However, α-methylenelactones are obtained if *syn* elimination cannot be achieved (equation 45).[105] The conjugate addition of sodium phenylselenide has been recommended for the protection of α-methylenelactones, the double bond being reintroduced by selenoxide elimination.[106]



Scheme 28

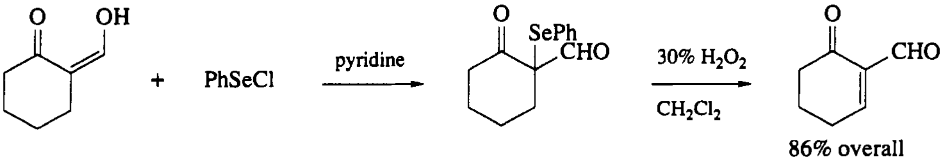


(44)

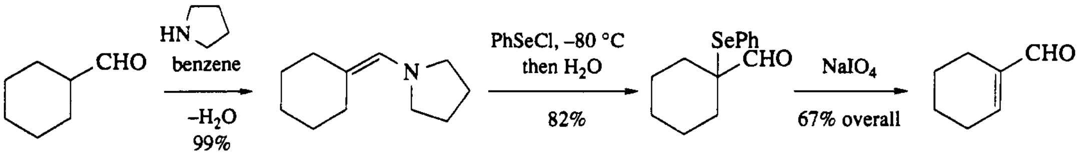


(45)

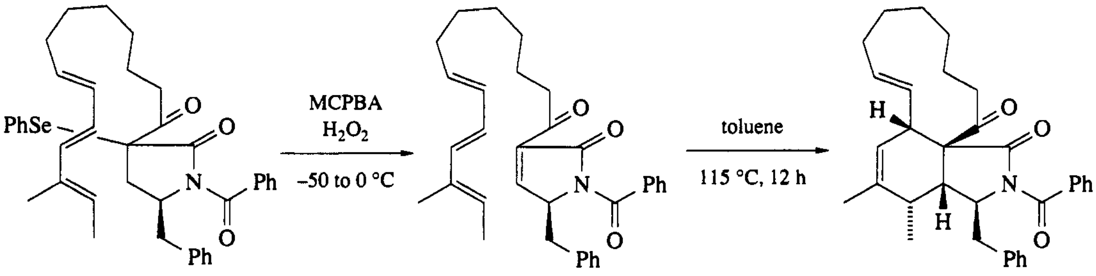
Procedures have been developed for the phenylselenenylation and oxidative elimination of β-formyl ketones[107] and aldehydes[108] to form the corresponding α,β-unsaturated aldehydes (Schemes 29 and 30). Other β-dicarbonyl compounds have also been oxidized to the corresponding α,β-unsaturated compounds by phenylselenenylation and oxidative elimination including 3-(1-oxotrienyl)pyrrolidinones, which give the corresponding pyrrol-2(5*H*)-one (*e.g.* **114**; Scheme 31). In this case the oxidative elimination was carried out using 1 mol equiv. of MCPBA at –50 °C, which selectively oxidized the selenide in the presence of the sensitive conjugated triene, with an excess of hydrogen peroxide present to trap the benzeneselenenic acid. The 3-(1-oxotrienyl)pyrrol-2(5*H*)-ones were unstable, undergoing intramolecular Diels–Alder cyclization, providing a route to the cytochalasans.[109]



Scheme 29



Scheme 30



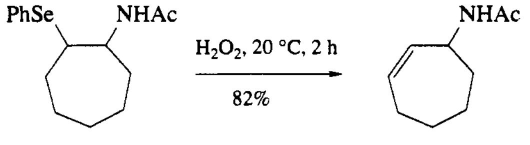
(114)

40% overall

Scheme 31

5.3.4.2.2 Synthesis of allylic alcohols, amines and derivatives

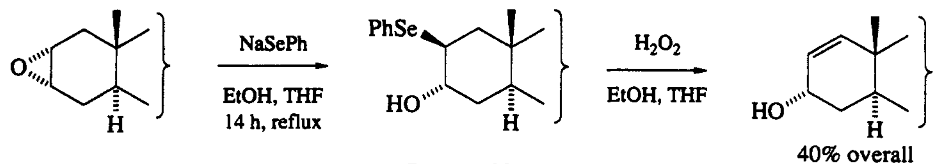
The selenoxide elimination of β-hydroxy selenoxides, which takes place regioselectively away from the hydroxy group, *e.g.* as in equation (41), has been developed into a useful synthesis of allylic alcohols.[81] Similar regioselective elimination is also observed for β-acyloxy selenoxides, as shown in equations (39) and (42), and for β-acylamino selenoxides (*e.g.* **115**; equation 46).[110] However, the regioselectivity of elimination is less useful for β-chloro and β-amino selenoxides.[81,111]



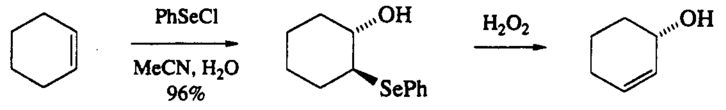
(46)

(115)

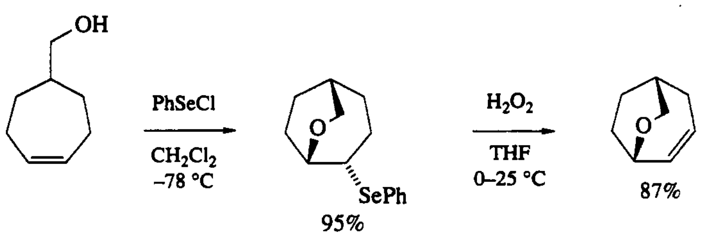
β-Hydroxy selenides are conveniently prepared from epoxides by treatment with sodium phenylselenide (Scheme 32)[85] and by the addition of benzeneselenenic acid and its derivatives to alkenes (Scheme 33),[86,87,112] although in some cases these reactions are not regioselective. Useful phenylseleno -etherification and -lactonization reactions have been developed which can be regioselective (equation 42 and Schemes 34 and 35).[94,113–115] Selenide- and selenoxide-stabilized carbanions have been used in addition reactions with aldehydes and ketones,[93,116] and the reduction of α-seleno ketones also provides a route to β-hydroxy selenides.[81]



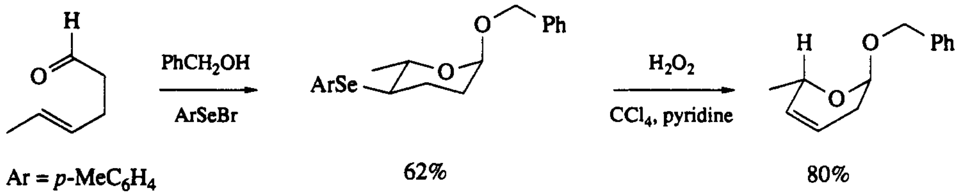
Scheme 32



Scheme 33

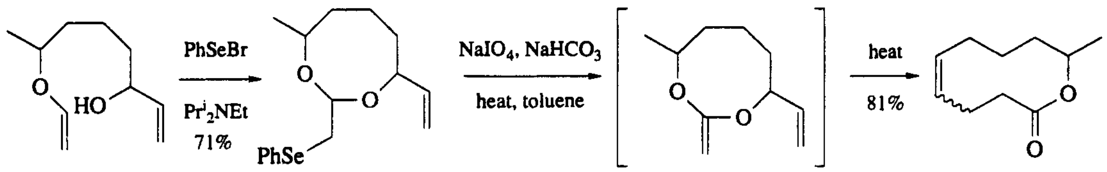


Scheme 34



Scheme 35

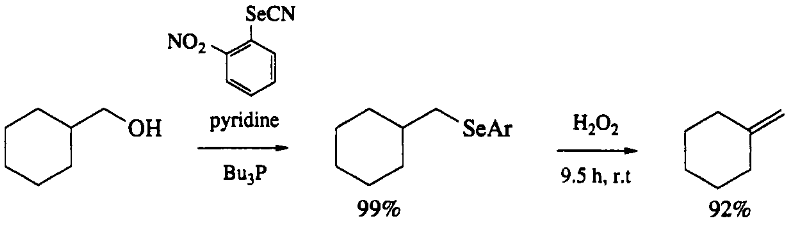
Although the preference for selenoxide elimination to take place away from a β-oxygen substituent is very marked, the elimination will still occur towards the oxygen substituent if there is no alternative. This has been used in elegant syntheses of ketene acetals derived from allylic alcohols, which are useful Claisen rearrangement precursors (Scheme 36)[117] and for the synthesis of phenylseleno methyl ketones.[118]



Scheme 36

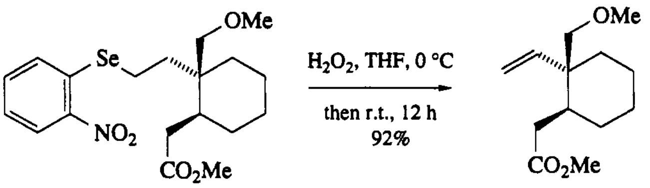
5.3.4.2.3 *Synthesis of terminal alkenes*

The oxidative elimination of primary selenides, readily available from the corresponding alcohol by treatment with an arylselenocyanate and tributylphosphine, is an attractive approach to the synthesis of terminal alkenes.[119] However these reactions are relatively slow when compared with other selenoxide eliminations allowing side reactions, in particular the addition of the areneselenenic acid to the newly formed double bond (Scheme 23), to compete. It has been found that arylselenides with electron-withdrawing substituents fragment more readily, giving improved yields of products,[120] in particular the use of *o*-nitrophenyl and 2-pyridyl selenides[121] has been recommended (Scheme 37). Often for the elimination of primary selenoxides, the solution containing the selenoxide is added to dichloromethane or carbon tetrachloride heated under reflux.[81]



Scheme 37

Following these guidelines, the selenoxide elimination procedure has proved particularly useful for the synthesis of terminal double bonds, for example the introduction of vinyl groups during sesquiterpene synthesis as illustrated in equation (47).[122,123]



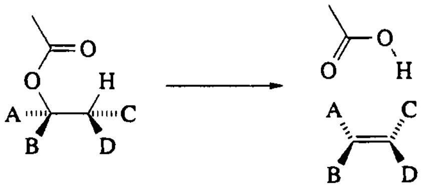
(47)

5.3.5 XANTHOGENATE AND ACETATE PYROLYSIS

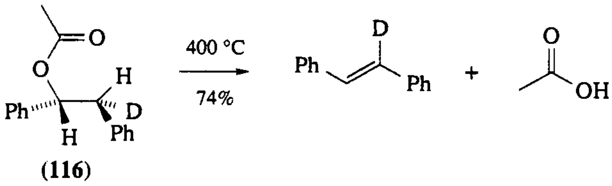
5.3.5.1 Introduction

Useful procedures for the synthesis of alkenes by pyrolysis of acetates and xanthogenates have been developed, and have been extensively reviewed.[124–127]

Acetate pyrolysis is normally carried out using a flow apparatus at temperatures in the region of 300–600 °C. The *syn* elimination mechanism (equation 48) was established by pyrolysis of the stereospecifically deuterium-labeled acetates (**116**) and (**117**), which gave labeled and unlabeled products as shown in equations (49) and (50).[128] 1,2-Disubstituted acyclic alkenes are normally obtained with the (*E*)-stereochemistry, as for the other eliminations discussed in this chapter.[129] However, the regioselectivity of acetate pyrolysis can be rather modest. This is because the regioselectivity is affected by several factors, in particular the stability of the product alkene and the number of available β-hydrogens. If these two factors oppose each other only low regioselectivity is observed, *e.g.* a 50:50 mixture of alkenes (**119**) and (**120**) was obtained from the pyrolysis of acetate (**118**; equation 51).[130]

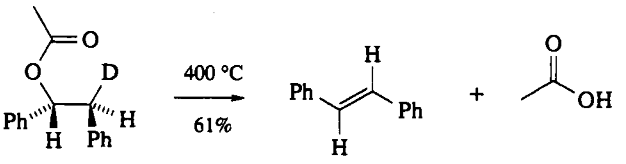


(48)



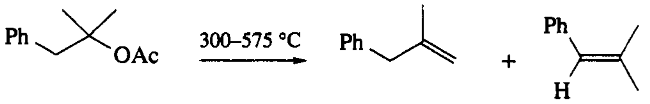
(**116**)

(49)



(117)

(50)

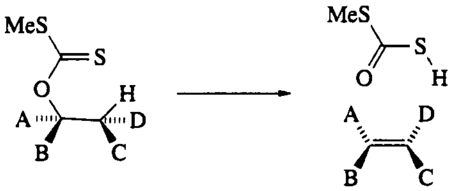


(118) **(119)** *ca.* 50:50 **(120)**

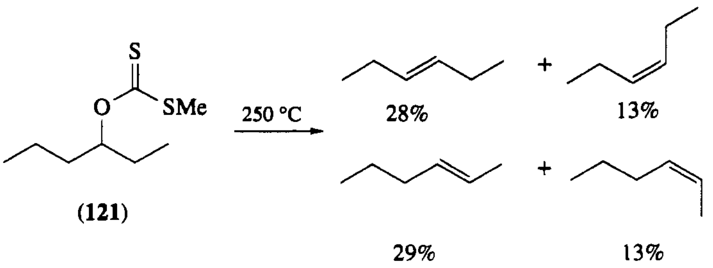
(51)

The rate of acetate fragmentation depends upon the nature of the alkyl group, with the relative rates of elimination of ethyl, isopropyl and *t*-butyl acetates being 1:26:1660, respectively, at 400 °C.[131] However, Hammett correlations for fragmentation of α- and β-aryl-substituted acetates show little sensitivity to aryl substituents.[124] The rates of fragmentation of esters derived from other carboxylic acids are dependent upon the pK_a of the parent acid, but this does not appear to influence significantly the regioselectivity of their fragmentation.[124,132]

Xanthogenate pyrolyses are usually carried out by distillation at temperatures in the region of 150–250 °C, *i.e.* lower than those required for the corresponding acetate pyrolyses, with the stereochemistry of the elimination corresponding to that of the *syn* process outlined in equation (52).[133] In acyclic systems there is a modest preference for 1,2-disubstituted products to be obtained with (*E*)-stereochemistry, but the regioselectivity is often rather weak because of the conflicting demands of product stability and statistical factors. For these reasons simple xanthogenates derived from acyclic secondary alcohols, *e.g.* **(121)** and **(122)**, often give mixtures of products, as illustrated in equations (53) and (54).[134]

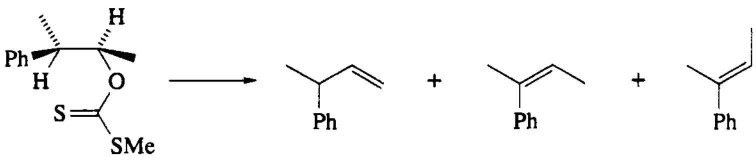


(52)



(121)

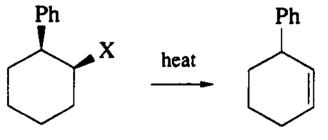
(53)



(122) 32% 45% 3%

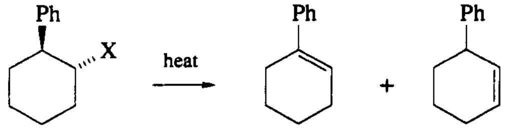
(54)

For xanthogenate and acetate elimination from cyclic systems, the regioselectivity is dependent upon the accessibility of the alternative *syn* elimination transition states. The *cis*-2-phenyl acetate (**123**; X = OAc) and xanthogenate (**123**; X = OCSSMe) both eliminate exclusively away from the phenyl substituent to give 3-phenylcyclohexene (**124**; equation 55), whereas the corresponding *trans*-2-phenyl compounds (**125**; equation 56) give mixtures of the 1- and 3-phenyl isomers (**126**) and (**124**).[124,127] The pyrolysis of 1-methylcyclohexyl acetate (**127**) differs from that of the corresponding amine oxide (**21**; *n* = 6) (Section 5.3.2.2) in that it gives predominantly the endocyclic alkene (equation 57).[135]

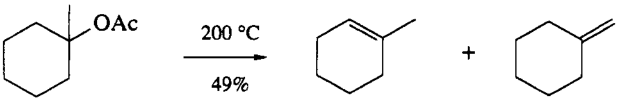


(**123**) (**124**) (55)

X = OAc, 450 °C, 65%; X = OCSSMe, 435 °C, 100%



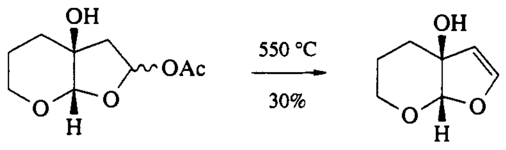
(**125**) (**126**) *ca.* 87:13 (**124**) (56)



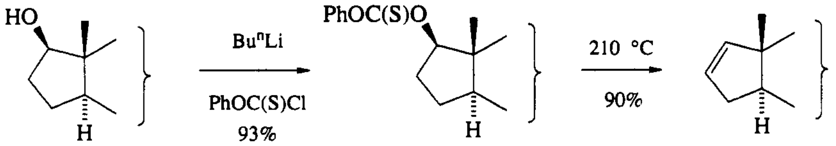
(**127**) 79:21 (57)

5.3.5.2 Applications in Synthesis

Despite the high temperatures required for acetate and xanthogenate pyrolysis, the accessibility of these compounds from the corresponding alcohols provides for a useful route to alkenes. One advantage is that as no acidic or basic reagents are required, rearrangement reactions, which can interfere with alcohol dehydration, are avoided. For example, pyrolysis of lactol acetates has been used to prepare 4,5-dihydrofurans, as illustrated in equation (58),[136,137] and pyrolysis of the corresponding thionocarbonate was used to dehydrate alcohol (**128**; Scheme 38).[138]



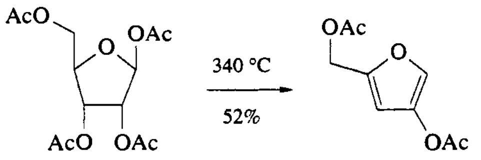
(58)



(**128**)

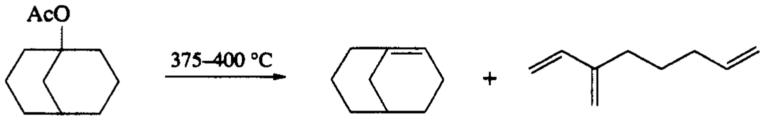
Scheme 38

Pyrolysis of peracetylated pyranose monosaccharides has been studied, and found to proceed *via* initial loss of the 1-acetoxy group followed in some cases by allylic rearrangement.[139] In contrast, peracetylated furanoses lose two acetoxy groups to give substituted furans, *e.g.* equation (59).[140]

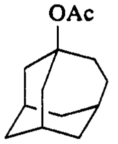


(59)

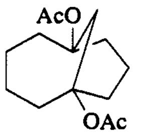
Thermolysis of acetates has been used to synthesize unstable bridgehead alkenes and dienes, which in some cases have been isolated by trapping at low temperatures. For example, the bicyclic acetate (**129**; equation 60) gave a mixture of bicyclo[3.3.1]non-1-ene (**130**) and its retro-Diels–Alder product (**131**) on pyrolysis at 375–400 °C,[141] and thermolysis of the 3-homoadamantyl acetate (**132**) gave a mixture of products whose formation may have been initiated by acetate elimination.[142,143] Bridgehead dienes are believed to be involved in the formation of products from the diacetate (**133**),[144] and novel dienes were isolated from pyrolysis of acetate (**134**).[145]



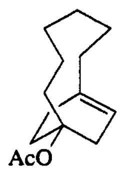
(**129**) (**130**) 66:34 (**131**) (60)



(**132**)



(**133**)



(**134**)

5.3.6 SUMMARY

The pyrolytic reactions discussed in this chapter play an important role in modern synthetic organic chemistry for the introduction of carbon–carbon double bonds into complex molecules. They are normally stereo- and regio-selective, and since they are carried out by simply heating the substrate to the required temperature, they avoid acid- and base-catalyzed rearrangements. The Cope elimination provides a useful alternative to the Hoffmann elimination, and the sulfoxide and selenoxide procedures are widely used, particularly for the synthesis of α,β-unsaturated carbonyl compounds, providing the preferred route to these compounds at the present time. The widespread use of xanthogenate, and more particularly acetate, pyrolyses, is limited by the high temperatures required; however, the ready availability of these compounds from alcohols, and the development of flash vacuum techniques, has encouraged their use in, for example, bridgehead alkene synthesis.

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5.4

Fragmentation Reactions

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5.4.1 INTRODUCTION

5.4.1.1 Definition

Fragmentation reactions, according to the definition of Grob,[1,2] are processes (equation 1) where the reacting molecule breaks into three fragments.

(1)

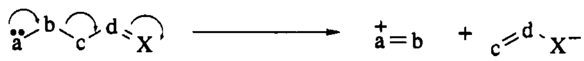
The electrofugal group a—b forms stable cations or neutral molecules depending on the initial charge. The middle group c—d gives an unsaturated fragment. The nucleofugal group X leaves the atom d with the bonding electron pair. There are many carbon or heteroatom groups containing electrofugal, middle, and nucleofugal groups which can be combined to give fragmentable systems.[1,2]

Fragmentation reactions have to be distinguished clearly from 1,2-elimination reactions (equations 2 and 3), where the electrofugal group is a single atom such as hydrogen or halogen, or an organometallic fragment such as MgBr.[1]

(2)

(3)

Furthermore, there is a class of reactions (retroaldol, retro-Claisen, *etc.*) which are similar to the fragmentations, but they are not to be considered as such. Here, the electron acceptor group X is double bonded to the atom d, and therefore two fragments rather than three are formed (equation 4).

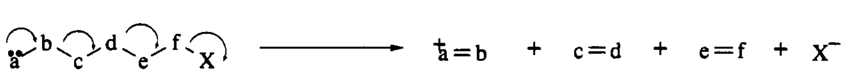


(4)

On the other hand, there are exceptions to the rule that a reaction must lead to three separate fragments when the potential fragments are ring members in cyclic reactants (equation 5).[1] This type is particularly useful in synthesis.

(5)

Finally, there are examples of a so-called seven center fragmentation (equation 6) which can lead to four fragments depending on the bonding situation.

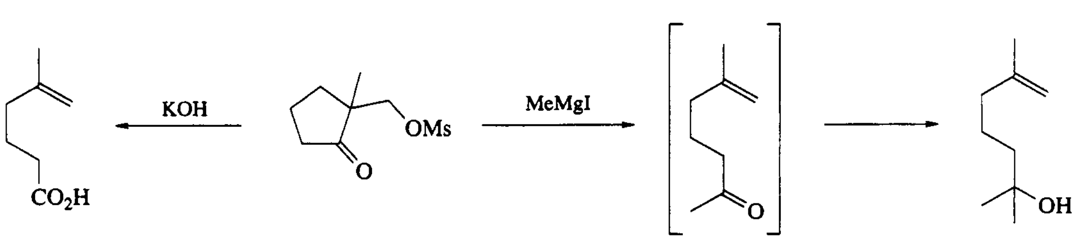


(6)

All the processes mentioned above are heterolytic fragmentations in solution. Homolytic fragmentations (preferably in the gas phase), by thermal energy or by electron impact (MS), will not be described. Unfortunately, the term 'fragmentation' is often confusingly used in the literature. Obviously, this is a semantic problem. Grob[2] first introduced 'Fragmentierung' in German language into the literature, employing this term in a well-defined sense. In English language 'fragmentation' is more or less synonymous with 'cleavage' or 'scission', and it is used in a broader sense. This chapter is limited to the 'real' fragmentations in the definition of Grob,[2] and some related reactions.

5.4.1.2 History

The first reactions of the type which we now call fragmentations had already been described in the last century, as Eschenmoser[3] realized in 1952 when he published the reaction of the β-mesyloxy ketone (**1**) with KOH or MeMgI to give the fragmentation products in over 80% yield (Scheme 1). He undoubtedly recognized the common principle, and gave the correct interpretation. It would therefore be justified for the fragmentation to bear his name. Coincidentally, he selected an appropriate educt, since even the next homolog of (**1**) with the six-membered ring yields mainly $S_{\mathrm{N}}\mathrm{i}$ substitution products under comparable conditions.[4–7]



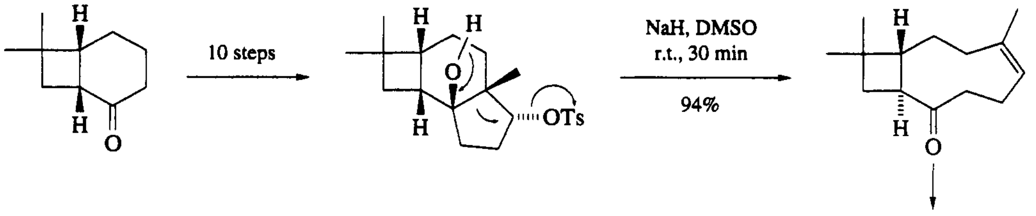
(**2**) (**1**) (**3**)

Scheme 1

Since the mid 1950s Grob has investigated these fragmentations in detail, and provided very much experimental material for the scope, mechanism and stereochemistry of this reaction type, summarized in some reviews.[1,2,8] Therefore, the term 'Grob fragmentation' is justified.

The great utility of fragmentations, especially those of 1,3-diol monosulfonates, for the construction of functionalized, medium-sized cycloalkenes was developed by Wharton,[9] by applying previous results.[10] In recognition of his important contributions to the chemistry of heterolytic fragmentations of cyclic 1,3-diol derivatives, this reaction type has been referred to in a recent review as the 'Wharton fragmentation'.[11]

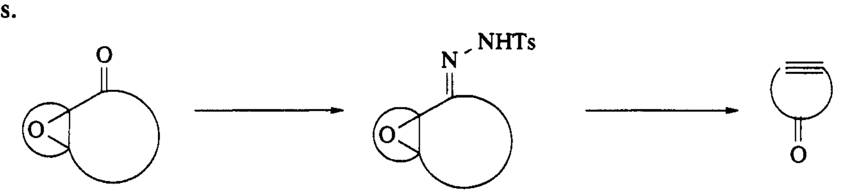
Corey utilized the reaction of appropriately substituted 1,3-hydrindanediol monotosylates for the introduction of the cyclononene moiety in an elegant synthesis of caryophyllene and its isomers (Scheme 2).[12] Some further examples will be found in two recent reviews.[11,13]



Scheme 2

Isocaryophyllene

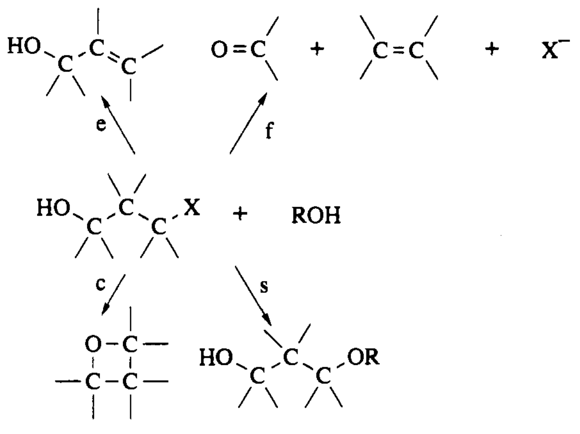
A special reaction type involves the α,β-epoxy ketone to alkynone fragmentation, often cited as the 'Eschenmoser fragmentation'. First published by Eschenmoser,[14] and a little later and independently by Tanabe,[15] the utility of this fragmentation for the synthesis of open-chained or cyclic alkynones (Scheme 3) is obvious.



Scheme 3

5.4.1.3 Mechanism and Stereochemistry

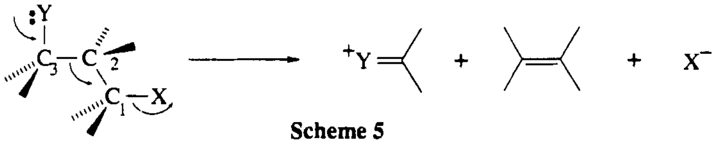
Candidates appropriate for fragmentation (equation 1) in general can also react *via* other pathways. γ-Nucleofuge-substituted alcohols, for example, in nucleophilic solvents are able to undergo substitutions, eliminations and ring closure reactions (Scheme 4). The real result depends on both electronic and steric factors.



f = fragmentation, s = substitution, e = elimination, c = ring closure

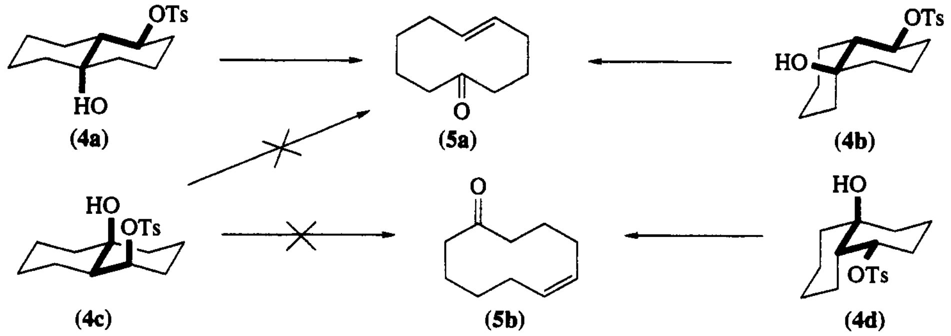
Scheme 4

The basic mechanism of fragmentation (equation 1) is a concerted one, with a contribution from each of the five centers to the transition state. Two-step carbonium ion or, very rarely, carbanion mechanisms mean in all cases that substitution, elimination or ring closure can take place rather than fragmentation. However, the one-step synchronous fragmentation is allowed only when the compound can adopt a conformation where the leaving group X as well as the electron pair of the electrofuge Y are antiperiplanar to the C(2)—C(3) bond (Scheme 5).[8]



Scheme 5

When this stereochemical arrangement cannot be achieved, substitution of the leaving group and elimination reactions take place. This behaviour has also been shown convincingly by Wharton[9] for the four stereoisomeric tosylates (**4**; Scheme 6). (**4a**), (**4b**) and (**4d**) show the crucial bonds to be *anti*, and in these cases fragmentation to the cyclodecenones (**5**) occurs in over 90% yield. The stereochemistry of the C—C bond forming the double bond is strictly retained (**4a** and **4b** give **5a**; **4d** gives **5b**). The isomer (**4c**), having the bonds which may undergo cleavage in a *gauche* orientation remains largely unchanged.



Scheme 6

However, there are some exceptions of this general rule[16a] if strained systems are involved. Together with the synthetic goals, mechanisms will be discussed where *syn* fragmentation apparently is concurrent[16b] or even preferred.[17]

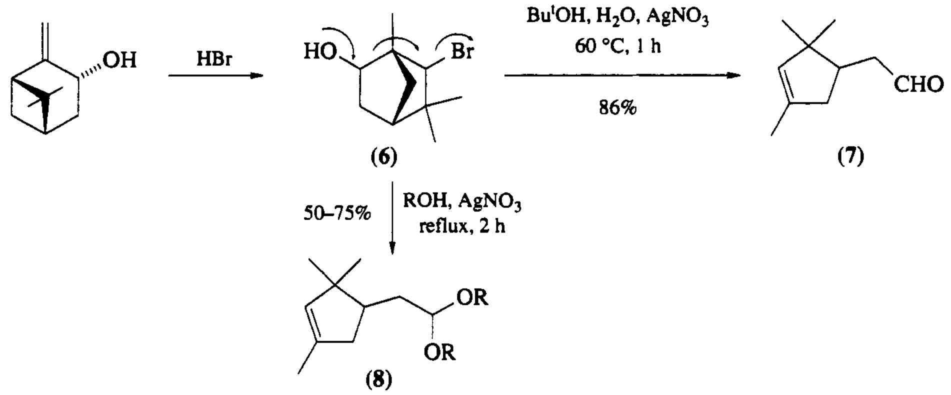
The electronic requirements for the Grob fragmentation from a molecular orbital viewpoint have been described,[18] and in a recent investigation mechanisms of borderline cases of fragmentations have been discussed.[19]

5.4.2 SYNTHESIS BY GROB FRAGMENTATION

5.4.2.1 Open Chains and Normal Rings

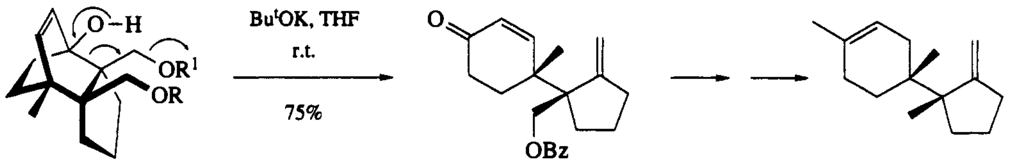
The aim of this section is to show how cyclic precursors can serve as an appropriate starting material for the construction of open-chained or monocyclic intermediates with defined regio- and/or stereospecifity. The nucleofuge usually is halide or sulfonate and the electrofuge an alkoxide, generated from an alcohol by base or from a keto group by attack of a nucleophile.

Fencholene aldehyde (**7**), an interesting starting material for the synthesis of sandalwood fragrance compounds, has been prepared by $AgNO_3$-assisted fragmentation of bromoisofenchol (**6**). The acetals (**8**) of fencholene aldehyde (**7**) are directly available in a one-pot reaction under anhydrous conditions.[20] Also, these acetals are useful as fragrances (Scheme 7).



Scheme 7

For the stereoselective total synthesis of bazzanene (**12**; Scheme 8),[21] a sesquiterpene isolated from the liverwort *Bazzania pompeana*, the fragmentation of the monoprotected mesylate (**10**) was used. The mesylate (**10**) is obtained from the triol (**9**), an intermediate in the synthesis of gymnomitrane sesquiterpenes.[22] Treatment of (**10**) with KOBu^t produces cleanly the expected cyclohexenone (**11**).



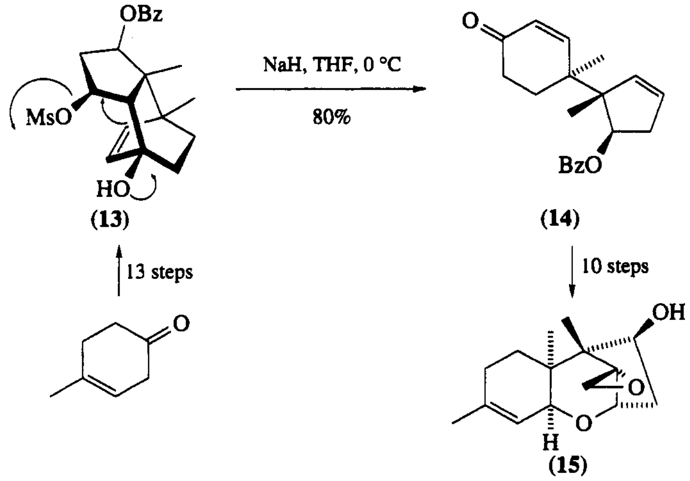
(**9**) R, R^1 = H
(**10**) R = Bz, R^1 = Ms

(**11**)

(**12**)

Scheme 8

The trichothecenes, *e.g.* (**15**), are a class of almost four dozen fungal metabolites that possess among them insecticidal, antifungal and cytotoxic activity. Related to the preceding fragmentation is a reaction sequence which was used by Still[23] in his trichodermol (**15**) synthesis, an outstanding piece of synthetic craftsmanship. Thirteen steps are necessary to obtain the tetracyclic triol derivative (**13**). Treatment with NaH under mild conditions gave stereoselectively the fragmentation product (**14**). After a further ten steps the target molecule (**15**) was obtained (Scheme 9).



(**13**)

(**14**)

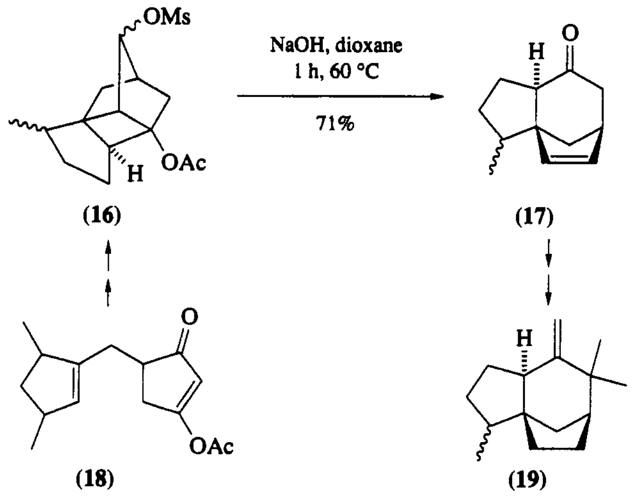
(**15**)

Scheme 9

The tricyclic ketone (**17**), a fragrant and volatile key compound of the zizaene (**19**) synthesis, results from a fragmentation of the tetracyclic mesylate (**16**).[24] This skeleton has also been formed by intramolecular photocycloaddition of the easily accessible enol acetate (**18**). Obviously, the ring strain of (**16**) is a strong driving force (Scheme 10).

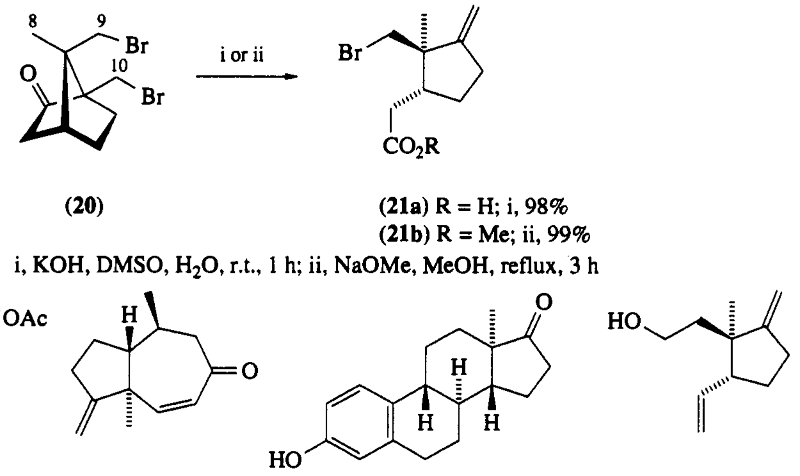
The use of (+)- or (–)-camphor as a chiral starting material in natural product synthesis[25a] is dependent on the availability of methods for the regiospecific and stereoretentive functionalization of camphor at the C-8, C-9 or C-10 position.[25b] Money[26] has shown that (+)-camphor can easily be converted to (+)-9,10-dibromocamphor (**20**), and that the latter compound undergoes facile, efficient fragmentation with base to provide monocyclic bromo acid (+)-(**21a**), or its methyl ester (**21b**),[29b] in almost quantitative yield. This versatile chiral synthon has been used for an enantiospecific formal synthesis[27] of one of the sex pheromones of female California red scale (**22**), for a synthetic route to bicyclic enone (**23**), which could be used as a key intermediate in pseudoguaianolide synthesis,[28] for a new enantiospecific synthesis of (–)-estrone (**24**), providing ring D;[29a] and for the valuable chiral intermediate (**24a**) in steroid synthesis (Scheme 11).[29b]

The first naturally occurring member of the class of fenestranes is the diterpene lauren-1-ene (**27**), isolated in 1979 from the essential oil of *Dacrydium cupressinum*. The intermediate (**26**) for Wender's[30] stereocontrolled synthesis of (**27**) is readily accessible by attack of KOH on the tosyloxy ketone (**25**) to give, *via* fragmentation, a carboxylate anion which undergoes immediate ring closure to the lactone (**26**; Scheme 12).



(16) **(17)** **(18)** **(19)**

Scheme 10



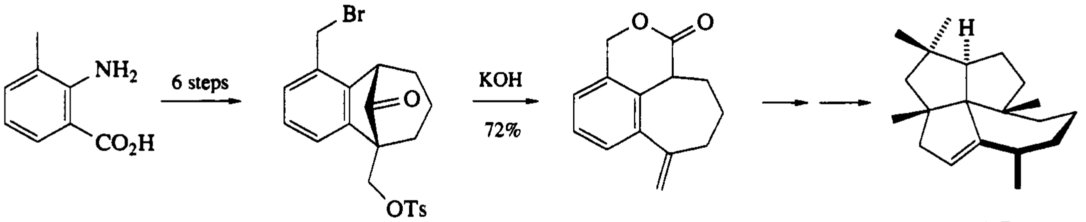
(20)

(21a) R = H; i, 98%
(21b) R = Me; ii, 99%

i, KOH, DMSO, H_2O, r.t., 1 h; ii, NaOMe, MeOH, reflux, 3 h

(22) **(23)** **(24)** **(24a)**

Scheme 11

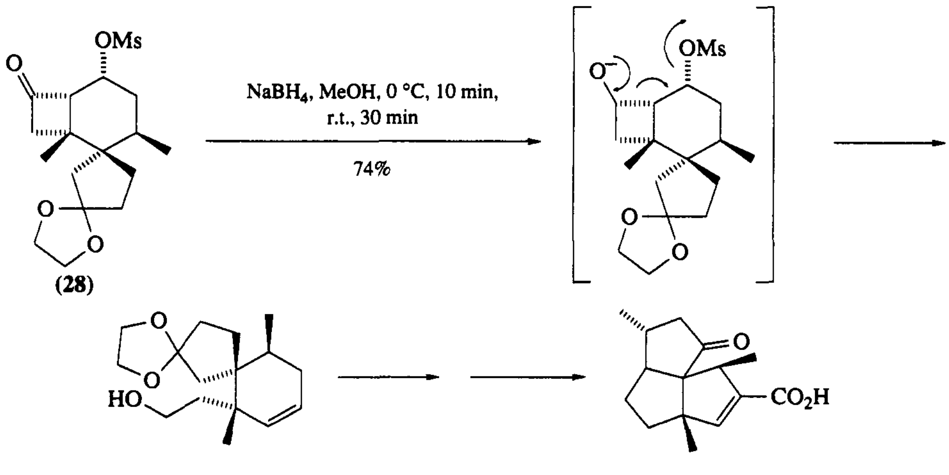


(25) **(26)** **(27)**

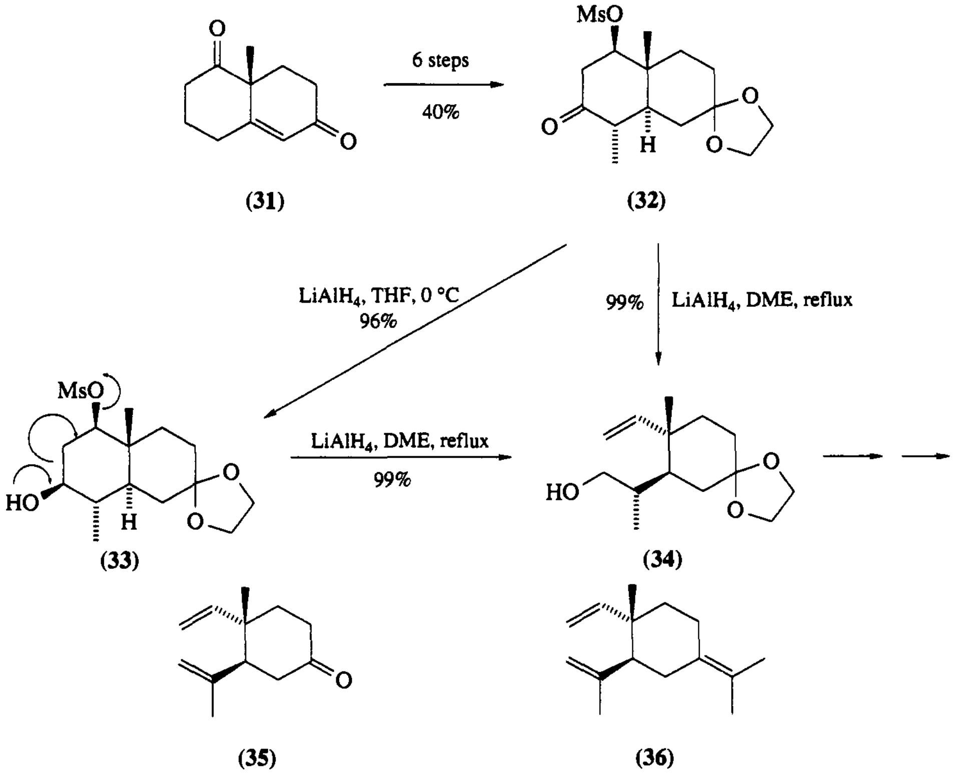
Scheme 12

Iwata's^{31} synthesis of subergorgic acid (**30**), a silphiperfolane derivative isolated from a gorgonian coral, involved the reductive fragmentation of the cyclobutanone (**28**) to the alcohol (**29**) *via* an intermediate aldehyde (Scheme 13).

Two of the side chains of the geijerone (**35**) or γ-elemene (**36**) system have been introduced by Yoshikoshi^{32a} by means of fragmentation of the appropriate bicyclus (**32**), synthesized from the Wieland–Miescher ketone (**31**). It is remarkable that reduction of ketone (**32**) under mild conditions allows the isolation of the hydroxy mesylate (**33**), which undergoes fragmentation to (**34**) at elevated temperatures (Scheme 14).



Scheme 13

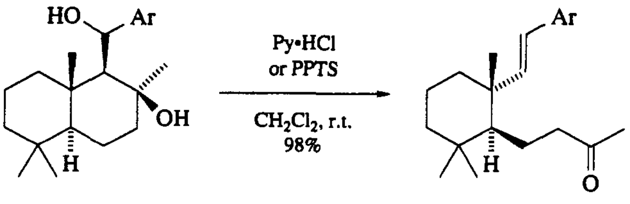


Scheme 14

Yoshikoshi[32b] recently reported a 1,3-diol fragmentation (Scheme 14a) under mild conditions, where a benzylic hydroxy group activated by the 2,6-dimethoxy-4-methylphenyl group proved to be a remarkably reactive nucleofuge.

In a synthesis which correlates (–)-β-pinene with (+)-hinesol (**41**; Scheme 15), Magnus[33] started with (+)-nopinone (**37**) which provided, after several steps, the sulfone (**38**) as the key compound. Under alkaline conditions, (**38**) gives the β-keto sulfone (**40**) *via* intramolecular attack of the carbanion of (**38**) forming the alkoxide (**39**). Release of ring strain is responsible for the domination of the fragmentation rather than typical alternatives such as oxetane formation, substitution, or other reaction pathways. Traces of water in the fragmentation step give rise to the formation of carboxylic acid (**42**).

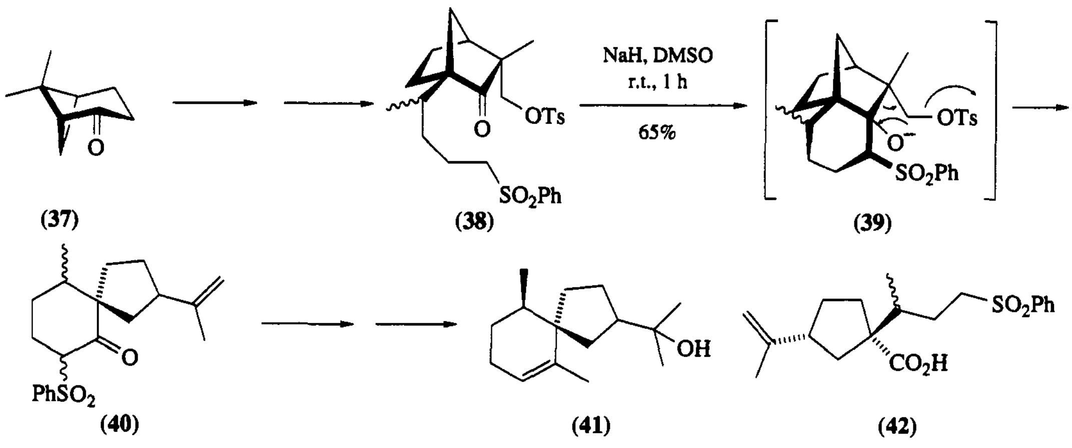
One of the very rare cases where a triple bond is formed by a normal Grob fragmentation is described by Corey[34] in the course of the synthesis of hybrida lactone (**45**), an eicosanoid, isolated from the marine alga *Laurencia hybrida*. The strained enol tosylate (**43**) yields the ethynyl ketone (**44**) under very mild



(36a) (36b)

Ar = 2,6-dimethoxy-4-methylphenyl

Scheme 14a

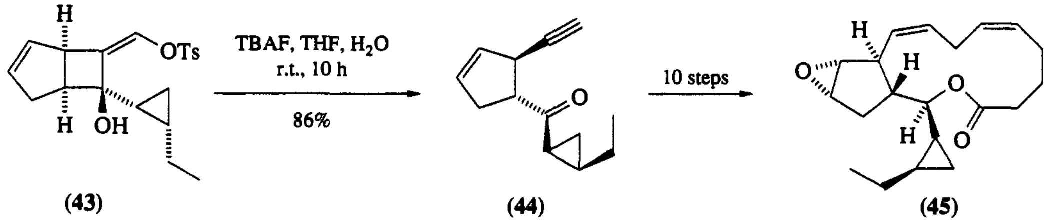


(37) (38) (39)

(40) (41) (42)

Scheme 15

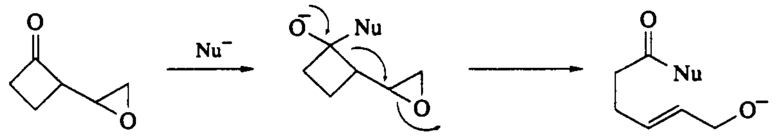
conditions. The initially formed *cis* isomer of (44) is equilibrated during the reaction time to a 9:1 *trans*:*cis* mixture (Scheme 16).



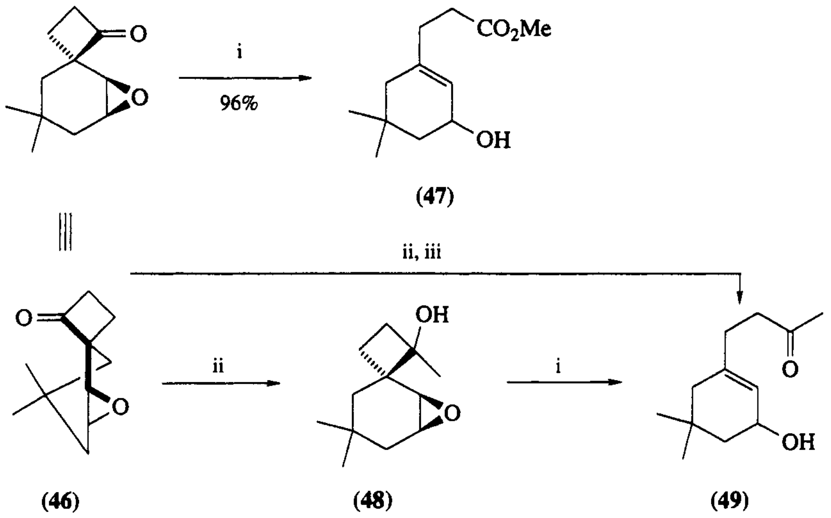
(43) (44) (45)

Scheme 16

The introduction of cyclobutanone units into organic substrates has been combined with the Grob fragmentation by Trost,[16] giving a useful approach to chain extension. This procedure has been termed generally 'secoalkylation'. In the case shown in Scheme 17, since one of the ring atoms is oxygen, it is termed 'oxasecoalkylation'. Thus, epoxy ketone (46) when treated with NaOMe gives hydroxy ester (47) in almost quantitative yield. MeLi addition to (46) at –78 °C followed by addition of water and allowing to warm to room temperature yields hydroxy ketone (49; Scheme 18). Alternatively, the epoxycyclobutanol (48) can be isolated if the reaction mixture is worked up immediately after quenching with water at low temperatures. Treatment of (48) with NaOMe then gives smooth fragmentation to the same hydroxy ketone (49).



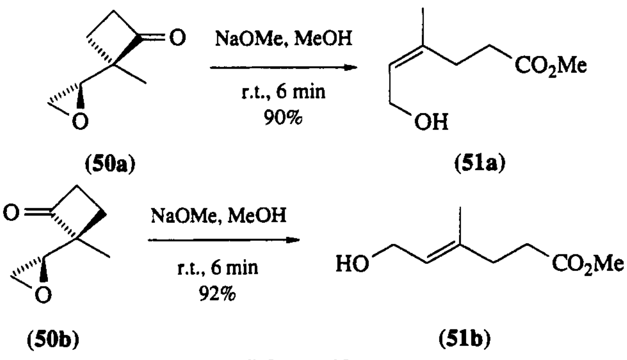
Scheme 17



i, NaOMe, MeOH, r.t.; ii, MeLi, –78 °C; iii, H_2O, r.t.

Scheme 18

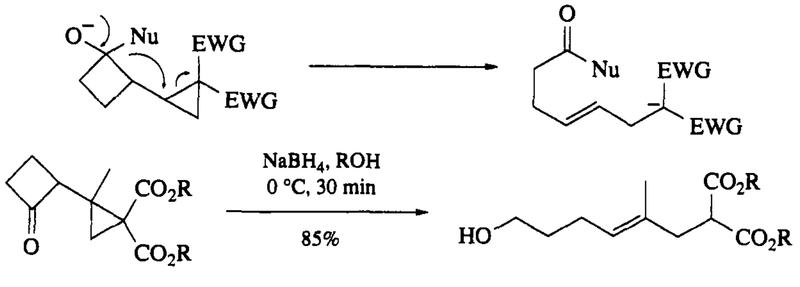
In the conformation of (**46**; Scheme 18), the cyclobutyl and epoxy bonds shown in bold bear an approximate *trans* diaxial relationship. Conversion of the carbonyl group into a good electron source by addition of nucleophiles should initiate fragmentation accompanied by the release of 54 kcal mol^{-1} (1 cal = 4.2 J), the combined strain energies of the cyclobutyl and epoxide rings. However, Trost has pointed out that fragmentation of cyclobutanols does not appear to require the *trans* orientation, since even in cases where a *trans* elimination is not possible fragmentation is smooth in all cases of sterically rigid systems. To investigate unstrained systems, both isomers of epoxycyclobutanone (**50**) were converted with NaOMe to the hydroxy esters (**51**; Scheme 19). (**50a**) leads cleanly to a single (*Z*)-ester (**51a**), and similarly (**50b**) produces a single (*E*)-ester (**51b**). Although the fragmentation is stereospecifically *anti* under the above conditions, with stronger Lewis acids such as $Mg(OMe)_2$ chelation occurs to favour *syn* fragmentation with mixtures of (**51a**) and (**51b**) deriving from both pure (**50a**) and (**50b**). These findings reflect a mixed mechanism between the concerted *anti* and concerted *syn* fragmentation, but even the possibility of a carbonium ion mechanism cannot be rigorously excluded.



Scheme 19

Similarly, Trost[35] has also shown that carbon can function as a nucleofugal atom in Grob fragmentation. These fragmentations occur when two electron-withdrawing groups are present. Thus, the diester (**52**; Scheme 20) gives hydroxy diester (**53**) through reductive fragmentation. The monoester does not react at all in this sense.

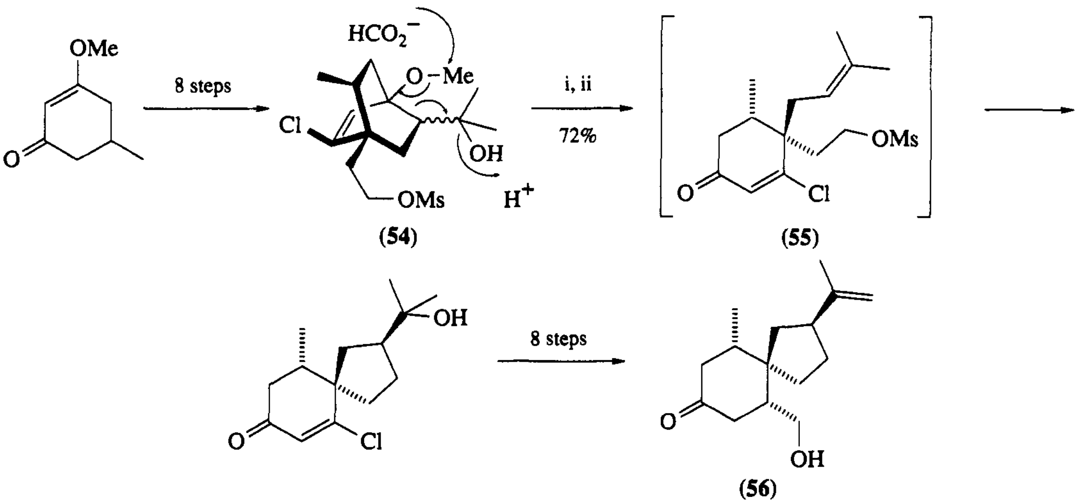
The acid fragmentation of suitably substituted bicyclo[2.2.2]octanes to cyclohexenones and subsequent ring closure to spirovetivanes *via* π-cation cyclization has been used by Murai[36] for a highly stereoselective isolubimin (**56**) synthesis. (**56**) has been considered to play an important role in the biogenetic pathway of various spirovetivane phytoalexins in the Solanaceae family. Treatment of methyl



(52) (53)

Scheme 20

ether (**54**) with formic acid gives enone (**55**) by acid fragmentation. The crude (**55**) is immediately cyclized to the spiroketone (Scheme 21).



(54) (55) (56)

i, HCO_2H, r.t., 2 h; ii, $(CO_2H)_2$, $MeCOBu^i$, H_2O, reflux, 8 h

Scheme 21

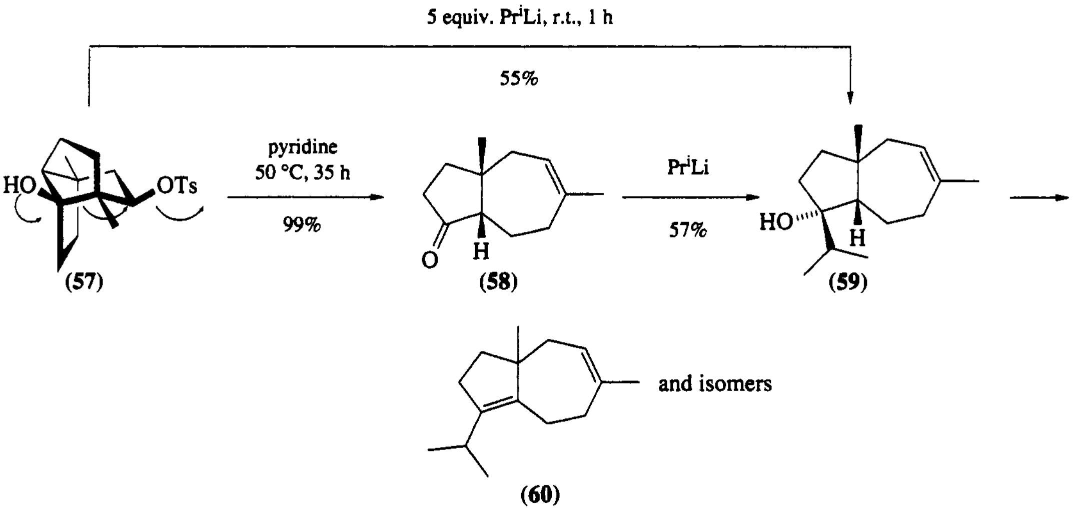
5.4.2.2 Medium-sized and Large Rings

Fragmentation of appropriate bicyclic sulfonyloxy alcohols or ketones is a general route towards cycloalkene ketones or carboxylic acids. Thus, the hydroazulene alcohol (**59**; Scheme 22), precursor for the synthesis of daucene (**60**), jaeschkeana diol and others, has been synthesized[37] by a one-pot reaction (fragmentation and isopropylation) of the hydroxy tosylate (**57**) with Pr^iLi. The fragmentation of (**57**) to give the ketone (**58**) as the primary product can be achieved by treatment with pyridine.

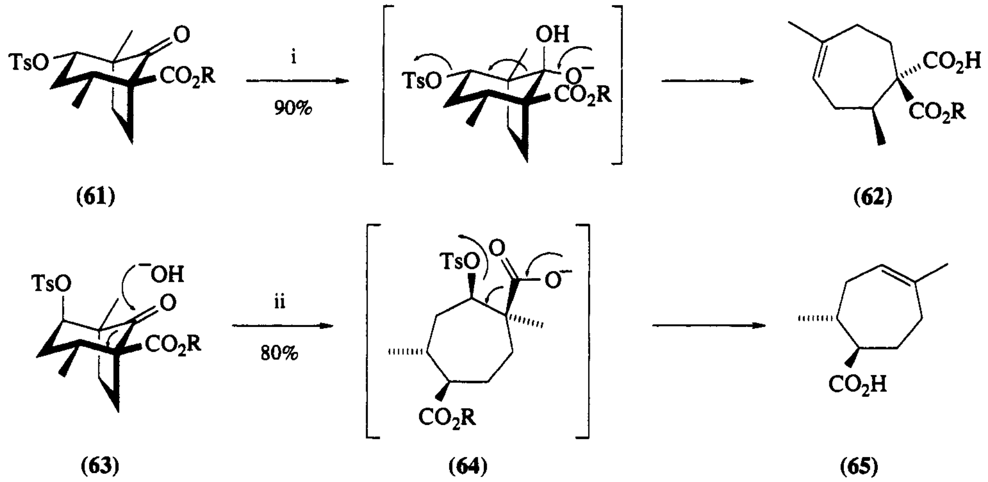
The equatorial tosylate (**61**; Scheme 23) is smoothly converted to the half-ester (**62**) by treatment with KOH. Similarly, reaction of (**61**) with NaOEt furnishes the corresponding diester, whilst under these conditions the axial epimer (**63**) is recovered in high yield.[38] The inertness of (**63**) is not unexpected, for compounds of this type are stereoelectronically incapable of a facile fragmentation. It is therefore of interest that when again KOH is used, the axial tosylate affords the acid (**65**) in excellent yield. This product must arise *via* (**64**) by a synperiplanar fragmentation.

The bridged hydroazulene dehydrokessane (**70**; Scheme 24) has been synthesized from the methylene ketone (**69**). The precursor is the diol (**67**), obtained from the readily accessible photoadduct (**66**). Treatment of (**67**) with TsCl in pyridine furnishes directly the ketone (**69**) in high yield.[39] Obviously, fragmentation of the intermediate tosylate (**68**) proceeds very rapidly due to the ring strain of the tricyclus.

A fragmentation of a similar tricyclus has been used by Oppolzer[40] for the synthesis of the hydroazulene ketone (**74**; Scheme 25), precursor of the bulnesenes (**75**). The tricyclic ketone (**71**), obtained by intramolecular photoaddition, is converted to the diol (**72**). Fragmentation is accomplished in one

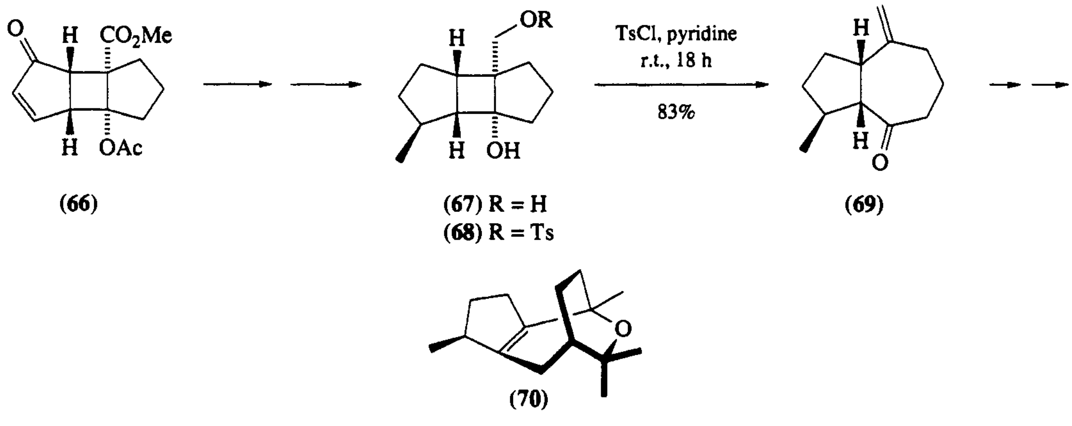


Scheme 22



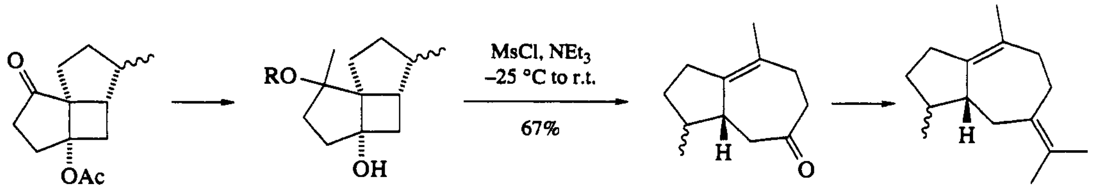
i, KOH, dioxane, H_2O, reflux, 30 min; ii, KOH, EtOH, reflux, 16 h

Scheme 23



Scheme 24

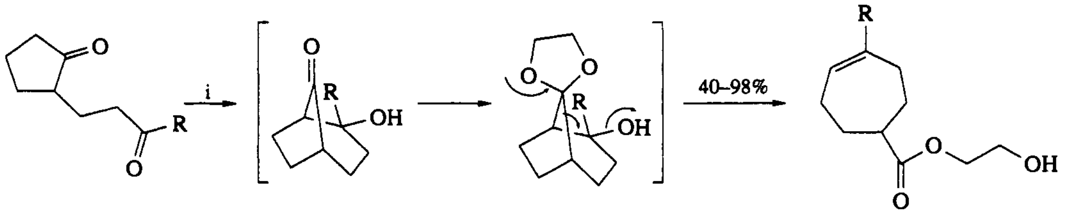
synthetic operation by reaction of (**72**) with MsCl, without isolation of the presumed intermediate mesylate (**73**), yielding (**74**).



(**71**) (**72**) R = H (**73**) R = Ms (**74**) (**75**)

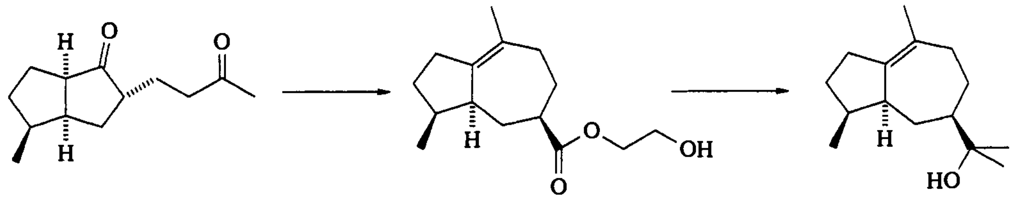
Scheme 25

Sakai[41] has reported that under acetalization conditions, cyclopentanones and cyclohexanones with carbonyl functions in an appropriate position in a side chain undergo facile ring cleavage to construct a new ring. Particularly useful is the reaction sequence starting from a cyclopentanone with the carbonyl function at the C-3 position of the α-position side chain (Scheme 26). After aldol condensation and acetalization, a fragmentation takes place which may be considered as one of the unusual cases of the Grob type.[42a] This ring expansion has been applied to the synthesis of bulnesol (**78**), with the sequence leading from (**76**) to (**77**) as the key step (Scheme 27). Similarly, bicyclo[*m*.*n*.0]alkanes are converted to spirocyclic skeletons.[42b]



i, $BF_3 \cdot Et_2O$, $HOCH_2CH_2OH$, r.t., 2 h

Scheme 26



(**76**) (**77**) (**78**)

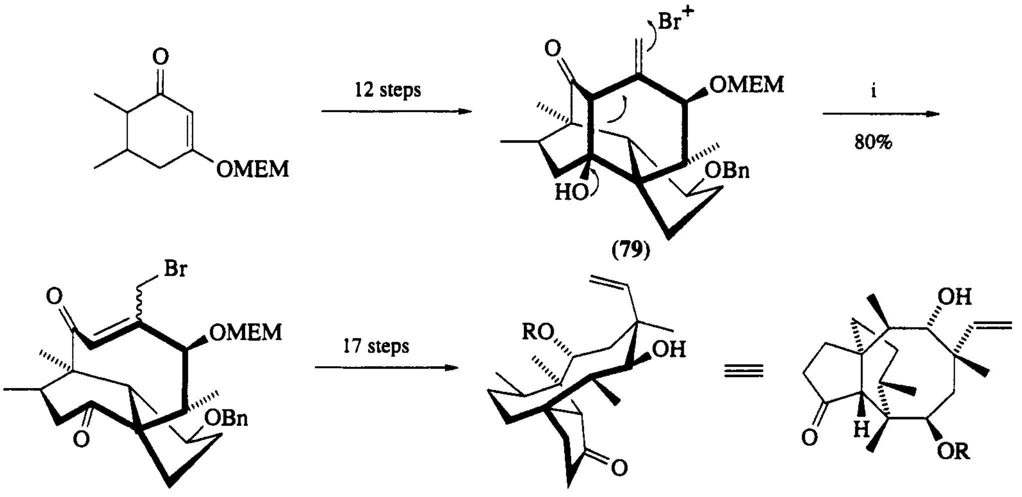
Scheme 27

Pleuromutilin (**81**; Scheme 28) an antibiotic isolated from several species of Basidiomycetes, *e.g. Pleurotus mutilis*, has been synthesized in a 30-step sequence.[43] One of the most important steps is the fragmentation of (**79**) to generate the required tricyclic skeleton of this diterpene. Direct retroaldol ring opening of (**79**) to the respective diketone is unsuccessful, but a two-step sequence *via* the ketoallyl bromide (**80**) results in the desired transformation.

The taxane family of diterpenes with a unique tricyclic ring system has attracted interest in both the biological and chemical communities. Particularly, taxol (**82**) exhibits singular biological activity through its ability to promote microtubule assembly. It is a most promising antitumor agent, now in phase II clinical trials, obtained from the bark of the pacific yew tree.

Holton's[44] plan for the synthesis of the AB ring system of taxanes (*e.g.* **83**) involves fragmentation of an easily accessible tricyclic compound derived from patchouli alcohol. Hydroxy-directed epoxidation of the tertiary alcohol (**84**) (from patchino **90**) gives an unstable substance which undergoes fragmentation *in situ* to provide the keto alcohol (**85**; Scheme 29).

Reactions similar to this type of fragmentation have been encountered by Sukh Dev[45] in longifolene chemistry. One noteworthy feature of the fragmentation leading to (**85**) is the synperiplanar orientation



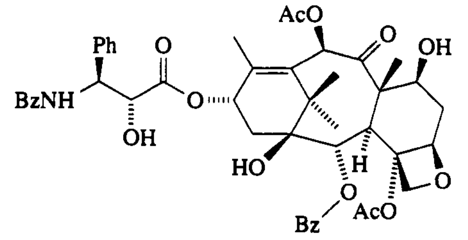
(79)

(80)

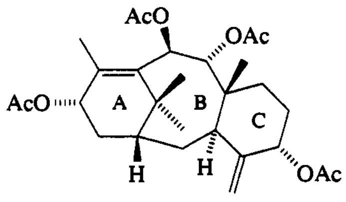
(81) R = $COCH_2OH$

i, NBA, MeOH, H_2O, r.t., 8 h

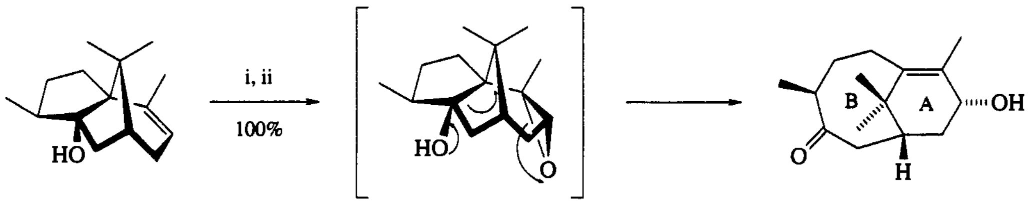
Scheme 28



(82)



(83)



(84)

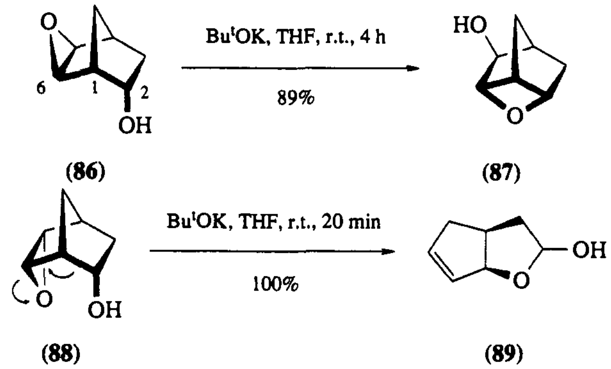
(85)

i, Bu^tO_2H, $Ti(OPr^i)_4$, CH_2Cl_2, 0 °C, 1 h; ii, Me_2S, reflux, 5–8 h

Scheme 29

of the breaking bonds. In ancillary studies it has been found that the synperiplanar relationship between breaking bonds is required for facile fragmentation in a related bridged bicyclic system.[17] Thus, the epoxy alcohol (**86**) with an antiperiplanar alignment of breaking bonds cyclizes to provide oxetane (**87**) in high yield. In contrast to this result, epoxide (**88**) reacts rapidly to provide a quantitative yield of lactol (**89**). These findings might be interpreted as a general preference for *syn* elimination of epoxides. However, the norbornane skeleton is constrained, so that the C(1)—C(2) bond and the C(6)—O bond are more nearly coplanar in *endo*-epoxide (**88**) than in *exo*-epoxide (**86**). This fact could be solely responsible for the above observations (Scheme 30).

The above results were again applied by Holton[46] in the even more challenging synthesis of taxusin (**83**). The cornerstone of the strategy is the fragmentation of the hydroxylated alkene (**91**) to the ketone (**92**) *via* the unstable epoxide (Scheme 31). This (–)-taxusin (**83**) synthesis requires more than 30

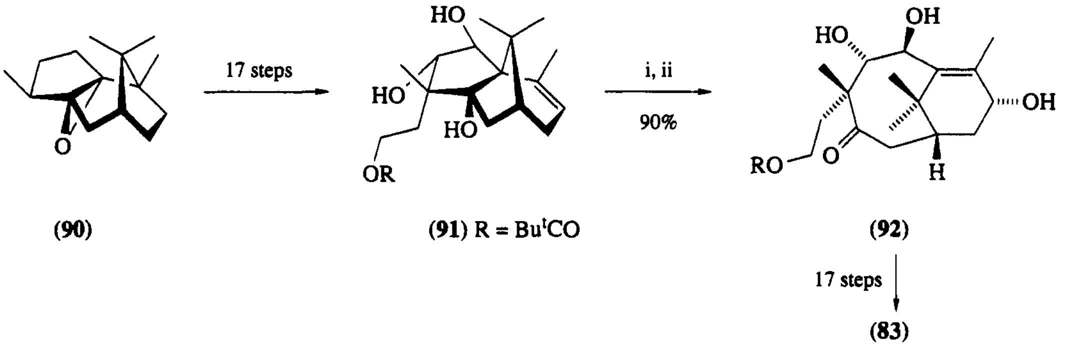


(86) (87)

(88) (89)

Scheme 30

reactions; however, it is most efficiently performed in approximately 24 laboratory operations in more than 20% overall yield from (–)-patchino (90).

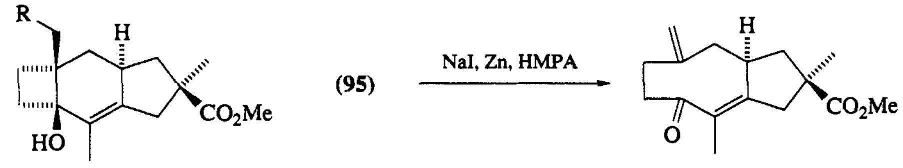


(90) (91) R = Bu^{t}CO (92) (83)

i, $MeCO_3H$ (large excess), CH_2Cl_2, r.t., 30 min; ii, $Ti(OPr^i)_4$, CH_2Cl_2, reflux, 45 min

Scheme 31

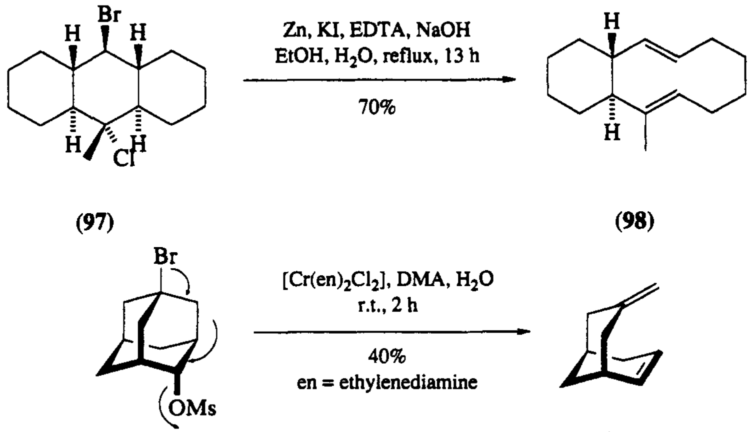
The fungus *Stereum purpureum*, the cause of the so-called silver leaf disease common on fruit trees, produces a new type of sesquiterpenoid (and derivatives) when grown in liquid culture, *viz.* sterpuric acid (93; Scheme 32). An undesired fragmentation reaction of a strained hydroxy tosylate (95) is observed during the synthesis of (93).[47] Attempts to transform the hydroxymethyl group of (94) to a methyl group have been unsuccessful, mainly because of the tendency of this system to undergo fragmentation. Tosylation of (94) provides (95) along with a small amount of the cyclooctenone (96). Several reactions designed to bring about replacement of the tosyloxy group with hydrogen (*e.g.* NaI/Zn) invariably lead to fragmentation.



(93) R = H; (94) R = OH; (95) R = OTs (96)

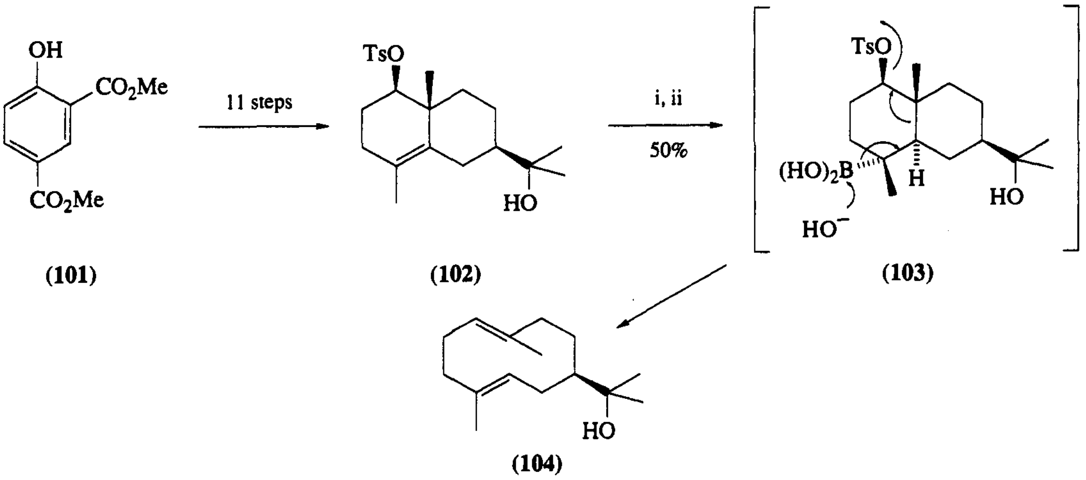
Scheme 32

Wharton[48] has described the fragmentation of the fused bromochlorodecalin (97; Scheme 33) with zinc dust in the presence of EDTA in boiling aqueous ethanol which gives the cyclodecadiene system (98). Babler[49] has suggested the use of chromium(II) complexes for similar reactions, *e.g.* the reaction of (99) to give (100). If successful, chromium(II) may be advantageous over zinc since fragmentation reactions involving the latter are generally run at elevated temperatures, conditions under which a Cope rearrangement of the diene product can occur.



Scheme 33

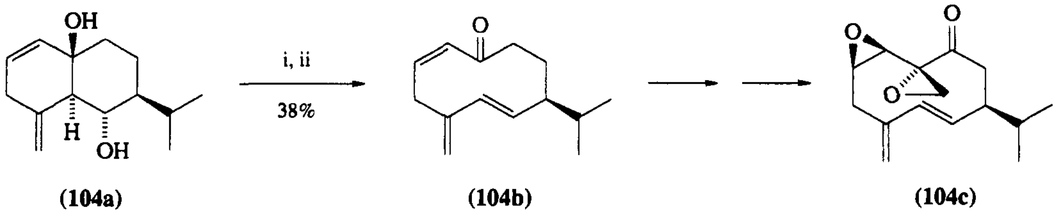
Boronates are excellent starting points for a Grob fragmentation,[50] particularly in hydroazulene synthesis.[51] Another example is given by Wharton's synthesis of hedycaryol (**104**).[52a] The requisite boronate (**103**; Scheme 34) is prepared in a straightforward manner from (**101**), proceeding *via* hydroboration of the unsaturated tosylate (**102**) and subsequent hydrolysis of the monoalkylborane. The latter step also brings about the fragmentation to give (**104**).



i, B_2H_6, THF, 0 °C, 2 h, r.t., 7 h; ii, 5 M NaOH, 65 °C, 13 h

Scheme 34

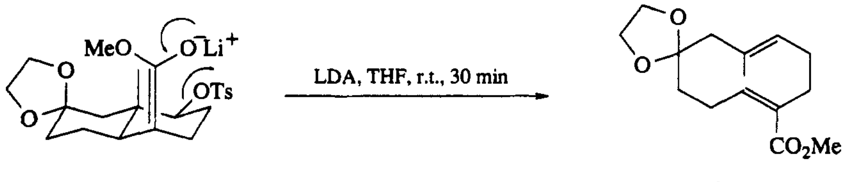
A very recent example of a Wharton-type fragmentation under modified conditions has been reported by De Clercq[52b] in an approach to the synthesis of periplanone B (**104c**) *via* diol (**104a**) and the 10-membered ketone (**104b**; Scheme 34a).



i, 2 equiv. BuLi, –30 °C, 30 min; ii, 3 equiv. TFAA, ether, –20 °C, 15 min

Scheme 34a

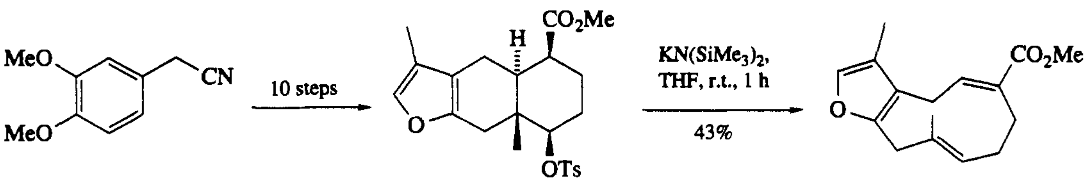
Mander[53] has provided the first example of an enolate-assisted fragmentation reaction. It was shown that the ester enolate (**105**), in which the activating ester is exocyclic to the ring, clearly undergoes intraannular fragmentation to yield the 1,5-diene ester (**106**; Scheme 35).



(105) **(106)**

Scheme 35

Another recent example for a similar enolate fragmentation to construct a 10-membered ring is represented by the last step of the sericenine (**108**; Scheme 36) synthesis.[54] (**108**) is a constituent of the essential oil of the leaves of *Neolitsea sericea* (Lauraceae), which grows in the southern parts of Japan and China. The tosyloxy ester (**107**) gives directly the furanogermacradiene (**108**), presumably *via* the neosericenine with the *cis*-α,β-unsaturated ester group, which isomerizes to the thermodynamically favored product.



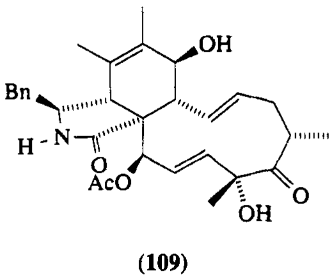
(107) **(108)**

Scheme 36

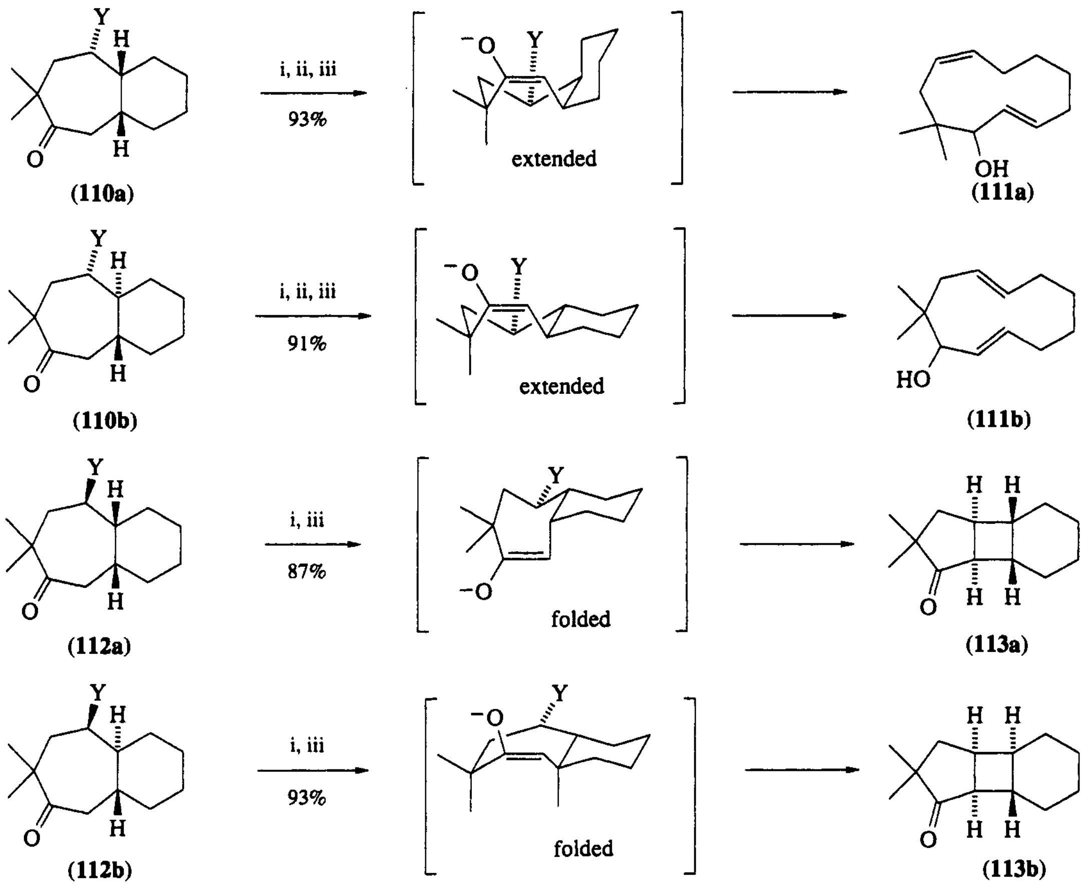
Fuchs[55] has used this reaction type for the construction of an 11-membered ring in the course of model studies for the [11]cytochalasin synthesis. These cytostatic compounds, *e.g.* cytochalasin C (**109**), are metabolites of microorganisms. Reductive fragmentation of the benzenesulfonates (**110**; Scheme 37) produces the dienols (**111**). In contrast, both the sulfonates (**112**) on treatment with LDA afford the tricyclic ketones (**113**), the products of internal alkylation. Less than 1% of (**111**) is formed. In conclusion, the author points out that the enolate conformation (Scheme 37, in parentheses) appears to be all important in determining the reaction products of the four diastereoisomers (**110**) and (**112**). Whenever the enolate can easily assume a folded conformation, the tricyclic cyclobutane (**113**) will result. Models of the enolates of (**110**), where the intraannular fragmentation successfully occurs, show that the folded conformations are more strained than are the extended conformations.

Unsaturated macrolides such as (**115**) or (**117**) (Scheme 38) have been synthesized by Eschenmoser using a fragmentation reaction as a key step. The tricyclic ketal carboxylate (**114**) can be cleaved as an amidinium salt to give (**115**) in excellent yield simply on heating.[56] Similarly, the macrolide (**117**) with (*E*,*E*)-configuration is obtained from (**116**).[57] This decarboxylative double fragmentation represents a nine-center Grob type.

Exaltone (cyclopentadecanone) (**118**; Scheme 39) and more so muscone (3-methylcyclopentadecanone) (**119**) are valuable musk fragrances of great commercial potential. Since the construction of a 15-membered ring by direct ring closure is quite difficult, ring extension methods possess particular

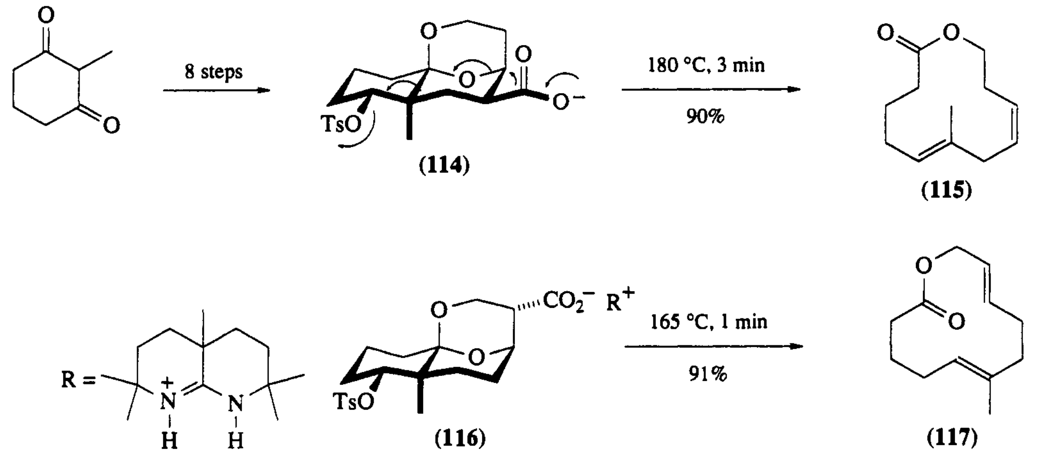


(109)



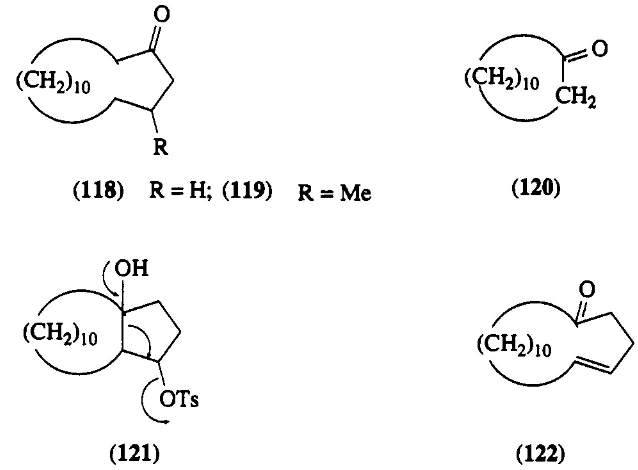
i, LDA, THF, –78 °C; ii, DIBAl-H, –78 °C; iii, warming to r.t., 2 h
Y = OSO_2Ph

Scheme 37



Scheme 38

interest. The most convenient and cheap starting material is cyclododecanone (**120**). There are numerous available syntheses of (**118**) and (**119**) and several of them use a fused 12-membered ring as the key compound in a fragmentation reaction.



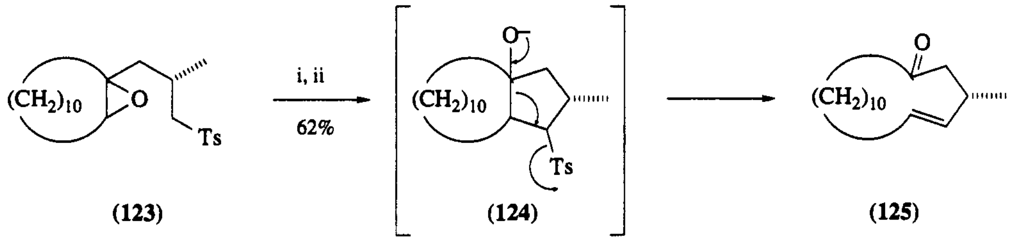
(118) R = H; **(119)** R = Me **(120)**

(121) **(122)**

Scheme 39

The pioneering work of Ohloff[58] in this field is shown by his historic paper on the synthesis of both **(118)** and **(119)**. *Inter alia*, the bicyclic tosylate **(121)** provides, by Grob fragmentation, the unsaturated ketone **(122)**, which also has a strong musk odour.

Fischli[59] has described a chiral, economic synthesis of (*S*)- and (*R*)-muscone **(119)** also starting from **(120)**. The key step is the epoxysulfonyl cyclofragmentation of **(123)** to (*E*,*Z*)-dehydromuscone (**125**; Scheme 40) in a one-pot procedure. The sulfone moiety serves as a carbanion stabilizer for the epoxide cleavage as well as a leaving group.



(123) **(124)** **(125)**

i, NaNH$_2$, toluene, reflux, 10 h; ii, Bu^{t}OK, Bu^{t}OH, HMPA, reflux, 16 h

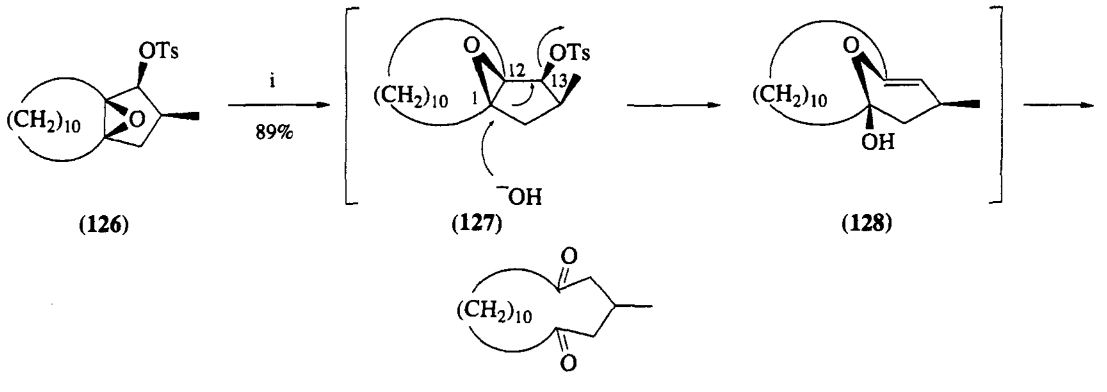
Scheme 40

Another fragmentation on the way to muscone **(119)** has been used by Dreiding,[60] starting with epoxy tosylate (**126**; Scheme 41) to furnish dione **(129)**. Possible mechanisms have been discussed in detail, with the most probable intermediates being **(127)** and **(128)** since the ^{1}H NMR data show that the C(1)—C(12) bond is almost antiperiplanar to the C(13)—OTs bond.

Hesse[61] has described an exaltolide (cyclopentadecanolide) (**134**; Scheme 42) synthesis starting from the readily available 2-cyanocyclododecanone **(130)**. The latter is converted to the quaternary ammonium salt **(131)**, which undergoes fragmentation under mild conditions to provide the lactone **(133)** *via* the lactole anion **(132)**. The methylene compound **(133)** exhibits similar musk odor, as does **(134)**.

5.4.2.3 Alkynones (Eschenmoser-type)

In his pioneering work, Eschenmoser[14] first described the epoxy ketone–alkynone fragmentation which now (usually) bears his name. Of course, this reaction is a special seven-center Grob-type reaction starting with the tosylhydrazone of an α,β-epoxy ketone (Scheme 43). Deprotonation leads to an alkoxide which immediately undergoes fragmentation to give four parts, a ketone, an alkyne, nitrogen and the leaving group toluenesulfinate. It is quite obvious that this reaction possesses synthetic value only if both the ketone and alkyne parts are connected to provide open-chained or cyclic alkynones (Scheme 43).

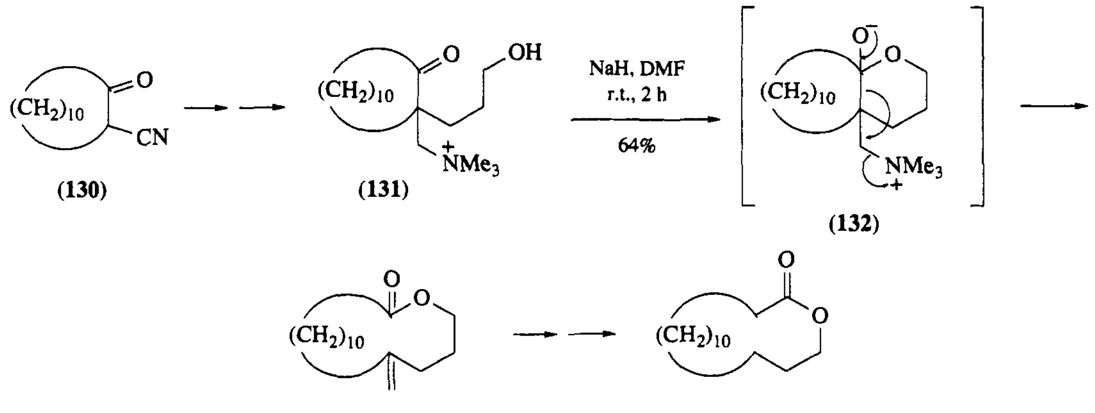


(126) (127) (128)

(129)

i, $CaCO_3$, dioxane, H_2O, reflux, 1 d

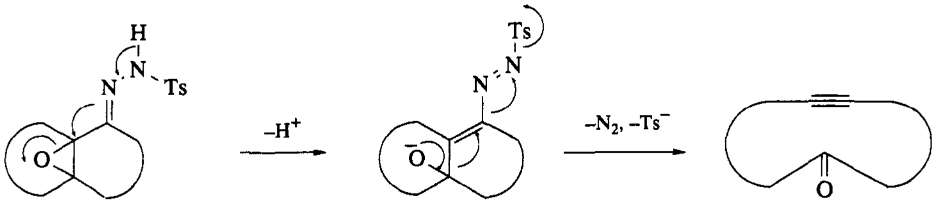
Scheme 41



(130) (131) (132)

(133) (134)

Scheme 42

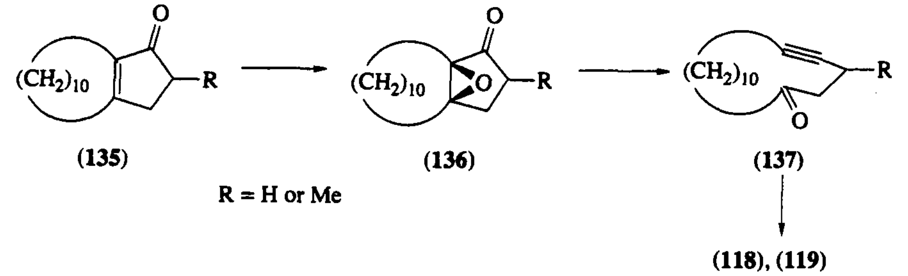


Scheme 43

The first examples to demonstrate the synthetic power of this method[62] were the preparations of exaltone (**118**) and muscone (**119**), starting from the α,β-unsaturated ketones (**135**) and proceeding *via* the epoxy ketones (**136**), the tosylhydrazones of which are cleaved to the cycloalkynones (**137**; Scheme 44). A little later, Tanabe[15] described the same reaction type starting from epoxydecalones, using this fragmentation for the synthesis of secosteroid alkynic ketones.[63]

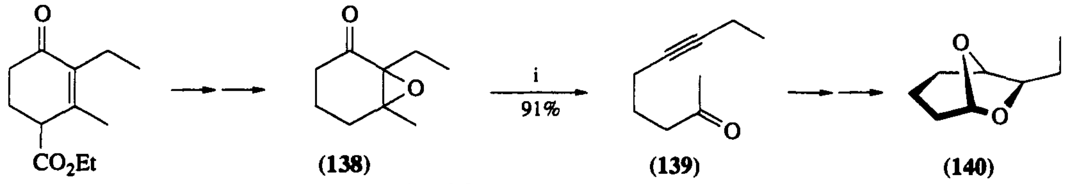
Eschenmoser,[62,64] together with groups from Firmenich, Geneva, and CIBA, Basle, gave an extended scope to the synthesis of various alkynones. Some preparative variations and improvements have been introduced by the use of oximes,[65] *N*-aminoaziridines,[66] 2,4-dinitrobenzenesulfonohydrazides[67] and 1,3,4-oxadiazolin derivatives.[68]

Some examples of the synthetic value of the Eschenmoser fragmentation should be given. Kocienski's economical and highly stereoselective synthesis[69] of both *endo*- and *exo*-brevicomin (**140**) uses the alkynone (**139**) as an intermediate, easily accessible by fragmentation of the keto epoxide (**138**; Scheme 45). Stevens[70] used this fragmentation during the course of studies on the synthesis of vitamin B_{12} precursors,



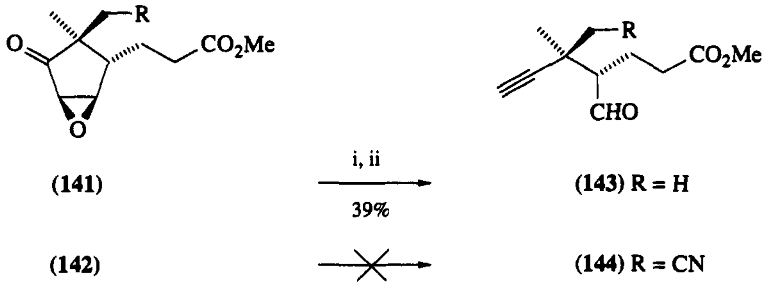
Scheme 44

with various degrees of success. The precursor of ring C, the alkynic aldehyde (**143**), can be obtained from the epoxy ketone (**141**; Scheme 46); numerous experiments were required to find a set of special conditions. However, in the course of the synthesis of the B-ring all attempts to cleave (**142**) *via* the tosylhydrazone or similar intermediate failed. In each case reaction was observed, but the resulting complex mixtures were devoid of aldehyde or alkyne protons.



i, $TsNHNH_2$, 0 °C, 3 h, r.t., 3 h

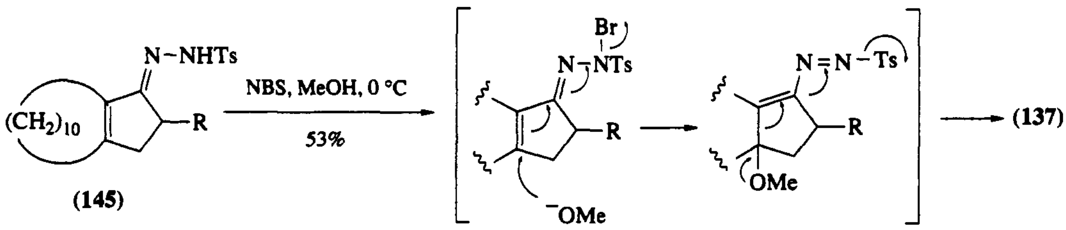
Scheme 45



i, $TsNHNH_2$, CH_2Cl_2, AcOH, 0 °C, 2 h; ii, $BF_3 \cdot Et_2O$, CH_2Cl_2, r.t.

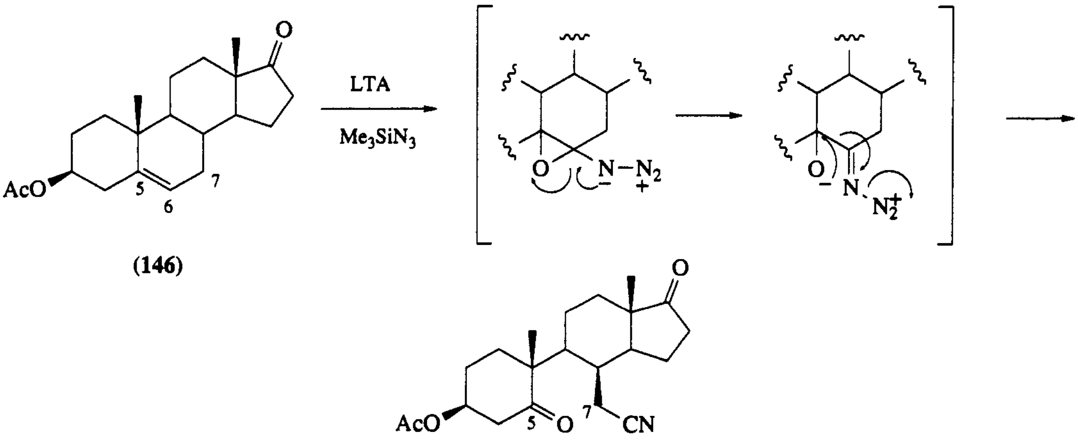
Scheme 46

The formation of epoxy ketones from sterically crowded enones is often difficult. Avoiding the epoxidation step, fragmentation to give the alkynone (**137**; Scheme 47) occurs on treatment of the unsaturated hydrazones (**145**) (from **135**) with an excess of NBS in methanol. Ohloff and Büchi[71] used this sequence for a further synthesis of exaltone (**118**) and muscone (**119**).



Scheme 47

Treatment of the steroid (**146**; Scheme 48) with LTA and TMS-N_3 gives the 5,6-seco-5-oxo-7-carbonitrile steroid (**147**) useful for the synthesis of ring B homoazasteroids. Zbiral[72] explains the mechanism as an aza analog of the Eschenmoser fragmentation *via* formation of the azido epoxide.

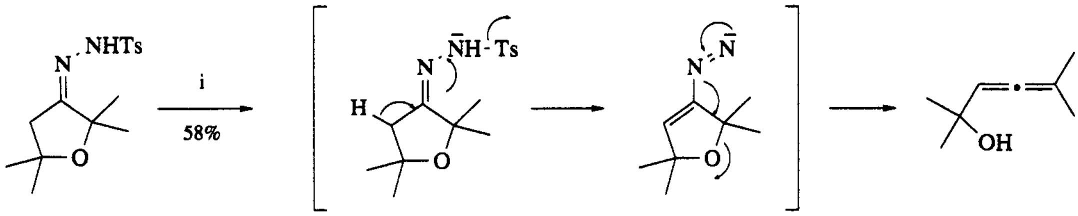


(**146**)

(**147**)

Scheme 48

α-Alkoxy tosylhydrazones without the ring strain of an epoxide react in a different way. Since there is insufficient driving force for immediate ring opening, these derivatives need two equivalents of strong base. Agosta[73] used this reaction for preparation of some allenes (**149**) from tosylhydrazones (**148**; Scheme 49).



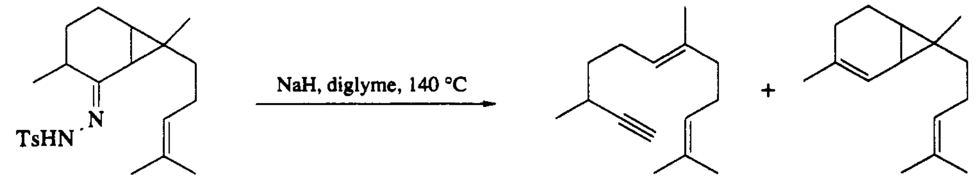
(**148**)

(**149**)

i, 2.5 equiv. BuLi, ether, r.t., 30 min

Scheme 49

Occasionally, the fragmentation is unexpected and unwanted. For the synthesis of sesquicarene (**152**), Coates[74] heated the sodium salt of tosylhydrazone (**150**). However, the main reaction was the carbon analog of the Eschenmoser fragmentation leading to the alkyne (**151**; Scheme 50).



(**150**)

(**151**) 53%

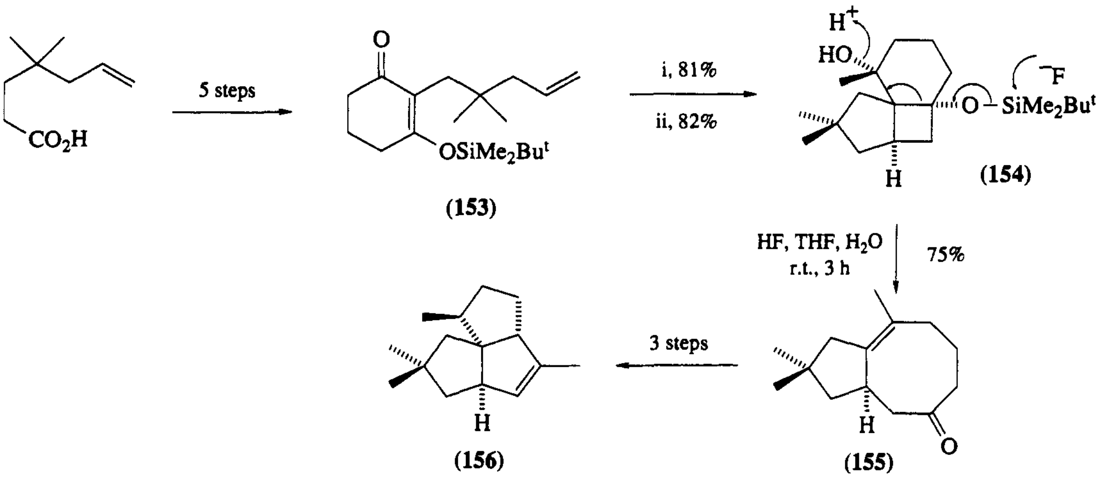
(**152**) 15%

Scheme 50

5.4.2.4 Silicon- and Metal-assisted Fragmentations

There seems to be no compelling reason to discuss silicon- and metal-assisted fragmentations in a special chapter, since they are mostly ordinary Grob types leading to medium-sized ring systems. However, justification is given by the fact that these reactions use unusual reagents under mild conditions or involve subsequent reactions.

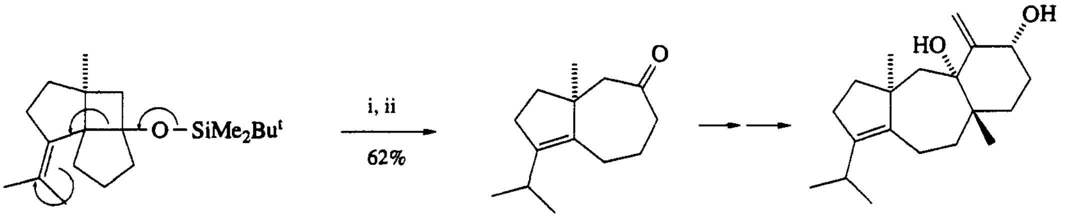
The bicyclo[6.3.0]undecenone (**155**) is elaborated from the silyl enol ether (**153**; Scheme 51) using a unique intramolecular [2 + 2] photocycloaddition–Grob fragmentation sequence.[75] When the silyl ether (**154**) is treated with aqueous hydrofluoric acid in THF, a smooth fragmentation ensues leading to the fused 5,8-ring enone (**155**) which is then converted to pentalenene (**156**), a triquinane isolated in 1980 from *Streptomyces griseochromogenes*. In the fragmentation step HF provides both the electrofugal and nucleofugal part by way of the F—Si affinity and by protonation of the hydroxy group.



i, 450 W Hg lamp, heptane, 7 h; ii, Me_3CuLi_2, ether, –68 °C, 1 h

Scheme 51

Isoamijiol (**159**; Scheme 52), a linear 5,7,6-ring-fused member of the dolastane group of diterpenes, is the principal secondary metabolite in the brown seaweed *Dictyota linearis*. In the course of the synthesis of (**159**), Pattenden[76] also used a photocycloaddition–fragmentation sequence. Treatment of (**157**) with HF as mentioned above yields the hydroazulenone portion (**158**) of (**159**), which then was elaborated to isoamijiol. This is the first example of a C=C bond and an Si—O bond being used as 'push–pull' partners in a fragmentation.



(157) (158) (159)

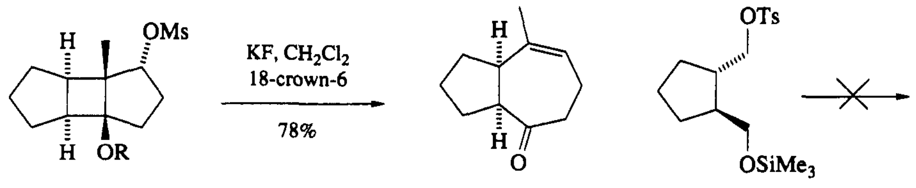
i, HF, THF, r.t., 1.5 h; ii, 60 °C, 2.5 h

Scheme 52

Whilst alkaline fragmentation of hydroxysulfonates such as (**160**; Scheme 53) is accompanied by isomerization to give *trans*-bicyclo[5.3.0]decenones, the fluoride-induced[77] fragmentation of the silyl ether (**161**) leads exclusively to the *cis* isomer (**162**). This reaction type is limited to strained systems. Thus, the silyl ether (**163**) does not react at all under similar conditions.

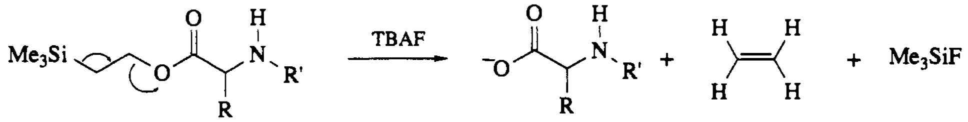
A mechanistically related and mild fragmentation is that of 2-trimethylsilylethyl esters (Tmse esters). The Tmse residue is a selectively cleavable carboxy-protecting group (see Volume 6, Chapter 3.2) Examples are known for the synthesis, *via* these esters, of peptides,[78] macrolides such as curvularin[79] and macrocyclic trichothecenes like verrucinol (Scheme 54).[80]

The reductive fragmentation with solvated electrons (metal in liquid ammonia) of strained rings bearing carbonyl groups in a 1,4-relationship leads to dicarbonyl systems with a lower number of fused rings (Scheme 55).

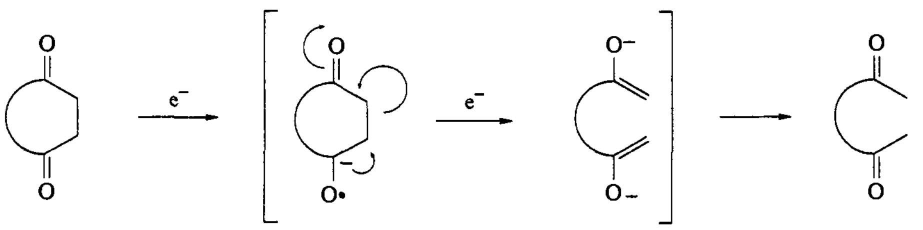


(160) R = H → **(161)** R = SiMe$_3$ **(162)** **(163)**

Scheme 53

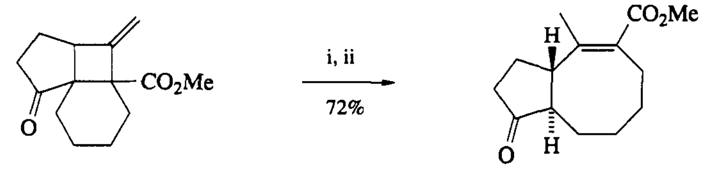


Scheme 54



Scheme 55

Valuable applications of this principle have been described by Paquette[81] for the synthesis of topologically spherical molecules. Coates[82] used this reductive fragmentation for the synthesis of bicyclo[6.3.0]undecenecarboxylates, compounds which bear a structural resemblance to the A–B rings of the fusicoccin and ophiobolane natural products. Reduction of the unsaturated keto ester (**164**) affords an isomeric mixture of esters, the equilibration of which effects conversion to the single ester (**165**; Scheme 56).



(164) **(165)**

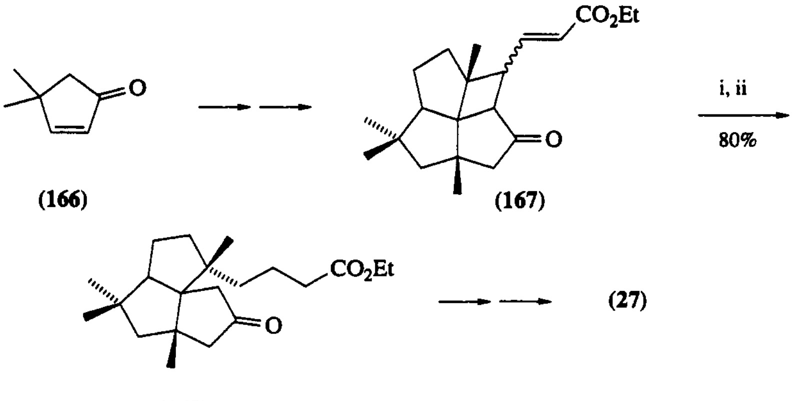
i, Li, NH$_3$, THF, 5 min; ii, NaOMe, MeOH, reflux, 19 h

Scheme 56

The sequence of intramolecular photocycloaddition–cyclobutane fragmentation has been used by Crimmins in an excellent manner for the synthesis of pentalenenes[83] and the even more sophisticated lauren-1-ene (**27**). The latter synthesis[84] was accomplished in 27 steps from cyclopentenone (**166**). One of the key steps is the reductive cleavage of the tetracyclic cyclobutane (**167**), followed by hydrogenation of the resulting β,γ-unsaturated ester to give keto ester (**168**; Scheme 57).

Quite related to the above reaction type is the reductive α,β-fragmentation of γ-halocyclobutyl ketones (Scheme 58).[85] Oppolzer[86] used this reaction in a new approach to the acorane system, and the mechanism was discussed. It remains to be clarified as to what extent this type of reaction entails similar stereoelectronic constraints as the classical Grob fragmentation.

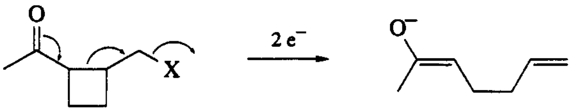
An elegant synthetic application of such a fragmentation has been described by Funk.[87] The ketone (**170**; Scheme 59) serves as a convenient precursor for 7,12-secoishwaran-12-ol (**171**), an antifertility



(166) **(167)** **(168)**

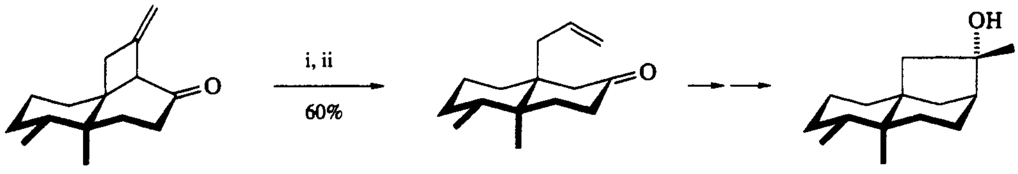
i, Na, NH_3, ether, –33 °C, 5 min; ii, H_2, Pd–C, EtOH

Scheme 57



Scheme 58

agent isolated from *Aristolochia indica*. For the preparation of (**170**) the known ketone (**169**) requires only the formal addition of H_2 to the cyclobutane α-keto carbon–vinyl carbon σ-bond. To this end, anti-Markownikow addition of HBr to alkene (**169**) and treatment of the crude mixture of bromides with Li/NH_3 gives the allyl decalone (**170**).



(169) **(170)** **(171)**

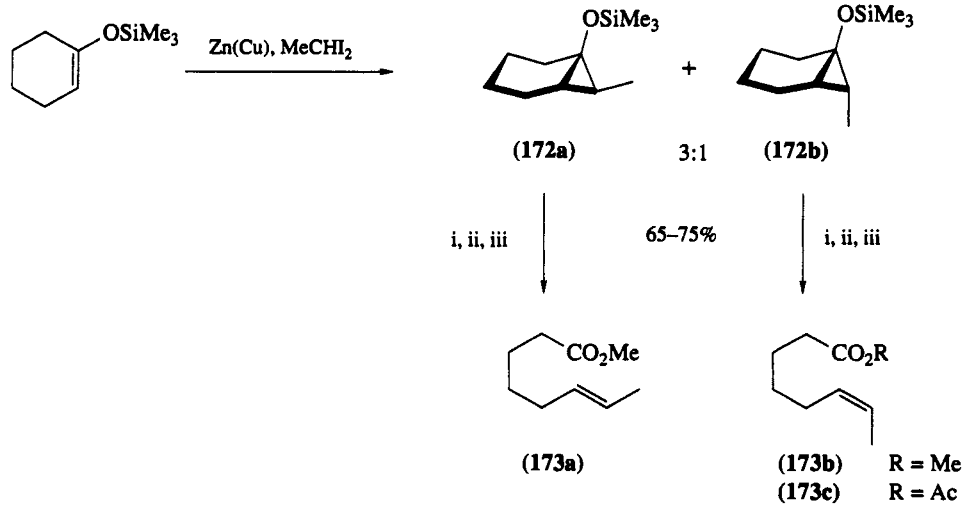
i, HBr, *h*ν; ii, excess Li, NH_3, THF

Scheme 59

The stereospecific synthesis of some methyl (*E*)- and (*Z*)-alkenoates (**173**; Scheme 60) has been carried out using lead-assisted oxidative fragmentation.[88] Starting from trimethylsilyloxyalkenes, a mixture of *exo*-methylated (**172a**) and *endo*-methylated (**172b**) cyclopropanes has been prepared. Treatment with LTA, then with CH_2N_2 gives (**173a**) and (**173b**). The fact that (**172a**) gives only (**173a**) and (**172b**) gives only (**173b**) proves that the fragmentation is stereospecific. The most reasonable explanation for this process involves initial solvolysis by AcOH to give the corresponding cyclopropanol (**172c**; Scheme 61). This reacts with lead(IV) to give the alkenoic acid anhydride (**173c**) through a series of reactions including ring cleavage with inversion at the carbon bonded to Pb, followed by fragmentation with $Pb(OAc)_2$ as the leaving group. The antiperiplanar relationship of the C(1)—C(6) and the C(7)—Pb bonds of (**172d**) is ideal for a Grob fragmentation.

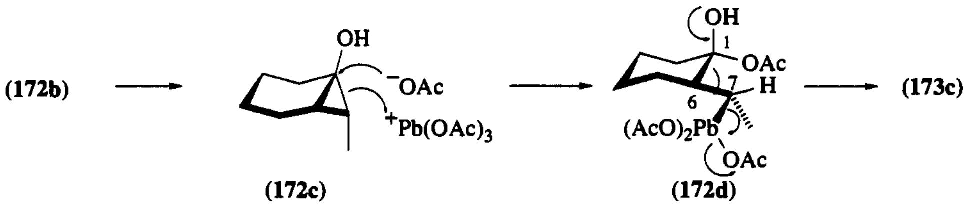
Treatment of patchoulol (**174**; Scheme 62), an olfactive component of patchouli oil, with LTA gives rise to a mixture from which the almost pure ketone (**175**) is distilled. Thomas[89] has postulated a free carbenium ion mechanism, but this reaction may be a regiospecific fragmentation facilitated by the fact that the proton on C(5) is oriented antiperiplanar to the C(1)—O bond.

The oxidative cleavage of γ-stannyl alcohols will be discussed in Volume 7, Chapter 4.2. Two recent examples of this so-called 'oxidative fragmentation' should be given. Posner[90a] has described a flexible and simple synthesis of macrolides involving this reaction to produce both ring enlargement and regio-

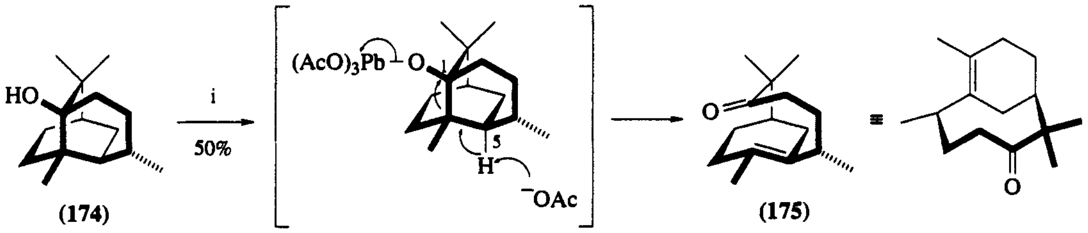


i, LTA, AcOH, r.t., 8 h; ii, H_2O, 20 min; iii, CH_2N_2

Scheme 60



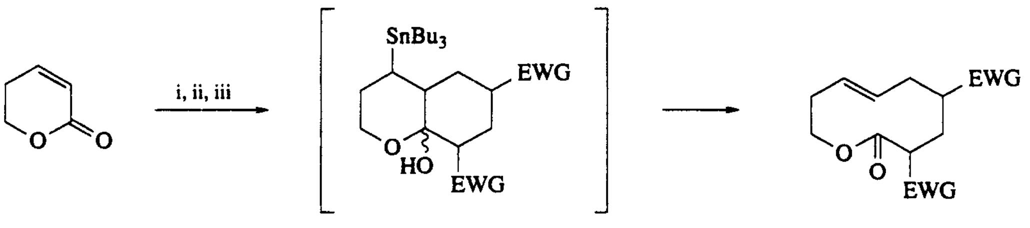
Scheme 61



i, LTA, $CaCO_3$, benzene, reflux, 3 h

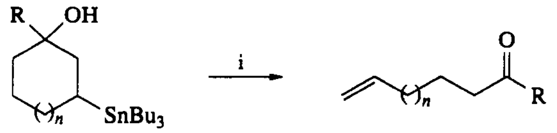
Scheme 62

specific formation of an alkenyl unit (Scheme 63). ω-Unsaturated carbonyl compounds have been obtained under modified Pfitzner—Moffatt (MOPMO) conditions (Scheme 63a).[90b]



i, $LiSnBu_3$; ii, $H_2C{=}CH\text{-}EWG$; iii, LTA, benzene, reflux

Scheme 63



R = alkyl, phenyl; n = 0, 1, 2

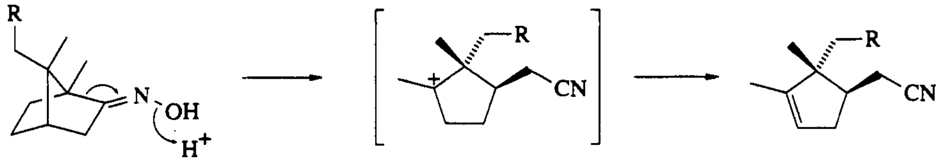
i, $(PhIO)_n$, DCC, $BF_3{\bullet}Et_2O$, CH_2Cl_2, 0 °C

Scheme 63a

5.4.3 BECKMANN FRAGMENTATION

The Beckmann fragmentation, as a special type of Beckmann rearrangement (see Volume 7, Chapter 5.2), occurs in particular when one of the alkyl groups attached to the oxime carbon is capable of stabilizing a positive charge, leading to a carbocation and a nitrile. Camphor oxime (**176**) is representative of the structural type which fragments to a tertiary carbocation, and its cleavage to α-campholenonitrile (**178**) with a variety of reagents was reported last century (Scheme 64). Hill[91] has done a historical review and investigated this reaction type in detail. With PPA, secondary reactions of the carbocation give rise to an array of novel products. Stevens has used the Beckmann fragmentation of the camphor derivative (**177**; Scheme 64) for an enantiospecific approach to the total synthesis of steroids[92] and precursors of vitamin B_{12}.[70] Under the reaction conditions the *endo*-alkene (**179**) is formed exclusively.

The key step in Ayer's[93] grandisol (**183**; Scheme 65) synthesis is the Beckmann fragmentation of oxime (**181**), which is prepared from eucarvone (**180**). Thus, nitrile (**182**) is readily accessible.

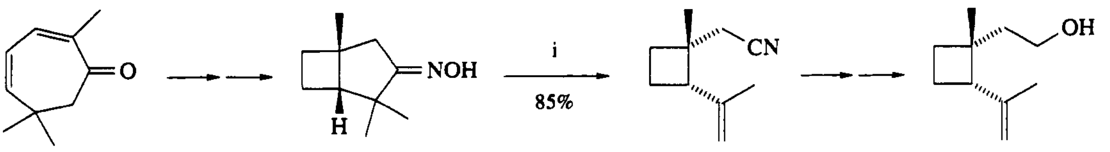


(**176**) R = H $\xrightarrow[80\%]{\text{i, ii}}$ (**178**) R = H

(**177**) R = CH_2CO_2Me (**179**) R = CH_2CO_2Me

i, TFAA, CH_2Cl_2, 0 °C to r.t., 4 h; ii, TFA, r.t., 24 h

Scheme 64

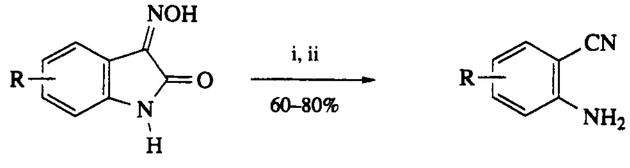


(**180**) (**181**) (**182**) (**183**)

i, PCl_3, lutidine, ether, 5 min

Scheme 65

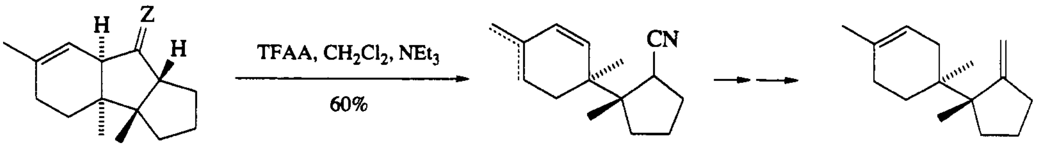
Isatin oxime triflates (**184**; Scheme 66) undergo facile fragmentation promoted by DBU to form anthranilonitriles (**185**) after hydrolytic work-up.[94] The ketone (**187**; Scheme 67), key compound of Harding's[95] highly stereoselective, convergent synthesis of trichodiene (**190**), has been prepared by Nazarov cyclization from simple starting materials. Numerous reaction sequences have been investigated to find conditions to cleave the central five-membered ring. The only useful reaction is the Beckmann fragmentation of the oxime (**188**) to yield the cyanodienes (**189**). The silicon-directed Beckmann fragmentation is a valuable addition to the available synthetic methods. It leads to the regio- and stereo-specific formation of alkenes.[96,97] Most interesting is a variation which uses only catalytic amounts of TMS-OTf, since this reagent is recycled by the reaction itself.[98] This sequence has been utilized for the synthesis of the acetate (**193**; Scheme 68), a component of the sex pheromone of the potato tuberworm moth *Phthorimaea operculella*. Treatment of the key compound (**191**) with catalytic amounts of TMS-OTf cleaves the oxime under very mild conditions to give the nitrile (**192**).



(184) (185)

i, TFAA, 2,6-lutidine, CH_2Cl_2, 0 °C, then 3 h reflux; ii, DBU, r.t., 1 h, then $NaHCO_3$

Scheme 66

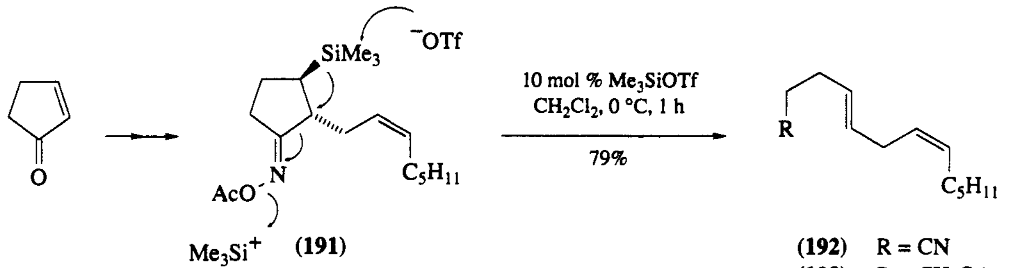


(187) Z = O
(188) Z = NOH

(189)

(190)

Scheme 67



(191)

(192) R = CN
(193) R = CH_2OAc

Scheme 68

5.4.4 MISCELLANEOUS

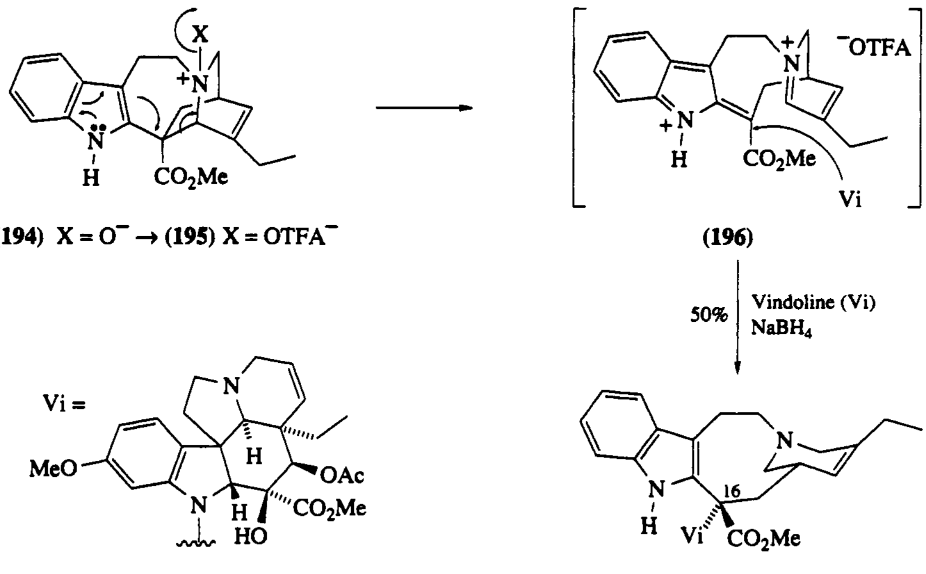
The Polonovski reaction (see Volume 6, Chapter 4.7) — the action of an acid anhydride on an *N*-oxide — can give rise both to elimination or fragmentation reactions.[99] Potier[100] has modified the fragmentation by use of TFAA rather than Ac_2O and has applied this version to a useful synthesis of compounds related to antitumor alkaloids of *Catharanthus roseus, e.g.* vinblastine and vincristine.

Treatment of catharanthine *N*-oxide (**194**; Scheme 69) with TFAA in CH_2Cl_2 at –78 °C in the presence of vindoline, and then with $NaBH_4$ in a one-pot reaction leads to anhydrovinblastine (**197**), in the natural (*S*)-configuration at C-16, in 50% yield. The reaction proceeds *via* the intermediate (**195**), its fragmentation to (**196**), and immediate attack of vindoline at the α-face of (**196**).

Despite that it is named as such quite often in the literature, the radical β-scission or β-cleavage is not a fragmentation in the sense considered in this chapter. The first example of a macrolide synthesis through such a reaction type was achieved by Ohloff[101] and resulted in an industrial synthesis of exaltolide (**134**; Scheme 70). Schreiber has described iron–copper-promoted fragmentation reactions of α-alkoxy hydroperoxides as a route to macrolides.[102,103] Two recent informative publications which cover the prior literature have been written by Suginome[104] and Macdonald.[105]

A short synthesis of ambrox (**202**; Scheme 71),[106] one of the most important ambergris fragrance compounds, has been performed, using natural sclareol (**198**) as starting material and involving β-cleavage as the key step. Iron(II) cleaves the hydroperoxide (**199**) to give the radical intermediate (**200**), which fragments into the alkyl radical (**201**) and methylvinyl ketone. Cyclization of (**201**) *via* the carbonium ion leads to ambrox (**202**). Similar results have been obtained by β-cleavage of other sclareol derivatives.[107]

Snowden has used the terminus fragmentation in his earlier papers for the β-cleavage of homoallylic alkoxides (Scheme 72). Such a reaction sequence (Scheme 73) has been used in particular for the synthesis of damascones (*e.g.* γ-damascone **203**) and related compounds.[108,109]

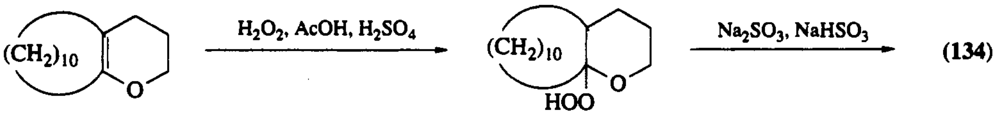


(194) X = O$^-$ → **(195)** X = OTFA$^-$

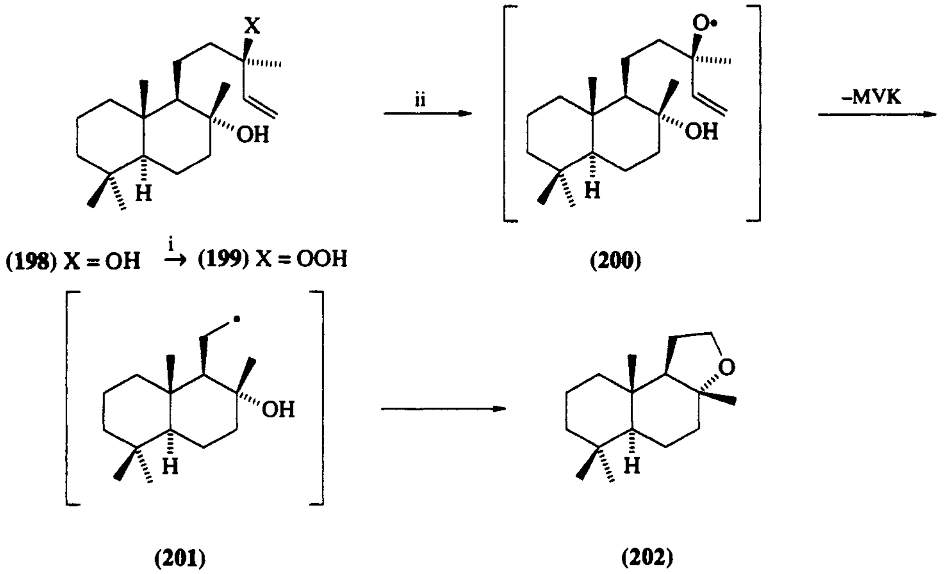
(196)

(197)

Scheme 69



Scheme 70



(198) X = OH $\xrightarrow{i}$ **(199)** X = OOH

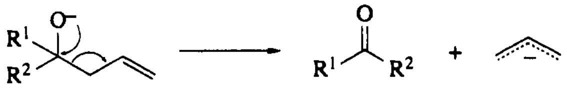
(200)

(201)

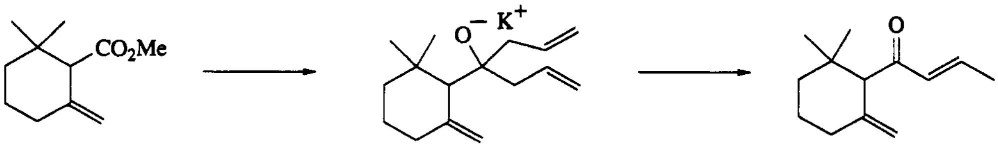
(202)

i, H$_2$O$_2$ (70%), CH$_2$Cl$_2$, r.t., 7 d; ii, Cu(OAc)$_2$, FeSO$_4$, MeOH, 50 °C, 2 h

Scheme 71



Scheme 72



(203)

Scheme 73

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Each entry consists of the author's name, followed by a list of numbers, each of which is associated with a superscript number. For example

Abbott, D. E., $6^{12,12c}$, 10^{40}, $573^{53,54}$

The numbers indicate the text pages on which references by the author in question are cited; the superscript numbers refer to the reference number in the chapter bibliography. Citations occurring in the text, tables and chemical schemes and equations have all been included.

Although much effort has gone into eliminating inaccuracies resulting from the use of different combinations of initials by the same author, the use by some journals of only one initial, and different spellings of the same name as a result of transliteration processes, the accuracy of some entries may have been affected by these factors.

Subject Index