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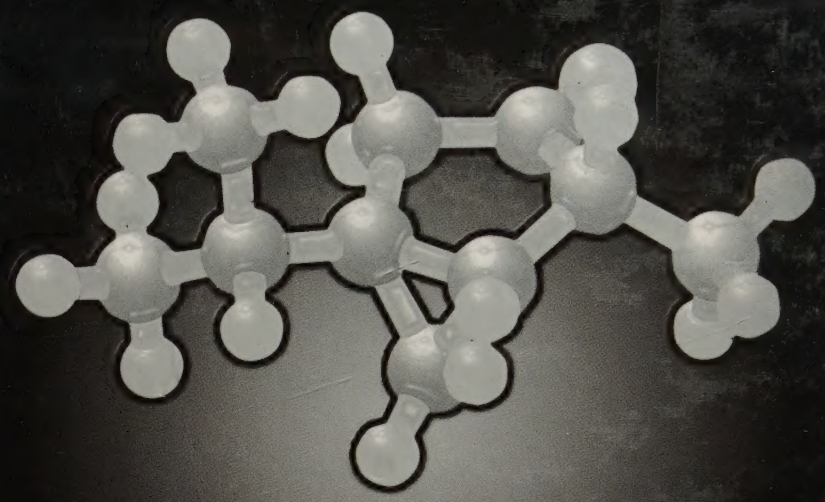

Handbook of Reagents for Organic Synthesis

Reagents for Direct Functionalization of C–H Bonds

Edited by
Philip L. Fuchs

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General Abbreviations

Ac	acetyl
acac	acetylacetonate
AIBN	2,2′-azobisisobutyronitrile
Ar	aryl
BBN	borabicyclo[3.3.1]nonane
BCME	dis(chloromethyl)ether
BHT	butylated hydroxytoluene (2,6-di-*t*-butyl-*p*-cresol)
BINAL-H	2,2′-dihydroxy-1,1′-binaphthyl-lithium aluminum hydride
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1′-bi-2,2′-naphthol
bipy	2,2′-bipyridyl
BMS	borane–dimethyl sulfide
Bn	benzyl
Boc	*t*-butoxycarbonyl
BOM	benzyloxymethyl
bp	boiling point
Bs	brosyl (4-bromobenzenesulfonyl)
BSA	*N,O*-bis(trimethylsilyl)acetamide
Bu	*n*-butyl
Bz	benzoyl
CAN	cerium(IV) ammonium nitrate
Cbz	benzyloxycarbonyl
CDI	*N,N′*-carbonyldiimidazole
CHIRAPHOS	2,3-bis(diphenylphosphino)butane
Chx	= Cy
cod	cyclooctadiene
cot	cyclooctatetraene
Cp	cyclopentadienyl
CRA	complex reducing agent
CSA	10-camphorsulfonic acid
CSI	chlorosulfonyl isocyanate
Cy	cyclohexyl
d	density
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	*N,N′*-diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DBAD	di-*t*-butyl azodicarboxylate
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N′*-dicyclohexylcarbodiimide
DCME	dichloromethyl methyl ether
DDO	dimethyldioxirane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAL	diisobutylaluminum hydride
DIEA	= DIPEA
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane
DIPEA	diisopropylethylamine
diphos	=dppe
DIPT	diisopropyl tartrate
DMA	dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
dmg	dimethylglyoximato
DMPU	*N,N′*-dimethylpropyleneurea
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DMTSF	dimethyl(methylthio) sulfonium tetrafluoroborate
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1′-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
DTBP	di-*t*-butyl peroxide
EDA	ethyl diazoacetate
EDC	1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide
EDCI	= EDC
ee	enantiomeric excess
EE	1-ethoxyethyl
Et	ethyl
ETSA	ethyl trimethylsilylacetate
EWG	electron withdrawing group
Fc	ferrocenyl
Fmoc	9-fluorenylmethoxycarbonyl
fp	flash point
Hex	*n*-hexyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoric triamide
HOBt	l-hydroxybenzotriazole
HOBT	=HOBt
HOSu	*N*-hydroxysuccinimide
Im	imidazole (imidazolyl)
Ipc	isopinocampheyl
IR	infrared
KHDMS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LD_{50}	dose that is lethal to 50% of test subjects

LDA	lithium diisopropylamide
LDMAN	lithium 1-(dimethylamino)naphthalenide
LHMDS	= LiHMDS
LICA	lithium isopropylcyclohexylamide
LiHMDS	lithium hexamethyldisilazide
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
LTMP	= LiTMP
LTA	lead tetraacetate
lut	lutidine
m-CPBA	*m*-chloroperbenzoic acid
MA	maleic anhydride
MAD	methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide)
MAT	methylaluminum bis(2,4,6-tri-*t*-butylphenoxide)
Me	methyl
MEK	methyl ethyl ketone
MEM	(2-methoxyethoxy)methyl
MIC	methyl isocyanate
MMPP	magnesium monoperoxyphthalate
MOM	methoxymethyl
MoOPH	oxodiperoxomolybdenum(pyridine)-(hexamethylphosphoric triamide)
mp	melting point
MPM	= PMB
Ms	mesyl (methanesulfonyl)
MS	mass spectrometry; molecular sieves
MTBE	methyl *t*-butyl ether
MTM	methylthiomethyl
MVK	methyl vinyl ketone
n	refractive index
NaHDMS	sodium hexamethyldisilazide
Naph	naphthyl
NBA	*N*-bromoacetamide
nbd	norbornadiene (bicyclo[2.2.1]hepta-2,5-diene)
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
NORPHOS	bis(diphenylphosphino)bicyclo[2.2.1]-hept-5-ene
Np	= Naph
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Pent	*n*-pentyl
Ph	phenyl
phen	1,10-phenanthroline
Phth	phthaloyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PMDTA	*N,N,N′,N″,N‴*-pentamethyldiethylene-triamine
PPA	polyphosphoric acid
PPE	polyphosphate ester
PPTS	pyridinium *p*-toluenesulfonate
Pr	*n*-propyl
PTC	phase transfer catalyst/catalysis
PTSA	*p*-toluenesulfonic acid
py	pyridine
RAMP	(R)-1-amino-2-(methoxymethyl)pyrrolidine
rt	room temperature
salen	bis(salicylidene)ethylenediamine
SAMP	(*S*)-1-amino-2-(methoxymethyl)pyrrolidine
SET	single electron transfer
Sia	siamyl (3-methyl-2-butyl)
TASF	tris(diethylamino)sulfonium difluorotrimethylsilicate
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAD	= DBAD
TBAI	tetrabutylammonium iodide
TBAP	tetrabutylammonium perruthenate
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TBHP	*t*-butyl hydroperoxide
TBS	= TBDMS
TCNE	tetracyanoethylene
TCNQ	7,7,8,8-tetracyanoquinodimethane
TEA	triethylamine
TEBA	triethylbenzylammonium chloride
TEBAC	= TEBA
TEMPO	2,2,6,6-tetramethylpiperidinoxyl
TES	triethylsilyl
Tf	triflyl (trifluoromethanesulfonyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran; tetrahydropyranyl
Thx	thexyl (2,3-dimethyl-2-butyl)
TIPS	triisopropylsilyl
TMANO	trimethylamine *N*-oxide
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
Tol	*p*-tolyl
TPAP	tetrapropylammonium perruthenate
TBHP	*t*-butyl hydroperoxide
TPP	tetraphenylporphyrin
Tr	trityl (triphenylmethyl)
Ts	tosyl (*p*-toluenesulfonyl)
TTN	thallium(III) nitrate
UHP	urea–hydrogen peroxide complex
Z	= Cbz

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Contents

Preface

As stated in its Preface, the major motivation for our undertaking publication of the *Encyclopedia of Reagents for Organic Synthesis* was "to incorporate into a single work a genuinely authoritative and systematic description of the utility of all reagents used in organic chemistry." By all accounts, this reference compendium succeeded admirably in approaching this objective. Experts from around the globe contributed many relevant facts that define the various uses characteristic of each reagent. The choice of a masthead format for providing relevant information about each entry, the highlighting of key transformations with illustrative equations, and the incorporation of detailed indexes serve in tandem to facilitate the retrieval of desired information.

Notwithstanding these accomplishments, the editors came to recognize that the large size of this eight-volume work and its cost of purchase often deterred the placement of copies of the *Encyclopedia* in or near laboratories where the need for this type of information is most critical. In an effort to meet this demand in a cost-effective manner, the decision was made to cull from the major work that information having the highest probability for repeated consultation and to incorporate the same into a set of handbooks. The latter would also be purchasable on a single unit basis.

The ultimate result of these deliberations was the publication of the *Handbook of Reagents for Organic Synthesis*, the first four volumes of which appeared in 1999:

Oxidizing and Reducing Agents
Edited by Steven D. Burke and Rick L. Danheiser

Acidic and Basic Reagents
Edited by Hans J. Reich and James H. Rigby

Activating Agents and Protecting Groups
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Reagents, Auxiliaries, and Catalysts for C–C Bond Formation
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Since 2003, the fifth, sixth, and seventh members of this series listed below have made their appearance:

Chiral Reagents for Asymmetric Synthesis
Edited by Leo A. Paquette

Reagents for High-Throughput Solid-Phase and Solution-Phase Organic Synthesis
Edited by Peter Wipf

Reagents for Glycoside, Nucleotide, and Peptide Synthesis
Edited by David Crich

Each of the volumes contains a selected compilation of those entries from the original *Encyclopedia* that bear on the specific topic. The coverage of the last three handbooks also extends to the electronic sequel *e-EROS*. Ample listings can be found to functionally related reagents contained in the original work. For the sake of current awareness, references to recent reviews and monographs have been included, as have relevant new procedures from *Organic Syntheses*.

The present volume entitled *Reagents for Direct Functionalization of C–H Bonds* constitutes the eighth entry in this continuing series of utilitarian reference works. As with its predecessors, this handbook is intended to be an affordable, enlightening compilation that will find its way into the laboratories of all practicing synthetic chemists. Every attempt has been made to be of the broadest possible relevance and the expectation is that our many colleagues will share in this opinion.

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Introduction

Syntheses requiring high material throughput are made even more challenging when targeting pure enantiomers. While asymmetric reactions employing chiral catalysts and prochiral substrates are highly attractive because one molecule of catalyst generates a multitude of chiral progeny, issues such as catalyst cost, and recovery may detract from this inherent advantage.[1] The problem is further compounded by syntheses requiring remote chiral centers, because one may have to access the chiral pool a number of times. Furthermore, if the chemist is forced to adopt one of the stoichiometric chiral strategies, the choice is often nonobvious (Fig. 1).

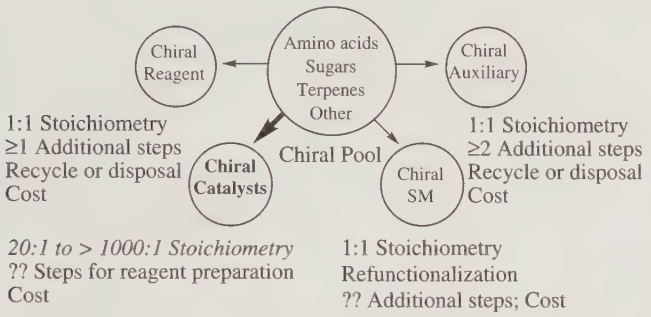
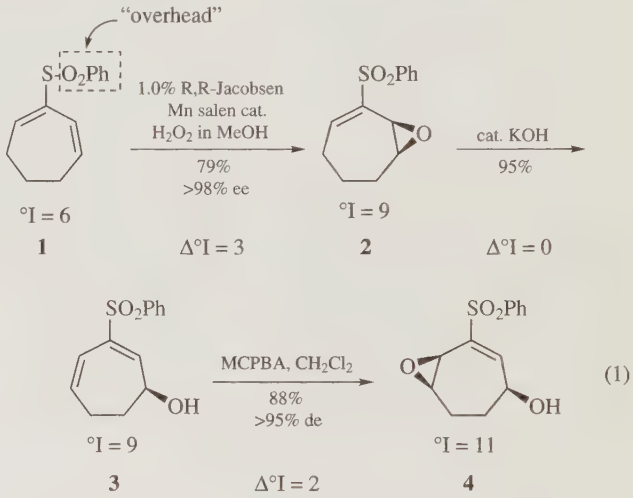


Figure 1 The chiral pool and strategies for enantiospecific synthesis.

Synthetic operations that increase molecular complexity, that is, *degree of intricacy* (°I), include arene and heteroarene functionalizations, introduction of heteroatoms, formation of chiral centers, rings, multiple bonds, and enantiogenesis.[2] In analyzing a synthesis it is useful to calculate Δ°I for each operation. Reactions having positive Δ°I factors (+3 being the theoretical maximum per transformation) indicate creation of new molecular complexity, while reactions with Δ°I equal to zero (protection/deprotection) or negative, signal a *status quo* or worse, *loss* of existing complexity. For example, consider the Jacobsen epoxidation of cross-conjugated dienyl sulfone **1**; this material has four stereogenic olefin centers, the seven-membered ring, and the directly attached sulfur heteroatom for a starting intricacy value of °I = 6. Epoxidation with the enantiopure catalyst converts two of the prochiral centers to chiral centers, introduces a ring, an oxygen, and transforms prochiral **1** to epoxyvinyl sulfone of >98% ee, thus increasing intricacy by three units. Base-catalyzed isomerization of **2** to dienylic alcohol **3** does not increase intricacy, but the subsequent directed epoxidation provides enantiopure **4** with an additional Δ°I increase of two units (eq 1).

The goal of increasing molecular intricacy is well served by reactions that target the functionalization of C–H bonds, since the oxidation of a prochiral C–H bond to an enantiopure molecule with a new chiral center is another example of a Δ°I = 3 process. The past several years have seen exponential growth in both the number of papers and complexity of substrate with regard to the subject area of C–H functionalization. A pair of outstanding monographs (ACS Symposium Series 885: *Activation and Functionalization of C–H Bonds;* Eds. Karen I. Goldberg and Alan S. Goldman, 2004) and the two volume *Handbook of C–H Transformations*, Ed. Gerald Dyker, Wiley-VCH, 2005) provide an extensive introduction for the current EROS reagent-based survey of the use of C–H functionalization strategies as applied to synthetic targets in the 21st century. In order to provide a sharp focus on this ever-expanding field, the current volume is restricted to the four major target areas, shown in the four quadrants of the diagram (Fig. 2).



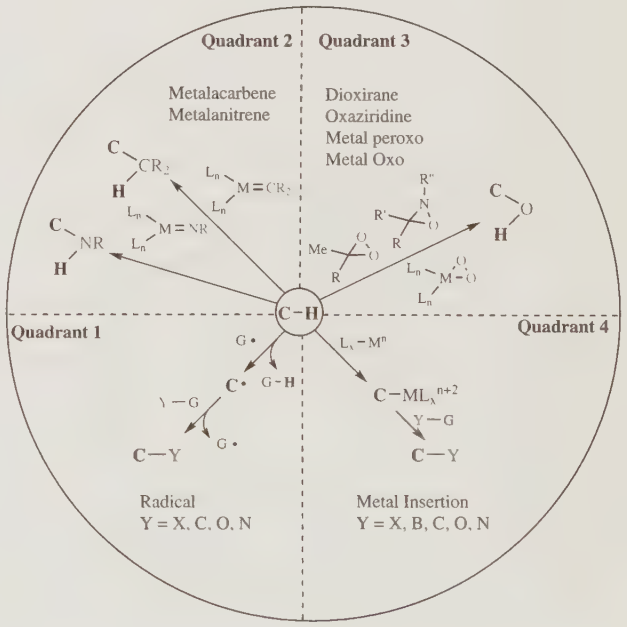
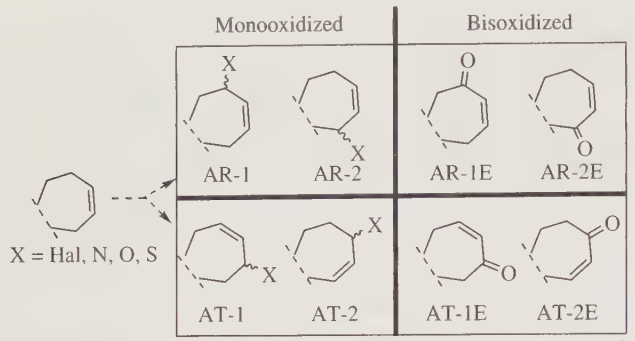


Figure 2 Four major approaches for C–H functionalization.

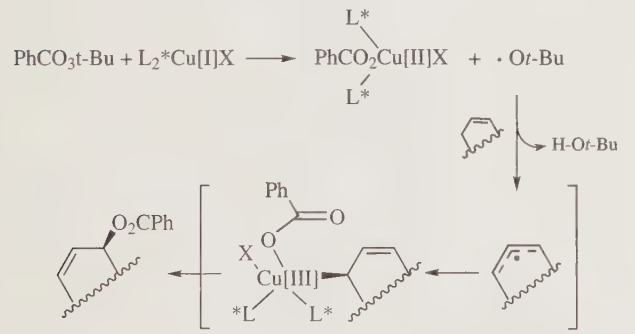
Quadrant 1: Radical Chemistry. Allylic oxidations, such as those employing *N*-**Bromosuccinimide**, are a traditional strategy to effect C–H functionalization relying upon the decreased bond strength of the allylic C–H bonds to dictate chemospecificity. These reactions can afford both allylically retained ("AR") and allylically transposed ("AT") oxidation products. Furthermore, depending upon the reagent selected and stoichiometry employed, both mono- and bisoxidation outcomes are possible (eq 2).

Because allylic functionalization reactions have the potential for generation of up to eight monooxidation products, they are most often conducted upon starting materials that generate a symmetric allylic intermediate.



(2)

The greatest intricacy increasing application of allylic oxidation involves the conversion of a simple symmetrical olefin to a highly enantioenriched allylic carboxylate. This transformation, now commonly termed the Kharasch–Sosnovsky reaction (Fig. 3),[3,4] usually involves the treatment of cyclopentene, cyclohexene, cycloheptene, or cyclooctene with a **copper(I)** or **copper(II)** salt in the presence of a enantiopure ligand and a **peroxyester** to prepare cyclic allylic carboxylates of high enantiomeric excess, although the process is still limited by slow rates and moderate yields.



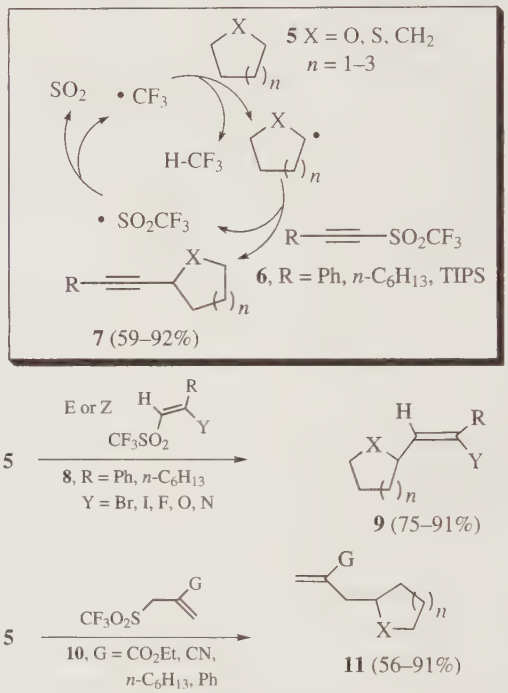
Substrate	Temp.(°C) time(days)	% ee/ % yield	Ligand/ oxidant	Ref.
Cyclopentene	−20/8	99/41	BOX/(a)	5d
Cyclopentene	−20/17	93/30	TOX/(b)	6a
Cyclohexene	−20/17	96/44	BOX/(a)	5d
Cyclohexene	0/8	91/45	BIPY/(b)	9b
Cycloheptene	−20/10	95/03	BOX/(a)	5d
Cycloheptene	−20/10	99/14	BOX/(c)	5d
Cycloheptene	−20/8	92/13	TOX/(c)	6b
1,4 cyclooctadiene	−20/10	94/13	BOX/(a)	5d

(a) *t*-Butyl *p*-nitroperbenzoate; (b) *t*-Butyl perbenzoate + sieves; (c) *i*-Propyl *p*-nitroperbenzoate.

Figure 3 The asymmetric Kharasch-Sosnovsky reaction.

This research area was opened in 1995 with the independent publication of a pair of landmark papers from the groups of Pfaltz[5] and Andrus,[6–10] with important contributions from Katsuki rapidly following.[11–13] Evolution of this strategy has been highly focused upon ligand development, with the initial class of C_2-symmetric enantiopure **bisoxazolines (BOX)** recently being supplemented with newer **BOX ligands**,[14,15] pyridine-linked bisoxazolines (pyBOX),[16–19] C_3-symmetrical trisoxazolines,[11–13] bipyridines,[20–23] and phenanthrolines.[24]

Reaction of ethers, sulfides, and hydrocarbons **5** with **acetylenic triflones 6** and β-heteroatom-substituted vinyl triflones **8** provides facile access to substituted alkynes **7** and alkenes **9**.[25–28] The reaction proceeds via radical C–H abstraction by the highly electrophilic trifluoromethyl radical[29,30] in a process involving subsequent addition of the substrate radical to the α-carbon of the acetylenic (or vinyl) triflone. Elimination of trifluoromethylsulfonyl radical, followed by fragmentation to sulfur dioxide and trifluoromethyl radical, propagates the chain. The power of this method lies in the fact that the chain transfer reaction (fragmentation) is rapid and unimolecular.[31] The scope of C–H bond functionalization was further extended using functionalized **allylic triflones 10**,[32] which also provide excellent yields of C–H functionalization products **11** (eq 3).



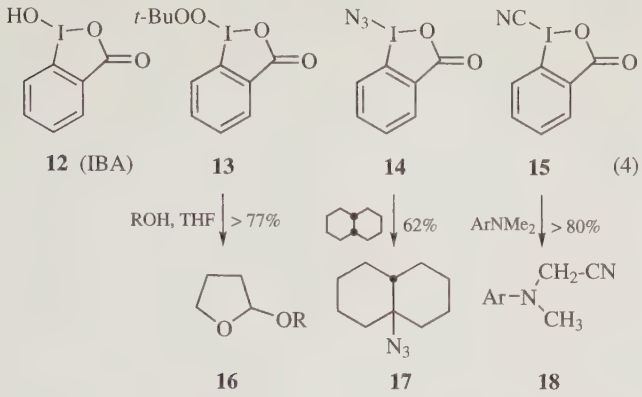
(3)

Other noteworthy stoichiometric radical C–H oxidants reviewed in this handbook include **copper(II) chloride/oxygen** or **copper(II) chloride** *t***butyl hydroperoxide, carbon tetrabromide , carbon tetraiodide, fluorine, hypofluorous acid in acetonitrile, gallium trichloride, triethylborane/oxygen**,[33] **di-benzoyl peroxide, di-*t*-butyl peroxide, ruthenium(II) tris [2-pyridylmethylamine] dichloride**, the Fenton–Gif related reagents **iron(II) perchlorate**, **iron(II) bispyridinecarboxylate**, and **iron(II) phthalocyanine**. Oxygen alkylation of **4-(4-chlorophenyl)-3-hydroxy-2(3H)thiazolinethione** provides entry to oxygen radicals that, in turn, regiospecifically afford carbon radicals via intramolecular C–H abstraction.

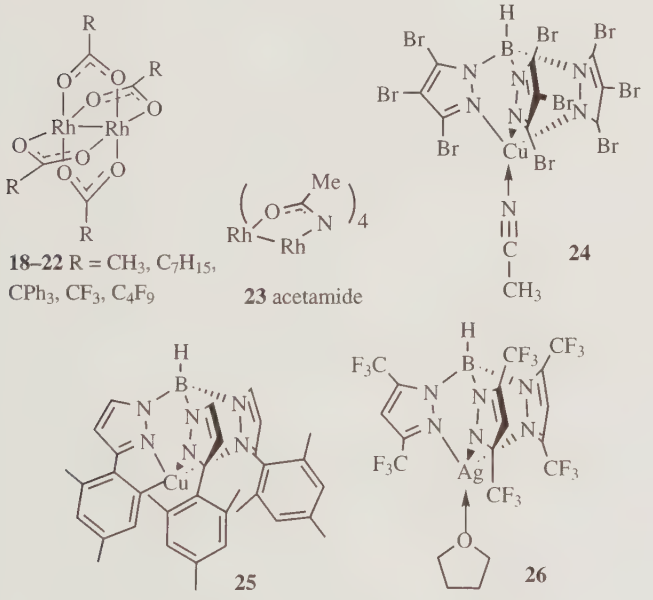
Special notice must be taken of ***ortho*-iodosyl benzoic acid (IBA) 12** and its **peroxy 13**, **azido 14**, and **cyano 15 derivatives**, as these reagents provide valuable entry to C–H functionalized substrates bearing O, N, and C groups (eq 4).

While not in the category of *radical chemistry*, the allylic oxidation of olefins by **di-*t*-butyl chromate**, **chromium(VI)-oxide-3,5-dimethylpyrazole**, and **dipyridine chromium(VI)-oxide** are of considerable value. Additionally, the ene reactions

of **selenium dioxide** and enantiopure **2-phenyl-1-cyclohexyldiazenedicarboxylate** afford allylic alcohols and allylic hydrazines with high selectivity, respectively.



Quadrant 2: Metalacarbene and Metalanitrene Chemistry. The achiral **dirhodium tetracarboxylates 18–22**, **acetamidate 23**, and the **copper and silver homoscorpionates 24–26** are an outstanding collection of catalysts for conversion of **diazo compounds** to their C–H intra- as well as *intermolecular* insertion products. A new hexamethyl copper catalyst analogous to **26** has been recently reported to be highly effective and recyclable for C–H insertions in the ionic liquid [bmin]BF_4.[34]



In addition to fostering the evolution of the achiral reagents, the groups of Michael Doyle and Huw Davies continue to make seminal contributions in the design and evaluation of enantiopure rhodium(II) catalysts for enantiocontrolled carbenoid insertion chemistry. Taken collectively, the discussions of enantiopure **dihordium reagents 27–34** provide a comprehensive overview of the current "state-of-the-art" in this rapidly evolving arena of synthetic research (Fig. 4).

A dramatic example highlighting the intricacy-increasing value of rhodium(II)-catalyzed intermolecular C–H insertion is seen in the synthesis of the childhood antipsychotic agent methylphenidate **37** (Ritalin™). Enantiopure rhodium(II) catalysts are used to achieve enantioselective C–H functionalization of Boc-piperidine **35**, providing a beautiful and efficient synthesis of the active *threo* (*R*,*R*)-enantiomer **37**. This chemistry *simultaneously creating two stereocenters with high enantiomeric excess* was independently disclosed in 1999 by the groups of Davies[35] and Winkler[36] and was further clarified in a 2003 full paper by Davies that also examined bridged catalyst **29**, which gave high enantioinduction in the formation of **37** (eq 5).[37]

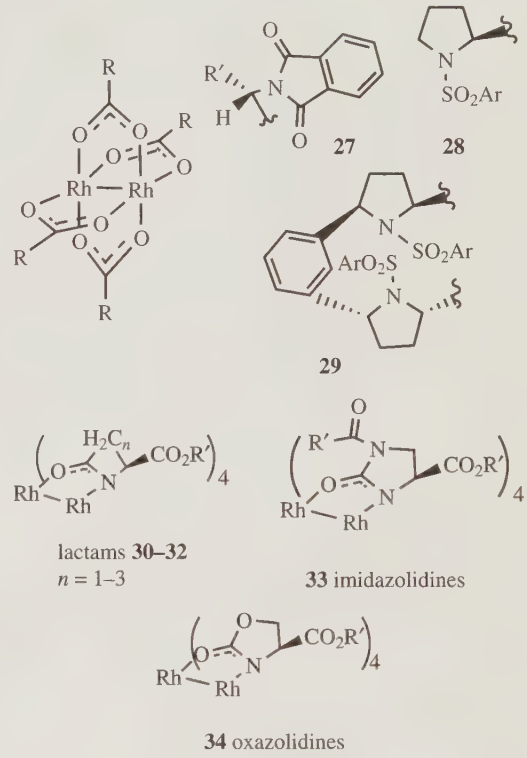
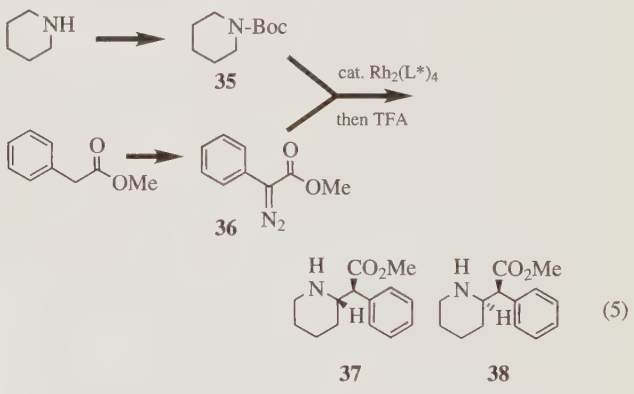
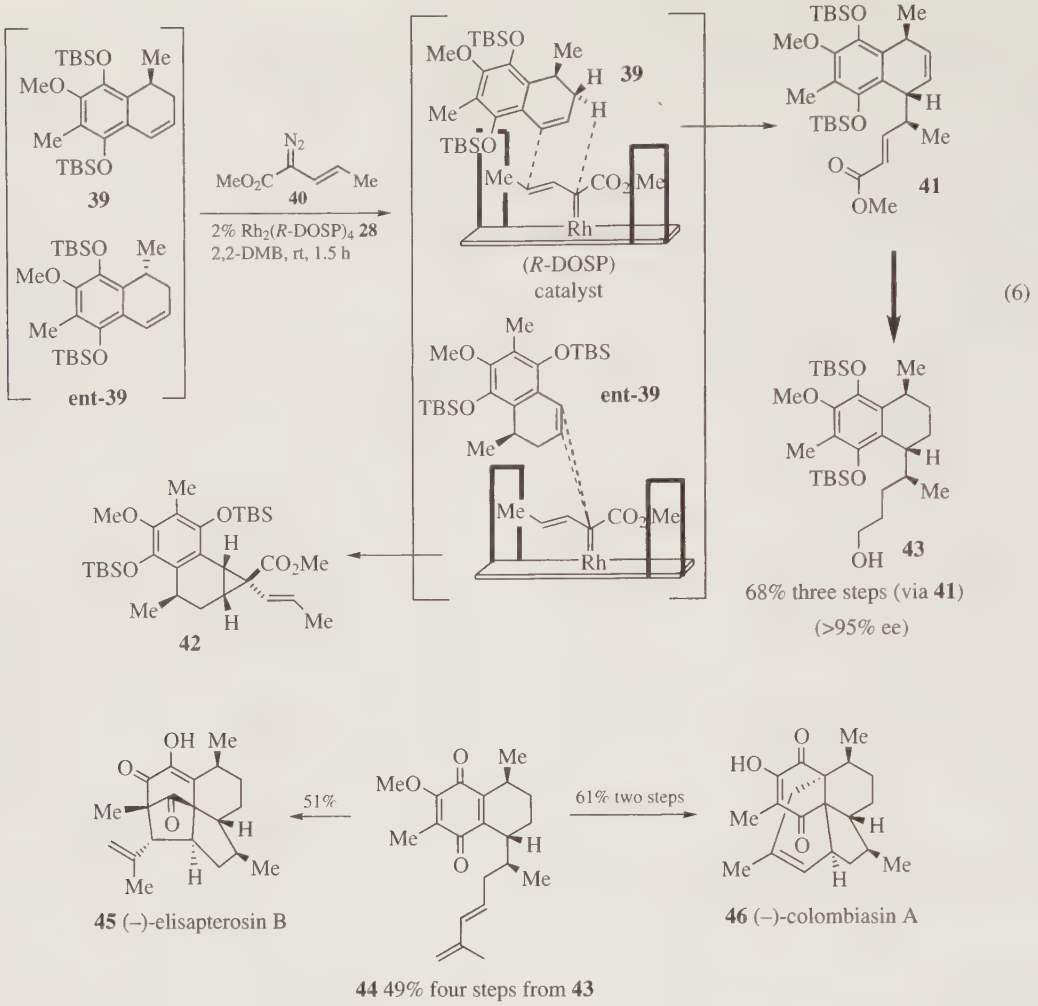


Figure 4 Dirhodium catalysts.



catalyst	yield **37** + **38** (ratio)	**37** (ee)
(*S*)-**31**	45% (96:4)	69%
(*S*)-**28**	44% (2:1)	89% (ent)
(*S*)-**29**	73% (2.7:1)	86%

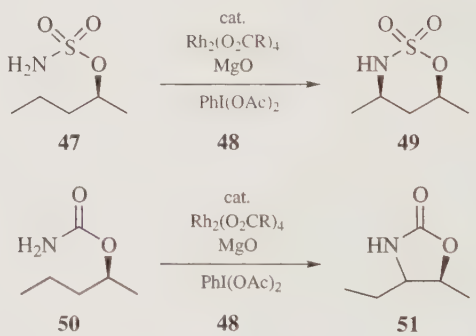
Another eye-catching example of the power of enantiocatalytic C–H activation has appeared just in time to include in this volume. Davies, Dai, and Long report treatment of racemic dihydronaphthalene **39** with α-diazo ester **40** in the presence of (*R*)-catalyst **28** enantiospecifically converts enantiomer **39** to adduct **41** bearing three relative stereocenters in addition to achieving complete asymmetric induction via a hybrid C–H activation/Cope reaction.[38] The cost of production of **41** with >95% ee is the simultaneous catalytic enantiodivergent transformation of **ent-39**



(6)

to cyclopropane **42**. A simple four-step sequence transformed **43** to the key intermediate quinone **44**, which was elaborated to (−)-elisapterosin B and (−)-colombiasin A by the method of Kim and Rychnovsky (eq 6).[39]

The area of nitrenoid chemistry is far less developed than the previously discussed carbenoid chemistry. Examples of intramolecular C–H functionalization are found in the update of **ethyl azidoformate** , but these moderate-yielding transformations are simply thermolysis reactions, presumably proceeding via the true acylnitrene intermediate. Application of the dirhodium catalysts in this area has been strongly advanced by the research group of Justin Du Bois at Stanford University.[40] Treatment of sulfamates **47** and carbamates **50** with **dirhodium tetracarboxylate** catalysts in the presence of magnesium oxide and **(diacetoxyiodo)benzene** **48** affords 6- and 5-membered sulfamates **49** and carbamates **51**, respectively (eq 7).[41–44] This C–H functionalization chemistry has been employed in total synthesis[45] and has recently been powerfully augmented by the synthesis and commercial availability of **52**,[46,47] a new bridged catalyst whose extended lifetime provides substantially improved performance. Additional examples giving very respectable ee values have been reported for both intra- and intermolecular benzylic and allylic amination using the above enantiopure dihrodium carboxylates.[48,49]



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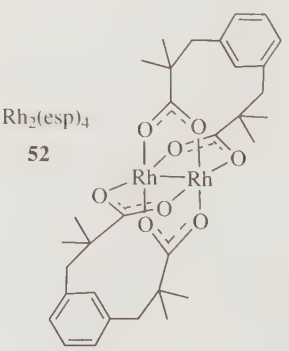


Quadrant 3: Dioxiranes, Oxaziridines, Metal Peroxy, and Metal Oxo Reagents. This group of oxidants formally deals with "oxenoid" type reagents that provide alcohols by C–H insertion of an oxygen atom. Although strongly centered on oxidations of tertiary C–H bonds, oxidations of methylene groups

afford alcohols that often suffer subsequent transformation to carbonyl groups. **Dimethyl dioxirane (DMDO) 53** and the very powerful **methyl(trifluoromethyl)dioxirane (TFDO) 54** have been extensively developed by the Curci group, and are typically the point of departure when seeking oxidants that operate under mild, almost neutral, reaction conditions. More recently, **3-fluoro-3-(heptafluoropropyl)-2-(nonafluorobutyl)-oxaziridne 55** and the recently reported benzo-fused trifluoromethyl oxaziridine **56**[50] (not yet reviewed in EROS) have joined the ranks of useful C–H oxidants. Rounding out the metal centered catalysts are the heteropolyanionic **tungstoboric acids**, **ruthenium tetroxide 57**, **ruthenium trichloride-periodate (57 in situ)**, **copper(II) chlorideoxygen**, **ruthenium-(II) bis-6,6′-dichloro2,2′-bipyridine ditriflate 58** (the precursor of the **ruthenium(VI) dioxo complex 59**), **methyloxydiperoxy rhenium(VII) 60** and the **aqua methyloxydiperoxy-rhenium(VII) 61**, **vanadium(V) diaquaoxyperoxy (2-pyridine-carboxylate) 62**, and **vanadium(VI) dioxobis(pyrazine-2-carboxylate) tetrabutylammonium salt 63** (Fig. 5).

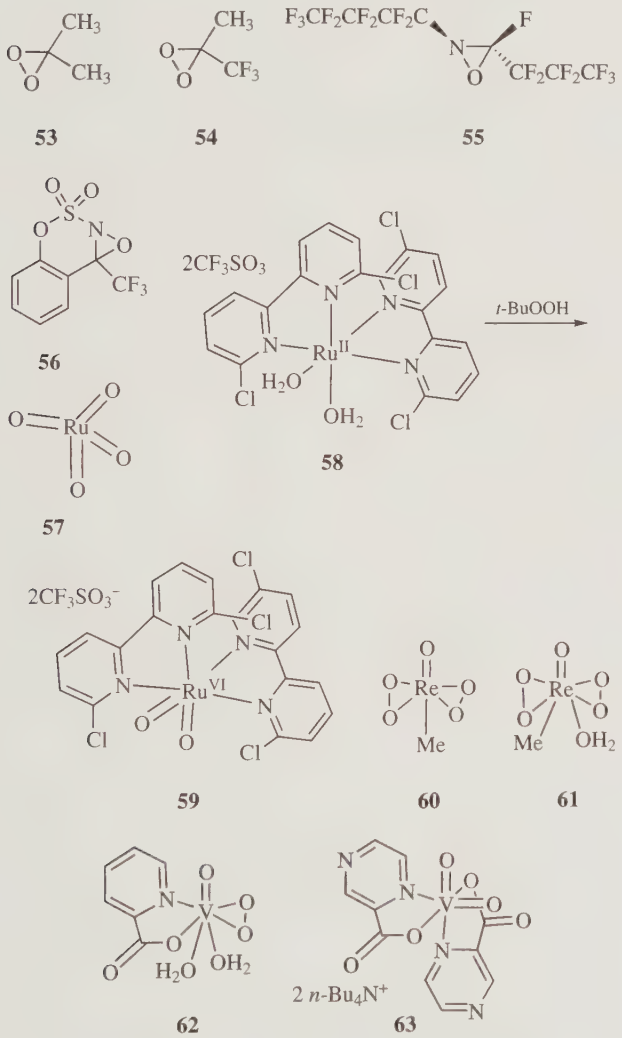


Figure 5 Oxenoid C–H oxidation reagents.

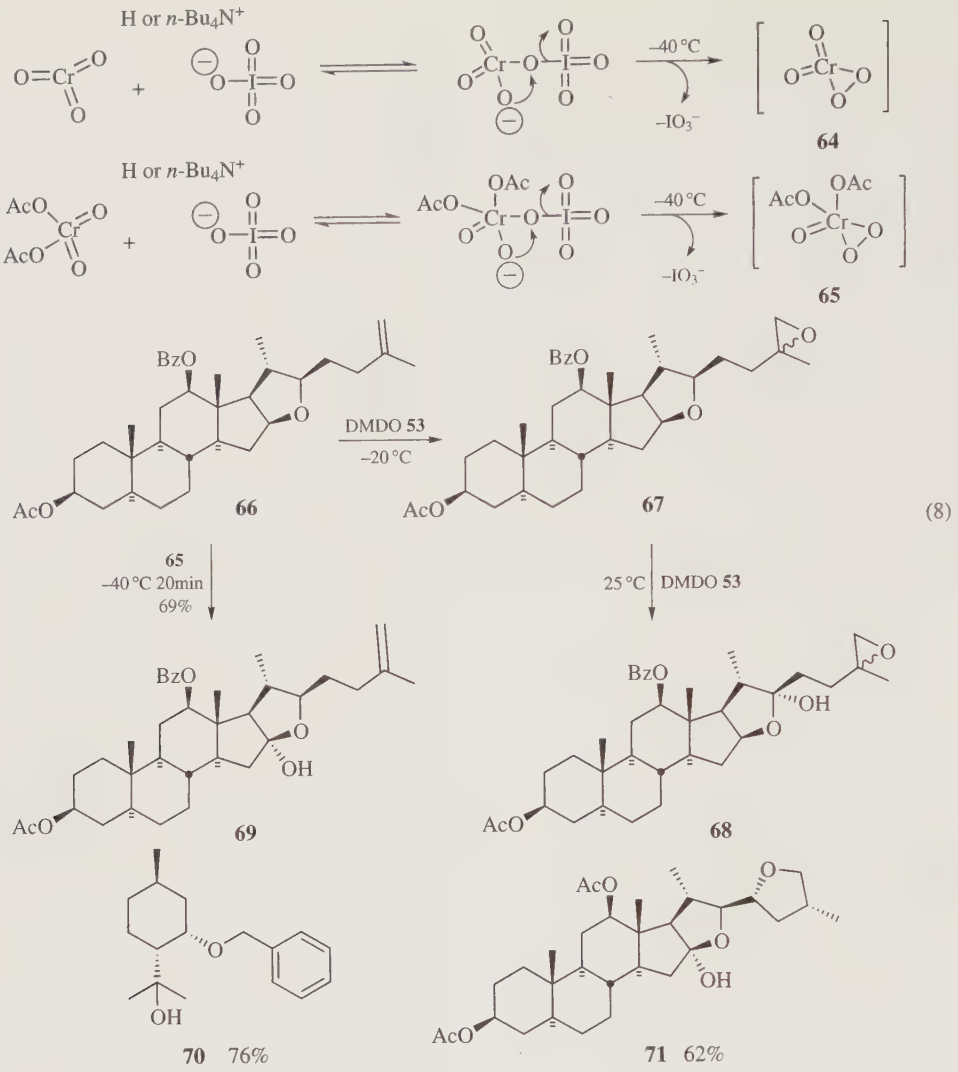
Although the enantiopure **manganese(III) metallosalen complexes** have received their greatest attention for olefin epoxidation, Katsuki has provided some striking examples of their catalytic uses for enantioselective oxidative desymmetrization of prochiral (*meso*) furans and pyrrolidines.[51–55] Recently, Murahashi has employed this catalyst for oxidative desymmetrization of prochiral benzylic methylenes and tertiary benzylic silyl ethers.[56]

Finally, the previously mentioned **di-*t*-butyl chromate**, **chromium(VI) oxide-3,5-dimethylpyrazole**, and **dipyridine chromium(VI) oxide** are joined by **chromium trioxideperiodate (64 in situ)**, and the more soluble **chromyl acetate-periodate (65 in situ)**. The latter reagent provides a striking contrast in chemospecificity to DMDO **53**. Reaction of steroidal olefin **66** with **53** initially affords a diastereomeric mixture of epoxides **67** followed by slow C–H oxidation to epoxy-lactols **68** upon warming the reaction medium. However, treatment of the same steroid with **65** gives lactol-olefin **69** without any trace of **67** or **68**. This is the *first example* of a reagent that will effect C–H insertion (admittedly at the oxygen-activated 3° center) *in preference to epoxidation of an olefin.* Alcohols **70** and **71** are two additional examples showing the selectivity achievable with this *new class* of low temperature C–H oxidants (eq 8).

Quadrant 4: Metal Insertion Chemistry. The final quadrant deals with transition metal reactions, now a standard part of the armamentarium of the synthetic organic chemist, with the seminal difference being that the starting materials for these reactions are C–H bonds rather that the more intricate halides, stannanes, and silanes that are more commonly employed in these fundamental organometallic processes.[57,58] Although seldom used, **pentahydridobis (triisopropylphosphine)iridium(V) 72** effects mild transfer dehydrogenation of cycloalkanes in the presence of a sacrificial olefin as hydrogen acceptor. While **sodium** and **potassium tetrachloroplatinate 73–74** have a long history of C–H activation, it is **dimethylplatinum dimethylsulfide dimer 75** that has recently become an important catalytic tool for C–H activation. The Sames group has employed **75** in the presence of a copper(II) chloride terminal oxidant to effect aqueous C–H oxidation of amino acids[59] as well as demonstrating the stoichiometric use of **75** with an enantiopure oxazoline to effect desymmetrization of two prochiral ethyl groups, thereby providing a concise total synthesis of (−)-rhazinilam **76**.[60]

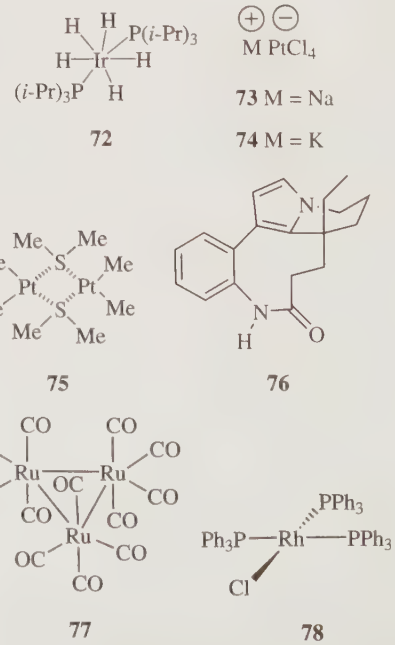
In addition to platinum, the currently most versatile catalysts for substrate directed metalation (SDM) by C–H activation are **triruthenium dodecacarbonyl 77**,[61] **chlorotris(triphenylphosphine)rhodium(I) (Wilkinson's catalyst) 78**, **carbonyl-(chloro)bis(triphenylphosphine)rhodium(I) 79**, **chloro(cyclooctene)rhodium dimer 80**, **palladium(II) acetate 81**, and **bis-(cyclopentadienyl)methylzirconium tetraphenylborate-tetrahydrofuran 82**. **2-Amino-3-picoline 83** is used for conversion of carbonyl groups to pyridyl imines, which provide proximal chelation of the catalyst to the C–H bonds of interest.

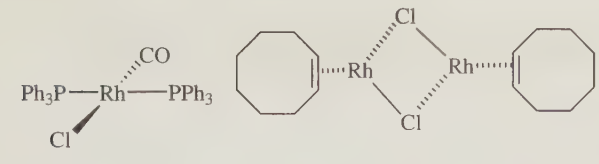
Complex **80** merits special attention by virtue of its ease of dissociation of the cyclooctene ligand. The Bergman–Ellman collaboration has been extremely active in developing the applications of this and other Rhodium(I) catalysts for SDM.[62,63] **Palladium(II) acetate 81** is continuing to see widespread growth as a palladium(0) precursor in methods development and application in total synthesis for the direct C–H functionalization of arenes and heteroarenes bearing imino, pyridine, and secondary amido ligating groups.[64–66] Very recent extensions of palladium-catalyzed C–H activation include oxime, pyridine, and oxazoline-directed oxidation of proximal methyl groups.[67–70]



Complementary to the above oxazoline-directed palladium-catalyzed methyl oxidation chemistry is the process of C–H borylation of aryl, heteroaryl, and *methyl groups*. While in terms of intricacy, activation of a terminal methyl group is not as high a "value added" process as are those reactions that convert prochiral secondary or tertiary C–H bonds, sterically controlled borylation chemistry is currently in a *class by itself* with respect to this valuable addition to the synthetic toolkit. **Iron reagent 84** and **tungsten reagent 85** both effect stoichiometric borylation reactions, but rhodium pre-catalyst **86** enables C–H borylation of arenes, heteroarenes, and functionalized alkanes both neat and in solution at 120–150 °C using **pinacolborane 88** and **dipinacoldiboron 89** as the boron source.[71–76] A major breakthrough involves using **bis cyclooctadienyl iridium methoxide dimer 87**[77–79] (and related alkoxy iridium species) for the *room temperature* catalytic borylation of arenes and heteroarenes using **89** in an inert solvent.

C–H functionalization strategies and the development of new catalysts that effect these intricacy-increasing reactions shall command the ever-increasing attention of synthetic, mechanistic, and medicinal chemists. This is the future of organic/organometallic chemistry.





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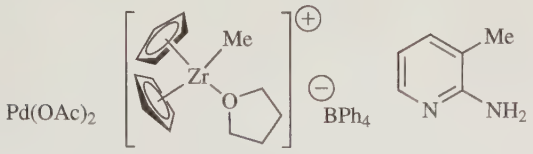

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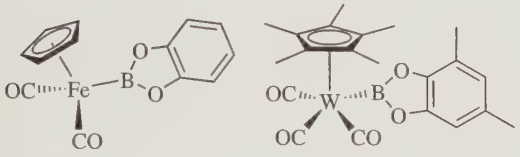

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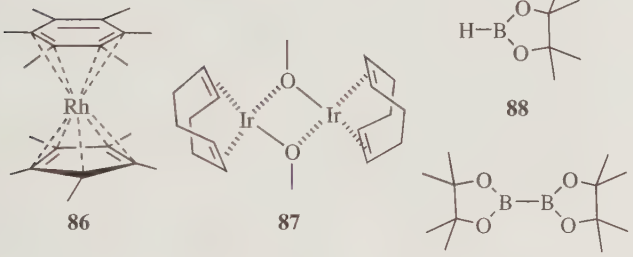

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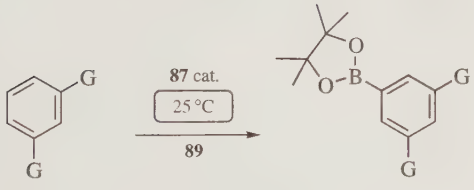
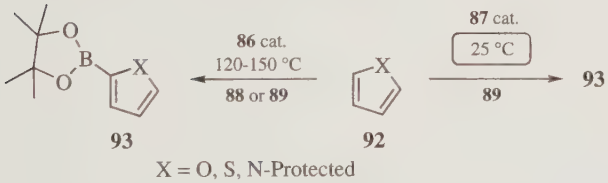


90 G = W, N, or D group 91



93 92 93

X = O, S, N-Protected

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Recent Review Articles and Monographs

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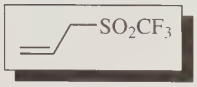
Allyl Triflone



[73587-48-1] $C_4H_5F_3O_2S$ (MW 174.14)

(allylating agent)

Alternate Names: 3-(trifluoromethylsulfonyl)prop-1-ene; allyl trifluoromethyl sulfone.
Physical Data: bp 171.5 °C.
Form Supplied in: colorless liquid; not commercially available.
Handling, Storage, and Precautions: moisture sensitive; thermally labile.

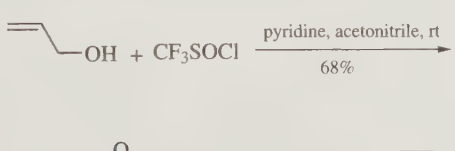
Free-radical allylations are powerful tools for the selective formation of carbon-carbon bonds under mild conditions. These transformations have been accomplished by reacting alkyl halides with allyl stannanes, allyl silanes, allyl sulfones, the title compound allyl trifluoromethanesulfone (allyl triflone), and its substituted derivatives. The strong electron withdrawing ability of the trifluoromethylsulfone group in allyl triflones facilitates the addition of an alkyl radical to an electron deficient triflone. The use of allyl triflones, together with other reagents such as allyl sulfones, avoids the toxicity and difficulty in removing tin residues from the products associated with stannane reagents.

Synthesis of Allyl Triflone. Alkyl triflones are formed in a clean, but slow, displacement reaction by nucleophilic substitution of primary halides by potassium triflinate with iodide catalysis in boiling acetonitrile (eq 1).[1]

$$RCH_2Br + KSO_2CF_3 \xrightarrow{KI,\ \text{acetonitrile reflux}} RCH_2SO_2CF_3 \quad (1)$$

1 **2** **3**

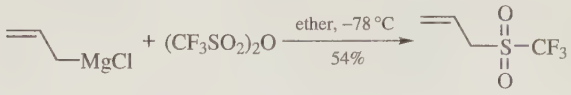
An alternative synthesis of allyl triflones is the triflination of allyl alcohols, which affords triflinates such as **4**, followed by thermal rearrangement in acetonitrile to give allyl triflone (**5**) (eq 2).[2]



(2)

4 **5**

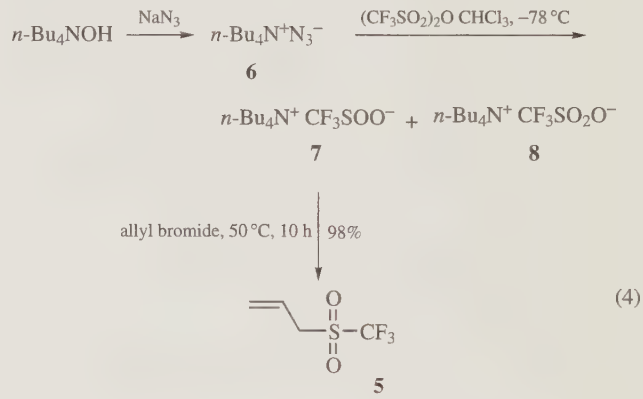
Creary reported the synthesis of allyl triflone in moderate yield by reacting allylmagnesium chloride with triflic anhydride (eq 3).[3]



(3)

5

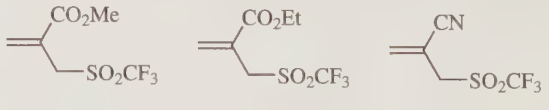
Hendrickson synthesized allyl triflones using tetrabutylammonium triflinate.[4] The quaternary ammonium system is more soluble and 20–40 times more reactive than the conventional potassium triflinate. Tetra-*n*-butylammonium azide (**6**) prepared from tetra-*n*-butylammonium hydroxide and sodium azide reacts with triflic anhydride in chloroform at −78 °C to give a 1:1 mixture of tetrabutylammonium triflinate (**7**) and tetrabutylammonium triflate (**8**) Treatment of this mixture with allyl bromide gives the corresponding allyl triflone (**5**) in almost quantitative yield. The water-soluble triflate coproduct (**8**) in the reaction mixture does not interfere with the formation of (**5**), which is readily isolated (eq 4).



(4)

5

Synthesis of Functionalized Allyl Triflones. The Hendrickson tetrabutylammonium triflinate reagent (**7**/**8**)[4] reported was used by Fuchs and Curran to prepare functionalized allyl triflones (**9**–**13**).[5]



9 **10** **11**

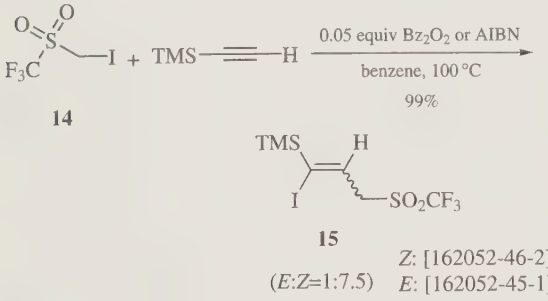
[210489-89-7] [210489-88-6] [210489-90-0]

12 **13**

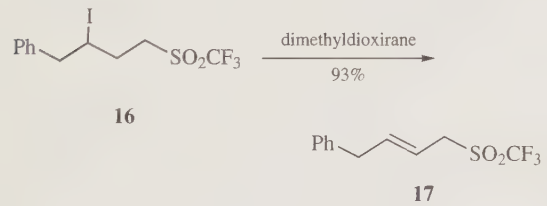
[210489-91-1] [210489-92-2]

Fuchs and co-workers used radical-mediated atom-transfer addition of iodomethyl triflone (**14**) [158530-86-0] to substituted alkynes to afford functionalized allyl triflones.[6] The reaction was complete within 5–10 h in most cases. For example, heating a

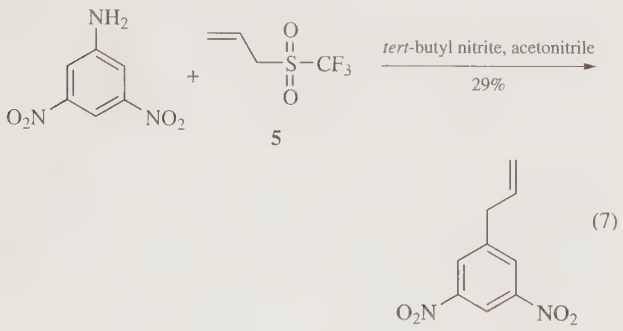
benzene solution of iodomethyl triflone (**14**) (1 equiv) and alkyne (2–3 equiv, to ensure an excess of the volatile substrate) in a sealed tube gave allyl triflone (**15**) in 99% yield (eq 5). The procedure was also extended to internal and terminal alkynes. Addition to 1-octyne and 4-octyne proceeded in over 70% yield, but resulted in a mixture of *E*- and *Z*-isomers.



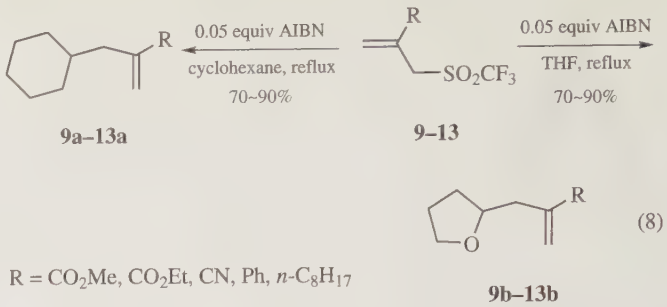
Fuchs also reported the preparation of allyl triflones through 1,2-elimination of the γ-iodoso triflone intermediate. γ-Iodoso triflone was prepared from γ-iodo triflones using dimethyldioxirane. In all of the cases, the elimination gave the corresponding allyl triflones regio- and stereoselectively (eq 6).[6] Formation of allyl triflone (**17**) demonstrates that the triflone moiety is more inductively activating than the phenyl ring in substrate **16**.



Allyl Triflone as an Allylating Agent. Frejd reported a low yield method using allyl triflone for aromatic allylation through a diazotization/allylation process (eq 7).[7]



Curran and Fuchs successfully reacted allyl triflones with THF and cyclohexane to give good to excellent yields of various allyl products through radical-mediated C–H bond functionalization (eq 8).[5]



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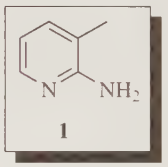
2-Amino-3-Picoline[1,2]



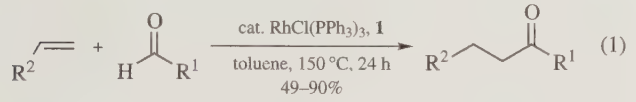
[1603-40-3] $C_6H_8N_2$ (MW 108.14)

(reagent used as a chelation-assisted auxiliary in various transition metal-catalyzed C-H and C-C bond activation processes, such as hydroacylation of olefins and alkynes, skeletal rearrangements of cyclic carbonyl compounds, cleavage of alkyne C-C triple bonds, etc.)

Alternate Name: 2-amino-3-methylpyridine.
Physical Data: mp 32–34 °C; bp 221–222 °C; *d* 1.073 g cm^{-3}.
Solubility: soluble in most organic solvents.
Form Supplied in: yellow liquid; commercially available.
Analysis of Reagent Purity: gas chromatography.
Purification: dried over KOH and distilled under reduced pressure.
Handling, Storage, and Precautions: hygroscopic, irritant, use in a fume hood; stored in a refrigerator protected from light and air.

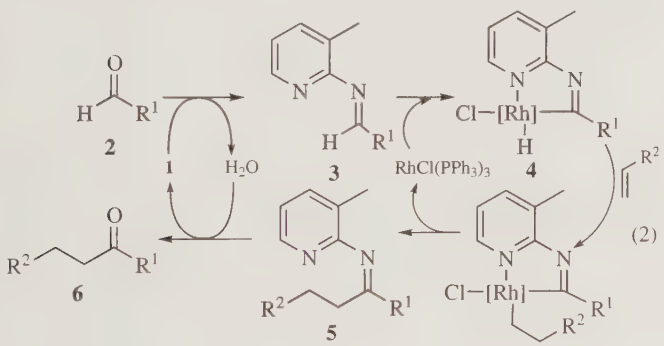
Chelation-Assisted Hydroacylation of Olefins with Aldehydes. Treatment of olefins with aldehydes in the presence of chlorotris(triphenylphosphine)rhodium(I) and 2-amino-3-picoline (**1**) gives the corresponding ketones in good to moderate yields (eq 1).[3] The Rh^I-catalyzed hydroiminoacylation of olefins with 2-aminopyridyl aldimines (**3**) was originally described by Suggs

in 1979 with the identification of an iminoacylrhodium(III) hydride intermediate (**4**).[4] Lacking the tedious steps of the formation of aldimines and the hydrolysis of ketimines, a convenient direct hydroacylation protocol has been developed using a co-catalyst system consisting of **1** and a Rh^I catalyst. In this protocol, 2-aminopyridine derivative **1** serves as an organic catalyst to assist chelation with the Rh^I catalyst, thus effectively preventing decarbonylation. The isolated yields of ketones are usually in the range of 49–92%. Notably, in the absence of **1**, no ketone is obtained and aldehyde decarbonylation occurs exclusively. This reaction represents one of the most practical one-step preparations of ketones from aldehydes via transition metal-catalyzed C-H bond activation, i.e., hydroacylation.



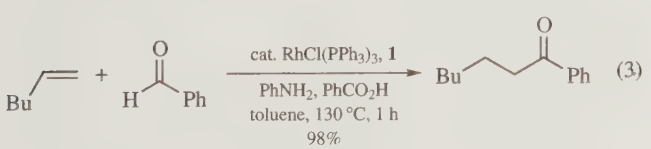
(1)

The proposed mechanism for the direct intermolecular hydroacylation of olefins with aldehydes is illustrated in eq 2.[3] As an in situ chelating auxiliary, **1** condenses with aldehyde **2** to generate **3** and H_2O. The catalytic cycle of the reaction involves the chelation-assisted hydroiminoacylation of the olefin with aldimine **3** via a stable five-membered metallacyclic complex (**4**). The resulting ketimine **5** can be easily hydrolyzed by H_2O generated during the condensation step to give ketone **6** as the final coupling product with regeneration of **1**.



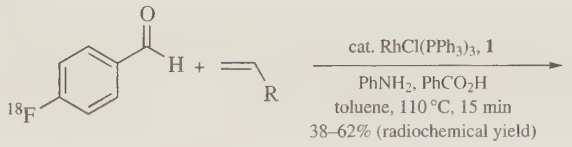
(2)

Two more additives, aniline and benzoic acid, dramatically accelerate the rate of intermolecular hydroacylation. The reaction of benzaldehyde with 1-hexene in the presence of $RhCl(PPh_3)_3$, **1**, $PhNH_2$, and $PhCO_2H$ gives heptanophenone in 98% yield (eq 3).[5] Control experiments have shown that the addition of $PhCO_2H$ likely accelerates the condensation of PhCHO and **1**, which is thought to be the rate-determining step of the overall reaction.



(3)

This catalytic system was successfully applied to the preparation of radiolabeled compounds (eq 4),[6] and in the total synthesis of indolizidine alkaloids such as (−)-167B and (−)-209D (eq 5).[7]



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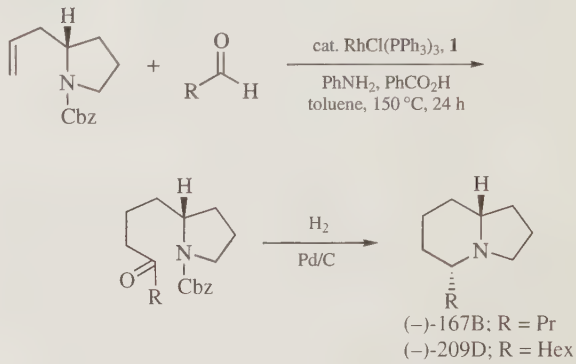
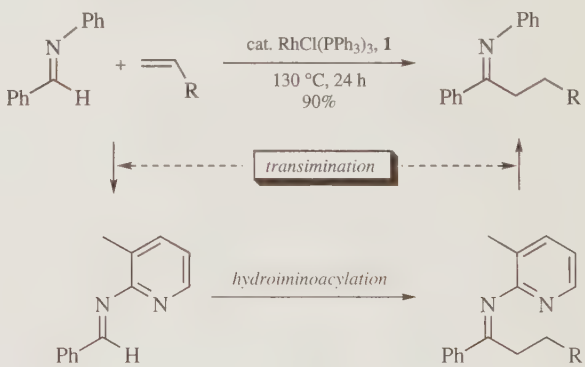


(5)

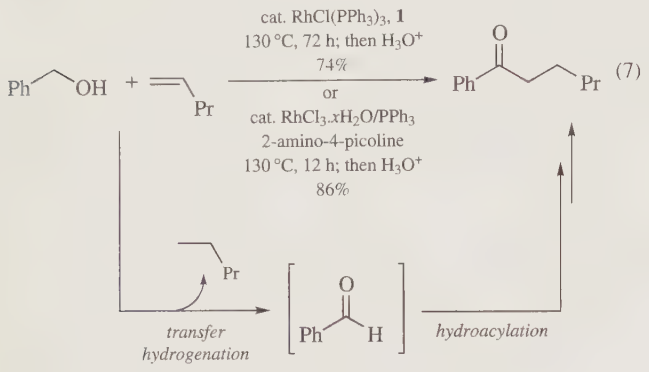
Hydroiminoacylation of Aldimines to Ketimines through Transimination. Direct conversion of a common aldimine such as benzylimine of benzaldehyde, which bears no special directing group, into a ketimine can be realized by a co-catalyst system of $RhCl(PPh_3)_3$ and **1** (eq 6).[8] The aldimine can be converted into a more reactive 2-aminopyridyl aldimine through transimination with **1**. Subsequent hydroiminoacylation followed by transimination of the resulting 2-aminopyridyl ketimine with aniline gives the corresponding ketimine.



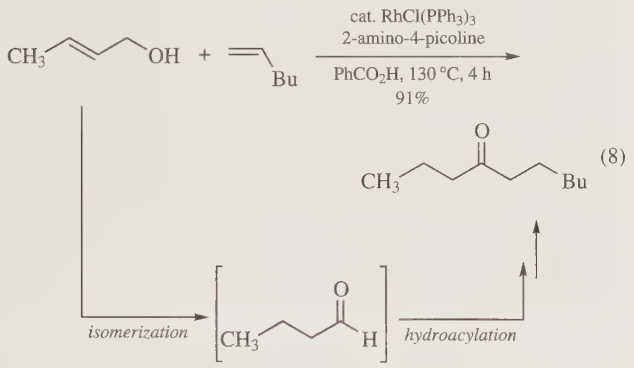
(6)

Chelation-Assisted Hydroacylation of Olefins with Some Alcohols and Amines. Some classes of alcohols such as benzyl alcohols[9–11] and allylic alcohols[12] also can be utilized as substrates in the chelation-assisted hydroacylation of olefins using 2-aminopyridine derivatives, since they can be easily converted into the corresponding aldehydes by transition metal complexes. The reaction of benzyl alcohol, which can be transformed into PhCHO through transition metal-catalyzed transfer hydrogenation, with excess 1-pentene in the presence of $RhCl(PPh_3)_3$ and **1** gives the corresponding ketone in a good yield (eq 7).[9] In this reaction, olefins serve not only as a substrate for hydroacylation but also

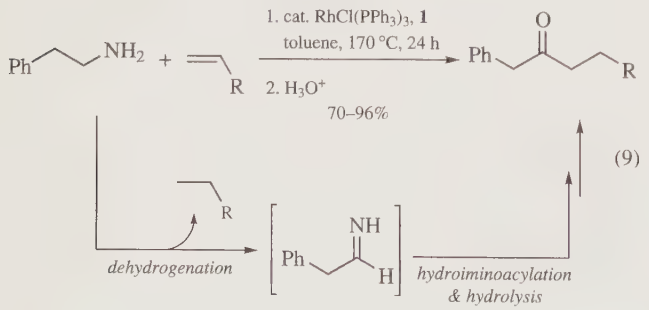
as a hydrogen acceptor for transfer hydrogenation. In the case of the reaction of some benzyl alcohols, 2-amino-4-picoline shows a higher reactivity than **1** when a mixture of $RhCl_3 \cdot xH_2O$ and PPh_3 is used as a catalyst precursor.[9]



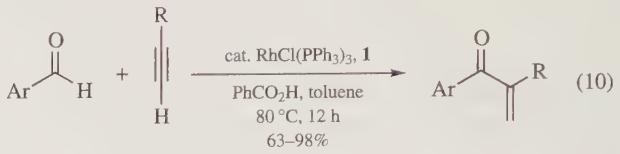
In a similar manner, various allylic alcohols are also applicable to the chelation-assisted hydroacylation due to their facile transition metal-catalyzed isomerization into the corresponding aldehydes. For instance, 2-buten-1-ol reacts with excess 1-hexene under a co-catalyst system of $RhCl(PPh_3)_3$, 2-amino-4-picoline, and $PhCO_2H$ to give a 91% yield of saturated ketone (eq 8).[12]



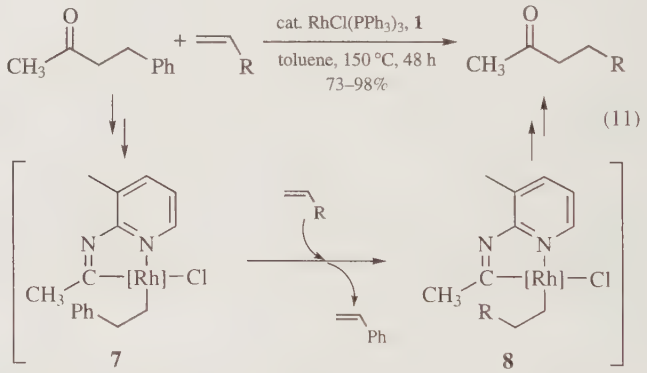
Primary amines, which can be dehydrogenated with a transition metal complex to afford the corresponding imines, may also be used as substrates in place of aldehydes and alcohols. Phenethylamine reacts with excess terminal olefins in the presence of $RhCl(PPh_3)_3$ and **1** to furnish ketones after hydrolysis of the resulting ketimines (eq 9).[13] In this reaction, the olefin acts as a hydrogen acceptor as well as a substrate for alkylation.



Chelation-Assisted Hydroacylation of Alkynes with Aldehydes. A co-catalyst system of $RhCl(PPh_3)_3$, **1**, and $PhCO_2H$ is extremely useful for the intermolecular hydroacylation of 1-alkynes with aldehydes.[14] A new C-C bond between sp^2-hybridized carbonyl group and sp^2-hybridized olefinic carbon can be constructed in a highly regio- and stereoselective manner through this catalytic reaction. In practice, this system seems to be highly efficient for the preparation of branched α,β-unsaturated ketones from aromatic aldehydes and 1-alkynes (eq 10).

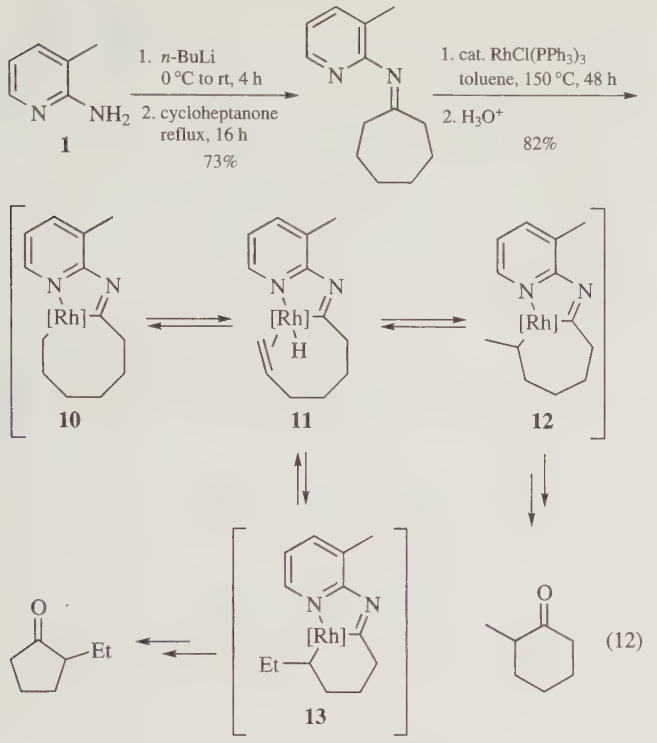


Chelation-Assisted C-C Bond Activation of Unstrained Ketones. By far the most significant application of **1** has been as a chelation auxiliary in the Rh^I-catalyzed C-C bond activation of unstrained carbonyl compounds. The treatment of benzylacetone possessing β-hydrogens with excess terminal olefin in the presence of $RhCl(PPh_3)_3$ and **1** gives the alkyl-exchanged ketone and a trace amount of styrene (eq 11).[15] The isolated yields of ketones are usually high. The key intermediate of this unusual transformation is iminoacylrhodium(III) alkyl **7**, which is formed through the chelation-assisted cleavage of the C-C bond α to the imino group. Metallacyclic complex **7** could be in equilibrium with another metallacyclic complex, i.e., **8**. The use of excess terminal olefin shifts the equilibrium toward iminoacylrhodium(III) alkyl **8** with the liberation of styrene, which is formed through a β-hydride elimination in **7**. Reductive elimination in **8** and subsequent hydrolysis of the resulting ketimine furnish the alkyl-exchanged ketone as the final product.



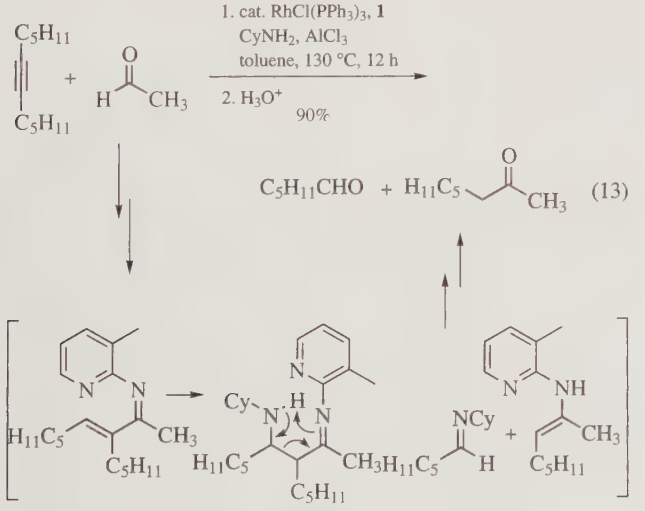
Chelation-Assisted C-C Bond Activation of Unstrained Cyclic Carbonyl Compounds. The employment of unstrained cycloalkanoketimines, such as cycloheptanoketimine derived from **1** and cycloheptanone, for chelation-assisted C-C bond activation with co-catalysis by $RhCl(PPh_3)_3$ and **1** results in a skeletal rearrangement to afford ring-contracted products, 2-methylcyclohexanone and 2-ethylcyclopentanone (eq 12), after hydrolysis.[16] β-Hydride elimination in metallacyclic iminoacylrhodium(III) complex **10**, which is formed through the chelation-assisted cleavage of the α C-C bond in cycloheptanoketimine, gives iminoacylrhodium(III) hydride (**11**). Hydride insertion into the coordinated terminal olefin in **11** in a Markovnikov fashion generates iminoacylrhodium(III) alkyl **12**. Reductive elimination in **12** produces 2-methylcyclohexanone after hydrolysis. Olefin isomerization in **11** and subsequent similar hydride insertion in the resulting metal

hydride species generates another iminoacylrhodium(III) alkyl **13**. Finally, reductive elimination in **13** gives 2-ethylcyclopentanone after hydrolysis.



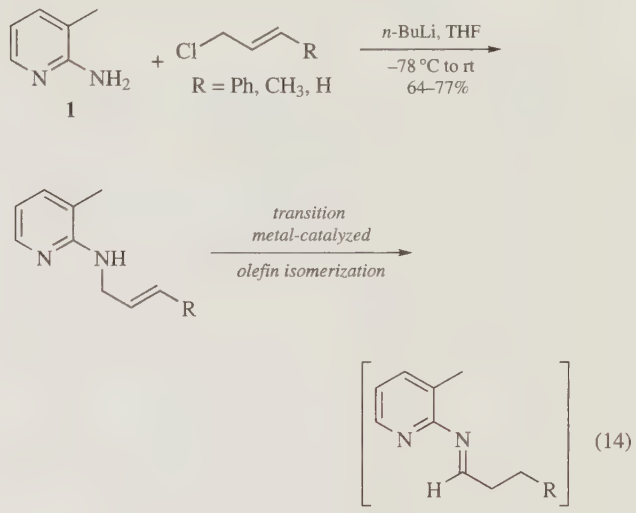
(12)

Cleavage of C-C Triple Bonds of Alkynes. The chelation-assisted hydroacylation of internal alkynes with aldehydes can be coupled with retro-Mannich-type fragmentation of the resulting α,β-unsaturated ketimines to bring about the cleavage of alkyne C-C triple bond. For instance, the reaction of acetaldehyde with 6-dodecyne in the presence of $RhCl(PPh_3)_3$, cyclohexylamine, aluminum chloride, and **1** affords 2-octanone in 90% yield after hydrolysis (eq 13).[17] As a whole, this reaction involves the cleavage of C-C triple bond of alkyne; the pentyl groups in both hexanal and 2-octanone are derived from 6-dodecyne.



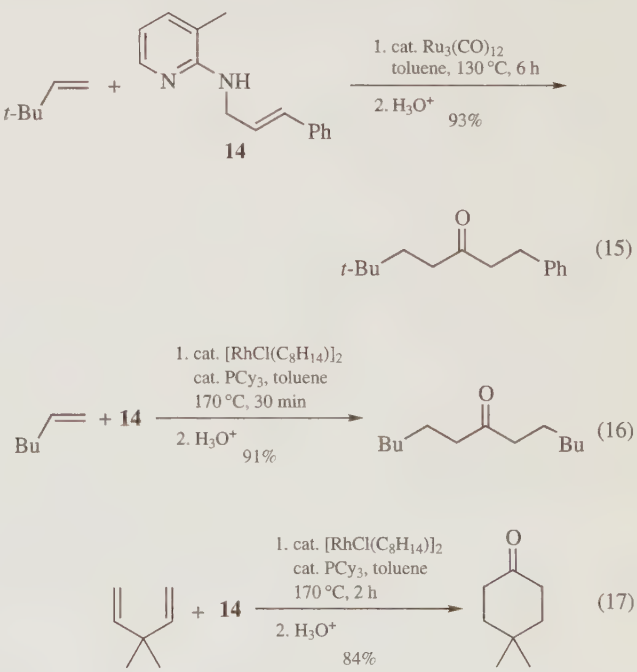
(13)

Synthesis of Allylamine Derivatives and Their Applications to C-H and C-C Bond Activation. Reaction of **1** with *n*-BuLi followed by treating the resulting lithio species with allyl chlorides (R = Ph, CH_3, H) gives allylamine derivatives, which can be easily converted into the corresponding aldimines through transition metal-catalyzed olefin isomerization (eq 14).[18]



(14)

Some useful transition metal-catalyzed C-H and C-C bond activation processes have been developed using these allylamine derivatives as substrates in place of aldehydes or aldimines. For example, cinnamylamine (**14**) can be successfully utilized in the synthesis of unsymmetrical ketones through Ru^0-catalyzed C-H bond activation (eq 15).[18] Symmetrical ketones also can be synthesized from **14** through Rh^I-catalyzed C-H and C-C bond activation (eq 16).[18] A variety of cycloalkanones are easily obtained from the reactions of **14**, as a masked form of formaldehyde, with dienes through Rh^I-catalyzed C-H and C-C bond activation (eq 17).[19] The cleavage of C-C triple bonds of alkynes was originally developed using **14** as a substrate for Rh^I-catalyzed hydroiminoacylation.[20]



(15)

(16)

(17)

Related Reagents. Chlorotris(triphenylphosphine)rhodium(I).

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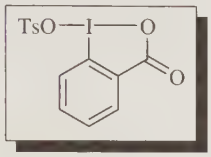
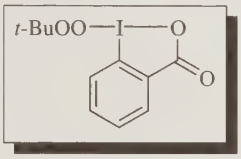
B

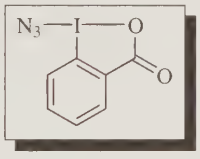
1,2-Benziodoxoyl-3(1*H*)-one Derivatives[1]



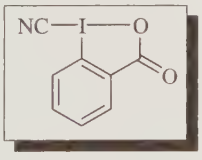
1-Tosyloxy-1,2-benziodoxol-3(1*H*)-one
[159950-96-6] $C_{14}H_{11}IO_5S$ (MW 418.2)



1-*tert*-Butylperoxy-1,2-benziodoxol-3(1*H*)-one
[142260-70-6] $C_{11}H_{13}IO_4$ (MW 336.12)



1-Azido-1,2-benziodoxol-3(1*H*)-one
[160732-56-9] $C_7H_4IN_3O_2$ (MW 289.03)



1-Cyano-1,2-benziodoxol-3(1*H*)-one
[172876-96-9] $C_8H_4INO_2$ (MW 272.96)

(oxidative iodination,[2] oxidation of ethers to esters,[3,4] oxidation at benzylic carbon,[3,5] oxidation of sulfides,[5] oxidation of amines and amides,[6,7] oxidation of phenols,[8] tetrahydrofuranylation of alcohols,[9] azidation of *N,N*-dimethylanilines,[10] azidation of alkanes,[10,11] cyanation of *N,N*-dimethylanilines[12])

Alternate Name: tosyloxybenziodoxole, *tert*-butylperoxybenziodoxole, azidobenziodoxole, cyanobenziodoxole.

Physical Data: tosyloxybenziodoxole: mp 178–180 °C (dec); *tert*-butylperoxybenziodoxole: mp 128–129 °C (dec); azidobenziodoxole: mp 138–140 °C (dec); cyanobenziodoxole: mp 173–175 °C (dec).

Solubility: all derivatives soluble in DMSO; *tert*-butylperoxybenziodoxole soluble in CH_2Cl_2; all derivatives insoluble in ether and nonpolar organic solvents.

Form Supplied in: white microcrystalline solids; typical impurities: 2-iodobenzoic acid and 2-iodosobenzoic acid.

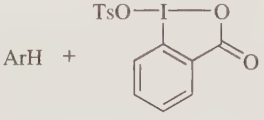
Analysis of Reagent Purity: iodometric titration, elemental analysis, ^1H NMR.

Preparative Methods: tosyloxybenziodoxole: from 1-hydroxy-1,2-benziodoxol-3(1*H*)-one and *p*-toluenesulfonic acid in acetic anhydride;[13] *tert*-butylperoxybenziodoxole: by treatment of 1-hydroxy-1,2-benziodoxol-3(1*H*)-one with *tert*-butyl hydroperoxide in the presence of boron trifluoride etherate at 0–25 °C;[3] cyanobenziodoxole: by the reaction of 1-hydroxy-1,2-benziodoxol-3(1*H*)-one with cyanotrimethylsilane in MeCN,[12] or by the reaction of 1-acetoxy-1,2-benziodoxol-3(1*H*)-one with cyanotrimethylsilane in CH_2Cl_2;[14] azidobenziodoxole: from 1-hydroxy-1,2-benziodoxol-3(1*H*)-one and azidotrimethylsilane in MeCN,[10] or by the reaction of 1-acetoxy-1,2-benziodoxol-3(1*H*)-one with azidotrimethylsilane in CH_2Cl_2.[14]

Purification: *tert*-butylperoxybenziodoxole can be purified by recrystallization from hexane-CH_2Cl_2.

Handling, Storage, and Precautions: all benziodoxole derivatives can be stored indefinitely in the dark; refrigeration should be used for long-term storage; azidobenziodoxole decomposes with explosion upon heating to 138–140 °C and should be handled with care.

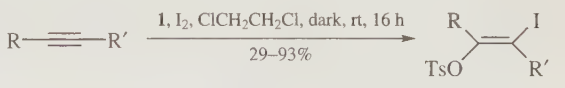
Oxidative Iodination with Tosyloxybenziodoxole/Iodine System. Tosyloxybenziodoxole (**1**) is used as an effective reagent for the oxidative halogenation of aromatic compounds. Treatment of various aromatic compounds with reagent **1** and I_2 gives the corresponding iodinated compounds in good yields (eq 1).[2] When a halide salt such as lithium bromide or lithium chloride is used instead of iodine, the corresponding aryl bromides and chlorides are also obtained in good yields. As compared with other oxidizing reagents (e.g., (diacetoxyiodo)benzene, [bis(trifluoroacetoxy)iodo]benzene, [hydroxy(tosyloxy)iodo]benzene), tosyloxybenziodoxole (**1**) shows the best reactivity as a halogenation reagent.



1

ArH = 1,3,5-$(MeO)_3C_6H_3$, 1,3,5-$(i\text{-}Pr)_3C_6H_3$, 1,3,5-$Me_3C_6H_3$, 1-MeO-4-$MeOC(O)C_6H_4$, 1-MeO-4-BrC_6H_4, 1,4-$Me_2C_6H_4$, 1,3-$Me_2C_6H_4$, $MeOC_6H_5$, *t*-BuC_6H_5, $AcOC_6H_5$, naphthalene, 2,3-benzothiophene, etc.

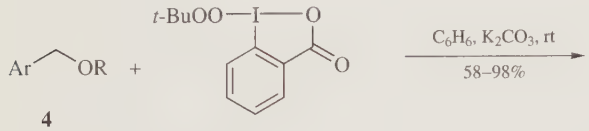
Tosyloxybenziodoxole (**1**)/iodine system can also be used for the iodotosyloxylation of alkynes (**2**) to give the addition products (**3**) in good yields (eq 2).[2b] These reactions presumably proceed via the intermediate formation of toluenesulfonyl hypoiodite.



2 **3**

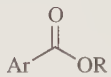
R = Ph, Pr, Bu, H
R′ = Ph, Pr, Me, H, CO_2Et

Oxidation of Ethers to Esters with *tert*-Butylperoxybenziodoxole. *tert*-Butylperoxybenziodoxole (**5**) oxidizes various benzyl ethers (**4**) and allyl ethers (**7**) to the respective esters (**6** and **8**) (eqs 3 and 4) under mild conditions in the presence of alkali metal carbonates.[3] This reaction is compatible with other protecting groups such as MOM, THP, TBDMS ethers, and acetoxy. Since esters are readily hydrolyzed under basic conditions, this method provides a convenient and effective alternative to the normal reductive deprotection.



4 **5**

Ar = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-PhC$_6$H$_4$, 3-ClC$_6$H$_4$, etc.
R = alkyl, cycloalkyl, aryl



(3)

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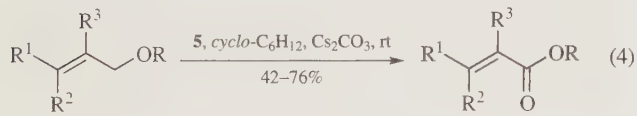
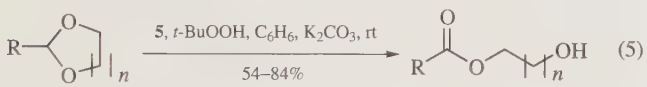


(4)

7 **8**

R^1, R^2, R^3 = H, Me or Ph
R = alkyl, cycloalkyl, aryl

Under similar mild conditions, peroxybenziodoxole (**5**) oxidatively cleaves cyclic acetals (**9**) to glycol monoesters (**10**) (eq 5).[4]

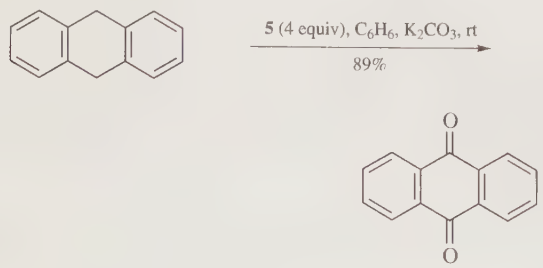


(5)

9 **10**

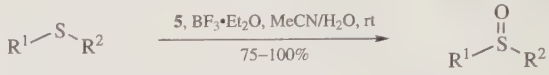
n = 1,2; R = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 2-furyl, PhCH$_2$, PhCH=CH, C$_9$H$_{19}$, *cyclo*-C$_6$H$_{11}$, etc.

Oxidation at Benzylic Carbon. Various arenes, such as indane, substituted indanes, tetrahydronaphthalene, diphenylmethane, fluorene, alkylbenzenes etc., can be oxidized with peroxybenziodoxole (**5**) under mild conditions to afford the respective ketones in good yields.[3] For example, 9,10-dihydroanthracene is oxidized to anthraquinone with excess of peroxybenziodoxole (**5**) at room temperature in benzene in the presence of potassium carbonate (eq 6).



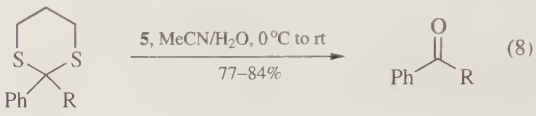
(6)

Oxidation of Organic Sulfur, Selenium, and Phosphorus Compounds with *tert*-Butylperoxybenziodoxole. Sulfides are oxidized with peroxybenziodoxole (**5**) under mild conditions to sulfoxides in high yields (eq 7).[5] A similar oxidation of dithioacetals (**11**) leads to the regeneration of the parent carbonyl compound (**12**) (eq 8) and thus can be useful as a method for selective deprotection.[5]



(7)

R^1 = Bu, *i*-Bu, *s*-Bu, PhCH$_2$, Me(CH$_2$)$_4$, CH$_2$=CHCH$_2$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, Ph
R^2 = PhCH$_2$, Ph, Me, CH$_2$P(O)(OEt)$_2$

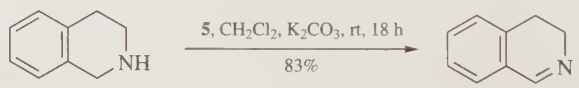


(8)

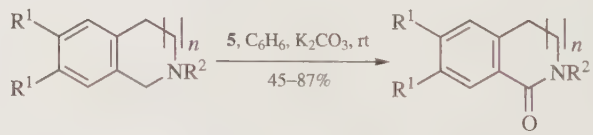
11 R = Me, C$_5$H$_{11}$ **12**

Diphenylselenide and triphenylphosphine are oxidized with peroxybenziodoxole (**5**) to the respective selenoxide and phosphine oxide in high yield at 0 °C.[15]

Oxidation of Amines and Amides with *tert*-Butylperoxybenziodoxole. The reaction of secondary amines with peroxybenziodoxole (**5**) in the presence of potassium carbonate affords imines (eq 9),[6] while amides (**13**) are oxidized by peroxybenziodoxole (**5**) at the methylene carbon yielding imides (**14**) as major products (eq 10).[7]



(9)

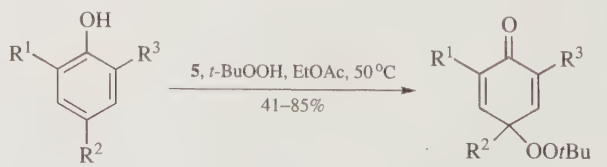


(10)

13 **14**

n = 0, 1
R^1 = H or OMe
R^2 = Ac, Ts, Boc

Oxidation of Phenols with *tert*-Butylperoxybenziodoxole. The oxidation of 4-alkylphenols (**15**) by peroxybenziodoxole (**5**) in the presence of *tert*-butyl hydroperoxide affords selectively 4-(*tert*-butylperoxy)-2,5-cyclohexadien-1-one (**16**) in good yields (eq 11).[8]

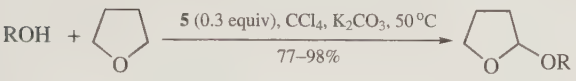


(11)

15 **16**

R^1, R^3 = H or *t*-Bu
R^2 = Me, *i*-Pr, *t*-Bu, CH$_2$Ph, OMe, etc.

Tetrahydrofuranylation of Alcohols Catalyzed by *tert*-Butylperoxybenziodoxole. The reaction of primary and secondary alcohols with THF and a catalytic amount of peroxybenziodoxole (**5**) in the presence of carbon tetrachloride provides an efficient method for protecting the hydroxy group as 2-tetrahydrofuranyl ethers (**17**) (eq 12).[9]

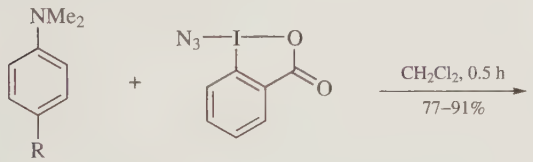


(12)

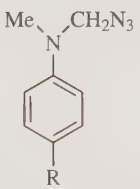
17

R = *n*-C_8H_{17}, $EtOCH_2CH_2$, $BrCH_2CH_2$, $NCCH_2CH_2$, $PhCH_2$, *cyclo*-C_6H_{11}, etc.

Azidation of *N,N*-Dimethylanilines with Azidobenziodoxole. Similarly to $PhIO/TMSN_3$ (see iodosylbenzene), azidobenziodoxole (**19**) can be used as an efficient azidating reagent towards various organic substrates. In particular, reagent **19** reacts with *N,N*-dimethylanilines (**18**) in dichloromethane at reflux to afford the respective *N*-azidomethyl-*N*-methylanilines (**20**) in high yield (eq 13).[6] The analogous reaction of *N,N*-dimethylanilines with the $PhIO/TMSN_3$ system[16] proceeds at −20 °C, which indicates lower reactivity of reagent **19** in comparison with the unstable $PhI(N_3)_2$ or $PhI(N_3)OTMS$ generated in situ from PhIO and $TMSN_3$. The main advantage of azidobenziodoxole (**19**) over the unstable $PhIO/TMSN_3$ reagent combination is high thermal stability allowing its storage and use at higher temperatures.



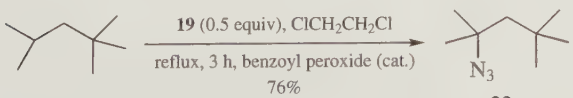
18 **19**



R = H or Br (13)

20

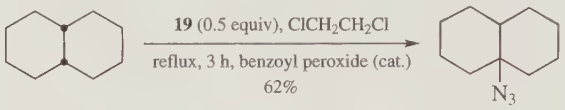
Azidation of Alkanes and Alkenes with Azidobenziodoxole. The relatively high thermal stability of azidobenziodoxole (**19**) allows its use for direct azidation of hydrocarbons at high temperatures in the presence of radical initiators.[10] Azidobenziodoxole (**19**) selectively reacts with isooctane (**21**) upon reflux in 1,2-dichloroethane in the presence of catalytic amounts of benzoyl peroxide to afford tertiary azide (**22**) and 2-iodobenzoic acid as the only products (eq 14).[10b] Azide (**22**) can be easily isolated in a good preparative yield by filtration of the reaction mixture through a short silica gel column using hexane as the eluent.



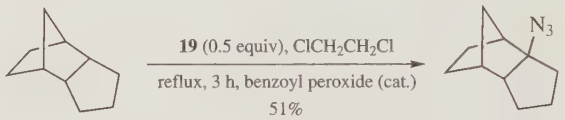
(14)

21 **22**

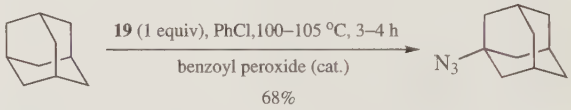
Various bicyclic and tricyclic hydrocarbons, such as *cis*-decalin (eq 15),[10b] tricyclo[5.2.1.0^{10,13}]decane (eq 16),[10b] adamantane (eq 17),[11] norbornane (eq 18)[11] undergo C–H activation by heating with azidobenziodoxole (**19**) in 1,2-dichloroethane or chlorobenzene at 83–132 °C in the presence of a catalytic amount of benzoyl peroxide. The reaction is generally completed in 3–4 h and the pure azides can be isolated in good yield by column chromatography on silica gel. Under similar conditions, cyclohexene is azidated in the allylic position to afford 3-azidocyclohexene in a relatively low yield (eq 19).[10b]



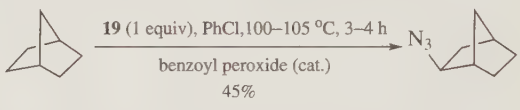
(15)



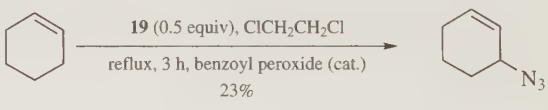
(16)



(17)

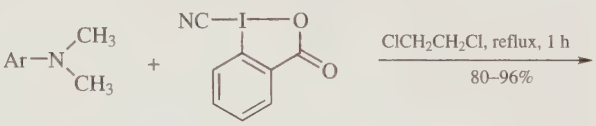


(18)

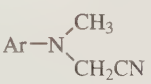


(19)

Cyanation of *N,N*-Dimethylanilines with Cyanobenziodoxole. The chemical reactivity of cyanobenziodoxole is generally similar to that of azidobenziodoxole and, in particular, it can be used as an efficient cyanating reagent towards *N,N*-dialkylarylamines. In a typical example, cyanobenziodoxole (**23**) reacts with *N,N*-dimethylanilines in 1,2-dichloroethane at reflux to afford the respective *N*-cyanomethyl-*N*-methylanilines in good yield (eq 20).[12] Products of this reaction can be easily separated from the side product, 2-iodobenzoic acid, by washing the reaction mixture with an aqueous basic solution. This reaction was applied to the synthesis of *N*-cyanomethyl-*N*-cyclopropylamine, which is an important metabolite of the cyclopropylamine-derived drugs.[17]



23



(20)

Ar = Ph, 4-BrC_6H_4, 4-MeC_6H_4, 1-naphthyl

Related Reagents. 1-Hydroxy-1,2-benziodoxol-3(1*H*)-one; iodosylbenzene; (diacetoxyiodo)benzene; IBX; DMP.

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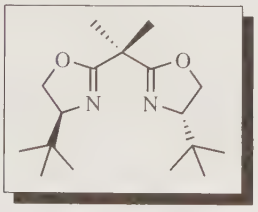
2,2-Bis{[2-[4(*S*)-*tert*-butyl-1,3-oxazinyl]}propane[1]



[131833-93-7] $C_{17}H_{30}N_2O_2$ (MW 294.44)

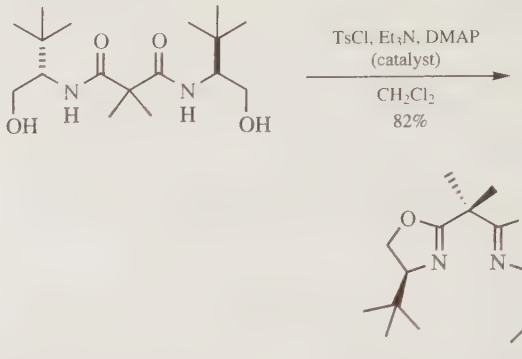
(reagent used as C_2-symmetric ligand for enantioselective catalysis[2])

Alternate Name: (*S,S*)-*t*-Bu-box.

Physical Data: mp 89–91 °C; $[\alpha]^{20}$ −120 (c = 5, $CHCl_3$).

Form Supplied in: white powder.

Preparative Methods: several methods for the synthesis of this ligand have been reported.[3] The preparation usually starts with the reduction of commercially available (*S*)-*tert*-leucine to the corresponding amino alcohol, followed by acylation with 0.5 equiv of dimethylmalonyl dichloride. The resulting dihydroxy malonodiamide is cyclized via the bis(alkyl chloride) or via the bis(tosylate) as described in an improved procedure (eq 1).[4]

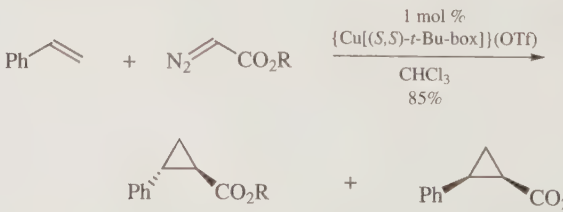


(1)

Handling, Storage, and Precautions: (*S,S*)-*t*-Bu-box is irritating to eyes, respiratory system and skin. In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. For the purification of (*S,S*)-*t*-Bu-box, crystallization from pentane can be used.

Cyclopropanation. The cationic Cu(I) complex, which is readily prepared from (*S,S*)-*t*-Bu-box and CuOTf, is the most efficient catalyst available today for the cyclopropanation of mono- and 1,1-disubstituted olefins with diazoacetates. For example, in the reaction of ethyl diazoacetate with 2-methylpropene, >99% ee and high yields can be obtained with this catalyst using substrate to catalyst ratios as high as 1000:1.

The reaction is carried out at ambient temperature and nearly complete enantioselectivity (>99%) is observed for mono- and 1,1-disubstituted olefins with diazoacetates.[5] With all copper catalysts, the *trans/cis* selectivities in the cyclopropanation of monosubstituted olefins are only moderate. The *trans/cis* ratio depends, in this case, mainly on the structure of the diazo ester rather than the chiral ligand (eq 2). It increases with the steric bulk of the ester group of the diazo compound. With the BHT ester, the more stable *trans* isomer is formed with selectivities up to >10:1. The steric hindrance usually prevents ester hydrolysis, but the BHT group can be removed by reduction with $LiAlH_4$. The *trans* isomer is even enriched by the reduction procedure because the *cis* isomer reacts more slowly.

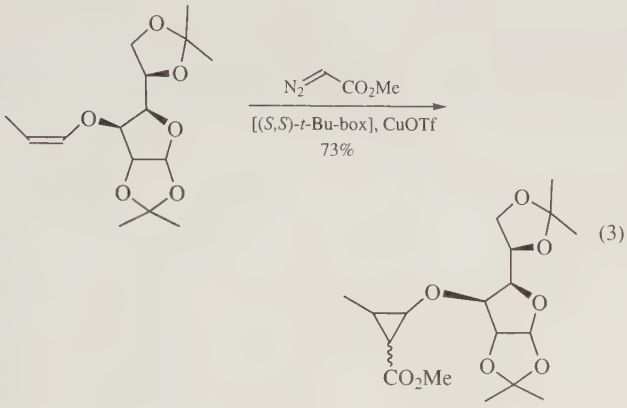


(2)

R = Et	99% ee	73:27	97% ee
R = BHT	99% ee	94:6	

On the other hand, with 1,2-disubstituted or certain trisubstituted olefins, the chiral ligand also influences the *trans/cis* selectivity. For example, treatment of a glucose-derived enol ether with

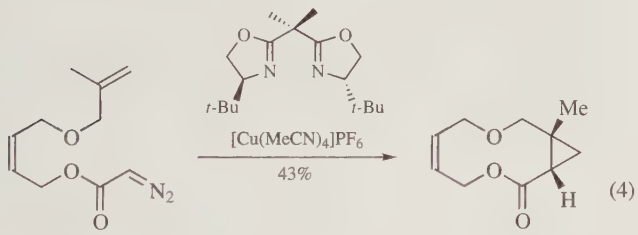
diazomethyl acetate in the presence of {Cu[(*S,S*)-*t*-Bu-box]}(OTf) complex affords the cyclopropanation product with an excellent *trans/cis* ratio but only moderate *trans*-enantioselectivity (eq 3).[6]



(3)

trans/cis >97:3
trans de 60%

Intramolecular reactions using (*S,S*)-*t*-Bu-box and $[Cu(MeCN)_4]PF_6$ complexes as catalysts have emerged as remarkably effective for the synthesis of macrocycles from *ω*-alkenyl diazoacetates. Also 10- and 15-membered ring lactones can be obtained in high enantiomeric purity with high efficiency.[7] If two double bonds are present in the molecule, the unique preference of copper-bisoxazoline catalysts to promote the formation of the larger ring is demonstrated (eq 4).[8]

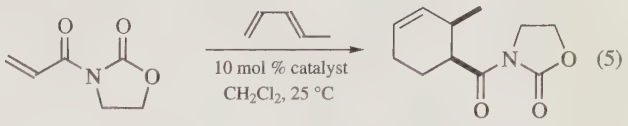


(4)

87% ee

Diels–Alder Reactions. It has been demonstrated that the ligand–metal complexes derived from (*S,S*)-*t*-Bu-box and a mild Lewis acid such as $Cu(OTf)_2$ are very efficient chiral catalysts for the Diels–Alder reaction with cyclopentadiene and substituted acylimide derivatives. Among various ligands examined, the (*S,S*)-*t*-Bu-box ligand consistently provided a very high level of *endo/exo* selectivity as well as *endo* enantioselectivity (90–98% ee with 5–10 mol % catalyst) and yield (82–92%) with a number of substituted dienophiles.

The counterion in these complexes plays a significant role for both catalyst activity and reaction enantioselectivity (eq 5). The hexafluoroantimonate-derived complex is 20 times more reactive in the Diels–Alder reaction than its triflate counterpart. This discovery resulted in a significantly broader scope (e.g. 1,3-cyclohexadiene, furan, isoprene and many other dienes can also be used successfully) of the reaction.[9] The crystalline aquo complexes $\{Cu[(S,S)\text{-}t\text{-Bu-box}](H_2O)_2\}(OTf)_2$ and $\{Cu[(S,S)\text{-}t\text{-Bu-box}](H_2O)_2\}(SbF_6)_2$ have also be evaluated as Lewis acid catalysts. The results indicate that hydration of the triflate complex effectively terminates catalysis. In contrast, hydration of the SbF_6 complex leads to a catalyst which is nearly as effective as its anhydrous counterpart.[10]



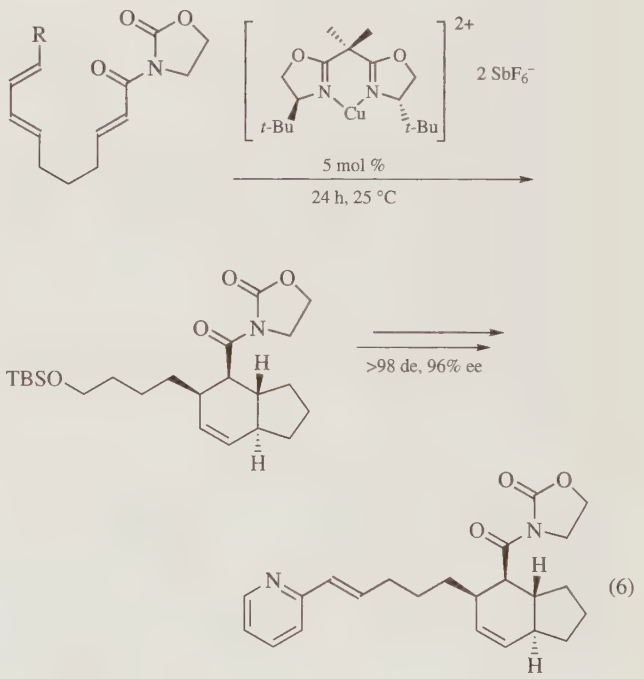
(5)

$\{Cu[(S,S)\text{-}t\text{-Bu-box}]\}(OTf)_2$: 15 h, 94% conversion, 84% ee

$\{Cu[(S,S)\text{-}t\text{-Bu-box}]\}(SbF_6)_2$: 50 min, 100% conversion, 95% ee

$\{Cu[(S,S)\text{-}t\text{-Bu-box}](H_2O)_2\}(SbF_6)_2$: 70 min, 100% conversion, 94% ee

For the enantioselective intramolecular Diels–Alder cycloaddition process, complex $\{Cu[(S,S)\text{-}t\text{-Bu-box}]\}(SbF_6)_2$ has also shown to be a very effective catalyst. In comparison, the complex prepared from $Cu(OTf)_2$ displays a very slow reaction, together with poor yields and selectivities. For example, the reaction of the substituted trienimide with 5 mol % of the hexafluoroantimonate complex provided the cycloaddition product as a single diastereomer within 5 h at 25 °C in good yield and 96% ee. The cycloadduct can afterwards be converted into (−)-isopulo'upone in a number of synthetic steps (eq 6).[11]

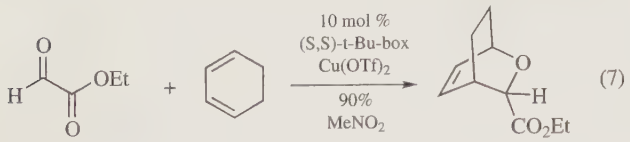


(6)

(−)-isopulo´upone

Hetero-Diels–Alder Reactions of Aldehydes. Cyclic conjugated dienes, such as 1,3-cyclohexadiene, are excellent substrates for the hetero-Diels–Alder reaction with ethyl glyoxylate catalyzed by $\{Cu[(S,S)\text{-}t\text{-Bu-box}]\}(OTf)_2$ (eq 7). The rate of this reaction is dependent on the counterion and the solvent. To obtain a highly diastereo- and enantioselective transformation, it is necessary to use $Cu[(S,S)\text{-}t\text{-Bu-box}](OTf)_2$ as a catalyst and $MeNO_2$

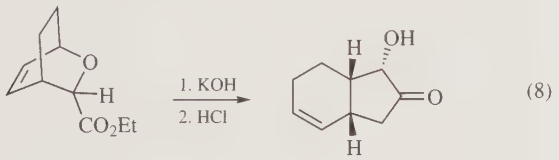
as a solvent, giving exclusively the *endo* adduct in more than 90% isolated yield with enantiomeric excess >97% ee.[12]



(7)

95% *endo*, > 97% ee

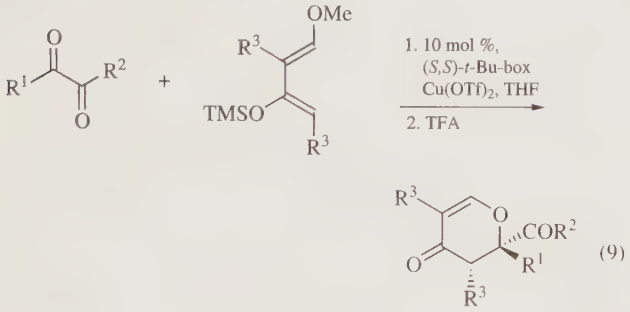
The product formed in this hetero-Diels–Alder reaction of ethyl glyoxylate with a cyclic diene catalyzed by (*S*,*S*)-*t*-Bu-box in combination with a copper(II) salt was used in the simple synthetic approach to enantiopure synthons for a class of natural products. Saponification of the bicyclic adduct followed by acidification with aqueous HCl provides the enantiopure (>99% ee) rearrangement product (eq 8).[13]



(8)

> 99% ee

Hetero-Diels–Alder Reactions of Ketones. Ketonic substrates such as ethyl pyruvate (eq 9, R^1 = Me, R^2 = OEt) do not react with simple dienes such as cyclopentadiene or 1,3-cyclohexadiene in the presence of (*S*,*S*)-*t*-Bu-box and a metal salt as catalyst. However, using activated dienes such as *trans*-1-methoxy-3-[(trimethylsilyl)oxyl]-1,3-butadiene (Danishefsky's diene), a hetero-Diels–Alder reaction with ethyl pyruvate and similar substrates catalyzed by 10 mol% of {Cu[(*S*,*S*)-*t*-Bu-box]}$(OTf)_2$ takes place in good yields and enantioselectivities (eq 9).[14] Surprisingly, it was even possible to reduce the catalyst loading to only 0.5 mol % without affecting the yield of the product, and in some cases the enantiomeric excess was even improved.

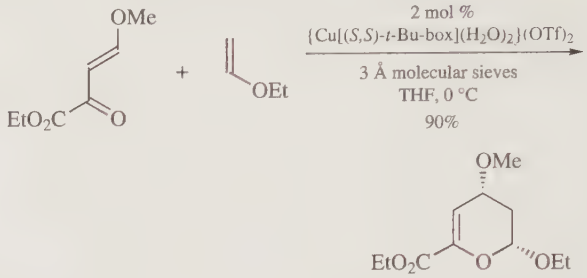


(9)

R^1 = R^2 = alkyl; yields up to 90%, up to 88% ee

R^1 = alkyl, aryl; R^2 = OEt; yields up to 96%, up to 99% ee

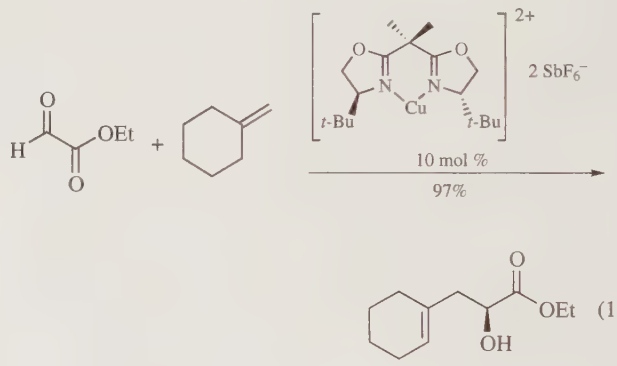
Inverse electron demand hetero-Diels–Alder reactions of acyl phosphonates[15] or α-keto ester heterodienes and enol ethers are also catalyzed by (*S*,*S*)-*t*-Bu-box complexes. High levels of enantioselectivity are obtained with γ-alkyl-, -aryl-, -alkoxy- and -thioalkyl-substituted β,γ-unsaturated α-keto esters using 2 mol % of the aquo complex {Cu[(*S*,*S*)-*t*-Bu-box]$(H_2O)_2$}$(OTf)_2$ (eq 10).[16] This reaction shows a number of practical advantages. First, the aquo complex, a bench-stable pale blue powder that can be stored indefinitely without special precaution, provides not only uniformly high levels of enantioselection but also excellent control of regioselectivity. A second feature is the possibility of reusing the catalyst following a simple recycling protocol involving hexane, a solvent in which the catalyst is apparently insoluble.



(10)

endo/*exo* 59:1, 98% ee

Ene Reaction. The dicarbonyl moiety of ethyl glyoxylate was found to react with a broad range of unactivated olefins to afford γ,δ-unsaturated α-hydroxy esters in high enantioselectivity and high yields (eq 11).



(11)

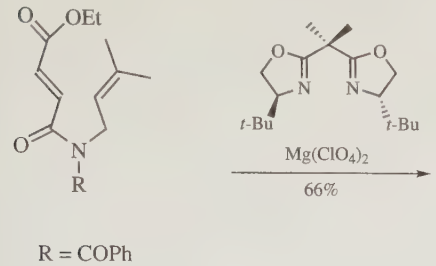
97% ee

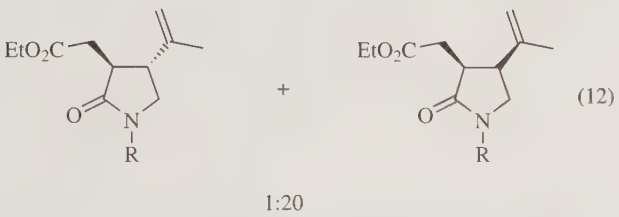
In this reaction, several attractive features can be noted. The bench-stable aquo {Cu[(*S*,*S*)-*t*-Bu-box]$(H_2O)_2$}$(SbF_6)_2$ complex was as effective as the analogous anhydrous {Cu[(*S*,*S*)-*t*-Bu-box]}$(SbF_6)_2$ complex, even with catalyst loadings as low as 0.1 mol %, without significant loss of yield and enantioselectivity. A testament for the Lewis acidity of the copper(II) (*S*,*S*)-*t*-Bu-box complexes is that weakly nucleophilic olefins such as hex-1-ene and cyclohexene had not been previously employed in catalytic asymmetric ene reactions.[17]

Besides the symmetrical 1,1-disubstituted alkenes, unsymmetrical 1,1-disubstituted, 1,2-disubstituted, and monosubstituted alkenes also react in a highly enantioselective manner in the presence of the copper(II) (*S*,*S*)-*t*-Bu-box catalyst.

A short and efficient asymmetric total synthesis of (−)-α-kainic acid, which is an important neurotransmitter, has been achieved by means of a metal-promoted, enantioselective ene reaction. This approach provides entry into the kainic acid ring system from a very simple precursor (eq 12).[18] One of the key steps involved (*S*,*S*)-*t*-Bu-box-promoted magnesium(II) catalysis. In this case,

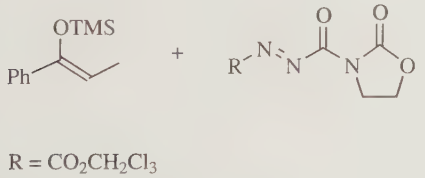
cyclization favored strongly the desired *cis*-diastereomer, which can be converted to the desired acid in a number of synthetic steps.

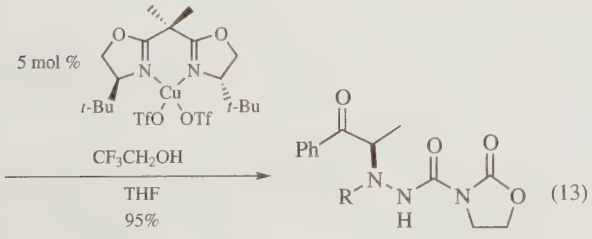




(12)

Enol Amination. The {Cu[(*S*,*S*)-*t*-Bu-box]}$(OTf)_2$ complex was found to be optimal for promoting the enantioselective conjugated addition of enolsilanes to azodicarboxylate derivatives (eq 13). This methodology provides an enantioselective catalytic route to differentially protected α-hydrazino carbonyl compounds. Isomerically pure enolsilanes of aryl ketones, acylpyrroles, and thioesters add to the azo-imide in greater than 95% ee. The use of an alcohol additive was critical to achieve catalyst turnover. Amination of cyclic enolsilanes was also possible. For example, the enolsilane of 2-methylindanone provides the adduct containing a tetrasubstituted stereogenic center in 96% ee and high yield. Acyclic (*Z*)-enolsilanes react in the presence of a protic additive with enantioselection up to 99%.[19]

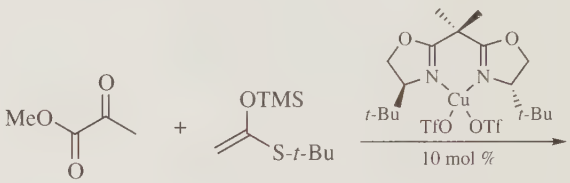


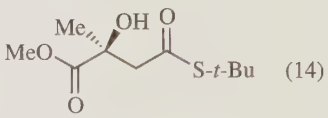


(13)

Aldol Addition. A catalyst generated upon treatment of $Cu(OTf)_2$ with the (*S*,*S*)-*t*-Bu-box ligand has been shown to be an effective Lewis acid for the enantioselective Mukaiyama aldol reaction.[20] The addition of substituted and unsubstituted enolsilanes at −78 °C in the presence of 5 mol % catalyst was reported to be very general for various nucleophiles, including silyl dienolates and enol silanes prepared from butyrolactone as well as acetate and propionate esters.

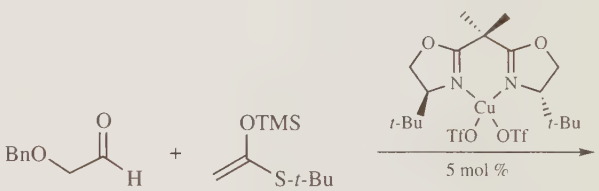
Mukaiyama aldol reactions of silylketene acetal and pyruvate ester (eq 14) in the presence of 10 mol % {Cu[(*S*,*S*)-*t*-Bu-box]}$(OTf)_2$ catalyst furnish the corresponding aldol product in excellent enantiomeric excess (98%). Furthermore, the addition reactions of ketene acetals derived from *t*-butyl thioacetate and benzyloxyacetaldehyde with only 5 mol % catalyst afford the aldol product in 91% ee (eq 15).[21] It is also noteworthy that the addition of both propionate-derived (*Z*)- and (*E*)-silylketene acetals stereoselectively forms the *syn*-adduct in 97% and 85% ee, respectively.

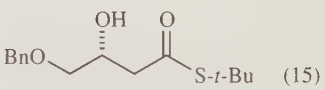




(14)

98% ee





(15)

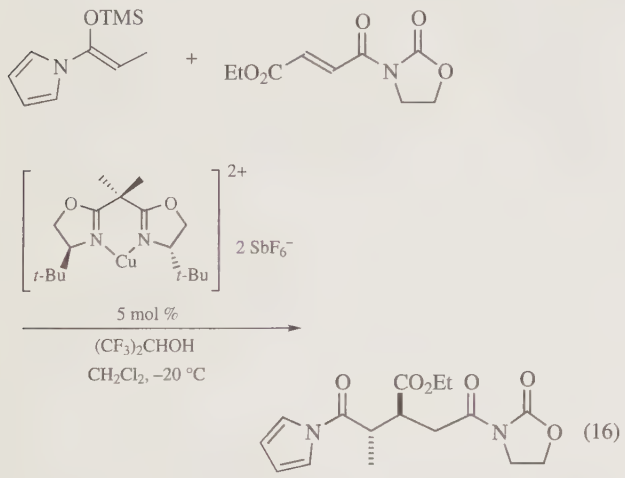
91% ee

Michael Additions. The {Cu[(*S*,*S*)-*t*-Bu-box]}$(SbF_6)_2$ complex catalyzes the enantioselective addition of enolsilanes to fumaroyl imides with enantioselectivities of up to 99% ee and in good yields (up to 91%).[22] Here, the diastereoselectivity correlates with the geometry of the nucleophile; (*E*)-silylketene acetals preferentially deliver *anti* adducts (eq 16), while (*Z*)-silylketene acetals afford *syn* products (eq 17).

Alkylidene malonates also react with silylketene thioacetals under catalysis by the {Cu[(*S*,*S*)-*t*-Bu-box]}$(SbF_6)_2$ complex. The reaction adducts are obtained with good efficiency (up to 91% yield) and high levels of enantiocontrol (up to 93% ee),[23] especially for alkylidene malonates bearing sterically demanding substituents in the β-position.

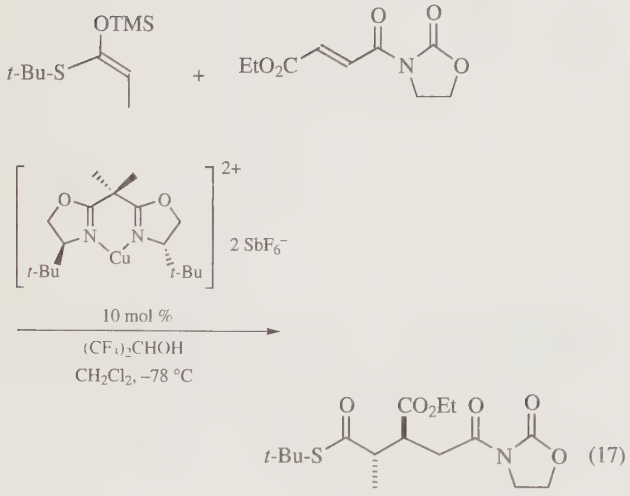
Oxidations. A widely used method for allylic oxidation is the Kharash–Sosnovsky reaction using a peroxide and a copper(I) salt system. Enantioselective allylic oxidations of cycloalkenes such as cyclopentene, cyclohexene and cycloheptene with *tert*-butyl perbenzoate were investigated with a variety of catalysts

derived from bis(oxazoline) ligands and copper(I) triflate complexes (eq 18). The ligand–copper(I) complexes from the *t*-Bu-box, Ph-box and *i*-Pr-box have shown comparable results.[24] In the presence of 5 mol % {Cu[(*S,S*)-*t*-Bu-box]}(OTf), a remarkable 84% ee (61% yield at 68% conversion) was achieved in the transformation of cyclopentene to 2-cyclopentenyl benzoate. Acetonitrile was the solvent of choice. The reactions were typically run at −20 °C for 5 days. At these temperatures acyclic olefins exhibited only very low or no optical activity. However, at 55 °C for 2 days, allylbenzene and oct-1-ene afforded 36% ee and 30% ee, respectively.[25]



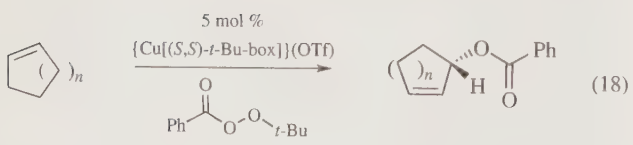
(16)

94% ee *anti/syn* 97:3



(17)

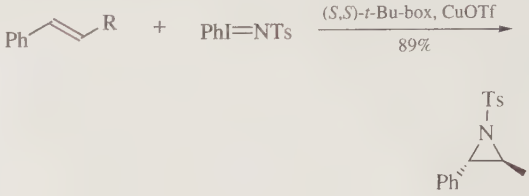
99% ee *anti/syn* 7:93



(18)

n = 1; 61%, 78% ee
n = 2; 44%, 79% ee

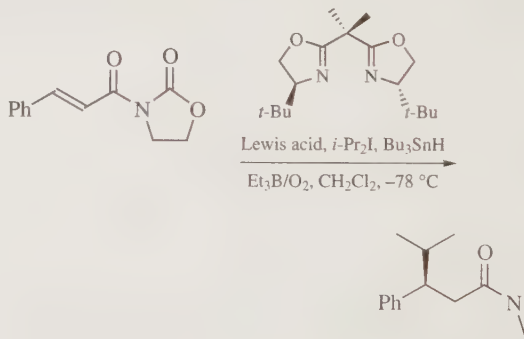
Aziridination Reactions. CuOTf–bis(oxazoline) complexes are efficient catalysts for the aziridination of olefins. Olefins with aryl substituents have proven to be the most efficient substrates for this reaction. For styrene, the corresponding *N*-tosylaziridine was obtained in good yield (89%), but only moderate enantiomeric excess (66% ee) (eq 19).[26] Catalysts derived from other bis(oxazoline) ligands, like for example Ph-box, have exhibited superior results over the sterically demanding (*S,S*)-*t*-Bu-box giving rise to enantioselectivities of up to 97% ee.[27]



(19)

R = H, 63% ee
R = Me, 70% ee

Radical Reactions. For radical additions, chiral Lewis acids can be complexed to radical traps which undergo enantioselective attack at the β-centers. One solution to the problem of acyclic diastereoselection in β-radical additions has been the use of bis(oxazolines) in conjunction with Lewis acid additives. (*S,S*)-*t*-Bu-box-derived, Lewis acid-promoted free radical conjugate additions to β-substituted, α,β-unsaturated *N*-oxazolidinone derivatives, with stoichiometric amounts of Lewis acid and ligand, proceed in excellent chemical yields and high enantioselectivities (eq 20). From the variety of tested Lewis acids for this reaction, usually magnesium or zinc salts, $MgBr_2$ gave the best results with the (*S,S*)-*t*-Bu-box ligand.[28]



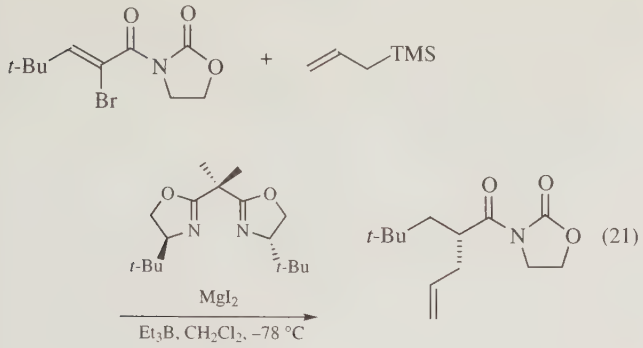
(20)

Lewis acid
$Zn(OTf)_2$, 37% ee
$MgBr_2$, 77% ee

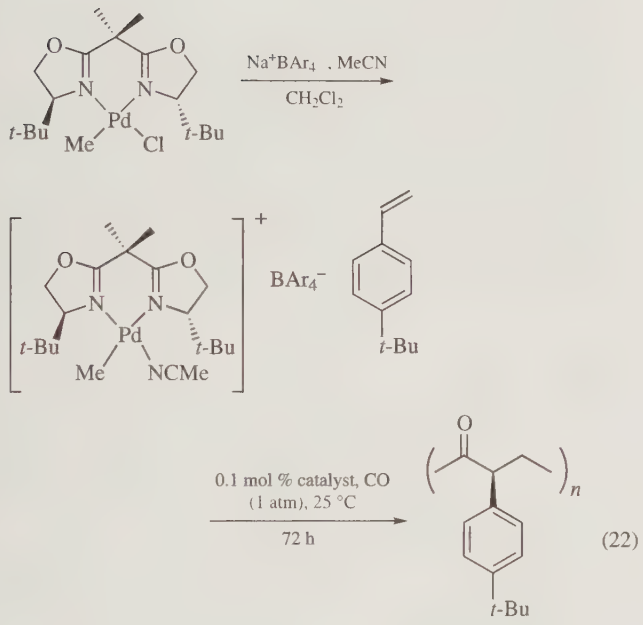
Radical allylation of bromides derived from β-substituted, α,β-unsaturated *N*-oxazolidinones with several allylsilanes have been carried out with 1 equiv of Lewis acid and ligand in dichloromethane initiated by Et_3B at −78 °C.[29] The use of the (*S,S*)-*t*-Bu-box ligand in combination with MgI_2 proceeds with good selectivity and yield (eq 21).

Polymerization Reactions. The enantioselective co-polymerization of styrenes and carbon monoxide has been achieved by the use of a palladium catalyst based on the (*S,S*)-*t*-Bu-box ligand. Co-polymerization of *p-tert*-butylstyrene (TBS) and carbon monoxide in the presence of 0.1 mol % chiral catalyst afforded the alternating co-polymer with a highly isotactic microstructure and excellent

optical purity (eq 22). The stereoregularity of the polymer is >98% and the polymer exhibits high molar rotation.[30]

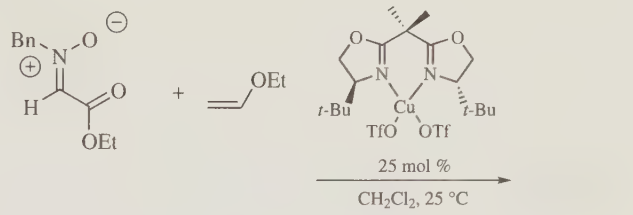


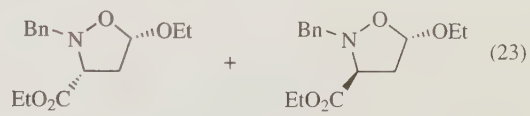
R/S 98:1



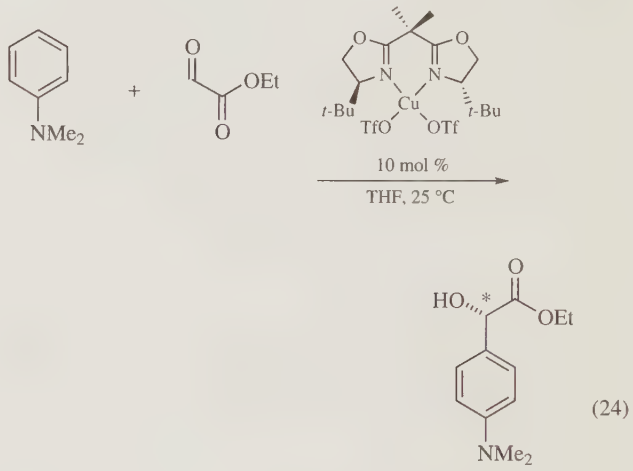
1,3-Dipolar Cycloadditions. 1,3-Dipolar cycloadditions provide a powerful method for the synthesis of five-membered heterocyclic rings. The use of (*S,S*)-*t*-Bu-box in combination with $Cu(OTf)_2$ as catalyst for the reaction of a nitrone with ethyl vinyl ether leads to the products in 93% yield (eq 23). The diastereoselectivity is *exo*-selective, as the product was obtained in an *endo*/*exo* ratio of 83:16. A change of the counterion in the catalyst from triflate to antimonate leads to a nonselective reaction. The use of a catalyst prepared from (*S,S*)-*t*-Bu-box and $Zn(OTf)_2$ displays weaker Lewis acidity than the corresponding copper(II) catalyst, which results in lower conversion (73%) and selectivity (*endo*/*exo* 66:34).[31]

Enantioselective Friedel–Crafts Reactions. The copper(II) complex of the (*S,S*)-*t*-Bu-box ligand has been used as catalyst for the reaction of *N,N*-dimethylaniline with ethyl glyoxylate and it has been found that a highly regio- and enantioselective Friedel–Crafts reaction takes place.[32] This reaction proceeds with the exclusive formation of the *para*-substituted isomer in up to 91% yield and 94% ee (eq 24).





84:16
89:35 % ee

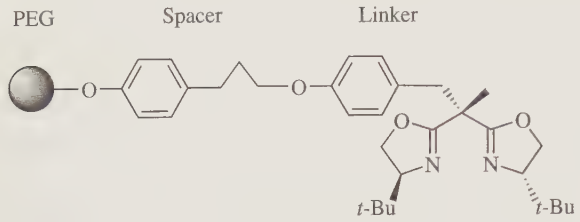


91%; 94% ee

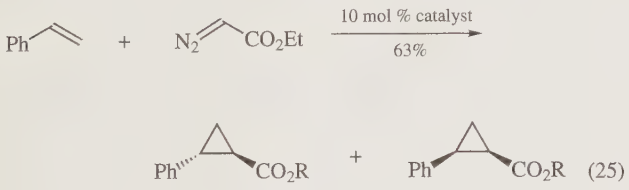
The reaction has been investigated for *N,N*-dimethylaniline under different reaction conditions and has been developed into a highly enantioselective catalytic reaction for *meta*-substituted *N,N*-dimethylanilines containing either electron-withdrawing or electron-donating substituents. The reaction also proceeds well for catalytic aromatic amines such as *N*-methylindoline, *N*-methyltetrahydroquinoline, and julolidine, where up to 91% yield and 93% ee are obtained. For polyaromatic amines, high yields but only moderate ee values for the Friedel–Crafts products are obtained. To enhance the potential of the reaction, the *N,N*-dimethyl- and *N*-methyl substituents, respectively, can be removed, successfully leading to the mono *N*-methyl product or the free amine, which allows the introduction of a variety of other substituents. Moreover, the catalytic enantioselective reaction also proceeds for heteroaromatic compounds such as 2-substituted furans, which react with ethyl glyoxylate as well as trifluropyruvates, giving up to 89% ee of the Friedel–Crafts products.

Poly(ethylene glycol)-supported (*S,S*)-*t*-Bu-box Ligands. (*S,S*)-*t*-Bu-box-supported on a modified poly(ethylene glycol) (PEG) has been prepared by a reaction sequence that involves formation of a suitably functionalized ligand and its attachment to the polymer matrix by means of a spacer and a linker. The solubility properties of PEG allowed the successful use of the supported ligand in the enantioselective cyclopropanation carried out under

homogeneous conditions, and allow recovery of the ligand as if bound to an insoluble support.



The cyclopropanation of styrene carried out with ethyl diazoacetate in the presence of 10 mol % supported ligand and 10 mol % CuOTf gave a 77:23 mixture of the *trans*/*cis* cyclopropane adducts in 63% yield and 91% ee for the major isomer (eq 25).[33] These results were comparable to those obtained with the free (*S*,*S*)-*t*-Bu-box ligand.[5a]



91% ee (77:23)

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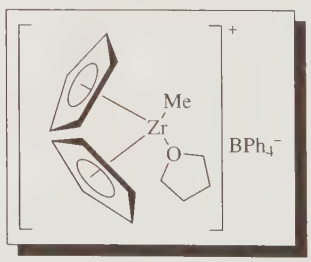
Bis(cyclopentadienyl)methylzirconium Tetraphenylborate–Tetrahydrofuran[1]



[100909-50-0] $C_{39}H_{41}BOZr$ (MW 627.78)

(alkene polymerization agent;[2] can insert carbon monoxide, nitriles, and alkynes;[3] can function as a Lewis acid[4])

Solubility: sol CH_2Cl_2 and 1,2-dichloroethane; reacts with protic solvents.

Analysis of Reagent Purity: ^1H NMR (CD_2Cl_2) δ 7.6–6.7 (m, 20H, BPh_4^-), 6.31 (s, 10H), 3.44 (m, 4H, THF), 1.80 (m, 4H, THF), 0.74 (s, 3H).

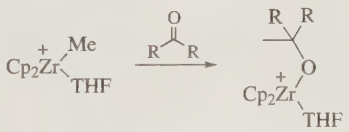
Preparative Methods: treatment of Cp_2ZrMe_2 with 1 equiv of $AgBPh_4$ in MeCN followed by recrystallization from THF gives $Cp_2ZrMe(THF)^+BPh_4^-$.[3a] Alternatively, it can be obtained directly by treating Cp_2ZrMe_2 with $[HNBu_3][BPh_4]$ or $[Cp'_2Fe][BPh_4]$ ($Cp' = C_5H_4Me$) in THF.[5]

Purification: recrystallization from hot THF gives a relatively stable pale yellow crystalline solid.

Handling, Storage, and Precautions: the dry solid is highly sensitive to moisture and oxygen and should be stored in a dry box; a coordinating solvent, such as MeCN, causes ligand exchange.

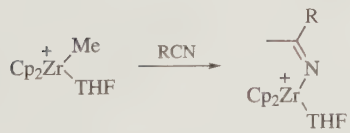
Ligand. Although complexes having ligands other than THF are known,[3a] most descriptions focus on the Lewis acidic THF complex due to there being abundant examples of its use in organic synthesis. The THF-free species Cp_2ZrMe^+, generated as a transient intermediate in CH_2Cl_2 solution, decomposes, principally to Cp_2MeCl.[2a] The THF ligand is labile and generally undergoes rapid exchange with nitriles, small phosphines, pyridine, and other heterocycles. In general, the cationic $Cp_2ZrMe(THF)^+$ complex is more reactive than neutral $Cp_2ZrMeCl$ or Cp_2ZrMe_2 complexes as a result of the increased unsaturation and charge.

Insertion Reaction. The high insertion reactivity of this complex has been noted and representative insertions are summarized in eqs 1–4.

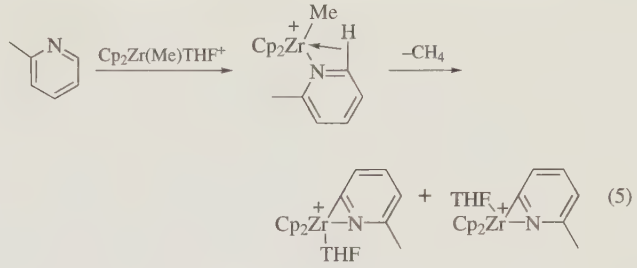

(1)


(2)

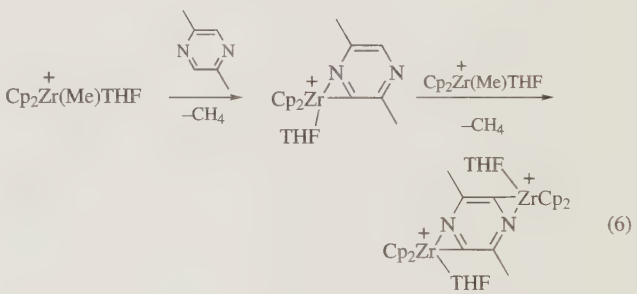

(3)


(4)

The Zr–CH_3 bond of this complex in THF can be cleaved by H_2 to yield the insoluble hydride $Cp_2Zr(H)(THF)^+BPh_4^-$.[6] The reaction of the cationic methyl complex with stoichiometric amounts of α-picoline yields the η^2-pyridyl complex, $Cp_2Zr(\eta^2\text{-}N,C\text{-picolyl})(THF)^+$, via initial ligand substitution followed by rapid C–H activation/CH_4 elimination ($t_{1/2}$ 6 min, 23 °C, CH_2Cl_2) (eq 5).[7]


(5)

Interestingly, use of pyridine itself causes a much slower reaction (hours, 50 °C, CH_2Cl_2). The acceleration of C–H activation by the α-methyl group of α-picoline is considered to be due to steric crowding which enhances the overlap of the *ortho* C–H bond with the Zr LUMO.[8] The C–H activation of a variety of N-heterocyclic compounds[9] can be achieved in CH_2Cl_2 as shown in eqs 6–8. These metallacycles react with alkenes and alkynes to give stable five- or six-membered metallacycles which can be converted to α-substituted heterocycles upon hydrolysis (eqs 9–11).[7a,9,10] The formation of these metallacycles was suggested to be both kinetically and thermodynamically favored.[10a] More importantly, alkenes and *ortho*-substituted pyridines are coupled by catalytic amounts of $Cp_2Zr(Me)^+$ in 1,2-dichloroethane under an H_2 atmosphere (eq 12).[7b]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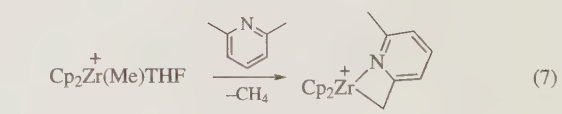
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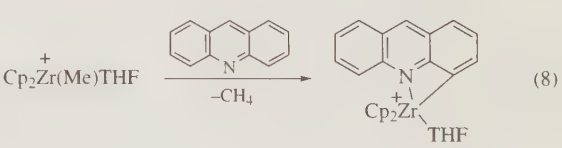
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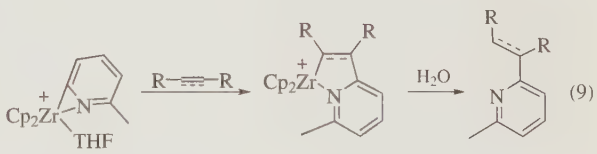
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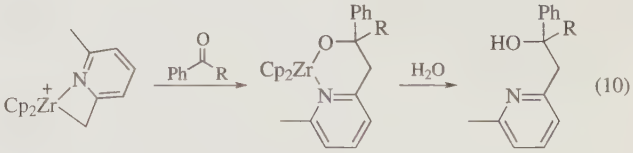
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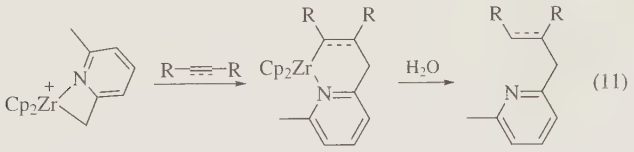

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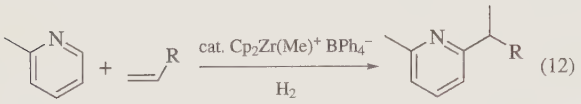
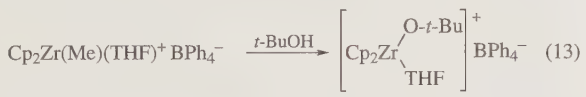


(12)

Lewis Acid Catalyst. Treatment of $Cp_2Zr(Me)(THF)^+BPh_4^-$ with *t*-BuOH gives $Cp_2Zr(O\text{-}t\text{-}Bu)(THF)^+$ (eq 13), which is an effective catalyst in the Diels–Alder (eq 14) and Mukaiyama aldol reactions (eq 15).[4]



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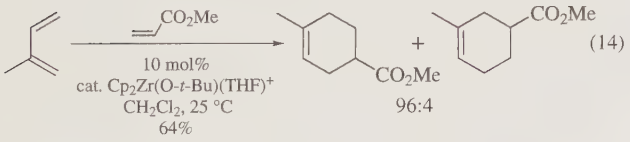

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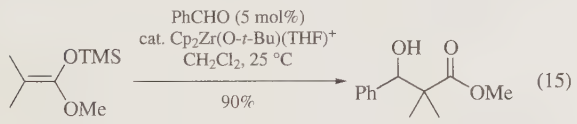

(15)

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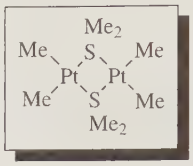
Bis[dimethyl(μ-dimethyl sulfide)-platinum(II)]



[79870-64-7] $C_8H_{24}Pt_2S_2$ (MW 574.56)

(reagent used for C–H functionalization)

Physical Data: mp 86 °C.

Solubility: very soluble in Et_2O, CH_2Cl_2 and moderately soluble in acetone.

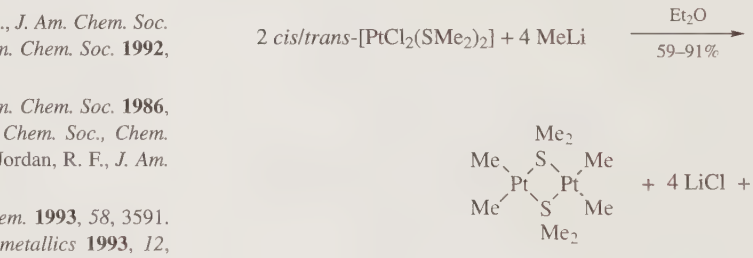
Form Supplied in: white solid; not commercially available.

Analysis of Reagent Purity: NMR and mp 86 °C.

Preparative Methods: synthesized from methyllithium treatment of a *cis/trans*-mixture of $PtCl_2(SMe_2)_2$ (see below).

Handling, Storage, and Precautions: compound can be handled in air, but should be stored under inert atmosphere at 0 °C. The product is stable for several weeks at 0 °C but decomposes rapidly at room temperature. Toxicological properties are unknown and the compound should be handled in a fume hood using gloves.

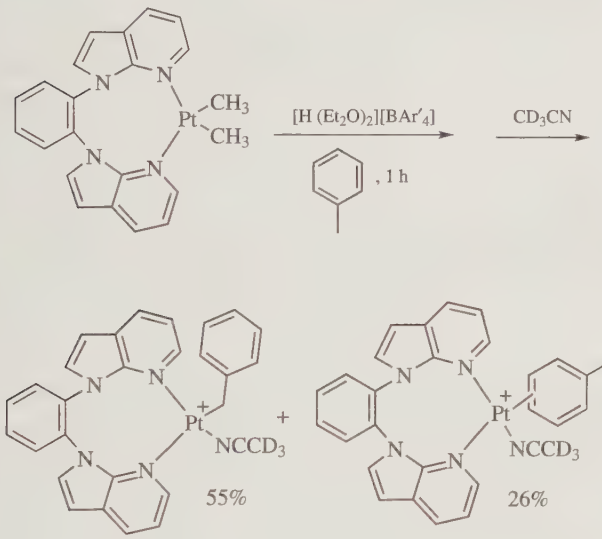
Synthesis. The first synthesis of $[Me_2(\mu\text{-}SMe_2)Pt]_2$ was given by Puddephatt in 1983,[1] and has recently been optimized.[2] This preparation relies on the treatment of a *cis/trans* mixture of $PtCl_2(SMe)_2$ with methyllithium (eq 1).



(1)

C–H Functionalization. C–H activation or as defined by Sames as C–H functionalization, a more convenient term and also of broader use,[3,4] holds fantastic potential for organic synthesis. While historically, radical reactions have been utilized for this purpose, homogeneous transition metal catalysis offer new options. In this context, platinum(II) complexes have already provided impressive results.[5] Two benchmark papers dating from the 1960s were given by Hodges and Garnett who described a homogeneous Pt(II)-catalyzed deuteration of arenes and alkanes and by Shilov who reported the oxidation of CH_4 into CH_3OH and CH_3Cl using a Pt(II) salt as catalyst with a stoichiometric Pt(IV) species as reoxidant.[4,6] These seminal works paved the way for important developments, while mechanistic studies have enabled critical understanding of this chemistry. Efforts to understand the initial C–H activation process, accompanied by the design and evaluation of more practical catalytic systems are major goals. Most approaches have involved Pt(II) complexes with bidentate

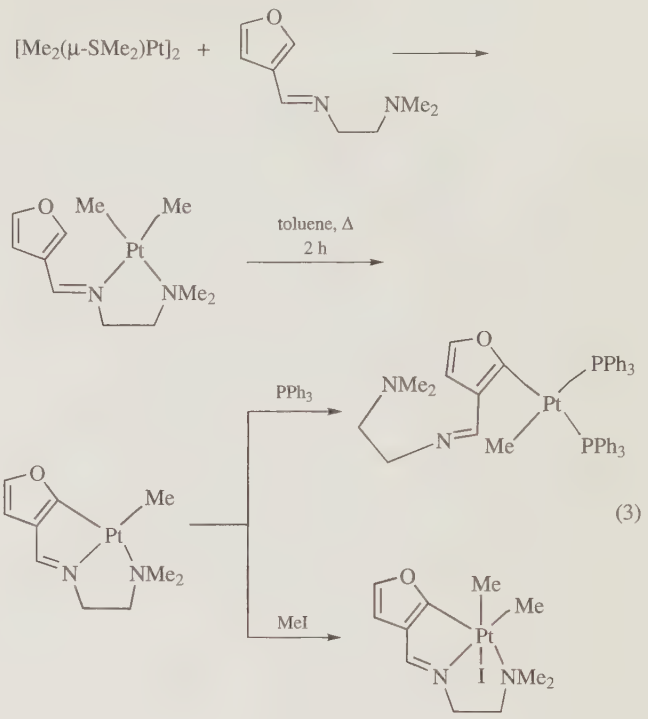
nitrogen ligands, notably diimine ligands[7] forming five- or six-membered complexes. The $[Me_2(\mu\text{-}SMe_2)Pt]_2$ complex has been adopted as an excellent source of Pt(II) for these endeavors, since complexation of the bidentate nitrogen ligands is typically accompanied by the loss of the SMe_2 ligands. Many studies have examined the ligation of platinum, systematically changing the electronic and steric environment by employing different heteroatoms. For example, complexes bearing mixed ligands (P, N) to platinum have been prepared by this exchange process.[8] A dimethyl Pt(II) 8-(methylthio)quinoline compound was further evolved by S-Pt(II) transmethylation, providing a binuclear Pt(IV) complex displaying stacked quinoline rings.[9] Recently, Wang has prepared two isomeric Pt(II) complexes using bis(*N*-7-azaindolyl)methane fluorescent ligands,[10] which have proven to be useful starting materials for C–H functionalization of aromatics, with C–H activation of alkanes under continuing investigation. Tethering two bis-*N*-7-azaindolyl fragments by a benzene ring generates a new dimethyl Pt(II) complex that reacts with 1 equiv of acid to activate toluene mainly at the benzylic position, accompanied by aromatic ring activation, principally at the *meta*-position (eq 2).[11]



(2)

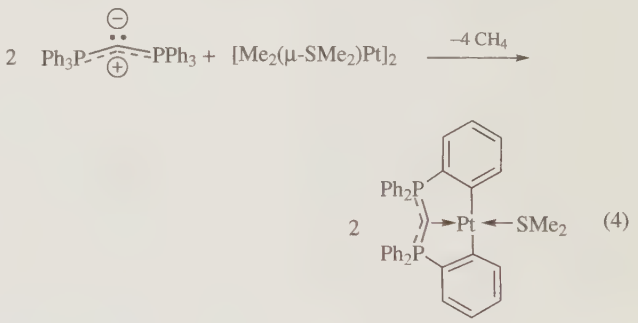
C–H bond activation is also achieved using unsymmetrical 2-(*N*-arylimino)pyrrolide Pt(II) complexes.[12] This reaction was highly sensitive to electronic and steric properties of the ligand as well as the substrate.

Intramolecular activation of aromatic substrates afford cyclometallated complexes. These compounds exhibit interesting photochemical properties and have potential use as molecular devices. Doubly cyclometallated binuclear Pt(II) complexes are generated from reaction of $[Me_2(\mu\text{-}SMe_2)Pt]_2$ with imine ligands derived from terephthalaldehyde.[13] Following studies on intramolecular C–H activation of aromatic systems, Anderson and Crespo examined furans and pyridines.[14] Reaction of $[Me_2(\mu\text{-}SMe_2)Pt]_2$ with a diaminofuran ligand proceeded smoothly at room temperature to give a remarkably stable complex. Only heating in toluene at reflux initiates cyclometallation with elimination of methane to provide an orthometallated complex. The diminished reactivity of furan towards cyclometallation was ascribed to a lower degree of aromaticity and not to the energy of the broken C–H bond. Interestingly, the cyclometallated complex easily reacted with triphenylphosphine and iodomethane (eq 3). In contrast, cyclometallated species were not isolated from pyridine ligands, which gave only intractable materials.



(3)

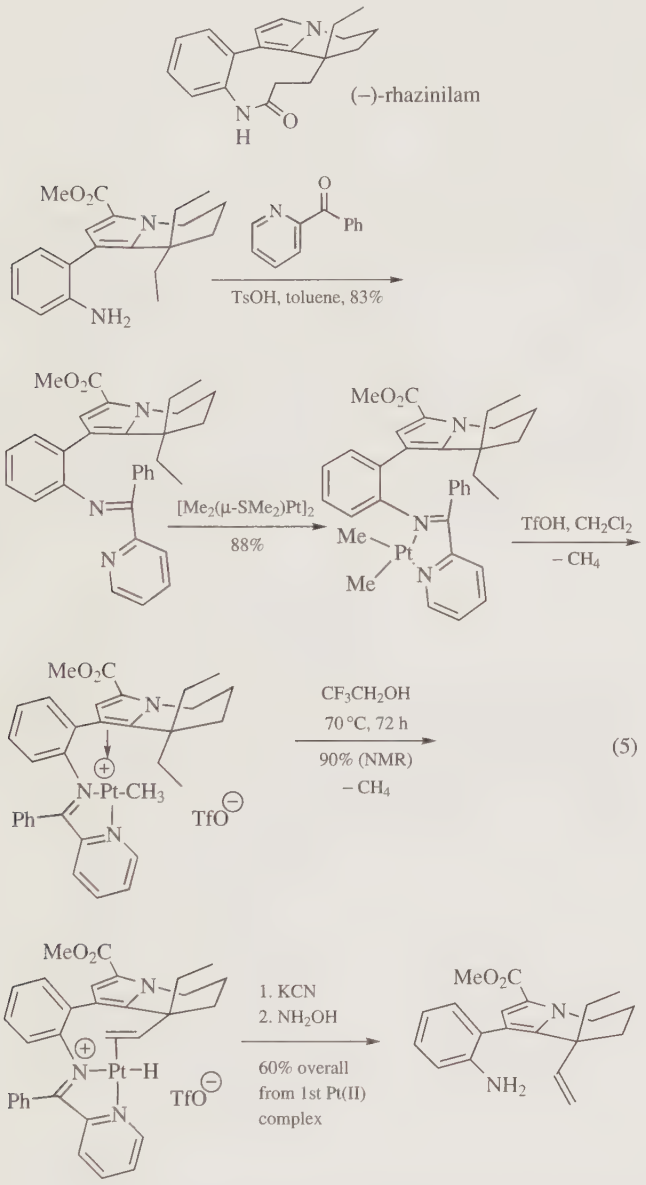
A very recent extension of this strategy is seen in the reaction of hexaphenylcarbodiphosphorane $PPh_3{=}C{=}PPh_3$ with $[Me_2(\mu\text{-}SMe_2)Pt]_2$, giving a C,C,C pincer carbene Pt(II) complex (eq 4). Formation of the complex involves a double orthometallation with elimination of two molecules of methane from each Pt atom.



(4)

An intriguing application of $[Me_2(\mu\text{-}SMe_2)Pt]_2$ was disclosed by Sames in connection with the total synthesis of the antimitotic rhazinilam.[15] The key step is a chemoselective C–H activation of an alkyl group. To complete this goal, several design elements were simultaneously achieved: A methyl carboxylate group on the pyrrole ring temporarily decreases its electrophilicity. Subsequently, a Schiff base serves as ligand for the platinum metal delivered from $[Me_2(\mu\text{-}SMe_2)Pt]_2$. Triflic acid generates a platinum cation accompanied by loss of methane, forming a Pt(II) complex featuring unusual coordination to the pyrrole ring. Thermolysis of this complex triggers ethyl group activation with concomitant methane loss. This is followed by β-elimination, providing a single new alkene-platinum hydride complex in excellent yield. The presence of the phenyl imine function is crucial, preventing pyrrole-aniline coplanearity while concurrently weakening platinum-pyrrole coordination. This looser complex is

perfectly suited for directed C–H activation. The platinum metal is removed by treatment with aqueous potassium cyanide and the Schiff base hydrolyzed. The resulting vinyl derivative is homologated by one carbon (carbonylation). Macrocyclization and deprotection of the methyl ester completes the total synthesis (eq 5).



(5)

Further refinement featured an asymmetric synthesis based on use of a chiral auxiliary to differentiate the two enantiotopic ethyl groups.[16] The cyclohexyloxazoline provided an ee of 62–76%.

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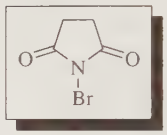
N-Bromosuccinimide[1]



[128-08-5] $C_4H_4BrNO_2$ (MW 177.99)

(radical bromination of allylic and benzylic positions; electrophilic bromination of ketones, aromatic and heterocyclic compounds; bromohydration, bromoetherification, and bromolactonization of alkenes)

Alternate Names: NBS; 1-bromo-2,5-pyrrolidinedione.

Physical Data: mp 173–175 °C (dec); *d* 2.098 g cm^{-3}.

Solubility: sol acetone, THF, DMF, DMSO, MeCN; slightly sol H_2O, AcOH; insol ether, hexane, CCl_4 (at 25 °C).

Form Supplied in: white powder or crystals having a faint odor of bromine when pure; widely available.

Purification: in many applications the use of unrecrystallized material has led to erratic results. Material stored for extended periods often contains significant amounts of molecular bromine and is easily purified by recrystallization from H_2O (AcOH has also been used). In an efficient fume hood (caution: bromine evolution), an impure sample of NBS (200 g) is dissolved as quickly as possible in 2.5 L of preheated water at 90–95 °C. As filtration is usually unnecessary, the solution is then chilled well in an ice bath to effect crystallization. After most of the aqueous portion has been decanted, the white crystals are collected by filtration through a bed of ice and washed well with water. The crystals are dried on the filter and then in vacuo. The purity of NBS may be determined by the standard iodide–thiosulfate titration method.

Handling, Storage, and Precautions: should be stored in a refrigerator and protected from moisture to avoid decomposition. One of the advantages of using NBS is that it is easier and safer to handle than bromine; however, the solid is an irritant and bromine may be released during some operations. Therefore, precautions should be taken to avoid inhalation of the powder and contact with skin. All operations with this reagent are best

conducted in an efficient fume hood. In addition, since reactions involving NBS are generally quite exothermic, large-scale operations (>0.1 mol) should be approached with particular caution.

Original Commentary

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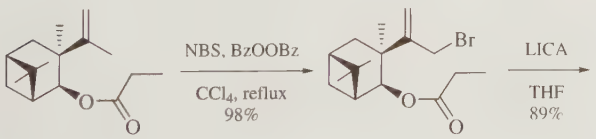
Massachusetts Institute of Technology, Cambridge, MA, USA

Introduction. *N*-Bromosuccinimide is a convenient source of bromine for both radical substitution and electrophilic addition reactions. For radical substitution reactions, NBS has several advantages over the use of molecular ***Bromine***, while ***1,3-Dibromo-5,5-dimethylhydantoin*** is another reagent of use. ***N-Chlorosuccinimide*** and ***N-Iodosuccinimide*** generally do not facilitate analogous substitution reactions. For electrophilic substitutions, ***Bromine***, ***N-Bromoacetamide***, ***Bromonium Di-sym-collidine Perchlorate***, ***1,3-Dibromoisocyanuric Acid***, and ***2,4,4,6-Tetrabromo-2,5-cyclohexadienone*** also have applicability and the analogous halogenation reactions are generally possible using NCS, NIS, and I_2. Possible impurities generated during NBS brominations include conjugates of succinimide and, if basic conditions are employed, β-alanine (formed by the Hofmann reaction) and its derivatives may be isolated.

Allylic Bromination of Alkenes.[2] Standard conditions for allylic bromination involve refluxing of a solution of the alkene and recrystallized NBS in anhydrous CCl_4 using ***Dibenzoyl Peroxide***, irradiation with visible light (ordinary 100 W light bulb or sunlamp[3]), or both to effect initiation. Both NBS and the co-product succinimide are insoluble in CCl_4 and succinimide collects at the surface of the reaction mixture as the reaction proceeds.[4] High levels of regioselectivity operate during the hydrogen-abstraction step of the chain mechanism, such that allylic methylene groups are attacked much more rapidly than allylic methyl groups.[5] However, a thermodynamic mixture of allylic bromides is generally isolated since both the allylic radical and the allylic bromide are subject to isomerization under the reaction conditions.[6] High levels of functional group selectivity are characteristic of this reaction, for example alkenic esters may be converted to allylic bromides prior to intramolecular cyclization (eq 1).[7] Brominations of α,β-unsaturated esters (eq 2)[8] and lactones (eq 3) are also successful.[9]



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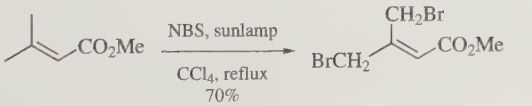

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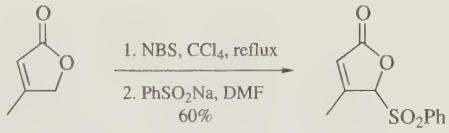
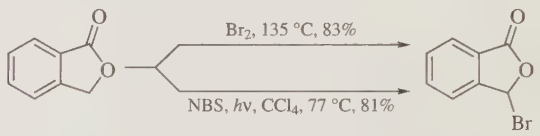


(3)

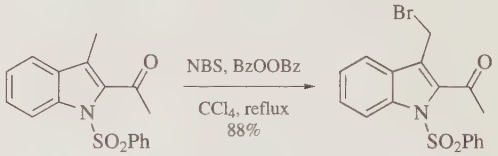
Benzylic Bromination of Aromatic Compounds. Using the conditions described above, NBS also effects the bromination of benzylic positions.[10] Bromine is also regularly used for benzylic bromination (eq 4);[11] however, many functional groups are sensitive to the generation of HBr during the reaction, including carbonyl groups which suffer competing acid-catalyzed bromination. These considerations render NBS as the reagent of choice for bromination of polyfunctional aromatic compounds. Selectivity can be anticipated with polyfunctional molecules based on the predicted stabilities of the radical intermediates (eq 5).[12] Accordingly, the use of NBS allows the bromination of alkyl groups attached to sensitive heterocyclic compounds (eq 6).[13] Complications which may arise from this method include *gem*-dibromination (eq 7)[14] of methyl substituents as well as in situ elimination of the product benzylic bromide (see also ***1,3-Dibromo-5,5-dimethylhydantoin***).



(4)

(5)

R = Me, 82%
R = TBDMS, 60%



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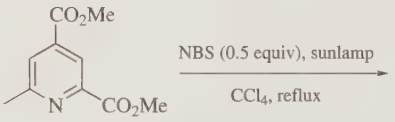
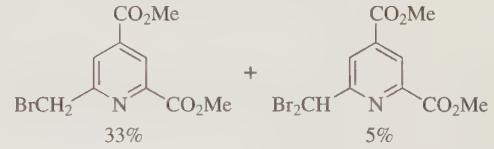
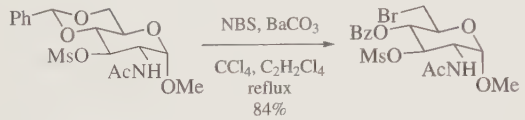




(7)

The regioselective cleavage of benzylidene acetals using NBS has been used widely in the synthesis of natural products from carbohydrates (eq 8)[15] and other chiral materials (eq 9).[16] It is rather important that the reaction be conducted in anhydrous CCl_4 (passage through activated alumina is sufficient), since in the presence of water the hydroxy benzoate is formed.[17] Barium carbonate is generally added to maintain anhydrous and acid-free conditions, and the addition of $Cl_2CHCHCl_2$ often improves solubility of the substrate. Selectivity is usually very high in cases in which a

primary bromide can be produced, but may also be obtained in systems such as shown in eq 10.[18] As alkoxy substituents serve to further stabilize the adjacent radicals, these reactions proceed with high selectivity in the presence of other functional groups. Other applications in the carbohydrate field include the cleavage of benzyl ethers and benzyl glycosides (to the corresponding glycosyl bromides) and the bromination of pyranoses in the 5-position.[19]



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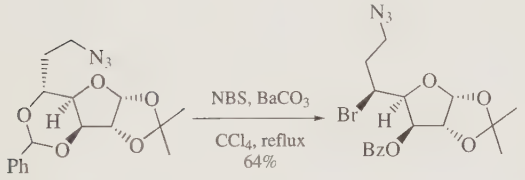
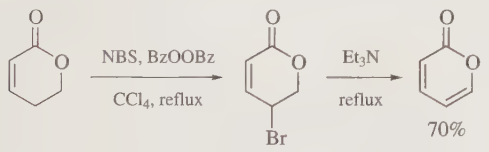


(10)

Unsaturation and Aromatization Reactions.[20] Unsaturated aldehydes, esters, and lactones can be accessed via strategies involving radical bromination and subsequent elimination. The allylic bromination of unsaturated lactones may be followed by elimination with base to obtain dienoic and trienoic lactones (eqs 11 and 12).[21] Conversion of an aldehyde to the enol acetate allows the radical bromination at the C_β position to proceed smoothly and, upon ester hydrolysis, the α,β-unsaturated aldehyde is obtained (eq 13).[22]



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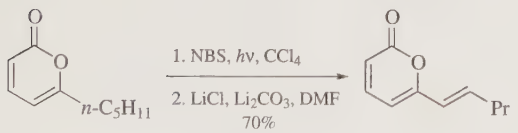

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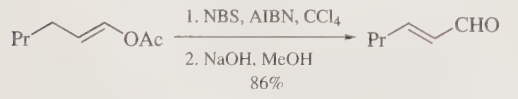
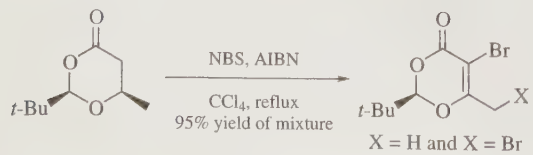


(13)

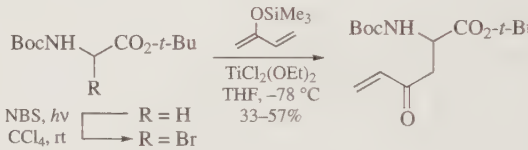
The direct bromination of β-alkoxylactones at the β position initially generates the α,β-unsaturated lactones (eq 14); however, the required radical abstraction is not so facile and further bromination of the α,β-unsaturated lactone proceeds competitively to afford the mono- and dibrominated products.[23] NBS is also used for the oxidative aromatization of polycyclic compounds, including steroids and anthraquinone precursors (eq 15).[24]



(14)

(15)

α-Bromination of Carbonyl Derivatives. Although simple carbonyl derivatives are not attacked in the α-position under radical bromination conditions, substitution by electron-donating groups stabilizes the radical intermediates by the capto-dative effect[25] and thus facilitates the substitution reaction which has been applied to a number of useful synthetic strategies. Protected glycine derivatives are easily brominated by NBS and benzoyl peroxide in $CHCl_3$ or CCl_4 at reflux to afford the corresponding α-bromoglycine derivatives.[26] These compounds are stable precursors of *N*-acyliminoacetates, which may be alkylated by silyl enol ethers in the presence of Lewis acids, organometallic reagents, and other nucleophiles to afford novel α-amino acids (eq 16).[27] Diketopiperazines and related heterocycles are also substituted in good yields (eq 17).[28] Furthermore, in contrast to aldehydes which undergo abstraction of the aldehydic hydrogen (see below), *O*-trimethylsilylaldoximes are readily brominated at the α-position under radical bromination conditions and can be converted to substituted nitrile oxides (*O*-trimethylsilylketoximes react similarly).[29]



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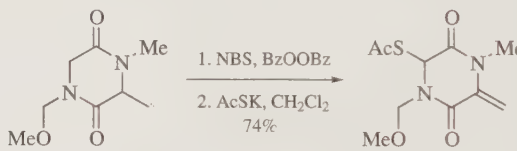
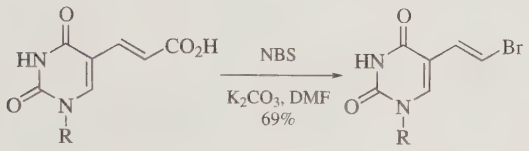


(17)

The use of NBS in the presence of catalytic ***Hydrogen Bromide*** has proven to be more convenient than Br_2 for the conversion of acid chlorides to α-bromo acid chlorides.[30] The reaction of the corresponding enolates, enol ethers, or enol acetates with NBS (and other halogenating agents) offers considerable advantages over direct acid-catalyzed halogenation of ketones and esters.[31] Although both reagents may afford the α-brominated products in high yields, NBS is more compatible than is bromine with sensitive functional groups and has been used in the asymmetric synthesis of α-amino acids.[32] The bromination of cyanoacetic acid proceeds rapidly with NBS to afford dibromoacetonitrile[33] and, similarly, β-keto esters, β-diketones, and β-sulfonyl ketones may be reacted with NBS in the presence of base to afford the products of bromination and in situ deacylation (see ***N-Chlorosuccinimide***).[34] (5*E*)-Bromovinyluridine derivatives are readily prepared by bromodecarboxylation of the corresponding α,β-unsaturated acids with NBS (eq 18).[35]

Reaction with Vinylic and Alkynic Derivatives. NBS is a suitable source of bromine for the conversion of vinylcopper and other organometallic derivatives to the corresponding vinyl bromides.[36] Vinylsilanes, prepared from the corresponding 1-trimethylsilylalkyne by reduction with ***Diisobutylaluminum***

Hydride, can be isomerized from the (*Z*) to the (*E*) geometry by irradiation with NBS and ***Pyridine***, thus making (*E*)-vinylsilanes readily available stereoselectively in three steps from the corresponding alkyne (eq 19).[37] Allylsilane can be brominated by NBS under radical conditions, whereas more reactive allylsilanes are bromodesilated by NBS in CH_2Cl_2 at −78 °C.[38] 1-Bromoalkynes can be prepared under mild conditions by reaction with NBS in acetone in the presence of catalytic ***Silver(I) Nitrate***.[39]



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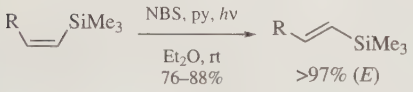
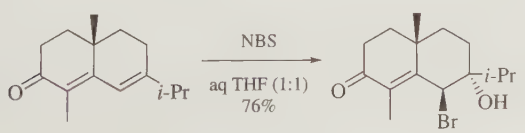


(19)

Bromination of Aromatic Compounds. Phenols, anilines, and other electron-rich aromatic compounds can be monobrominated using NBS in DMF with higher yields and higher levels of *para* selectivity than with Br_2.[40] *N*-Trimethylsilylanilines and aromatic ethers are also selectively brominated by NBS in $CHCl_3$ or CCl_4.[41] *N*-Substituted pyrroles are brominated with NBS in THF to afford 2-bromopyrroles (1 equiv) or 2,5-dibromopyrroles (2 equiv) with high selectivity, whereas bromination with Br_2 affords the thermodynamically more stable 3-bromopyrroles.[42] The use of NBS in DMF also achieves the controlled bromination of imidazole and nitroimidazole.[43] Thiophenes are also selectively brominated in the 2-position using NBS in acetic acid–chloroform.[44]

Bromohydration, Bromolactonization, and Other Additions to C=C.[45] The preferred conditions for the bromohydration of alkenes involves the portionwise addition of solid or predissolved NBS (recrystallized) to a solution of the alkene in 50–75% aqueous DME, THF, or *t*-butanol at 0 °C. The formation of dibromide and α-bromo ketone byproducts can be minimized by using recrystallized NBS. High selectivity for Markovnikov addition and *anti* stereochemistry results from attack of the bromonium ion intermediate by water. Aqueous DMSO can also be used as the solvent; however, since DMSO is readily oxidized under the reaction conditions, significant amounts of the dibromide byproduct may be produced.[46,47] In the bromohydration of polyalkenic compounds, high selectivity is regularly achieved for attack of the most electron-rich double bond (eq 20).[48] With farnesol acetate, squalene, and other polyisoprenes, choice of the optimum proportion of water is used to effect the selective bromohydration at the terminal double bond (eq 21),[49] and the two-step sequence shown is often the method of choice for the preparation of the corresponding epoxides.[50]



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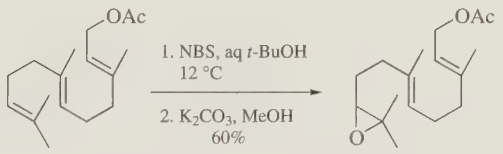
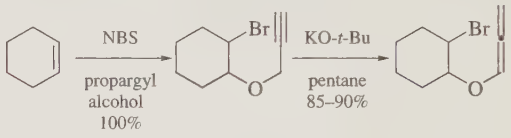


(21)

Bromoetherification of alkenes can be achieved using NBS in the desired alcohol as the solvent. The reaction of 1,3-dichloropropene with NBS in methanol yields an α-bromo dimethyl acetal in the first step in a convenient synthesis of cyclopropenone.[51] Using propargyl alcohol the reaction depicted in (eq 22) has been extended to an annulation method for the synthesis of α-methylene-γ-butyrolactones.[52] Intramolecular bromoetherification and bromoamination reactions are generally very facile (eq 23).[53] In natural products synthesis, bromoetherification has been used for the synthesis of cyclic ethers (by subsequent debromination, see ***Tri-n-butylstannane***) and for the protection of alkene appendages as cyclic bromoethers (regenerated by reaction with zinc).[54]



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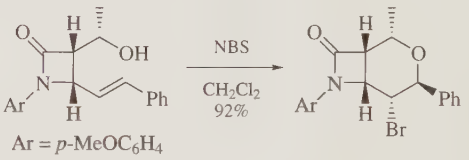
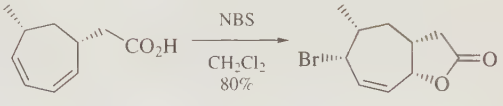


(23)

NBS is also an effective reagent for bromolactonization of unsaturated acids and acid derivatives with the same high stereo- and Markovnikov selectivity (see also ***Iodine***). Dienes, such as the cycloheptadiene derivative shown, may react exclusively via *syn*-1,4-addition (eq 24).[55] Alkynic acids are converted to the (*E*)-bromo enol lactones by NBS in a biphasic medium, whereas the combination of bromine and silver nitrate afford the (*Z*)-bromo enol lactones (eq 25).[56] α,β-Unsaturated acylprolines react with NBS in anhydrous DMF to afford the corresponding bromolactones having diastereomeric excesses up to 93%, which can be converted to chiral α-hydroxy acids by debromination followed by acidic hydrolysis (eq 26).[57] In contrast to alkenic amides, which generally react with NBS to afford bromolactones (via the cyclic iminoether derivatives), alkenic sulfonamides readily undergo cyclization on nitrogen when reacted with NBS to afford the bromosulfonamides in high yields.[58] *N*-Methoxyamides have also proven effective for bromolactamization, leading to diketopiperazines (eq 27)[59] (see also ***Bromonium Di-sym-collidine Perchlorate***).



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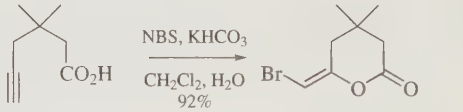

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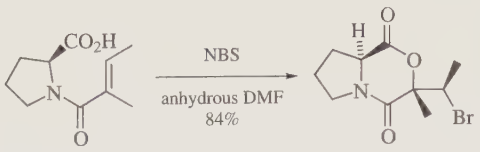

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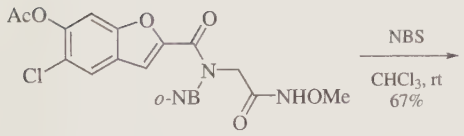
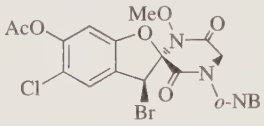
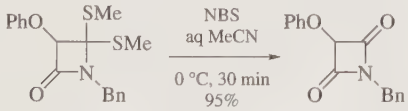




(27)

Addition of NBS to an alkene in the presence of aqueous ***Sodium Azide*** affords fair yields of the corresponding β-bromoazides, which can be converted by ***Lithium Aluminum Hydride*** reduction to aziridines.[60] Intermolecular reactions of alkenes with NBS and weaker nucleophiles can be achieved if conducted under anhydrous conditions to avoid the facile bromohydration reaction. In this manner, bromofluorination of alkenes has been extensively studied using ***Pyridinium Poly(hydrogen fluoride)***, triethylammonium dihydrogentrifluoride or tetrabutylammonium hydrogendifluoride as the fluoride ion source.[61]

Oxidation and Bromination of Other Functional Groups. Conjugate bases of other functional groups can be α-brominated with NBS. Nitronate anions of aliphatic nitro compounds react with NBS to afford the *gem*-bromonitro compounds in high yield.[62] The α-bromination of sulfoxides can be performed in the presence of pyridine and proceeds more satisfactorily using NBS in the presence of catalytic Br_2 than with either reagent alone.[63] NBS also reacts with sulfides to afford sulfoxides when methanol is used as a solvent, or to form α-bromo sulfides in anhydrous solvents.[64] NBS is a favored reagent for the deprotection of dithianes and dithioacetals to regenerate carbonyl groups (eq 28)[65] (see also ***N-Chlorosuccinimide*** and ***1,3-Diiodo-5,5-dimethylhydantoin***).



(28)

In polar media, NBS effectively oxidizes primary and secondary alcohols to carbonyl compounds via hypobromite or alkoxysuccinimide intermediates. Although this transformation is more commonly effected by the use of chromium reagents or activated ***Dimethyl Sulfoxide***, the most notable application of NBS and related reagents lies in its selectivity for the oxidation of axial vs. equatorial hydroxy groups in steroid systems (see ***N-Bromoacetamide***).[66] Often, a single secondary alcohol may be converted to the ketone in the presence of many other alcohol groups.

Under radical conditions, aldehydes are readily oxidized by NBS to acid bromides.[67] The oxidation of aldoximes to nitrile oxides using NBS and ***Triethylamine*** in DMF is superior to the use of aqueous hypochlorite.[68] Tosylhydrazones are cleaved by reaction with NBS in methanol,[69] and hydrazines and hydrazides are oxidized to azo compounds.[70]

First Update

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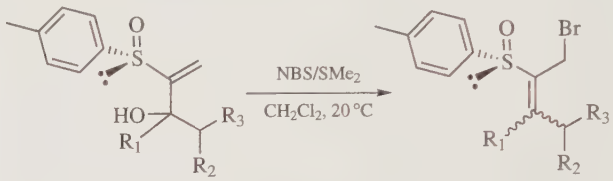
University of Leicester, Leicester, UK

Allylic Bromination of Alkenes. The alcohols (**1**) were converted into the rearranged primary allylic bromides (**2**) via S_N2' displacement by treatment with NBS/Me_2S (eq 29).[71] A well researched procedure for the allylic bromination of 1,5-cyclooctadiene has also appeared.[72] NBS and water react with allylic ethers to regenerate alcohols.[73]

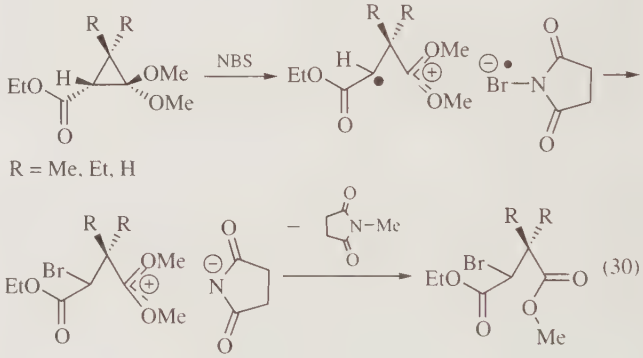


(29)

1 **2**

R_1 = H, Me, i-Pr, PH R_2 = H, Me R_3 = Me, H

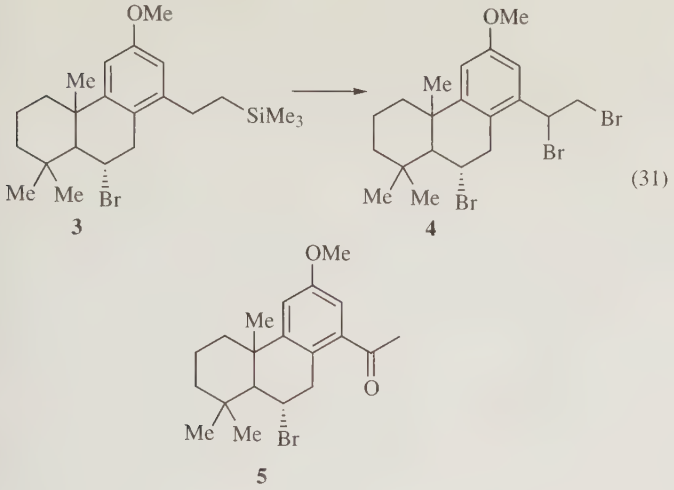
Bromination of Cyclopropanes. NBS gives bromination of donor-acceptor cyclopropanes by an electron-transfer (ET) mechanism (eq 30).[74]

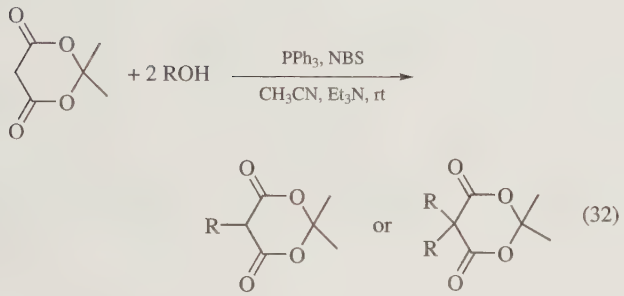


(30)

Benzylic Bromination of Aromatic Compounds. An efficient and fast microwave-assisted method for the preparation of benzylic bromides has appeared.[75] The 2-trimethylsilylethyl substituent on the benzenoid ring of **3** undergoes benzylic bromination followed by elimination of Me_3SiBr and addition of bromine to produce the dibromo compound (**4**) (eq 31). The ketone (**5**) is also observed from the hydrolysis of **4**.[76]

α-Bromination of Carbonyl Derivatives. Reaction of a complex silyl enol ether with NBS leads to an α-bromo ketone in the Ogasawara synthesis of (−)-morphine.[77] Amberlyst-15® promotes the bromination of 1,3-keto esters and cyclic ketones with NBS.[78] α-Bromination of carbonyl compounds has been achieved using NBS in the presence of silica-supported sodium hydrogen sulfate as a heterogeneous catalyst.[79] *C*-Alkylation of Meldrum's acid is possible using triphenylphosphine and NBS (eq 32).[80]

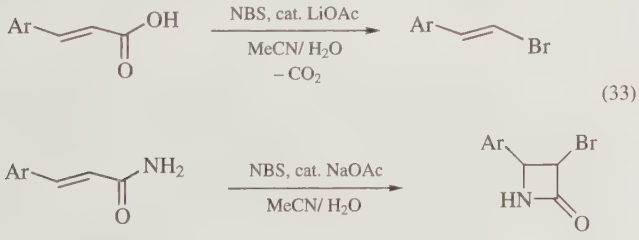




A process of selenocatalytic α-halogenation using NBS has been reported.[81] A catalytic enantioselective bromination of β-keto esters has been achieved using a combination of NBS and $TiCl_2$(TADDOLato) complexes as enantioselective catalyst;[82] modest enantiomeric excesses were obtained.

Decarboxylation. Bromodecarboxylation (Hunsdiecker reaction) of α,β-unsaturated carboxylic acids was achieved employing IBD or IBDA as catalysis.[83] Manganese(II) acetate[84] and lithium acetate[85] (eq 33) can also catalyze this kind of reaction.

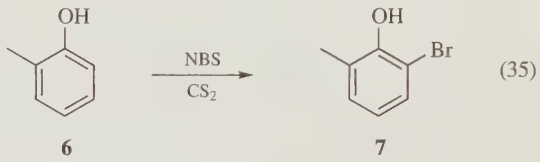
On the other hand, a slight modification of the latter reaction protocol can be employed for the synthesis of α-bromo-β-lactams when the starting material is a α,β-unsaturated aromatic amide, with catalysis by NaOAc instead of LiOAc (eq 33).[86]



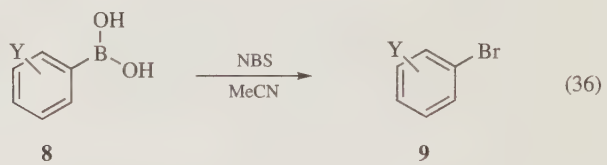
Reaction with Vinylic and Alkynic Derivatives. Vinylic boronic acids are converted with good yields to alkenyl bromides, keeping the same geometry, by treatment with NBS (eq 34).[87]

Propiolates can be brominated with or without decarboxylation.[88,89]

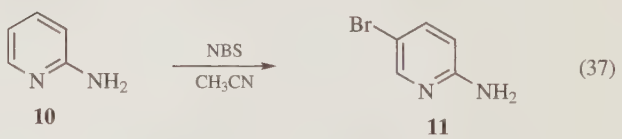
Bromination of Aromatic Compounds. Studies on the bromination of monocyclic and polycyclic aromatic compounds with NBS have continued[90,91] and in particular the bromination of phenols and naphthols has received attention,[92,93] e.g., the conversion of **6** into **7** (eq 35).



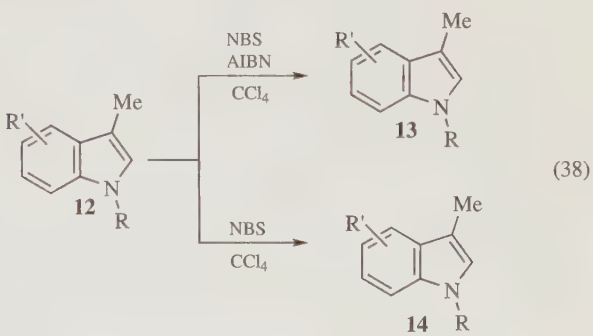
Aromatic bromination is also achieved using NBS,[94] in some cases using strong acids as catalysts.[95] Deactivated aromatic compounds are brominated by NBS in trifluoroacetic acid and sulphuric acid.[96] NBS and aqueous sodium hydroxide is used to brominate activated benzoic acid derivatives.[97] An intriguing effect of lithium perchlorate dispersed on silica gel on the bromination of aromatic compounds with NBS has been reported.[98] Finally a method for the *ipso*-substitution of phenyl boronic acids (**8**) with NBS leading to the aromatic bromides (**9**) has appeared (eq 36).[99]



Heterocyclic Bromination. Pyridines with electron-donating groups undergo regioselective bromination with NBS under mild acidic conditions as shown by the conversion of **10** into **11** (eq 37).[100]



A range of "pyridine-type" hydroxyl heterocycles are brominated effectively with NBS/PPh_3[101] while NBS is used as a synthesis of pyridines.[102] Polysubstituted pyrroles,[103] furans,[104] pyrrolidin-2-ones,[105] thiophenes,[106] and 3,4-disubstituted indoles[107] have also been prepared using NBS as a key reagent. 3-Methyl indole derivatives of general structure **12** are brominated in the methyl group to **13** with NBS under radical conditions. Under ionic conditions bromination occurs at the 2-position of the indole structure (**12**) to give products with general structure **14** (eq 38).[108]



NBS is used as a reagent for phenylselenyl activation in a route to aziridines and oxazolidin-2-ones.[109] The synthesis of 5-bromoisoquinoline and 5-bromo-8-nitroisoquinoline has been achieved using NBS.[110] 3-Bromo-*N*-methylpyrrole can be obtained from *N*-methylpyrrole by the use of NBS and a catalytic amount of PBr_3.[111] A new synthetic route to indoloquinones has appeared in which 2-methoxy-2*H*-azepine derivatives react with NBS to form 3*H*-azepines.[112] Convenient methods for the bromination of 3,5-diarylisoxazoles[113] and for the synthesis of 3-halogeno-1-methylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones[114] using NBS have appeared.

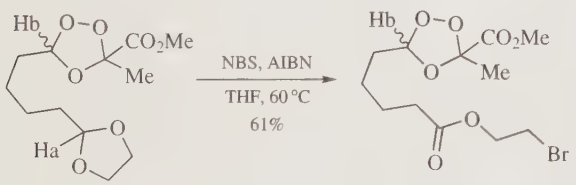
Purine derivative (**15**) undegoes regioselective bromination with NBS in DMF to give the brominated product (**16**) (eq 39).[115]

15 **16** (39)

***N*-Thiosuccinimide Formation.** The reagent **17** is prepared from NBS (eq 40) and is very useful in the synthesis of cyanoethyl-protected nucleotides due to its solubility in pyridine. It is also used in the selective reactions of *H*-phosphonate derivatives.[116]

17 (40)

Acetal Bromination and Formation. The bromination of an acetal by NBS under radical conditions does not require the presence of an aromatic group (eq 41).[117]



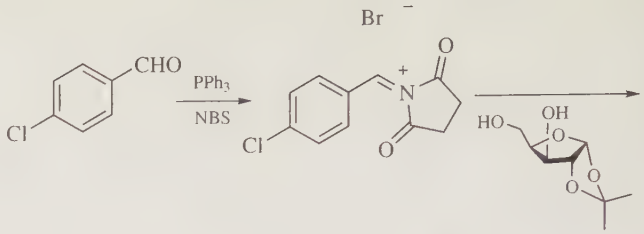
(41)

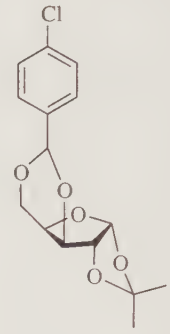
NBS can also be used to make acetals: the reaction of *para*-chlorobenzaldehyde, NBS and PPh_3 produces a reagent which forms an acetal with 1,2-*O*-isopropylidene-α-D-xylofuranose (eq 42).[118]

1,2,4-Trioxones are produced by reaction of aldehydes with allylic peroxide (**18**) (eq 43); yields are in the range 25–35%, when R = Me, Et and Pr.[119]

In the carbohydrate area, two important uses of the reagent have appeared: one uses NBS-Me_3SiOTf as the promoter for the glycosidic bond formation and simultaneous bromination of an activated aryl aglycon.[120] In the second, the synthesis of branched polysaccharides by polymerization of 6-*O*-*t*-butyldimethylsilyl-D-glucal through stereoregular bromoglycosylation was achieved by the use of NBS.[121]

NBS is a chemoselective catalyst for the acetalization of carbonyl compounds using triethyl orthoformate under almost neutral conditions (eq 44).[122,123]





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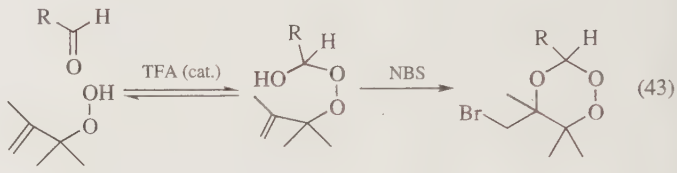

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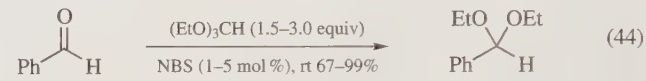


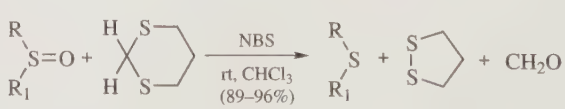
(44)

NBS is an effective catalyst for the acetalation of alcohols under mild conditions:[124] aldehydes are converted to 1,1-diacetates by reaction of acetic anhydride with NBS as a catalyst.[125]

Reactions of Thioacetals. The ring expansion of aromatic thioacetals can be achieved using NBS: initial bromination α to the thioacetal is followed by ring expansion and proton transfer (eq 45).[126]

(45)

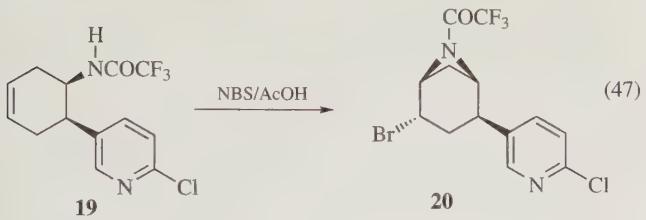
The use of NBS as an alternative for $HgCl_2$ in the deprotection of 2-silyl-1,3-dithianes into the corresponding acylsilanes has been investigated;[127] trithioorthoesters are converted to α-oxo thiolcarboxylates.[128] Sulfoxides are reduced to sulfides by the reaction of a thioacetal and NBS (eq 46),[129] and 1,3-oxathioacetals and dithioacetals are converted into acetals using NBS.[130]



(46)

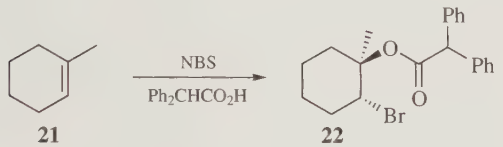
1,3-Oxathiolanes may be synthesised from aldehydes and mercaptoethanol using NBS as a catalyst;[131] the reverse reaction is also possible in aqueous acetone.[132] Glycosidation can be achieved using thioglycosides activated by NBS and a catalytic amount of strong acid salts.[133]

Bromination of Olefins. In the Corey synthesis of epibatidine[134] the cyclohexene (**19**) reacts with NBS to give bromination with neighboring group participation, producing **20** (eq 47). This reaction has been studied in detail by Vasella.[135]



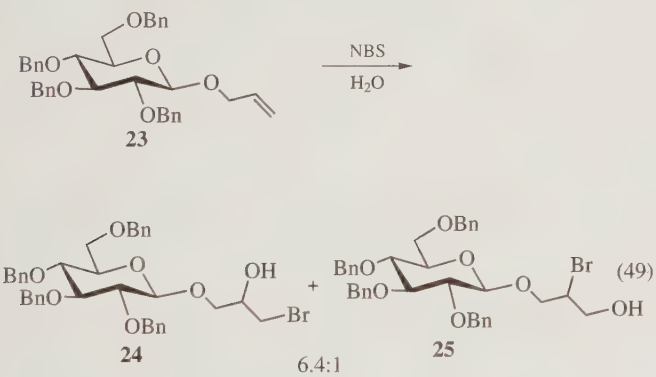
19 20 (47)

NBS and diphenylacetic acid add regiospecifically to olefins, e.g., the conversion of **21** to **22** (eq 48).[136]



21 22 (48)

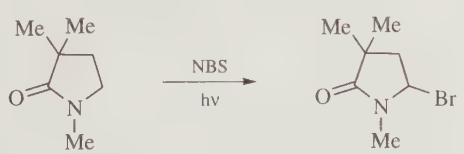
ω-Alkenyl glycoside (**23**) reacts with aq NBS to give bromo alcohols (**24** and **25**) (eq 49).[137] The observed selectivity is explained by the formation of a cyclic bromonium ion intermediate.



23 24 25 6.4:1 (49)

Transition metal-catalyzed regio- and stereoselective aminobromination of olefins with $TsNH_2$ and NBS as nitrogen and bromine sources.[138] Studies have appeared on the use of NBS in additions to alkenes[139] and in the isomerization of alkenes.[140]

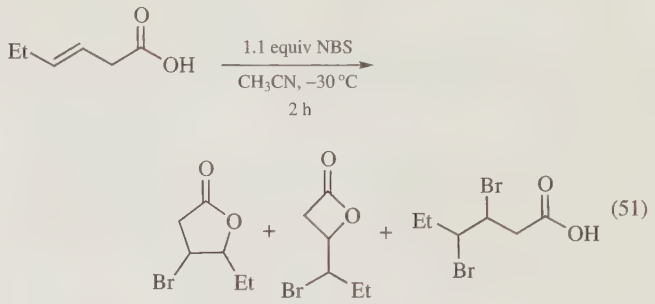
Bromination of Amides and Amines. Although yields are low, radical bromination α to nitrogen is possible (eq 50) and indicates a novel use of NBS.[105]



(50)

Secondary or tertiary amides are prepared in good yield from amines and alcohols using an in situ generated *N*-bromophosphonium salt from the reaction of NBS and PPh_3.[141] Benzylamines are debenzylated by NBS and AIBN[142] and the conversion of amides into carbamates was achieved in a Hofmann rearrangement using NBS/NaOMe,[143] or NBS/DBU/MeOH.[144]

Bromohydration, Bromolactonization and Other Additions to C=C. The first catalytic method for the halolactonization of olefins has appeared.[145] The selenium-catalyzed method using NBS leads to a mixture of regioisomers depending on the reaction conditions (eq 51).



(51)

No catalyst	2	1	0
5 mol% PhSeSePh	17	1	1

Oxidations.

Oxidation and Bromination of Other Functional Groups. Selective oxidation of alcohols may be achieved using a 1:1 complex of NBS and tetrabutylammonium iodide,[146] whereas 1,2-diols are converted into 1,2-diketones using *N*-bromosuccinimide.[147] An efficient and mild procedure has been reported for the preparation of benzoic acids via oxidation of aromatic carbonyl compounds by employing NBS and mercuric acetate.[148] Selective and efficient oxidation of sulfides to sulfoxides has been achieved with NBS in the presence of β-cyclodextrin in water.[149] Epoxides and aziridines are conveniently oxidized to the corresponding α-hydroxy or α-amino ketones using cerium(IV) ammonium nitrate and NBS.[150]

New Reaction Techniques Involving NBS. Several new reaction techniques have been applied to NBS reactions to develop potentially useful new synthetic methods, a selection of these are outlined below.

Solid State and Related Reactions. The area of solid/solid organic reactions has been explored.[151–153] Results on the solid state nuclear bromination of aromatic compounds with NBS as well as some theoretical insights into the mechanism of the reaction have been reported. NBS on a solid support has been used to sythesize benzylic bromides under neutral conditions[154] and for the functionalization of α-oxoaldehyde-supported silicas.[155]

Microwave Reactions. Side chain bromination of mono and dimethyl heteroaromatic and aromatic compounds by a solid phase *N*-bromosuccinimide reaction without radical initiator under microwave conditions was developed.[156] The stereoselective synthesis of (*E*)-β-arylvinyl bromides by microwave-induced Hunsdiecker-type reaction has also appeared.[157]

Reactions in Ionic Liquids. NBS in an ionic liquid has been used to oxidize benzylic alcohols to carbonyl compounds[158] to convert olefins to *vic*-bromohydrins[159] and for the regioselective monobromination of aromatic substrates.[160]

NBS as a Ligand in Organometallic Chemistry. Bromo-bis (triphenylphosphine)(*N*-succinimide)palladium(II) has been reported as a novel catalyst for Stille cross-coupling reactions.[161]

NBS in Water with Cyclodextrin. NBS in water with cyclodextrin has been used as a deprotecting agent for silyl ethers[162] and THP ethers[163] in the conversion of oxiranes to α-hydroxylmethyl aryl ketones,[164] in the conversion of aryl aziradines to α-tosyl amino ketones[165] and in the conversion of oximes into a carbonyl compounds.[166]

Related Reagents. *N*-Bromosuccinimide–dimethylformamide; *N*-bromosuccinimide–dimethyl sulfide; *N*-bromosuccinimide–hydrogen fluoride; *N*-bromosuccinimide–sodium azide; triphenylphosphine–*N*-bromosuccinimide.

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Carbon Tetrabromide

[558-13-4] CBr_4 (MW 331.65)

(brominating agent used in synthesis of α-acetoxycarboxylic acids[4] and allenes;[5–8] radical additions to alkenes[12–28])

Alternate Name: tetrabromomethane.
Physical Data: shining plates, mp 88–90 °C; bp 190 °C (dec).
Solubility: insol in water, sol in organic solvents.
Form Supplied in: white solid; widely available.
Analysis of Reagent Purity: FT–IR data.[1]
Preparative Method: carbon tetrabromide is most conveniently prepared by the exhaustive bromination of acetone in the presence of alkali.[2]
Purification: can be sublimed in vacuo; bromide removal via reflux with dil aq Na_2CO_3, followed by steam-distillation and EtOH recrystallization.[29]
Handling, Storage, and Precautions: safety data are available.[3]

Original Commentary

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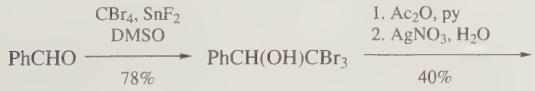
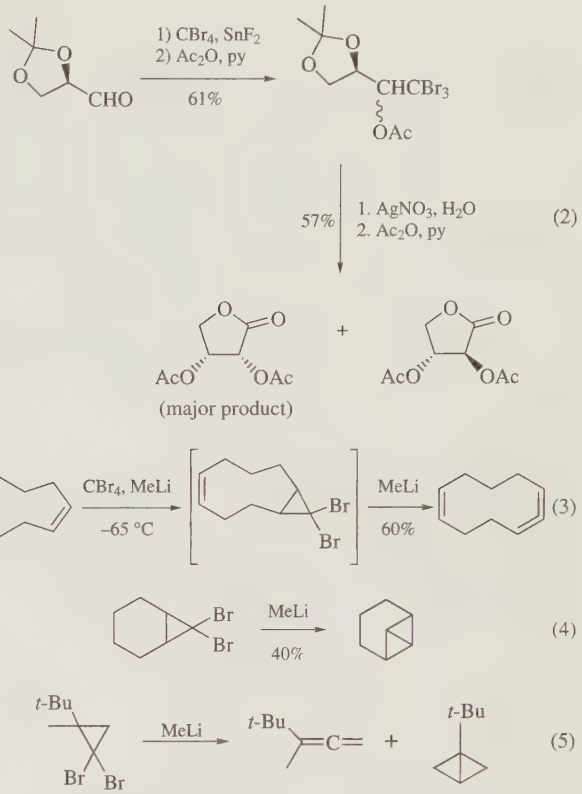
Carbon Tetrabromide–Tin(II) Fluoride. The reaction of aldehydes with CBr_4 and SnF_2 in DMSO at 25 °C gives 1-substituted 2,2,2-tribromoethanols in moderate to good yields. The acetate of the product can be hydrolyzed to an α-acetoxycarboxylic acid by $AgNO_3$ (eq 1).[4]



(1)

2,3-Diacetyl-D-erythronolactone[4] has been prepared in a similar fashion (eq 2).



(2)

Allene Synthesis. The system of carbon tetrabromide (1 equiv) with methyllithium (2 equiv) converts C_n alkenes into C_{n+1} allenes.[5–8] The synthesis of 1,2,6-cyclodecatriene from *cis,cis*-1,5-cyclononadiene[7] serves as an example (eq 3).

(3)

When 1 equiv of MeLi is used, the intermediate dibromocyclopropane can be isolated (eqs 4 and 5). Bicyclobutanes are the sole products when the resulting allene would be highly strained (eq 4),[9] or they are significant byproducts (eq 5) when the allene possesses two bulky geminal groups.[10]

(4)

(5)

Dehalogenation of dibromocyclopropanes with an alkyllithium in the presence of (−)-sparteine gives optically active allenes of low optical purity.[11]

Radical Reactions. The addition of CBr_4, or other halogenocarbons, to alkenes is known as the Kharasch reaction. The reactions of terminal alkenes furnish the addition products in the highest yields (eq 6).

(6)

The reaction can be initiated by photoirradiation,[12] radical initiators,[13] inorganic salts,[14,15] ruthenium complexes,[16–19] other transition metal complexes,[20–24] samarium diiodide,[25] or by a manganic salt generated electrochemically in situ.[26] The scope and limitations of this reaction have been reviewed in two monographs.[27,28]

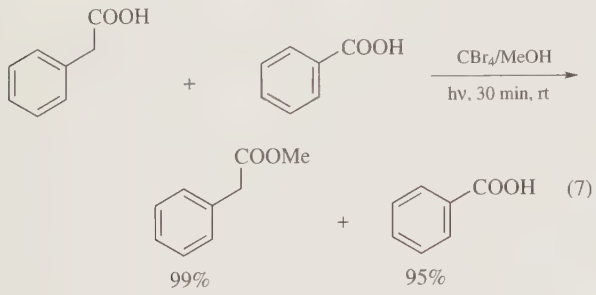
For related chemistry using CBr_4, see the entries ***Triphenylphosphine–Carbon Tetrabromide***, ***Triphenylphosphine–Carbon Tetrabromide–Lithium Azide***, ***Tribromomethyllithium*** and ***1,2-Bis(diphenylphosphino)ethane***.

First Update

Andrey A. Fokin
Kiev Polytechnic Institute, Kiev, Ukraine
Peter R. Schreiner
Justus-Liebig University, Giessen, Germany

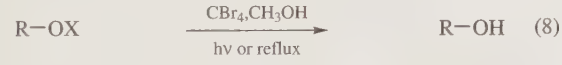
Carbon Tetrabromide–CH_3OH. The selective transformation of carboxylic acids to corresponding methyl or ethyl esters can be accomplished in the presence of 0.05 equiv of carbon

tetrabromide in the respective alcohol. The rates of the esterifications are very sensitive to electronic effects: Chemoselectivity can, for instance, be achieved between phenylacetic and benzoic acid (eq 7).[30]



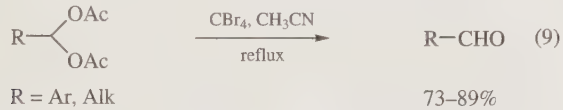
(7)

Carbon tetrabromide in methanol is also useful for the simple and efficient deprotection of methoxymethyl-, methoxyethoxymethyl-,[31] *p*-methoxybenzyl ethers,[32] and some other protecting groups, which are especially valuable for carbohydrate chemistry (eq 8).[33,34]



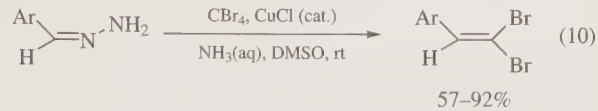
(8)

Carbon Tetrabromide–CH_3CN. The deprotection of diacetates with carbon tetrabromide in acetonitrile gives aldehydes (eq 9) in good to high yields under neutral conditions.[35]

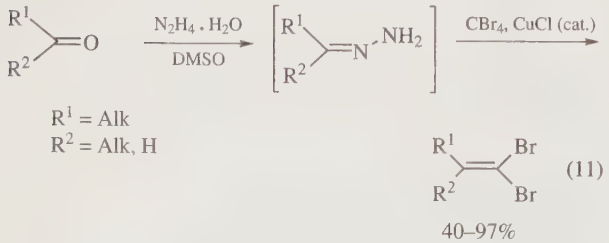


(9)

Carbon Tetrabromide–Copper(I) Chloride. The reaction of *N*-arylhydrazones with carbon tetrabromide in the presence of aqueous ammonia under copper catalysis in DMSO gives the corresponding *gem*-dibromoalkenes in good yields (eq 10).[36] The direct transformation of aldehydes and ketones to *gem*-dibromoalkenes is also elaborated (eq 11).[37]

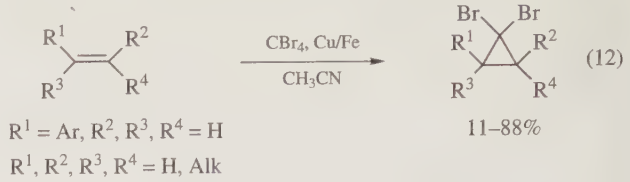


(10)



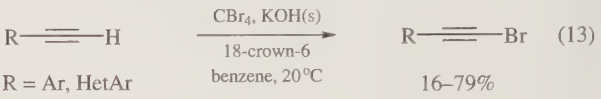
(11)

Carbon Tetrabromide–Iron/Copper. The activation of carbon tetrabromide by a bimetallic iron/copper couple in acetonitrile is an inexpensive, nontoxic, and efficient procedure for *gem*-dibromomethylenation of nucleophilic alkenes in moderate to good yields (eq 12).[38]



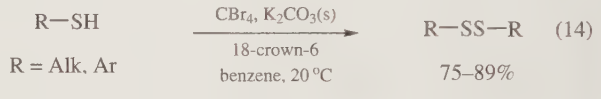
(12)

Carbon Tetrabromide–KOH. Terminal acetylenes bearing aromatic substituents can be brominated in moderate to good yields under the phase-transfer conditions using CBr_4 with solid KOH in the presence of a phase-transfer catalyst (18-crown-6) in benzene at room temperature (eq 13).[39,40]



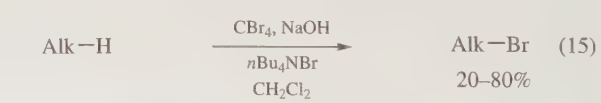
(13)

Carbon Tetrabromide–K_2CO_3. The synthesis of disulfides from thiols or their sodium salts in the phase-transfer catalytic system CBr_4/18-crown-6/benzene or toluene gives the target products in 75–89% yields (eq 14).[41]



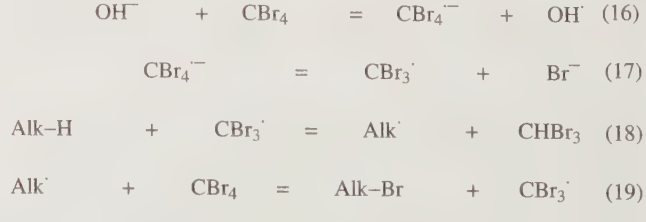
(14)

Carbon Tetrabromide–NaOH. The bromination of unactivated aliphatic hydrocarbons, which may be linear, branched, (poly)cyclic, strained as well as unstrained, can be achieved under phase-transfer conditions with CBr_4 in the presence of NaOH (either solid or 50%-aqueous). The phase-transfer system avoids overfunctionalizations and simplifies the workup; the selectivities of the C–H brominations are excellent and the reaction progresses in moderate to good yields (eq 15).[42–44]



(15)

The proposed mechanism involves the reduction of CBr_4 in the initiation step (eq 16). The CBr_4^{-} radical anion thus formed gives the tribromomethyl radical (eq 17), which carries the radical chain C–H substitution process (eqs 18,19).[42,44]



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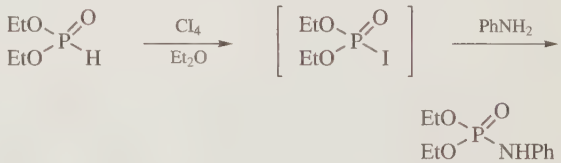
Carbon Tetraiodide

[507-25-5] CI_4 (MW 519.63)

(reagent used for C–H iodinations, preparation of *gem*-diiodoalkenes from carbonyl compounds, as well as for C–OH/C–I exchange reactions)

Alternate Name: tetraiodomethane.
Physical Data: red crystals, mp 171 °C (dec).
Solubility: soluble in organic solvents.
Form Supplied in: fine crystals.
Analysis of Reagent Purity: mass,[2] as well as ^{13}C NMR spectra.[3,4]
Preparative Method: from CCl_4 and EtI in presence of $AlCl_3$,[5] also may be generated in situ from iodoform and NaOH.[6]
Purification: recrystallization from benzene.[1]
Handling, Storage, and Precautions: light-sensitive corrosive solid. Store at 2–8 °C, keep tightly closed. Incompatible with oxidizing reagents. Causes skin irritation, may be harmful if inhaled. Toxicity (intravenous, mouse) LD_{50}: 178 mg kg^{-1}.

Carbon Tetraiodide. Carbon tetraiodide is used as the reagent in the synthesis of phosphoramidates via the Todd–Atherton reaction (eq 1).[7]



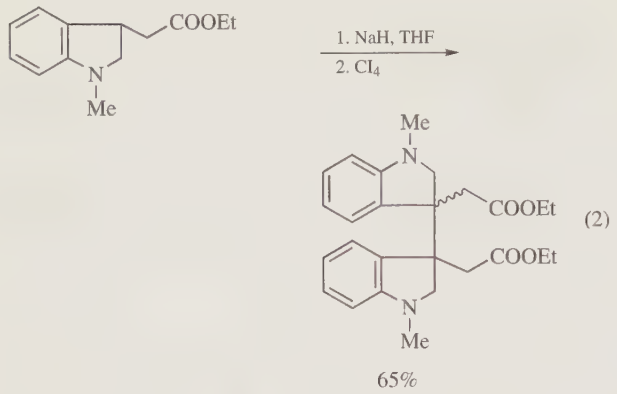
(1)

74%

The dimerizations of oxinolides occur efficiently in the presence of strong base and carbon tetraiodide in good yields (eq 2).[8]

The reaction involves a radical anion chain process, where carbon tetraiodide plays an active part in the dimerization.[8] The proposed mechanism involves the reduction of CI_4 with the carbanion (eq 3), single-electron transfer to $R–CI_3$ (eq 4), radical and anion coupling (eq 5), and the oxidation of the dimerization product by back electron transfer to $R–CI_3$ (eq 6).

Carbon Tetraiodide–KOH. Phenylacetylene is iodinated in high yield under phase-transfer conditions using carbon tetraiodide with solid KOH in presence of catalyst (18-crown-6) in benzene at room temperature (eq 7).[9]



(2)

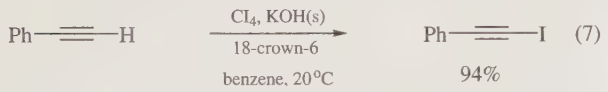
65%

$$R^- + CI_4 \rightleftharpoons R\text{–}CI_3 + I^- \quad (3)$$

$$R\text{–}CI_3 + R^- \rightleftharpoons R\text{–}CI_3^{\bullet -} + R^\bullet \quad (4)$$

$$R^\bullet + R^- \rightleftharpoons R\text{–}R^{\bullet -} \quad (5)$$

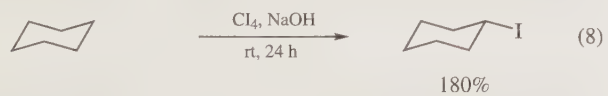
$$R\text{–}R^{\bullet -} + R\text{–}CI_3 \rightleftharpoons R\text{–}R + R\text{–}CI_3^{\bullet -} \quad (6)$$



(7)

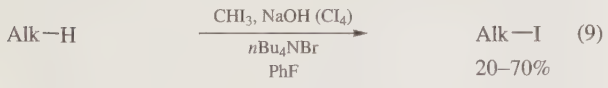
94%

Carbon Tetraiodide–NaOH. The system of carbon tetraiodide–sodium hydroxide converts cyclohexane into iodocyclohexane with 180% yield based on CI_4 (eq 8).[6] This reagent, generated in situ from iodoform and NaOH,[6] is used for the direct iodination of a number of alkanes, including *n*-pentane, *n*-hexane, cycloalkanes, as well as adamantane and its derivatives (eq 9).[10] Iodination of unactivated aliphatic hydrocarbons with HCI_3 and solid NaOH can be accelerated with ultrasonication.[11]



(8)

180%



(9)

20–70%

The proposed mechanism involves the reduction of CI_4 with hydroxide with formation of a radical anion (eq 10), which then gives the triiodomethyl radical (eq 11). The latter abstracts a hydrogen from the alkane (eq 12), forming an alkyl radical that carries the radical chain (eq 13).[10,12] Hence, this process is akin to the radical coupling mechanism proposed for the preparation of oxinolide dimers (vide supra).

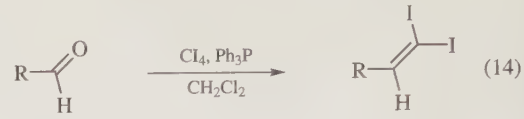
$$OH^- + CI_4 \rightleftharpoons CI_4^{\bullet -} + OH^\bullet \quad (10)$$

$$CI_4^{\bullet -} \rightleftharpoons CI_3^\bullet + I^- \quad (11)$$

$$Alk\text{–}H + CI_3^\bullet \rightleftharpoons Alk^\bullet + HCI_3 \quad (12)$$

$$Alk^\bullet + CI_4 \rightleftharpoons Alk\text{–}I + CI_3^\bullet \quad (13)$$

Carbon Tetraiodide–Triphenylphosphine. Various diiodoalkenes can be prepared from the corresponding aldehydes and carbon tetraiodide with triphenylphosphine (eq 14). Reactions occur usually in CH_2Cl_2 under mild conditions;[13,14] using Zn-powder in the work-up procedure usually improves the yields.[15,16]

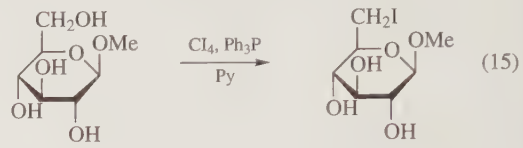


(14)

R = Alk, Ar

60–98%

This reagent is also useful for selectively replacing hydroxymethyl groups for iodine in sugars and nucleosides (eq 15).[17]



(15)

97%

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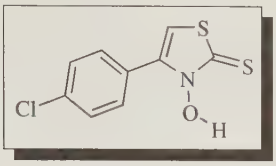
4-(4-Chlorophenyl)-3-hydroxy-2(3*H*) thiazolethione



[105922-93-8] $C_9H_6NOClS_2$ (MW 243.72)

(starting material for the synthesis of *N*-alkoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thiones[1,2]—compounds that liberate alkoxyl radicals under neutral (i.e., non-oxidative) conditions, if subjected to microwave irradiation, heated in the presence of an initiator, or photolyzed with either intense visible or UV/A light.[1,3,4] *N*-Alkoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thiones exhibit significantly improved characteristics as sources of oxygen-centered radicals for synthetic purposes[4–6] or for the investigation of mechanistic aspects of *O*-radical chemistry,[7] if compared to equivalent reagents such as *N*-alkoxypyridine-2(1*H*)-thiones,[8,9] *N*-alkoxyphthalimides,[10] or *N*-alkoxydithiocarbamates;[11] reagent for the generation of the hydroxyl radical, e.g., for photobiological applications;[12] starting material for the synthesis of *N*-acyloxy-4-(*p*-chlorophenyl)thiazole-2(3*H*)-thiones[1,13] which serve as carbon radical precursors)

Alternate Name: *N*-hydroxy-4-(*p*-chlorophenyl)thiazole-2(3*H*)-thione, CPTTOH.

Physical Data: decomposes at 138 ± 2 °C in an exothermic reaction without melting; UV/Vis (EtOH): λ_{max} (log ϵ) = 309 (4.16), 240 nm (4.20); ^1H, ^{13}C NMR data; FT-IR, single crystal X-ray crystallography; and electronic spectrum have been investigated.[1,14]

Solubility: soluble in many organic solvents (dimethylsulfoxide, dimethylformamide, ethyl acetate, chloroform, dichloromethane, benzene); slightly soluble in THF, methyl *tert*-butyl ether, diethyl ether, and EtOH; almost insoluble in water.

Preparative Methods: CPTTOH and a number of closely related derivatives thereof, such as 4-(*p*-methoxyphenyl)-, 4-(*p*-methylphenyl)-, 4-phenyl-, and 4-(*p*-nitrophenyl)-substituted *N*-hydroxythiazole-2(3*H*) thione, *N*-hydroxy-4-methylthiazole-2(3*H*) thione (commercially available), and *N*-hydroxy-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*) thione are prepared from the corresponding α-haloketones in three synthetic steps.[15–17] The yields for the most important reagents of this type are in the range 59–68% (eq 1). Polymer-supported derivatives of CPTTOH have been immobilized on a Wang resin.[18]

(1)

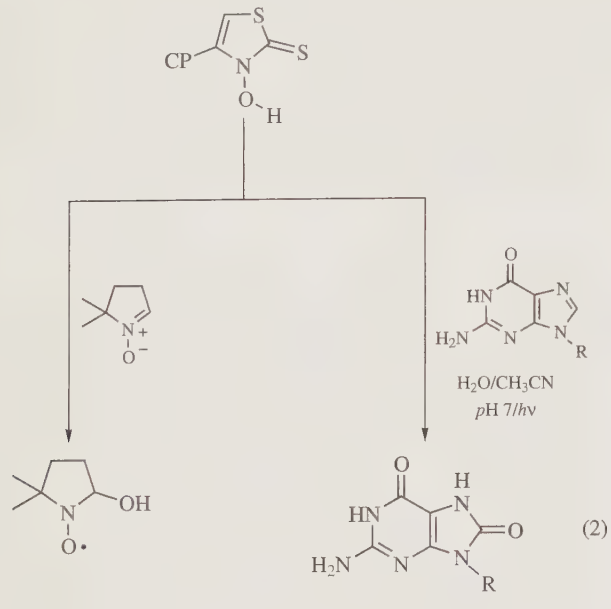
R^1	R^2	X	Yield (%)
p-ClC_6H_4 (CP)	H	Br	67
CH_3	H	Cl	59
CH_3	*p*-$H_3COC_6H_4$ (An)	Cl	68

Handling, Storage, and Precautions: colorless crystalline material (bulk); faces of single crystals shimmer, depending on their orientation towards light, from green to brown. Purification of CPTTOH is achieved by recrystallization of the crude product from hot 2-propanol. The title compound has a musty odor. Inhalation of CPTTOH dust and contact with eyes should be avoided; wearing of protective gloves while handling CPTTOH in a well-ventilated hood and storage in amber-colored vials at temperatures below 20 °C is recommended.

***N*-Hydroxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thione.** The reagent is a weak acid which forms monovalent anions if treated with alcoholic solutions of alkaline hydroxides or tetraalkylammonium hydroxides. The derived NEt_4-salts (hygroscopic) are commonly used for the preparation of *N*-alkoxy-4-(*p*-chlorophenyl) thiazole-2(3*H*) thiones.[1,4] Syntheses and X-ray crystallography of bis[*N*-oxy-4-methylthiazole-2-thiolato(–1)]copper(II) and zinc(II) from *N*-hydroxy-4-methylthiazole-2(3*H*) thione have been reported.[19] CPTTOH is an efficient source of the hydroxyl radical under neutral conditions when photolyzed in aq CH_3CN.[12] The hydroxyl radical has been trapped under these conditions with DMPO and identified via the characteristic EPR spectrum of its derived nitroxyl radical adduct (eq 2). Photolysis of CPTTOH in the presence of 2′-deoxyguanosine affords 8-oxo-2′-deoxyguanosine in up to 6% yield (eq 2). Further, the reagent induces strand breaks in supercoiled pBR322 DNA via intermediate photogenerated hydroxyl radicals.[12] In a more recent application, the transformation of CPTTOH and cyclodecyne has been reported to furnish products of transannular cyclization, presumably via addition of a photochemically generated HO • radical to the triple bond in one of the initial steps.[20]

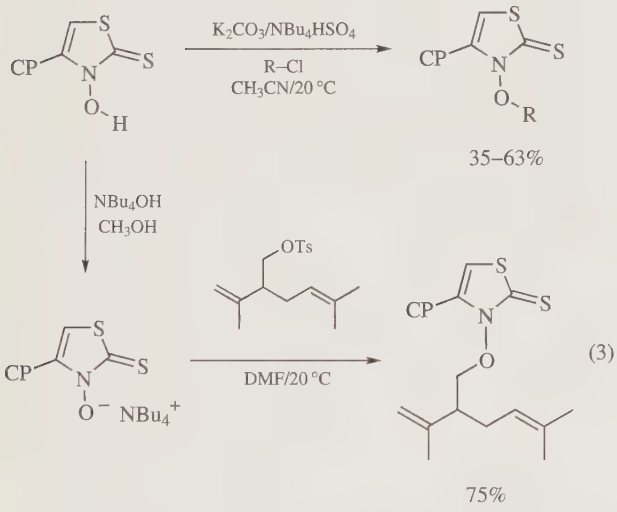
***N*-Alkoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thiones (CPTTOR).** Selective *O*-alkylation of CPTTOH is achieved by treatment of derived NBu_4- or NEt_4-salts[2,4] with hard alkylating reagents such as primary or secondary alkyl chlorides, bromides, tosylates, and brosylates as well as allylic or benzylic chlorides (eq 3). 2-Alkylsulfanyl-4-(*p*-chlorophenyl)thiazole-*N*-oxides, i.e., compounds of *S*-selective alkylation of the ambident thiohydroxamate anion, are formed in minor amounts (<5–10%). The only exception is seen when CPTTOH is treated with an excess of CH_3I thus leading to 2-methylsulfanyl-4-(*p*-chlorophenyl)thiazole-*N*-oxide as major product.[21,22] The synthesis of chiral *N*-alkoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thiones from secondary alkyl tosylates and *N*-hydroxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thione tetraalkylammonium salts proceeds under S_N2-conditions. The enantiomeric purity of chiral *N*-alkoxythiazole-2(3*H*) thiones is preferentially verified by CD-spectroscopy. A direct application of CPTTOH in the synthesis of *N*-alkoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thiones, which circumvents a separate synthesis of hygroscopic NBu_4- and NEt_4-salts, has been developed. The latter procedure applies K_2CO_3 as base, NBu_4HSO_4 as phase transfer catalyst, CH_3CN as solvent, and preferentially alkyl chlorides or tosylates as alkylating reagents (eq 3).[2] The synthesis of *N*-(1-pentyloxy)-4-(*p*-chlorophenyl)thiazole-2(3*H*) thione (47%) has been achieved starting from 1-pentanol, CPTTOH, DIAD, PPh_3 in CH_2Cl_2.[23] The latter procedure has, however, been more effectively adapted for the synthesis of *N*-alkoxy-4-

methylthiazole-2(3*H*) thiones using DEAD as azo compound and C_6H_6 as solvent.[24]



(2)

R = 2′-deoxy-1′-ribosyl



(3)

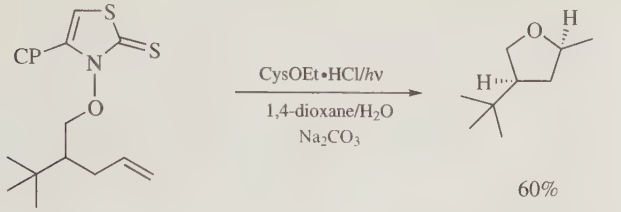
75%

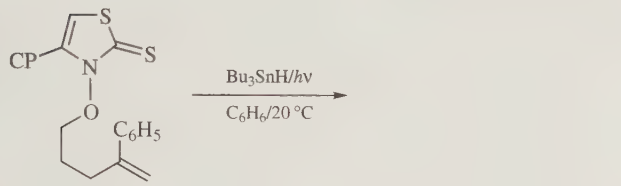
N-Alkoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thiones are colorless to tan crystalline compounds which may generally be stored for years in a refrigerator. Selected *N*-alkenoxy-4-(*p*-chlorophenyl) thiazole-2(3*H*) thiones have been heated in C_6H_6 ($T = 80\,^{\circ}C$) for 2 h in the presence of α-tocopherol without significant decomposition. Rare examples of thermal transformations of CPTTOR, which proceed at ~5 °C in the dark, refer to fragmentations or isomerizations of selected neat samples. Thus, *N*-(5-methyl-1-phenyl-4-hexenoxy)-4-(*p*-chlorophenyl)thiazole-2(3*H*) thione fragments upon longer storage into 5-methyl-1-phenyl-4-hexen-1-one and 4-(*p*-chlorophenyl)thiazole-2(3*H*) thione. *N*-Methoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thione rearranges into 2-methylsulfanyl-4-(*p*-chlorophenyl)thiazole, and *N*-(3-*tert*-butyl-4-penten-1-oxy)-4-(*p*-chlorophenyl)thiazole-2(3*H*) thione isomerizes into 2-[*cis*-(4-*tert*-butyltetrahydrofuryl-2-methylsulfanyl)]-4-(*p*-chlorophenyl)thiazole.[21] A rare instance of thiazolethione ring cleavage, which afforded among other products a derived isothiocyanate, has been observed in photochemical experiments starting from *N*-isopropoxy-4-(*p*-methylphenyl)thiazole-2(3*H*) thione.[25] Photochemical excitation (250 W, visible light discharge lamp or Rayonet®-chamber reactor equipped with 350 nm light bulbs), treatment with BEt_3/O_2, or heating of solutions of CPTTOR in the presence of an initiator (e.g., AIBN) affords alkoxyl radicals RO• that have been applied in efficient chain reactions for selective C–O bond formations (synthesis of cyclic ethers), β-C-C cleavages (formation of aldehydes), and remote functionalizations. Efficient transformations of all three types require the use of appropriate mediators that furnish after carbon radical trapping suitable chain carrying radicals. In this sense, •CCl_3 (from, e.g., $BrCCl_3$), *n*-•C_4F_9 (from *n*-C_4F_9I), •$SnBu_3$ (from $HSnBu_3$), and •$Si(SiMe_3)_3$ [from $HSi(SiMe_3)_3$] are favorable intermediates because they readily add to the C=S π-bond in *N*-alkoxythiazole-2(3*H*) thiones thus inducing selective N-O-homolysis and therefore alkoxyl radical generation. Primary and secondary alkyl radicals are generally not suited for this purpose.[7]

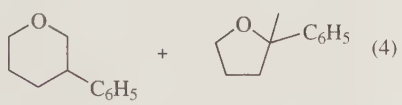
Carbon-Oxygen Bond Formation. Photolysis of δ-unsaturated *N*-alkenoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thiones in the presence of trapping reagents leads to the formation of substituted tetrahydrofurans and/or tetrahydropyrans. The key step of this reaction is associated with an intramolecular C–O bond formation of intermediate substituted 4-penten-1-oxyl radicals. Cyclized radicals are preferentially trapped with L-cysteine derivatives (in aqueous solvents) or Bu_3SnH, $(Me_3Si)_3SiH$ (in organic solvents) (eq 4). 1- or 3-Substituted 4-penten-1-oxyl radicals afford 2,5-*trans*- or 2,3-*trans*-disubstituted tetrahydrofurans as major products. The observed diastereoselectivity increases with the steric size in the series Me < Et < *i*-Pr < *t*-Bu < 2,4,6-mesityl for 1-substituted radicals. Cyclizations of 2-substituted 4-penten-1-oxyl radicals provide 2,4-*cis*-disubstituted tetrahydrofurans. The *cis*-selectivity improves in going from Me via Ph to *t*-Bu.[26] A minor fraction of 6-*endo* cyclized products (i.e., substituted tetrahydropyrans) is formed in most cases. The ratio of 5-*exo*:6-*endo* cyclized products is determined by the substituent at position 4 of the 4-penten-1-oxyl radical and increases in the sequence 4-Me < 4-*t*-Bu < 4-Ph from 82:18 to 7:93 at 30 °C.

For synthetic purposes, cyclized radicals are preferentially trapped with halogen atom donors such as CCl_4, $BrCCl_3$, *n*-C_4F_9I, $I(Me)C(CO_2Et)_2$.[4,9] The latter reaction, which constitutes a radical version of the halocyclization, is a synthetically useful transformation. It is the only known method so far for selectively converting 5,5-dimethyl-substituted bis-homoallylic alcohols, a widespread structural motif among naturally occurring terpenols, into 5-*exo*-halocyclized products without notable interference of tetrahydropyran formation (eq 5).[4,5] In other instances, complementary diastereoselectivities of alkoxyl radical based bromocyclizations have been observed, if compared to the polar equivalent starting from bis-homoallylic alcohols and, e.g., NBS. For example, photolysis of (2*R*,3*S*)-*N*-(3-benzoyloxy-5-hexen-2-oxy)-4-methylthiazole-2(3*H*) thione in the presence of $BrCCl_3$ furnishes (2*R*,3*S*,5*S*)-3-benzoyloxy-5-bromomethyl-2-methyltetrahydrofuran as the major product and the corresponding (2*R*,3*S*,5*R*)-isomer as the minor. These building blocks were converted into enantiomerically pure (+)-*allo*-muscarine (from the major alkoxyl radical cyclization product) and (–)-muscarine (from the minor product) (eq 6). The polar bromocyclization of (2*R*,3*S*)-3-benzoyloxy-5-hexen-2-ol exhibits a reversed

diastereoselectivity thus leading to (2*R*,3*S*,5*R*)-3-benzoyloxy-5-bromomethyl-2-methyltetrahydrofuran, i.e., the precursor of (−)-muscarine, as major product.[27,28]







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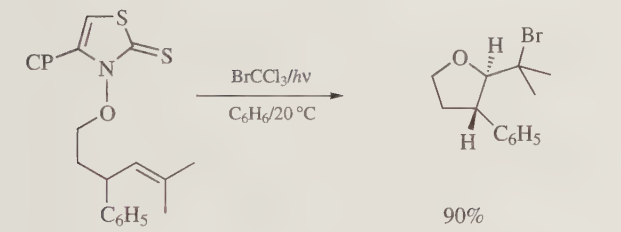

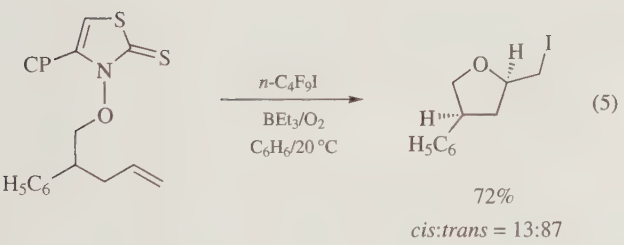

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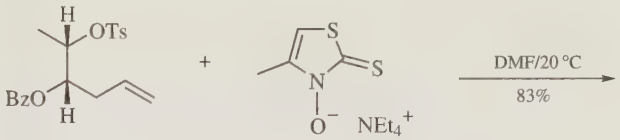

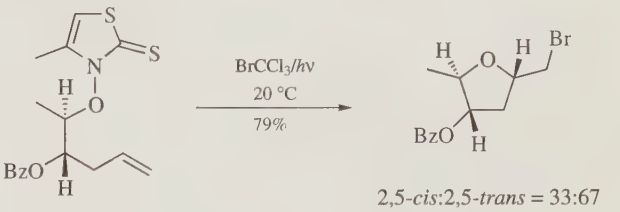

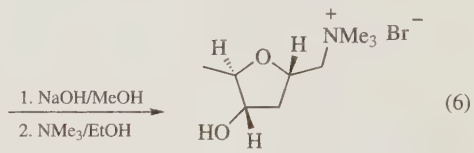

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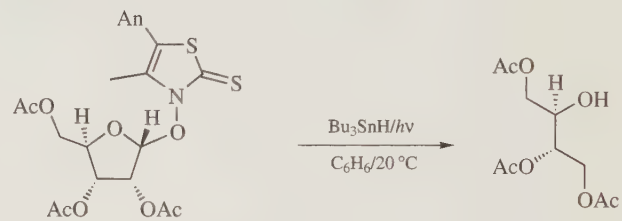
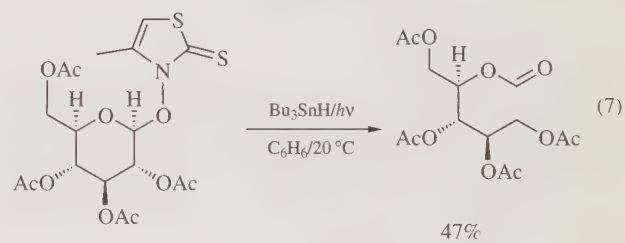




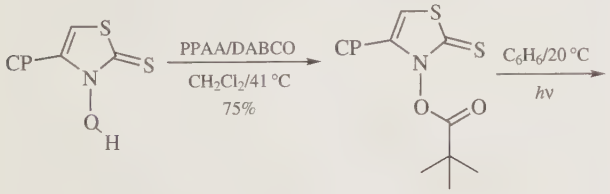
(7)

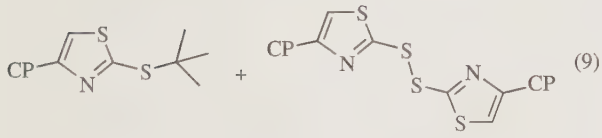
β-Carbon-Carbon Bond Cleavage. Thermal or photochemical excitation of strained *N*-(cycloalkoxy)thiazole-2(3*H*) thiones, preferentially in the presence of Bu_3SnH or $(Me_3Si)_3SiH$, leads to the formation of synthetically useful aldehydes or ketones (eq 7). Acetal-derived oxyl radicals generally provide the corresponding substituted formates as crude products which are frequently converted in the course of the chromatographic work-up into the derived alcohols (eq 7).[7,17,24] Most of such transformations have been performed either with 4-methyl- or with 5-(*p*-methoxyphenyl)-4-methyl-substituted thiazole-2(3*H*) thiones. This is due to (i) improved yields for the synthesis of such alkoxyl radical precursors and (ii) favorable characteristics especially of 5-(*p*-methoxyphenyl)-4-methyl-substituted thiazolethiones.[17] The alkoxyl radical-induced C–C cleavage is particularly useful for degrading carbohydrate-derived hydroxyl groups with subsequent heteroatom trapping or C–C-bond formation.[29,30]

Remote Functionalization: C–H Activation. Substituted *N*-(alkoxy)thiazolethiones have been applied in selective C–H activation reactions. For example, δ-bromohydrins that serve as starting materials for succeeding polar transformations have been prepared from *N*-(1-pentyloxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*) thione and $BrCCl_3$ (eq 8). This reaction is preferentially conducted under thermal conditions since the effectiveness of the underlying 1,5-hydrogen translocation benefits from elevated temperatures.[17]

(8)

***N*-Acyloxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thiones [CPTTOC(O)Rs].** Treatment of *N*-hydroxy-4-(*p*-chlorophenyl) thiazole-2(3*H*) thione potassium salt with acyl chlorides or alkyl chloroformates furnishes CPTTOC(O)Rs.[4,20] Polymer-supported derivatives of CPTTOH have been transformed via intermediate salt formation into the corresponding *N*-acyloxy derivatives.[18] A direct conversion of carboxylic acids, for instance pivaloic acid, and CPTTOH into the derived *N*-acyloxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thiones is feasible if propane trisphosphonic acid anhydride (PPAA) is used as dehydrating reagent.[13,31] *N*-(Pivaloyloxy)-4-(*p*-chlorophenyl)thiazole-2(3*H*) thione, or solid-phase supported derivatives thereof, liberate upon heating or photochemical excitation *tert*-butyl radicals that have been trapped with, e.g., $BrCCl_3$ to furnish *tert*-butyl bromide.[18] In the absence of a suitable trapping reagent, *N*-(pivaloyloxy)-4-(*p*-chlorophenyl) thiazole-2(3*H*) thione is converted into 2-*tert*-butylsulfanyl-4-(*p*-chlorophenyl)thiazole as major and 2,2′-bis[4-(*p*-chlorophenyl) thiazyl]disulfane as minor product (decarboxylative rearrangement) (eq 9).[1]





(9)

70% 10%

Related Reagents. *N*-Hydroxypyridine-2-thione; 4-methyl-3-hydroxythiazole-2-thione; 5-(*p*-methoxyphenyl)-4-methyl-3-hydroxythiazole-2-thione; (diacetoxyiodo)benzene; *N*-hydroxyphthalimide.

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Chromium(VI) Oxide[1]

[1333-82-0]	CrO_3	(MW 99.99)
Tetrabutylammonium periodate		
[65201-77-6]	Bu_4NIO_4	(MW 433.37)
Periodic acid		
[10450-60-9]	H_5IO_6	(MW 227.94)

(reagent for oxidizing carbon–hydrogen bonds to alcohols, oxidizing alkylaromatics to ketones and carboxylic acids, converting alkenes to α,β-unsaturated ketones, oxidizing carbon–carbon double bonds, oxidizing arenes to quinones, oxidizing alcohols to aldehydes, ketones, acids, and keto acids)

Alternate Names: chromic anhydride; ***Chromic Acid*** in aqueous media.

Physical Data: mp 196 °C; *d* 2.70 g cm^{-3}.

Solubility: sol ether, H_2O, HNO_3, H_2SO_4, DMF, HMPA.

Form Supplied in: red crystals.

Handling, Storage, and Precautions: **caution**: chromium(VI) oxide is a highly toxic cancer suspect agent. All chromium(VI) reagents must be handled with care. The mutagenicity of Cr^{VI} compounds is well documented.[7] HMPA is also a highly toxic cancer suspect agent. Special care must always be exercised in adding CrO_3 to organic solvents. Add CrO_3 in small portions to HMPA in order to avoid a violent decomposition. This reagent must be handled in a fume hood.

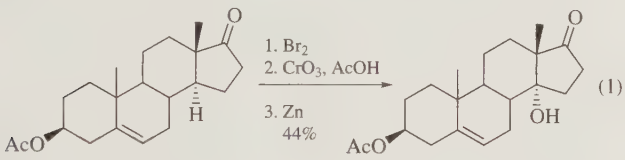
Each mol of chromium(VI) oxide has 1.5 equivalents of oxygen. The oxidizing power of the reagent increases with

decreasing water content of the solvent medium. The oxidizing medium may be aqueous acetic acid,[2,3] anhydrous acetic acid (Fieser reagent),[4] or concentrated[5] or aqueous[6] sulfuric acid.

Original Commentary

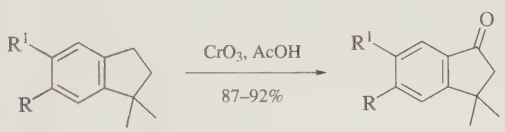
Fillmore Freeman
University of California, Irvine, CA, USA

Oxidation of Carbon–Hydrogen Bonds to Alcohols. Chromium(VI) oxide in 91% acetic acid oxidizes the methine hydrogen of (+)-3-methylheptane to (+)-3-methyl-3-heptanol with 70–85% retention of configuration.[8] 3β-Acetoxy-14α-hydroxyandrost-5-en-17-one is obtained by direct introduction of an α-hydroxyl group at C-14 in the dibromide of 3β-acetoxyandrost-5-en-17-one (eq 1).[9]



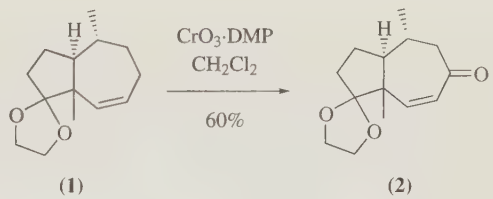
(1)

Oxidation of Alkylaromatics to Ketones and Carboxylic Acids. Chromium(VI) oxide in concentrated sulfuric acid oxidizes 3,4-dinitrotoluene to 3,4-dinitrobenzoic acid (89%).[5] Under milder conditions, with longer alkyl chains, the benzylic position is converted to carbonyl. Chromium(VI) oxide in acetic acid oxidizes ethylbenzene to acetophenone and benzoic acid. More rigorous oxidizing experimental conditions convert longer chain alkyl groups to carboxyl, thus yielding benzoic acid or its derivatives. Methylene groups between two benzene rings are oxidized to carbonyl derivatives in preference to reaction at alkyl side chains.[10] Indans are oxidized to 1-indanones by use of a dilute (10%) solution of chromium(VI) oxide in acetic acid at room temperature (eq 2).[11]



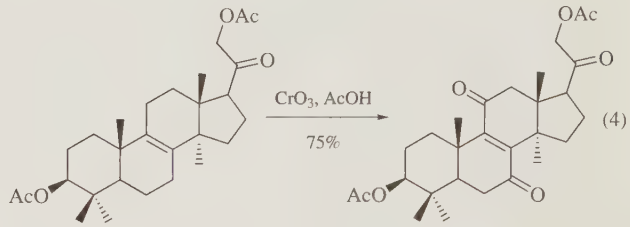
(2)

Allylic Oxidations. Allylic oxidations may be complicated by carbonyl formation at either one or both allylic positions. Although chromium(VI) oxide appears to be useful for allylic oxidation in steroid chemistry, better results may be obtained in other systems with ***Di-t-butyl Chromate*** or ***Dipyridine Chromium(VI) Oxide*** (Collins reagent). However, the ***Chromium(VI) Oxide–3,5-Dimethylpyrazole*** complex (CrO_3·DMP) is useful for allylic oxidations. The complex oxidized the allylic methylene group in (**1**) to the α,β-unsaturated ketone (**2**) which was used in the synthesis of the antibacterial helenanolide (+)-carpesiolin (eq 3).[12] Chromium(VI) oxide in glacial acetic acid oxidizes 3,21-diacetoxy-4,4,14-trimethyl-Δ^8-5-pregnene to the enetrione (eq 4).[13] Complex product mixtures are formed when epoxidation competes with the allylic oxidation.[14]



(3)

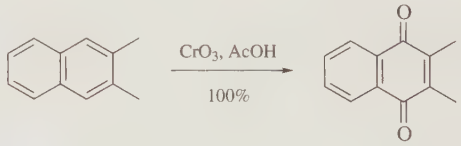
(**1**) (**2**)



(4)

Oxidation of Carbon–Carbon Double Bonds. Chromium(VI) oxide in aqueous sulfuric acid generally cleaves carbon–carbon double bonds. Rearrangements may further complicate the oxidation. In anhydrous acetic acid, chromium(VI) oxide oxidizes tetraphenylethylene to the oxirane (70% yield) and benzophenone (11%).[15] The yield is lower and more double bond cleavage occurs in aqueous acetic acid. However, use of acetic anhydride as solvent (see ***Chromyl Acetate***) affords the oxiranes from tri- and tetrasubstituted alkenes in 50–88% yields, along with benzopinacols.[16,17] Many steroidal and terpenic cyclic alkenes react with chromium(VI) oxide in acetic acid to give oxiranes, and saturated, α,β-unsaturated, α-hydroxy, and α,β-epoxy ketones which arise from the initially formed oxirane.[18,19] A synthetically useful cleavage of double bonds involving chromium(VI) oxide is the Meystre–Miescher–Wettstein degradation[20] which shortens the side chain of a carboxylic acid by three atoms at one time. This procedure is a modification of the Barbier–Wieland degradation.[21,22]

Oxidation of Arenes to Quinones. In contrast to alkylaromatics, which undergo oxidation at the side chain with some chromium(VI) oxidants, polynuclear aromatic arenes undergo ring oxidation to quinones with chromium(VI) oxide. This chemoselectivity is shown in the chromium(VI) oxide in anhydrous acetic acid (Fieser reagent) oxidation of 2,3-dimethylnaphthalene to 2,3-dimethylnaphthoquinone in quantitative yield (eq 5).[23] In some cases, depending on experimental conditions, both benzylic and ring oxidations occur[24] or the alkyl groups may be eliminated (eq 6).[25] The oxidation of anthracene derivatives is important in the total synthesis of anthracycline antibiotics.[26,27]



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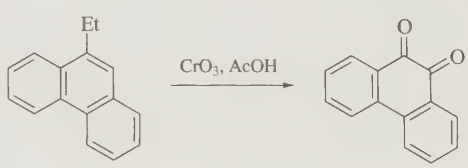
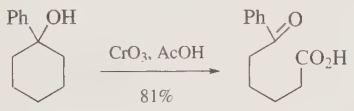
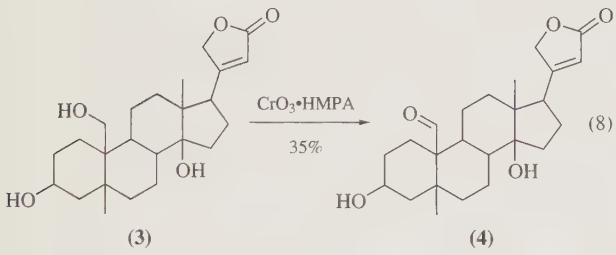


(6)

Oxidation of Alcohols to Aldehydes, Ketones, Acids, and Keto Acids. Chromium(VI) oxide in acetic acid oxidizes primary alcohols to aldehydes and acids, and secondary alcohols to ketones and keto acids (Fieser reagent) (eq 7).[28] Chromium(VI) oxide in water or aqueous acetic acid oxidizes primary alcohols to carboxylic acids.[29,30] Chromium(VI) oxide–***Hexamethylphosphoric Triamide*** (CrO_3·HMPA) selectively oxidized the primary hydroxyl group of strophanthidol (**3**) to an aldehyde group in the final step in the synthesis of strophanthidin (**4**) (eq 8).[31] The CrO_3·HMPA complex oxidizes saturated primary alcohols to aldehydes in about 80% yield.[32,33] The yields are lower with secondary alcohols and highest with α,β-unsaturated primary and secondary alcohols. It is possible to selectively oxidize certain allylic and benzylic hydroxyl groups in the presence of other unprotected saturated groups (eq 9; cf eq 8). Chromium(VI) oxide in DMF in the presence of catalytic amounts of sulfuric acid oxidizes steroidal alcohols to ketones.[34] Chromium(VI) oxide on graphite selectively oxidizes primary alcohols in the presence of secondary and tertiary alcohols.[35]

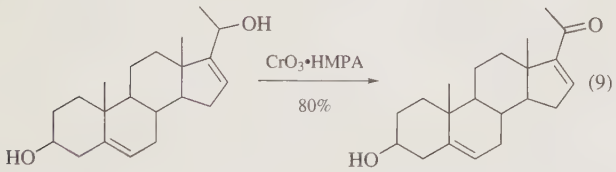


(7)



(8)

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



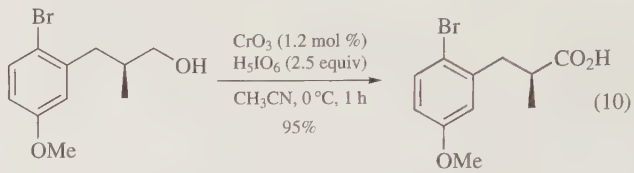
(9)

Other Applications. Chromium(VI) oxide in aqueous acetic acid converts α-chlorohydrindene to α-hydrindanone (50–60%).[36] Suitably protected methylene or benzylidene acetals of alditols are cleaved by chromium(VI) oxide in glacial acetic acid to derivatives of ketoses.[37] Chromium(VI) oxide in anhydrous acetic acid converts methyl ethers into the corresponding formates, which can be hydrolyzed by base to alcohols (demethylation).[38]

First Update

Seongmin Lee
Purdue University, West Lafayette, IN, USA

Oxidation of Alcohols. Catalytic chromium(VI) oxide (1.2 mol %) together with 2.5 equiv of periodic acid as co-oxidant in wet acetonitrile converts various primary alcohols to the carboxylic acids in excellent yields (eq 10).[39] Notably, chiral alcohols are cleanly oxidized to carboxylic acids without racemization at the adjacent chiral centers (eq 11). Cr^{VI}-catalyzed oxidation of secondary alcohols give the corresponding ketones in a nearly quantitative yield (eq 12). No product formation was observed in the absence of chromium(VI) oxide or when acetone was used as solvent.



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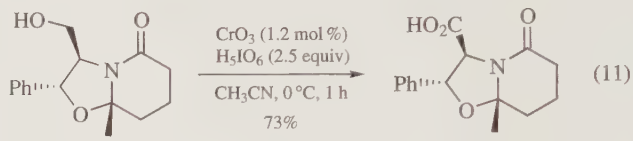
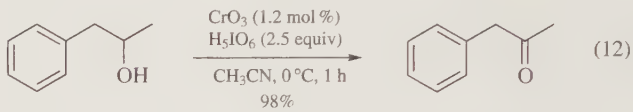
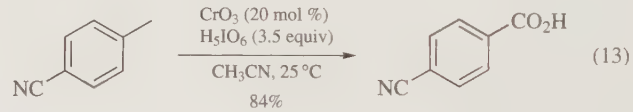


(11)



(12)

Benzylic Oxidation. Chromium(VI) oxide acts as an efficient catalyst for the benzylic oxidation with periodic acid as the terminal oxidant in acetonitrile at 25 °C. Various substituted toluenes are converted to the corresponding benzoic acids (eq 13).[40] Cyclic benzyl ethers are oxidized to the lactones in excellent yields.[40] Isochroman is oxidized to 3,4-dihydroisocoumarin quantitatively by using 2 equiv of periodic acid and 1 mol % of chromium(VI) oxide (eq 14). 4-Ethyl-3-nitro-benzoic acid is efficiently transformed into 4-acetyl-3-nitro-benzoic acid by 3 mol % chromium(VI) oxide and periodic acid.[41]



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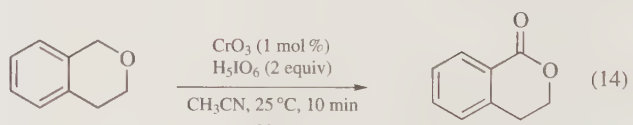
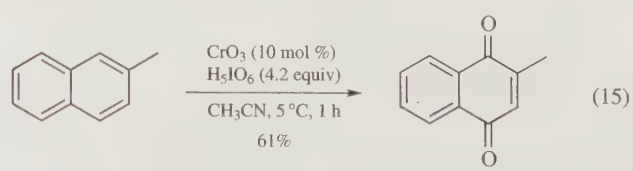


(14)

Oxidation of Arenes to Quinones. Chromium(VI) oxide catalyzes the oxidation of arenes to the corresponding quinones with excess periodic acid in good to excellent yield.[42] 2-Methylnaphathalene is smoothly converted to 2-methyl-1,4-naphthoquione (vitamin K_3) at 5 °C in the presence of 10 mol % of chromium(VI) oxide and 4.2 equiv of periodic acid (eq 15). 1,3,5-Trimethoxybenzene is transformed into 2,6-dimethoxy-1,4-benzoquinone in 90% yield with 3 mol % catalyst (eq 16).



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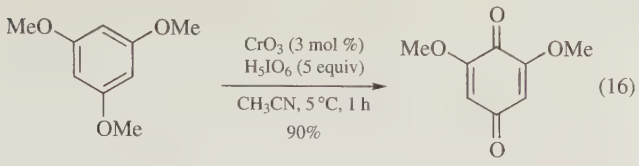
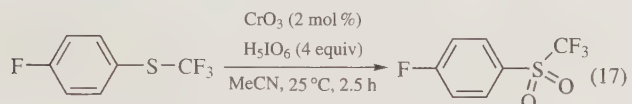
vitamin K_3

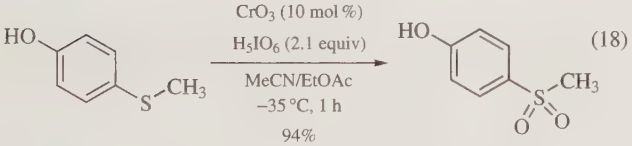


(16)

Oxidation of Sulfides to Sulfones. Chromium(VI) oxide/periodic acid is an excellent catalytic system for the oxidation of sulfides to sulfones.[43] A myriad of electron-rich and electron-deficient sulfides are oxidized to sulfones with 2 mol % chromium(VI) oxide and 2 equiv periodic acid at low temperature (eq 17). Higher catalyst loading (10 mol %) led to shorter reaction time and a highly chemoselective oxidation of sulfides to sulfones in the presence of readily oxidized functional groups. Both carbon-carbon double bonds and triple bonds are unaffected by this catalytic system. Sulfides containing phenol, primary alcohol, and aldehyde are converted to the corresponding sulfones (eq 18). However, benzylic alcohol and secondary alcohol moieties are not tolerated under the oxidation conditions and give very poor yields of the desired sulfones due to competing oxidation of hydroxyl group. Amide and heterocyclic nitrogen atoms are not affected by the oxidation condition.



(17)



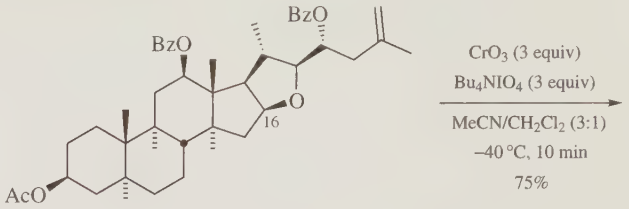
(18)

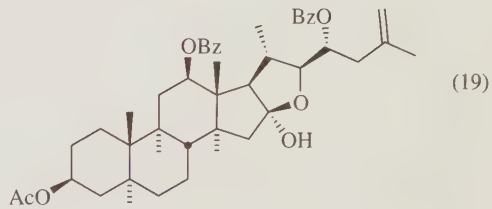
Direct Functionalization of C–H Bonds. Stoichiometric chromium(VI) oxide (3 equiv) together with tetrabutylammonium periodate (3 equiv) efficiently oxyfunctionalizes C–H bonds of various activated and nonactivated hydrocarbons. It oxidizes steroidal cyclic ethers to the corresponding hydroxylated cyclic ethers.[43] It is proposed that a monoperoxo Cr^{VI} species structurally similar to the dioxiranes, is generated in situ by the reaction of chromium(VI) oxide with Bu_4NIO_4 and serves as the active C–H oxidant. The generated oxidant is stable at −40 °C and has an orange color typical of Cr^{VI}.

The value of this oxidation is its extremely mild conditions combined with high selectivity. The Cr^{VI}-mediated C–H oxidations occur at about −40 °C and are typically complete within 10 min. The observed retention of configuration strongly suggests that the C–H oxidation proceeds through a concerted "three-center two-electron" oxenoid insertion into C–H bonds rather than through radical intermediates.

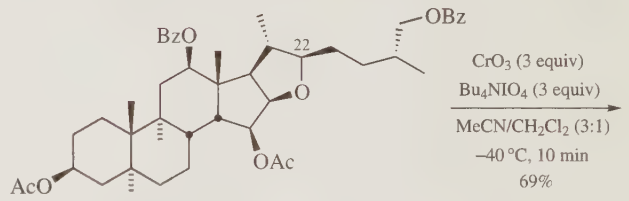
Several impressive oxyfunctionalization reactions on steroid substrates illustrate the scope of this process. Oxidation-susceptible olefin and iodide moieties, which ultimately give epoxides under the influence of dimethyldioxirane or *m*-CPBA, are unreactive under these oxidation conditions, highlighting the chemoselectivity of the Cr-mediated C–H oxidation. The unusual chemoselectivity for C–H oxidation over epoxidation is in keeping with a theoretical study that Cr^{VI} peroxo species have higher calculated activation barriers for oxygen transfer to ethylene; they are less prone to epoxidation than similar Mo^{VI} and W^{VI} species.

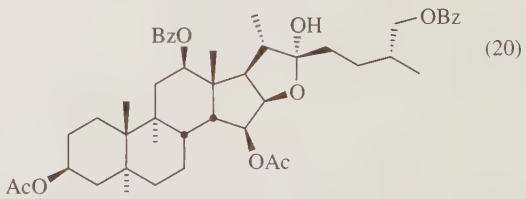
The C–H bond at either C16 (eq 19) or C22 (eq 20) in steroid cyclic ethers is oxidized in excellent yield to give the corresponding hemiacetals as a function of their electronic environments.[44]





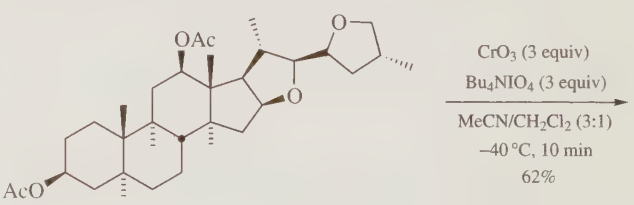
(19)

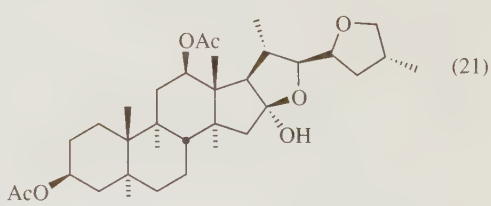




(20)

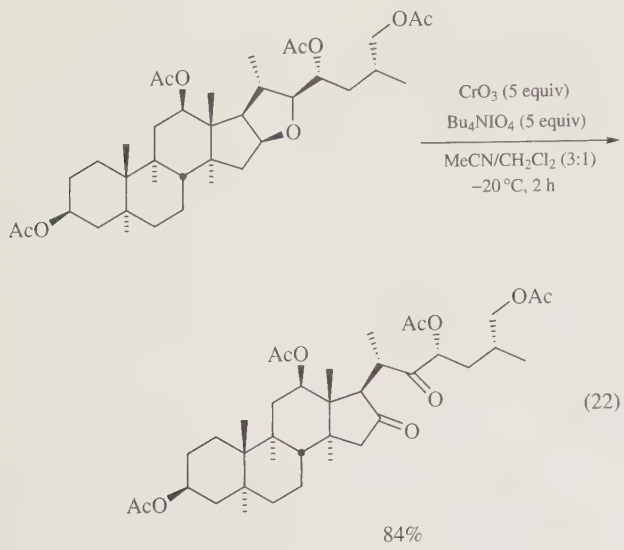
The regioselectivity of these C–H oxidations is illustrated in the oxidation of bistetrahydrofuran. Out of many potential products, C16 hemiacetal is obtained as the major product (eq 21).



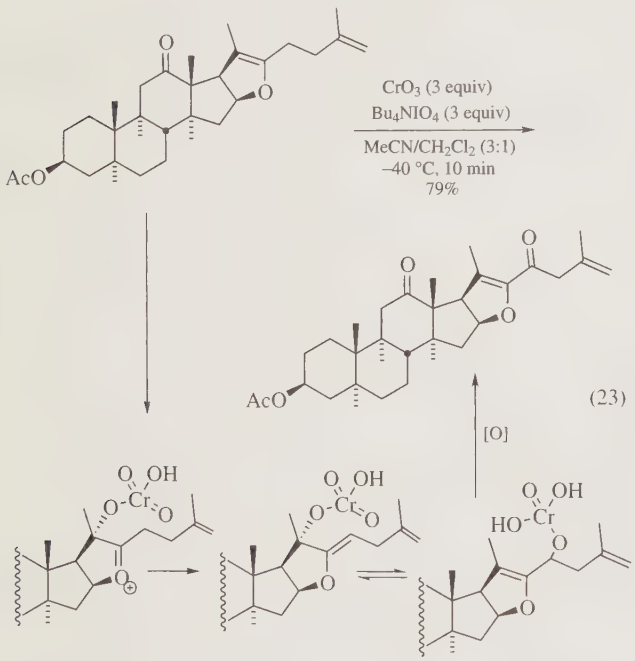


(21)

A diketone is obtained in 84% yield via the bishemiacetal intermediate from the oxidation of E-ring tetrahydrofuran at an elevated reaction temperature (eq 22). The absence of epimerization α to the carbonyl illustrates the mildness of this oxidation.



In the case of an E-ring cyclic enol ether, an allylic oxidation product is obtained, presumably via sequential enol ether attack on Cr^{VI} species, [3,3]-sigmatropic rearrangement, and allylic oxidation (eq 23).

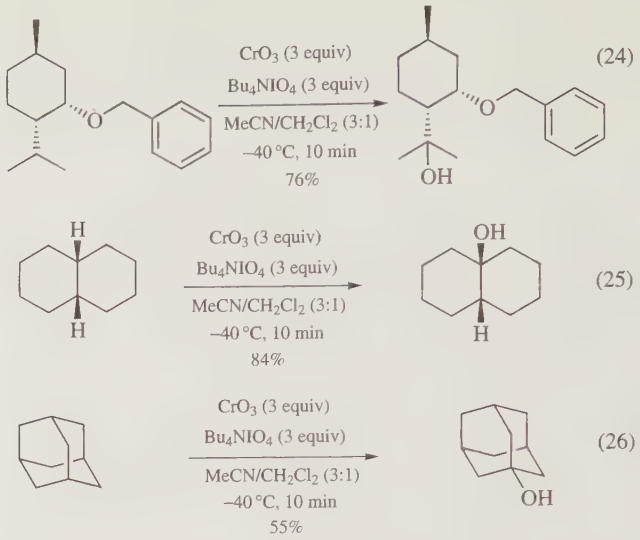


Substrates for chromium(VI) oxide/Bu_4NIO_4-mediated C–H oxidation are not limited to steroidal cyclic ethers. C–H bonds of nonactivated hydrocarbons are readily oxidized to give tertiary alcohol or ketone.

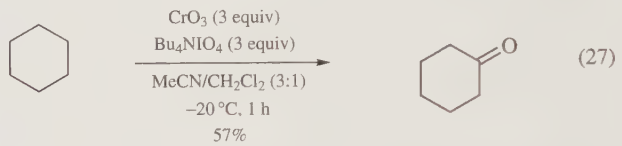
The sterically less hindered tertiary C–H bond of a menthol derivative has been preferentially oxidized over secondary benzylic position also adjacent to oxygen, the tertiary α position of the acyclic ether, and the sterically more hindered tertiary C–H bonds (eq 24).[44]

The C–H oxidation is stereospecific with retention of stereochemistry of the C–H bond oxidized. So the oxidation of *cis*-decalin results in the formation of *cis*-decanol (eq 25).

Preference of tertiary C–H bond over secondary is seen in the oxidation of adamantane (eq 26).



Secondary C–H bonds are also oxidized to give the corresponding ketones. Cyclohexane is oxidized to cyclohexanone, but the reaction requires an elevated reaction temperature and prolonged reaction time (eq 27).



Related Reagents. Chromium(VI) Oxide–3,5-dimethylpyrazole; Chromium(VI) oxide–quinoline; Chromium(VI) oxide–silica gel; dimethyldioxirane; methyl(trifluoromethyl)dioxirane; chromylacetate.

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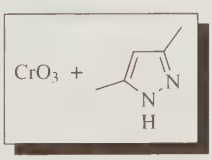
Chromium(VI) Oxide-3,5-Dimethylpyrazole



(CrO_3)
[1333-82-0] CrO_3 (MW 99.99)
($C_5H_8N_2$)
[67-51-6] $C_5H_8N_2$ (MW 96.13)

(oxidizing agent for alcohols;[1] oxidant for saturated carbons α to unsaturation[2–5])

Physical Data: see ***Chromium(VI) Oxide***.

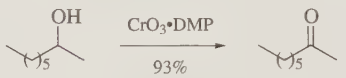
Solubility: sol dichloromethane; slightly sol ether and pentane.

Form Supplied in: formed in situ from widely available reagents.

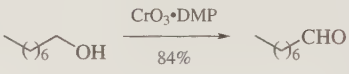
Preparative Method: drying of the CrO_3 over P_2O_5 is recommended; rapid addition of DMP (1 equiv) to a suspension of chromium(VI) oxide (1 equiv) in dry CH_2Cl_2 (−20 °C) results in a dark red homogeneous solution after 10 min; the solution is then treated with the organic substrate (0.05–0.5 equiv).[1,2]

Handling, Storage, and Precautions: chromium salts are carcinogenic; this reagent should be used in a fume hood.

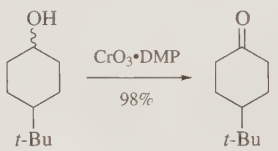
Oxidation of Alcohols. The oxidation of primary and secondary alcohols is typically effected by treating the alcohol (1 equiv) with CrO_3·DMP (1–10 equiv) at rt (eqs 1–3).[1] Notably similar to ***Pyridinium Chlorochromate*** (PCC), the title reagent system has been shown to oxidize primary alcohols to aldehydes efficiently (eq 2). The ease of oxidation of both equatorial and axial alcohols using this complex has been demonstrated (eq 3); the reactions of both are complete within 40 min when stirred at room temperature. The authors suggest the intermediacy of a cyclic chromate ester species through which rapid intramolecular oxidation may occur.[1]



(1)

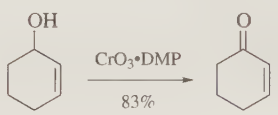


(2)



(3)

Oxidation of Unsaturated Alcohols.[1] Allylic, benzylic, and propargyl alcohols readily interact with CrO_3·DMP to provide the expected carbonyl compounds in good to excellent yield. Allylic alcohols can be oxidized with little or no competing oxidation of allylic methylene positions within the same molecule (eqs 4 and 5).



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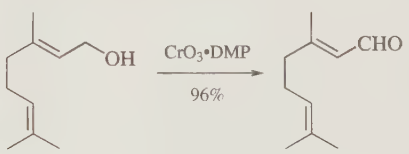
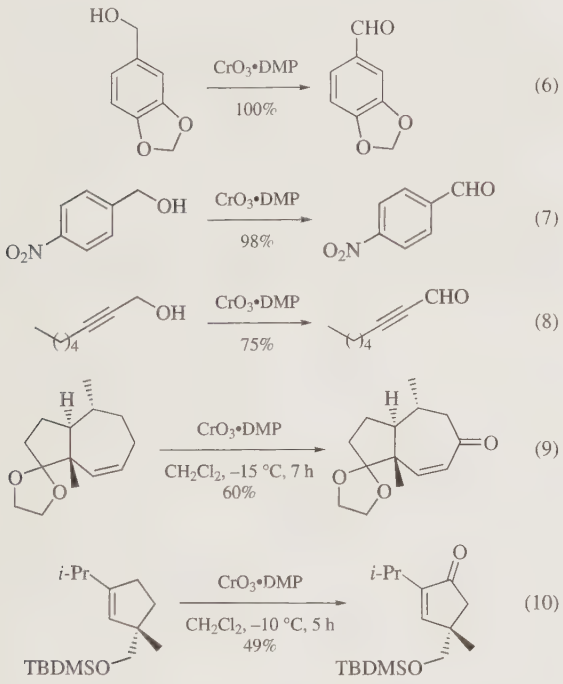


(5)

Benzylic alcohols are oxidized with comparable efficiency and the reaction is not sensitive to the electronic nature of the aromatic ring (eqs 6 and 7). Propargyl alcohols with both internal and terminal triple bonds are oxidized in good yield using CrO_3·DMP (eq 8).

Oxidation of Saturated Allylic and Benzylic Carbons. The CrO_3·DMP complex appears to offer two unique advantages over

PCC: an empty Lewis acidic coordination site on chromium, and an internal basic nitrogen that may aid in cleavage of a carbon–hydrogen bond.[2] As a result, for allylic and benzylic oxidations, CrO_3·DMP is superior to more conventional chromium oxidants which often suffer from low yields, practical complications, and/or inconvenient and extended reaction times. In the total synthesis of (±)-carpesiolin, CrO_3·DMP was used to install an enone from an alkene precursor (eq 9).[3] It was used once more for a similar transformation in the total synthesis of (−)-retigeranic A and several of its derivatives, where it was found to be the most efficient reagent for the purpose (eq 10).[4]



Observations made in the course of studies toward the synthesis of Δ^5-7-keto steroids provide some insight into the mechanism of CrO_3·DMP-mediated allylic oxidation.[2] Here, axial hydrogens were found to be predisposed to more facile cleavage by this reagent, a common observation with chromium oxidants. The allylic oxidation of cholesteryl benzoate was complete within 30 min when CrO_3·DMP was used in 20-fold excess. Alternatively, use of only a 12-fold excess of CrO_3·DMP provided 74% conversion following stirring for 4 h at 0 °C. Benzylic methylenes are also susceptible to oxidation by this reagent.[5]

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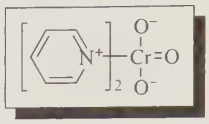
Chromium(VI) Oxide-Dipyridine[1]



[26412-88-4] $C_{10}H_{10}CrN_2O_3$ (MW 258.22)

(reagent for oxidizing alcohols to carbonyl compounds)

Alternative Names: Collins reagent; chromium(VI) oxide–pyridine.

Solubility: sol CH_2Cl_2; (*Z*)-1,2-dichloroethylene; pyridine; $CHCl_3$.

Form Supplied in: red crystals; not commercially available.

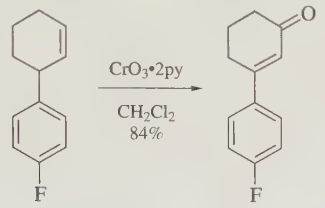
Preparative Methods: prepared in 85–91% yield from ***Chromium(VI) Oxide*** and ***Pyridine***.[2,3] Caution: the reaction is extremely exothermic. The chromium(VI) oxide should be added to dry pyridine at such a rate that the temperature does not exceed 20 °C and in such a way that the oxide mixes rapidly with pyridine. Other chromium(VI) oxide–pyridine complexes are known. These include the Ratcliffe reagent (dipyridine chromium(VI) oxide prepared in situ in CH_2Cl_2),[4,5] and the Sarett reagent (CrO_3·$(C_5H_5N)_2$ in pyridine).[6] The preparation and workup of the Sarett reagent is sometimes tedious. The hygroscopic nature of the Collins reagent and its propensity to inflame may be avoided by the in situ preparation of the complex according to the Ratcliffe procedure.

Handling, Storage, and Precautions: Caution: the Collins reagent is extremely hygroscopic; exposure to moisture rapidly converts it to the yellow dipyridinium dichromate. The reagent should be stored at 0 °C under nitrogen or argon in a sealed container, protected from light. All chromium(VI) reagents must be handled with care; their mutagenicity is well documented.[7] This reagent should be prepared and handled in a fume hood.

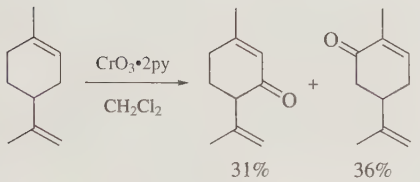
Allylic Oxidation to Form α,β-Unsaturated Ketones. Although a solution of chromium(VI) oxide in pyridine is not very useful for allylic oxidation, the isolated dry chromium(VI) oxide–dipyridine complex in dichloromethane oxidizes allylic methylene groups to enones at rt in good to excellent yields. Δ^5-Androsten-7-one-3β,17β-diol diacetate is thus obtained (82%) from the oxidation of Δ^5-androstene-3β,17β-diacetate.[8] Attack at an allylic methine position yields the isomeric enone when possible; for example, 3-(4-fluorophenyl)cyclohexenol is oxidized to the isomeric enone (eq 1).[8] Similar rearrangements occur in methylene systems with steric hindrance.[8] If more than one allylic methylene group is present in a conformationally flexible molecule, isomeric enones resulting from attack at both positions are formed (eq 2).[8] Selectivity is observed in conformationally rigid molecules.[8] Methyl groups are not easily oxidized. In general, the Collins reagent gives higher yields and less overoxidation than ***Di-t-butyl Chromate*** or ***Chromium(VI) Oxide*** in acetic acid.

Alkynes are oxidized to conjugated alkynic ketones (ynones) by the Collins reagent.[9] The Collins reagent oxidizes 4-octyne to 4-octyn-3-one (eq 3). Oxidation of alkynes by ***t-Butyl Hydroperoxide*** and catalytic amounts of ***Selenium(IV) Oxide***[10] effects oxidation at both centers adjacent to a triple bond. A catalytic

amount of chromium(VI) oxide in benzene and *t*-butyl hydroperoxide selectively oxidizes alkynes to ynones in about 50% yield.[11]



(1)



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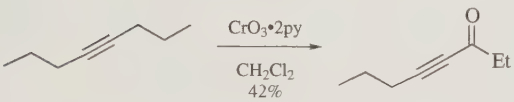
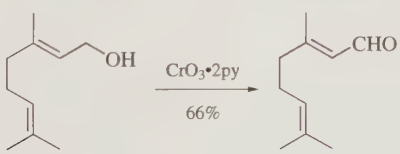


(3)

Oxidation of Primary Alcohols to Aldehydes. The oxidation of alcohols is generally performed in dichloromethane with a sixfold excess of the Collins reagent. The Collins reagent[3] gives higher yields than the Sarett reagent[6] and comparable yields to the Ratcliffe reagent.[5] The Collins reagent oxidizes 1-heptanol to 1-heptanal in 70–84% yield[3] and the Ratcliffe reagent oxidizes 1-decanol to 1-decanal in 83% yield.[4,5] The Collins reagent oxidizes the primary allylic alcohols geraniol (eq 4) and nerol (eq 5) to geranial and neral, respectively, without isomerization.[12] The Ratcliffe reagent oxidizes cinnamyl alcohol to cinnamaldehyde in 96% yield.[5] The Collins reagent has been used to oxidize primary hydroxy groups of sugars to aldehydes in 50–75% yield.[13] Although the Sarett reagent is useful for the conversion of primary allylic and benzylic alcohols to their corresponding aldehydes, its use for primary saturated alcohols (with the exception of some steroidal ones) is less effective than the Collins or Ratcliffe reagent.



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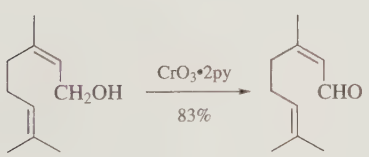
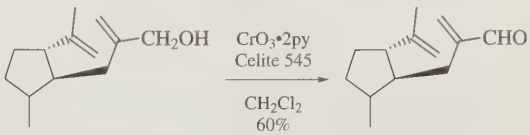


(5)

The oxidation of allylic alcohols to aldehydes is facilitated by use of Celite-supported Collins reagent (eq 6).[14,15] This method has been used to prepare intermediates in the synthesis of bulnesol[14] and guaiol.[15] A modified Ratcliffe reagent, $CrO_3 \cdot 2py$ in acetonitrile on Celite, was used to oxidize primary alcohols to aldehydes.[16]

The (*S*)-alcohol (**1**) is oxidized by the Collins reagent to the aldehyde (**2**) with no more than 5% racemization (eq 7).[17]

Primary alcohols are converted to the corresponding *t*-butyl esters by Collins reagent in CH_2Cl_2/DMF/Ac_2O and a large excess of *t*-butyl alcohol (eq 8).[18] This conversion is probably general except for aromatic aldehydes.



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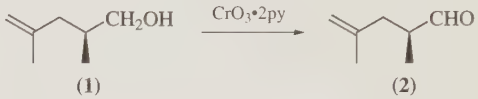

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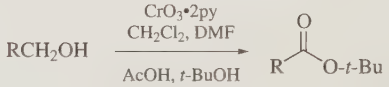
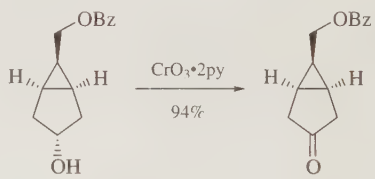


(8)

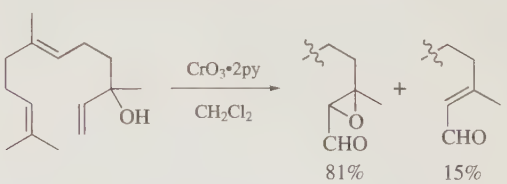
Oxidation of Secondary Alcohols to Ketones. The Collins reagent (eq 9),[19] the Ratcliffe reagent,[5] and the Sarett reagent[20,21] are effective in oxidizing secondary alcohols to ketones. Generally, acid sensitive functional groups such as acetals, double bonds, oxiranes, and thioethers are not affected, although there are exceptions. The Collins reagent oxidizes *exo*-7-hydroxybicyclo [4.3.1]deca-2,4,8-triene to bicyclo[4.4.1]deca-2,4,8-triene-7-one (64%).[22] Collins reagent oxidizes the secondary alcohol functional groups in β-hydroxy-(*Z*)-*O*-alkyloximes to the corresponding β-keto-*O*-alkyloximes.[23]



(9)

A number of alternative reagents are available for the oxidation of primary and secondary alcohols to aldehydes and ketones. Related chromium-based reagents include ***Chromium(VI) Oxide–3,5-Dimethylpyrazole***, ***Chromium(VI) Oxide–Quinoline***, ***Pyridinium Chlorochromate***, and ***Pyridinium Dichromate***.

Oxidation of Tertiary Allylic Alcohols to Epoxy Aldehydes. The Collins reagent oxidizes tertiary allylic alcohols to epoxy aldehydes (eq 10).[24]

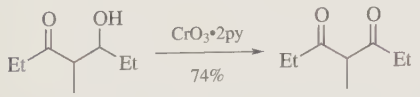


(10)

Oxidation of Carbohydrates. Addition of acetic anhydride to the Collins reagent increases the yields (>90%) for the oxidation of secondary hydroxy groups to carbonyl groups in carbohydrates.[13,25,26]

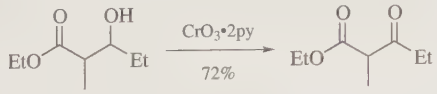
Oxidation of β-Hydroxy Ketones to 1,3-Diketones. Collins reagent oxidizes β-hydroxy ketones to 1,3-diketones (eq 11).[26,27]

Higher yields are generally obtained with ***Dimethyl Sulfoxide–Oxalyl Chloride*** (Swern reagent).



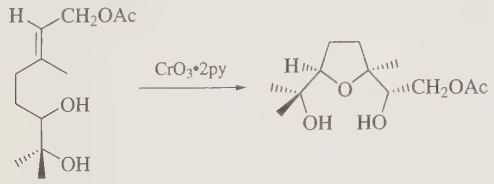
(11)

Oxidation of β-Hydroxy Esters to β-Keto Esters. Collins reagent oxidizes β-hydroxy esters to β-keto esters (eq 12).[27]



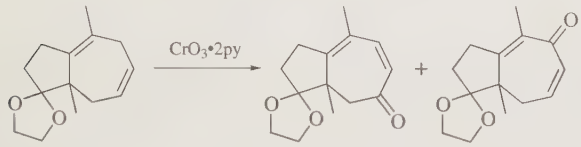
(12)

Oxidative Cyclization of 5,6-Dihydroxyalkenes. Collins reagent oxidizes the unsaturated diols (**3**) to the corresponding *cis*-tetrahydrofurandiols (**4**) (eq 13).[28]



(3) (4) (13)

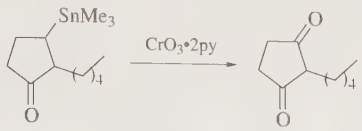
Oxidation of 1,4-Dienes. Oxidation of the 1,4-diene (**5**) with Collins reagent or ***Di-t-butyl Chromate*** yields dienones (**6**) and (**7**) in the ratio of 1:3 (~65% total yield) (eq 14).[29] Complementary regioselectivity (**6**)/(**7**) = 9:1 (~70% total yield) is obtained with ***Pyridinium Chlorochromate*** (PCC).



(5) (6) (7) (14)

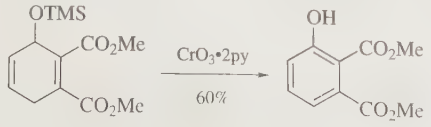
Other Applications. Collins reagent, Jones' reagent, and chromic acid in 50% acetic acid oxidatively deoximate ketoximes to the corresponding carbonyl compounds.[30]

Secondary alkylstannanes are converted into the corresponding carbonyl compounds by oxidation with Collins reagent (eq 15).[31,32] Mixtures of alcohols and dehydration products are obtained from tertiary alkylstannanes.



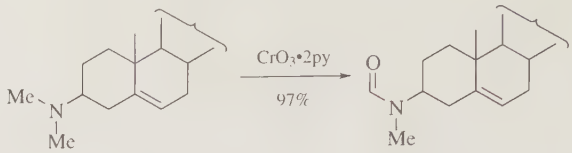
(15)

Collins reagent oxidizes trimethylsiloxy-substituted 1,4-cyclohexadienes to phenols (eq 16).[32]



(16)

Collins reagent oxidizes steroidal tertiary amines to *N*-formyl derivatives (eq 17).[3]



(17)

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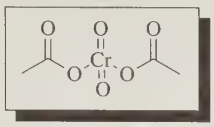
Chromyl Acetate[1]



[4112-22-5] $C_4H_6CrO_6$ (MW 202.10)

(oxidizing agent for carbon–hydrogen bonds, carbon–carbon double bonds, macrocyclic lactones, and alcohols)

Physical Data: mp 30.5 °C.

Solubility: sol CCl_4, Ac_2O, HOAc; slowly oxidizes many solvents.

Purification: spectrophotometrically or titrimetrically.[2–5]

Preparative Method: prepared in situ from CrO_3 and Ac_2O or Ac_2O/HOAc. Slow addition of CrO_3 to a cooled solution of Ac_2O is recommended in order to avoid a highly exothermic reaction.

Handling, Storage, and Precautions: best results are obtained from the freshly prepared oxidant. Chromium compounds are toxic and should be handled with care and disposed of in conformance with established procedures. This reagent should be handled in a fume hood.

Original Commentary

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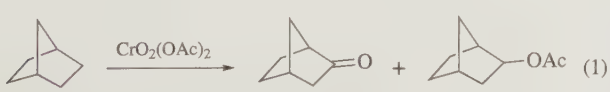
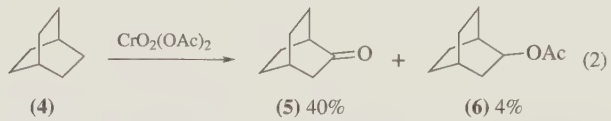
This powerful oxidant, which is sometimes called chromium (VI) oxide–acetic anyhdride or chromium(VI)–acetic anhydride–acetic acid, oxidizes carbon–hydrogen bonds in bicycloalkanes and polycycloalkanes to form alcohols and ketones.[6–12] The initially formed alcohol may also be acetylated or oxidized to the ketone in the reaction mixture. Methylbenzenes are oxidized to the corresponding benzoic acids[12] and, in the presence of sulfuric acid (Thiele reagent), benzylidene diacetates (aldehyde precursors) are obtained.[13–15] Alkenes are oxidized to oxiranes[16–18] and diol carbonates.[19] Diarylmethanes and secondary alcohols are oxidized to ketones.[12,20]

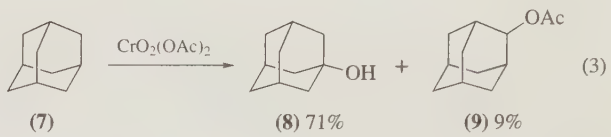
Oxidation of Carbon–Hydrogen Bonds to Form Alcohols and Ketones. Chromyl acetate oxidizes bicyclo[2.2.1]heptane (**1**) to (**2**) and (**3**) (eq 1),[6] bicyclo[2.2.2]octane (**4**) to (**5**) and (**6**) (eq 2),[6] and adamantane (**7**) to (**8**) and (**9**) (eq 3).[6] Tricyclo[3.3.0.0^{2,6}]octane (**10**) is oxidized to (**11**) and (**12**) in a 9:1 ratio (eq 4).[7] (−)-Isobornyl acetate (**13**) is regioselectively oxidized to (**14**) and (**15**) (4:1; eq 5), which is useful in the synthesis of nojigku acid.[8] Similarly, (−)-bornyl acetate (**16**) is oxidized to (**17**) and (**18**) (eq 6).[9] 3β-Acetoxy-5α,6β-dichloroandrostan-17-one (**19**) is oxidized by chromyl acetate to the corresponding 14α-hydroxy compound (**20**) (eq 7)[10] and 3,5α-cycloandrostane is oxidized to a mixture of three ketones.[11] The latter reaction involves oxidation and carbonyl formation α to a cyclopropane ring.



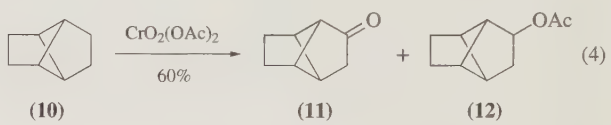
(1) (2) 23% (3) 6% (1)



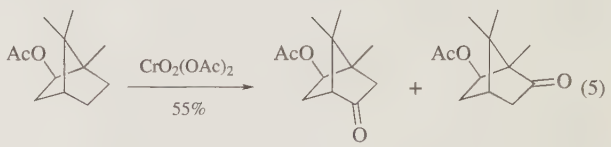
(4) (5) 40% (6) 4% (2)



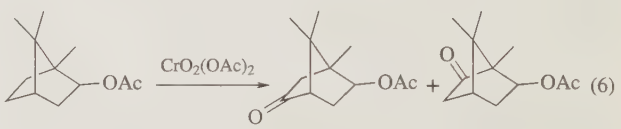
(7) (8) 71% (9) 9% (3)



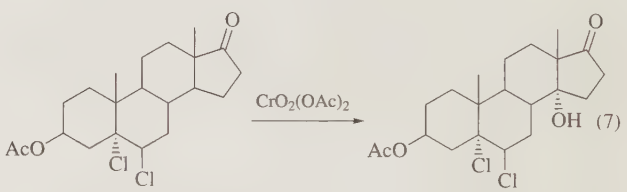
(10) (11) (12) (4)



(13) (14) (15) (5)

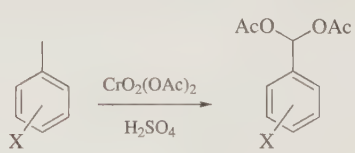


(16) (17) 40% (18) 16% (6)



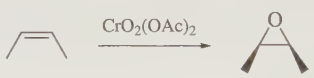
(19) (20) (7)

Oxidation of Benzylic Carbon–Hydrogen Bonds to Alcohols, Aldehydes, Carboxylic Acids, and Ketones. Chromyl acetate in the presence of sulfuric acid converts methyl-substituted aromatic and heteroaromatic compounds to the corresponding benzylidene diacetates in fair to excellent yields (eq 8).[13–15] The benzylidene diacetates are easily hydrolyzed to aldehydes. Diphenylmethane and triphenylmethane are oxidized to benzophenone and triphenylcarbinol, respectively, in near quantitative yields.[12]

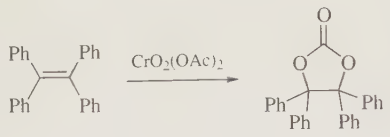


(8)

Oxidation of Carbon–Carbon Double Bonds to Oxiranes. Chromyl acetate[16–18] and chromyl nitrate[19] stereospecifically oxidize carbon–carbon double bonds to oxiranes (eq 9). Tetraphenylethylene is converted to the oxirane, benzophenone, and benzopinacol (eq 10).[20]



(9)



(10)

Other Applications. Unlike the ***Dipyridine Chromium(VI) Oxide*** complex and ***Pyridinium Chlorochromate*** which gave nearly exclusive α-oxidation of alkynes, chromyl acetate oxidized the α-position and the triple bond.[21] Macrocyclic lactones are oxidized to monoketo lactones with some regioselectivity. The preferred conformation of the lactone probably influences the site of oxidation.[22] New oxygenated derivatives of 1,8-epoxy-*p*-menthane were obtained by the chromyl acetate oxidation of 1,8-cineole.[23]

First Update

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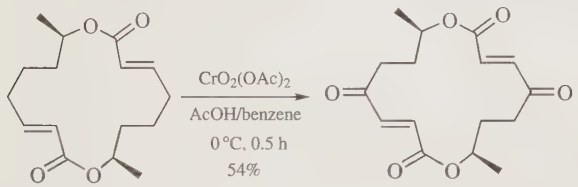
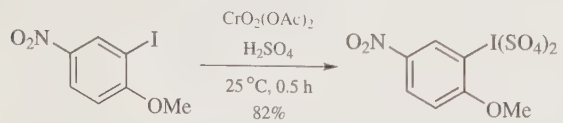
Oxidation of Allylic C–H bonds to α,β-Unsaturated Ketones. Chromyl acetate is useful for allylic oxidations. Allylic oxidations of simple alkenes may be complicated by carbonyl formation at either one or both allylic positions. The use of α,β-unsaturated esters as substrates removes the complication. Antibiotic macrodiolide (−)-pyrenophorin (**22**) is prepared by chromyl acetate-mediated allylic oxidation of α,β-unsaturated ester (**21**) in 54% yield (eq 11).[24]



21 **22**

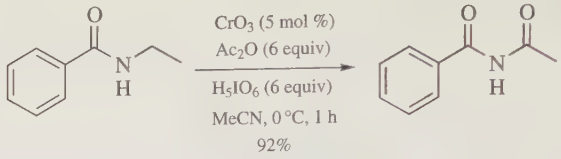
(11)

Oxidation of Iodoarenes. Chromyl acetate in the presence of sulfuric acid effectively oxidizes various iodoarenes to the corresponding $ArI(SO_4)_2$ in good to excellent yields (eq 12). $ArI(SO_4)_2$ is readily converted to $ArI(OAc)_2$ by aqueous ammonium acetate.[25]



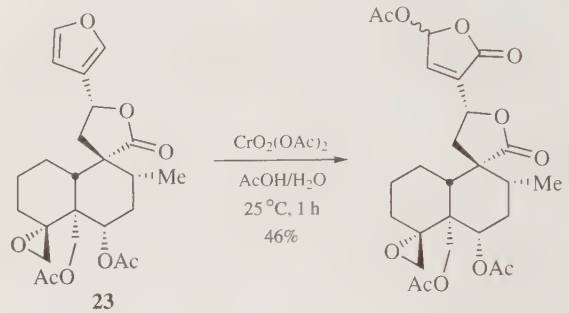
(12)

Oxidation of *N*-Alkylamides to Imides. Chromyl acetate catalyzes the oxidation of *N*-alkylamides to the corresponding imides with periodic acid as co-oxidant in acetonitrile (eq 13).[26] Unlike RuO_4-catalyzed alkylamide oxidation, various functional groups such as carbon-carbon double bonds, carbon-carbon triple bonds, and aromatic rings remain intact under chromyl acetate-catalyzed oxidation.



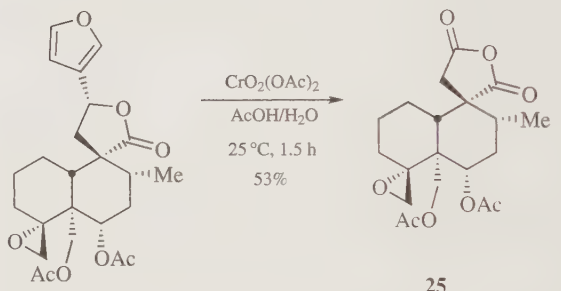
(13)

Oxidation of Heterocyclic Rings. Chromyl acetate oxidatively cleaves various heterocyclic rings effectively. Treatment of montanin C (**23**) with chromyl acetate in acetic acid results in the formation of allylic acetate (**24**) (eq 14). Using the same reagent, but a slightly different procedure, Montanin C (**23**) was converted to anhydride (**25**) (eq 15).[27]



23 **24**

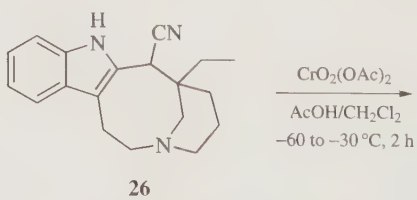
(14)



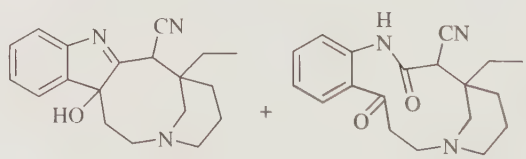
23 **25**

(15)

Oxidation of 3α-cyano-*C*-norquebrachamine (**26**) with chromyl acetate in dichloromethane/acetic acid at low temperature results in β-hydroxy indolenine (**27**) in 52% yield. Further oxidation of the indolenine (**27**) with the same reagent affords indole ring-opened product (**28**) in low yield (eq 16).[28]



26



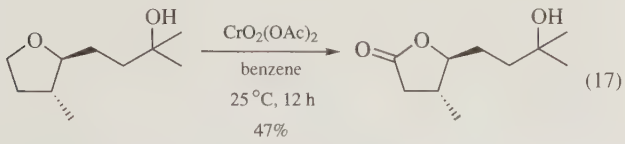
27 **28**

52% 10%

(16)

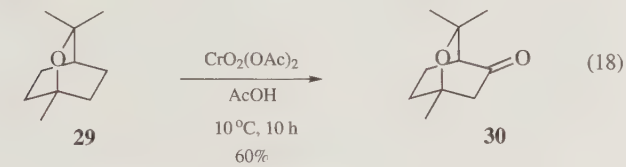
C–H Oxidation of Cyclic Ethers. Chromyl acetate selectively oxidizes C–H bonds adjacent to an oxygen atom. Cyclic

ethers like tetrahydrofuran yield lactones by four-electron chromyl acetate oxidation. In the synthesis of eldanolide, transformation of the tetrahydrofuran-alcohol into the γ-lactone is achieved by the oxidation with chromyl acetate in benzene (eq 17).[29]



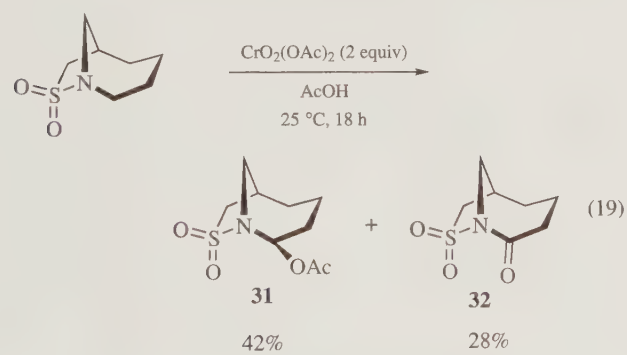
(17)

C–H Oxidation of 2-Oxabicyclo[2.2.2]octane. Chromyl acetate is known to oxidize C–H bonds in bridged polycyclic hydrocarbons. Chromyl acetate attacks the unactivated C-5 methylene group of oxabicyclooctane (**29**) in a highly regioselective way, producing oxabicyclo[2.2.2]octane-5-one (**30**) in 60% yield (eq 18).[30]



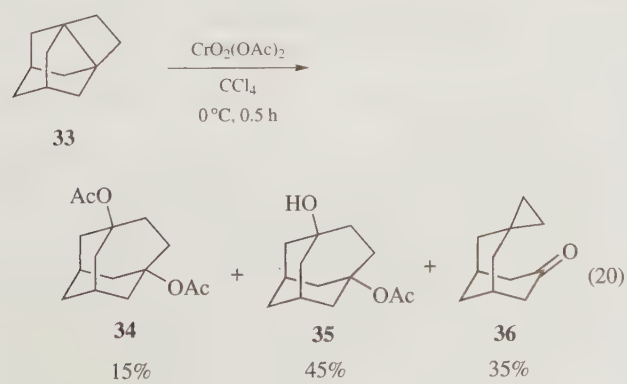
(18)

C–H Oxidation of Bridgehead Sulfonamide. Chromyl acetate is capable of oxidizing nitrogen-activated C–H bonds in bicycloalkanes and polycycloalkanes to give alcohols, acetates, and ketones. Typically, attack occurs at tertiary C–H bonds more rapidly than methylene groups, with methyl groups being unreactive. When tertiary hydrogen is positioned at bridgehead site, the methylene group α to nitrogen in the largest bridge is most reactive, providing acetate (**31**) and keto-sultam (**32**) (eq 19).[31]



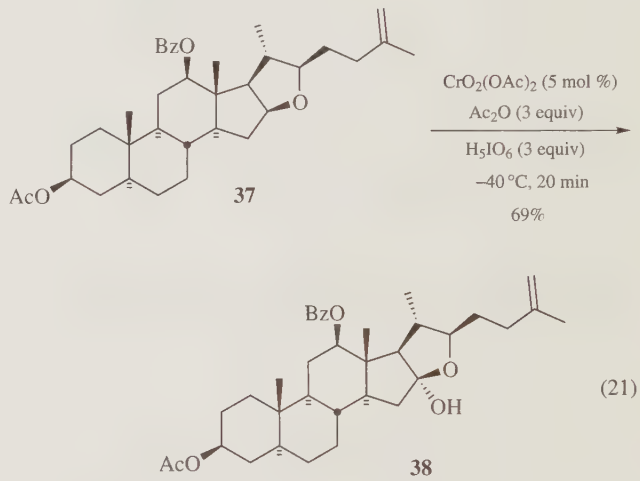
(19)

C–H Oxidation of Propellanes. Propellane (**33**) reacts with chromyl acetate to afford diacetate (**34**), hydroxyacetate (**35**), and spirocyclopropane (**36**). The spirocyclopropane results from the oxidative cyclobutane ring contraction (eq 20).[32]



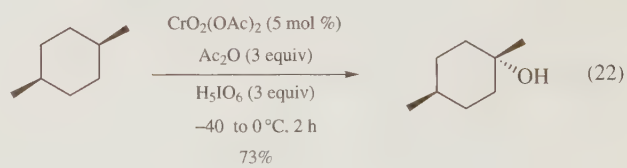
(20)

Catalytic C–H Oxidation with $CrO_2(OAc)_2$ and Periodic Acid. Chromyl acetate together with periodic acid generates a strong C–H oxidant, which enables regio-, stereo-, and chemoselective oxidation of various C–H bonds at low temperature in good to excellent yields.[33] It is proposed that the reactive intermediate is Cr^{VI} monoperoxo species formed from nucleophilic attack of periodic acid on chromyl acetate, followed by loss of iodic acid. It is noteworthy that chromyl acetate-mediated C–H oxidation occurs at −40 °C and the reaction is catalytic in chromium. The C16 position of steroidal cyclic ether (**37**) is oxidized to give hemiacetal (**38**) in good yield. The oxidation-susceptible olefin is inert under these reaction conditions, highlighting the chemoselectivity of the Cr-mediated C–H oxidation (eq 21).

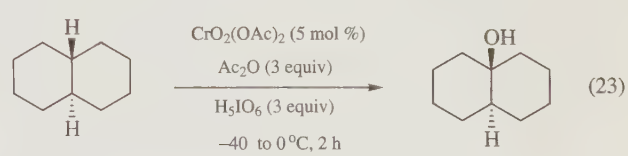


(21)

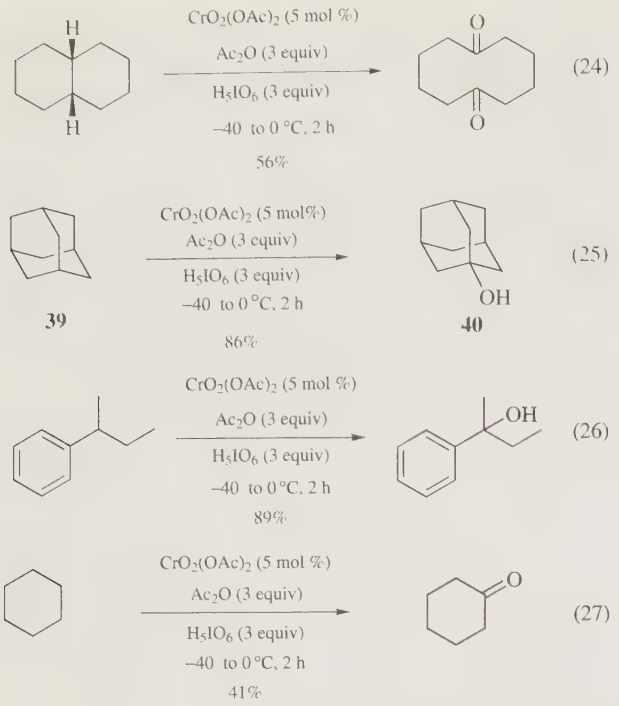
C–H bonds of nonactivated hydrocarbons are readily oxidized to tertiary alcohols or ketones. The reaction is stereospecific with the retention of stereochemistry of the C–H bonds oxidized (eq 22). Unlike *trans*-decalin (eq 23), the oxidation of *cis*-decalin results in diketone formation due to oxidative ring cleavage of the 1,2-diol by periodate (eq 24). Adamantane is an informative substrate for oxidation by chromyl acetate. The bridgehead C–H bond in adamantane is preferentially *mono* oxyfunctionalized to give tertiary alcohol (eq 25). Chromyl acetate oxidizes benzylic C–H bonds to give tertiary alcohols (eq 26). While substantially preferred, the oxidation is not limited to tertiary C–H bonds. Cyclohexane is oxidized to cyclohexanone (eq 27).[33]



(22)



(23)



Related Reagents. Chromium(VI) oxide; dimethyldioxirane (DDO); methyl(trifluoromethyl)dioxirane; periodic acid.

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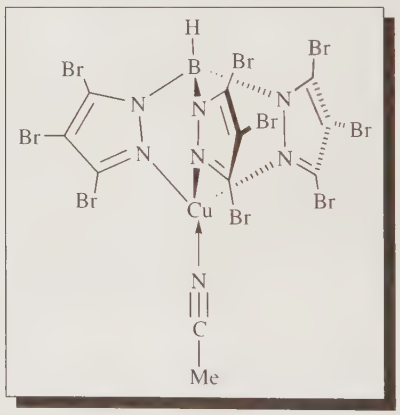
Copper(I){Hydrotris(3,4,5-tribromo)-pyrazolylborate}(acetonitrile)



[501930-73-0] $BBr_9C_{11}CuH_4N_7$ (MW 1027.45)

(reagent used in catalytic transfer of carbenes, from diazo compounds, and nitrenes, from iminoiodinanes)

Solubility: soluble in most common organic solvents, partially soluble in hexane.

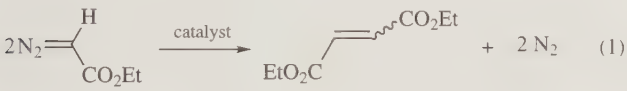
Preparation: this complex was prepared by the direct reaction of CuI and $TlTp^{Br3}$ in acetonitrile. One mmol of the copper salt was reacted with 1 equiv of the thallium salt[1] of the homoscorpionate ligand.[2] The resulting suspension, containing a yellow-greenish solid of thallium iodide, was stirred for 8 h, filtered, and the resulting colorless solution was evaporated under reduced pressure to give the desired complex as a white solid in 80–90% yield.

Purification: the crude solid obtained as described above can be crystallized from saturated acetonitrile solutions upon cooling at −20 °C overnight. White microcrystalline material of analytical purity was collected in 80% yield, suitable for X-ray studies to unambiguously establish the structure in the solid state.[3]

Handling, Storage, and Precautions: this complex is stable toward atmospheric oxygen both in the solid state and in acetonitrile or methylene chloride solutions.

Catalytic Properties.

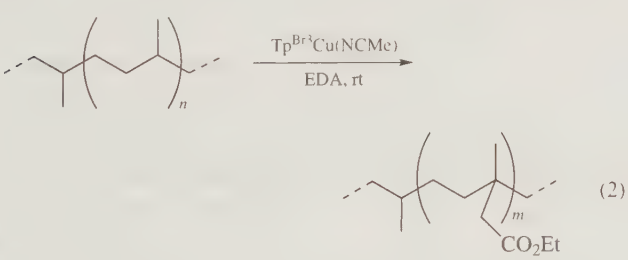
Diazo Decomposition. This compound exhibits catalytic activity toward the decomposition of ethyl diazoacetate N_2CHCO_2Et (EDA) and the subsequent transfer[4] of the $:CHCO_2Et$ unit to a number of saturated and unsaturated substrates. In general, a solution of EDA in methylene chloride is slowly added to a solution containing the catalyst and the substrate (neat or dissolved in methylene chloride). This method is employed to avoid unwanted dimerization of two $:CHCO_2Et$ units to give diethyl fumarate and maleate (eq 1).[4] In other cases, the slow addition can be avoided, and the EDA can be added in one portion.



(1)

Insertion of EDA into Carbon-Hydrogen Bonds: Alkanes and Polyolefins. When alkanes are employed as substrates, insertion of the $:CHCO_2Et$ group into carbon-hydrogen bonds is observed. This procedure has been applied to several alkanes such as pentane, hexane, 2-methylbutane, 2-methylpentane, or 2,3-dimethylbutane (Table 1). Other substrates that undergo similar transformations are cyclic ethers and methyl alkyl ethers. In the latter cases, insertion takes place into C–H bonds adjacent to the oxygen atom.[5]

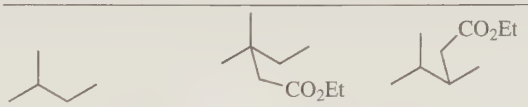
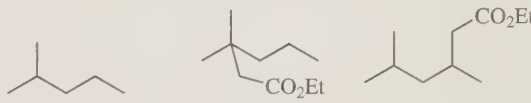
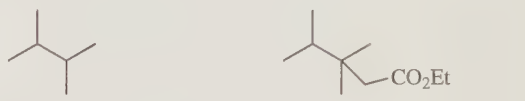
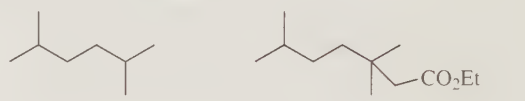
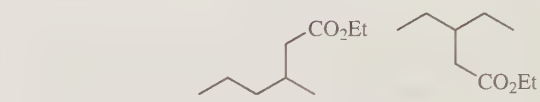
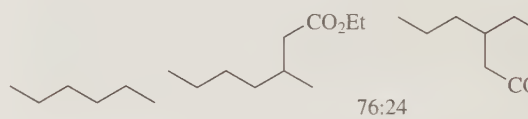
Polyolefins have also been modified following this methodology. The reaction of EDA with polybutene (obtained using Brookhart's catalysts)[6] yields materials with a ca. 10 CO_2Et/1000C ratio of incorporation, exclusively into tertiary C–H bonds (eq 2).[7]



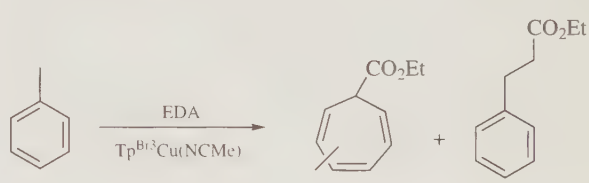
(2)

Other polyolefins such as commercial polyethylene-1-octene (40% w/w in 1-octene) and synthetic polypropylene can also be functionalized by this procedure, with variable degrees of insertion of the polar groups depending on the reaction conditions. Polymer analyses reveal another important feature of this system: the values of M_w, M_n, and PDI of the modified polymers are nearly equal to those of the starting materials, e.g., no C–C scission takes place during the functionalization process.

Table 1 Insertion of ethyl diazoacetate into C–H bonds of alkanes catalyzed by $Tp^{Br3}Cu(NCMe)$

Alkane	Products	Yield (%)
	80:20	53
	62:38	73
		56
		71
	78:22	50
	76:24	60

Reactions of EDA with Arenes and Furans. Arenes[8] and furans[9] have also been treated with EDA in the presence of $Tp^{Br3}Cu(NCMe)$ catalyst. In the case of benzene, a cycloheptatriene derivative is formed via addition of the $:CHCO_2Et$ group to the arene, followed by electrocyclic ring expansion of the bicyclic intermediate. When alkylbenzenes were employed (eq 3), this reaction competes with insertion of EDA into the C–H bonds of the alkyl groups (Table 2).



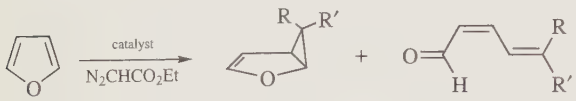
(3)

Table 2 Reactions of ethyl diazoacetate with alkylaromatic substrates with $Tp^{Br3}Cu(NCMe)$ as the catalyst

Substrate	Insertion (%)	Addition (%)
Toluene	8	62
Mesitylene	12	75
Ethylbenzene	30	18

The reaction of EDA and furan in the presence of $Tp^{Br3}Cu(NCMe)$ yields two products, cyclopropanes and dienes,

with two isomers of each type (eq 4) being observed. The activity of this catalyst is comparable to that of dirhodium tetraacetate. The addition of elemental iodine at the end of the reaction induces the well-known transformation of the mixture of dienes in eq 4 into the *E,E*-isomer.



(4)

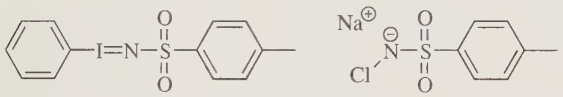
exo: R = H; R′ = CO_2Et 30% R = CO_2Et; R′ =H, *Z,Z isomer* 8%

endo: R = CO_2Et; R′ = H 5% R= H; R′ = CO_2Et, *E,Z isomer* 43%

Reactions of EDA with Alcohols. Alcohols can be readily converted into ethers upon reaction with EDA in the presence of $Tp^{Br3}Cu(NCMe)$ as the catalyst.[10] This procedure provides quantitative yields (based on EDA) of the corresponding ethers, and has been applied to a group of alcohols including linear, branched, allylic, and fluorine-containing alcohols (eq 5).

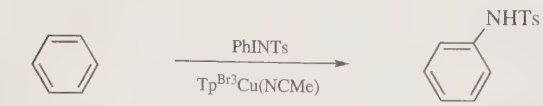
(5)

Nitrene Transfer. In addition to the functionalization of organic substrates by carbene addition or insertion, the complex $Tp^{Br3}Cu(NCMe)$ also displays catalytic activity toward the decomposition of some nitrene sources and the concomitant transfer of the NR group to saturated and unsaturated organic substrates.[11] PhI=NTs (Ts = tosyl) and chloramine-T have both been employed as nitrene sources.



PhINTs Chloramine-T

Amination Reactions by Nitrene Insertion. When catalytic amounts of $Tp^{Br3}Cu(NCMe)$ are added to a suspension of PhI=NTs in benzene or cyclohexane at room temperature, the nitrene unit NTs is transferred into the C–H bonds of both substrates[12] (eqs 6 and 7) in 40% and 65% yield, respectively. The use of toluene or mesitylene leads to a similar transformation, in which the insertion takes place into the methyl C–H bonds in quantitative yield (eqs 8 and 9).



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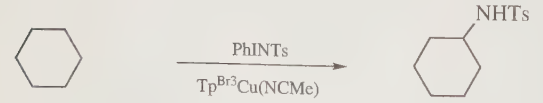

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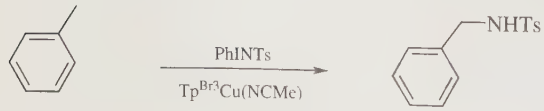

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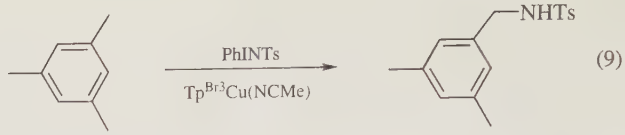
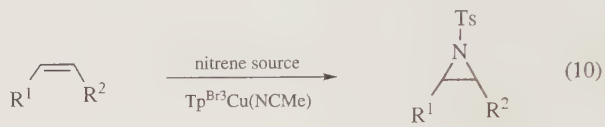


(9)

Olefin Aziridination. The complex $Tp^{Br3}Cu(NCMe)$ also catalyzes the addition of the nitrene unit NTs to unsaturated substrates, such as olefins, in the olefin aziridination reaction (eq 10).[13] In this case, the nitrene sources are the previously mentioned PhI=NTs and the commercially available chloramine-T, which has the advantage of forming environmentally benign sodium chloride as the sole by-product. Yields are quite high for styrene and cyclooctene, but low with the less reactive 1-hexene (Table 3). It is possible to use stoichiometric amounts of the latter nitrene source, but the yield with styrene decreases to 55%.



(10)

Table 3 Olefin aziridination with $Tp^{Br3}Cu(NCMe)$ as the catalyst with chloramines-T as the nitrene source

Entry	Cat.:Chlor.-T	Chlor.-T:Olefin	Styrene	*cis*-Coe	1-Hexene
1	1:20	1:10	96	88	34
2	1:40	1:1	55	-	-

1. Rheingold, A. L.; Liable-Sands, L. M.; Incarvito, C. K.; Trofimenko, S., *J. Chem. Soc. Dalton Trans.* **2002**, 2297.
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5. (a) Caballero, A.; Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J., *J. Am. Chem. Soc.* **2003**, *125*, 1446. (b) Caballero, A.; Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J., *Organometallics* **2003**, *22*, 4145.
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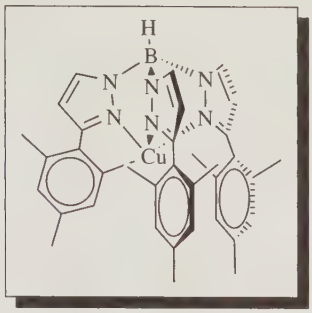
Copper(I),[Hydrotris[3-(2,4,6-trimethylphenyl)-1*H*-pyrazolato-N_1]borato(1-)-$N_2,N'_2N''_2$



[216496-49-0] $BC_{36}CuH_{40}N_6$ (MW 630.36)

(reagent used in the catalytic transfer of carbene, from diazo compounds, and nitrene, from iminoiodinanes, groups)

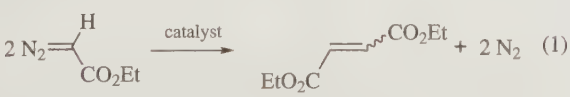
Solubility: soluble in most common organic solvents, partially soluble in hexane.

Preparation: this complex is prepared by the direct reaction of CuI and $TlTp^{Ms}$ in methylene chloride.[1] One mmol of the copper salt was reacted with 1 equiv of the thallium salt of the homoscorpionate ligand.[2] The resulting suspension, containing a yellow-greenish solid of thallium iodide, was stirred for 8 h, filtered, and the resulting colorless solution was evaporated under reduced pressure to give the desired complex as a white solid in 80–90% yield.

Purification: the crude solid obtained as described above can be crystallized from saturated methylene chloride-hexane solutions upon cooling at −20 °C overnight. White microcrystalline material of analytical purity was collected in 85% yield.

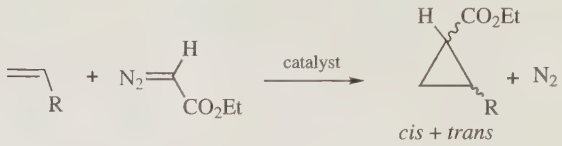
Handling, Storage, and Precautions: this complex is stable toward atmospheric oxygen in the solid state, but somewhat unstable when dissolved in organic solvents.

Diazo Decomposition. This compound exhibits catalytic activity toward decomposition of ethyl diazoacetate N_2CHCO_2Et (EDA) and subsequent transfer[3] of the $:CHCO_2Et$ unit to a number of saturated and unsaturated substrates. In general, a solution of EDA in methylene chloride is slowly added to a solution containing the catalyst and the substrate (neat or dissolved in methylene chloride). This method is employed to avoid unwanted dimerization of two $:CHCO_2Et$ units to give diethyl fumarate and maleate (eq 1).[3] In other cases, the slow addition can be avoided, and the EDA added in one portion.



(1)

Olefin Cyclopropanation. The complex Tp*Cu is known to catalyze the conversion of olefins and ethyl diazoacetate into cyclopropanes.[4] The $Tp^{Ms}Cu$ complex also catalyzes this transformation (eq 2) and provides 96% diastereomeric excess of the *cis*-isomer, in reaction with styrene.[5] This catalytic behavior is general with an array of terminal olefins, giving preferential *cis*-cyclopropanation with these substrates (Table 1).[6] The amounts of diethyl fumarate and maleate, formed from catalytic coupling of ethyl diazoacetate, are quite low.



(2)

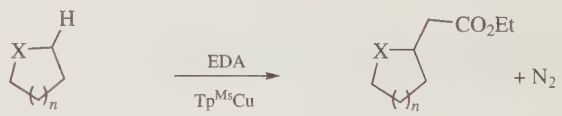
Table 1 Olefin cyclopropanation reaction catalyzed by $Tp^{Ms}Cu$

Olefin	Yield (%)	*cis*:*trans*	de[a]
3,3′-Dimethyl-1-butene	82	65:35	30
2,5-Dimethyl, 2,4-hexadiene	97	78:22	56
1-Hexene	84	77:23	54
1-Octene	80	75:25	50
Vinyl-acetate	87	92:8	84
n-Butyl vinyl ether	97	79:21	58
Styrene	>98	98:2	96
α-Methylstyrene	98	97:3	94

[a]Diastereomeric excess.

This complex can also be employed as the catalyst for the cyclopropenation of 3-hexyne,[7] although the yields are lower than in reactions using 3-alkyl-pyrazolyl-containing Tp^x ligands.

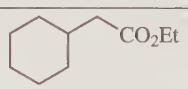
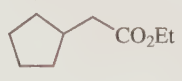
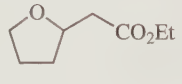
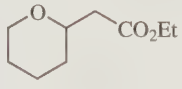
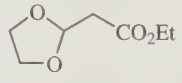
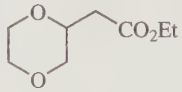
Insertion of EDA Into Carbon Hydrogen Bonds. The complex $Tp^{Ms}Cu$ is capable of inducing the insertion of EDA into the C–H bonds of cycloalkanes in moderate yield, as well as for insertion into the α-C–H bonds of cyclic ethers in high yield (eq 3, Table 2).[8]



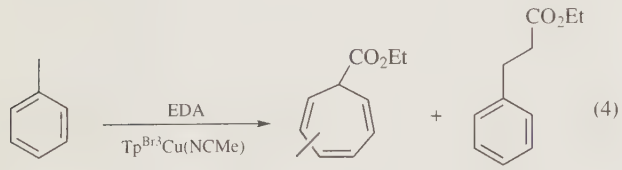
(3)

X = O, CH_2 X = O, CH_2

Table 2 C–H functionalization by carbene insertion with $Tp^{Ms}Cu$

Substrate	Product	Yield (%)
Cyclohexane		54
Cyclopentane		50
Tetrahydrofuran		95
Tetrahydropyran		84
Dioxolane		95
Dioxane		20

Reactions of EDA with Arenes and Furans. Arenes[9] and furans[10] have also been treated with EDA in the presence of $Tp^{Ms}Cu$ as the catalyst. In the case of benzene, a cycloheptatriene derivative is formed via addition of the :$CHCO_2Et$ group to the arene, followed by electrocyclic ring expansion of the bicyclic intermediate. When alkylbenzenes were employed (eq 4), this reaction competes with insertion of EDA into the C–H bonds of the alkyl groups (Table 3).

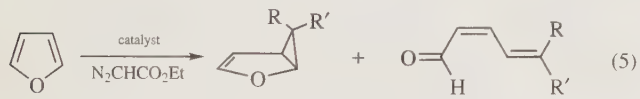


(4)

Table 3 Reactions of ethyl diazoacetate with alkylaromatic substrates with $Tp^{Ms}Cu$ as the catalyst

Substrate	Insertion (%)	Addition (%)
Toluene	20	nd
Mesitylene	30	<5
Ethylbenzene	56	nd

The reaction of EDA and furan in the presence of $Tp^{Ms}Cu$ yields two products, cyclopropanes and dienes, with two isomers of each type (eq 5) being observed. The activity of this catalyst is comparable to that of dirhodium tetraacetate. The addition of elemental iodine at the end of the reaction induces the well-known transformation of the mixture of dienes in eq 5 into the *E,E*-isomer.



(5)

exo: R = H; R′ = CO_2Et 30% R = CO_2Et; R′ =H, *Z,Z isomer* 9%

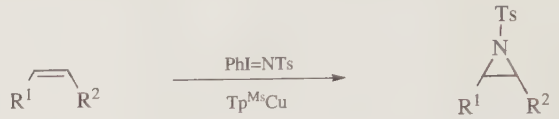
endo: R = CO_2Et; R′ = H 6% R= H; R′ = CO_2Et, *E,Z isomer* 32%

Reactions of EDA with Amines and Alcohols. Alcohols and amines can be functionalized at the X–H bond upon reaction with EDA in the presence of $Tp^{Ms}Cu$ as the catalyst.[11,12] This procedure provides very high yields (based on EDA) in the corresponding ethers or amino acid derivatives (eqs 6 and 7), respectively.

(6)

(7)

Nitrene Transfer. In addition to the functionalization of organic substrates by carbene addition or insertion, the complex $Tp^{Ms}Cu$ also displays catalytic activity toward the decomposition of some nitrene sources and the concomitant transfer of the NR group to olefins, in the aziridination reaction (eq 8).[13] Styrene, *cis*-cyclooctene, and 1-hexene were converted into the corresponding aziridines, using PhI = NTs as the nitrene source, in 95%, 82%, and 62% yield, respectively.



(8)

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13. Mairena, M. A.; Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J., *Organometallics* **2004**, *23*, 253.

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Copper(II) Acetate[1]

$Cu(OAc)_2$

[142-71-2] $C_4H_6CuO_4$ (MW 181.64)

(oxidizes carbanions,[2] radicals[3] and hydrocarbons;[4] for oxidative coupling and solvolytic cleavage of Si–C,[5] Bi–C, Pb–C, and Sb–C bonds; rapid radical scavenger; catalyst for cyclopropanation of alkenes with diazo esters;[6] Lewis acid catalyst)

Alternate Name: cupric acetate.

Physical Data: blue crystals, mp 130–140 °C (dec); *d* 1.92–1.94 g cm^{-3}.[7]

Solubility: soluble in H_2O (6.79 g/100 mL, 25 °C); soluble in AcOH, pyridine; insoluble in ether.

Form Supplied in: widely available; the anhydrous salt can be prepared from the usually available monohydrate $Cu(OAc)_2 \cdot H_2O$ *[6046-93-1]* by heating to 90 °C until constant weight[7,8] or by refluxing $Cu(OAc)_2 \cdot H_2O$ in acetic anhydride and washing the insoluble product with Et_2O.[9]

Analysis of Reagent Purity: iodometric titration;[10] atomic absorption spectroscopy.[11]

Purification: recrystallize (as monohydrate) from warm dil HOAc.[57]

Handling, Storage, and Precautions: must be stored in the absence of moisture; is decomposed on heating to hydrogen and $Cu^{I}OAc$.[7] Irritating to skin, eyes, and respiratory system. May be dissolved in a combustible solvent for incineration.

Original Commentary

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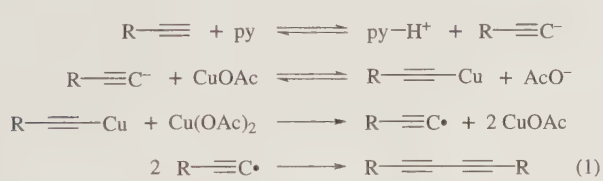
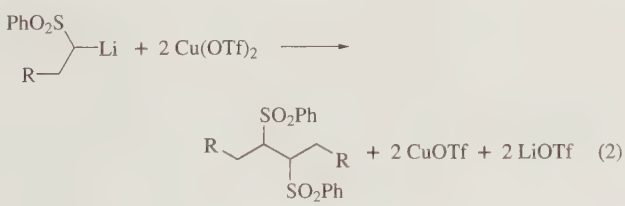
Oxidation of Carbanions. Oxidative coupling of terminal alkynes to diynes (eq 1) with $Cu(OAc)_2$ and ***Pyridine*** can be carried out in MeOH or in benzene/ether.[2] The reaction requires the presence of copper(I) salt; the rate-determining step corresponds to the formation of the Cu^{I} acetylide.[12]

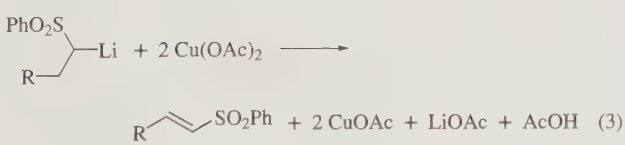


(1)

While α-sulfonyl lithiated carbanions are oxidatively coupled with ***Copper(II) Trifluoromethanesulfonate*** (eq 2), $Cu(OAc)_2$ oxidizes them to the corresponding (*E*)-α,β-unsaturated sulfones (eq 3).[13]



(2)

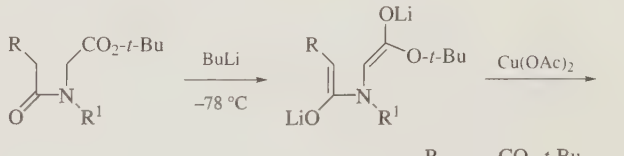


(3)

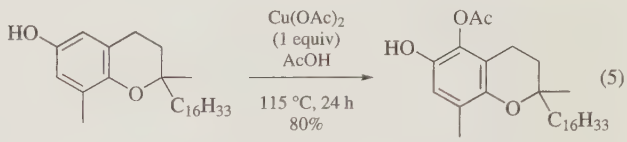
Other carbanions can be coupled oxidatively by $Cu(OAc)_2$, as shown in the synthesis of β-lactams (eq 4).[14]

In the presence of ***1,4-Diazabicyclo[2.2.2]octane*** in DMF, the complex of $Cu(OAc)_2$ and 2,2′-bipyridyl catalyzes the oxygenation of α-branched aldehydes with O_2 to ketones.[15]

Carbon–Hydrogen Bond Oxidations. *Ortho* hydroxylation of phenols with O_2 is catalyzed by a complex of $Cu(OAc)_2$ and ***Morpholine*** (soluble in EtOH).[16] In the absence of O_2, *ortho* acetoxylation of phenols can be induced with equimolar amounts of $Cu(OAc)_2$ in AcOH (eq 5).[17]

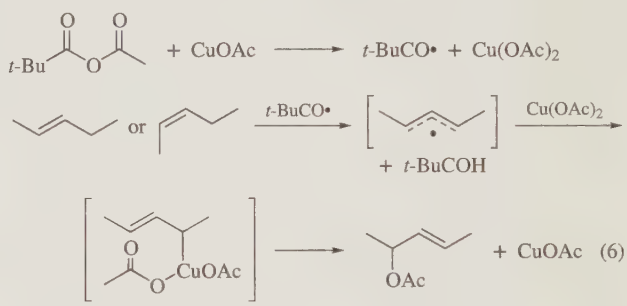


(4)



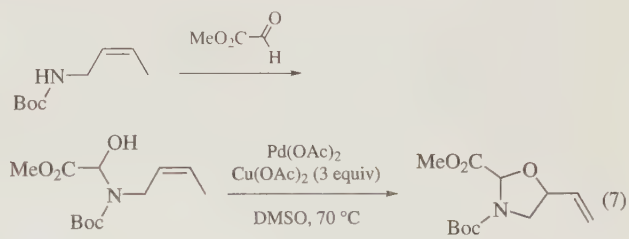
(5)

Allylic hydrogens are replaced by acyloxy groups by reaction of peroxy esters in the presence of catalytic amounts of copper salts, including $Cu(OAc)_2$.[18] The reaction probably proceeds via the formation of an allylic radical, which reacts quickly with Cu^{II} to form a Cu^{III} intermediate that generates the most substituted alkene, probably via a pericyclic transition state (eq 6).[19] Allylic oxidation can be enantioselective when performed in AcOH and ***Pivalic Acid*** in the presence of $Cu(OAc)_2$ and an L-amino acid.[20]



(6)

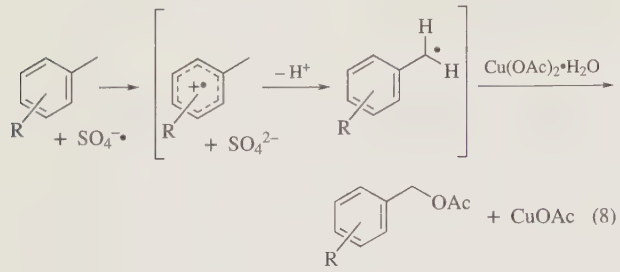
Allylic oxidation of cyclohexene and related alkenes can be achieved with catalytic amounts of ***Palladium(II) Acetate***, $Cu(OAc)_2$, hydroquinone, and O_2 as oxidant in AcOH, leading to allylic acetates.[21] Methyl glyoxylate adducts of *N*-Boc-protected allylic amines cyclize, in the presence of catalytic $Pd(OAc)_2$ and an excess of $Cu(OAc)_2$ in DMSO at 70 °C, to 5-(1-alkenyl)-2-(methoxycarbonyl)oxazolidines (eq 7).[22]



(7)

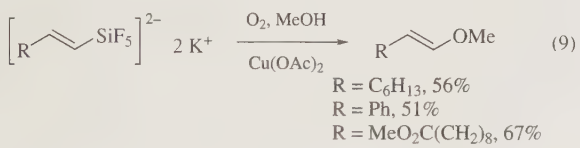
Methyl substituted benzene derivatives are oxidized in boiling AcOH to the corresponding benzyl acetates (eq 8) with sodium, potassium, or ***Ammonium Peroxydisulfate***, $Cu(OAc)_2 \cdot H_2O$, and NaOAc.[4] The peroxydisulfate radical is responsible for the primary oxidation, whereas $Cu(OAc)_2$ prevents dimerization of the intermediate benzylic radical by oxidizing it to benzyl acetate.

The benzylic acetoxylation of alkyl aromatics can also be carried out with O_2 using $Pd(OAc)_2$ and $Cu(OAc)_2$ as catalysts.[23]

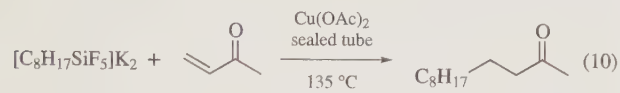


Cycloalkanes are transformed into the corresponding cycloalkenes by treatment with ***t-Butyl Hydroperoxide*** in pyridine/AcOH solution containing $Cu(OAc)_2 \cdot H_2O$. When Fe^{III} salts are used instead of $Cu(OAc)_2 \cdot H_2O$, the major product is the corresponding cycloalkanone.[24] Cyclohexanone is the main product of cyclohexane oxidation with H_2O_2, $Cu(OAc)_2 \cdot H_2O$ in pyridine, and AcOH (GoCHAgg system).[25] $Cu(OAc)_2$ also catalyzes the oxidation of secondary alcohols by ***Lead(IV) Acetate***.[26]

Carbon–Metal Bond Oxidations. In MeOH and under O_2 atmosphere, a catalytic amount of $Cu(OAc)_2$ promotes the cleavage of the Si–C bond of (*E*)-alkenylpentafluorosilicates to give alkenyl ethers (eq 9). The reaction is highly stereoselective and leads to the (*E*)-enol ethers. In the presence of H_2O the corresponding aldehydes are obtained.[5]

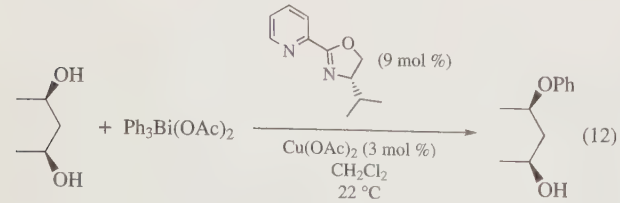


In the presence of $Cu(OAc)_2$, 1,4-additions of alkylpentafluorosilicates to α,β-unsaturated ketones take place on heating (eq 10).[5] This reaction proceeds probably by initial one-electron oxidation with formation of an alkyl radical (eq 11), which then adds to the enone.



$$RSiF_5^{2-} + CuX_2 \longrightarrow R\bullet + [XSiF_5]^{2-} + CuX \quad (11)$$

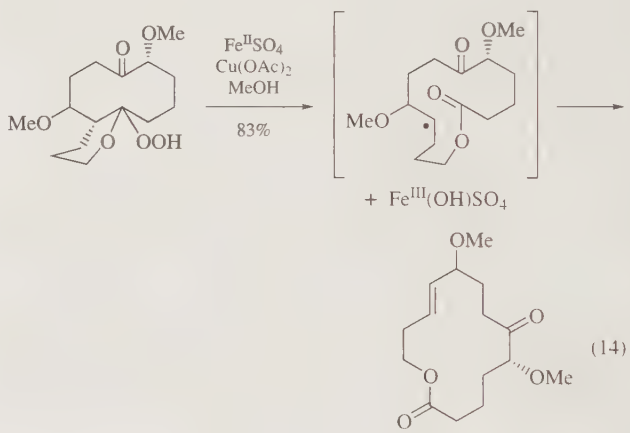
The monophenylation of 1,*n*-diols with ***Triphenylbismuth Diacetate***[27] is greatly accelerated by catalytic amounts of $Cu(OAc)_2$.[28] This reaction can be enantioselective in the presence of optically active pyridinyloxazoline ligands as cocatalysts (eq 12).[29] Reaction of alcohols (ROH) with ***Triphenylbismuthine*** and $Cu(OAc)_2$ gives the corresponding phenyl ethers (PhOR) and benzene.[30] The treatment of Ph_5Sb with a catalytic amount of $Cu(OAc)_2$ in toluene at 20 °C gave 100% yields of Ph_3Sb, Ph–Ph, and PhH.[31] $Cu(OAc)_2$ catalyzes the arylation of amines by diaryliodonium salts,[32] aryl halides,[33] $Ph_3Bi(OCOCF_3)_2$,[34] and aryllead triacetates.[35]



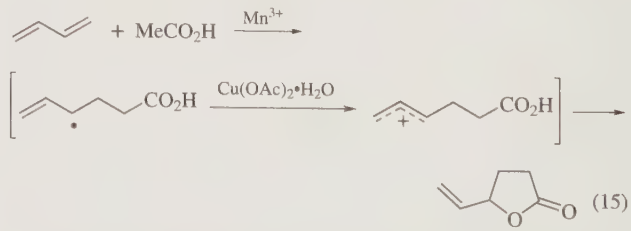
Fast Radical Scavenging and Oxidation. Rates of oxidative decarboxylation by $Pb(OAc)_4$ of primary and secondary carboxylic acids to alkenes[36] are enhanced in the presence of catalytic amounts of $Cu(OAc)_2$ or $Cu(OAc)_2 \cdot H_2O$. This effect is attributed to the fact that the rate of one-electron-transfer oxidation of alkyl radicals by Cu^{II} salts (eq 13) approaches a diffusion-controlled rate.[3] Oxidative decarboxylation of carboxylic acids can also be carried out with ***(Diacetoxyiodo)benzene*** in the presence of a catalytic amount of anhydrous $Cu(OAc)_2$.[37]

$$\begin{aligned} RCO_2Pb(OAc)_3 &\longrightarrow R\bullet + CO_2 + Pb(OAc)_3 \\ R\bullet + Cu(OAc)_2 &\longrightarrow \text{alkene} + CuOAc + AcOH \\ CuOAc + RCO_2Pb(OAc)_3 &\longrightarrow Cu(OAc)_2 + RCO_2Pb(OAc)_2 \\ RCO_2Pb(OAc)_2 &\longrightarrow R\bullet + CO_2 + Pb(OAc)_2 \end{aligned} \quad (13)$$

The case of radical oxidation with $Cu(OAc)_2$ has been exploited by Schreiber[38] in the fragmentation of α-alkoxyhydroperoxides, as in eq 14.[38b]

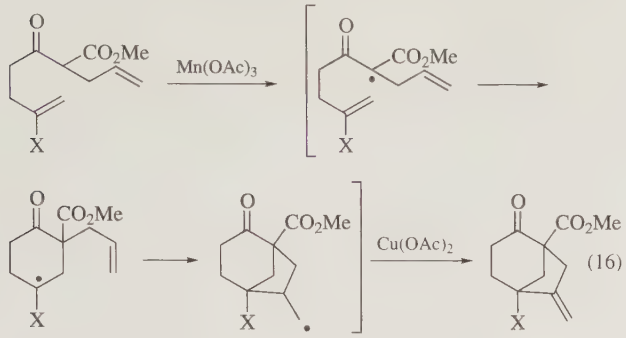


In an electrochemical system containing ***Manganese(III) Acetate***, acetic acid is added to butadiene to generate an allylic radical intermediate that is oxidized with $Cu(OAc)_2 \cdot H_2O$ to the corresponding allylic cation, leading to γ-vinyl-γ-butyrolactone (eq 15),[39] a precursor in the industrial synthesis of sorbic acid.



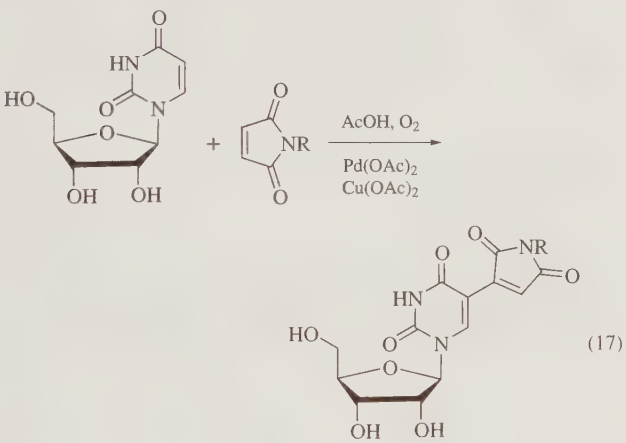
β-Oxoesters are oxidized with $Mn(OAc)_3$ to the corresponding radicals that can add intermolecularly[40] or intramolecularly (eq 16)[41] to generate alkyl radicals. In the presence of $Cu(OAc)_2$ the latter are rapidly quenched and oxidized to give alkenes. Radical arylation with alkyl iodides can be induced with ***Dibenzoyl Peroxide***; the yield of the reaction can be improved using a catalytic amount of $Cu(OAc)_2 \cdot H_2O$,[42] which minimizes hydrogen

abstraction by the intermediate radical but introduces a competitive electron-transfer oxidation of the intermediate radical. The oxidative addition of disulfides to alkenes (Trost hydroxysulfenylation[43]) can be promoted by catalytic amounts of $Cu(OAc)_2$.[44]



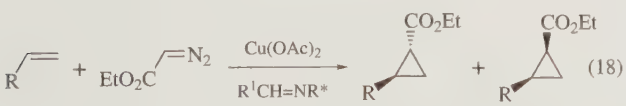
(16)

Reoxidant in Palladium-Catalyzed Reactions. $Cu(OAc)_2$ has been used as a reoxidant in the Wacker oxidation ($CH_2=CH_2 + O_2 \rightarrow CH_3CHO$)[45] and in the $Pd(OAc)_2$-catalyzed alkenylation of aromatic compounds with alkenes[46] (eq 17).[47] $Pd(OAc)_2$ and $Cu(OAc)_2$ are effective catalysts for the reactions of nitrosobenzenes with carbon monoxide, dioxygen, and alcohols that give the corresponding *N*-alkylcarbamates.[48]



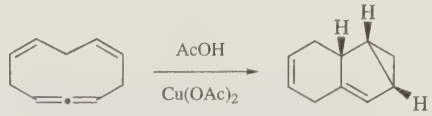
(17)

Enantioselective Cyclopropanation. $Cu(OAc)_2$ has been used as procatalyst in the asymmetric cyclopropanation[49] of alkenes with alkyl diazoacetates with optically pure imines as cocatalyst (eq 18).[6]



(18)

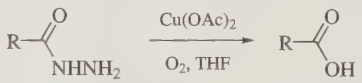
$Cu(OAc)_2$ as Lewis Acid. Decarboxylation of L-tryptophan into L-tryptamine proved most effective in HMPA in the presence of $Cu(OAc)_2$.[50] In boiling MeCN and under $Cu(OAc)_2 \cdot H_2O$ catalysis, aldoximes are converted smoothly into nitriles.[51] In the presence of various Lewis acids including $Cu(OAc)_2$, cyclodeca-1,2,5,8-tetraene is rearranged to *cis,syn*-tricyclo[4.4.0.$0^{2,4}$]deca-5,8-diene (eq 19).[52]



(19)

The Michael reaction of $O_2NCH_2CO_2R$ (R = Me, Bn) with $R^1COCH{=}CHR^2$ (R^1 = Me, Et, R^2 = H; $R^1 = R^2$ = Me) is catalyzed by $Cu(OAc)_2$ and gives $R^1COCH_2CHR^2CH(NO_2)CO_2R$ in dioxane at 100 °C.[53] Knoevenagel condensation of *t*-butyl malonate with ***Paraformaldehyde*** to give di-*t*-butyl methylidenemalonate can be achieved in the presence of KOH and $Cu(OAc)_2$.[54] Lithium imine anions of α-amino esters undergo $Cu(OAc)_2$-catalyzed reactions with α,ω-dihalogenoalkanes to give the corresponding ω-halogenoalkylimines.[55] $Cu(OAc)_2$ catalyzes the coupling of PhYbI with *n*-BuI, giving *n*-BuPh and Ph–Ph.[56]

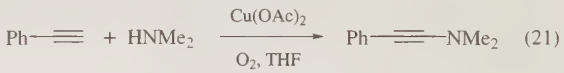
Acyl hydrazides are converted to the corresponding carboxylic acids by bubbling oxygen through a THF or MeOH solution containing the hydrazide and a catalytic amount of $Cu(OAc)_2$ (eq 20).[58]



R = alkyl, aryl

(20)

Synthesis of Ynamines. Phenylacetylene reacts with dimethylamine under $Cu(OAc)_2$ catalysis to produce *N,N*-dimethyl-2-phenylethynylamine (eq 21).[59] The reaction is effected by bubbling oxygen through a benzene solution of the reagents and $Cu(OAc)_2$; in the absence of oxygen, 1,4-diphenylbutadiyne is the sole product. This may be suppressed by adding a reducing agent, such as hydrazine, to the reaction mixture.

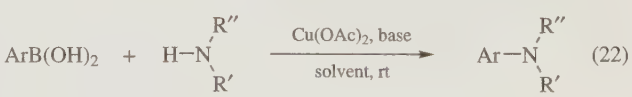


(21)

First Update

Jiri Srogl
Emory University, Atlanta, GA, USA

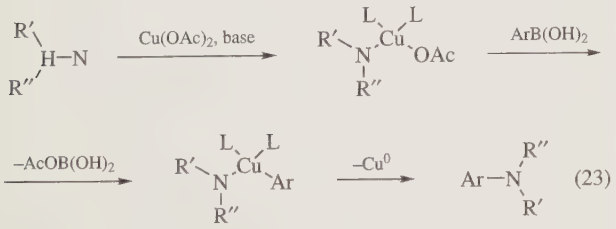
Oxidative N-Arylation. $Cu(OAc)_2$ has been shown to facilitate synthetically useful oxidative formation of carbon-nitrogen bonds. The amination of various boronic acids, pioneered by Lam et al.,[60] has been employed as a mild alternative to aromatic amination of aryl halides.[61] Various aryl and vinylboronic compounds were aminated in presence of a base and either a stoichiometric[60,62] or a catalytic[63,64] amount of $Cu(OAc)_2$; in the latter case with air as the oxidant and myristic acid as a co-catalyst (eq 22).[63,64] Dichloromethane or toluene were the solvents of choice. The influence of various oxidants and co-oxidants on the reaction process was also examined.[64]



(22)

Nitrogen substrates such as aliphatic amines,[63] α-aminoesters,[62b] nitrogen containing heteroaromatics,[60,62a,c,d] amides,[62a] aziridines,[65] and sulfonamides[62a] were used with success in this mild reaction. In a pursuit of combinatorial libraries the process was also successfully extended to various solid supported nitrogen-bearing substrates.[66]

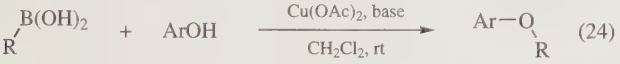
The suggested mechanism (eq 23) of the *N*-arylation starts with formation of a copper (II) –amine complex. Transmetallation by the arylboronic acid followed by reductive elimination finally affords the *N*-aryl product.[62d]



(23)

Other organometaloids also undergo similar reactions. Analogous $Cu(OAc)_2$ mediated reaction of aryltins,[62d] arylsiloxanes,[67] arylbismuth compounds,[68] and arylleads[69] with various amines leads to arylated products in good yields. An interesting modification of amine or amide arylation by aryl boronic acids mediated by *polymer supported* $Cu(OAc)_2$ was reported:[70] immobilization of $Cu(OAc)_2$ on Wang resin provided the air stable catalyst which could be recycled without loss of activity.

O-Arylation and O-Vinylations. When aryl[62a,71] or vinyl boronic[64,72] acids are treated with $Cu(OAc)_2$ in the presence of base and a phenol, *O*-arylation occurs giving aromatic aryl or vinyl ethers in good to excellent yields under very mild conditions (eq 24). As in the *N*-arylation case, both catalytic[64] and stoichiometric[71,72] versions were developed. Air, TEMPO, or pyridine *N*-oxide were used as the oxidants/co-oxidants in the catalytic version of the reaction.[64]



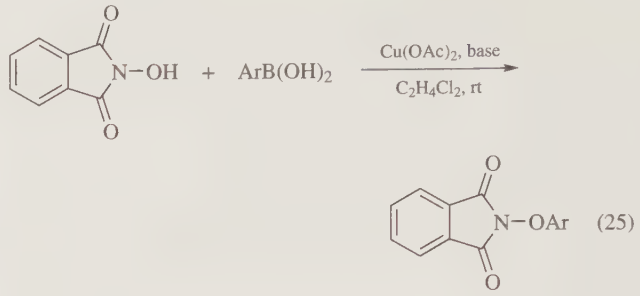
(24)

R = aryl, vinyl

The reaction was also extended to aliphatic alcohols. In this case more reactive aryltrifluoroborates had to be used instead of boronic acids to give good to excellent yields of arylalkyl ethers.[73] As with amination, successful results were obtained with $Cu(OAc)_2$ immobilized on a solid support.[70] *N*–Substituted hydroxylamines were also employed as substrates in the oxidative *O*-arylation. Thus *N*-hydroxyphthalimide was treated with excess arylboronic acids in the presence of $Cu(OAc)_2$, base, and molecular sieves to give *O*-aryloxyamines in good to excellent yields (eq 25).[74]

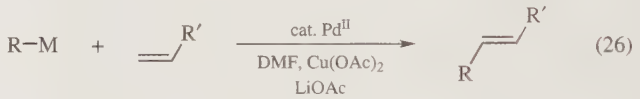
Oxidative S-Arylation. When arylboronic acids were treated with thiols in the presence of $Cu(OAc)_2$ and base in refluxing DMF, sulfides were formed in good to excellent yields.[75]

Oxidative Dimerization of Arylboronic Acids. $Cu(OAc)_2$ was shown to mediate dimerization of various arylboronic acids forming symmetric biaryls in good yields.[76] The oxidative homocoupling proceeds smoothly at rather elevated temperatures with $Cu(OAc)_2$ present in catalytic or stoichiometric amounts. In an earlier case air was employed as an oxidant. The mechanism presumably involves transmetallation of arylboronic acids by copper followed by dimerization of the organocopper intermediate, followed by reductive elimination to give the product.[76]



(25)

Oxidations. $Cu(OAc)_2$ has been used as a reoxidant in Pd catalyzed reactions of aryl and alkenyl boronic acids with alkenes and alkynes,[77] aryltins,[78] and aryl or alkenyl silanols with electron deficient olefins (eq 26).[78a,79] This Mizoroki-Heck type reaction supposedly[77–79] proceeds through a Pd(II)-boron transmetallation step, followed by addition across the double (triple) bond and final β-hydride elimination. $Cu(OAc)_2$ serves as the final reoxidant of Pd(0). LiOAc has been typically added as a co-catalyst.

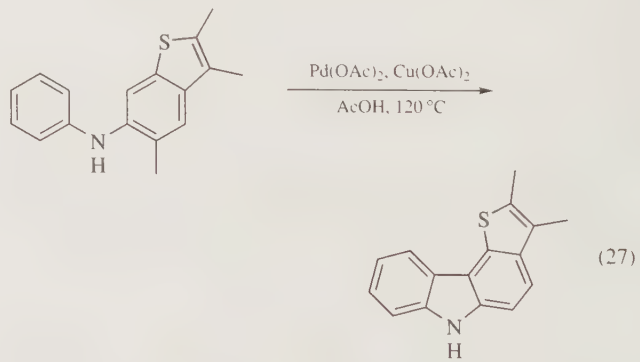


(26)

R = aryl, vinyl

M = $B(OH)_2$, $SnBu_3$, $SiMe_2OH$

$Pd(OAc)_2$ catalyzed intramolecular aromatic annulation with oxidative C–H bond activation was reported.[80] $Cu(OAc)_2$ was used as the reoxidant for the Pd catalyst (eq 27).

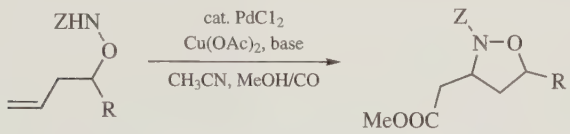


(27)

In cyclization reactions, isooxazolidines were obtained when *O*-homoallylhydroxylamides possessing a terminal double bond were treated with MeOH and CO in the presence of $PdCl_2$, $Cu(OAc)_2$, and base (eq 28).[81] When unprotected *O*-homoallylhydroxylamines were used as substrates no cyclization occurred. In this chemistry $Cu(OAc)_2$ again plays the role of palladium reoxidant.

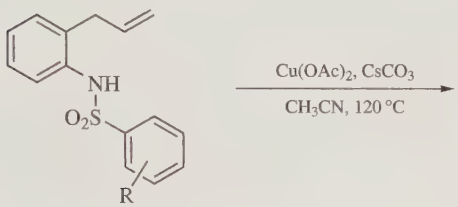
An interesting oxidative cyclization reaction mediated by $Cu(OAc)_2$ has been reported in which, unlike previous cases, the cyclic product was formed in absence of a Pd based catalyst

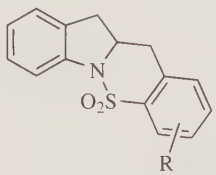
(eq 29).[82] Both, radical and ionic, mechanisms have been elaborated: the first begins with one electron oxidation of sulfonamidic nitrogen while the second one includes formation of a nitrogen-copper bond, followed by migratory insertion to the double bond.



(28)

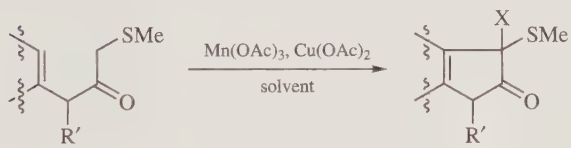
Z = COOMe, Ns, Cbz, Boc





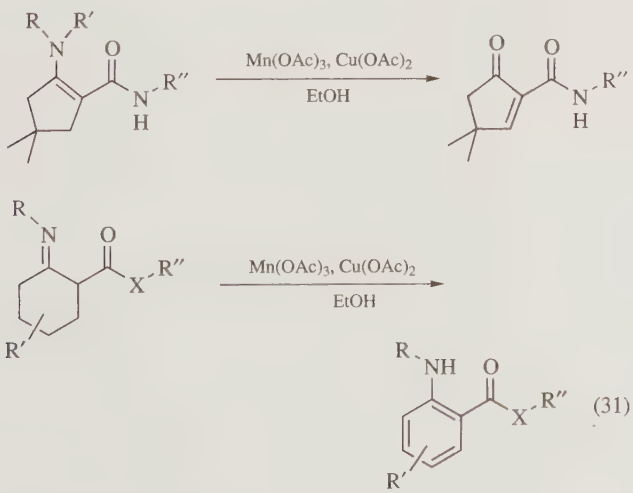
(29)

Oxidative radical cyclization of various substituted α-methylthioacetamides has been facilitated by $Cu(OAc)_2$ in the presence of $Mn(OAc)_3$ (eq 30).[83] Although the reaction proceeded to some extend with $Cu(OAc)_2$ alone, the omission of $Mn(OAc)_3$ led to considerably lower yields of the desired product(s).[83a]



(30)

The $Cu(OAc)_2$, $Mn(OAc)_3$ dyad was found to facilitate oxidative transformation of cyclic β-enaminoamides and β-enamidoesters to α,β-unsaturated imines, azadienes, and anilines (eq 31).[84]

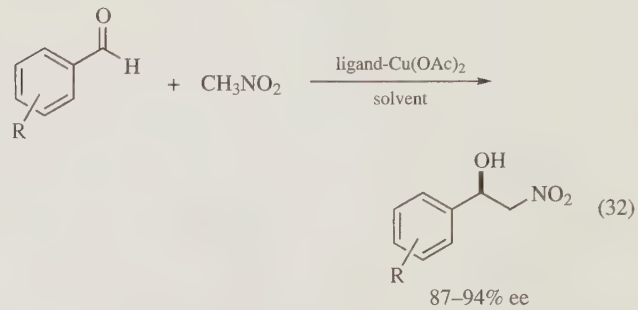


(31)

Enantioselective Cyclopropanation. Chiral $Cu(OAc)_2$ based complexes of Schiff bases have been used as carbene transfer reagents in an asymmetric cyclopropane forming reaction.[85]

$Cu(OAc)_2$ as Lewis Acid.

Henry Reactions. An enantioselective nitroaldol reaction was catalyzed by a $Cu(OAc)_2$ -oxazoline complex.[86] Various aldehydes were treated with nitromethane in the presence of the copper catalyst giving the desired β-nitroalcohols in good to excellent yields and enantiomeric excesses (eq 32).

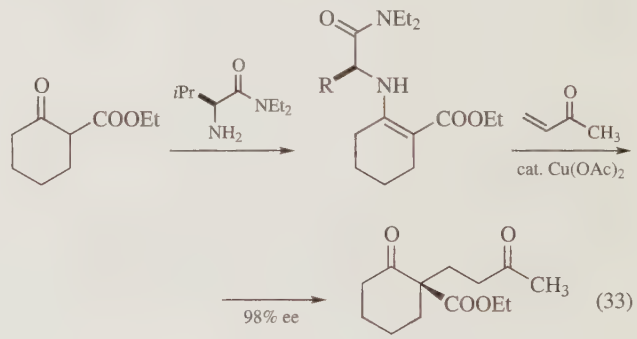


(32)

87–94% ee

Under the reaction conditions the featured copper complex was found to be superior to Mn, Co, Ni, Mg, and Zn complexes.

Michael Additions. $Cu(OAc)_2$ in combination with chiral ligands has been extensively utilized as a catalyst for enantioselective conjugate-additions of organometallics[87] and active methylene substrates[88] to α,β-unsaturated systems. The latter process, in particular, has been very useful synthetically, leading to the formation of quaternary chiral centers under mild, neutral conditions.[88a] Easily accessible natural α-amino acids or their derivatives were employed as efficient chiral auxiliaries and these could be recovered at the end of the reaction (eq 33).[88a]



(33)

R configuration

Related Reagents. Copper(I) acetate; copper(II) acetate–Iron(II) sulfate; iodine–copper(II) acetate; lead(IV) acetate–copper(II) acetate; manganese(III) acetate–copper(II) acetate; sodium hydride–copper(II) acetate–sodium t-pentoxide; zinc–copper(II) acetate–silver nitrate.

1. *Fieser & Fieser* **1967**, *1*, 157, 159; **1969**, *2*, 18, 84; **1972**, *3*, 65; **1974**, *4*, 105; **1975**, *5*, 156; **1977**, *6*, 138; **1979**, *7*, 126; **1982**, *10*, 103; **1986**, *12*, 140; **1990**, *15*, 99.
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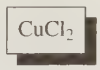
Copper(II) Chloride



[7447-39-4]	$CuCl_2$	(MW 134.45)
$(\cdot 2H_2O)$		
[10125-13-0]	$Cl_2CuH_4O_2$	(MW 170.48)

(chlorinating agent; oxidizing agent; Lewis acid)

Physical Data: anhydrous: *d* 3.386 g cm^{-3}; mp 620 °C (reported mp of 498 °C actually describes a mixture of $CuCl_2$ and CuCl); partially decomposes above 300 °C to CuCl and Cl_2; dihydrate *d* 2.51 g cm^{-3}; mp 100 °C.

Solubility: anhydrous: sol water, alcohol, and acetone; dihydrate: sol water, methanol, ethanol; mod sol acetone, ethyl acetate; sl sol Et_2O.

Form Supplied in: anhydrous: hygroscopic yellow to brown microcrystalline powder; dihydrate: green to blue powder or crystals; also supplied as reagent adsorbed on alumina (approx. 30 wt % $CuCl_2$ on alumina).

Analysis of Reagent Purity: by iodometric titration.[70]

Purification: cryst from hot dil aq HCl (0.6 mL g^{-1}) by cooling in a $CaCl_2$–ice bath.[71]

Handling, Storage, and Precautions: the anhydrous solid should be stored in the absence of moisture, since the dihydrate is formed in moist air. Irritating to skin and mucous membranes.

Original Commentary

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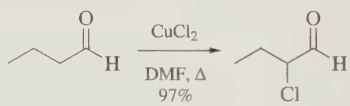
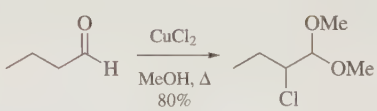
Chlorination of Carbonyls. Copper(II) chloride effects the α-chlorination of various carbonyl functional groups.[1] The reaction is usually performed in hot, polar solvents containing ***Lithium Chloride***, which enhances the reaction rate. For example, butyraldehyde is α-chlorinated in DMF (97% conversion, eq 1) while the same reaction in methanol leads to an 80% yield of the corresponding α-chloro dimethyl acetal (eq 2).[2]

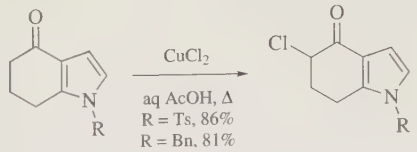


(1)

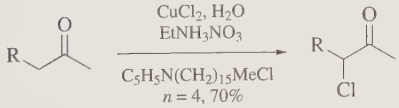


(2)

The process has been extended to carboxylic acids, anhydrides, and acid chlorides by using an inert solvent such as sulfolane.[3] 4-Oxo-4,5,6,7-tetrahydroindoles are selectively α-chlorinated, allowing facile transformation to 4-hydroxyindoles (eq 3).[4] The ability of the reaction to form α-chloro ketones selectively has been further improved by the use of trimethylsilyl enol ethers as substrates.[5] Recently, phase-transfer conditions have been employed in a particularly difficult synthesis of RCH(Cl)C(O)Me selectively from the parent ketones (eq 4).[6]



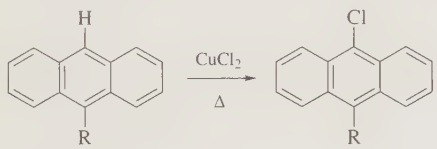
(3)



(4)

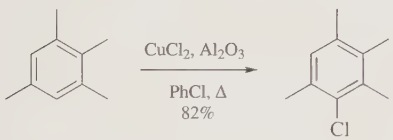
R = $Me(CH_2)_n$, n = 2–5, 8

Chlorination of Aromatics. Aromatic systems may be chlorinated by the reagent. For example, 9-chloroanthracene is prepared in high yield by heating anthracene and $CuCl_2$ in carbon tetrachloride (eq 5).[7] When the 9-position is blocked by a halogen, alkyl, or aryl group, the corresponding 10-chloroanthracenes are formed by heating the reactants in chlorobenzene.[8,9] Under similar conditions, 9-acylanthracenes give 9-acyl-10-chloroanthracenes as the predominant products.[10] Polymethylbenzenes are efficiently and selectively converted to the nuclear chlorinated derivatives by $CuCl_2$/***Alumina*** (eq 6).[11]



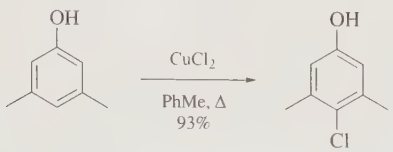
(5)

R = H, Me, Ph, Ac

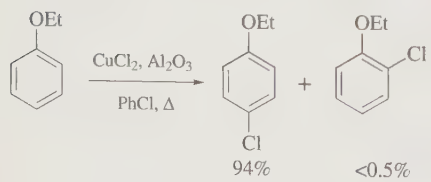


(6)

Reactions with Alkoxy and Hydroxy Aromatics. Hydroxy aromatics such as phenols and flavanones undergo aromatic nuclear chlorination with copper(II) chloride.[12] Thus heating 3, 5-xylenol with a slight excess of the reagent in toluene at 90 °C gave a 93% yield of 4-chloro-3,5-xylenol (eq 7).[13] 2-Alkoxynaphthalenes are similarly halogenated at the 1-position.[14] Attempted reaction of $CuCl_2$ with anisole at 100 °C for 5 h gave no products; in contrast, it was found that alkoxybenzenes were almost exclusively *para*-chlorinated (92–95% *para*:0.5–3% *ortho*) using $CuCl_2/Al_2O_3$ (eq 8).[15] Anisole reacts with benzyl sulfides in the presence of equimolar $CuCl_2$ and ***Zinc Chloride*** to give anisyl(phenyl)methanes (*para*:*ortho* = 2 : 1, eq 9).[16,17]



(7)



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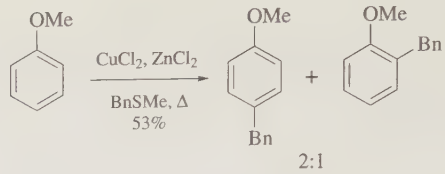
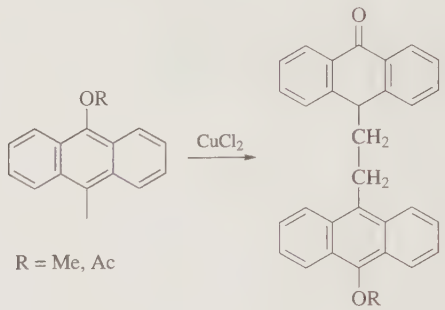


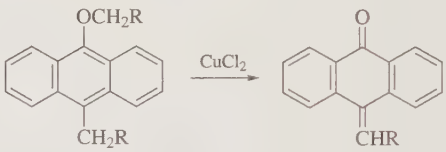
(9)

Reactions with Active Methylene-Containing Compounds. 9-Alkoxy(or acyloxy)-10-methylanthracenes react with $CuCl_2$ to give coupled products (eq 10), while the analogous 9-alkoxy(or acyloxy)-10-benzyl(or ethyl)anthracenes react at the alkoxy or acyloxy group to afford 10-benzylidene(or ethylidene)anthrones (eq 11).[18] The reactions are believed to proceed via a radical mechanism.



(10)

R = Me, Ac

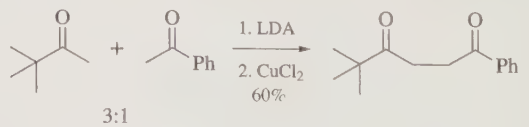


(11)

R = Me, Ph

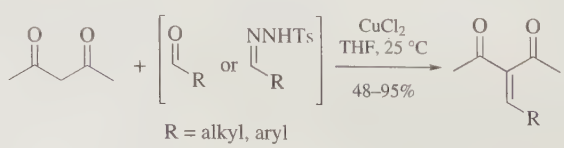
Under similar conditions, 9-alkyl(and aryl)-10-halogenoanthracenes give products resulting from replacement of the halogen, alkyl, or aryl groups with halogen from the $CuCl_2$.[19] Boiling toluene reacts with $CuCl_2$ to yield a mixture of phenyltolylmethanes.[20]

Lithium enolates of ketones[21] and esters[22] undergo a coupling reaction with copper(II) halides to afford the corresponding 1,4-dicarbonyl compounds. Thus treating a 3:1 mixture of *t*-butyl methyl ketone and acetophenone with ***Lithium Diisopropylamide*** and $CuCl_2$ gives a 60% yield of the cross-coupled product (eq 12).



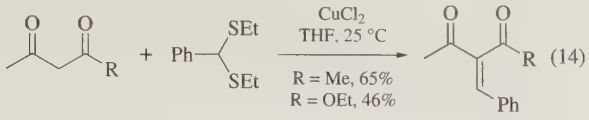
(12)

The intramolecular variant of this reaction producing carbocyclic derivatives has been reported.[23] Copper(II) chloride catalyzes the Knoevenagel condensation of 2,4-pentanedione with aldehydes and tosylhydrazones (eq 13).[24] The reagent also catalyzes the reaction of various 1,3-dicarbonyls with dithianes such as benzaldehyde diethyl dithioacetal to give the corresponding condensation products (eq 14).[25]

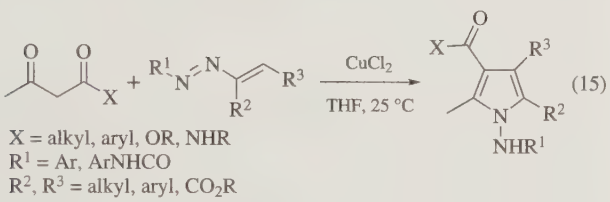


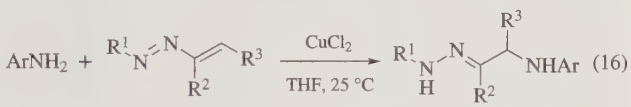
(13)

R = alkyl, aryl

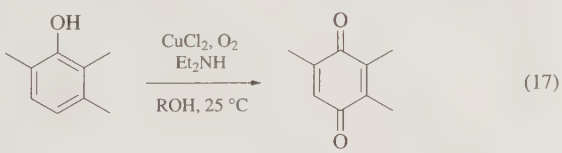


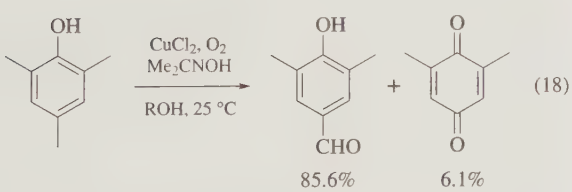
Catalyst for Conjugate Additions. The catalytic effect of copper(II) chloride on the 1,4-addition of β-dicarbonyl compounds to (arylazo)alkenes[26,27] and aminocarbonylazoalkenes[28,29] has been studied in some detail. The reactions proceed at ambient temperature in THF and afford the corresponding pyrrole derivatives (eq 15). This mild method requires no other catalyst and succeeds with β-diketones, β-ketoesters, and β-ketoamides. Copper(II) chloride also catalyzes the addition of water, alcohols, phenol, and aromatic amines to arylazoalkenes (eq 16).[30]



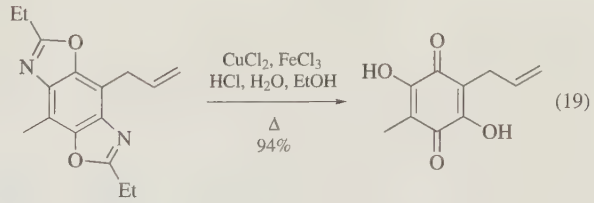


Oxidation and Coupling of Phenolic Derivatives. In the presence of oxygen, copper(II) chloride converts phenol derivatives to various oxidation products. Depending on the reaction conditions, quinones and/or coupled compounds are formed.[31] Several groups have examined different sets of conditions employing $CuCl_2$ to favor either of these products. Thus 2,3,6-trimethylphenol was selectively oxidized to trimethyl-*p*-benzoquinone with $CuCl_2$/amine/O_2 as the catalyst (eq 17),[32] while 2,4,6-trimethylphenol was converted to 3,5-dimethyl-4-hydroxybenzaldehyde using a catalytic system employing either acetone oxime or amine (eq 18).[33,34]

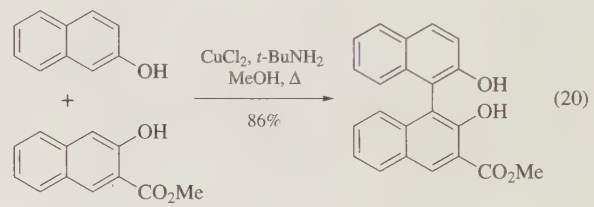




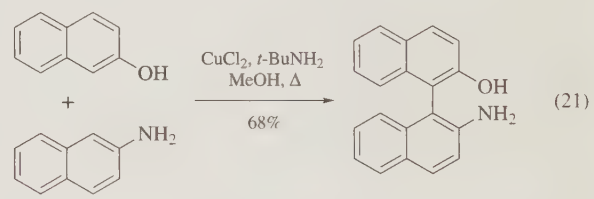
The oxidation of alkoxyphenols to the corresponding quinones has been studied,[35] and even benzoxazole derivatives are oxidized by a mixture of copper(II) chloride and ***Iron(III) Chloride*** (eq 19).[36] A $CuCl_2/O_2$/alcohol catalytic system has been used for the oxidative coupling of monophenols.[37]



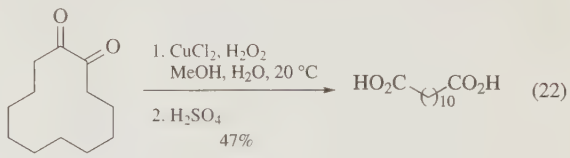
Copper(II) amine complexes are very effective catalysts for the oxidative coupling of 2-naphthols to give symmetrical 1,1′-binaphthalene-2,2′-diols.[38] Recent work has extended this methodology to the cross-coupling of various substituted 2-naphthols.[39,40] For example, 2-naphthol and 3-methoxycarbonyl-2-naphthol are coupled under strictly anaerobic conditions using $CuCl_2$/***t-Butylamine*** in methanol to give the unsymmetrical binaphthol in 86% yield (eq 20).



Other ligands such as methoxide are also effective; a mechanistic study indicates that the selectivity for cross- rather than homo-coupling is dependent upon the copper:ligand ratio.[41] A 1:1 mixture of 2-naphthol and 2-naphthylamine is cross-coupled with $CuCl_2$/benzylamine to give 2-amino-2′-hydroxy-1,1′-binaphthyl (68% yield, eq 21).[42] The cross-coupled products from these reactions are important in view of their use as chiral ligands for asymmetric synthesis.

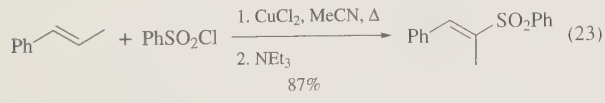


Dioxygenation of 1,2-Diones. 1,2-Cyclohexanedione derivatives have been converted to the corresponding 1,5-dicarbonyl compounds by oxidation with O_2 employing copper(II) chloride as the catalyst.[43] More recently, $CuCl_2$–***Hydrogen Peroxide*** has been used to prepare terminal dicarboxylic acids in high yield.[44] While 1,2-cyclohexanedione afforded α-chloroadipic acid in 85% yield, 1,2-cyclododecanedione was converted to 1,12-dodecanedioic acid in 47% yield under identical conditions (eq 22).



Addition of Sulfonyl Chlorides to Unsaturated Bonds. The addition of alkyl and aryl sulfonyl chlorides across double and triple bonds is catalyzed by copper(II) chloride.[45–51] The reaction appears to be quite general and proceeds via a radical chain

mechanism. The 2-chloroethyl sulfones produced in the reaction with alkenes undergo base-induced elimination to give vinyl sulfones (eq 23).[45–48] 1,3-Dienes similarly react, yielding 1,4-addition products (eq 24) which may be dehydrohalogenated to 1,3-unsaturated sulfones.[45,49]



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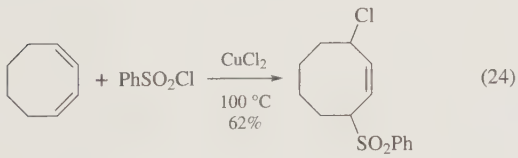
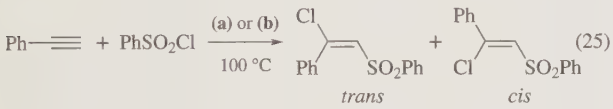


(24)

The stereoselectivity of the addition to alkynes can be controlled by varying the solvent or additive, and thus favoring either the *cis* or *trans* β-chlorovinyl sulfone.[50,51] For example (eq 25), when benzenesulfonyl chloride is reacted with phenylacetylene in acetonitrile with added triethylamine hydrochloride, the *trans*:*cis* ratio is 92:8, while the same reaction performed in CS_2 without additive favors the *cis* isomer (16:84).



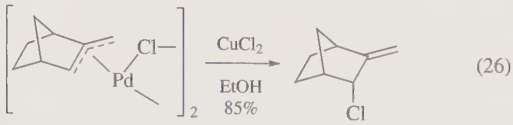
(25)

(a) = $CuCl_2$, NEt_3HCl, MeCN **(a)** *trans*:*cis* = 92:8
(b) = $CuCl_2$, CS_2 **(b)** *trans*:*cis* = 16:84

Acylation Catalyst. *N*-Trimethylsilyl derivatives of (+)-bornane-2,10-sultam (Oppolzer's chiral sultam) and chiral 2-oxazolidinones (the Evans chiral auxiliaries) are *N*-acylated with a number of acyl chlorides including acryloyl chloride in refluxing benzene in the presence of $CuCl_2$.[52] The *N*-acylated products were prepared in high yields; the method does not require an aqueous workup, making it advantageous for large-scale preparations.

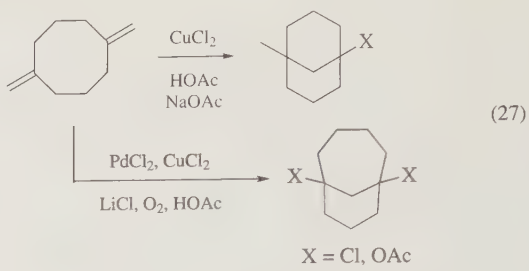
Racemization Suppression in Peptide Couplings. A mixture of copper(II) chloride and ***Triethylamine*** catalyzes the formation of peptide bonds.[53] Furthermore, when used as an additive, $CuCl_2$ suppresses racemization in both the carbodiimide[54] and mixed anhydride[55] peptide coupling methods. Recently it was shown that a combination of ***1-Hydroxybenzotriazole*** and $CuCl_2$ gives improved yields of peptides while eliminating racemization.[56,57]

Reaction with Palladium Complexes. π-Allylpalladium complexes undergo oxidative cleavage with copper(II) chloride to form allyl chlorides with the concomitant release of $PdCl_2$ (eq 26).[58]



(26)

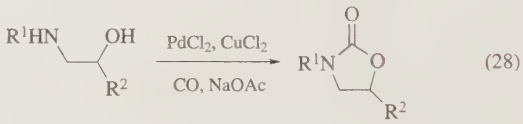
This methodology has been used in the dimerization of allenes to 2,3-bis(chloromethyl)butadienes.[59] 1,5-Bismethylenecyclooctane was transformed into the bridgehead-substituted bicyclo[3.3.1]nonane system using $CuCl_2$/HOAc/NaOAc, while the same substrate produced bicyclo[4.3.1]decane derivatives (eq 27) with a ***Palladium(II) Chloride***/$CuCl_2$ catalytic system.[60]



(27)

While reaction of a steroidal π-allylpalladium complex with AcOK yields the allyl acetate arising from *trans* attack, treatment of a steroidal alkene with $PdCl_2$/$CuCl_2$/AcOK/AcOH gave the allyl acetate arising from *cis* attack.[61]

Reoxidant in Catalytic Palladium Reactions. Copper(II) chloride has been used extensively in catalytic palladium chemistry for the regeneration of Pd^{II} in the catalytic cycle. In particular, the reagent has found widespread use in the carbonylation of alkenes,[62–64] alkynes,[65] and allenes[66,67] to give carboxylic acids and esters using $PdCl_2$/$CuCl_2$/CO/HCl/ROH, and in the oxidation of alkenes to ketones with a catalytic $PdCl_2$/$CuCl_2$/O_2 system (the Wacker reaction).[68] The $PdCl_2$/$CuCl_2$/CO/NaOAc catalytic system has been used in a mild method for the carbonylation of β-aminoethanols, diols, and diol amines (eq 28).[69]



(28)

Cyclopropanation with $CuCl_2$–$Cu(OAc)_2$ Catalyst. ***Ethyl Cyanoacetate*** reacts with alkenes under $CuCl_2$–***Copper(II) Acetate*** catalysis to give cyclopropanes.[72] Thus heating cyclohexene in DMF (110 °C, 5 h) with this reagent combination gives a 53% yield of the isomeric cyclopropanes. The reaction also proceeds with styrene, 1-decene, and isobutene. Byproducts formed from the addition to the alkene are removed with ***Potassium Permanganate***.

First Update

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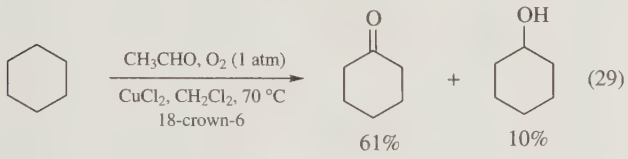
Copper(II) Chloride-catalyzed Oxidation of Hydrocarbons with Molecular Oxygen.

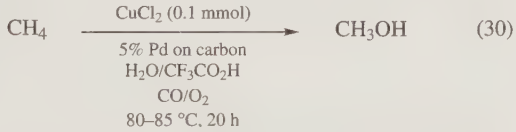
Oxidation of Hydrocarbons to Alcohols and Ketones. A combination of $CuCl_2$ and a crown ether is an efficient catalytic system for the aerobic oxidation of alkanes in the presence of acetaldehyde.[73,74] For example, oxidation of cyclohexane in the presence of $CuCl_2$ (2.5×10^{-4} mol %), 18-crown-6 (2.5×10^{-4} mol %), and acetaldehyde (10 mol %) at 70 °C under O_2 at 1 atmosphere gave cyclohexanone (61% yield based on acetaldehyde)

and cyclohexanol (10%). This catalytic system has high turnover number of 1.62×10^4 for the aerobic oxidation of cyclohexane (eq 29). The presence of crown ether forms a complex with copper ions which enhances the catalytic activity of the copper chloride. Thus, the $CuCl_2$-18-crown-6 complexes catalyze oxidation of acetaldehyde with molecular oxygen to give peracid. The reaction of copper complexes with peracid then gives the oxo-copper intermediate. Hydrogen abstraction of alkane by the oxo-copper complex, followed by oxygen transfer yields the corresponding alcohol. The alcohol suffers further oxidation to the corresponding ketone under the reaction conditions.



(29)

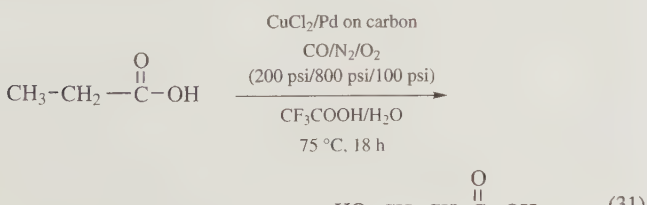
A highly catalytic bimetallic system for the low temperature selective oxidation of methane, ethane, and butane with oxygen as the oxidant has been reported.[75] The catalytic system consists of a mixture of copper chloride and metallic palladium in a 3:1 mixture (v/v) of trifluoroacetic acid-water in the presence of oxygen and carbon monoxide. For example, methane can be selectively converted to methanol at 80–85 °C for 20 h in a bomb (eq 30), pressurized to 200 psi with carbon monoxide, 1200 psi with methane, then 1300 psi with oxygen. An increase in reaction temperature significantly increases the rate of methane to methanol conversion. The rate of formation of methanol is ca. 65×10^{-4} M min^{-1} at 145–150 °C.



(30)

For oxidation of ethane and *n*-butane under similar oxidation conditions, products derived from C–C bond cleavage compete with or dominate those derived from C–H bond cleavage on a per bond basis. The overall transformation encompasses three catalytic steps: (1) Pd-catalyzed reaction between CO and H_2O to form CO_2 and H_2; (2) Combination of H_2 and O_2 to yield hydrogen peroxide; and (3) Cu-catalyzed oxidation of the alkane by hydrogen peroxide. This catalytic system shows interesting synergism, in that the principle role of metallic Pd is to generate hydrogen peroxide in situ, and the $CuCl_2$ activates hydrogen peroxide for oxidation of the substrates.

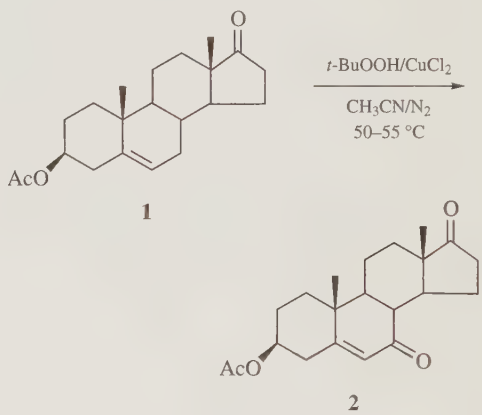
This catalytic system has been extended to the hydroxylation of remote primary C–H bonds of various acids, alcohols, and aliphatic halides.[76] For example, propionic acid can be converted to 3-hydroxypropionic acid in 22% yield (eq 31). This catalytic system exhibits two important features: (1) Reactions are very specific, and only hydroxylation is observed; further oxidation to aldehyde and carboxylic acid does not occur; (2) C–C bond cleavage and overoxidation can be minimized under suitable conditions.



(31)

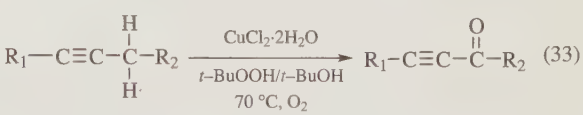
Copper(II) Chloride-catalyzed Oxidation of Hydrocarbons with *t*-Butyl Hydroperoxide.

Oxidation of Allylic Compounds. Allylic oxidation reaction of various types steroids have been preformed in the presence of *t*-butyl hydroperoxide (*t*-BuOOH) catalyzed by copper(I),(II) or copper metal.[77] For example, allylic oxidation of the Δ^5-3β-acetoxy steroid (**1**) was catalyzed with $CuCl_2$ in the presence of *t*-BuOOH at 50–55 °C for 20 h to give 81% yield of **2** (eq 32). No oxidation is detected in the absence of copper catalyst.



(32)

Oxidation of Alkynes to α,β-Acetylenic Ketones. Various alkynes have been converted to the corresponding α,β-acetylenic ketones by oxidation with oxygen and *t*-BuOOH using copper(II) chloride as the catalyst (eq 33).[78] The catalytic system gives both high conversion and selectivity in the formation of the α,β-acetylenic ketones. This selectivity results from rapid oxidation of the intermediate acetylenic alcohol, RC≡CCH(OH)R′, to ketone under the reaction conditions. The resulting acetylenic ketone is deactivated from further oxidation.

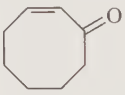


(33)

R_1=H, aliphatic, or aromatic group
R_2=aliphatic group

Copper(II) chloride not only catalyzes the decomposition of *t*-BuOOH, but also plays a key role in converting the acetylenic alcohol intermediates to α,β-acetylenic ketones. To obtain both high conversion and selectivity towards α,β-acetylenic ketones, optimal reaction conditions are determined to be $CuCl_2 \cdot 2H_2O$: alkyne:*t*-BuOOH in a 1:25:50 ratio in *t*-BuOH at 70 °C under an oxgen atmosphere. The reaction has broad substrate applicability, where R and R′ can be a variety of aliphatic or aromatic groups (Table 1).

Table 1 Oxidation of alkynes catalyzed by $CuCl_2 \cdot 2H_2O$/*t*-BuOOH under oxygen[a]

Substrate	Conv.[b] (%)	Product	Yield[c] (%)
$CH_3CH_2C{\equiv}CCH_2CH_3$ 3-hexyne	91	$CH_3C(O)C{\equiv}CCH_2CH_3$	59
$CH_3(CH_2)_2C{\equiv}C(CH_2)_2CH_3$ 4-octyne	99	$CH_3CH_2C(O)C{\equiv}C(CH_2)_2CH_3$	74
$CH_3(CH_2)_3C{\equiv}C(CH_2)_3CH_3$ 5-decyne	95	$CH_3(CH_2)_2C(O)C{\equiv}C(CH_2)_3CH_3$	66
$CH_3CH_2C{\equiv}CCH_2CH_2CH_3$ 3-heptyne	100	$CH_3C(O)C{\equiv}CCH_2CH_2CH_3$	37
		$CH_3CH_2C{\equiv}CC(O)CH_2CH_3$	31
$CH_3(CH_2)_2C{\equiv}C(CH_2)_3CH_3$ 4-nonyne	99	$CH_3CH_2C(O)C{\equiv}C(CH_2)_3CH_3$	39
		$(CH_2)_2C{\equiv}C(O)(CH_2)_2CH_3$	37
$CH_3C{\equiv}C(CH_2)_6CH_3$ 2-decyne	84	$CH_3C{\equiv}CC(O)(CH_2)_5CH_3$	70
$HC{\equiv}C(CH_2)_5CH_3$ 1-octyne	61	$HC{\equiv}CC(O)(CH_2)_4CH_3$	51
$C_6H_5C{\equiv}C(CH_2)_2CH_3$ 1-phenyl-1-pentyne	85	$C_6H_5C{\equiv}C(O)CH_2CH_3$	78
$C_5H_{11}C{\equiv}CCOOCH_3$ Methyl-2-octynoate		No reaction	
$C_5H_{11}C{\equiv}C\text{-}COOH$ 2-Octynoic acid		No reaction	
 *cis*-Cyclooctene	97		42
$CH_3CH(OH)C{\equiv}CCH(OH)CH_3$[d] 3-hexyn-2,5-diol	100	$CH_3C(O)C{\equiv}CCH(OH)CH_3$	65
		$CH_3C(O)C{\equiv}C(O)CH_3$	15

[a]Reaction conditions: $CuCl_2 \cdot 2H_2O$:substrate:*t*-BuOOH = 1:25:50 (molar ratio). Reaction was carried out at 70 °C under O2.

[b]Conversion was determined by GC analysis using an internal standard, *t*-butylbenzene. By-products were mainly acetylenic alcohol.

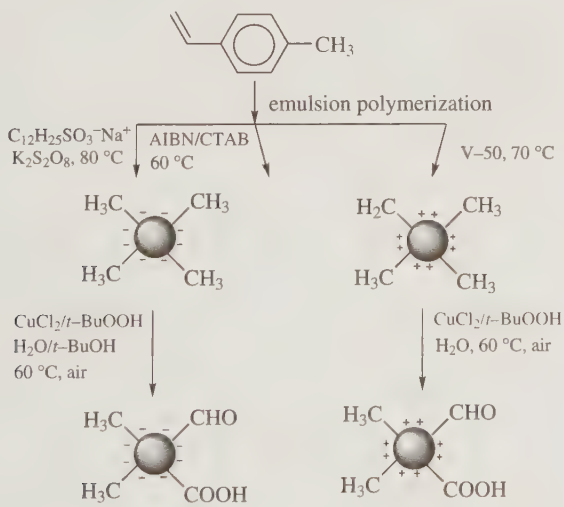
[c]Isolated yield.

[d]10 h reaction.

The oxidation to the α,β-acetylenic ketone proceeds with both high conversion and selectivity. The only major side-product after 24 h is the acetylenic alcohol. If a longer reaction time is employed, this side-product is completely converted to the α,β-acetylenic ketone. Alkyne reactivities correlate with the ease of C–H atom abstraction. Symmetric internal aliphatic alkynes, such as 3-hexyne, 4-octyne, and 5-decyne, give excellent conversion and selectivity for ketone formation. The aliphatic chain length has little effect on the reactivity and selectivity. Unsymmetrical internal aliphatic alkynes, such as 3-heptyne and 4-nonyne, afford a pair of acetylenic ketones with approximately equal distribution, indicating that the system cannot distinguish between the two chemically similar α-CH_2 groups of the substrate. However, the oxidation of 2-decyne is regiospecific, yielding 2-decyn-3-one in 70% yield with no C–H abstraction from the C-1 methyl group. Terminal acetylenes also yield acetylenic ketones although the substrate reactivity is diminished. Besides the aliphatic alkynes, aromatic alkynes such as 1-phenyl-1-pentyne can be oxidized to the corresponding conjugated acetylenic ketone in good yield. The reaction conditions can also be employed for oxidation of other related substrates, such as *cis*-cyclooctene, which yields 3-cyclooctenone with lower selectivity. Adjacent carboxylate groups severely inhibit the alkyne reactivity. No apparent substrate oxidation is observed for methyl-2-octynoate or 2-octynoic acid after 24 h. By contrast, 3-hexyn-2,5-diol is rapidly converted to 3-hexyn-2-ol-5-one in high yield with some further oxidation to 3-hexyn-2,5-dione. Acetylenic alcohols, while not typically as reactive as 3-hexyn-2,5-diol, are still activated for further reaction to acetylenic ketones. However, like acetylenic esters or acids, the acetylenic ketones are strongly deactivated.

Oxidation of Poly(Methyl styrene). Anionic or cationic poly(methyl styrene) (PMS) latex particles can be functionalized via oxidation of the benzylic methyl group to the corresponding aldehyde and carboxylic acid in water. The oxidation of PMS latex dispersion has been achieved using *t*-butyl hydroperoxide as an oxidant catalyzed by a small amount of copper(II) chloride under air (Scheme 1).[79–83] The oxidation mechanism involves initial copper(II) chloride-catalyzed decomposition of *t*-BuOOH to both *t*-BuO· and *t*-BuOO. radicals. These reactive radicals abstract benzylic hydrogens to generate benzylic radicals, which are oxidized to the corresponding aldehyde groups under air. Since the aldehyde groups are easily oxidized to the carboxylic acid under the oxidative conditions, a mixture of aldehyde and carboxylic acid functionalities result. The distribution of these two functional groups can be controlled by varying reaction conditions such as concentration of *t*-BuOOH, type of surfactant, reaction temperature, and time. Since the $CuCl_2$/*t*-BuOOH/O_2 is an effective system for benzylic C–H oxidation in aqueous media, it is environmentally benign. This aqueous functionalization method for opens up a new route to the preparation of a potentially large class of functionalized latex particles, which may find useful applications in various fields.

Related Reagents. Chlorine; N-Chlorosuccinimide; copper(I) chloride; copper(II) chloride–copper(II) oxide; iodine–copper(II) chloride copper(I) chloride–oxygen; copper(I)chloride-tetrabutylammonium chloride copper(I) chloride–sulfur dioxide iodine–aluminum(III) chloride–copper(II) chloride; iodine–copper(I) chloride–copper(II) chloride; methylmagnesium iodide–copper(I) chloride; palladium(II) chloride–copper(I) chloride; palladium(II) chloride–copper(II) chloride; phenyl selenocyanate–copper(II) chloride; vinylmagnesium chloride–copper(I) chloride; zinc–copper(I) chloride



Scheme 1

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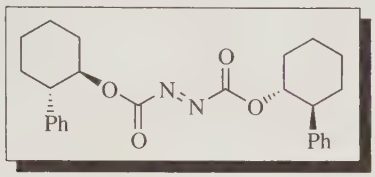
D

Di-(−)-(1*R*,2*S*)-2-phenyl-1-cyclohexyl Diazenedicarboxylate



[206359-91-3] $C_{26}H_{30}N_2O_4$ (MW 434.53 (*E*))

(reagent used as a chiral azo-enophile in asymmetric azo-ene reactions)

Alternate Name: (1*R*-1α[*E*(1*R**,2*S**)],2β)-Bis(2-phenylcyclohexyl) diazenedicarboxylate.

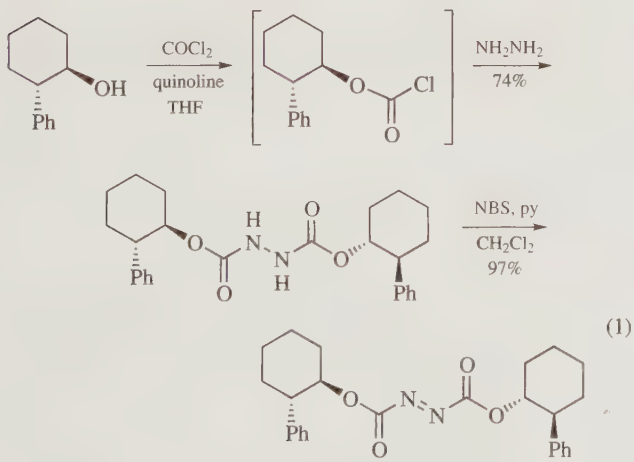
Physical Data: $[\alpha]_D$ −56.9 (*c* 0.65, $CHCl_3$).

Solubility: soluble in CH_2Cl_2, diethyl ether, and most organic solvents.

Form Supplied in: yellow oil.

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

Preparative Methods: The title reagent is prepared[1] by reaction of (1*R*, 2*S*)-2-phenyl-1-cyclohexanol with excess phosgene in the presence of quinoline to afford a chloroformate which is treated directly with hydrazine monohydrate (0.5 equiv) to afford di-(−)-(1*R*, 2*S*)-2-phenyl-1-cyclohexyl diazanedicarboxylate. Oxidation of the diazanedicarboxylate to the diazenedicarboxylate is then readily effected using *N*-bromosuccinimide and pyridine (eq 1).



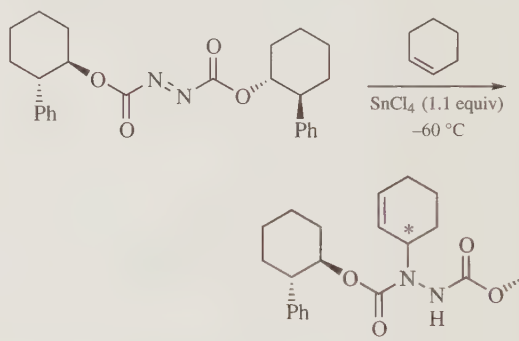
(1)

Purification: flash chromatography using hexane–ethyl acetate (9:1) as eluent.

Handling, Storage, and Precautions: store in closed vessels under an inert atmosphere in the refrigerator. Protect from light.

Azo-ene reactions. The ene reaction[1] provides a powerful method for C–C bond formation with concomitant activation of an allylic C–H bond. A variety of functionalized carbon skeletons can be constructed due to the range of enophiles which can be used. For example, carbonyl compounds give homoallylic alcohols[2] and imino derivatives of aldehydes afford homoallylic amines.[3] The azo-ene reaction offers a method for effecting allylic amination by treatment of an alkene with an azo-diester to afford a diacyl hydrazine which upon N–N cleavage furnishes a carbamate. Subsequent hydrolysis of the carbamate provides an allylic amine. Use of chiral diazenedicarboxylates provides a method for effecting stereoselective electrophilic amination.

Lewis acid-mediated ene reaction of di-(−)-(1*R*,2*S*)-2-phenyl-1-cyclohexyl diazenedicarboxylate with cyclohexene using tin(IV) chloride in dichloromethane at −60 °C for 5 min afforded the azo-ene adduct in 80% yield after purification by flash chromatography (eq 2).[4] The ^{1}H NMR spectrum of the azo-ene adduct recorded at 380 K in deuterated toluene established the presence of only one diastereomer. Further analysis of the ene adduct by HPLC on a Whatman Partisil 5 normal phase silica column using hexane–ethyl acetate (9:1) as eluent confirmed the presence of only one diastereomer.



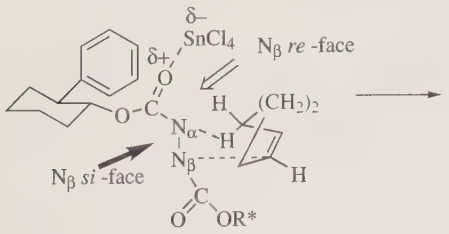
(2)

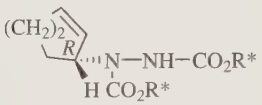
80% > 97:3

Use of cyclopentene, *trans*-hex-3-ene and *trans*-oct-4-ene afforded the ene adducts in good yield with a diastereomeric excess of 86:14 in each case. The diastereoselectivity observed using di-(−)-(1*R*,2*S*)-2-phenyl-1-cyclohexyl diazenedicarboxylate as a chiral azo-enophile offered a significant improvement over the use of di-(−)-menthyl azodicarboxylate where the level of asymmetric induction achieved in Lewis acid-mediated ene reactions with simple alkenes was not impressive.[5] Moreover, it proved difficult to cleave the N–N bond in the menthyl ester azo-ene adducts whereas sodium/liquid ammonia was used to smoothly cleave the N–N bond in the diacylhydrazine adducts formed using di-(−)-(1*R*,2*S*)-2-phenyl-1-cyclohexyl diazenedicarboxylate as azo-enophile.

The absolute stereochemistry at the newly formed stereogenic carbon of the major diastereomer of the ene adduct can be predicted by analysis of the transition model for the ene reaction (eq 3). The (1*R*,2*S*)-2-phenyl-1-cyclohexyl chiral auxiliary adopts a chair conformation with equatorial placement of the bulky phenyl group. Complexation of the carbonyl group to the Lewis acid affords the more stable *s-trans* conformation about the C–N sigma bond. In this conformation, the phenyl group shields the N_β-*re*-face. Therefore the cyclic alkene preferentially attacks from the less hindered N_β-*si*-face. Ene reaction proceeds through a six-

membered cyclic transition state affording the (1′*R*)-diastereomer of the ene adduct.





(3)

Related Reagents. The synthesis of chiral diazenedicarboxylates as potential chiral electrophilic aminating agents has received little attention. A series of chiral bornyl, isobornyl and menthyl diazenedicarboxylates has been reported[6] and their reaction with achiral enolates of esters and *N,N*-dimethyl amides afforded α-hydrazino acid derivatives with little or no selectivity. Incorporation of a chiral azodicarboxamide unit into a chiral bridging binaphthyl moiety afforded α-hydrazino acid derivatives with high stereoselectivity in reactions with achiral oxazolidinone anions.[7]

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2. (a) Snider, B. B. The Prins and Carbonyl-Ene Reactions, in *Comprehensive Organic Synthesis*, Trost, B. M., Ed., Pergamon: Oxford, 1991, Vol. 2, p 527; (b) Mikami, K.; Shimizu, M., *Chem. Rev.* **1992**, *92*, 1021.
3. Borzilleri, R. M.; Weinreb, S. M., *Synthesis* **1995**, *4*, 347.
4. Brimble, M. A.; Lee, C. Y. K., *Tetrahedron: Asymmetry* **1998**, *9*, 873.
5. Brimble, M. A.; Heathcock, C. H.; Nobin, G. N., *Tetrahedron: Asymmetry* **1996**, *7*, 2007.
6. Harris, J. M.; Bolessa, E. A.; Mendonca, A. J.; Feng, S.-C.; Vederas, J. C., *J. Chem. Soc. Perkin Trans. 1* **1995**, 1945.
7. Harris, J. M.; McDonald, R.; Vederas, J. C., *J. Chem. Soc. Perkin Trans. 1* **1996**, 2669.

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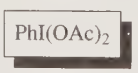
(Diacetoxyiodo)benzene[1–3]



[3240-34-4] $C_{10}H_{11}IO_4$ (MW 322.10)

(transannular carbocyclization,[6] *vic*-diazide formation,[7] α-hydroxy dimethyl acetal formation,[8,10,11,13] oxetane formation,[9] chromone, flavone, chalcone oxidation,[11,12] arene–$Cr(CO)_3$ functionalization,[14] phenolic oxidation[16] and coupling,[17,18] lactol fragmentation,[19] iodonium ylides and intramolecular cyclopropanation,[20] oxidation of amines[24–28] and indoles,[30,31] hydrazine derivatives (diimide[32] and azodicarbonyls[33]) and radical type intramolecular oxide formation[44–46])

Alternate Names: phenyliodine(III) diacetate; DIB; iodobenzene diacetate; IBD.

Physical Data: mp 163–165 °C.

Solubility: sol AcOH, MeCN, CH_2Cl_2; in KOH or $NaHCO_3$/MeOH it is equivalent to $PhI(OH)_2$.

Form Supplied in: commercially available as a white solid.

Preparative Methods: by reaction of iodobenzene with ***Peracetic Acid***.[4,5]

Purification: recrystallization from 5 M acetic acid.[4]

Handling, Storage, and Precautions: a stable compound which can be stored indefinitely.

Original Commentary

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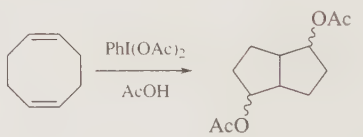
Jerome W. Kosmeder II
University of Illinois at Chicago, IL, USA

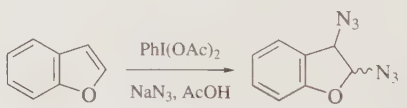
Reactions with Alkenes. Reactions of simple alkenes with $PhI(OAc)_2$ are not synthetically useful because of formation of multiple products.

Transannular carbocyclization in the reaction of *cis,cis*-1,5-cyclooctadiene yields a mixture of three diastereomers of 2,6-diacetoxy-*cis*-bicyclo[3.3.0]octane, a useful precursor of *cis*-bicyclo[3.3.0]octane-2,6-dione (eq 1).[6]



(1)

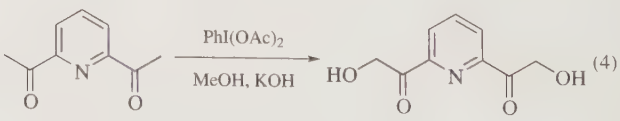
$PhI(OAc)_2/NaN_3$/AcOH yields vicinal diazides (eq 2).[7]



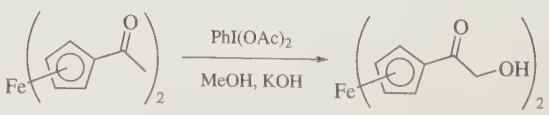
(2)

Oxidation of Ketones to α-Hydroxyl Dimethyl Acetals. Ketones are converted to the α-hydroxy dimethyl acetal upon reaction with $PhI(OAc)_2$ in methanolic potassium hydroxide (eqs 3–5).[8]

(3)

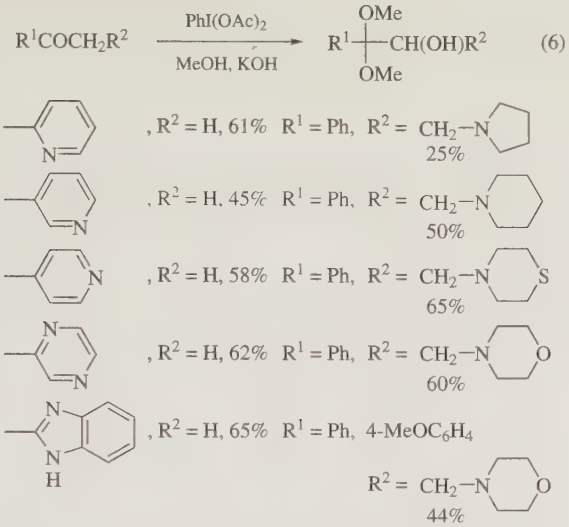


(4)

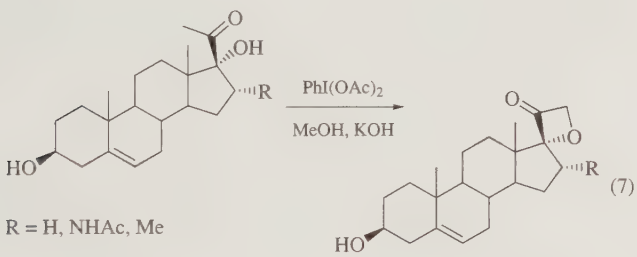


(5)

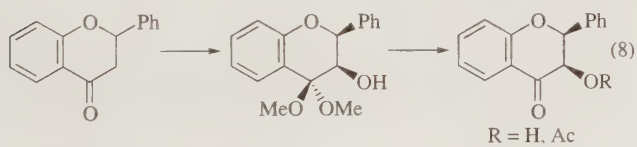
Several potentially oxidizable groups are unaffected in this reaction (eq 6).[13]



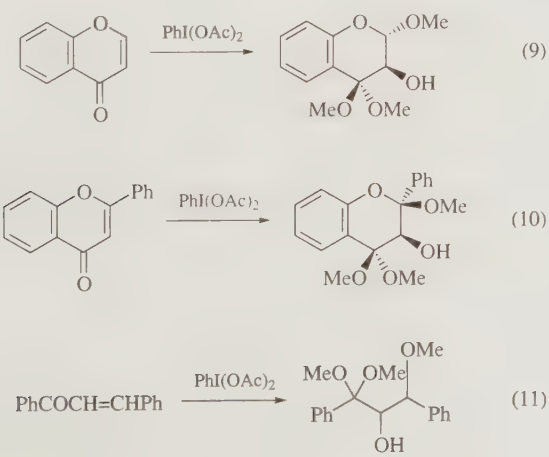
In the case of a 17α-hydroxy steroid the hydroxy group acts as an intramolecular nucleophile to yield the 17-spirooxetan-20-one. It is noteworthy that the 3β-hydroxy-Δ^5-system is unaffected (eq 7).[9]



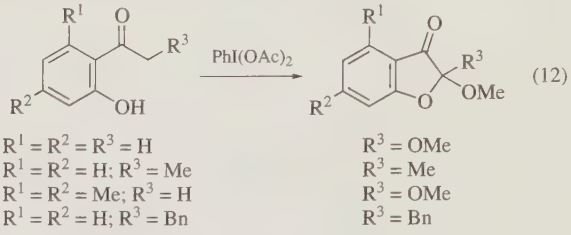
cis-3-Hydroxyflavonone is obtained via acid-catalyzed hydrolysis of *cis*-3-hydroxyflavone dimethyl acetal, which is formed upon treatment of flavanone with $PhI(OAc)_2$ (eq 8).[10,11]



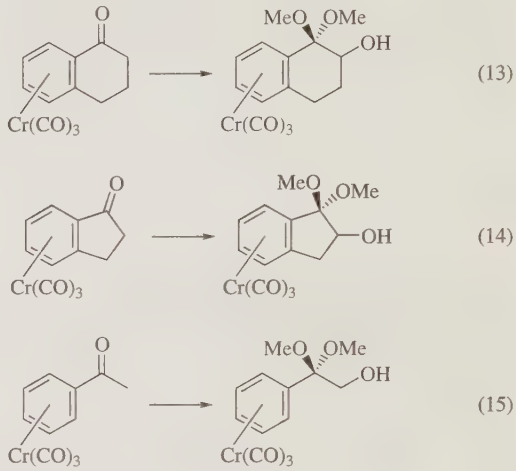
α,β-Unsaturated ketones, such as chromone, flavone, chalcone, and flavanone, yield α-hydroxy-β-methoxy dimethyl acetal products (eqs 9–11).[12a]



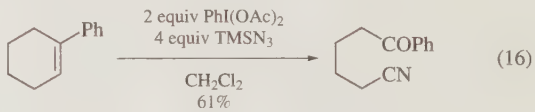
Intramolecular participation by the *ortho* hydroxy group occurs in the reaction of substituted *o*-hydroxyacetophenones, yielding the corresponding coumaran-3-ones (eq 12).[12b]



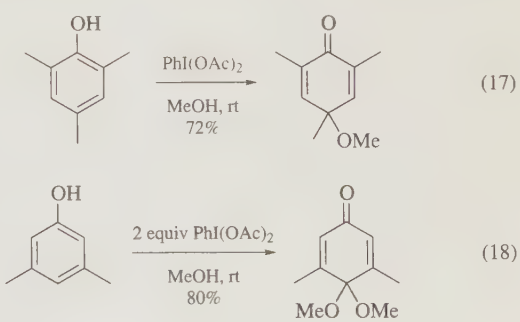
Formation of the α-hydroxy dimethyl acetal occurs without reaction of the $Cr(CO)_3$ complex of η^6-benzo-cycloalkanones (eqs 13–15).[14]

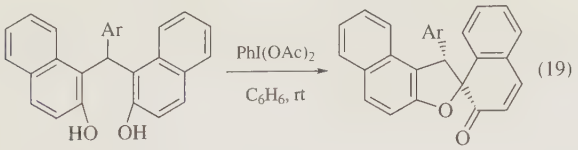


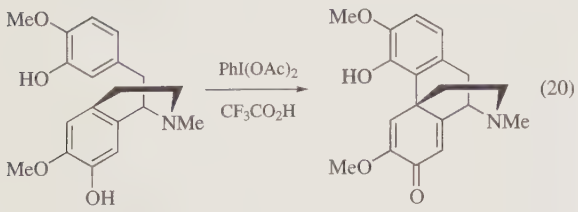
Carbon–Carbon Bond Cleavage with $PhI(OAc)_2$/$TMSN_3$. $PhI(OAc)_2$/*Azidotrimethylsilane* reacts with unsaturated compounds even at −53 °C to yield keto nitriles (eq 16).[15]



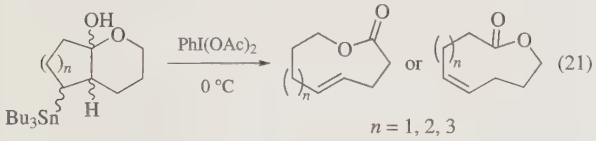
Oxidation of Phenols. Phenols are oxidized using $PhI(OAc)_2$ with nucleophilic attack by solvent (eqs 17 and 18),[16] or with intramolecular nucleophilic addition amounting to an overall oxidative coupling as with the bisnaphthol (eq 19)[17] and also with the conversion of reticuline to salutaridine (eq 20).[18]







Fragmentation of Lactols to Unsaturated Medium-Ring Lactones. Ring cleavage to form a medium-sized ring lactone with a transannular double bond has been observed (eq 21).[19]



Reactions with β-Dicarbonyl Systems; Formation of Iodonium Ylides; Intramolecular Cyclopropanation. β-Dicarbonyl compounds upon reaction with $PhI(OAc)_2$ and KOH/MeOH at 0 °C yield isolable iodonium ylides (eq 22).[20] This is a general reaction which requires two stabilizing groups flanking the carbon of the C=I group, such as NO_2 and SO_2Ph.[21] Decomposition of unsaturated analogs in the presence of ***Copper(I) Chloride*** proceeds with intramolecular cyclopropanation (Table 1).[20]

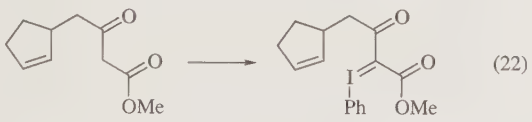
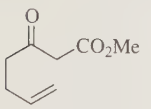
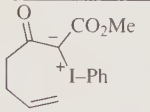
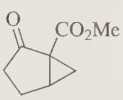
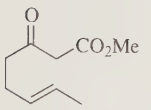
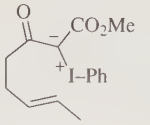
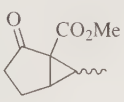
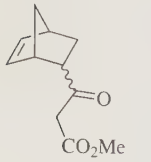
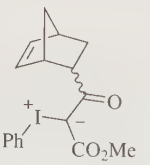
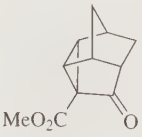
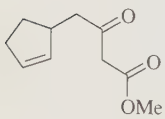
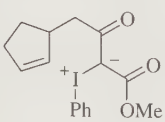
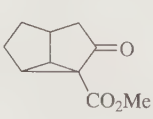
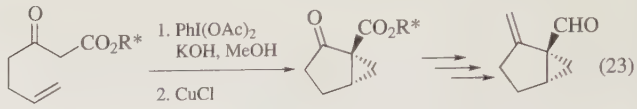


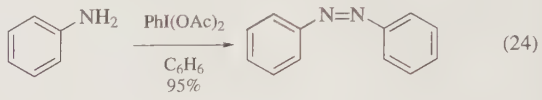
Table 1 Intramolecular cyclopropanation of iodonium ylides

Reactants	Iodonium ylide	Product	Yield (%)
			76
			81
			85
			82

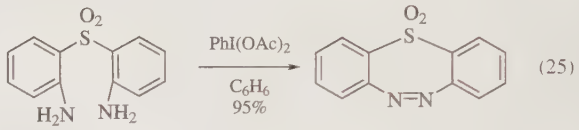
An asymmetric synthesis of a vitamin D ring A synthon employed this intramolecular cyclopropanation reaction (eq 23).[22]

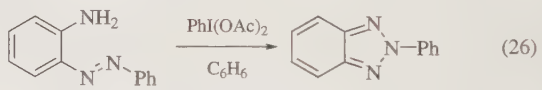


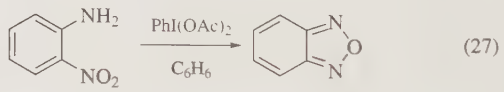
Oxidation of Amines. Aromatic amines are oxidized with $PhI(OAc)_2$ to azo compounds in variable yield. $PhI(OAc)_2$ in benzene oxidizes aniline in excellent yield (eq 24);[23] however, substituted anilines give substantially lower yields.

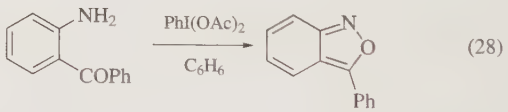


Intramolecular azo group formation is a useful reaction for the formation of dibenzo[*c*,*f*]diazepine (eq 25).[24,25] Other *ortho* groups may react intramolecularly to yield the benzotriazole (eq 26), benzofuroxan (eq 27), or anthranil (eq 28) derivatives.[24–28]

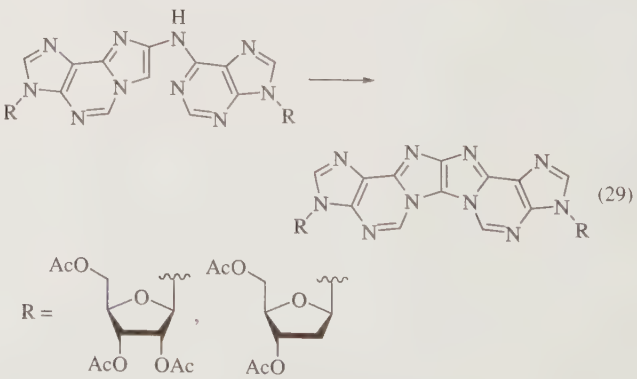






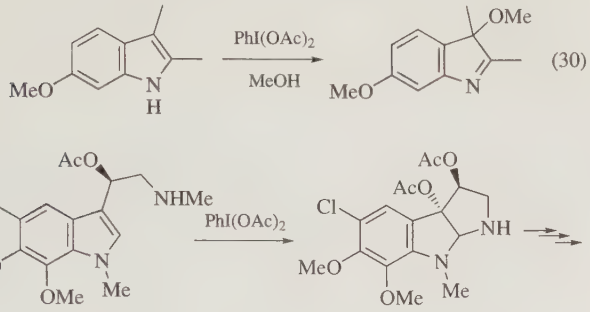


A number of examples of oxidative cyclization of 2-(2′-pyridylamino)imidazole[1,2-*a*]pyridines to dipyrido[1,2-*a*:2′,1′-*f*]-1,3,4,6-tetraazapentalenes with $PhI(OAc)_2/CF_3CH_2OH$ have been reported (eq 29).[29]



In the case of the oxidation of indole derivatives, nucleophilic attack by solvent may occur (eq 30).[30] Reserpine undergoes an

analogous alkoxylation.[30] In the absence of a nucleophilic solvent, intramolecular cyclization occurs, an example of which is illustrated in the total synthesis of sporidesmin A (eq 31).[31]



(30)

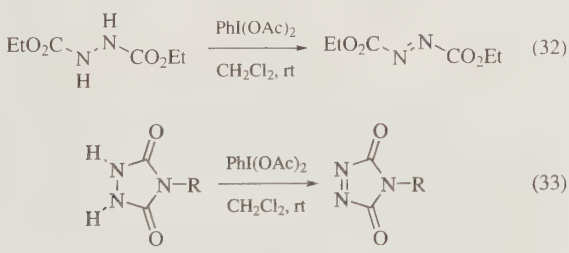
(31)

Hydrazine is oxidized by $PhI(OAc)_2$ to diimide, which may be used to reduce alkenes and alkynes under mild conditions (Table 2).[32]

Table 2 Diimide reduction of various compounds

Compound	Product	Yield (%)
$PhSCH{=}CH_2$	$PhSCH_2Me$	85
cis-$EtO_2CCH{=}CHCO_2Et$	$EtO_2CCH_2CH_2CO_2Et$	94
$EtO_2C{-}N{=}N{-}CO_2Et$	$EtO_2CNH{-}NHCO_2Et$	90
Maleic anhydride	$(MeCO)_2O$	83
$PhC{\equiv}CPh$	*cis*-$PhCH{=}CHPh$	80
$PhCH{=}CHCO_2Et$	$PhCH_2CH_2CO_2Et$	96
$CH_2{=}CHCN$	$MeCH_2CN$	97

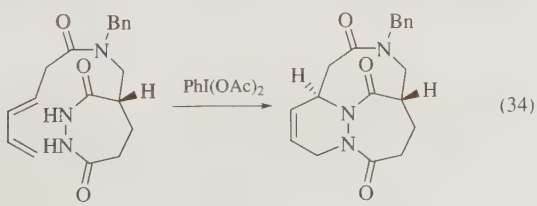
The hydrazodicarbonyl group is smoothly oxidized by $PhI(OAc)_2$ to the azodicarbonyl group (eqs 32 and 33).[33]



(32)

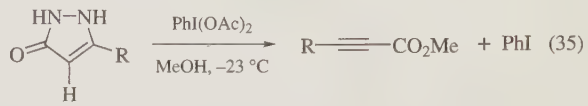
(33)

An intramolecular application of this reaction was used in a tandem sequence with $PhI(OAc)_2$ oxidation and a Diels–Alder reaction in the synthesis of nonpeptide β-turn mimetics (eq 34).[34,35]



(34)

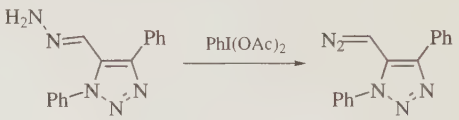
Oxidation of 5-Substituted Pyrazol-3(2*H*)-ones; Formation of Alkynyl Esters. Oxidation of various 5-substituted pyrazol-3(2*H*)-ones proceeded with fragmentative loss of molecular nitrogen to yield methyl-2-alkynoates (eq 35).[36] An analogous fragmentation process with pyrazol-3(2*H*)-ones occurs with ***Thallium(III) Nitrate Trihydrate***[37,38] and ***Lead(IV) Acetate***.[39]



(35)

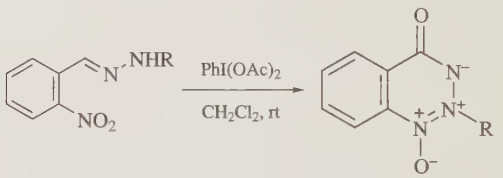
R = Me, 60%
R = Et, 63%
R = CO_2Me, 59%
R = CH_2CO_2Me, 62%
R = Ph, 59%
R = *p*-ClC_6H_4, 61%
R = *p*-MeC_6H_4, 59%
R = *p*-$MeOC_6H_4$, 64%

Oxidation of Hydrazones, Alkylhydrazones, *N*-Amino Heterocycles, *N*-Aminophthalimidates, and Aldazines. The oxidation of hydrazones to diazo compounds is not a generally useful reaction but it was uniquely effective in the oxidation of a triazole derivative (eq 36).[40]

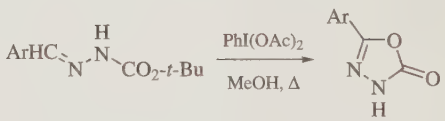


(36)

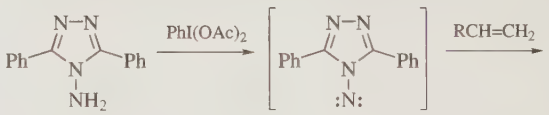
Oxidation of arylhydrazones proceeds with intramolecular cyclizations (eqs 37 and 38)[41] and aziridines may be formed via nitrene additions (eq 39).[42]

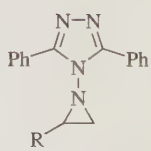


(37)



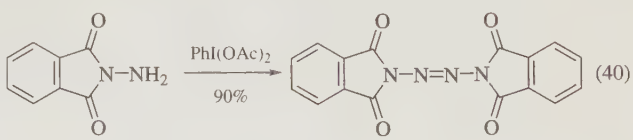
(38)





(39)

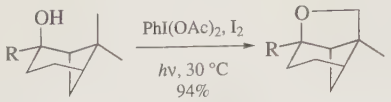
A linear tetrazane is formed in the oxidation of *N*-aminophthalimide (eq 40).[43]



(40)

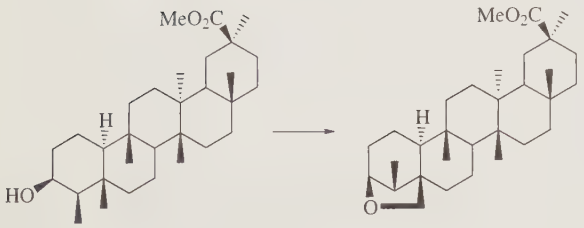
(Diacetoxyiodo)benzene/***Iodine*** is reported to be a more efficient and convenient reagent for the generation of alkoxyl radicals

than Pb^{IV}, Hg^{II}, or Ag^{I}, and this system is useful for intramolecular oxide formation (eqs 41 and 42).[44]



(41)

R = H, CH_2CO_2Et



(42)

Fragmentation processes of carbohydrate anomeric alkoxyl radicals[45] and steroidal lactols[46] using $PhI(OAc)_2/I_2$ have been reported.

First Update

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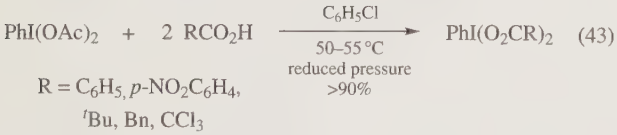
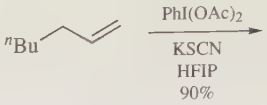
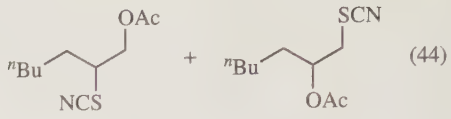
Preparation. Methods for the synthesis of $PhI(OAc)_2$ and aryl-substituted derivatives involve oxidation of iodoarenes with CH_3CO_3H, $NaBO_3$, $NaIO_4$, and CrO_3.[47–49] Peracid oxidation is typically employed to prepare the title reagent as well as solid-supported forms;[50] reactions with $NaBO_3$ and CrO_3, however, appear to be more versatile and have been used to synthesize both arene and heteroarene iodine(III) reagents. Alternatively, ligand exchange between $PhI(OAc)_2$ and a variety of carboxylic acids is quite facile and proceeds in high yield (eq 43).[51] Derivatives of stronger acids (i.e., *p*-TsOH) are also accessible starting from $PhI(OAc)_2$.[52,53]



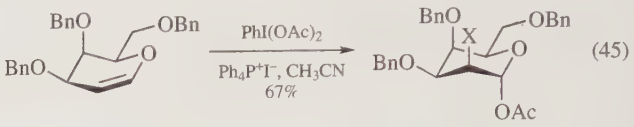
(43)

Reactions with Alkenes. The combination of $PhI(OAc)_2$ with nucleophilic reagents including KSCN, Me_3SiSCN, $(PhSe)_2$, and $Et_4N^+Br^-$ provides for the *trans*-selective functionalization of alkene derivatives (eq 44).[54,55] Good levels of regiocontrol are often observed in such reactions employing unsymmetrical olefins.[56,57] Treatment of $PhI(OAc)_2$ with halogen salts is known to generate $(AcO)_2X^-$, thought to be the active oxidant in reactions with glycals and other unsaturated materials (eq 45).[58] Alternatively, activation of $PhI(OAc)_2$ with catalytic $BF_3{\cdot}OEt_2$ enables the conversion of protected glycals to *trans*-1,2-bis(acetoxy)-glycosides.[59]





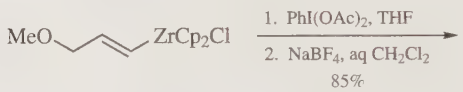
(44)



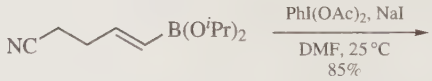
(45)

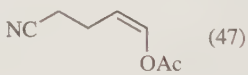
Ligand exchange of $PhI(OAc)_2$ with $Mg(ClO_4)_2$ and subsequent introduction of terminal or cyclic alkenes has been reported to give vicinal-bis(perchlorato)alkanes.[60] Reaction with cyclohexene selectively affords the *cis*-product.

Alkene derivatives such as alkenylboronic acids and alkenylzirconanes reacht with $PhI(OAc)_2$ to furnish alkenyliodonium salts (eq 46).[61] These transformations proceed with retention of olefin configuration.[62] Similarly, alkenylboron species add to $PhI(OAc)_2$ in the presence of NaI to give vinyl acetate products (eq 47). In these examples, (*E*)-alkenylboronates give stereochemically pure (*Z*)-configured enol acetates.[63]



(46)

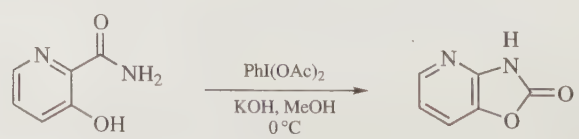




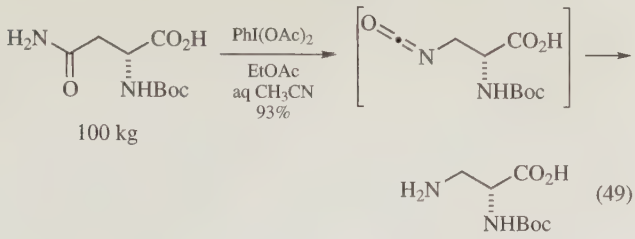
(47)

stereospecific

Rearrangement and Fragmentation Reactions. Hoffmann-type rearrangements of 1° amides were described originally using $PhI(OAc)_2$ in methanolic KOH solution.[64] Under such conditions, benzo-fused azolones are conveniently prepared (eq 48).[65] The need for strong base, however, does not appear essential for conducting such oxidations, as highlighted in the reaction of *N*-Boc asparagine (eq 49).[66] The mildness of these conditions for effecting the Hoffmann rearrangement and the inexpensive cost of $PhI(OAc)_2$ facilitate the large scale preparation of important amine derivatives. Similar transformation of *N*-substituted amidines with $PhI(OAc)_2$ leads to urea products via the corresponding carbodiimide intermediate.[67]

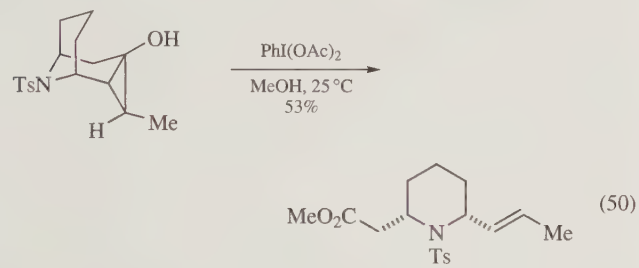


(48)



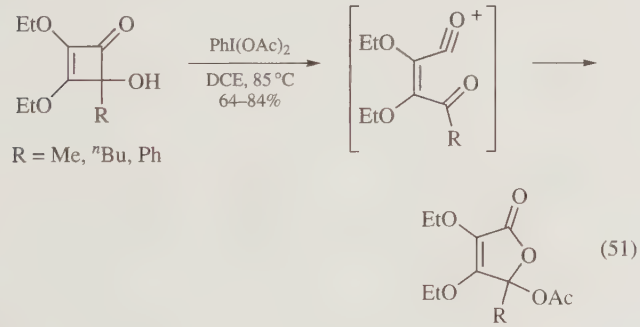
(49)

Rearrangement reactions of three- and four-membered cycloalkanols have been demonstrated in a number of notable contexts.[48] In the former case, fragmentation occurs with $PhI(OAc)_2$ in MeOH to yield the unsaturated ester product (eq 50).[68] Other combinations of hypervalent iodine reagents with Brønsted acids have also proven effective for this transformation.



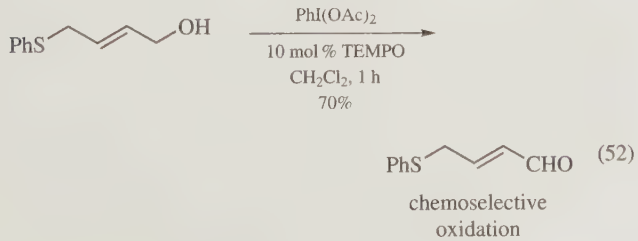
(50)

Synthesis of substituted furanones is made possible starting from squaric ester derivatives (eq 51).[69] Ring-expansion occurs through a putative acylium species, which may be trapped with either AcOH or MeOH depending on the choice of reaction solvent.



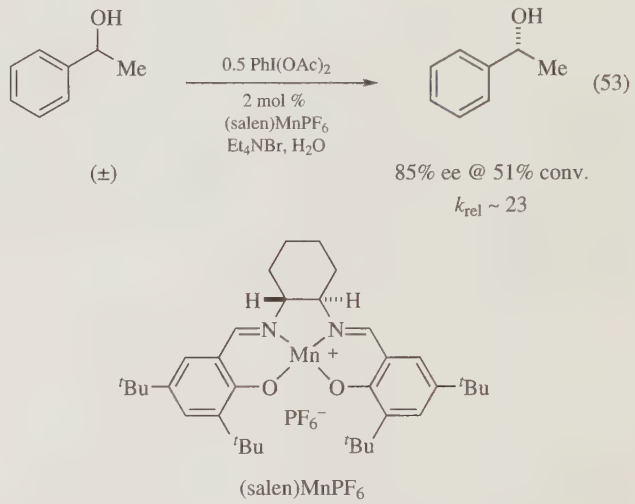
(51)

Alcohol Oxidation. Catalytic 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO), employed in combination with $PhI(OAc)_2$, will effect the oxidation of 1° and 2° alcohols to aldehydes and ketones, respectively (eq 52).[70,71] Reactions are generally high yielding and complete in a few hours. A related protocol uses polymer-supported $PhI(OAc)_2$ with KBr in H_2O to generate carboxylic acids from 1° alcohols.[50,72] Ketones may also be prepared in excellent yield with this latter method.



(52)

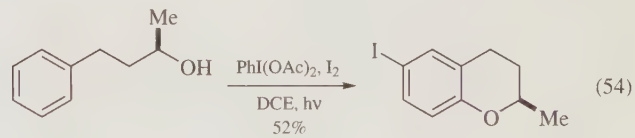
Alcohol oxidation has been described using (salen)CrCl (10 mol %) and $PhI(OAc)_2$.[73] Over-oxidation of 1° alcohols to carboxylic acids is not observed under these conditions. Chemoselective synthesis of α,β-unsaturated enones from allylic alcohols is also possible. Optically active (salen)$MnPF_6$ catalysts perform with $PhI(OAc)_2$ for the kinetic resolution of a small collection of chiral 2° alcohols (eq 53).[74]



(53)

In the absence of TEMPO or a metal catalyst, benzylic alcohols can be oxidized with alumina-supported $PhI(OAc)_2$ using microwave irradiation.[75] The reaction is conducted without solvent and is completed in 1–3 min.

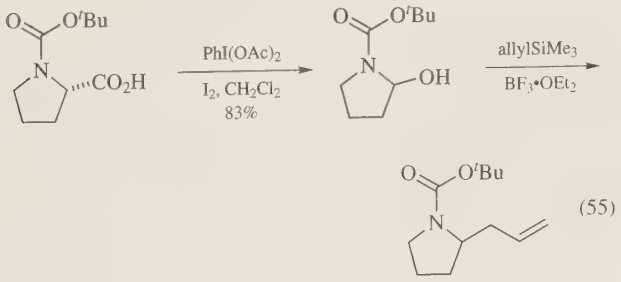
Decarboxylation and Related Radical Processes. Oxidation of alcohols and sulfonamides with $PhI(OAc)_2$ and I_2 under irradiation from a Hg- or W-lamp results in the formation of oxygen- and nitrogen-centered radicals, respectively.[76] Chroman derivatives may be synthesized in this manner from simple 3-arylpropan-1-ol starting materials (eq 54).[77] *N*-Alkylsaccharin products have been assembled in a similar fashion.[76] The $PhI(OAc)_2/I_2$ conditions also make available benzo-fused lactones from *ortho*-substituted benzoic acids.



(54)

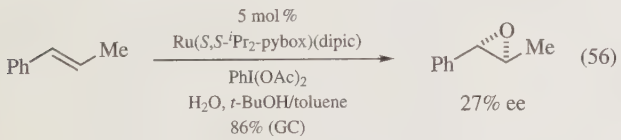
Decarboxylation of α-heteroatom-functionalized carboxylic acids occurs smoothly using $PhI(OAc)_2$ and I_2 without the requirement for photolysis.[78] When proline derivatives are employed for this reaction, the intermediate *N,O*-acetal may be treated with nucleophilic agents to give 2-substituted pyrrolidine products (eq 55).

Treatment of both aliphatic and electron-withdrawn aromatic carboxylic acids with $PhI(OAc)_2$, Br_2, and light affords alkyl- and aryl bromides, respectively.[79]



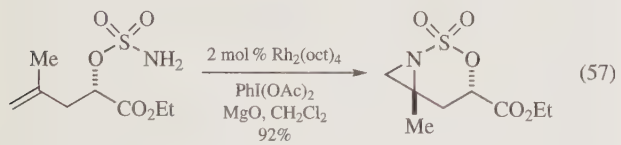
(55)

Alkene Epoxidation/Aziridination. Olefin epoxidation, principally of styrene derivatives, using a chiral Ru(II)-bisoxazoline catalyst and $PhI(OAc)_2$ takes place with modest enantiomeric induction (eq 56).[80,81] The rate of this reaction is enhanced by the presence of H_2O. An electron-deficient Fe-porphyrin complex also serves as a catalyst for *O*-atom transfer using $PhI(OAc)_2$ as the terminal oxidant.[82]

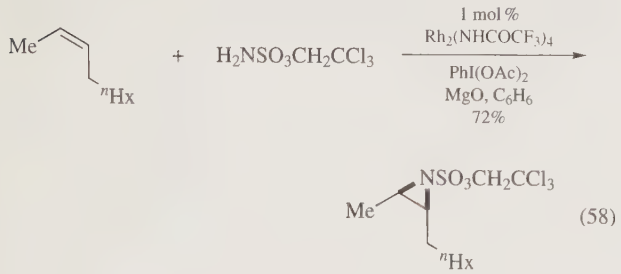


(56)

Both intra- and intermolecular aziridination of alkenes can be accomplished with $PhI(OAc)_2$ and an appropriate nitrogen source (eqs 57 and 58).[83,84] The former reactions have been described using carbamate, sulfonamide, and sulfamate substrates. Typical catalysts utilized for these processes include Ru, Rh, and Cu complexes.[85–88] By employing chiral transition metal catalysts, asymmetric induction has been realized in both intra- and intermolecular reactions.

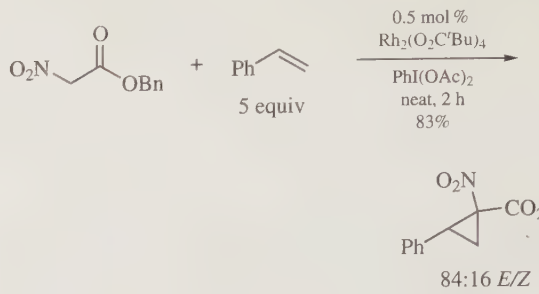


(57)



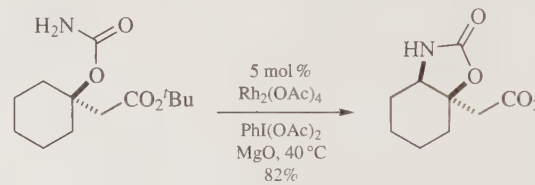
(58)

Alkene Cyclopropanation. Olefin cyclopropanation is possible in selected cases through in situ generation of stabilized phenyliodonium ylides using $PhI(OAc)_2$ and enolate equivalents such as Meldrum's acid or methyl nitroacetate (eq 59).[89] The intermediate ylide decomposes in the presence of $Rh_2(O_2CR)_4$ catalysts to generate a putative metallo-carbene species as the reactive cyclopropanating agent. With methyl nitroacetate, substituted cyclopropanes are formed with good levels of *cis/trans* stereocontrol.[90] PhI=O has also been employed for related reactions using both Rh and Cu complexes.[91,92]



(59)

C–H Amination. A number of amine-based starting materials will react with $PhI(OAc)_2$ and a transition metal catalyst to promote selective C–H bond amination.[84] Intramolecular oxidation of substrates such as carbamates, ureas, sulfamates, sulfonamides, and sulfamides affords the corresponding heterocycles in high yields and, in many cases, with excellent diastereocontrol (eqs 60 and 61).[93–95] Insertion into optically active 3° C–H centers is reported to be stereospecific (eq 62).[96,97] Chiral Ru, Mn, and Rh catalysts have all been utilized for asymmetric C–H amination, though product enantiomeric induction is variable. Many of the heterocyclic structures furnished from these reactions function as versatile precursors to 1,2- and 1,3-amine derivatives.



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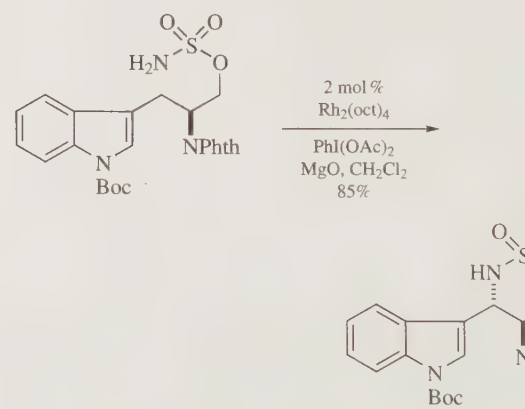
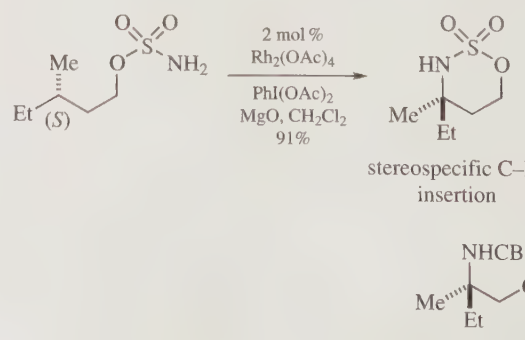
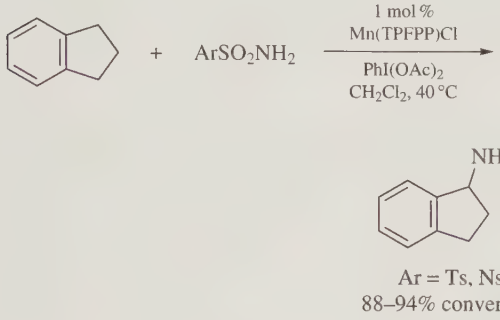


(61)



(62)

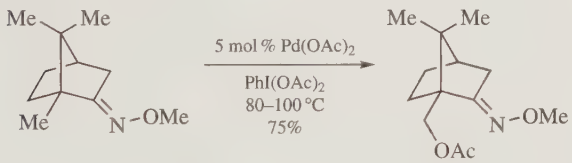
Intermolecular C–H amination has been demonstrated using primarily *p*-$TsNH_2$ or 2,2,2-trichloroethoxysulfonamide as the nitrogen source (eq 63).[93,95,98] Reactions operate most effectively with benzylic hydrocarbons, although C–H amination of 3° and 2° C–H bonds is possible. Other sulfonamides as well as certain acyl amides can be employed in this unique oxidation reaction.[99] These methods generally function with limiting amounts of the starting hydrocarbon and a slight excess of both the nitrogen source and $PhI(OAc)_2$.



(63)

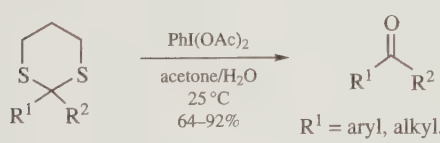
Ar = Ts, Ns
88–94% conversion

C–H Oxygenation. The combination of $PhI(OAc)_2$ and catalytic $Pd(OAc)_2$ can be used with functionalized aromatic and aliphatic hydrocarbons for the directed oxygenation of C–H bonds (eq 64).[100,101] Substrates containing pyridine, azole, imine, and oxime groups function under these reaction conditions to afford acetoxylated or methoxylated compounds. Oxidation of 1° methyl centers is strongly preferred over 2° and 3° C–H sites.



(64)

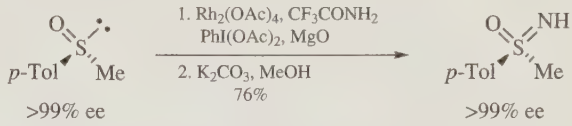
Heteroatom Oxidation. Oxidation of organosulfur compounds with $PhI(OAc)_2$ is noted in a number of different contexts. A particularly useful method for deprotection of dithiane-derived aldehydes and ketones employs $PhI(OAc)_2$ in aq acetone (eq 65).[102] Related to this process, organosulfides may be selectively oxidized to sulfoxides by employing the supported reagent $PhI(OAc)_2/Al_2O_3$ or with a combination of $PhI(OAc)_2$ and Ac_2O.[103]



(65)

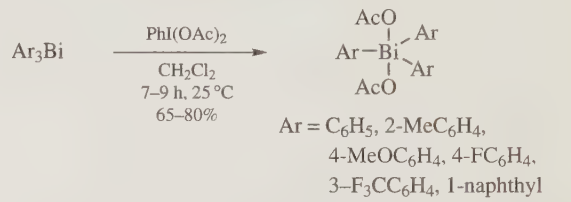
R^1 = aryl, alkyl, vinyl
R^2 = H, alkyl

Synthesis of sulfilimines and sulfoximines from sulfides and sulfoxides, respectively, may be accomplished with $PhI(OAc)_2$ and *o*-$NsNH_2$ or CF_3CONH_2 as the nitrogen source.[104] $Rh_2(OAc)_4$ was found to be an optimal catalyst for this process (eq 66). Removal of the CF_3CO-protecting group from the products is facilitated with methanolic base, thereby affording the *N*-unsubstituted products. Under these conditions, reaction of a chiral sulfoxide is stereospecific. *N*-Sulfonyl sulfilimine formation has also been reported using arenesulfonamides and $PhI(OAc)_2$ in the absence of a metal catalyst.[105]



(66)

Diacetoxyiodobenzene has been utilized for the oxidation of organic derivatives of both bismuth and antimony.[103] Reactions of triaryl species proceed under mild, neutral conditions to yield the corresponding pentavalent diacetates (eq 67).[106]



(67)

Ar = C_6H_5, 2-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 3-$F_3CC_6H_4$, 1-naphthyl

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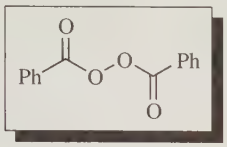
Dibenzoyl Peroxide[1–4]



[94-36-0] $C_{14}H_{10}O_4$ (MW 242.23)

(initiator for radical reactions such as allylic and benzylic halogenation,[5] radical addition to carbon–carbon multiple bonds to form C–heteroatom (halogen, S, Si, Ge, P, and N) bonds,[2] C–H additions across multiple bonds[4] in an intermolecular[1] and intramolecular[6] fashion, homolytic aromatic substitution in electron-deficient heteroaromatics;[7] reagent for benzoyloxylation of enolates, enamines, and other electron-rich systems;[8] oxidizing agent for N, P, Si, S, and Se compounds; oxidizing agent in redox chain reactions with transition metals[9])

Alternate Name: DBP.

Physical Data: mp 103–106 °C (dec).

Solubility: sparingly sol water or alcohol; sol benzene, chloroform, and ethers.

Form Supplied in: white crystalline powder.

Analysis of Reagent Purity: the peroxide content can be established by iodometric titration.[10]

Handling, Storage, and Precautions: explosive; harmful if exposed by ingestion or skin contact; strong oxidizer; susceptible to explosion by shock, friction or heat; autoignition temperature 79 °C. *Caution*: all experiments involving peroxy compounds should be carried out behind a safety shield. Excess peroxide should be destroyed before working up the reaction.[11]

Original Commentary

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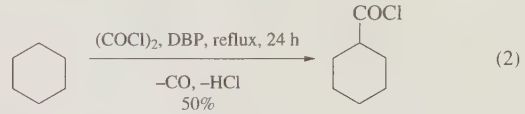
Introduction. Dibenzoyl peroxide is a widely used initiator for radical reactions. It undergoes thermal homolytic cleavage of the O–O bond with a half-life of about 1 h at 95 °C (eq 1).[12] This homolysis may also be effected by light as well as transition metal catalysts.[9]

$$(PhCO_2)_2 \longrightarrow 2\,PhCO_2\bullet \longrightarrow Ph\bullet + CO_2 \qquad (1)$$

Initiator for Halogenation Reactions. Even though DBP has been used as an initiator for functionalization of unactivated hydrocarbons (eq 2), more common are the applications for halogenations of allylic (eqs 3 and 4)[5,13] and benzylic (eq 5)[14] positions. DBP also serves as an initiator for halogenation of silanes by replacement of a Si–H bond.[15]

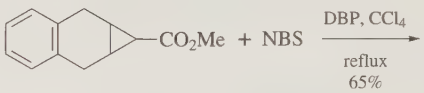
Initiator for Radical Additions to Unsaturated Compounds. The primary steps in the radical addition of X–Y to unsaturated compounds are shown in eqs 6–10. By far the largest application of this reagent[16] is in radical chain polymerization of vinyl compounds such as vinyl chloride, vinyl acetate, butadiene derivatives, styrene, and various acrylic monomers. The topic of polymerization is beyond the scope of this article. Excellent monographs and reviews dealing with this subject are available.[17]

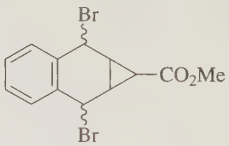


(2)

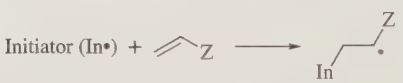
(3)

(4)

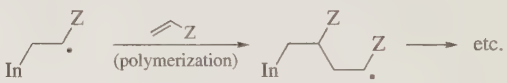




(5)

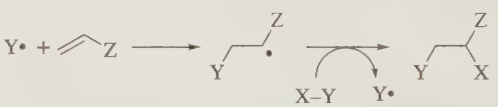


(6)



(7)

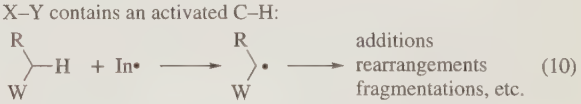
(8)



(9)

repeat ⟶ 1:1 adduct of the alkene and X–Y

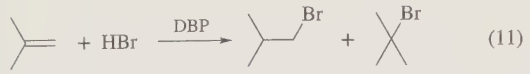
when X–Y contains an activated C–H:



(10)

Formation of a 1:1 adduct (eq 9) will be favored when X–Y is an efficient chain transfer agent. For reactions of short chain lengths, an excess of X–Y and a steady concentration of the initiator should be present in the reaction medium.[2] Since the original discoveries of the anti-Markovnikov addition of HBr (eq 11),[18] and of carbon tetrachloride to alkenes (eq 12),[1] a large number of related reactions have been reported. DBP catalyzes the addition of a wide variety of X–Y type compounds to carbon–carbon multiple bonds. These include H–Br, thiols, mercapto acids, thiophosphoric acids, hydrogen sulfide, silanes, germanes, phosphorus halides,

phosphorus acids and esters, and various oxides of nitrogen.[2] The important C–C bond-forming reactions are described below.



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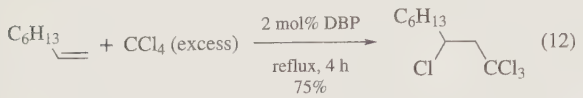
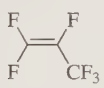
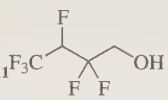
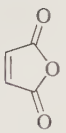
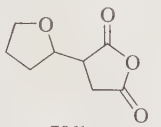
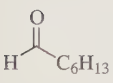
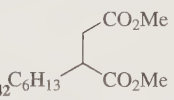
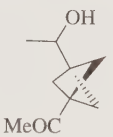
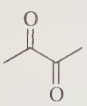
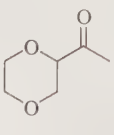
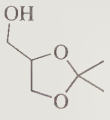


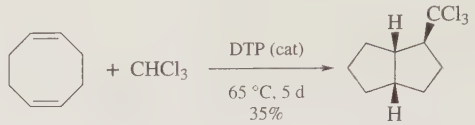
(12)

Intermolecular Carbon–Carbon Bond Forming Reactions. When the compound X–Y contains an activated C–H bond, initiators such as DBP and di-*t*-butyl peroxide initiate the radical reactions by abstraction of this hydrogen (eq 10) from the substrate, and the resultant radical enters the radical chain cycle. Substrates of this kind are poor chain transfer agents and typically a higher concentration of the substrate and a steady supply of the initiator are needed for a viable reaction. Representative examples of carbon–carbon bond forming reactions initiated by DBP are listed in Table 1[11,41,42,43,44,45] (see also ***1,1-Di-t-butyl Peroxide***). A more complete list is available in two excellent reviews.[1,4]

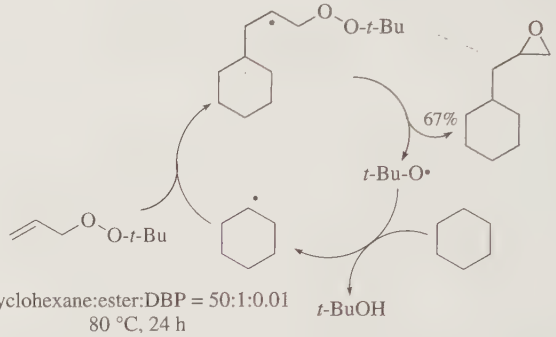
Table 1 Intermolecular C–C forming reactions via radicals

Precursor	Alkene	Reaction conditions	Product
MeOh		DBP (cat), 120 °C, 3 h[11]	 67%
		DBP (cat), 65 °C[41]	 70%
		DBP (cat), 87 °C, 24 h[42]	 71%
		DBP[43]	 Yield not given
		DBP, 80 °C, 2 h[44]	 48%
	CH_2O	DBP, *hν*[45]	 86%

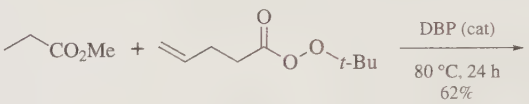
The intermolecular additions may be coupled to an intramolecular cyclization (eq 13)[19] or an S_H2 reaction.[20] The S_H2 reactions are useful for the synthesis of epoxy compounds (Scheme 1) or lactones (eq 14). Radicals from nitriles, ketones, ethers, and polyhaloalkanes also undergo similar addition–substitution reactions.

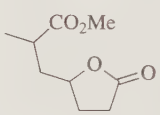


(13)



Scheme 1 Intermolecular addition–S_H2 reaction of peresters

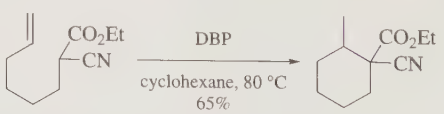




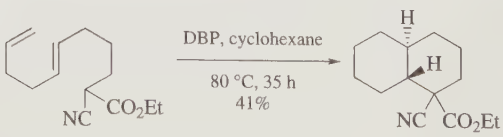
(14)

Addition of various α-carboxyl radicals to alkenes is best carried out with a high temperature initiator such as di-*t*-butyl peroxide, although reports of using DBP are known. This subject has been extensively reviewed.[21]

Intramolecular Additions. The intramolecular versions of the C–H additions mentioned above have been extensively studied by Julia and co-workers (eqs 15 and 16).[6] These reactions, while not very practical from a synthetic standpoint, nonetheless have played a key role in the development of radical synthetic methodology.[22,23] A related cyclization (eq 17) was used by Barton and co-workers for the synthesis of a tetracycline intermediate.[24] An interesting variant of this reaction is the cyclization of geranyl acetate to a benzoyloxyfarnesyl acetate (eq 18).[25] The radical reaction is initiated by DBP and the Cu salt serves as an oxidant for the final cyclized radical.



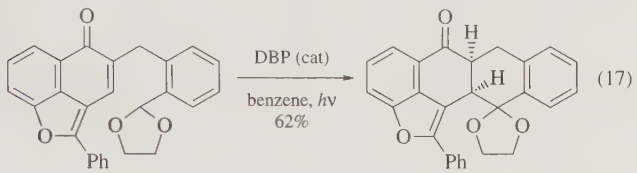
(15)

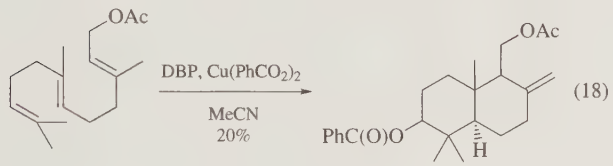


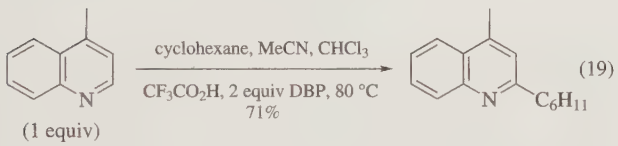
(16)

Initiator for Radical Additions to Electron-Deficient Heteroaromatic Compounds. Minisci and co-workers have developed

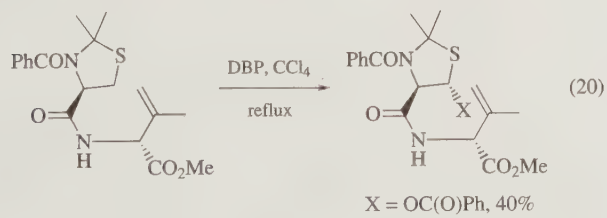
radical-mediated homolytic substitution reactions for various electron-deficient aromatic nuclei.[7] Radicals derived from alkyl halides, dioxane,[26] dimethylformamide,[27] and even cyclohexane[26] can be added to protonated heteroaromatic compounds. The addition of a cyclohexyl radical (eq 19) proceeds in good yields even when the reaction medium contains a large excess of chloroform and acetonitrile. The highly electrophilic nature of the $\bullet CCl_3$ and $\bullet CH_2CN$ completely inhibits the reaction towards the protonated heterocycle. Under these conditions, ethyl acetate gives the electrophilic radical $\bullet CH_2CO_2Et$ and the nucleophilic radical $MeCO_2CHMe$, but only the latter adds.

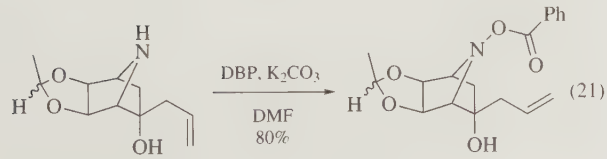


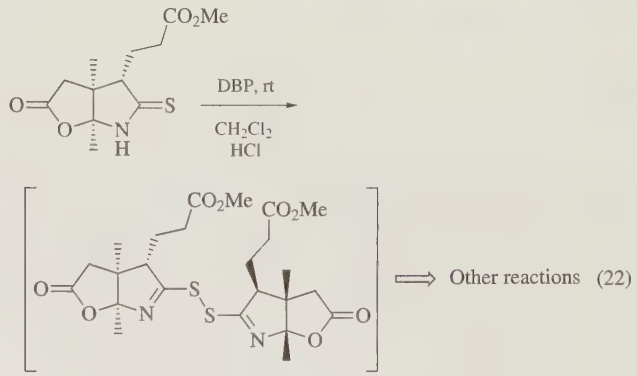


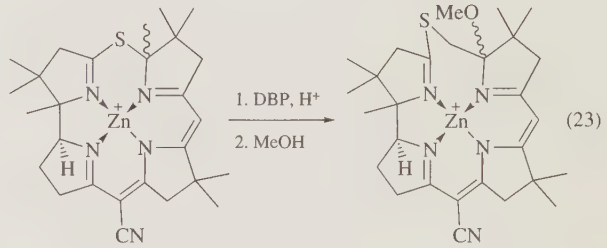


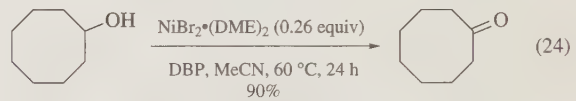
As an Oxidant. Benzoyl peroxide oxidizes ethers to α-benzoyloxy ethers, and alkyl sulfides to α-benzyloxy sulfides (eq 20).[28] Tertiary amines are oxidized to amine oxides, while secondary amines give *N*-benzoyloxy amines (eq 21).[29] In the presence of a mild base, DBP acts as a very selective oxidizing agent for hydroquinones.[30] Aldehydes and benzylic positions are not affected. Two key steps in the Eschenmoser synthesis of the corrin nucleus make use of DBP (eqs 22 and 23).[31] Secondary alcohols are oxidized to ketones with dibenzoyl peroxide and ***Nickel(II) Bromide*** (eq 24).[32] A benzoyl peroxide-mediated annulation used by Kishi in the synthesis of sporidesmin B (eq 25)[33] is likely to be an ionic (vis-á-vis radical) reaction. A 1:1 mixture of DBP and ***Hexamethyldisilazane*** has been used as an epoxidizing agent for acid-sensitive alkenic substrates.[34]

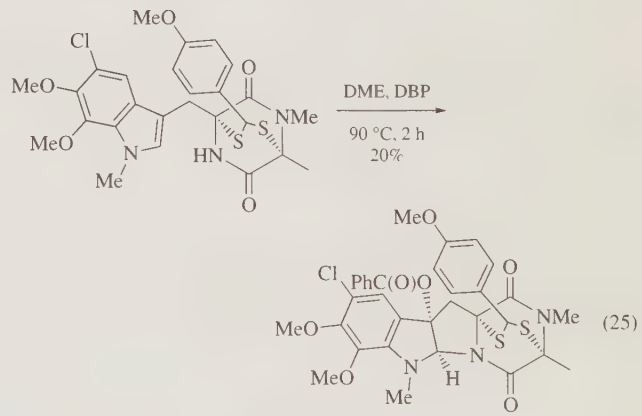






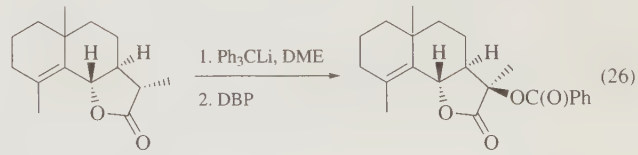






As a Benzoyloxylation Agent[8]. Under catalysis by ***Iodine***, benzoyloxylation of aromatic and heteroaromatic compounds takes place. Nucleophilic compounds such as malonates,[35] phenols,[36] enamines, and indoles[37] also react with DBP to give benzoyloxylation products. Secondary amines are converted into *N*-benzyloxy amines (eq 20).[29] An improved protocol[38] for this reaction and an application for synthesis of N^5-hydroxy-L-ornithine[39] have appeared in the literature.

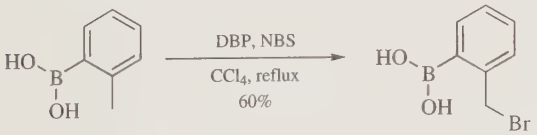
Benzoyl peroxide has been used for α-benzoyloxylation of an enolate (eq 26).[40]



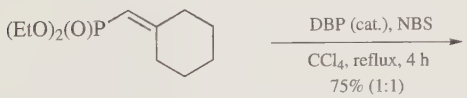
First Update

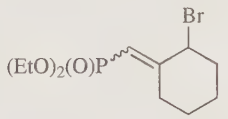
Fabien Gagosz
Ecole Polytechnique, Palaiseau, France

Initiator for Halogenation Reactions. DBP is commonly used as an initiator in the radical halogenation of a wide variety of substrates. In combination with NBS or NCS in refluxing CCl_4, benzylic (eq 27),[46] allylic (eq 28),[47] and α-carbonyl positions (eq 29)[48] are easily halogenated in generally good yield.

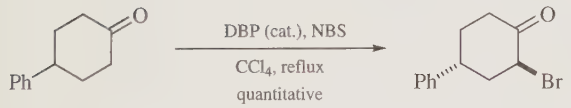


(27)



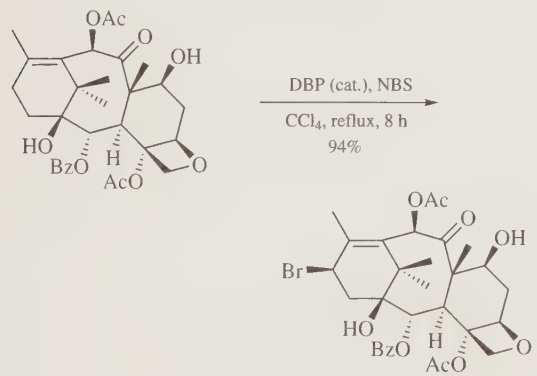


(28)



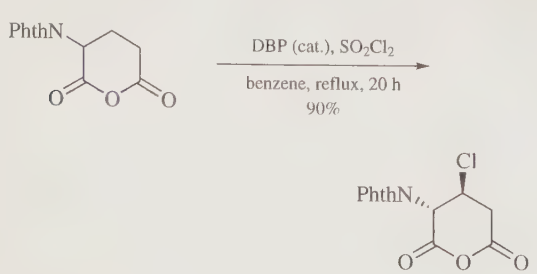
(29)

An impressive example is the diastereoselective bromination of 13-deoxybaccatine reported by Georg and co-workers (eq 30), which emphasizes the mildness of the reaction conditions employed.[49]

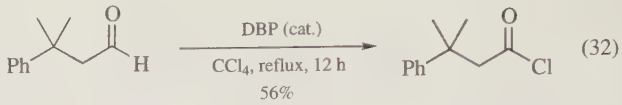


(30)

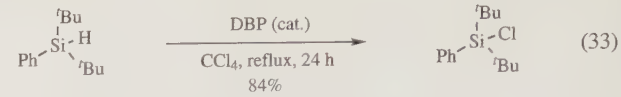
Less activated positions may also be selectively chlorinated using sulfuryl chloride in refluxing benzene (eq 31).[50] Aldehydes or silanes can thus be converted into the corresponding acyl chlorides or chlorosilanes using the couple DBP/CCl_4 (eqs 32 and 33).[51,52]



(31)

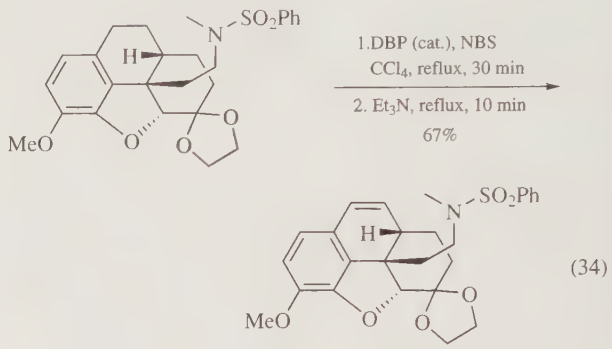


(32)



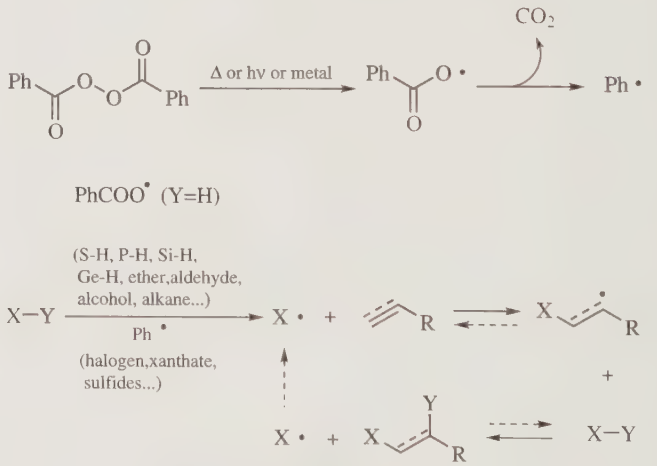
(33)

The radical halogenation step can be followed by an additional dehydrobromination reaction leading to the corresponding alkene as exemplified by the synthesis of (−)-dehydrocodeinone by Mulzer and co-workers (eq 34).[53]



(34)

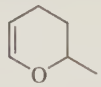
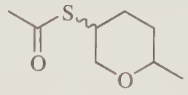
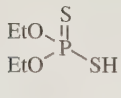
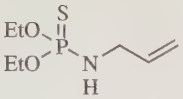
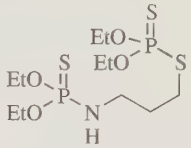
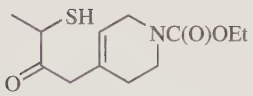
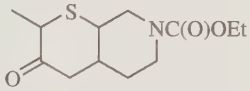
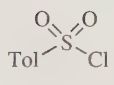
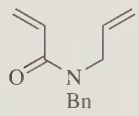
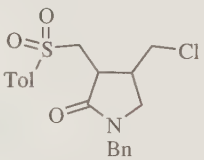
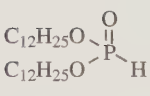
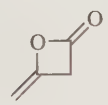
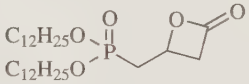
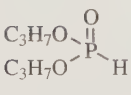
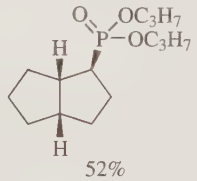
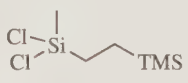
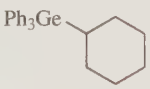
Initiator for Radical Additions to Unsaturated Compounds. Initiation of the "Kharasch-type" reaction is by far the largest application of DBP in organic synthesis.[54,55,1,2] This radical chain transformation, which is an atom or group transfer process, typically allows the creation of a new heteroatom-carbon bond or carbon-carbon bond by addition of a wide variety of radical precursors to an olefinic bond (Scheme 2).[56]



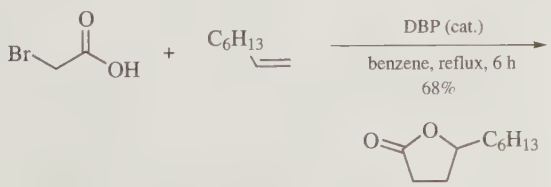
Scheme 2 Generalized Kharasch-type reaction mechanism

This transformation has been applied to the introduction of diverse sulphur,[57–60] phosphorus,[61,62] silicon,[63] and even germanium[64] moieties as illustrated by the examples listed in Table 2. However, the more synthetically useful application deals with the formation of carbon-carbon bonds. Benzoyloxy radicals ($PhCOO^{\bullet}$) derived from DBP may abstract an activated hydrogen atom from a defined substrate such as an ether,[65] an aldehyde,[66] an alcohol,[67] or even an alkane.[68] The resulting radical $X^{\bullet}$ then adds to an activated radical trap to give diversely functionalized adducts (Table 3). Alternatively, loss of carbon dioxide from benzoyloxy

Table 2 C-Heteroatom bond formation via radicals

Precursor	Alkene	Reaction conditions	Product
		DBP (cat.), 0 °C, 12 h[57]	 90% (70:30)
		DBP (cat.), 80 °C, 16 h[58]	 74%
		DBP (cat.), 100 °C[59]	 Yield not given
		DBP (cat.), rt, hv[60]	 60% (90:10)
		DBP (cat.), 120 °C, 1 h[61]	 65%
		DBP (cat.), 80 °C, 8 h[62]	 52%
		DBP (cat.), 45 °C, 9 d[63]	 74%
Ph_3GeH		DBP (cat.), hv, 48 h[64]	 Yield not given

radicals leads to the formation of phenyl radicals ($Ph^{\bullet}$), which are efficient radical chain initiators when the substrate possesses a halogen atom (Cl, Br, I) or a dithiocarbonate functionality. The DBP initiated radical addition of polyhalomethane derivatives to an unsaturated substrate is by far the most popular transformation of this family (last example in Table 3).[69] When the reaction is performed with an α-halocarbonyl precursor, the presence of the halogen in the adduct may be used to implement another "one-pot" ionic transformation such as the formation of lactones from α-bromoacetic acid and an olefin (eq 35).[70]

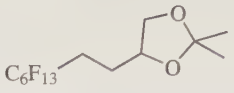
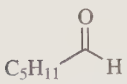
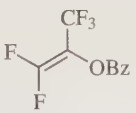
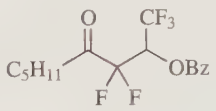
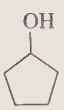
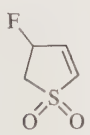
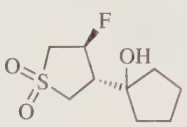
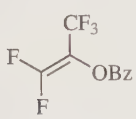
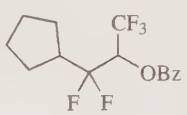
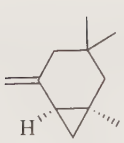
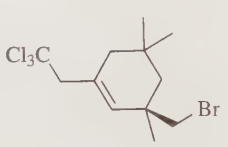


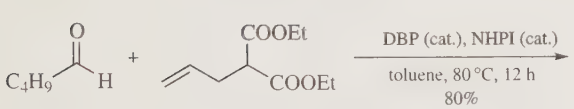
(35)

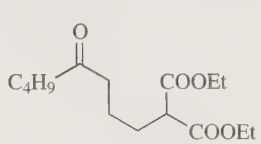
However, this transformation suffers from severe limitations. Indeed, when the initiation step involves a hydrogen abstraction, the substrate is generally a poor radical chain carrier. It therefore needs to be used in large excess and the adduct radical has to be rather electrophilic in character (use of electron poor olefin). It should be noted that an improved protocol using DBP as the initiator and a catalytic amount of a polar reversal catalyst (*N*-hydroxyphthalimide = NHPI) has been developed recently for the hydroacylation of unactivated alkenes, thus opening new perspectives for this transformation (eq 36).[71]

Although the reaction conditions are subjected to some severe constraints, several synthetic applications of the Kharasch reaction have appeared in the literature.[72] A typical example has been reported by Wender and co-workers in the total synthesis of (±) subergorgic acid (eq 37).[73]

Table 3 C–C bond formation via radicals

Precursor	Alkene	Reaction conditions	Product
		DBP (cat.), reflux, 4 h[65]	 91%
		DBP (cat.), 60 °C, 3d[66]	 85%
		DBP (cat.), 110 °C[67]	 87%
		DBP (cat.), 60 °C[68]	 68%
$BrCCl_3$		DBP (cat.), 100 °C[69]	 87%

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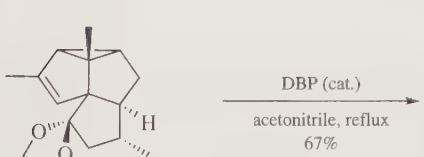
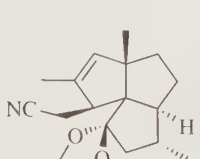
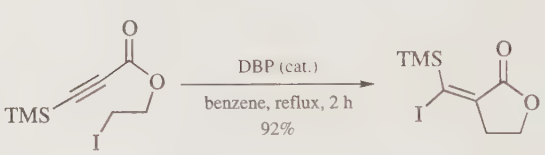
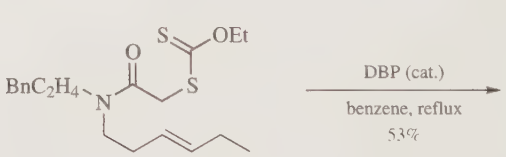
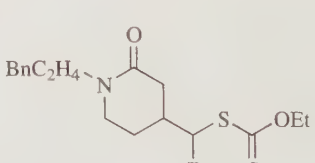


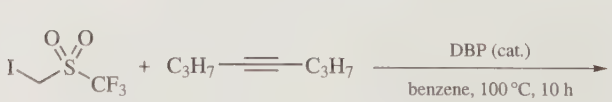

(37)

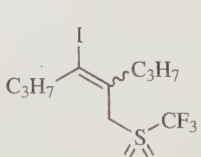


(38)



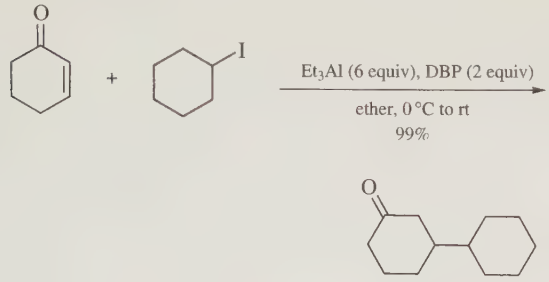

(39)




(40)

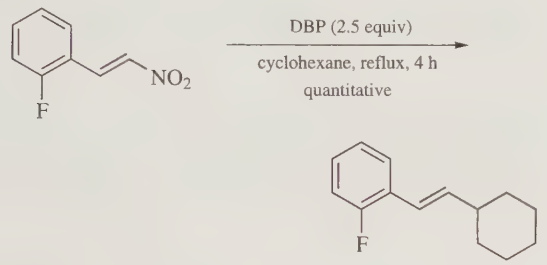
New developments in the field of carbon-carbon bond formation have appeared recently. For example, alkyl iodides or dithiocarbonates have been used as radical precursors in the presence of DBP to effect various kinds of radical ring closures (eqs 38 and 39),[74,75] while iodomethyltriflones were found to add efficiently onto alkenes and alkynes (eq 40).[76]

Interestingly, DBP has been employed in excess as a co-initiator with triethylaluminum to induce free radical reaction of alkyl iodides with α,β-unsaturated compounds (eq 41).[77]

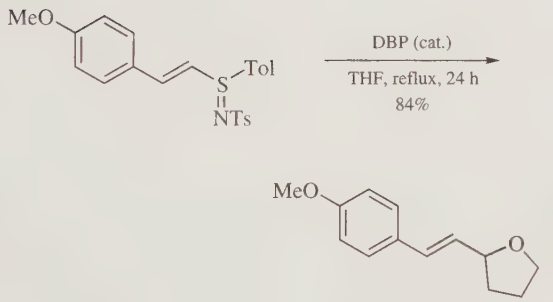


(41)

Very recently, interest has focused on "vinylation-type" radical reactions and several processes involving DBP, used either in a sub- or over-stoichiometric amount, and alkyl iodides, ethers, or alkanes as radical precursors have been developed (eqs 42 and 43).[78,79]



(42)

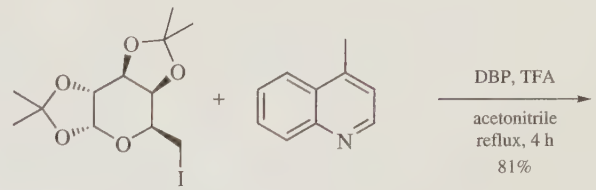


(43)

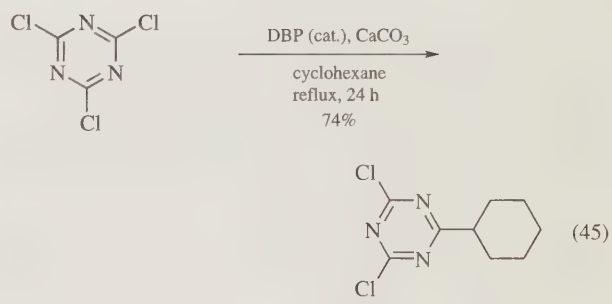
Two recent papers have reported an acceleration of the Reformatsky reaction of bromomalonates with aromatic aldehydes in the presence of DBP under wet conditions. Although the authors have postulated a plausible radical pathway, the effect of DBP on the course of the reaction is not yet clear.[80]

Initiator for Radical Additions to Electron-Deficient Aromatic Compounds. The Minisci radical alkylation reaction offers a unique and complementary means of functionalizing electron-deficient aromatic compounds.[81] The main importance of this reaction derives from the large variety of radical types (*σ-type radicals* such as acyl, carbamoyl, and alkoxycarbonyl radicals or *π-type radicals* without electron-withdrawing groups directly attached to the radical center), the high regio- and chemoselectivity and the simple experimental conditions. For instance, 6-iodogalactose was reacted regioselectively with 4-methyl-quinoline in the presence of DBP and TFA in refluxing acetonitrile to give the corresponding adduct in excellent yield (eq 44).[82]

Minisci and co-workers also reported a variant of the classical transformation involving substitution of chlorine atoms on aryl and vinyl chlorides in the presence of DBP and $CaCO_3$, the latter being used as a base to trap the HCl formed during the course of the reaction (eq 45).[83]



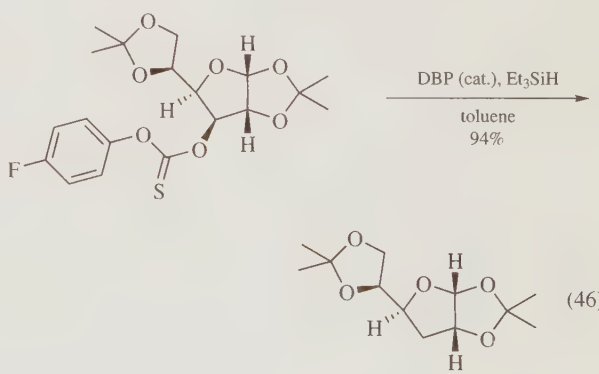
(44)



(45)

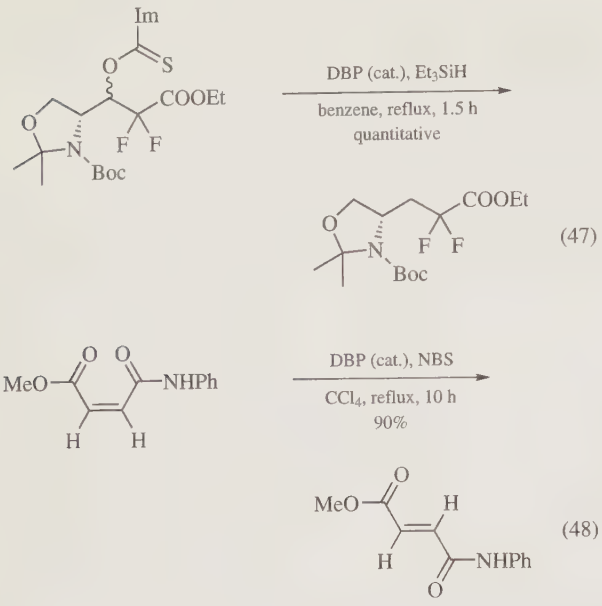
A new method using DBP as the initiator in the presence of a catalytic amount of copper (II) acetate was developed to effect the homolytic aromatic substitution by *n*-perfluoroalkyl radicals.[84]

Miscellaneous Radical Transformations. Even though the couple AIBN/ Bu_3SnH is generally employed for the Barton-McCombie deoxygenation reaction, DBP was found to be an efficient radical initiator in the reduction of *p*-fluorophenoxylthiocarbonates (eq 46),[85] imidazolylthiocarbonates (eq 47),[86] or dithiocarbonates[87] to the corresponding alkanes in the presence of a trialkylsilane.

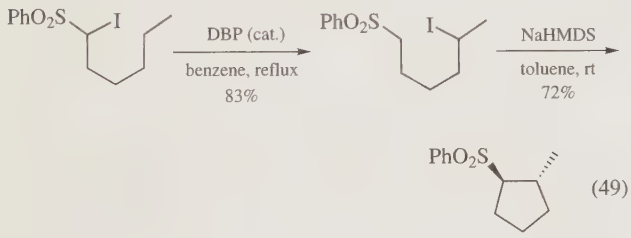


(46)

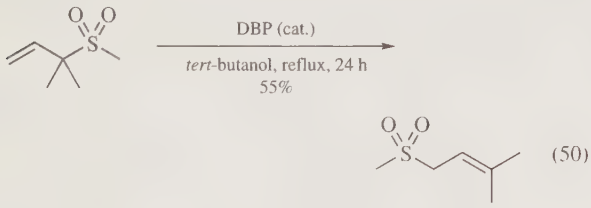
In the presence of NBS, DBP also mediates several types of *Z*- to *E*- carbon–carbon double bond isomerizations in nearly quantitative yield (eq 48).[88]



A radical rearrangement of an α-iodoalkyl sulfone using DBP as initiator has been reported. This reaction, which involves a 1,5-hydrogen atom transfer, is practical and leads to convenient precursors for the synthesis of cyclopentane derivatives (eq 49).[89]

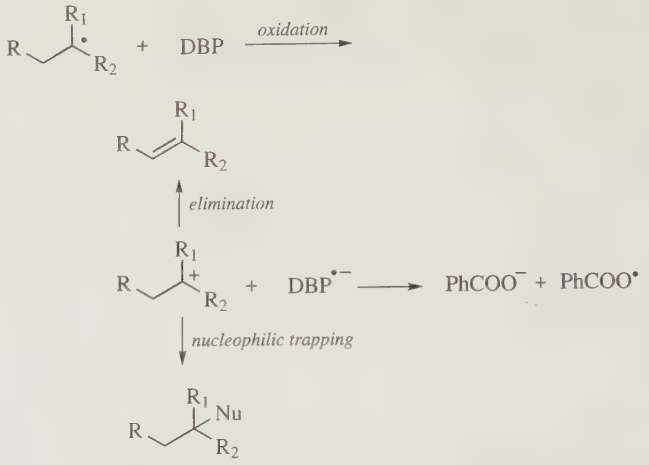


DBP also proved to be an efficient catalyst for the isomerization of allylic sulfones (eq 50).[90] This simple transformation has been extended to numerous radical cascades of high synthetic interest.[91]

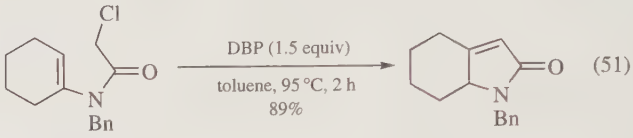


As an oxidant. When DBP is used as the initiator in a radical transformation such as a cyclization, the radical obtained after the addition step is sometimes too stable to efficiently propagate the chain. This latter can therefore be oxidized by an excess of DBP to generate a cation which can evolve in various ways (Scheme 3).

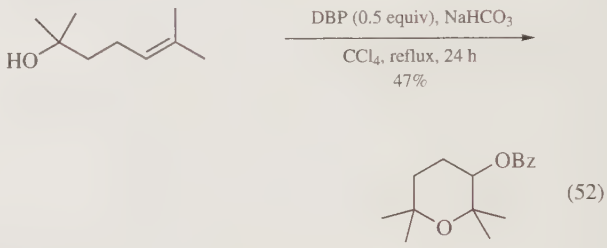
A number of oxidative radical cyclizations using DBP as an initiator and oxidant have been reported by Miranda and co-workers. An example of a 5-*endo* oxidative radical cyclization on an enamide system is shown in (eq 51).[92]



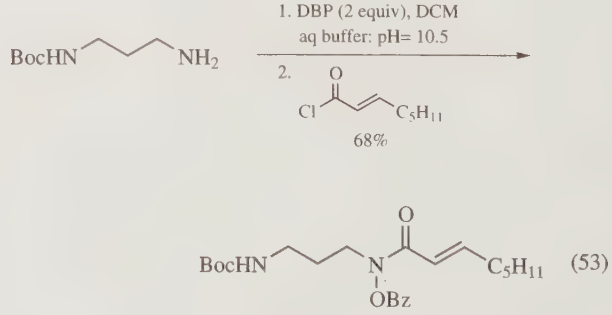
Scheme 3 Oxidation of a radical by DBP



Another example of a 6-*endo* oxidative radical cyclization, followed by the internal capture of the resulting cation by the benzoic acid present in the reaction medium, has been described by Bugarcic et al. (eq 52).[93]

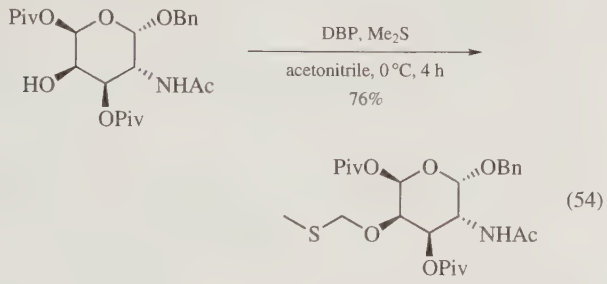


The nature of the products resulting from the oxidation of amines with DBP depends on the degree of substitution of the substrate. Tertiary amines are oxidized to amine oxides, while secondary amines are converted into *N*-benzoyloxy amines.[29] Depending on the reaction conditions employed, primary amines are either transformed to the corresponding benzamide or to the benzoyloxy compound.[94] An improved protocol for the benzoyloxylation of primary amines[95] with DBP in an aqueous buffered medium has been applied to the total synthesis of acinetoferrin (eq 53) as reported by Phanstiel and co-workers.[96]



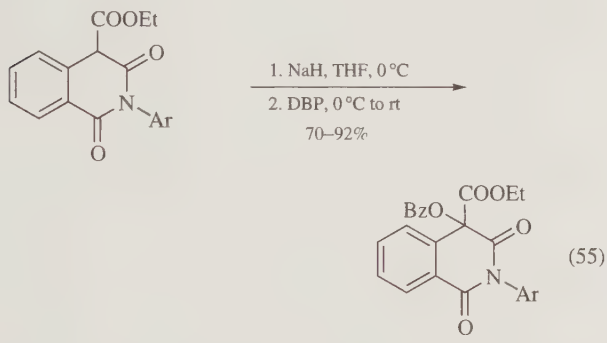
DBP also oxidizes thioethers to α-benzoyloxysulfides.[97] This transformation has been exploited by Kyler and co-workers for

the protection of alcohols as methylthiomethylethers (MTM).[98] This mild method, compatible with a wide variety of other protecting groups (triphenylmethyl, tetrahydropyranyl, silyl ...), is largely employed in the synthesis of sugar derivatives (eq 54).[99] The use of an additional non-nucleophilic hindered base such as 2,6-lutidine is sometimes required to neutralize the benzoic acid released during the course of the reaction, thus preventing the degradation of reactants and products.



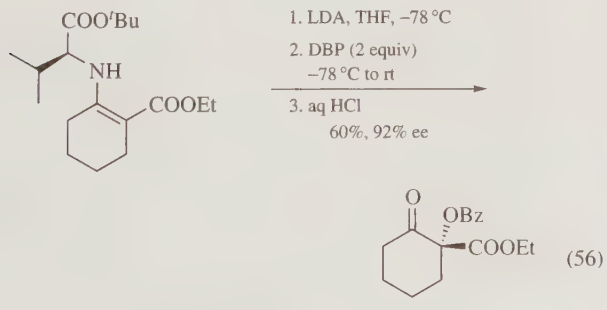
(54)

1,3-Diketones,[100] 1,3-ketoesters,[101] and 1,3-ketoamides[102] react with DBP to give the corresponding 2-benzoyloxy derivatives (eq 55).



(55)

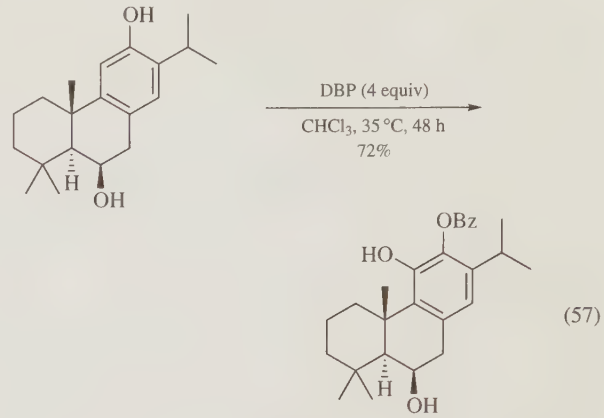
An efficient asymmetric version of this transformation starting from chiral ketoenamines has been published by Snyder and coworkers[103] (eq 56) and used in the synthesis of tanshindiol A.[104]



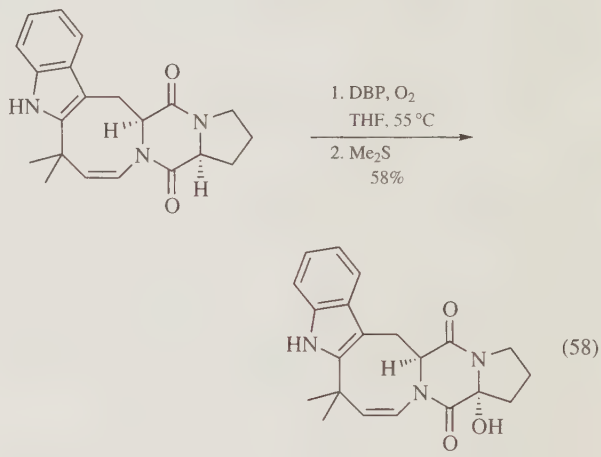
(56)

Although simple lithium[105] or aluminum[106] enolates are less commonly employed as nucleophiles, they can be reacted with DBP to give oxidized products in moderate to good yields. Enamines[107] and indoles[108] are generally oxidized with difficulty while phenols give benzoyloxy derivatives (eq 57),[109] and hydroquinones are transformed into benzoquinones.[110]

Several substrates are oxidized by DBP in the presence of oxygen. They can lead to α,β-unsaturated ketones when the oxidized position is allylic[111] or to compounds bearing an hydroperoxy functionality as in the case of indoles.[112] An example of this transformation applied to the total synthesis of (+)-deoxyisoaustamide and leading to the α-hydroxylation of a proline subunit after reduction of the hydroperoxy moiety with DMS has been reported recently by Corey and co-workers (eq 58).[113]



(57)



(58)

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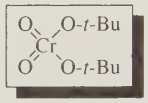
Di-*t*-butyl Chromate[1]

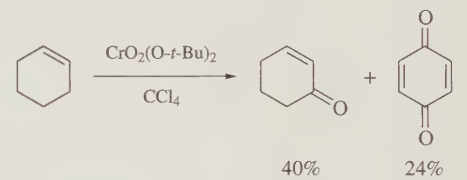


[1189-85-1] $C_8H_{18}CrO_4$ (MW 230.22)

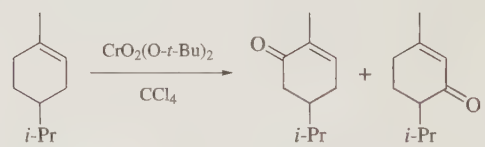
(selectively oxidizes allylic methylene groups to carbonyl groups; oxidizes alcohols to aldehydes and ketones)

Alternate Names: *t*-butyl chromate.
Physical Data: red crystals; oil at rt; mp −5 to 0 °C.
Solubility: sol CH_2Cl_2, C_6H_6, BuOH, *t*-BuOH, CCl_4, petroleum ether, C_6H_6 or CCl_4 or $Cl_2C{=}CCl_2/Ac_2O/HOAc$.
Preparative Method: prepared from *t*-butanol and ***Chromium(VI) Oxide*** or ***Chromyl Chloride***.
Handling, Storage, and Precautions: should be used as prepared. Chromium(VI) compounds are toxic and should be handled with care; the mutagenicity of Cr^{VI} compounds is well documented.[1f] Use in a fume hood.

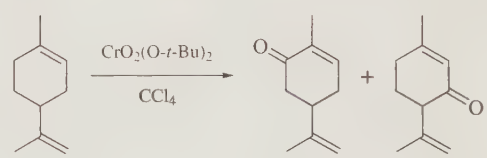
Oxidation of Allylic Methylene Groups to Carbonyl Groups. Good to excellent yields of α,β-unsaturated ketones have been obtained from the di-*t*-butyl chromate oxidation of allylic methylene groups.[2–4] The oxidation of cyclohexene affords cyclohexen-3-one and benzoquinone (eq 1).[2] Carvomenthene (**1**) is oxidized to carvotanacetone (**2**) and piperitone (**3**) (eq 2).[5–7] Similarly, verbenone may be obtained from β-pinene in 40% yield[7] and limonene (**4**) affords carvone (**5**) and isopiperitenone (**6**) (eq 3).[8]



(1)



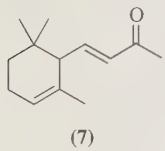
(1) (2) 50% (3) 16%
(2)



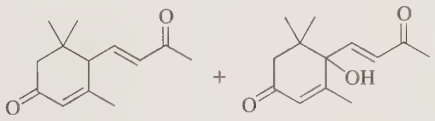
(4) (5) 21% (6) 13%
(3)

Di-*t*-butyl chromate, in refluxing *t*-butanol, oxidizes α-ionone (**7**) to small amounts of the α,β-unsaturated ketone (**8**) and 1-hydroxy-4-keto-α-ionone (**9**) in 23–27% yield (eq 4).[9] Allylic methine carbon–hydrogen bonds are more resistant to oxidation than methylene carbon–hydrogen bonds in nonpolar solvents. Ketone (**8**) is obtained (14%, 14 days) in tetrachloromethane at 0 °C. The hydroxy ketone (**9**) was converted into abscisic acid, which is a plant hormone involved in flower and leaf abscission.

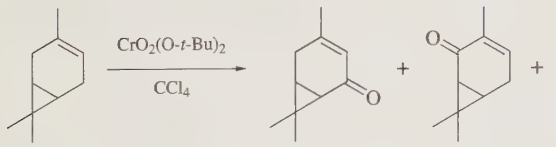
Di-*t*-butyl chromate is superior to ***Chromium(VI) Oxide*** or ***Potassium Permanganate*** for oxidation of (+)-car-3-ene (**10**) to (−)-car-3-en-5-one (**11**) (eq 5).[10] Di-*t*-butyl chromate does not attack methylene groups adjacent to the cyclopropane ring, as (−)-*cis*-carane and (+)-caren-3-ol are stable under the experimental conditions.



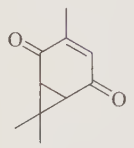
(**7**)



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

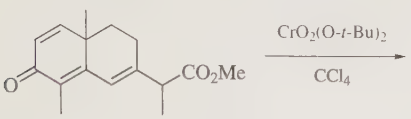


(**10**) (**11**) 50% (**12**) 12%

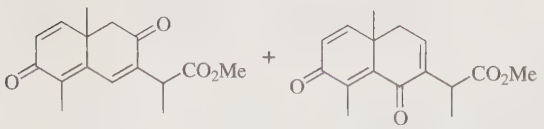


(**13**) 12% (5)

Di-*t*-butyl chromate was found superior to ***Selenium(IV) Oxide*** or ***Dipyridine Chromium(VI) Oxide*** for oxidation of the trienone (**14**) to (**15**) (eq 6).[11] Compound (**16**) is used in the synthesis of yomogin. Oxidation of the 1,4-diene (**17**) affords dienones (**18**) and (**19**) in the ratio 1:3 (65% total yield, eq 7).[12] Complementary regioselectivity (**18/19** = 9:1, 70% yield) is obtained with ***Pyridinium Chlorochromate*** (PCC). Chromium(VI) oxide–pyridine gave results similar to di-*t*-butyl chromate.



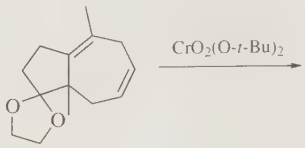
(**14**)



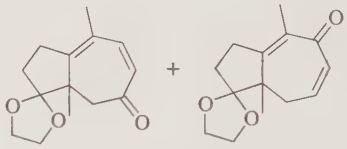
(**15**) 39% (**16**) 20% (6)

The 17β-epimer of Δ^1-5β-pregnen-20-one (**20**) was converted to progesterone (**21**) by oxidation with di-*t*-butyl chromate in tetrachloroethylene/Ac_2O/HOAc (eq 8).[13] Selective hydrogenation of progesterone (**21**) afforded 5β-pregnane-3,20-dione. Pregnenolone acetate (**22**) is oxidized at the C-7 position to afford (**23**) (eq 9).[4] Similarly, 3β,21-diacetoxypregn-5-ene-20-one has been oxidized to 3β,21-diacetoxypregn-5-ene-7,20-dione (71%).[4]

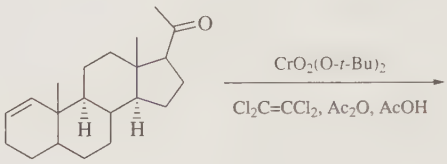
Di-*t*-Butyl chromate oxidizes cholesteryl acetate (**24**) to (**25**) (eq 10).[2,14–16] 3β-Substituted (20*S*)-20-[(benzenesulfonyl) methyl]pregn-5-en-7-ones, which are useful as intermediates for hormones, growth regulators, and calcium metabolism, were prepared by allylic oxidation of the pregn-5-enes with di-*t*-butyl chromate in acetic anhydride/acetic acid.[17]



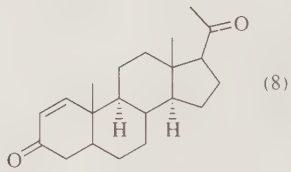
(**17**)



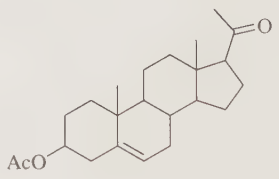
(**18**) (**19**) (7)



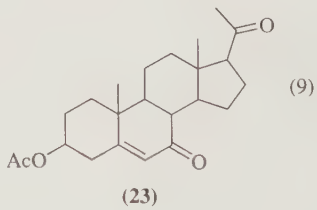
(**20**)



(**21**) 60% (8)



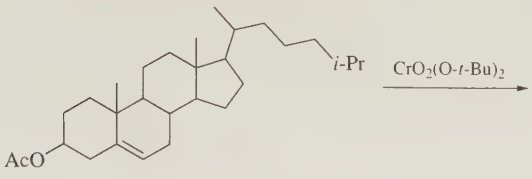
(**22**)



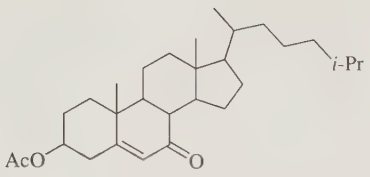
(**23**) (9)

Allylic oxidation of steroidal glycosides by di-*t*-butyl chromate affords the corresponding carbonyl compounds in high yields.[18] Oxidation of a methylene group adjacent to a double bond or aromatic ring to a carbonyl group was effected in a group of diterpenes and triterpenes.[19]

Oxidation of tetrasubstituted alkenes generally leads to a mixture of products. For example, methyl 13β-abiet-8(9)-en-18-oate is oxidized to five products in tetrachloromethane.[20]

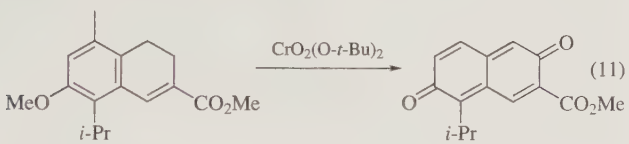


(24)



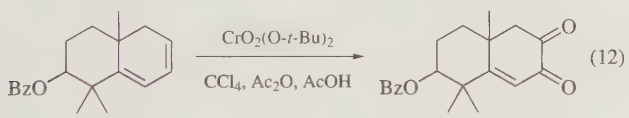
(25) (10)

Di-*t*-butyl chromate oxidizes the substituted ether (**26**) to the 2,6-naphthoquinone derivative (**27**) in low yield (eq 11).[6] Presumably the methyl group is oxidized to a carboxyl group which undergoes decarboxylation.



(26) (27) (11)

Conjugated homoannular dienes are oxidized to α-diketones. 3β-Benzoyloxy-4,4,9-trimethyl-1,2,3,4,8,9-hexahydronaphthalene (**28**) is oxidized to the corresponding 6,7-dione (**29**) in tetrachloromethane containing acetic anhydride and acetic acid (eq 12).[21] Similarly, (+)-occidentalol, a sesquiterpene containing a homoannular diene, is oxidized to four products in benzene containing acetic anhydride and glacial acetic acid.[22]



(28) (29) (12)

Oxidation of Alcohols to Aldehydes and Ketones. Di-*t*-butyl chromate oxidizes alcohols in nonpolar solvents.[23,24] Although aliphatic primary alcohols are oxidized to the corresponding aldehydes in low yields, allylic and benzylic primary alcohols give aldehydes in good to excellent yields. Cyclohexanol affords cyclohexanone (89%), cyclohexane-1,2-diol yields adipic acid, and cyclic vicinal glycols with one secondary and one tertiary hydroxy group are oxidized at the secondary position to give the corresponding hydroxy ketones.[25] The ultrasound-mediated di-*t*-butyl chromate ester oxidation of alcohols in dichloromethane affords aldehydes and ketones in excellent yields.[26]

The oxidation of alcohols with anhydrous ***Di-t-butyl Chromate –Pyridine*** gives high yields of aldehydes and ketones and permits large scale reactions.[27,28] The use of excess di-*t*-butyl chromate in the presence of 3,5-dimethylpyrazole selectively oxidized an allylic methylene position to a carbonyl group in the final step in the synthesis of (−)-solavetivone.[29]

Other Applications. In CCl_4/Ac_2O/HOAc, di-*t*-butyl chromate is more effective than ***Ruthenium(IV) Oxide*** in converting spiroethers to spirolactones.[30]

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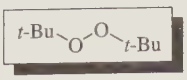
Di-*t*-butyl Peroxide[1–3]



[110-05-4] $C_8H_{18}O_2$ (MW 146.23)

(radical initiator, initiates anti-Markovnikov addition of HX to alkenes (X = halogen, S, Si, P);[4] initiates, by H-abstraction, the following radical reactions of compounds with an activated C–H bond: (a) dehydrodimerization;[5,6] (b) intra-[7] and intermolecular additions[3,8,9] to alkenes, alkynes, and carbonyl compounds; (c) addition to protonated heterocycles;[10,11] (d) fragmentation;[12,13] mediates alcohol deoxygenation via silane reduction of esters[14] and chlorohydrin formation by reaction with $TiCl_4$ and alkene[15])

Alternative Names: *t*-butyl peroxide; DTBP.
Physical Data: bp 109 °C/760 mmHg, 63 °C/119 mmHg; *d* 0.796 g cm^{-3}.
Solubility: freely soluble in organic solvents.
Form Supplied in: clear colorless liquid.
Analysis of Reagent Purity: Kropf describes various procedures (chemical and chromatographic) for the analysis of peroxides.[1b]
Handling, Storage, and Precautions: explosive; harmful if exposed by inhalation or skin contact; strong oxidizer; flammable; keep away from heat. Caution: All experiments involving peroxy compounds should be carried out behind a safety shield. Use in a fume hood.

Original Commentary

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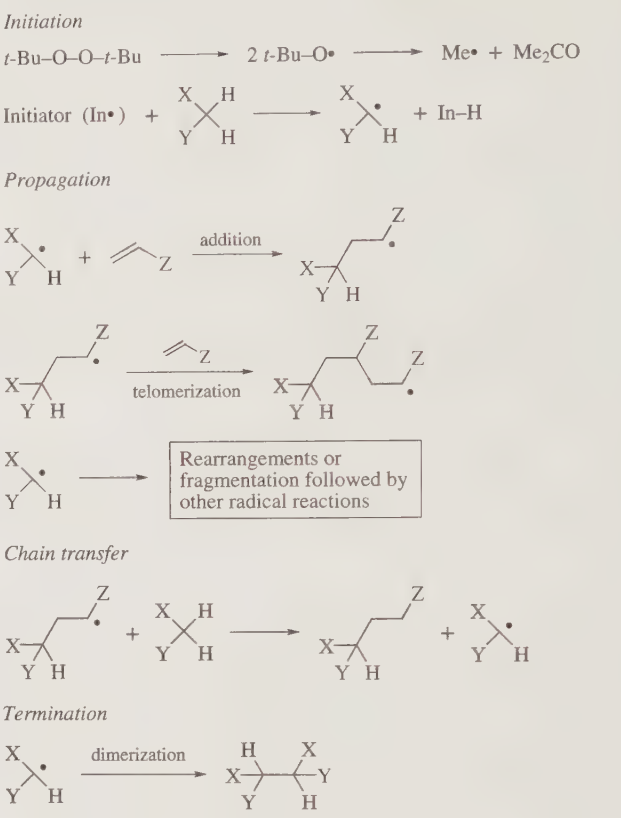
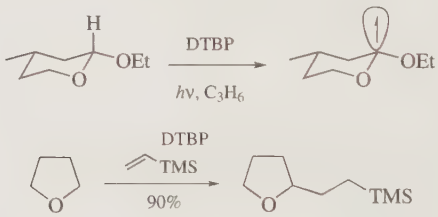
Nigel S. Simpkins
University of Nottingham, Nottingham, UK

General Discussion. Di-*t*-butyl peroxide is a commonly used initator for radical reactions. It undergoes facile unimolecular thermal decomposition to the *t*-butoxy radical, which in turn fragments to a methyl radical and acetone. The half-lives of DTBP are approximately 3 h at 140 °C and 24 h at 120 °C.[2] Accordingly, radical reactions that proceed at 110–150 °C can be initiated by DTBP, since a steady concentration of the initiating radical would be available for the reactions. Alkoxy radicals are electrophilic and they initiate the reaction by abstraction of a C–H bond α to a heteroatom. The resultant radicals undergo a variety of carbon–carbon bond forming reactions, including polymerization.[16] Scheme 1 shows the primary steps involved in useful C–C bond forming reactions. Use of precursors having an activated C–H bond is advantageous for this purpose, since the chain-transfer step also produces the primary adducts along with the propagating radical, which is also one of the reactants. However, because of the high bond energy associated with the C–H bond, these types of compound are poor H-atom donors. Chain lengths of these reactions are generally short; the use of a large excess of the C–H precursor and a steady supply of the initiator are important for success in many instances.

Abstractions of H adjacent to ethers and amines are important examples, the heteroatom adjacent to the site of reaction providing a favorable polar contribution to the transition state for abstraction by the electrophilic oxy radical, and providing stabilization for the product radical. Examples of the use of DTBP in this way include the study of anomeric radicals by Ingold and co-workers (eq 1),[17] and a synthesis of substituted tetrahydrofurans (eq 2).[18]



Scheme 1 Primary radical processes



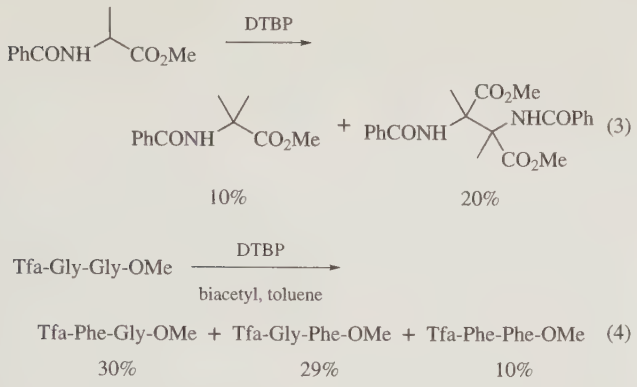
(1)

(2)

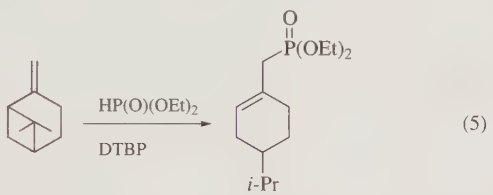
In the first case the radicals were generated by UV photolysis of the reaction mixture in the cavity of the NMR instrument used for studying the configuration at the anomeric center. By contrast, the substitution of THF was carried out under more typical thermal conditions by heating in a sealed autoclave. In this study it was found that similar substitution of tetrahydro-2-furanone could also be carried out, although generally in modest yield.

Hydrogen atom abstraction from amino acid derivatives is especially facile, since the resulting captodative radicals are highly stabilized. Treatment of an alanine derivative with DTBP led to a mixture of an α-methylated product and a diastereomeric mixture of dimers (eq 3).[19] The first product is formed as a result of radical combination between the captodative amino acid radical and a methyl radical formed by scission of a *t*-butoxy radical. Substitution of protected dipeptides can be carried out using this approach, by including an alkylating agent such as toluene in the reaction medium (eq 4).[20] The reaction relies on the action of biacetyl

(***2,3-Butanedione***) as a photoinitiator, hydrogen atom abstraction occurring preferentially at glycine residues.



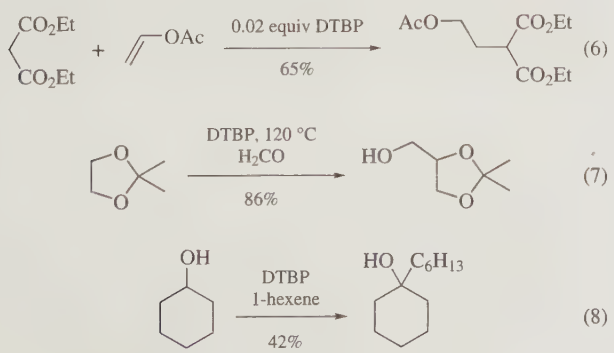
Reactions involving phosphorus centered radicals derived from diethyl hydrogen phosphite are also initiated by DTBP under thermal conditions (eq 5).[21] Under modified reaction conditions, diphosphonate products, resulting from further addition to the initially formed unsaturated phosphonate, were also observed.

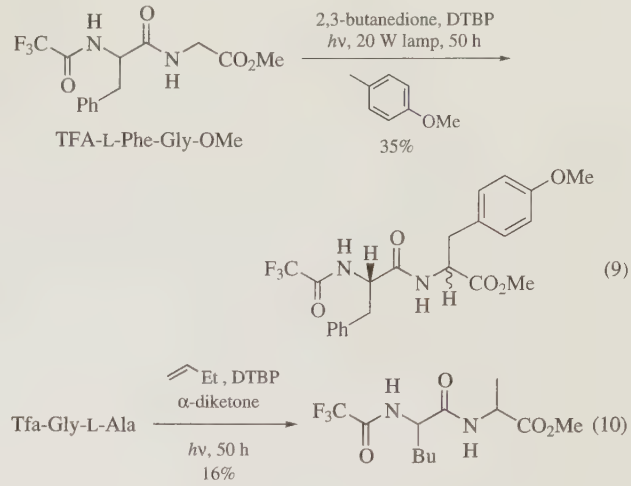


Typical reactions of radicals with alkene acceptors, initiated by DTBP and used in synthesis, are listed below.

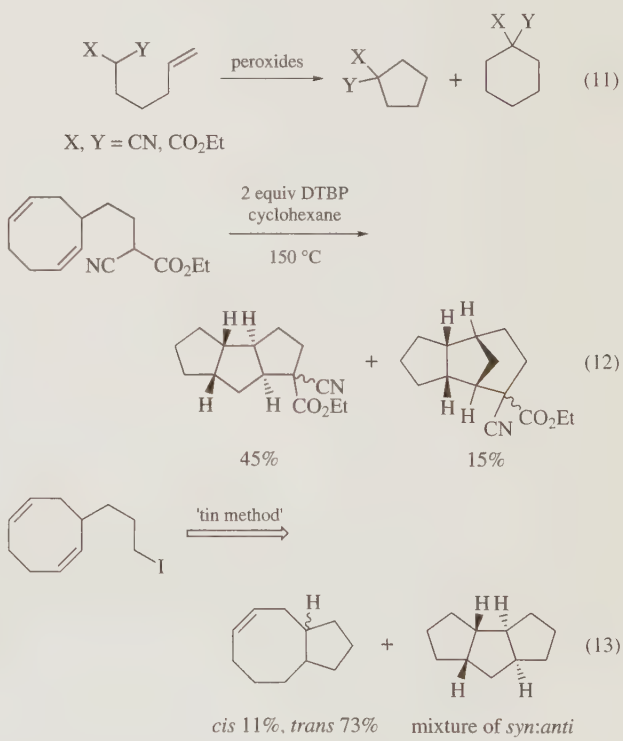
Intermolecular Additions. The radical chain nature and the anti-Markovnikov regiochemistry of radical addition reactions were originally discovered by Kharasch in the 1930s. Since then, these reactions have been used extensively for the formation of carbon–carbon[3,8] and carbon–heteroatom[4] bonds. Substrates that are suitable for the former include polyhalomethanes, alcohols, ethers, esters, amides, and amines. The prototypical examples compiled in Table 1 are from reviews by Walling[8] and Ghosez et al.[3]

Among the other notable applications are addition of the radical from diethyl malonate to alkynes and alkenes (eq 6),[9] addition of a 1,3-dioxalane-derived radical to formaldehyde (eq 7),[22] and addition of *s*-alcohols to alkenes (eq 8).[23] Novel radical mediated alkylations of a dipeptide makes use of DTBP as an initator (eqs 9 and 10).[20]



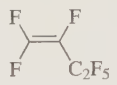
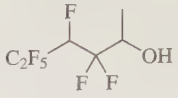
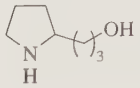
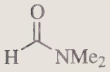
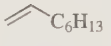
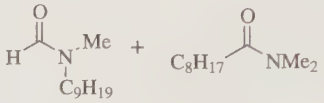
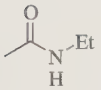
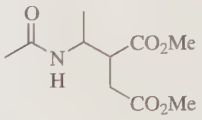
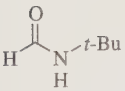
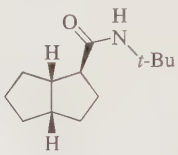
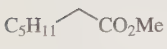
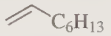
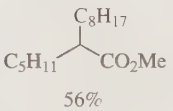
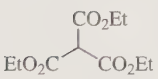
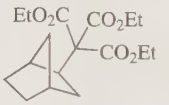
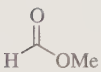
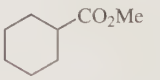
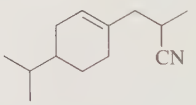


Intramolecular Addition Reactions. Early studies by Julia and his co-workers on the cyclization of hexenyl (eq 11) and heptenyl radicals played a key role in the development of radical synthetic methodology, and many of the earlier studies were conducted with peroxides as initiators.[7] Cyclization of stabilized radicals such an malonates and cyanoesters are reversible, and the course of ring closure can be controlled by the appropriate choice of precursors and reaction conditions. Thus the cyanoacetate in (eq 12)[24] with 2 equiv of DTBP gives the products shown, whereas under kinetic conditions, using the tin hydride method, a different product distribution is obtained (eq 13).



Dehydrodimerization. Radicals that are stabilized by an α-heteroatom, when produced in sufficiently high concentrations, will undergo dimerization. Use of DTBP is particularly effective for dehydrodimerizations of polyhaloalkanes,[25] alcohols, ethers,[5,25] amides, and esters (Table 2).[5,6] Viehe, who pioneered

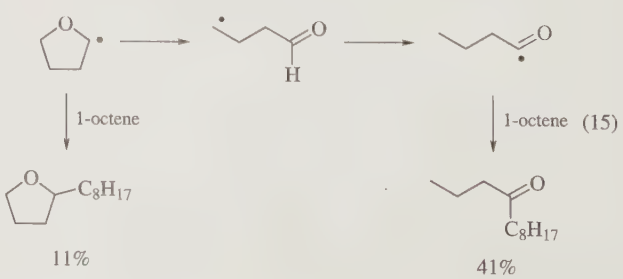
Table 1 Intermolecular C–C bond forming reaction via radicals

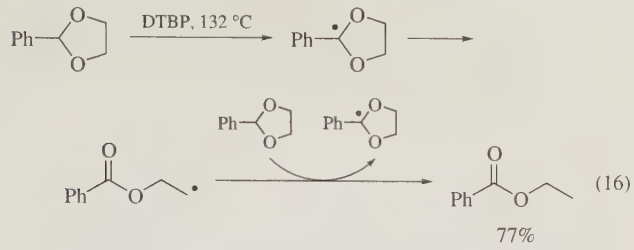
Precursor	Alkene	Reaction conditions	Product(s)
EtOH		DTBP, 120 °C, 48 h	 60%
		DTBP, 120 °C, 48 h	 54%
		DTBP, 132 °C, 48 h	 22% 34%
		DTBP, 0.01 equiv, 6 h	 87%
		DTBP, 137 °C, 24 h	
		DTBP, 150 °C	 56%
		DTBP, 150 °C	 62%
		DTBP	 36%
EtCN		DTBP, 6 h, 140–150 °C	 77%

this work, has used α-*t*-butylmercaptoacrylonitrile as a trapping agent for the above mentioned C-centered radicals.[26] The adduct radical is stabilized by 'captodative effects'[27] and do not participate in further chain transfer chemistry. These radicals undergo ready dimerization, thereby providing a facile route to compounds with a four-carbon bridge between the original radicals (eq 14).


(14)

Fragmentation Reactions. The tetrahydrofuranyl radical undergoes fragmentation at 140 °C to give an open-chain acyl radical. The THF radical as well as the rearranged radical are trapped by excess of alkene (eq 15).[12] Benzylidene acetals undergo similar fragmentation to give a benzoate ester (eq 16).[13]


(15)

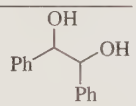
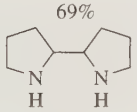
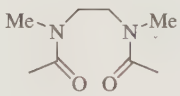
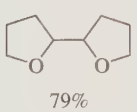
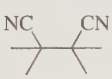
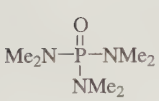
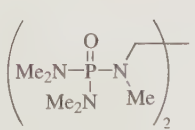
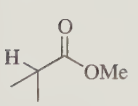
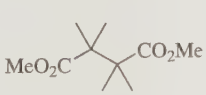
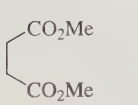
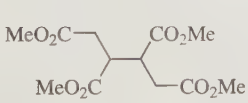


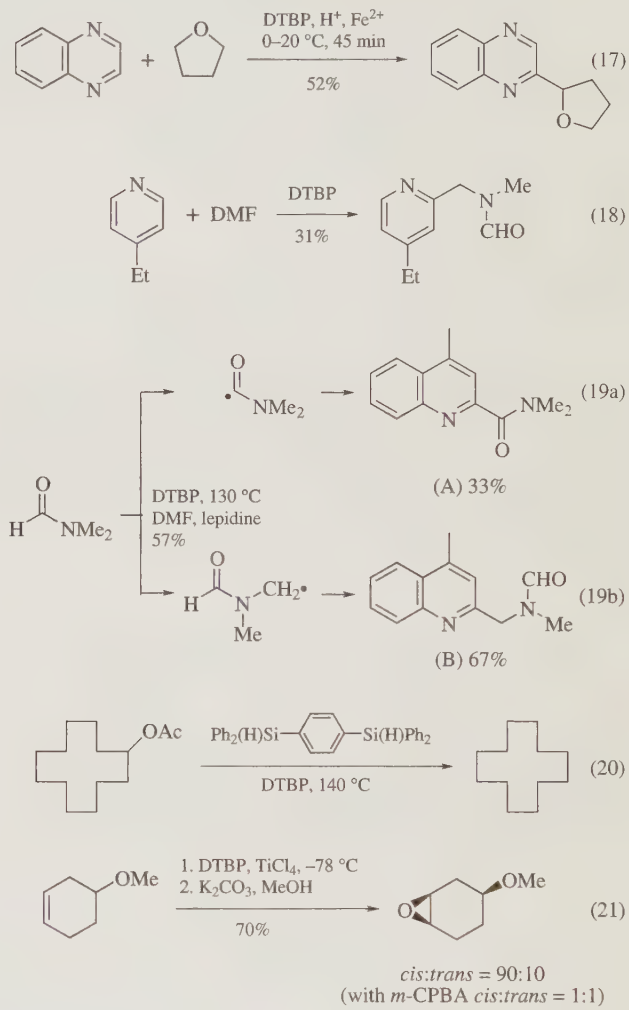
(16)

Homolytic Substitution Reactions. Alkylation of electron-deficient heteroaromatic compounds developed by Minisci and co-workers is a powerful method for their functionalization.[10,28] Three examples are illustrated in eqs 17–19. The product distribution often depends on the oxidant used. For example, as shown in eq 19, DTBP gives a 1:2 mixture of two products (A and B) upon alkylation of 4-methylquinoline. ***t-Butyl Hydroperoxide*** and Fe^{II} salts give almost exclusively the dimethylaminocarbonyl radical adduct A (eq 19).[11]

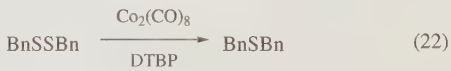
Miscellaneous Reactions. DTBP has been used as a hydrosilylation catalyst,[4] even though catalysis[29] by transition metal complexes have largely replaced the radical methods. DTBP has also been used as an oxidant for silanes.[30,31] Other applications of DTBP include its use as an initiator for radical mediated deoxygenation of alcohols via the corresponding chloroformate[32] or acetate ester[14] (eq 20). It has also been used as an initiator for the reduction of lactones and esters to ethers using ***Trichlorosilane***.[33] In a rare example of a nonradical reaction, DTBP has been used in conjunction with ***Titanium(IV) Chloride*** for the formation of chlorohydrin from alkenes (eq 21).[15]

Table 2 Dimerization of radicals

Precursor	Reaction conditions	Products
$PhCH_2OH$	DTBP, 140 °C, 10 h	 69%
	DTBP, 135 °C	 73%
$MeCONMe_2$	DTBP (5 mole %), 140 °C	 100%
	DTBP (5 mole %), 140 °C	 79%
	DTBP (5 mole %), 140 °C	 84%
	DTBP (5 mole %), 140 °C	
	DTBP,160 °C, 8 h	
	DTBP,160 °C, 8 h	

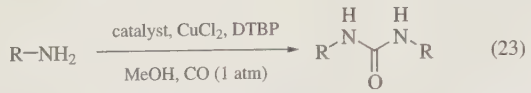


The carbonylation reaction of disulfides, catalyzed by ***Octacarbonyldicobalt***, normally leads to the production of thioesters. However, in the presence of DTBP and in the absence of CO the reaction takes an alternative course, with benzyl disulfides undergoing clean desulfurization to give the corresponding sulfides (eq 22).[34]



(22)

DTBP has also been employed in palladium catalyzed carbonylation reactions. Depending on the type of catalyst used, or on the reaction conditions, the carbonylation reaction of primary amines can be used to prepare either ureas (eq 23)[35] or carbamate esters (eq 24).[36]



(23)

catalyst = montmorillonite(bipyridyl)palladium(II) acetate

(24)

Using the ***Palladium(II) Chloride*** system, the reaction involving secondary amines was found to give mixtures of carbamate ester and an oxamate ester resulting from double carbonylation.[36] Analogous carbonylations of alcohols can lead to a range of products, including dialkyl carbonates, oxalates, and succinates.[37]

First Update

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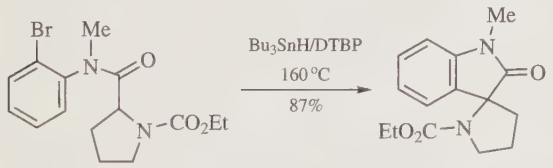
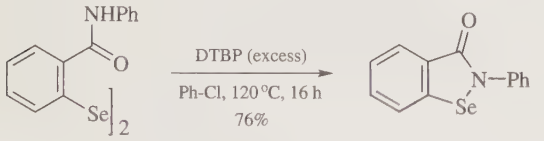
Intramolecular Addition/Homolytic Substitution Reactions. *o*-Bromo-*N*-methylanilides are converted into oxindoles in good to excellent yields upon treatment with tri-*n*-butylstannane and DTBP (eq 25).[38] The reaction involves the initial formation of an aryl radical, translocation of the radical, and subsequent intramolecular homolytic aromatic substitution.



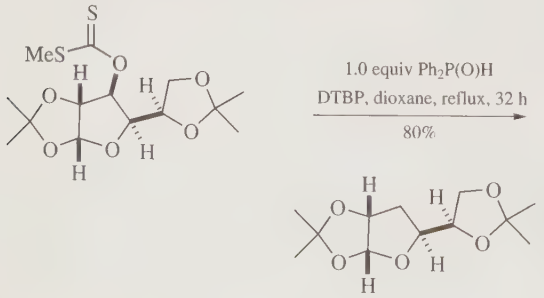
(25)

DTBP in excess has been used to carry out homolytic radical substitution at Se by an amidyl radical (eq 26).[39] Analogs of the anti-inflammatory agent ebselen have been prepared by this route.



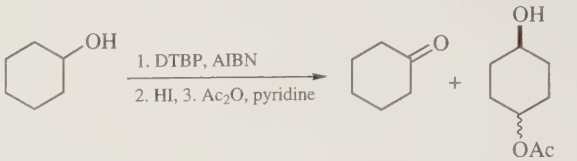
(26)

Deoxygenation of Alcohols. A new application of DTBP is its use as an initiator for radical-mediated deoxygenation of alcohols via the corresponding xanthate using diphenylphosphinous acid as the hydrogen source (eq 27).[40]



(27)

Miscellaneous Reactions. Despite considerable research on the use of DTBP and related peroxides in C–H oxidations, the selectivity still remains poor. In this context, the reactivity of C–H bonds in cyclohexanol with *t*-BuO· radical has been examined using DTBP as the source of the radical.[41] The resulting peroxides are reduced with HI and subsequently acylated with acetic anhydride in pyridine (eq 28). The –OH group activates the α-CH bond, deactivates the β- and γ-CH bonds. The reactivity of the δ-CH bond is close to the reactivity of the C-H bond in cyclohexane.

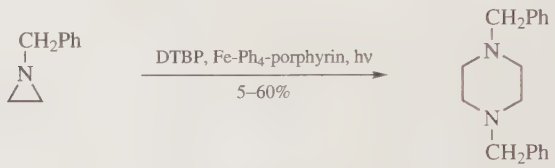


(28)

(97.5%) (1.9%)

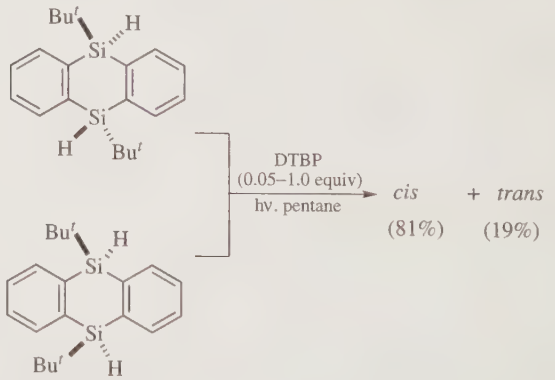
+ other products

A low-yielding, unusual oxidative dimerization of an aziridine, mediated by DTBP (and other peroxides) and iron-tetraphenylprophyrin (eq 29) has also been reported.[42]



(29)

DTBP has been used to equilibrate *cis*- and *trans*-9,10-di-*tert*-butyl-9,10-dihydro-9,10-disilaanthracenes.[43] Thus a pentane solution of a mixture of the two compounds reaches a photostationary equilibrium with 81 % cis and 19 % trans isomers at various times, depending on the amount of DTBP used (eq 30).



(30)

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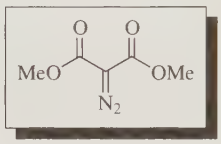
Dimethyl Diazomalonate[1]



[6773-29-1] $C_5H_6N_2O_4$ (MW 158.13)

(carbene or carbenoid precursor;[1] cyclopropanation;[2] synthesis of oxazoles[3] and furans;[4] ring expansion;[5] deoxygenation of epoxides;[6] alkenation;[7] *C*-glycosidation;[8] etherification[9])

Physical Data: bp 60–61 °C/2 mmHg.

Solubility: sol ether, THF, halocarbon and hydrocarbon solvents.

Form Supplied in: not commercially available.

Preparative Methods: diazomalonates are generally prepared by diazo transfer reaction of malonates and sulfonyl azides.[10a] A recent modification employs polystyrene-supported trialkylammonium azide (generated in situ) under phase-transfer catalysis conditions and allows for facile isolation.[10b]

Handling, Storage, and Precautions: dimethyl diazomalonate has been utilized more extensively than has diethyl diazomalonate due to the explosion hazard of the latter. Nonetheless, care should be taken in preparation and handling of dimethyl diazomalonate. Storage at low temperature is recommended. The decomposition of dimethyl diazomalonate evolves nitrogen and can result in high pressures.

Original Commentary

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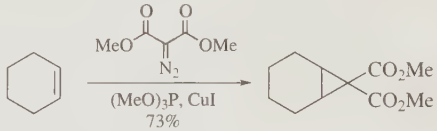
Eli Lilly and Company, Indianapolis, IN, USA

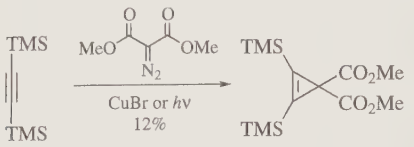
Cyclopropanation. Decomposition of dimethyl diazomalonate by direct photolysis or by transition metal catalysis in the presence of alkenes leads to cyclopropanation (eq 1).[2a] The use of alkynes to trap the carbenoid species affords cyclopropenes (eq 2).[2b] Rhodium(II) acetate-catalyzed reaction with allenes allows ready access to methylenecyclopropanes, which form the basis for a methylenecyclopentane annulation protocol (eq 3).[2c]



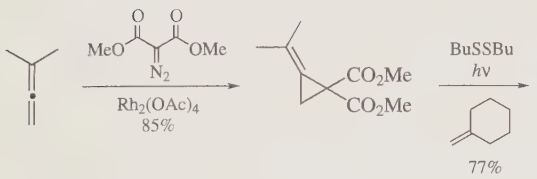
(1)

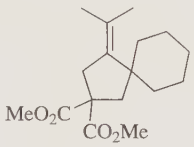
Synthesis of Oxazoles and Furans. Dimethyl diazomalonate reacts with a variety of nitriles in the presence of rhodium(II)

acetate to afford 2-substituted 5-methoxy-4-methoxycarbonyl-1,3-oxazoles (eq 4).[3] This reaction is fairly general in scope, although cyclopropanation and insertion can be competing processes.

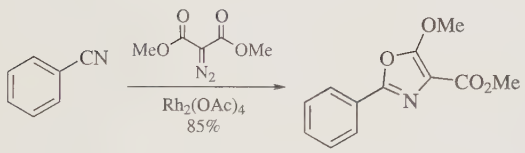


(2)



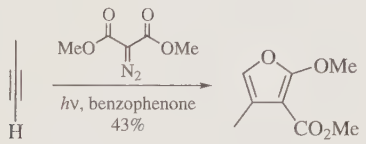


(3)



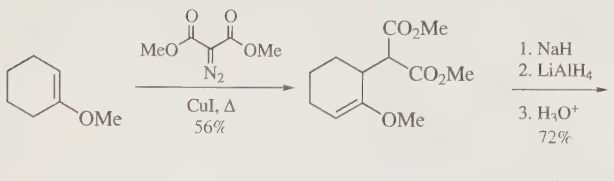
(4)

In contrast to the direct photolytic cyclopropanation of alkynes with dimethyl diazomalonate, benzophenone-sensitized photolysis in the presence of alkynes affords furans as the major products in moderate yields (eq 5).[4a]

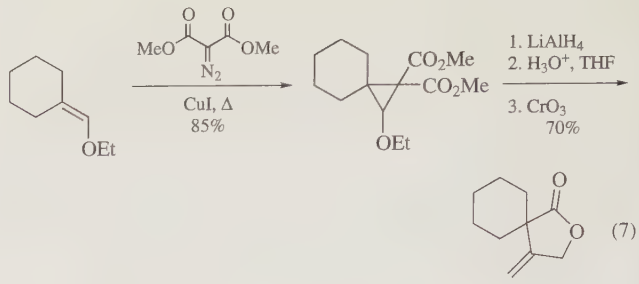


(5)

An alternative furan synthesis is based upon allylic C–H insertion upon reaction with a ketone-derived enol ether.[4b] Reduction and hydrolysis affords the furan (eq 6). With aldehyde-derived enol ethers, copper(I) induced reaction with dimethyl diazomalonate yields an alkoxycyclopropane diester, whose reduction, hydrolysis, and oxidation affords a spiro-β-methylene-γ-lactone (eq 7).

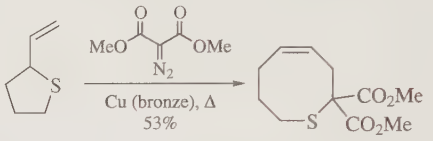


(6)



(7)

Ring Expansion. Sulfonium ylides can be prepared from sulfides and dimethyl diazomalonate under rhodium(II) or copper catalysis. Subsequent [2,3] or [1,2] rearrangement of the ylides derived from cyclic sulfides allows for ring expansion. Examples include the synthesis of *cis*-thiacyclooctene (eq 8),[5a] dihydrothiazinones (eq 9),[5b] and homocephems (eq 10).[5c]



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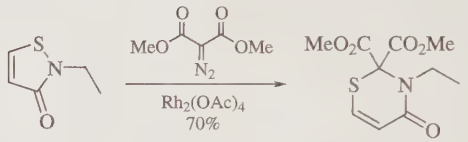

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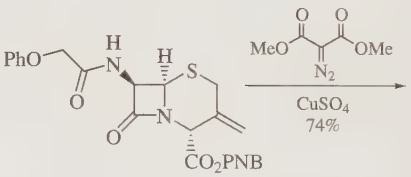
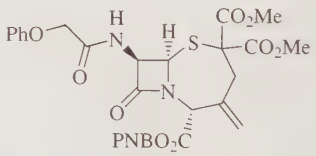
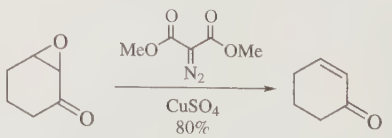




(10)

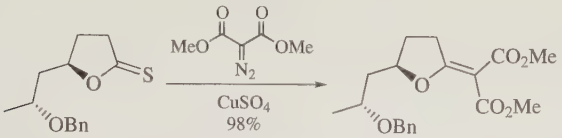
Deoxygenation of Epoxides. In the presence of catalytic rhodium(II) acetate, dimethyl diazomalonate deoxygenates epoxides under neutral conditions (eq 11).[6] This reaction tolerates functionality such as ketones, esters, alkyl and silyl ethers and halogen substituents, although alcohols and aldehydes undergo competing insertion reactions.



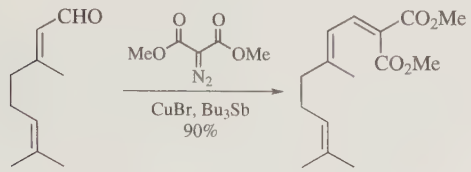
(11)

Alkenation. Alkenation of thiolactones can be achieved by rhodium(II) acetate-catalyzed reaction with dimethyl diazomalonate (eq 12).[7a] Recently, an efficient alternative alkenation protocol has been demonstrated to be applicable to a variety of ketones and aldehydes by reaction with ***Tri-n-butylstibine*** and dimethyl diazomalonate in the presence of ***Copper(I) Bromide***

(eq 13).[7b] This process is proposed to occur via tributylstibonium bis(methoxycarbonyl)methylide.

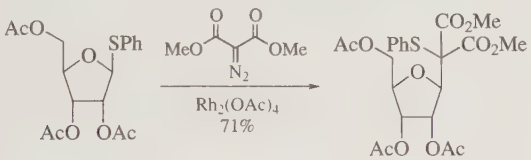


(12)

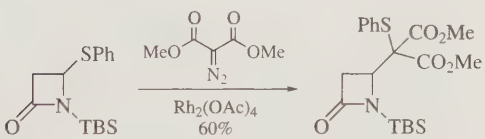


(13)

***C*-Glycosidation.** Reaction of phenyl thioglycosides with dimethyl diazomalonate in the presence of rhodium(II) acetate allows for the construction of *C*-glycosyl linkages in moderate yields under neutral conditions (eq 14).[8a] The methodology is applicable to both thiofuranosides and thiopyranosides. A related insertion process allows for a mild carbon extension of 4-phenylthioazetidinones (eq 15).[8b]

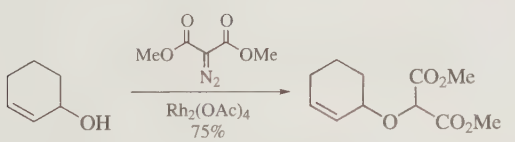


(14)



(15)

Etherification. Rhodium(II) acetate-catalyzed O–H insertion of dimethyl diazomalonate is exceedingly facile, resulting in an efficient, neutral etherification in the presence of other sensitive functionality (eq 16).[9]

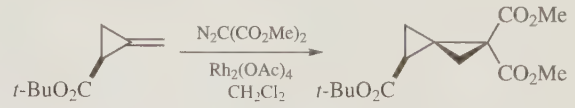


(16)

First Update

Vladimir Gevorgyan & Michael Rubin
University of Illinois at Chicago, Chicago, USA

Cyclopropanation ([2 + 1] Cycloaddition). Cu^{II}- and Rh^{II}-catalyzed cyclopropanation[11,12] of olefins with dimethyldiazo malonate was used efficiently for the preparation of cyclopropane dicarboxylates. Methylenecyclopropanes were employed in this reaction to afford bicyclopentane derivatives in moderate yields and high diastereoselectivity (eq 17).[13] Utilization of dimethyl diazomalonate in enantioselective cyclopropanation is a very challenging task. Thus the highest ee's obtained in the presence of $Rh_2(4S\text{-MEAZ})_4$ did not exceed 50% (eq 18).[14] Cyclopropanation of olefins was also performed in the presence of catalytic amounts of copper(II)[15] and osmium(II).[16]



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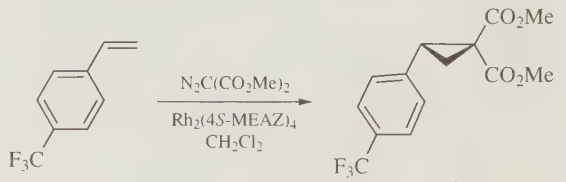
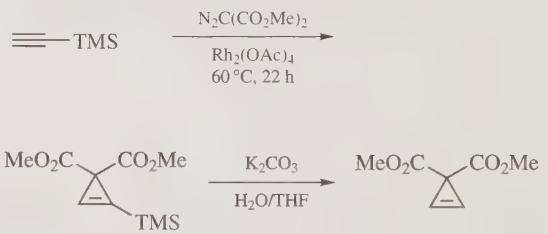
33%



(18)

73%
50% ee

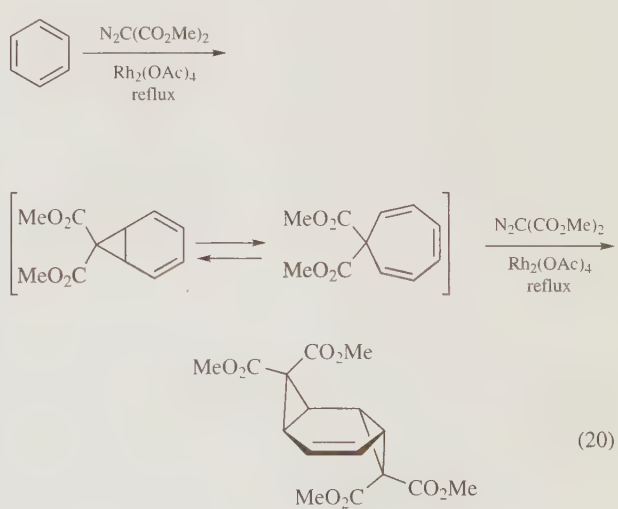
Rhodium(II) catalysts were demonstrated to give higher yields in cyclopropenation of alkynes[17] compared to earlier reported reactions in the presence of copper (eq 19).[2b,18]



(19)

73%

When Buchner-type cyclopropanation of benzene with dimethyl diazomalonate was carried out, unexpectedly the double cyclopropanation product was obtained as the major product (eq 20). This reaction represents the most efficient to date synthesis of bis-σ-homoaromatic compounds.[19]

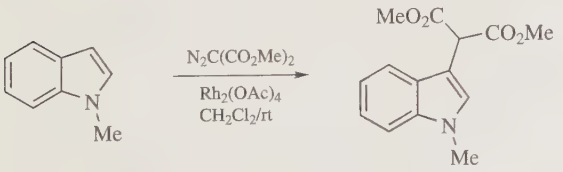


(20)

58%

Cyclopropanation of aromatic and heteroaromatic compounds with dimethyl diazomalonate in the presence of $Rh_2(OAc)_4$ is usually accompanied by dissociation of one of the cyclopropane bonds. In reaction of *N*-protected indoles this led to a very efficient introduction of a malonate substituent at position

3 (eq 21). When the 3-position was substituted, the malonate moiety was installed into the 2-position, however, yields were significantly diminished. Remarkably, no cyclopropanation of the α-olefin at the side chain was observed (eq 22).[20] Although the reactions featured here represent a formal insertion of the carbenoid species into the C–H bond, it was demonstrated that they proceed via a cyclopropanation/nitrogen-assisted ring-opening sequence. True C–H insertion reactions will be discussed below.



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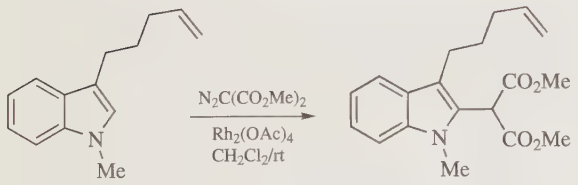
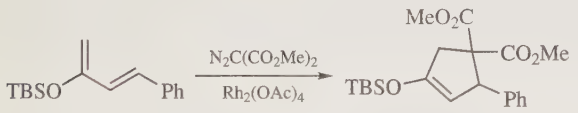


(22)

18%

[4+1] Cycloaddition. [4+1] Cycloaddition of dimethyl diazomalonate with conjugated dienes[21] and enones[22] proceeds in the presence of catalytic amounts of Rh^{II} or Cu^{II}, affording cyclopentenes or dihydrofurans in fair yields (eqs 23 and 24).



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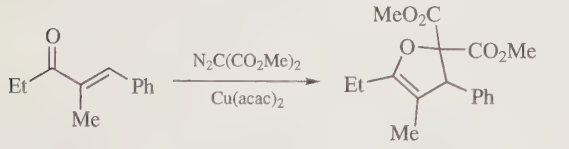
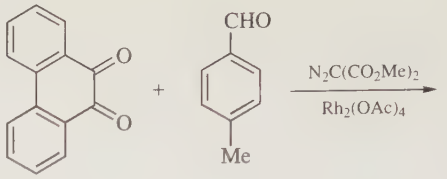


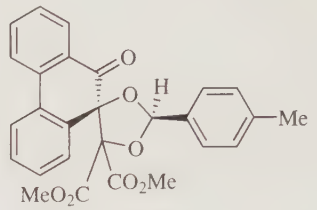
(24)

32%

Synthesis of Heterocycles. A novel synthesis of 1,3-dioxolanes was suggested, which starts with the formation of an intermediate carbonyl ylide from dimethyl diazomalonate and a carbonyl compound (aldehyde or quinone) in the presence of catalytic amounts of Rh^{II}.[23] Once formed, the ylide undergoes dipolar [3+2] cycloaddition with another equivalent of carbonyl compound to furnish a five-membered heterocycle (eqs 25 and 26). Employment of aldimines in this reaction allowed for preparation of 1,3-imidazolidines (eq 27) and 1,3-oxazolidines (eq 28).[24]

Reaction of dimethyldiazomalonate with diaminogermanium(II) lead to the formation of germaimine, which spontaneously cyclized into oxadiazagermine derivative (eq 29).[25]





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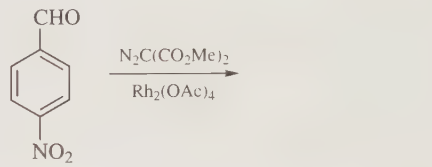

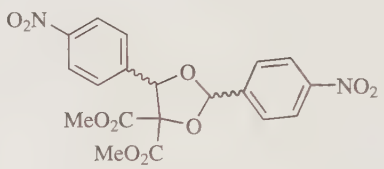

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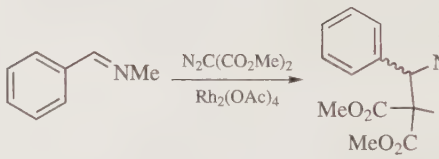

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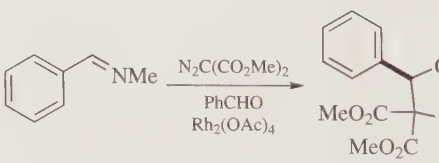

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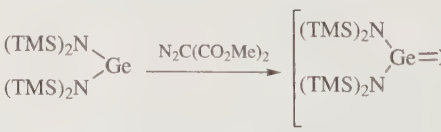
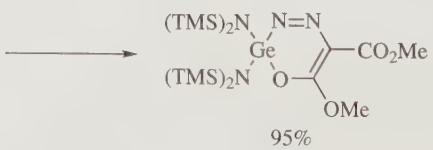


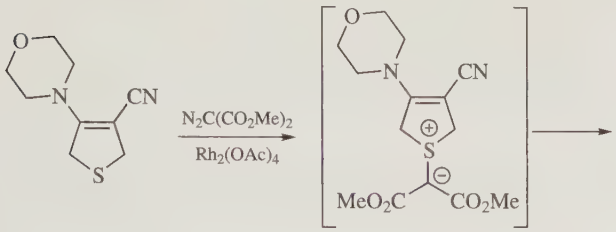


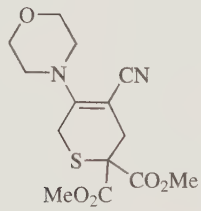
(29)

95%

Ring Expansion. Formation of sulfur ylides from cyclic sulfides and dimethyl diazomalonate in the presence of Rh^{II} catalyst

is accompanied by 1,2-ring expansion. This reaction was used for preparation of dihydrothiopyranes (eq 30).[26] Ring expansion of azirinium ylides under similar conditions afforded the corresponding 2,3-dihydroazete (eq 31).[27]





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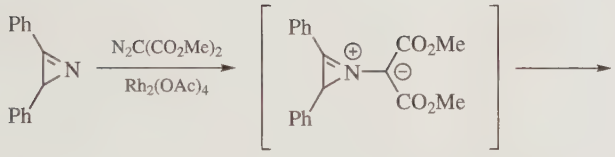
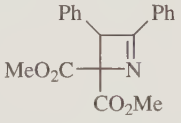
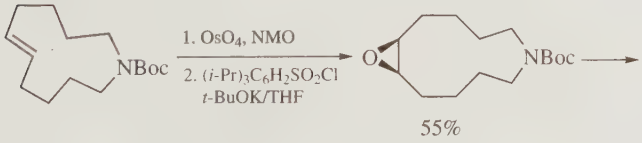




(31)

73%

Deoxygenation of Epoxides. Rh^{II}-catalyzed deoxygenation of epoxides with dimethyl diazomalonate was shown to occur stereoselectively. This reaction feature was used for efficient inversion of double bond configuration in azacycloundecene fragment in the total synthesis of manzamine C (eq 32).[28]



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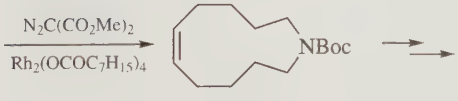

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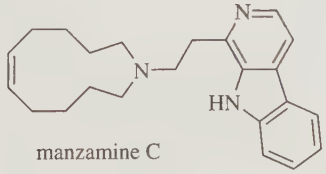
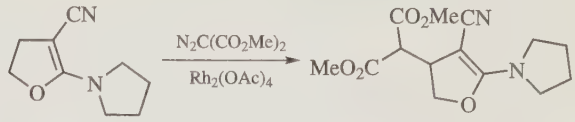


(32)

manzamine C

C–H Insertion. Insertion of carbenoid species generated from dimethyl diazomalonate in the presence of Rh^{II} into activated C–H bonds proceeds in moderate yields (eq 33).[29] Sometimes undesired insertion into the C–H bond adjacent to a heteroatom complicates the utilization of Ganem epoxide deoxygenation[6] procedure (eq 34).[30]



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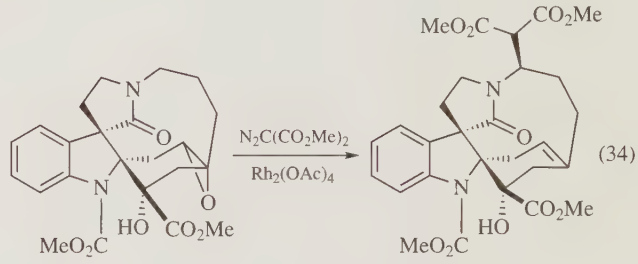
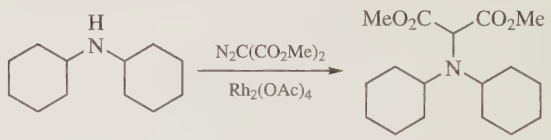


(34)

46%

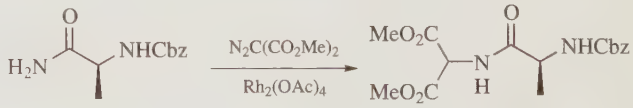
N–H Insertion. Dimethyl diazomalonate reacts with variety of secondary amines in the presence of catalytic amounts of Rh^{II} to afford tertiary amines in good yields. This method was suggested for efficient preparation of variety of hindered amines (eq 35).[31]



(35)

85%

Although Rh^{II}-catalyzed reaction of dimethyl diazomalonate with nitriles to afford 1,3-oxazoles (eq 4) generally gives high yields,[3,32] it is incompatible with an α-amino function. Thus, an alternative route was proposed for preparation of oxazole derivatives of α-amino acids. This method involves Rh^{II}-catalyzed insertion into the N–H bond of an amide, derived from the amino acid, followed by intramolecular condensation (eq 36).[33]



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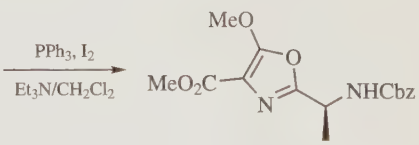


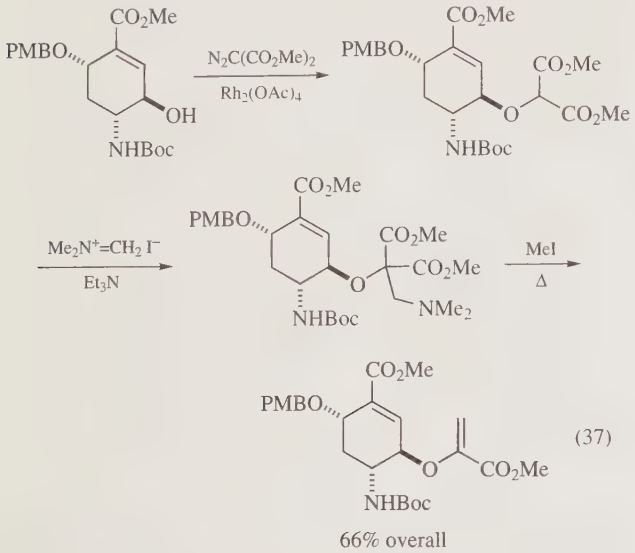
(36)

66%

O–H Insertion (Etherification). Rh^{II}-catalyzed insertion of the malonate-derived carbenoid into an O–H bond followed by Mannich condensation with Eschenmoser's salt and subsequent

elimination proved to be a very convenient method for installation of the sensitive enol pyruvyl group (eqs 37 and 38).[34]

Alkenylation. Rh^{II}-catalyzed reaction of dimethyl diazomalonate with thioketones and dithiolactones leads to the formation of sulfur ylides, which rearrange into thiiranes followed by spontaneous desulfurization to alkenes (eqs 39 and 40).[35,36]



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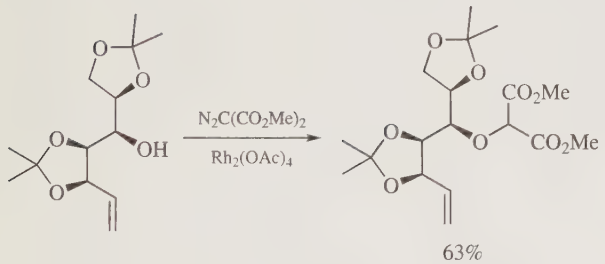

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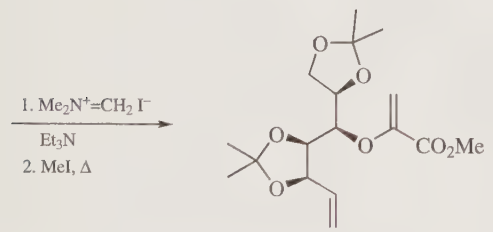

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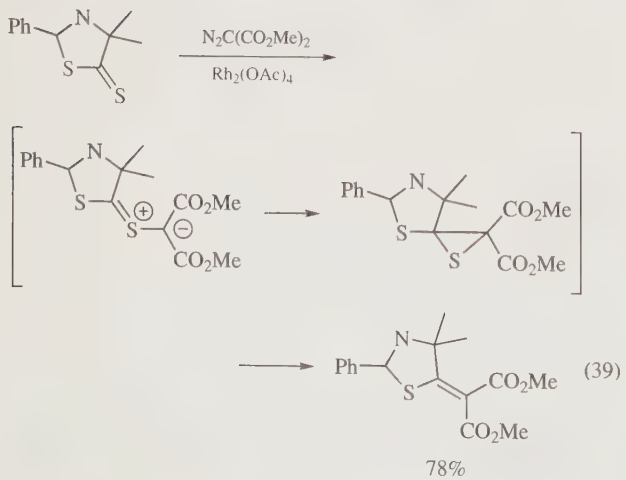

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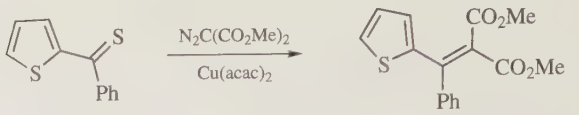

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Dimethyldioxirane[1]

[74087-85-7] $C_3H_6O_2$ (MW 74.09)

(selective, reactive oxidizing agent capable of epoxidation of alkenes and arenes,[11] oxyfunctionalization of alkanes,[19] and oxidation of alcohols,[23] ethers,[21] amines, imines,[32] and sulfides[35])

Alternate Name: DDO.

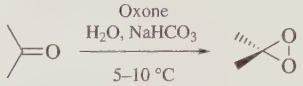
Physical Data: known only in the form of a dilute solution.

Solubility: soluble in acetone and CH_2Cl_2; soluble in most other organic solvents, but reacts slowly with many of them.

Form Supplied in: dilute solutions of the reagent in acetone are prepared from Oxone and acetone, as described below.

Analysis of Reagent Purity: the concentrations of the reagent can be determined by classical iodometric titration or by reaction with an excess of an organosulfide and determination of the amount of sulfoxide formed by NMR or gas chromatography.

Preparative Methods: the discovery of a convenient method for the preparation of dimethyldioxirane has stimulated important advances in oxidation technology.[1] The observation[2] that ketones enhance the decomposition of the monoperoxysulfate anion prompted mechanistic studies that implicated dioxiranes as intermediates.[3] Ultimately, these investigations led to the isolation of dilute solutions of several dioxiranes.[4] DDO is by far the most convenient of the dioxiranes to prepare and use (eq 1). Several experimental set-ups for the preparation of DDO have been described,[4–6] but reproducible generation of high concentration solutions of DDO (ca 0.1M) is aided by a well-formulated protocol.[6] The procedure involves the portionwise addition of solid Oxone (***Potassium Monoperoxysulfate***) to a vigorously stirred solution of $NaHCO_3$ in a mixture of reagent grade ***Acetone*** and distilled water at 5–10 °C. The appearance of a yellow color signals the formation of DDO, at which point the cooling bath is removed and the DDO–acetone solution is distilled into a cooled (−78 °C) receiving flask under reduced pressure (80–100 Torr). After preliminary drying over reagent grade anhydrous $MgSO_4$ in the cold, solutions of DDO are stored over molecular sieves in the freezer of a refrigerator at −10 to −20 °C. In instances where the concentration of DDO is crucial, analysis is typically based on reaction with an excess of an organosulfide monitored by NMR.[4,7,8]



(1)

Concentrated solutions of DDO in chlorinated solvents may be obtained by a simple extraction technique.

A fresh solution (50 mL) of isolated DDO (0.06–0.08 M in acetone), prepared as reported, is diluted with an equal volume of cold water (0–5 °C) and extracted in a chilled separatory funnel with four 10 mL portions of cold CH_2Cl_2, $CHCl_3$, or CCl_4 to yield a total volume of ca. 35 mL of extract (pale yellow DDO solution). In order to concentrate this DDO solution, the combined extracts in chlorinated solvent are washed three times in a separatory funnel at 0–5 °C with an equal volume of cold 0.01 M phosphate buffer (pH 7). The resulting solution is 0.19–0.36 M in DDO. Its concentration can be estimated by iodometry; the recovery of dioxirane from the initial acetone solution is 35–45% in most cases. ^{1}H NMR spectroscopy analysis reveals that initial solvent acetone is not completely eliminated.

Handling, Storage, and Precautions: solutions of the reagent can be kept in the freezer of a refrigerator (−10 to −20 °C) for as long as a week. The concentration of the reagent decreases relatively slowly, provided solutions are kept from light and traces of heavy metals. These dilute solutions are not known to decompose violently, but the usual precautions for handling peroxides should be applied, including the use of a shield. All reactions should be performed in a fume hood to avoid exposure to the volatile oxidant.

Original Commentary

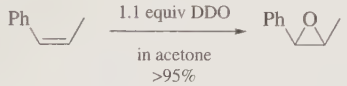
Jack K. Crandall
Indiana University, Bloomington, IN, USA

Introduction. Reactions with DDO are typically performed by adding the cold reagent solution to a cold solution of a reactant in acetone or some other solvent. CH_2Cl_2 is a convenient solvent which facilitates reaction in a number of cases. After the reactant has been consumed, as monitored by TLC, etc., the solvent and excess reagent are simply removed to provide a nearly pure product. An excess of DDO is often used to facilitate conversion, provided further oxidation is not a problem. Where the product is especially sensitive to acid, the reaction can be run in the presence of solid ***Potassium Carbonate*** as an acid scavenger and drying agent. When it is important to minimize water content, the use of powdered molecular sieves in the reaction mixture is recommended. Reactions can be run from ambient temperatures down to −78 °C.

Dimethyldioxirane is a powerful oxidant, but shows substantial selectivity in its reactions. It has been particularly valuable for the preparation of highly reactive products, since DDO can be employed under neutral, nonnucleophilic conditions which facilitate the isolation of such species. Whereas DDO performs the general conversions of more classic reagents like ***m-Chloroperbenzoic Acid***, it generates only an innocuous molecule of acetone as a byproduct. This is to be contrasted with peracids whose acidic side-products can induce rearrangements and nucleophilic attack on products. Although several other dioxiranes have been prepared, these usually offer no advantage over DDO. An important exception is ***Methyl(trifluoromethyl)dioxirane***, whose greater reactivity is advantageous in situations where DDO reacts sluggishly, as in the oxyfunctionalization of alkanes.

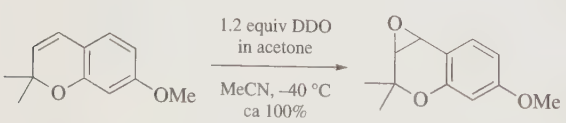
The need to prepare DDO solutions beforehand, the low yield of the reagent based on ***Potassium Monoperoxysulfate*** (Oxone) (ca. 5%),[6] and the inconvenience of making DDO for large-scale reactions are drawbacks that can be avoided when the product has good stability. In these instances, an in situ method for DDO oxidations is recommended.

Oxidation of Alkenes and Other Unsaturated Hydrocarbons. The epoxidation of double bonds has been the major area for the application of DDO methodology and a wide range of alkenes are effectively converted to epoxides by solutions of DDO.[4,7] Epoxidation is stereospecific with retention of alkene stereochemistry, as shown by the reactions of geometrical isomers; for example, (*Z*)-1-phenylpropene gives the *cis*-epoxide cleanly (eq 2), whereas the (*E*) isomer yields the corresponding *trans*-epoxide. Rate studies indicate that this reagent is electrophilic in nature and that alkyl substitution on the double bond enhances reactivity.[7] Interestingly, *cis*-disubstituted alkenes react 7–9 times faster than the *trans* isomers, an observation that has been interpreted in terms of a 'spiro' transition state.[9]

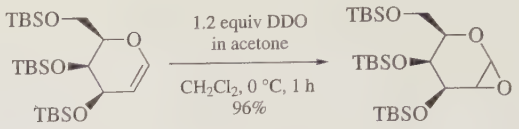


(2)

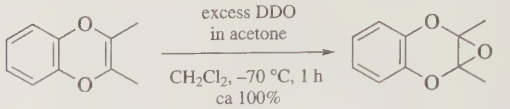
From a preparative viewpoint, the use of DDO solutions, while efficient and easy to perform, are generally not needed for simple alkenes that give stable epoxides. Rather, in situ methodology is suggested. However, the extraordinary value of isolated DDO has been amply demonstrated for the generation of unstable epoxides that would not survive most epoxidation conditions.[1] A good example of this sort of application is the epoxidation of precocenes, as exemplified in eq 3.[10] A number of impressive epoxidations have been reported for oxygen-substituted alkenes, including enol ethers, silyl enol ethers, enol carboxylates, etc.[1] Examples include a number of 1,2-anhydro derivatives of monosaccharides.[11] Steric features often result in significant stereoselection in the epoxidation, as illustrated in eq 4.[11] Conversions of alkenes with two alkoxy substituents have also been achieved (eq 5), even when the epoxides are not stable at rt.[12]



(3)

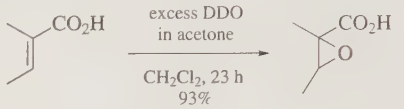


(4)

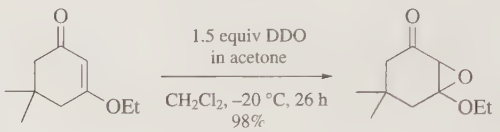


(5)

Although reactions are much slower with conjugated carbonyl compounds, DDO is still effective for the epoxidation of these electron-deficient double bonds (eq 6).[13] Alkoxy-substitution on such conjugated alkenes can also be tolerated (eq 7).[14]

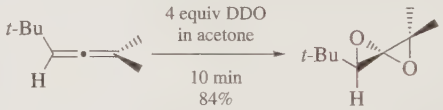


(6)



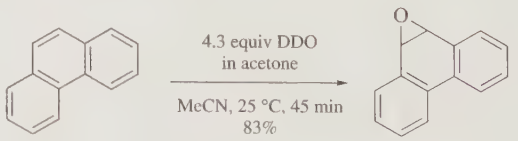
(7)

Allenes react with DDO by sequential epoxidation of the two double bonds to give the previously inaccessible, highly reactive allene diepoxides.[15] In the case of the *t*-butyl-substituted allene shown in eq 8, a single diastereomer of the diepoxide is generated, owing to steric control of the *t*-butyl group on reagent attack.

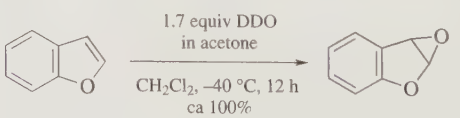


(8)

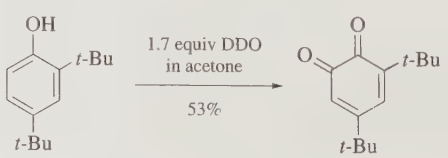
Certain polycyclic aromatic hydrocarbons can be converted to their epoxides, as typified by the reaction of phenanthrene with DDO (eq 9).[4] Aromatic heterocycles like furans and benzofurans also give epoxides, although these products are quite susceptible to rearrangement, even at subambient temperatures (eq 10).[16] The oxidation of heavily substituted phenols by DDO leads to quinones, as shown in eq 11, which illustrates the formation of an orthoquinone.[17] The corresponding hydroquinones are intermediates in these reactions, but undergo ready oxidation to the quinones.



(9)

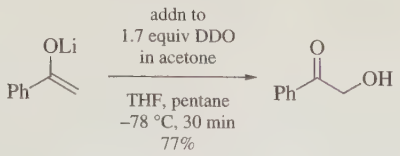


(10)



(11)

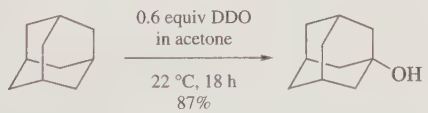
Finally, preformed lithium enolates are converted to α-hydroxy ketones by addition to a cold solution of DDO (eq 12).[18]



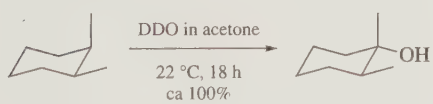
(12)

Oxidation of Saturated Hydrocarbons, Ethers, and Alcohols. Surely the most striking reaction of dioxiranes is their ability to functionalize unactivated C–H bonds by the insertion of an oxygen atom into this σ-bond. This has opened up an important new area of oxidation chemistry.[1] While DDO has been used in a number of useful transformations outlined below, the more reactive ***Methyl(trifluoromethyl)dioxirane*** is often a better reagent for this type of conversion, despite its greater cost and difficulty of preparation.

The discrimination of DDO for tertiary > secondary > primary C–H bonds of alkanes is more pronounced than that of the *t*-butoxide radical.[19] Good yields of tertiary alcohols can be secured in favorable cases, as in the DDO oxidation of adamantane to 1-adamantanol, which occurs with only minor reaction at C-2 (eq 13). Of major significance is the observation that these reactions are stereospecific with high retention of configuration, as illustrated by the oxidation of *cis*-dimethylcyclohexane shown in (eq 14); the *trans* isomer gives exclusively the diastereomeric alcohol. This and other data have been interpreted in terms of an 'oxenoid' mechanism for the insertion into the C–H bond. Several interesting applications in the steroid field involve significant site selectivity as well.[20] The slower reactions of DDO with hydrocarbons without tertiary hydrogens are less useful and lead to ketones owing to a rapid further oxidation of the initially formed secondary alcohol. For example, cyclododecane is converted to cyclododecanone.

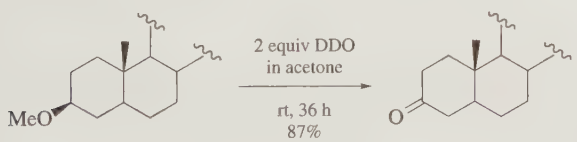


(13)



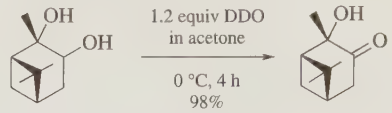
(14)

Ethers and acetals are slowly converted by DDO to carbonyl compounds. This serves as a nontraditional method for deprotection of these derivatives, an example of which is shown in (eq 15).[21,22] Hemiacetals are presumed intermediates in these transformations.

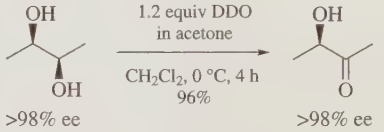


(15)

While DDO has been little used for the oxidation of simple alcohols, it has found application in useful conversions of vicinal diols. The oxidation of tertiary–secondary diols to α-hydroxy ketones occurs without the usual problem of oxidative cleavage between the two functions (eq 16).[23] DDO has also been used to convert appropriate optically active diols selectively into α-hydroxy ketones of high optical purity; for example, see (eq 17).[24]



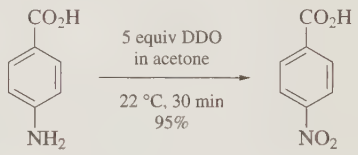
(16)



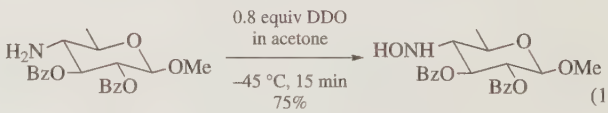
(17)

Finally, the Si–H bond of silanes suffers analogous oxidation to silanols upon reaction with DDO. This reaction takes place with retention of configuration and is, as expected, more facile than C–H oxidations.[25]

Oxidation of Nitrogen Functional Groups. Selective oxidations of nitrogen compounds are often difficult to achieve, but DDO methodology has been shown to be very useful in a number of instances. For example, one of the first applications of this reagent was in the conversion of primary amines to the corresponding nitro compounds (eq 18).[26] This process probably proceeds by successive oxidation steps via hydroxylamine and nitroso intermediates. Complications arise with unhindered primary aliphatic amines, owing to dimerization of the intermediate nitrosoalkanes and their tautomerization to oximes.[27] In oxidations of amino sugar and amino acid derivatives, it is possible to isolate the initially formed hydroxylamines (eq 19).[28]

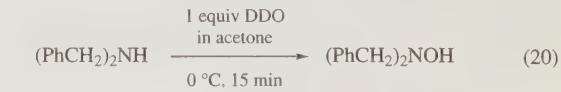


(18)

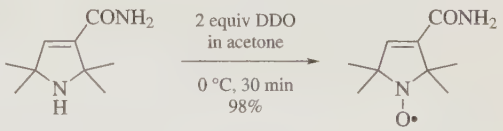


(19)

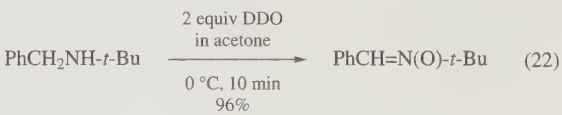
The oxidation of secondary amines to hydroxylamines is readily achieved with 1 equiv of DDO (eq 20).[29] The use of 2 equiv of DDO results in further oxidation, the nature of which depends on the structure of the amine. Thus cyclic secondary amines which do not possess α-hydrogens are converted to nitroxides,[30] as illustrated in (eq 21). Secondary benzylamines give nitrones (eq 22).[31]



(20)



(21)

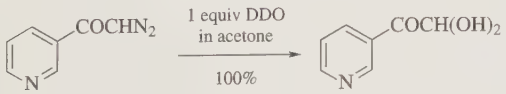


(22)

A related transformation is the oxidation of imines to nitrones by DDO (eq 23).[32] It is interesting that the isomeric oxaziridines are not produced here, given that peracids favor these heterocycles.

$$C_6Me_5CH{=}NMe \xrightarrow[CH_2Cl_2,\ 0\ °C,\ 2\ h\ 71\%]{1.1\ equiv\ DDO\ in\ acetone} C_6Me_5CH{=}N(O)Me \quad (23)$$

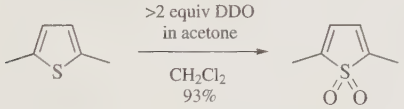
Reaction of α-diazo ketones with DDO leads to α-keto aldehyde hydrates (eq 24).[33] Oximes are converted to the free ketones by DDO.[34]



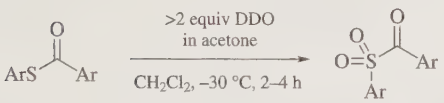
(24)

Oxidation of Sulfur Functional Groups. Dimethyldioxirane rapidly oxidizes sulfides to sulfoxides and converts sulfoxides to sulfones (eq 25).[4,35] The partial oxidation of sulfides to sulfoxides can be controlled by limiting the quantity of DDO. Since Oxone is one of the many reagents that can perform these reactions, the extra effort involved in preparing DDO solutions is often not warranted. An exception involves the transformation of thiophenes to the corresponding sulfones (eq 26).[36] A similar procedure gives α-oxo sulfones by DDO oxidation of thiol esters (eq 27).[37]

$$PhSMe \xrightarrow{DDO} PhSOMe \xrightarrow{DDO} PhSO_2Me \quad (25)$$



(26)



(27)

Alkanethiols are selectively oxidized to alkanesulfinic acids by DDO (eq 28).[38] Air oxidation of an intermediate species appears to be important in this transformation.

$$Me(CH_2)_4SH \xrightarrow[in\ acetone]{DDO} \xrightarrow{O_2} Me(CH_2)_4SO_2H \quad (28)$$

First Update

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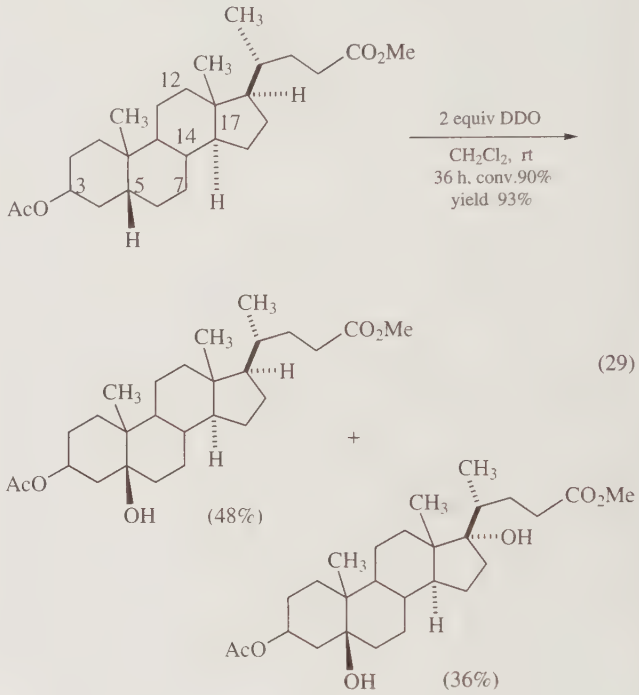
Direct Functionalization of C–H Bonds by Dimethyldioxirane.[1,39] The efficient oxyfunctionalization of simple, "unactivated" C–H bonds of alkanes under extremely mild conditions is undoubtedly one of the major highlights of dioxirane chemistry.[1,39]

Although less effective than methyl(trifluoromethyl)dioxirane (TFDO), oxyfunctionalization of unactivated methine C–Hs with dimethyldioxirane (DDO) is feasible for various substituted steroids related to the 5β-cholane and 5α-cholestane series to give novel mono- and dihydroxylated steroids.[40] The reactivity and site selectivity of oxyfunctionalization is affected conspicuously by the structural and steric environments of the target methine carbon atoms. This nonenzymatic procedure may be advantageously applied to selective and short-course syntheses of bioactive steroids. Thus, the major reaction product of methyl 3α-acetoxy-5α-cholan-24-oate with DDO in 36 h was the corresponding 5β-hydroxylated compound in 48% yield, while concurrent double oxyfunctionalization at the C-5 and C-17 produced the corresponding dihydroxylated derivative in comparable yield (36%) (eq 29).[40]



(29)

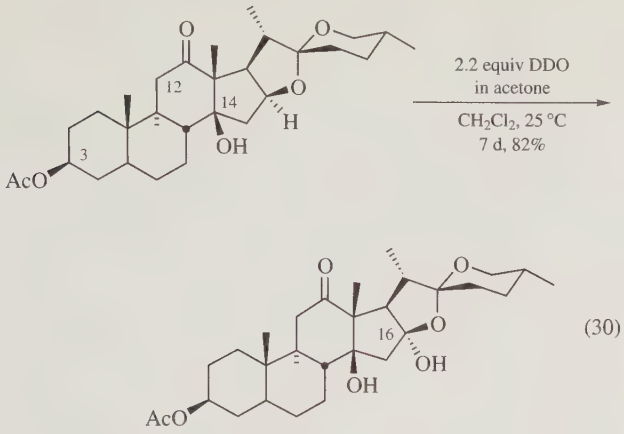
Both the 5β- and 17α-hydroxylation proceeded stereoselectively and the configuration of the resulting C–OH was the same as that of the original methine C–H bond. In order to accelerate the reaction of *O*-insertion (otherwise rather sluggish), instead of the usual DDO solution (up to 0.11 M) in acetone, the aforementioned concentrated DDO solutions (0.33–0.35 M) in $CHCl_3$ were employed.[40] These are obtained by following a procedure of extraction (outlined above) of the dioxirane into the chlorinated solvent,[41] similar to that devised to obtain ketone-free TFDO solutions.[42]

In another study where DDO was employed for *tert*-C–H hydroxylation of several di- and triacetates of (5β)-bile acid methyl esters, it was reported that derivatives bearing a 7-acetoxy group give 17α- or 14α-hydroxylated products in addition to the 5β-hydroxylated ones.[43]

For bile acid esters, the DDO oxidation of *sec*-CHOH groups of hydroxy cholate methyl esters to the corresponding carbonyls (via *gem*-diols) occurs readily; the positional order of reactivity C3 ≅ C7 > C6 > C12 was established.[44]

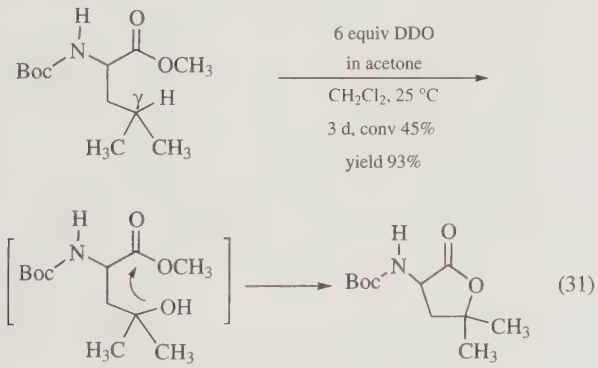
In line with the effective oxyfunctionalizations recorded for steroids, the DDO hydroxylation of cephalostatin derivatives provide another interesting example. In fact, the DDO oxidation hecogenin acetate β-hydroxyketone in (eq 30) results in *O*-insertion

into C16–H to yield the corresponding hemiketal with amazing site-selectivity.[45a] This key transformation paves the road for synthesis of the cephalostatin North 1 hemisphere.[45]



(30)

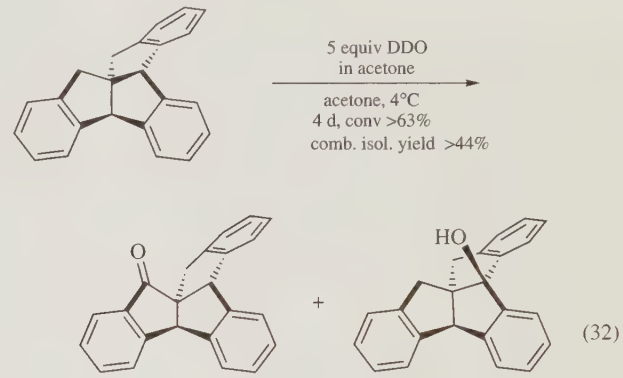
Remarkable site-selectivity is often observed in the hydroxylation of protected *N*-Boc derivatives of α-amino acid esters bearing an alkyl side chain (Boc-Gly-OMe, Boc-Ala-OMe, Boc-Val-OMe, Boc-Ile-OMe, Boc-Phe-OMe); this results in different products depending on the structure.[46] Although these reactions are rather sluggish, requiring long reaction times for sizable substrate conversion, they offer a novel entry to side-chain modified α-amino acids and peptides that avoids multi-step synthetic approaches. The reactivity and site-selectivity depends on the steric environments and electron density of the target C–H bonds in the side chain; high regioselectivity for the *O*-insertion into the γ-C–H bond of leucine (Leu) residues with respect to the weaker α-C–H bonds is observed. Thus, Boc-Leu-OMe was found to yield the corresponding 4,4-dimethyl-4-butanolide derivative; the latter is formed by selective *O*-insertion into the tertiary γ-C–H bond of Leu followed by cyclization (eq 31).



(31)

A position selectivity in the oxidation of peptides containing more than one Leu residue was also reported.[46] However, it should be noted that the same transformation in eq 31 gave a markedly lower yield in γ-butanolide using a lower DDO excess.[47] The reaction occurs more rapidly (6 h, 91% conv) using the powerful TFDO (6 equiv); it gives the *N*-hydroxy derivative of the butanolide in 21% yield, along with the uncyclized *N*-hydroxy derivative of the starting Boc-Leu-OMe as the major product (57%).[47]

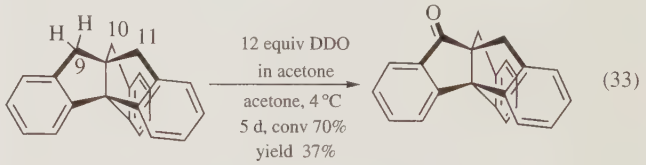
In general, benzhydrylic C–H bonds (only slightly more reactive than *tert*-C–Hs) are distinctly more reactive than benzylic C–H bonds toward dioxirane *O*-insertion.[39,48,49] However, special situations arise in the selective hydroxylation of complex polycyclic indan hydrocarbons, i.e., the centropolyindans.[50] For instance, the rigidity of the polycyclic framework and steric factors in the angular centrotriindan 1,1′-(*o*-phenylene)-2,2′-spirobiindan moderate the otherwise distinct selectivity for benzhydrylic vs. benzylic C–H *O*-insertion by DDO; so then, spirobiindanone is formed along with the tertiary 4bα-alcohol (eq 32).[50]



(32)

(28%) (16%)

Triptindane, another propellane-type centropolyindan, was found to react with excess DDO yielding triptindan-9-one as the major product (37% yield) at the conditions given in (eq 33).[50]

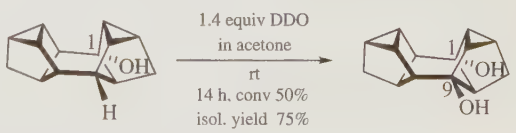


(33)

The monoketone thus obtained was fully characterized. The formation of sizeable amounts of more highly oxidized products (triptindan-9,10-dione and triptindan-9,10,11-trione) was detected by mass spectrometry.

Turning to polycyclic saturated hydrocarbons, the shown (eq 13) selective oxyfunctionalization of adamantane (*requiring 6 equiv of the powerful TFDO for exhaustive bridgehead hydroxylation*)[11] serves well to illustrate the high tertiary vs. secondary selectivities that are customarily observed. The ratio of tertiary to secondary carbons and the different reactivity towards oxidation for each type of C–H bond in Binor S renders it an attractive probe for the study of regioselectivity of oxyfunctionalization. In fact, this saturated heptacyclic hydrocarbon (the head-to-head dimer of norbornadiene) consists of two nortricyclane units, each containing one three-membered ring and three five-membered rings; it presents two symmetric methylene groups and 12 tertiary carbons ordered in four different geometries.

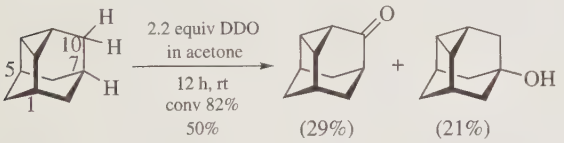
Treatment of Binor S in CH_2Cl_2 with aqueous (pH 7) monoperoxosulfate (caroate)/acetone (DDO in situ) afforded Binor S 1-ol in 98% yield.[51] Further oxidation of this material with isolated DDO gives the symmetrical 1,9-diol as the major product (eq 34).[51]



(34)

The examples above further demonstrate that dioxirane reactions are characterized by high selectivity and that *tert*-C–H bonds are considerably more reactive towards dioxirane *O*-insertion than their *sec*-C–H complements.[39] However, the cyclopropane moiety, if suitably oriented,[52,53] can have a marked influence in activating proximal α-C–H bonds towards dioxirane oxyfunctionalization.[52]

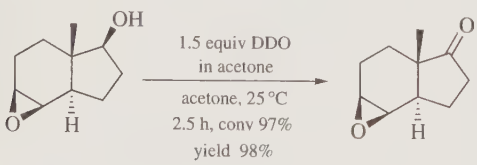
This is illustrated by the application of dioxiranes to polycyclic alkanes possessing a sufficiently rigid framework, such as the 2,4-didehydroadamantane case. For this substrate the reaction with DDO proceeds with 82% conversion during 12 h, yielding the expected 2,4-didehydroadamantan-7-ol, but also the precious 2,4-didehydroadamantan-10-one in comparable yield (eq 35).[54] The ketone derives from competitive dioxirane attack at the methylene positions α to the cyclopropyl moiety; the latter is encompassed in the rigid 2,4-didehydroadamantane framework to lay constrained into a "bisected"[52] orientation relative to the neighboring methylene C–H bonds.



(35)

Hydroxylation at the bridgehead C1 and C5 does not take place because the bridgehead *tert*-C–H bonds are deactivated by the proximal cyclopropyl moiety lying perpendicularly. It is worth of note that, at variance with what is observed with other oxidants (e.g., dry ozone), no rearranged products are observed in the reaction of DDO with this target compound.[54]

It was mentioned that oxidation by DDO allows the clean conversion of secondary alcohols into carbonyls under mild conditions. In this transformation the dioxiranes rank high with respect to transition-metal oxidants because of their efficiency, superior versatility, and ease of operations. Based on kinetic data and the application of reaction probes,[55] the oxidation proceeds via a substantially concerted *O*-insertion by the dioxirane into the C–H bond "alpha" to the OH functionality generating a *gem*-diol $C(OH)_2$, hence the carbonyl. As shown by the example in eq 36, remarkable chemoselectivity is achieved in the oxidation of epoxy alcohols in that the corresponding epoxy ketones are formed in high yield, while the epoxy functionality remains untouched.[56] The epoxy ketone in eq 36 is a key intermediate in the convergent synthesis of active 1α,25-dihydroxyvitamin D_3 analogs.[57]



(36)

Both open chain and cyclic epoxy alcohols can be neatly transformed into the corresponding epoxy ketones with high conversions and yields using just 1.1–1.5 equiv of DDO oxidant. Also, the conversion of optically active epoxy alcohols into epoxy ketones occurs selectively leaving the configuration at the chiral center(s) at the oxirane ring unaffected.[56]

Related Reagents. Potassium monoperoxosulfate (Oxone); potassium monoperoxosulfate (Oxone)/acetone (DDO in situ); methyl(trifluoromethyl)dioxirane.

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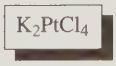
Dipotassium Tetrachloroplatinate(II)[1]



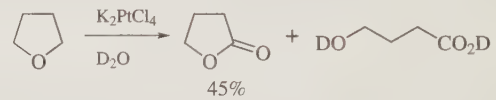
[10025-99-7] Cl_4K_2Pt (MW 415.08)

(homogeneous hydrogen isotope exchange catalyst;[2] selective oxidative functionalization of alkane C–H bonds;[3] used for the synthesis of various platinum complexes)

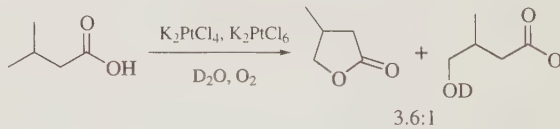
Physical Data: dark red crystals; *d* 3.38 g cm^{-3}.
Solubility: sol H_2O (0.93 g/100 mL at 15 °C, 5.3 g/100 mL at 100 °C); insol ethanol, acetone.
Form Supplied in: solid; widely available.
Drying: at 120 °C/0.1 mmHg for 24 h.
Handling, Storage, and Precautions: should be stored in the absence of moisture; irritating to skin, eyes, and respiratory organs; corrosive.

Hydrogen Isotope Exchange Catalyst. Aromatic and aliphatic compounds undergo exchange of isotopic hydrogen with a catalytic amount of this reagent. This system is valuable for labeling compounds with deuterium and/or tritium in one step and constitutes the homogeneous equivalent of the well-known heterogeneous platinum technique. A wide range of compounds, including alkanes,[4] cycloalkanes,[5] saturated carboxylic acids,[6] benzoic acid,[7] benzyl alcohol,[8] β-phenylpropionic acid,[9] phenylalanine, phenylglycine,[10] and tyrosine[11] have been D and/or T labeled using this technique (see also ***Disodium Tetrachloroplatinate(II)***).

Functionalization of Saturated Hydrocarbons. K_2PtCl_4 or the combination K_2PtCl_4/K_2PtCl_6 in aqueous medium is often used for the selective oxidation of isolated C–H bonds of saturated hydrocarbons (see also ***Disodium Tetrachloroplatinate(II)***). Ethane can be selectively oxidized to acetic or glycolic acid.[12] Tetrahydrofuran is oxidized to γ-butyrolactone (eq 1),[13] and isovaleric acid to γ-valerolactone (eq 2).[14]

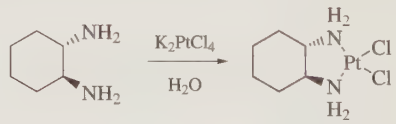


(1)



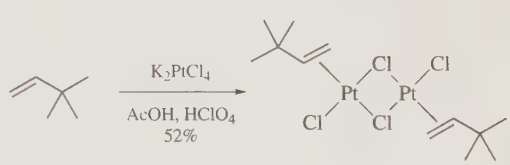
(2)

Complexes. The reaction of 1,2-diamines and similar ligands with K_2PtCl_4 is widely used for the synthesis of cisplatin analogs, powerful antitumor agents (eq 3).[15]



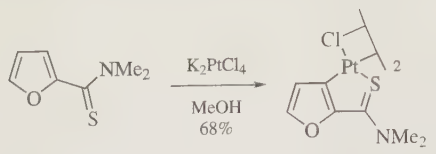
(3)

Alkenes,[16] including ethylene,[17] and dienes,[18] readily coordinate with K_2PtCl_4, forming complexes (eq 4). These complexes readily undergo displacement reactions with free alkene in the solution.[19]



(4)

A number of aromatic and heteroaromatic compounds, substituted with suitable donor ligands, undergo cycloplatination reactions when treated with K_2PtCl_4 (eq 5).[20]



(5)

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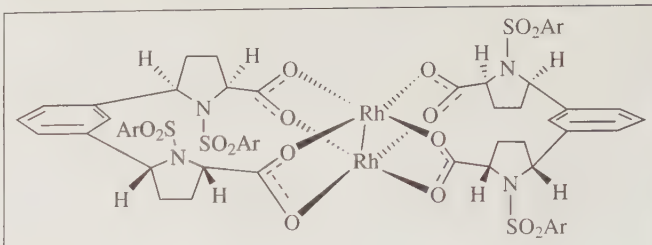
Dirhodium(II) bis-{1,3-[*N*,*N*′-di (4-Dodecyl-Benzenesulfonyl)-(2*S*,2′*S*),(5*R*,5′*R*)-5,5′-Prolinate]Benzene}



Rh_2(*S*-biDOSP)$_2$: Ar = *p*-$C_{11-13}H_{23-27}C_6H_4$

Rh_2(*S*-biTISP)$_2$: Ar = 2,4,6-tri-^{i}PrC_6H_2

Rh_2(*S*-biTBSP)$_2$: Ar = *p*-^{t}BuC_6H_4

Rh_2(*S*-biDOSP)$_2$
[232946-37-1] $C_{104}H_{148}O_{16}N_4S_4Rh_2$ (MW 2044)

Rh_2(*S*-biTISP)$_2$
[244240-94-6] $C_{92}H_{124}O_{16}N_4S_4Rh_2$ (MW 1876)

Rh_2(*S*-biTBSP)$_2$
[244240-93-5] $C_{72}H_{84}O_{16}N_4S_4Rh_2$ (MW 1596)

(catalysts for carbenoid reactions of diazo compounds)

Physical Data: IR (neat) 2962, 2925, 2857, 1602, 1417, 1332, 1157, 1099 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (bs, 4H), 7.52 (bs, 4H), 7.08 (bs, 8H), 6.95–6.65 (bm, 8H), 4.73 (bs, 4H), 4.57 (bs, 4H), 2.8–0.6 (bm, 116H).

Solubility: soluble in CH_2Cl_2, *n*-alkanes, most hydrocarbon solvents.

Form Supplied in: not commercially available.

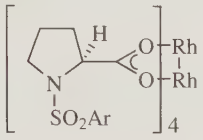
Preparative Methods:[1] Rh_2(*S*-biDOSP)$_2$ can be prepared by ligand exchange from dirhodium(II) tetraacetate dimer. A typical procedure is as follows: A stirred solution of 1,3-[*N*,*N*′-di (4-dodecylbenzenesulfonyl)-(2*S*,2′*S*),(5,5′-prolinate]benzene[1] (2.0 g, 2.2 mmol) and dirhodium(II) tetraacetate dimer (0.44 g, 1.0 mmol) in chlorobenzene (65 mL) was heated at reflux through a soxhlet extractor containing calcium carbonate for 72 h. The solution was cooled to room temperature and concentrated under reduced pressure. The product was purified by silica gel chromatography (hexanes/EtOAc, 4:1) to give a green solid (1.0 g, 49% yield).

Purification: the title compound can be readily purified by column chromatography on silica gel with a hexanes/EtOAc solvent system to give a green solid.

Handling, Storage, and Precautions: air stable, stored in dessicator.

Introduction. Rh_2(*S*-biDOSP)$_2$ is a member of a family of dirhodium tetracarboxylate catalysts that contain two bridging phenyl units that link the proline groups together in a rigid manner. Other catalysts of this type include bis-{1,3-[*N*,*N*′-di(4-*tert*-butylbenzenesulfonyl)-(2*S*,2′*S*),(5*R*,5′*R*)-5,5′-prolinate]benzene} dirhodium(II) (Rh_2(*S*-biTBSP)$_2$) and bis-{1,3-[*N*,*N*′-di(2,4,6-triisopropyl-benzenesulfonyl)-(2*S*,2′*S*),(5*R*,5′*R*)-5,5′-prolinate]benzene} dirhodium(II) (Rh_2(*S*-biTISP)$_2$) both of which differ from

Rh_2(*S*-biDOSP)$_2$ in the structure of the arylsulfonyl groups attached to the proline units. These catalysts were developed as second-generation versions of their unbridged analogs Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-TBSP)$_4$ (Figure 1) and have been very effective at catalyzing carbenoid reactions. These catalysts have some distinct advantages over their predecessors, especially with regard to turnover numbers (TON) and immobilization on a solid phase polymer resin.



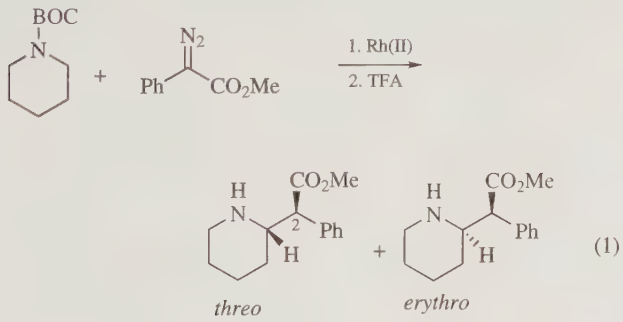
Rh_2(*S*-DOSP)$_4$: Ar = *p*-$C_{11-13}H_{23-27}C_6H_4$

Rh_2(*S*-TBSP)$_4$: Ar = *p*-^{t}BuC_6H_4

Figure 1

Metal Carbene Transformations.

C–H Activation. The rhodium prolinate catalysts described above are very effective at catalyzing carbenoid reactions with high asymmetric induction only when donor/acceptor-type carbenoids are utilized. Several reviews are available describing in detail the subtle electronic effects that make this class of compounds distinct from traditional carbenoids that do not contain a stabilizing donor group.[2–4] In addition to undergoing cyclopropanation reactions, these carbenoids are capable of highly regioselective intermolecular C–H insertions. Sites α to heteroatoms are electronically favored as the positive charge that is built up at the carbon undergoing C–H insertion can be effectively stabilized. A very practical example of this type of reaction is in the synthesis of *threo*-methylphenidate (Ritalin) by Davies shown in eq 1.[5,6]



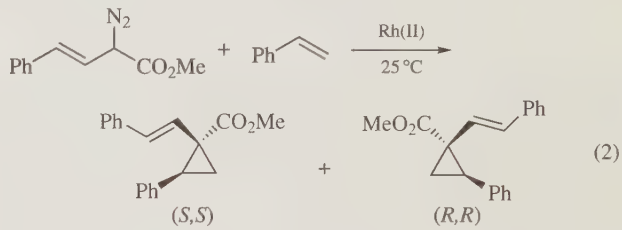
(1)

	threo:*erythro*	ee % (*threo*)
Rh_2(*S*-biDOSP)$_2$	71:29	86(2*R*)
Rh_2(*S*-DOSP)$_4$	50:50	25(2*S*)

In this case, the asymmetric induction achieved by the Rh_2(*S*-DOSP)$_4$ catalyst was poor, with an equal amount of the two diastereomers produced and the desired biologically active *threo*-diastereomer formed with poor enantioselectivity. The same reaction performed with Rh_2(*S*-biDOSP)$_2$ resulted in much better stereocontrol favoring the *threo*-isomer. Interestingly, the sense of the enantioinduction observed with Rh_2(*S*-biDOSP)$_2$ is opposite to that obtained when Rh_2(*S*-DOSP)$_4$ is used as the catalyst. This is a general trend for the bridged versus the unbridged catalysts and is believed to result from the binding of the carbenoid in a different staggered orientation to the bridged catalysts.[1]

Cyclopropanation.

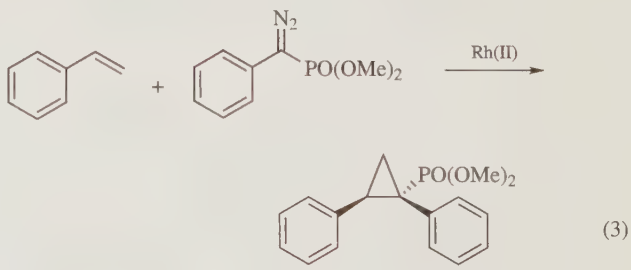
Solvent Effects. Solvent effects also play an important role in the level of asymmetric induction achieved in carbenoid reactions. The unbridged Rh_2(*S*-DOSP)$_4$ catalyst performs best in nonpolar hydrocarbon solvents and generally a drop in enantioselectivity is observed for reactions carried out with this catalyst in solvents such as dichloromethane. Just the opposite has been observed with the bridged catalysts as shown in eq 2 for the cyclopropanation of styrene.[1] This is very important for reactions involving polar substrates that are relatively insoluble in nonpolar solvents.



(2)

	ee % in *n*-alkane	ee % in CH_2Cl_2
Rh_2(*S*-biDOSP)$_2$	53 (*S*,*S*)	68 (*S*,*S*)
Rh_2(*S*-biTISP)$_2$	74 (*S*,*S*)	90 (*S*,*S*)
Rh_2(*S*-DOSP)$_4$	90 (*R*,*R*)	74 (*R*,*R*)

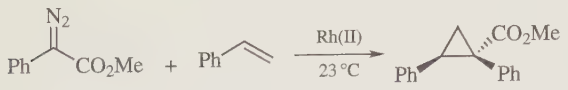
Phosphonate Diazo Compounds. In cases where the electron-withdrawing component (acceptor) of the carbenoid is different from the typical ester group, the bridged catalysts can be superior to the unbridged versions. An interesting example is given in eq 3 involving a phosphonate diazo compound.[7] Rh_2(*S*-DOSP)$_4$ failed to give good enantioselectivity with this carbenoid, while the bridged catalyst Rh_2(*S*-biTISP)$_2$ resulted in a much improved ee and yield.



(3)

catalyst	yield (%)	de (%)	ee (%)
Rh_2(*S*-DOSP)$_4$	69	95	34
Rh_2(*S*-biTISP)$_4$	89	98	88

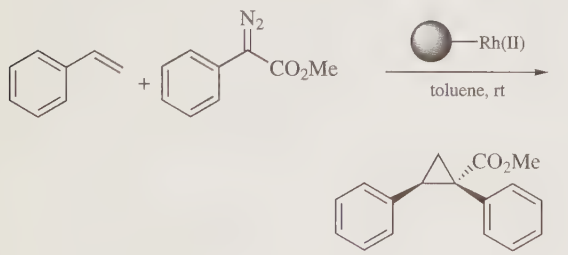
Turnover Numbers. The unbridged catalyst Rh_2(*S*-DOSP)$_4$ is capable of effectively catalyzing carbenoid reactions at low (1:1000) catalyst to substrate ratios. In a direct comparison, however, the bridged catalyst Rh_2(*S*-biTISP)$_2$ was able to perform well even at substrate to catalyst ratios approaching 1 000 000:1 as shown in eq 4.[8]



(4)

	substrate/catalyst ratio	yield (%)	ee (%)	time (h)
Rh_2(*S*-DOSP)$_4$ (hexanes)	1000	97	91	1
	10 000	96	85	16
	100 000	14	10	>192
Rh_2(*S*-biTISP)$_2$ (DCM)	1000	82	89	1
	10 000	79	89	3
	100 000	85	83	28
	1 000 000	75	74	>240

Immobilization. In addition to these examples of homogeneous reactivity, there is an evidence that Rh_2(*S*-biDOSP)$_2$ would be conducive to immobilization upon a solid-support polystyrene resin. For example, Rh_2(*S*-biTISP)$_2$ has been linked to an Argopore-Wang resin and has shown similar catalytic activity to the homogeneous version[9,10] (eq 5). As expected from the homogeneous reaction data, the bridged catalyst produced the opposite enantiomer of the product as compared to the unbridged catalyst. One surprising feature of the solid-supported bridged catalyst Rh_2(*S*-biTISP)$_2$ is that in comparison with the solid-supported unbridged version, the enantioselectivities of the products remain unchanged after 15 cycles. In contrast, studies with an unbridged catalyst Rh_2(*S*-TBSP)$_4$ showed a decrease in product enantiomeric excess from 82% to 70% after four cycles.[9] The former observation is an attractive feature in that much higher turnover numbers can be realized, which would prove economical in the synthesis of a library of compounds. It may also indicate that bridged carboxylate dirhodium catalysts in general are superior to unbridged versions for solid-supported carbenoid chemistry.



(5)

	Rh_2(*S*-TBSP)$_4$			Rh_2(*S*-biTISP)$_2$		
cycle	time (min)	yield (%)	ee (%)	cycle	time (min)	yield (%)	ee (%)
1	10	92	82	1	18	91	85
4	14	89	70	4	36	90	87
				15	92	89	88

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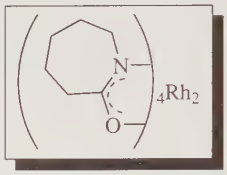
Dirhodium(II) Tetra(caprolactamate)



[138984-26-6] $C_{24}H_{40}N_4O_4Rh_2$ (MW 658.44)

(catalyst for selective carbenoid reactions of diazo compounds[1])

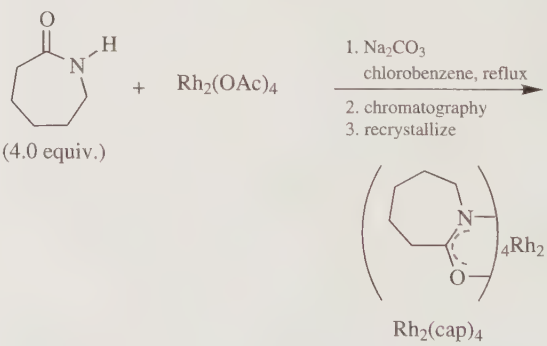
Alternate Name: Rh_2(Cap)$_4$.

Spectral Data: λ 607 nm, ε 250 (CH_2Cl_2).

Solubility: soluble in methanol, acetonitrile; slightly soluble in CH_2Cl_2, $ClCH_2CH_2Cl$, toluene.

Form Supplied in: purple powder as the bisacetonitrile complex, blue solid after removal of the axial nitrile ligands. Note: Johnson-Matthey does not supply Rh_2(cap)$_4$ as the bisacetonitrile complex.

Preparative Methods: from dirhodium tetraacetate by ligand substitution with caprolactam (eq 1).[2]



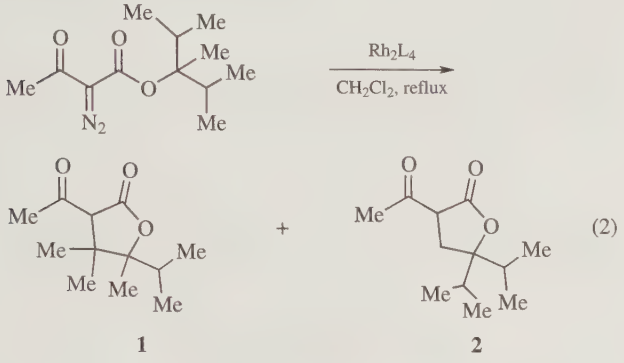
(1)

Handling, Storage, and Precautions: air stable, weakly hydroscopic; stored in a desiccator.

Preparation. Dirhodium(II) tetra(caprolactamate) Rh_2(cap)$_4$ was prepared from dirhodium(II) tetraacetate.[3] The preferred procedure is ligand substitution on $Rh_2(OAc)_4$ with caprolactam in refluxing chlorobenzene; liberated acetic acid is trapped by sodium carbonate in a Soxhlet extraction apparatus.[3] Four caprolactam molecules ligate one dirhodium(II) nucleus; each rhodium is bound to two nitrogen and two oxygen donor atoms arranged in a *cis*-geometry.[4]

Metal Carbene Transformations. The principal advantages of $Rh_2(cap)_4$ are its solubility in organic solvents and its selectivity for product formation from reactions with diazocarbonyl compounds relative to dirhodium(II) tetra(carboxylates).

Regioselectivity in Carbon-Hydrogen Insertion Reactions. The use of $Rh_2(cap)_4$ provides exceptional regiocontrol in intramolecular C–H insertion reactions of diazoacetoacetates and diazoacetoacetamides (e.g., eq 2, Table 1).[3]



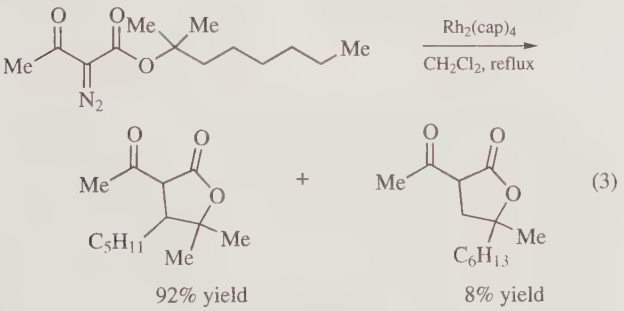
(2)

1 2

Table 3 Dirhodium(II) catalysts for intramolecular C–H insertion

	Yield (%)	
Catalyst	**1**	**2**
$Rh_2(pfb)_4$	39	61
$Rh_2(OAc)_4$	90	10
$Rh_2(cap)_4$	>99	<1

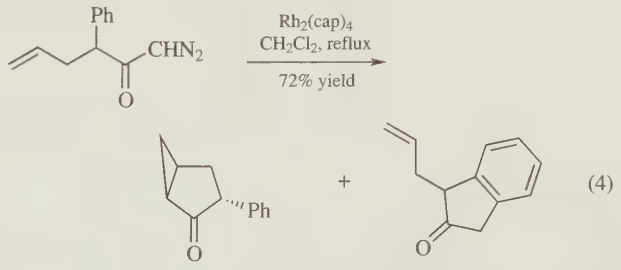
Similarly, when competition for C–H insertion is between primary and secondary C–H bonds, $Rh_2(cap)_4$ directs insertion to the secondary C–H bonds with high selectivity (eq 3) compared to rhodium(II) carboxylates.[3]



(3)

92% yield 8% yield

Chemoselectivity in Metal Carbene Transformations. When there are two reaction centers for intramolecular metal carbene reactions, the use of $Rh_2(cap)_4$ often leads to the production of only one product.[5,6] Cyclopropanation is favored over aromatic substitution (eq 4), over tertiary C–H insertion (eq 5), and over aromatic cycloaddition (eq 6). Product yields are high in each case. The order of reactivity for metal carbenes generated from $Rh_2(cap)_4$ decomposition of diazoketones is cyclopropanation > tertiary C–H insertion > secondary C–H insertion > aromatic cycloaddition.[6]



(4)

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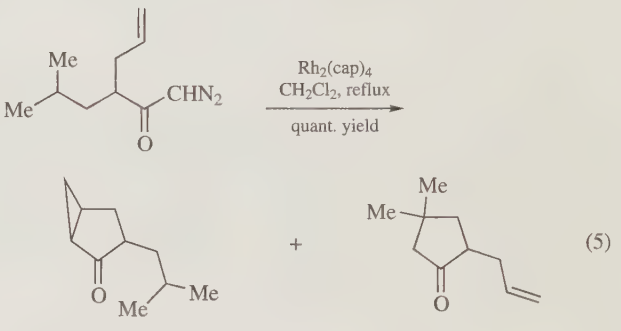

(5)

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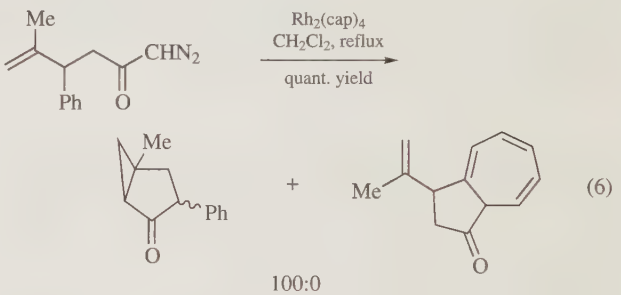

(6)

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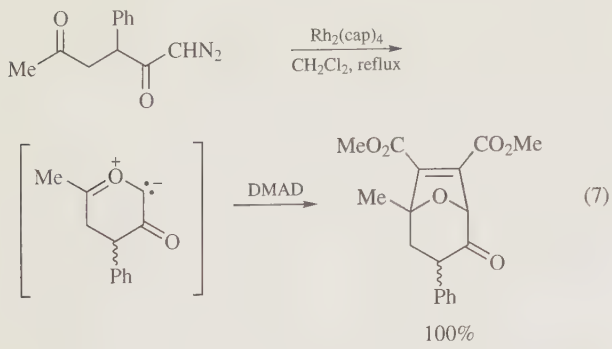
$Rh_2(cap)_4$ affected selective cyclopropanation of the allylic double bond of *trans,trans*-farnesyl diazoacetate, whereas with $Rh_2(OAc)_4$, a 13-membered cyclopopane-fused lactone was formed.[7] Further studies revealed that when competition exists between proximal allylic and remote olefinic cyclopropanantion, macrocyclization is favored by (catalyst ordered by increasing electrophilicity) $Rh_2(pfb)_4 > Rh_2(OAc)_4 \gg Rh_2(cap)_4$.[8]

Ylide Chemistry. Carbonyl ylide generation is favored over aromatic substitution with $Rh_2(cap)_4$ (eq 7, DMAD = dimethyl acetylenedicarboxylate),[9,10] but in competition with cyclopropanation both ylide generation and alkene cycloaddition occur with equivalent facility.[5,11,12] The selectivities achieved with changes in dirhodium(II) ligands are due, in part, to the degree of charge localization on the carbene center.[6] However, conformational restrictions from the carbene system bound to dirhodium(II) can also influence selectivity, so broad generalizations regarding selectivities with $Rh_2(cap)_4$ are inappropriate.[13]

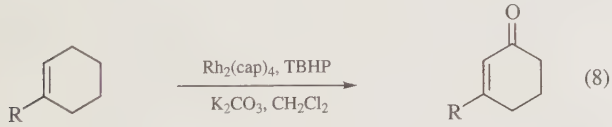
Allylic Oxidation. Allylic oxidation, whereby a single methylene unit is converted directly into a carbonyl group is a highly value added process. Recently, a new method for this process has been achieved using dirhodium(II) caprolactamate [$Rh_2(cap)_4$]. Doyle and co-workers reported that $Rh_2(cap)_4$ in combination with *tert*-butyl hydroperoxide (TBHP, terminal oxidant) effectively catalyzes the allylic oxidation of a variety of olefins and enones.



(7)

100%

Dirhodium(II) caprolactamate readily undergoes oxidation to $Rh_2(cap)_4^{5+}$ when treated with organic oxidants. This low, 1-electron oxidation ($E_{1/2}$ = 11 mV) allows $Rh_2(cap)_4$ to traverse the Rh_2^{4+}–Rh_2^{5+} oxidation states making it a suitable catalyst for allylic oxidation (eq 8, Table 2).[14,15] Using mild conditions (5 equiv TBHP and 50 mol % K_2CO_3), olefins were rapidly converted to enones in 1 h with only 0.1 mol % $Rh_2(cap)_4$.[16] Complete selectivity was observed in all cases.



(8)

Table 4 Dirhodium(II) tetra(caprolactamate)-catalyzed allylic oxidation

R	mol %	Time (h)	Yield (%)
H	0.1	1	60
tert-butyl	0.1	1	94
Ph	0.1	1	77
CO_2Me	1.0	1	92
Me	0.1	0.3	89

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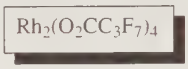
Dirhodium(II) Tetrakis(perfluorobutyrate)



[73755-28-9] $C_{16}F_{28}O_8Rh_2$ (MW 1057.98)

(catalyst for carbenoid reactions of diazo compounds,[1] hydrosilylation of alkenes and alkynes,[2] and silylcarbonylation of alkynes[3])

Physical Data: λ 626 nm, ε 248 (CH_2Cl_2).[4]

Solubility: sol MeCN, DMSO, pyridine, benzene, CH_2Cl_2, alkenes.

Form Supplied in: anhydrous form is green; hydrate is blue.

Preparative Methods: from ***Dirhodium(II) Tetraacetate*** by ligand displacement in refluxing perfluorobutyric acid containing perfluorobutyric anhydride.[5]

Handling, Storage, and Precautions: air stable, very hygroscopic; stored in desiccator.

Metal Carbene Transformations.

Alkene Coordination. Dirhodium(II) tetrakis(perfluorobutyrate), $Rh_2(pfb)_4$, and ***Dirhodium(II) Tetrakis(trifluoroacetate)***, $Rh_2(tfa)_4$, are unique among dirhodium(II) carboxylates and carboxamides in their ability to form association complexes with alkenes and alkynes in solution.[2,4] Equilibrium constants range from 70 M^{-1} (styrene) to 932 M^{-1} (2-methoxypropene). However, alkene coordination with $Rh_2(pfb)_4$ has no effect on relative reactivity or selectivity in cyclopropanation reactions with ethyl diazoacetate. Being more soluble in weakly polar solvents than is $Rh_2(tfa)_4$, removal of $Rh_2(pfb)_4$ from reaction solutions by simple chromatography on silica is more difficult.

Stereoselectivity and Regioselectivity. The strongly electron-withdrawing perfluorobutyrate ligands render $Rh_2(pfb)_4$ significantly more electrophilic than ***Dirhodium(II) Tetraacetate*** or ***Dirhodium(II) Tetraacetamide***. As a result, reactivity towards diazo compounds is substantially increased, relative to

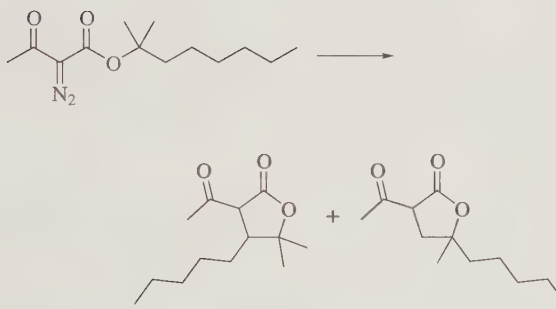
$Rh_2(OAc)_4$, and stereoselectivity and regioselectivity in cyclopropanation and carbon–hydrogen insertion reactions are greatly diminished (e.g. eqs 1–3).[6] Regioselectivity for C–H insertion into primary and secondary carbon–hydrogen bonds (eq 3) is nearly statistical, demonstrating that relative reactivities for insertion are essentially equal.[7–11]

(1)

	anti:*syn*
$Rh_2(pfb)_4$	1.9:1
$Rh_2(OAc)_4$	3.8:1
$Rh_2(acam)_4$	10:1

(2)

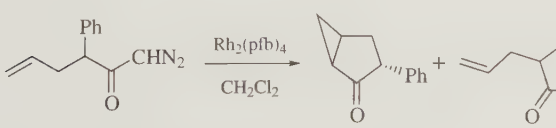
	%	%
$Rh_2(pfb)_4$	21	79
$Rh_2(OAc)_4$	12	88
$Rh_2(acam)_4$	7	93



(3)

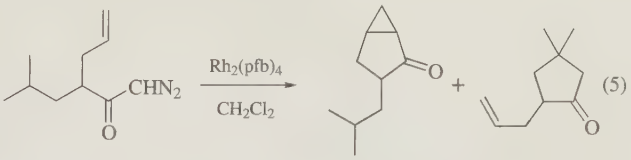
	%	%
$Rh_2(pfb)_4$	34	66
$Rh_2(OAc)_4$	75	25
$Rh_2(acam)_4$	92	8

Chemoselectivity. Dirhodium(II) perfluorobutyrate has proven to be highly selective in competitive intramolecular metal carbene transformations.[12] In contrast to results with ***Dirhodium (II) Tetra(caprolactam)***, the use of $Rh_2(pfb)_4$ favors aromatic substitution over cyclopropanation (eq 4),[13] insertion over cyclopropanation (eq 5),[13] and aromatic substitution over carbonyl ylide generation (eq 6).[14] Product yields are high in each case. The order of reactivity for metal carbenes generated from $Rh_2(pfb)_4$ is aromatic substitution > tertiary C–H insertion > cyclopropanation ≈ aromatic cycloaddition > secondary C–H insertion, and the rate differences between them are as much as 100-fold.[13]



(4)

0% 100%



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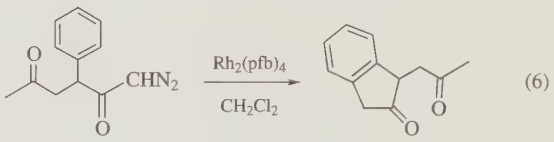
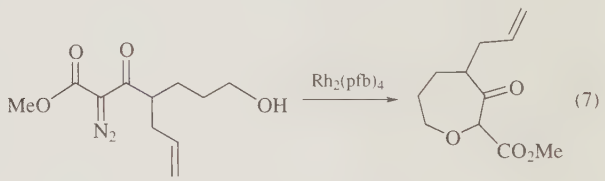


(6)

85%

Additional applications of $Rh_2(pfb)_4$ to metal carbene transformations include intramolecular O–H insertion (eq 7),[14] where intramolecular cyclopropanation would also be a viable pathway. For intramolecular cyclopropenation reactions of diazo ketones which undergo subsequent vinylcarbene formation, use of $Rh_2(pfb)_4$ leads to different products than those from dirhodium(II) octanoate.[15] In contrast to the use of rhodium(II) octanoate in pentane which effects exclusive cyclopropanation, $Rh_2(pfb)_4$ in CH_2Cl_2 promotes [3 + 2] annulation in reactions of a vinyldiazomethane with vinyl ethers (eq 8),[16] and this result further exemplifies the influence of the highly electrophilic $Rh_2(pfb)_4$ on selectivity.



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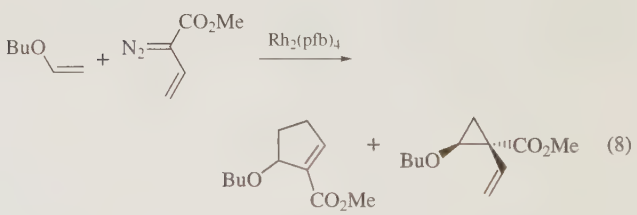
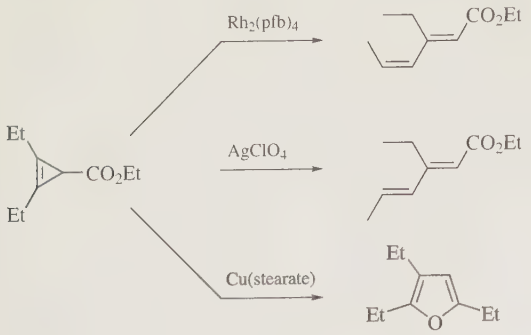


(8)

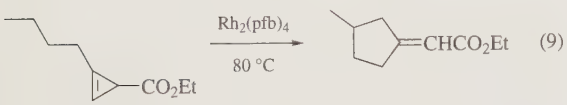
32% 0%

Isomerizations of Cyclopropenes. Cyclopropenes undergo facile rearrangements catalyzed by $Rh_2(pfb)_4$ to yield products that are structurally different from those obtained with the use of copper, platinum, or silver catalysts.[17] The selectivity achieved with $Rh_2(pfb)_4$ is remarkable (Scheme 1), and, as suggested by eq 9, the involvement of $Rh_2(pfb)_4$ is consistent with the generation of a vinylcarbene intermediate.

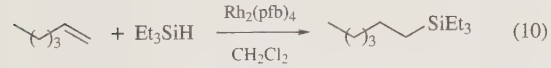
Hydrosilylation of Alkenes and Alkynes. Hydrosilylation of 1-alkenes is catalyzed by $Rh_2(pfb)_4$ under mild conditions.[18] The mode of addition determines the products that are formed. When the alkene is added to triethylsilane in the presence of $Rh_2(pfb)_4$, 'normal' hydrosilylation (eq 10) occurs; reversed addition causes the formation of vinyl- or allylsilanes (eq 11). Alkene isomerization catalyzed by the combination of $Rh_2(pfb)_4$ with triethylsilanes has also been reported.[18]



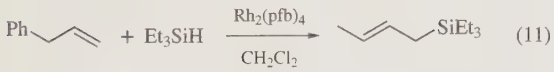
Scheme 1



(9)

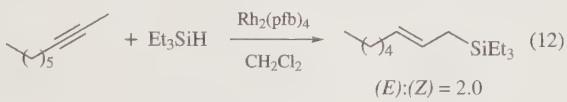


(10)



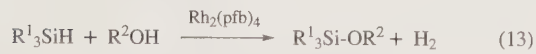
(11)

Hydrosilylation of 1-alkynes catalyzed by $Rh_2(pfb)_4$ forms either vinylsilanes (*trans* addition) or allylsilanes in moderate to high isolated yields, dependent on the mode of addition.[19] Addition of triethylsilane to 1-alkynes in dichloromethane containing $Rh_2(pfb)_4$ results in the formation of vinylsilanes, whereas addition of the alkynes to triethylsilane produces allylsilanes (eq 12) in high yield. Product dependence on the mode of addition is associated with organosilane coordination with $Rh_2(pfb)_4$. Organosilane alcoholysis is also catalyzed by $Rh_2(pfb)_4$ (eq 13);[20] primary alcohols react with triethylsilane approximately five times faster than do secondary alcohols.



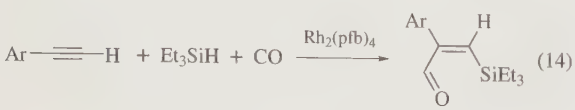
(12)

(E):*(Z)* = 2.0



(13)

Silylcarbonylation of Alkynes. $Rh_2(pfb)_4$ is a highly effective catalyst for silylation of terminal alkynes in reactions performed at atmospheric pressure or at 10 atm CO pressure and at or below rt.[3] At atmospheric CO pressure, addition of the alkyne to the organosilane is critical to the success of this transformation (eq 14), which is characterized by virtually complete regioselectivity and (*Z*/*E*) selectivity that is greater than 10:1, often reaching >30:1. ***Dirhodium(II) Tetraacetate*** is relatively ineffective as a catalyst for silylcarbonylation. The advantages of $Rh_2(pfb)_4$ as a catalyst for silylcarbonylation of alkynes lie in the mild conditions employed, high catalysts turnovers, and exceptional (*E*/*Z*) ratios.



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Dirhodium(II) Tetrakis(trifluoroacetate)

[31126-95-1] $C_8F_{12}O_8Rh_2$ (MW 657.90)

(highly electron deficient catalyst for carbenoid reactions of diazo compounds[1])

Physical Data: λ 610 nm, ε 210 (CH_2Cl_2).[2]

Solubility: sol MeCN, DMSO, pyridine; slightly sol dichloromethane, benzene.

Form Supplied in: anhydrous form is green; hydrate is blue.

Preparative Method: from ***Dirhodium(II) Tetraacetate*** by ligand displacement in refluxing trifluoroacetic acid containing trifluoroacetic anhydride.[3]

Handling, Storage, and Precautions: air stable, very hygroscopic; stored in desiccator.

Original Commentary

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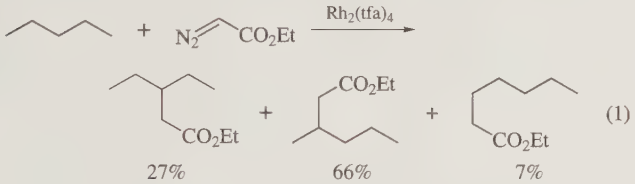
Alkene Coordination. Dirhodium(II) tetrakis(trifluoroacetate), $Rh_2(tfa)_4$, like the corresponding ***Dirhodium(II) Tetrakis(perfluorobutyrate)***, $Rh_2(pfb)_4$, forms π-complexes with alkenes.[2,4] Equilibrium constants for alkene coordination are 2–3 times less than those for $Rh_2(pfb)_4$, and they are relatively insensitive to steric influences. Coordination causes substantial changes in chemical shifts for vinyl protons.[4] A determination of chirality has been made through an axial bis-alkene complex of $Rh_2(tfa)_4$.[5] Nitroxide and phosphine complexes have also been characterized.[6,7]

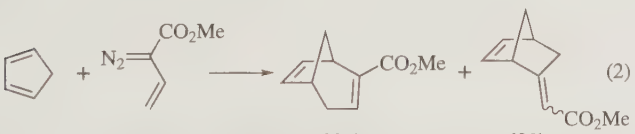
Metal Carbene Transformations. Fluoroalkanoate complexes of dirhodium(II) were first employed to effect intermolecular carbon–hydrogen insertion reactions (eq 1).[8,9] Although insertion product yields are relatively high, selectivity is low. A similar low level of selectivity occurs in intermolecular cyclopropanation of alkenes[10,11] and dienes.[12] However, relative to $Rh_2(tfa)_4$, $Rh_2(pfb)_4$ exhibits even lower levels of stereocontrol and regiocontrol in cyclopropanation reactions.



(1)

Both reactivity and solubility in weakly polar solvents render $Rh_2(pfb)_4$ superior to $Rh_2(tfa)_4$ for metal carbene transformations.

The cationic character of the intermediate metal carbene formed from a vinyldiazo compound is evident in the formation of the bicyclo[2.2.1]heptene system in eq 2.[13] Here, use of $Rh_2(tfa)_4$ favors this carbocation addition product even in pentane, whereas use of ***Dirhodium(II) Tetraacetate*** in pentane reduces the yield of this product to only 5%. Electrophilic substitution products have also been reported from $Rh_2(tfa)_4$-catalyzed reactions of vinyldiazomethane derivatives with *N*-(methoxycarbonyl)pyrrole.[14] Overall $Rh_2(tfa)_4$ is not as effective as $Rh_2(pfb)_4$, nor is its selectivity in reactions of metal carbenes significantly different.



(2)

$Rh_2(tfa)_4$, CH_2Cl_2	32%	68%
$Rh_2(tfa)_4$, pentane	46%	54%
$Rh_2(OAc)_4$, CH_2Cl_2	67%	33%
$Rh_2(OAc)_4$, pentane	95%	5%

First Update

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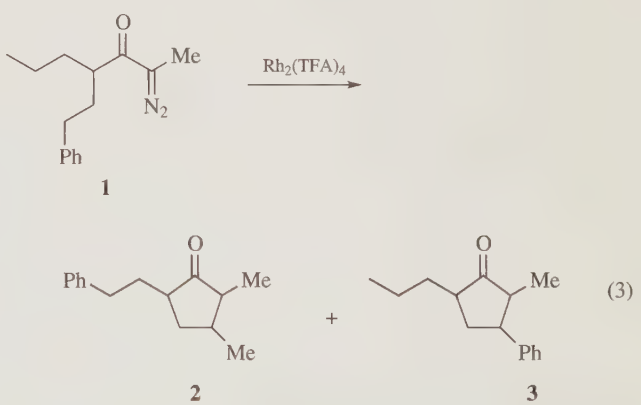
Introduction. Dirhodium tetrakis(trifluoroacetate) [$Rh_2(TFA)_4$] and the related dirhodium tetrakis(perfluorobutyrate) [$Rh_2(pfb)_4$] [*73755-28-9*] are the most electron deficient members of the dirhodium tetracarboxylates. These reagents are very effective at catalyzing carbenoid reactions of diazo compounds. Due to its highly electron deficient character, $Rh_2(TFA)_4$ readily coordinates ligands at the axial position. Although $Rh_2(TFA)_4$ is typically drawn lacking axial ligands, this is most likely not the case because the axially free complex requires isolation by sublimation and is highly hygroscopic.[15] It behaves as a highly Lewis acidic species capable of unusual coordination to a range of substrates including aromatic systems.[16–19] The carbenoid chemistry is probably conducted with hydrated or other axially coordinated complexes of $Rh_2(TFA)_4$ that readily undergo axial ligand exchange to allow formation of rhodium carbenoid intermediates.

Metal Carbene Transformations. $Rh_2(TFA)_4$ is highly electron deficient and this greatly influences its reactivity. The resulting rhodium carbenoid is highly electrophilic and tends to react through an earlier transition state than the conventional rhodium carbenoids,[20] which impacts the type of products that are formed. A few examples of this modified reactivity profile were described in the original e-EROS report, but more recently a number of interesting new applications have been published.

One of the most impressive reactions of rhodium carbenoids is the C–H activation chemistry by means of carbenoid induced C–H insertions. Highly electrophilic carbenoids facilitate C–H insertions, making $Rh_2(TFA)_4$ a very effective catalyst. In the early studies by Teyssié, the highest yields of intermolecular C–H insertion of ethyl diazoacetate into alkanes were obtained using $Rh_2(TFA)_4$ as catalyst, but the high reactivity was accompanied by low selectivity.[21] A recent intramolecular example is the $Rh_2(TFA)_4$-catalyzed reaction of **1** to form **2** and **3** (eq 3).[22] The same reaction catalyzed by dirhodium tetraacetate [$Rh_2(OAc)_4$] or dirhodium tetraacetamide failed to give any product.

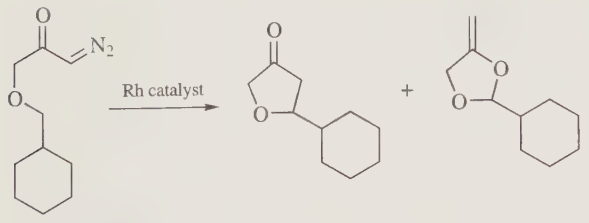


(84% yield, 2:1 ratio)

(3)

Pathways proceeding through zwitterionic intermediates are prevalent in $Rh_2(TFA)_4$-catalyzed reactions and these can compete with the more common concerted reactions.[23–26] This is because the trifluoroacetate ligands can more effectively stabilize increased negative charge on rhodium compared to the standard catalysts such as $Rh_2(OAc)_4$. An example is the reaction of diazoketone (**4**).[23] The $Rh_2(OAc)_4$-catalyzed reaction preferentially forms the C–H insertion product **5**, whereas the $Rh_2(TFA)_4$-catalyzed reaction gives a 1:1 mixture of **5** and the ketal **6**, the

latter being formed by a stepwise mechanism initiated by a hydride shift (eq 4).

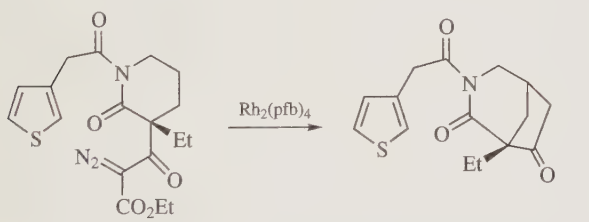


4 5 6

$Rh_2(OAc)_4$ (**5**: 55% yield, **6**: 8% yield)

$Rh_2(TFA)_4$ (**5**: 35% yield, **6**: 40% yield)

In competition reactions, the perfluorinated catalysts tend to enhance the formation of C–H insertion products compared to the less electron deficient catalysts. An impressive example of this effect is the rhodium-catalyzed decomposition of **7**.[27] Under the $Rh_2(pfb)_4$-catalyzed conditions, C–H insertion occurs followed by decarboxylation to form **8** (eq 5). In contrast, dirhodium tetrapivalate [$Rh_2(piv)_4$] catalysis affords pentacycle (**9**) derived from carbonyl ylide formation followed by an intramolecular 1,3-dipolar cycloaddition (eq 6).



7 8

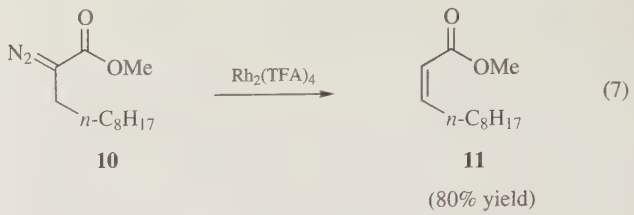
(51% yield)

7 9

(35% yield)

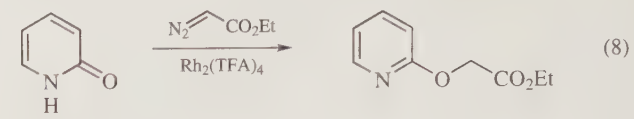
1,2-Hydride shifts are common reactions for alkyl-substituted rhodium carbenoids and this is further enhanced by electron deficient catalysts.[28] The carbenoid formed in the $Rh_2(TFA)_4$-catalyzed reaction of alkyl-substituted diazoacetate (**10**) readily undergoes a 1,2-hydride shift to form the *cis*-α,β-unsaturated ester (**11**) (eq 7). Similar reactions catalyzed by $Rh_2(OAc)_4$ give considerable amounts of intramolecular C–H insertion products.

The highly electrophilic character of the $Rh_2(TFA)_4$-derived carbenoids has been exploited for the *O*-alkylation of pyridones.[29] The reaction of 2-pyridione (**12**) with ethyl diazoacetate generated *O*-alkylated product (**13**) in 87% yield (eq 8). This strategy was used for the selective formation of enol ethers in a variety of substrates where the enol form is the minor tautomer.



10 11

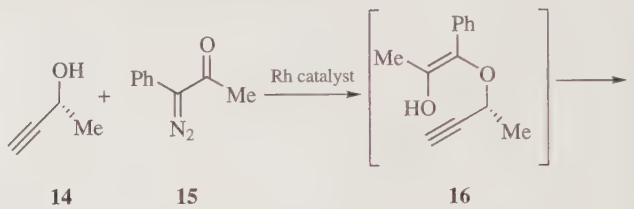
(80% yield)



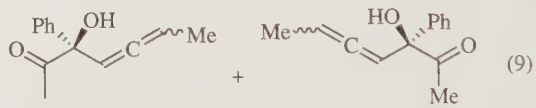
12 13

(87% yield)

Due to the highly Lewis acidic character of $Rh_2(TFA)_4$, Lewis acid-catalyzed transformations can compete with carbenoid chemistry. This type of behavior is seen in the reaction of propargylic alcohol (**14**) with phenyldiazoketone (**15**) (eq 9).[30,31] The initial product is enol (**16**), which undergoes an uncatalyzed [3,3] sigmatropic rearrangement to form **17** as the dominant product when $Rh_2(OAc)_4$ is used in the carbenoid reaction. In contrast, $Rh_2(TFA)_4$ catalyzes a [2,3] sigmatropic rearrangement of **15** to form **18** as the major product.



14 15 16



17 18

$Rh_2(OAc)_4$ (10.5:1)

$Rh_2(TFA)_4$ (1:57)

In summary, $Rh_2(TFA)_4$ and $Rh_2(pfb)_4$ are currently the most electron deficient dirhodium tetracarboxylate catalysts known. On occasion, they lead to different products compared to those obtained with the more standard catalyst, $Rh_2(OAc)_4$.

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Dirhodium(II) Tetrakis(triphenylacetate)

$Rh_2(O_2CCPh_3)_4$

[142214-04-8] $C_{80}H_{60}O_8Rh_2$ (MW 1355.14)

(catalyst for carbenoid reactions of diazo compounds)

Physical Data: mp >300 °C; IR ($CHCl_3$) 1590, 1365 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.5–7.2 (m, 60H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.14, 126.66, 127.30, 127.60, 130.41, 130.51, 142.99, 193.29.

Solubility: soluble in CH_2Cl_2.

Form Supplied in: not commercially available.

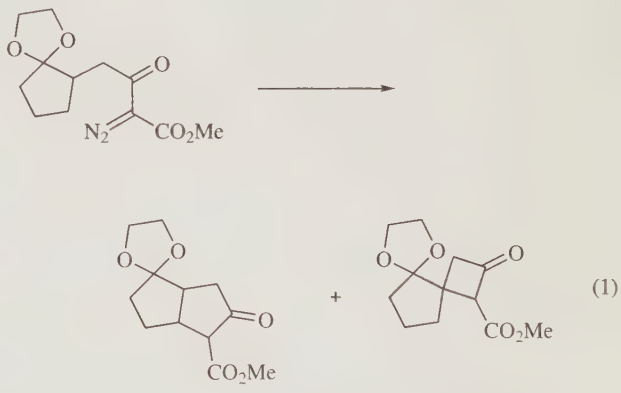
Preparative Methods[1]: a mixture of dirhodium(II) tetraacetate $Rh_2(OAc)_4$ (700 mg, 1.58 mmol), triphenylacetic acid (3.61 g, 12.5 mmol), and chlorobenzene (200 mL) was heated at reflux with vigorous stirring, while the solvent was distilled off at a rate such that 30 mL of the solvent was removed per hour. After completion of the reaction (3 h), which could be confirmed by TLC analysis, the mixture was concentrated to ca. 30 mL followed by diluting with CH_2Cl_2 (100 mL). The resulting dark green solution was washed with saturated aq $NaHCO_3$, water, and brine, and then dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crystalline residue, which was recrystallized from CH_2Cl_2 followed by drying in vacuo at 80 °C for 10 h to give $Rh_2(TPA)_4 \cdot 2H_2O$ (1.86 g, 85%) as dark green prisms. Further drying of the dihydrate complex in vacuo (150 °C, 20 h) gave the anhydrous $Rh_2(TPA)_4$ as yellow-green powder, which readily absorbs water from the atmosphere.

Purification: recrystallization from CH_2Cl_2 gives the title compound as dark green prisms in the dihydrate form.

Handling, Storage, and Precautions: air stable, very hygroscopic; stored in dessicator.

Metal Carbene Transformations.

Regioselectivity in Intramolecular Reactions. Dirhodium(II) tetra(triphenylacetate) $Rh_2(TPA)_4$ has been used for the decomposition of various diazo compounds to form a highly reactive rhodium carbenoid species that can undergo C–H insertion and cyclopropanation reactions. This readily prepared catalyst is one of the most sterically demanding dirhodium tetracarboxylates. Its primary usage has been to provide regioselectivity in intramolecular C–H insertion reactions where one C–H bond is more sterically hindered than another. A notable example of the regioselectivity obtainable with this catalyst is from the seminal studies by Ikegami and co-workers.[1] In their attempts to synthesize a bicyclic β-keto ester as an intermediate for the synthesis of (+)-isocarbacyclin, $Rh_2(OAc)_4$ yielded predominantly the spirocyclic compound. $Rh_2(TPA)_4$ reversed this selectivity to yield the desired bicyclic compound in a 96:4 ratio over the spirocycle (eq 1).

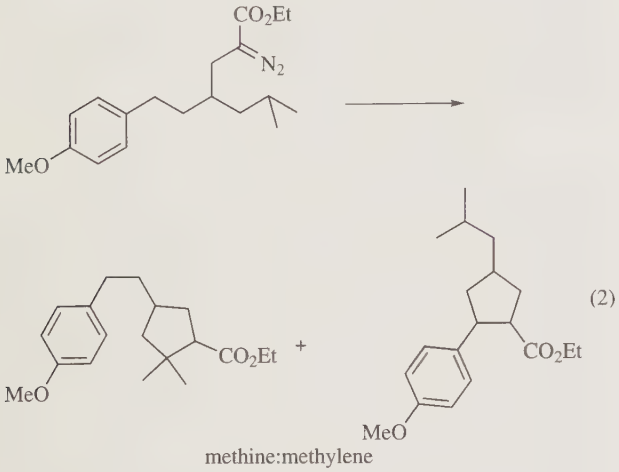


(1)

	cyclopentanone:cyclobutanone
$Rh_2(OAc)_4$	37:63
$Rh_2(O_2CPh)_4$	54:46
$Rh_2(O_2CCHPh_2)_4$	64:36
$Rh_2(O_2CCMePh_2)_4$	82:18
$Rh_2(TPA)_4$	96:4

As methine C–H insertion is favored electronically over methylene C–H insertion,[2] the selectivity can be attributed to the bulky bridging ligand of $Rh_2(TPA)_4$. This is supported by the degradation in selectivity as electronically similar but sterically less demanding catalysts are used. It should be noted, however, that the

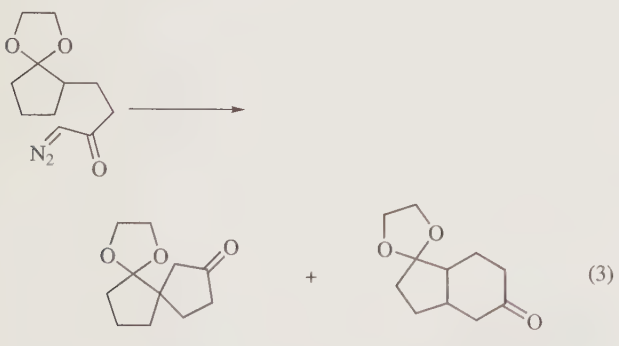
comparison was between forming a strained spirocyclobutanone via methine C–H insertion versus forming a cyclopentanone via methylene C–H insertion. Indeed, later work by Taber studied the direct intramolecular competition between an activated methylene site and a methine site for C–H insertion where a cyclopentane would be the product in either case.[3] A variety of rhodium(II) catalysts were studied and $Rh_2(TPA)_4$ was found to exclusively produce insertion into the methine site over the methylene site while $Rh_2(OAc)_4$ gave approximately equal amounts of both products (eq 2).



(2)

	methine:methylene
$Rh_2(OAc)_4$	1.03:1
$Rh_2(TPA)_4$	100:0

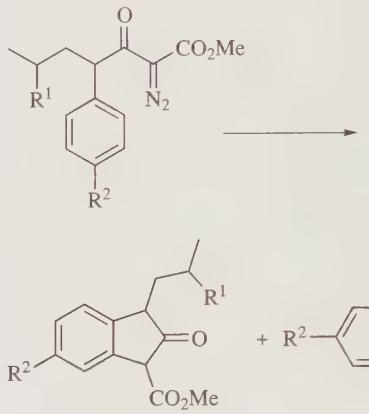
A striking example of the ability of $Rh_2(TPA)_4$ to catalyze formation of the sterically favored product is seen in the synthesis of α,β′-dioxospiranes by Undheim and co-workers.[4] $Rh_2(OAc)_4$ produced the spirane exclusively by C–H insertion into the electronically favored methine C–H bond, while $Rh_2(TPA)_4$ favored insertion into the less sterically congested methylene C–H bond to give the ring annulated cyclohexanone in an 86:14 ratio. $Rh_2(TPA)_4$ also catalyzed the reaction more quickly, requiring only 1.5 h at 0 °C for complete consumption of the starting material as compared to 12 h at room temperature for $Rh_2(OAc)_4$ (eq 3).



(3)

	spirocycle:cyclohexanone
$Rh_2(OAc)_4$	100:0
$Rh_2(TPA)_4$	14:86

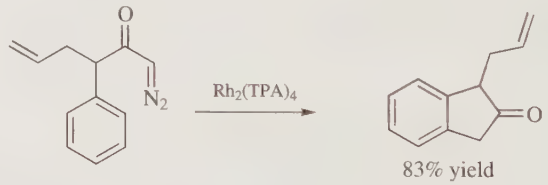
$Rh_2(TPA)_4$ has also been used to promote selective intramolecular insertion into an aryl C–H bond over a comparable methylene C–H bond.[5] Competitive studies have shown that insertion into either of these types of bonds is similar in energy.[2] $Rh_2(OAc)_4$ displayed a slight preference for aryl C–H insertion while $Rh_2(TPA)_4$ favored aryl C–H insertion by a ratio of 96:4. An even greater preference for aryl C–H insertion was displayed when the competition was with an electronically favored but sterically disfavored methine C–H bond. $Rh_2(OAc)_4$ favored methine insertion while $Rh_2(TPA)_4$ exclusively gave aryl C–H insertion. Remarkably, in a substrate with an electronically deactivating *para*-fluoro substituent on the aromatic ring the reactions catalyzed by either $Rh_2(OAc)_4$ or $Rh_2(TPA)_4$ resulted in complete reversal of selectivity (eq 4).



(4)

Catalyst	R^1	R^2	aryl:alkyl
$Rh_2(OAc)_4$	H	H	54:46
$Rh_2(TPA)_4$	H	H	96:4
$Rh_2(OAc)_4$	Me	H	38:62
$Rh_2(TPA)_4$	Me	H	>99:<1
$Rh_2(OAc)_4$	Me	F	<1:>99
$Rh_2(TPA)_4$	Me	F	>99:<1

Aryl C–H insertion was also favored over cyclopropanation of the terminal olefin when $Rh_2(TPA)_4$ was used as catalyst (eq 5).[5] In contrast, $Rh_2(OAc)_4$ gave a 26% yield of C–H insertion product and a 63% yield of cyclopropanation product.

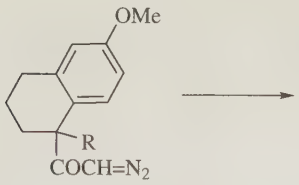


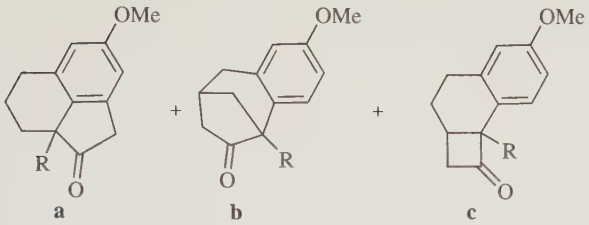
(5)

83% yield

Although $Rh_2(TPA)_4$ was shown in the above cases to prefer aryl over alkyl C–H insertion over cyclopropanation, the steric environment of the substrate can override this preference. Mander desired production of the aromatic C–H insertion product in preference to the aliphatic C–H insertion product.[6] Surprisingly, $Rh_2(TPA)_4$ favored methylene insertion instead of aryl insertion except in the case where R was hydrogen. This reversal in selectivity was attributed to the steric crowding of the aryl C–H bond by the quaternary center and became increasingly pronounced with increasing bulk of the R group (eq 6).

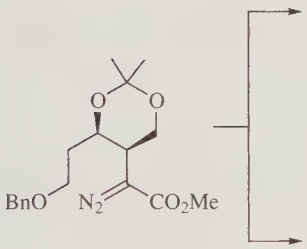
Taber and co-workers illustrated an interesting example of the subtle balance between sterics and electronics in the synthesis of a *cis*-isoprostane synthon.[7] Formation of the *cis*-product was expected to be favored on the basis of sterics while formation of the *trans*-product was expected to be favored electronically (eq 7).

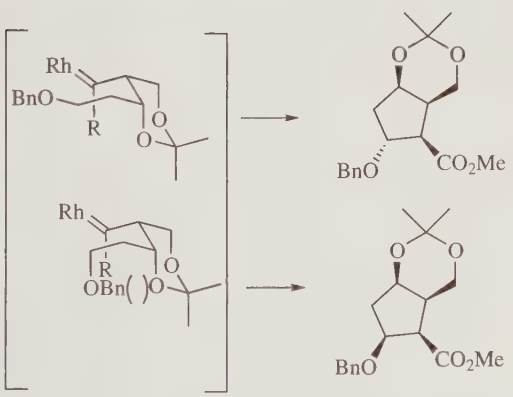




(6)

R	$Rh_2(OAc)_4$ a:b:c	$Rh_2(TPA)_4$ a:b:c
H	>10:1:0	2:1:0
Me	1:1.5:0	1:3:0
Et	1:1.5:0	1:8:0
$CH_2CH(=CH_2)Me$	1:1.5:0	0:3:1
CH_2CHMe_2	1:1.5:0	0:2:1

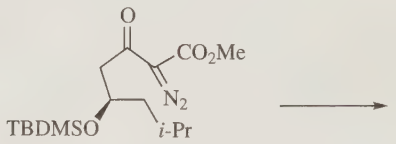


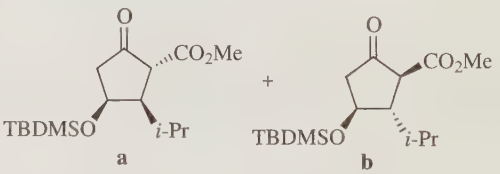


(7)

	cis:trans
$Rh_2(piv)_4$	1.2:1
$Rh_2(TFA)_4$	1:6.4
$Rh_2(TPA)_4$	6.5:1

Use of dirhodium(II) tetrapivalate $Rh_2(piv)_4$ resulted in approximately equal amounts of the *cis*- and *trans*-products while use of the less sterically demanding but more reactive dirhodium(II) tetra(trifluoroacetate) $Rh_2(TFA)_4$ catalyst resulted in a decreased ratio of *cis:trans*-product (1:6.4). $Rh_2(TPA)_4$, the most sterically demanding and least reactive catalyst completely reversed the selectivity, resulting in a 6.5:1 ratio of *cis:trans*-product. In cases where intramolecular C–H insertion results in new stereocenters, stereocontrol can be achieved via the interaction between the bulky $Rh_2(TPA)_4$ catalyst and an adjacent stereocenter. Ikeda and co-workers demonstrated that the yield can be improved in the synthesis 2,3-*cis*-2-alkyl-3-(*tert*-butyldimethylsilyloxy)-5-oxocyclopentanecarboxylates when $Rh_2(TPA)_4$ is used as the catalyst for diazo decomposition instead of $Rh_2(OAc)_4$ (eq 8).[8]

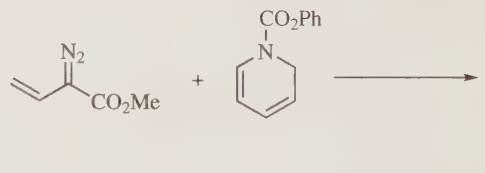


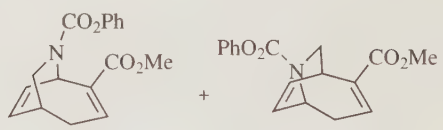


(8)

	Combined Yield	a:b
$Rh_2(OAc)_4$	30	>95:5
$Rh_2(TPA)_4$	52	97:3

Intermolecular Reactions. The use of $Rh_2(TPA)_4$ as a catalyst for intermolecular carbenoid reactions has thus far been very limited. A practical example of its application was in the synthesis of the 6-azabicyclo[3.2.2]nonane nucleus by Davies and co-workers (eq 9).[9] Use of dirhodium(II) tetraoctanoate $Rh_2(OOct)_4$ produced equal amounts of the regioisomers, while $Rh_2(TPA)_4$ resulted in a >15:1 selectivity for one regioisomer over the other.





(9)

	Yield (%)	Yield (%)
$Rh_2(OOct)_4$	30	29
$Rh_2(OPiv)_4$	56	12
$Rh_2(TPA)_4$	50	3

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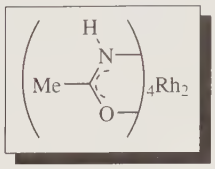
Dirhodium(II) Tetraacetamide



[87985-40-8] $C_8H_{16}N_4O_4Rh_2$ (MW 438.10)

(catalyst for selective carbenoid reactions of diazo compounds[1])

Alternate Name: dirhodium(II) tetraacetamidate.

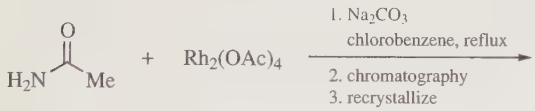
Physical Data: UV/vis (MeCN) 500 (2.2), 345 (shoulder) nm.[2] NMR (CD_3CN): δ 2.20 (s).[3]

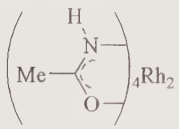
Spectral Data: λ 500, 345 (shoulder) nm (CH_3CN).[2] ^1H NMR (CD_3CN) of $Rh_2(acam)_4$-$(CH_3CN)_2$: δ 2.20 (s, 12 H).

Solubility: sol MeOH, MeCN, pyridine, DMSO; insol CH_2Cl_2, $ClCH_2CH_2Cl$, toluene.

Form Supplied in: blue solid for anhydrous form and after removal of axial nitrile ligands; purple solid as hydrate and as the bisacetonitrile complex.

Preparative Method: from dirhodium tetraacetate by ligand substitution with acetamide (eq 1).[3]





(1)

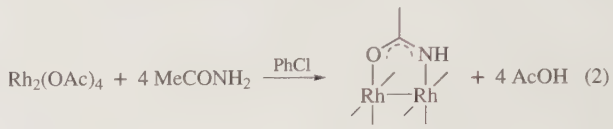
$Rh_2(acam)_4$

Handling, Storage, and Precautions: air stable, weakly hygroscopic; stored in desiccator.

Original Commentary

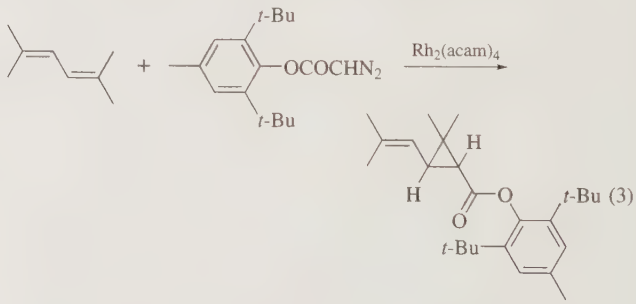
Michael P. Doyle
University of Maryland, College Park, MD, USA

Introduction. Dirhodium(II) tetraacetamide, $Rh_2(acam)_4$, was first prepared from ***Dirhodium(II) Tetraacetate*** in a melt of acetamide.[4] However, this method gave a mixture of $Rh_2(OAc)_{4-n}(acam)_n$, of which $Rh_2(acam)_4$ was the dominant product but could not be conveniently separated. The preferred procedure is to treat $Rh_2(OAc)_4$ with acetamide in refluxing chlorobenzene under conditions where acetic acid is trapped by sodium carbonate in a Soxhlet extraction apparatus (eq 2).[3] Four acetamidates are ligated to one dirhodium(II) nucleus, and each rhodium is bound to two nitrogen and two oxygen donor atoms arranged in a *cis* geometry.[5] Incomplete substitution, when only three acetamides have replaced acetate, yielding $Rh_2(acam)_3(OAc)$, produced a catalyst whose selectivity is not optimum.

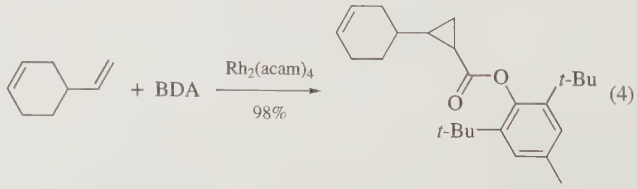


Metal Carbene Transformations. Although insoluble in the solvents in which catalytic metal carbene transformations are performed, $Rh_2(acam)_4$ enters solution after addition of the diazo compound. The principal advantage of this catalyst is its selectivity for product formation from reactions with diazocarbonyl compounds, but its reactivity towards dinitrogen extrusion is less than that of dirhodium(II) tetra(carboxylates).

Stereoselectivity in Cyclopropanation Reactions. Use of $Rh_2(acam)_4$ for intermolecular cyclopropanation of alkenes results in higher *trans* (*anti*) selectivity which, when the diazo compound is 2,6-di-*t*-butyl-4-methylphenyl diazoacetate (BDA), is exceptional (e.g. eq 3: 98% *trans*).[3] Product yields are high (75–96%), and byproducts are often minimal. Relative reactivities are also enhanced by $Rh_2(acam)_4$, which has made possible highly regioselective cyclopropanation of selected dienes (e.g. eq 4).[3] However, $Rh_2(acam)_4$ is unsuitable, relative to ***Dirhodium(II) Tetraacetate***, for intermolecular cyclopropanation of styrene by the pantolactone ester of *trans*-2-diazo-4-phenyl-3-butenoate.[6] Substitution of $Rh_2(acam)_4$ by the more soluble ***Dirhodium(II) Tetra(caprolactam)***, $Rh_2(cap)_4$, does not provide any obvious advantage in reactivity or selectivity for cyclopropanation.



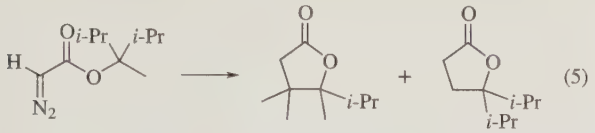
98% *trans*



trans:*cis* = 67:1

Carbon–Hydrogen Insertion Reactions. Use of $Rh_2(acam)_4$ provides an increase in regioselectivity for competitive insertion

into carbon–hydrogen bonds (tertiary > secondary > primary) that result in the formation of five-membered ring carbonyl compounds (e.g. eq 5; pfb = perfluorobutyrate).[7,8]

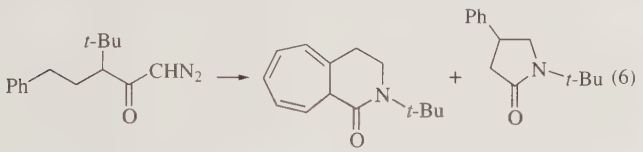


(5)

$Rh_2(pfb)_4$	32%	68%
$Rh_2(OAc)_4$	53%	47%
$Rh_2(acam)_4$	>99%	<1%

Both diazoacetoacetates and diazoacetates show exceptional selectivity enhancement with $Rh_2(acam)_4$. However, the same degree of control is not evident in the competition from diazoacetoacetamides for β-lactam versus γ-lactam formation.[9–11] The use of $Rh_2(cap)_4$ in place of $Rh_2(acam)_4$ does not provide any obvious advantage in regioselectivity for carbon–hydrogen insertion.

Chemoselectivity. Few comparisons have been made with $Rh_2(acam)_4$ and $Rh_2(cap)_4$, but those that have suggest that $Rh_2(cap)_4$ holds an advantage.[11] *N*-(2-Arylethyl)-*N*-*t*-butyldiazoacetamides, for example, exhibit competition between aromatic cycloaddition and carbon–hydrogen insertion (e.g. eq 6), and chemoselectivity for C–H insertion with $Rh_2(cap)_4$ is greater than with $Rh_2(acam)_4$, but both are more selective than is $Rh_2(OAc)_4$.



(6)

$Rh_2(acam)_4$	23%	77%
$Rh_2(cap)_4$	3%	97%

First Update

Michael P. Doyle & Raymond E. Forslund
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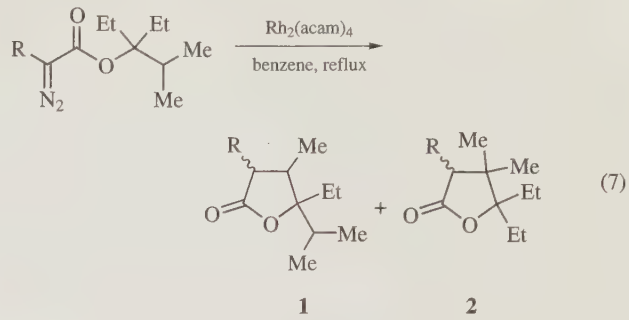
Preparation. Dirhodium(II) tetraacetamidate, $Rh_2(acam)_4$, was first prepared from dirhodium(II) tetraacetate in a melt of acetamide.[4] However, this method gave a mixture of $Rh_2(OAc)_{4-n}(acam)_n$. The preferred procedure is ligand substitution on $Rh_2(OAc)_4$ with acetamide in refluxing chlorobenzene; liberated acetic acid is trapped by sodium carbonate in a Soxhlet extraction apparatus.[3] Four acetamide molecules ligate one dirhodium(II) nucleus; each rhodium is bound to two nitrogen and two oxygen donor atoms arranged in a *cis*-geometry.[5]

Carbon-Hydrogen Insertion Reactions. Rhodium(II)-catalyzed reaction of α,α′-*O*-alkyl-α-(alkoxycarbonyl)-α-diazoacetates (eq 7, Table 1) showed that insertion into the tertiary C–H bond was the preferred pathway, however, when R = acetyl, a modest preference was observed for **1**.[12]

When $Rh_2(acam)_4$ was used in competition reactions between cyclopropanation and C–H insertion reactions (eq 8, Table 2); cyclopropanation of the double bond was the major pathway when $n = 1$ and also accounted for a significant amount of product when $n = 2$. This observation is in agreement with previous findings that have shown that amide-based catalysts favor cyclopropanation over tertiary C–H insertion.[13]

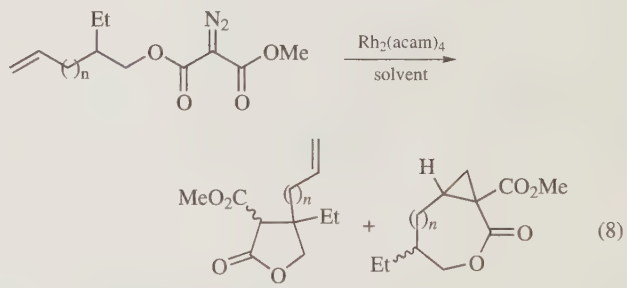


(7)

1 **2**

Table 1 Dirhodium(II) tetraacetamidate-catalyzed C–H insertion of α,α′-*O*-alkyl-α-(alkoxycarbonyl)-α-diazoacetates

R	Isolated Yield	Relative Yield (**1**:**2**)
CO_2Me	90	42:58
$CO_2CH_2CF_3$	87	41:59
$C(O)CH_3$	83	77:23



(8)

3 **4**

Table 2 C–H Insertion versus cyclopropanation with dirhodium(II) tetraacetamidate

n	Solvent	Temp (°C)	Yield (%)	Relative Yield (**3**:**4**)
1	CH_2Cl_2	25	80	29:60
1	benzene	25	62	34:66
2	CH_2Cl_2	40	87	73:26

Other. Wang and co-workers have used $Rh_2(acam)_4$ and other dirhodium catalysts to probe for mechanistic details concerning the metal-mediated intramolecular metal carbene C–H insertion reaction[14] as well as reactivities of α-diazo esters towards these catalysts.[15]

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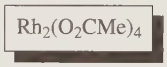
Dirhodium(II) Tetraacetate



[15956-28-2] $C_8H_{12}O_8Rh_2$ (MW 442.02)

(catalyst for carbenoid reactions of diazo compounds,[1] hydroboration of alkenes and alkynes,[2] hydrocarbon oxidation;[3] nitrene reactions, and miscellaneous reactions)

Physical Data: λ 590 nm, ε 210 (EtOH); λ 552 nm, ε 235 (MeCN).[4] IR ν^- (CO_2) 1585 cm^{-1}.[5]

Solubility: sol MeOH, acetic acid, MeCN, acetone; slightly sol toluene; insol Et_2O, 1,2-dichloroethane, CH_2Cl_2.

Form Supplied in: emerald-green solid for anhydrous form.

Preparative Method: prepared from $RhCl_3 \cdot xH_2O$.[6]

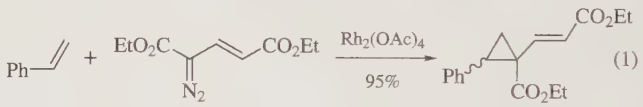
Handling, Storage, and Precautions: air stable, moderately hygroscopic; stored in desiccator. Removal of axially coordinated solvent can be achieved in vacuum oven at 60–80 °C.

Original Commentary

Michael P. Doyle
University of Maryland, College Park, MD, USA

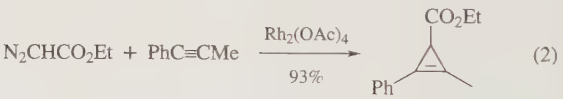
Metal Carbene Transformations. When used in amounts as low as 0.05 mol %,[7] $Rh_2(OAc)_4$ serves as a highly effective and efficient catalyst for dinitrogen extrusion from diazo carbonyl compounds and subsequent metal carbene directed alkene[1,8] and alkyne[9] addition reactions, σ-bond insertion reactions,[1,10] ylide generation,[1,11] and carbene coupling processes,[12] among others. With diazoacetates and diazo ketones, catalytic reactions are generally performed in dichloromethane at rt. The diazo compound is added at such a rate so as to minimize its concentration in the reaction solution.[6] The less reactive α-diazo-β-carbonyl alkanoates, including diazomalonates and diazoacetoacetates, and related diazo dicarbonyl compounds require refluxing 1,2-dichloroethane or refluxing benzene for efficient catalyst turnovers. In laboratory scale reactions, $Rh_2(OAc)_4$ is removed from the reaction solution by filtering through a short column of silica or alumina, or the product(s) are distilled directly from the catalyst-containing mixture. (Rhodium acetate undergoes thermal decomposition at temperatures near 250 °C).

Cyclopropanation/Cyclopropenation. Its catalytic uses for intermolecular cyclopropanation and cyclopropenation reactions, discovered only recently by Teyssié and co-workers,[9,13] have been the standard through which mechanistic[14] and synthetic (selectivity)[8,15] understanding of metal carbene addition reactions have been derived.[1] Intermolecular addition reactions of diazoacetates with alkenes occur at 25 °C in high yield. Their stereoselectivities and regioselectivities[16] are lower than those achieved with the use of ***Dirhodium(II) Tetraacetamide***,[8] but high selectivities are observed with vinylcarbenoid addition (eq 1)[17] and nitrocarbenoid addition[18] to alkenes. Cyclopropene formation occurs with a broad selection of alkynes (eq 2),[19a] but not phenylacetylene.[9,19] Neither cyclopropanation nor cyclopropenation occurs readily with α,β-unsaturated carbonyl compounds or nitriles.[20]



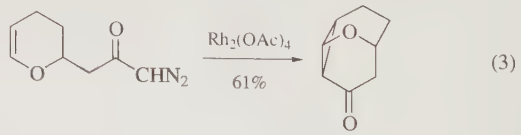
(1)

(E):*(Z)* = 92:8



(2)

Intramolecular analogs of these reactions suggest the overall viability of $Rh_2(OAc)_4$ catalysis (eqs 3 and 4),[21–23] although for alkyne addition the presumed cyclopropene intermediate is unstable and undergoes reactions characteristic of vinylcarbenoid species,[22,23] of which the most frequently encountered involve rearrangement to furans. The intramolecular Büchner reaction of aryl diazoketones (eq 5)[24] is, formally, cyclopropanation of an aromatic ring, for which $Rh_2(OAc)_4$ is especially suitable;[24] the diazoamide analog of this transformation is particularly facile.[25]



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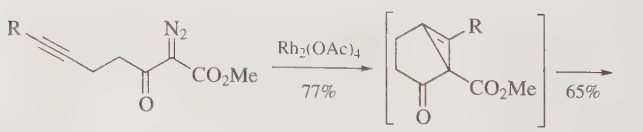

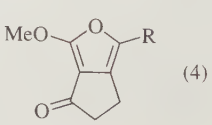

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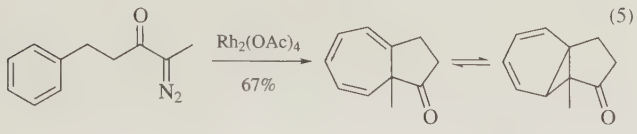
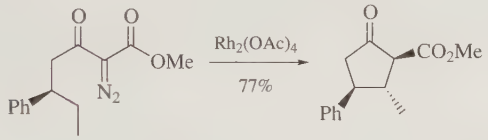


(5)

Carbon–Hydrogen Insertion. The utility of $Rh_2(OAc)_4$ as a catalyst for metal carbene transformations is most evident in its ability to effect insertion into unactivated carbon–hydrogen bonds.[1,10] Preference for the formation of five-membered rings is pronounced (eq 6),[26] and selectivity for insertion into tertiary C–H bonds is usually greater than for insertion into secondary C–H bonds, and primary C–H bonds are the least reactive.[27] Although these controlling influences are pervasive, an increasing number of examples suggest that the factors which control regioselectivity in these reactions are complex (e.g. eq 7).[28]



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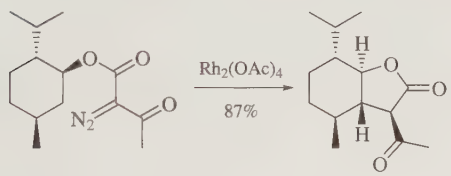
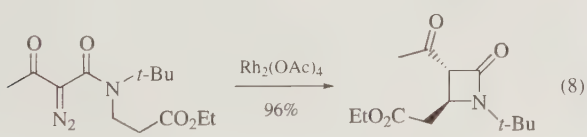


(7)

Heteroatom activation of adjacent C–H bonds[29] has made possible the construction of β-lactam derivatives from diazoacetoacetamides (eq 8)[30] and of β-lactones from selected diazomalonates.[31] With *N*-benzyl derivatives, the presence or absence of an acyl group uniquely defines the course of the catalytic reaction (eq 9; R = *t*-Bu; S = H, Me, OMe, Br).[32] Both electronic and conformational (steric) effects are responsible for the selectivity in these reactions.



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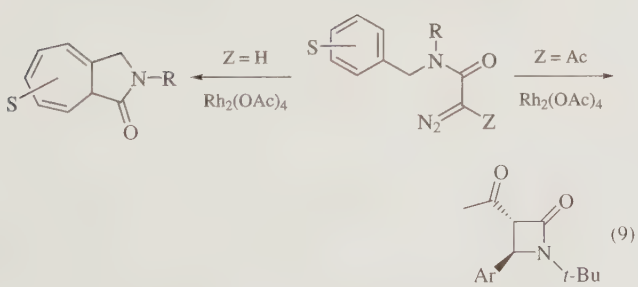
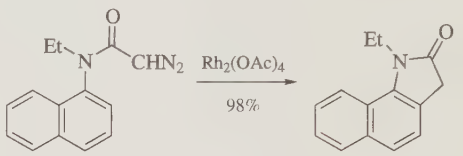


(9)

Intermolecular variants of carbon–hydrogen insertion reactions are generally of limited value because of lower reactivity and selectivity.[1] Insertion into vinylic or alkynic C–H bonds is not competitive with cyclopropanation or cyclopropenation under ordinary circumstances. The so-called 'allylic C–H insertion reaction', commonly observed in copper-catalyzed reactions of diazomalonates or β-diazo-α-keto esters,[33] is not common with $Rh_2(OAc)_4$ catalysis.[14b]

In contrast to the paucity of examples for C–H insertion into vinylic or alkynic C–H bonds, intramolecular 'insertion' into aromatic C–H bonds is well documented.[1] These reactions are most pronounced when the aromatic ring is activated for substitution by oxygen[34] or nitrogen[35] (e.g. eqs 10 and 11),[34,35a] and they are more suitably described as aromatic substitution reactions than as C–H insertion reactions. Aryl-substituted diazo ketones,[36] diazoacetates,[34] diazoacetoacetates,[34] and their corresponding amide derivatives[35] are all effective. The formation of a five-membered ring is preferred, but, with suitable structural demands in the diazo carbonyl reactant, six-membered ring formation occurs.[37]



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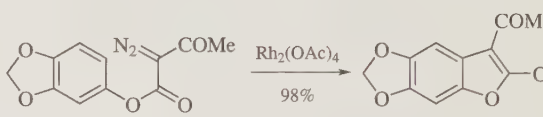
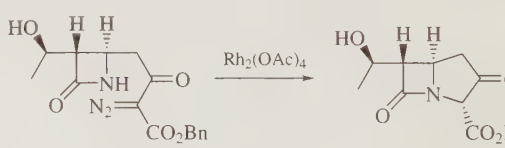


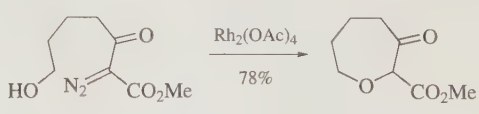
(11)

Heteroatom–Hydrogen Insertion. One of the most important applications of metal carbene chemistry has been in the syntheses of penems, exemplified in eq 12, which is key step in the total synthesis of the carbapenem thienamycin.[38] This reaction has become the method of choice for the synthesis of bicyclic β-lactams from 2-azetidinones substituted through the 4-position to a diazocarbonyl group.[39]



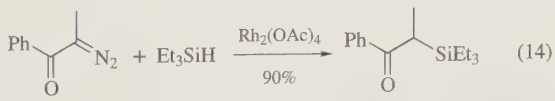
(12)

Oxygen–hydrogen insertion (with water) is a common undesirable side reaction in $Rh_2(OAc)_4$ catalyzed transformations, but its synthetic importance is evident in intramolecular processes. Cyclization via O–H insertion occurs readily and in high yield for five-, six-, and seven-membered ring formation (eq 13),[40] but C–H insertion becomes competitive in attempts to effect eight-membered ring formation. Intermolecular processes have also been examined,[41] but they have more limited usefulness.



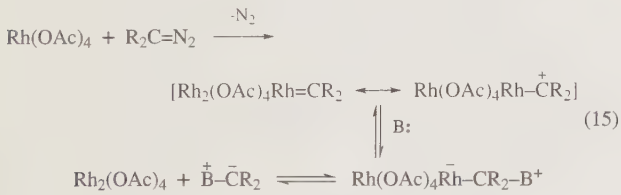
(13)

Thiol insertion also occurs in both intermolecular and intramolecular transformations,[42,43] but these reactions are more difficult to perform because of the facile coordination of thiols and sulfides with $Rh_2(OAc)_4$. Intermolecular silicon–hydrogen insertion provides a convenient methodology for the synthesis of α-silyl esters and ketones (eq 14).[44] Overall, $Rh_2(OAc)_4$ is generally suitable, and often the catalyst of choice, for heteroatom–hydrogen insertion reactions of diazo esters and ketones.[43]



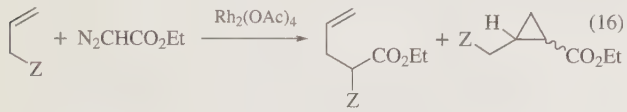
(14)

Ylide Generation. Metal carbenes produced by $Rh_2(OAc)_4$-catalyzed dinitrogen extrusion from diazo compounds are electrophilic.[1] Reactions of these reactive intermediates, which resemble metal-stabilized carbocations, with Lewis bases constitute a generally effective methodology for ylide generation (eq 15).[11] The relative reactivity of Lewis bases towards ylide generation follows the expected order of basicity for carbon–heteroatom compounds. Ylide products are further transformed by insertion, sigmatropic rearrangement, or dipolar addition reactions, dependent on the design of the ylide. Heteroatom–hydrogen insertion is reasonably regarded as an ylide transformation.



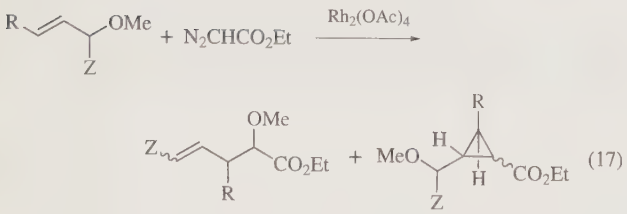
(15)

The relative reactivity for ylide generation, determined from subsequent [2,3]-sigmatropic rearrangement of the initially formed ylide in competition with cyclopropanation (eq 16),[45,46] shows that ylide formation increases in the order RI > RBr > RCl, $R_3N > R_2O$, and $R_2S > R_2O$. Allyl substituents facilitate ylide generation (eq 17),[46,47] and their influences on relative reactivities suggest that the formation of the metal-stabilized ylide and metal dissociation (eq 15) are equilibrium processes.



(16)

Z	Yield (%)	
NMe_2	95	100:0
SMe	96	100:0
I	98	100:0
Br	76	28:72
Cl	95	5:95
OEt	88	10:90

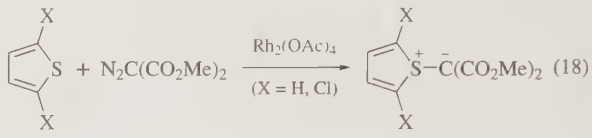


(17)

R	Z		Yield (%)
H	H	10:90	88
Me	H	92:8	86
Ph	H	73:27	95
TMS	H	94:6	68
H	OMe	77:23	75

Rhodium(II) acetate has two axial coordination sites at which reactions with diazo compounds occur. Strongly coordinating compounds, either reactants or solvents, occupy these sites and inhibit electrophilic addition to diazo compounds. Consequently, whereas reactions with diazo compounds that possess chloride, bromide, iodide, or ether functional groups take place at rt, those with sulfide or amine functional groups require higher temperatures for dinitrogen extrusion.

Stable sulfonium ylides have been produced by intermolecular reactions of thiophenes with dimethyl diazomalonate, catalyzed by $Rh_2(OAc)_4$ (eq 18),[48] as well as by intramolecular reactions (eq 19).[49] The formation of four- to seven-membered rings has been possible,[49,50] but C–H insertion is competitive with seven-membered ring ylide generation. The stability of the ylide is dependent on the sulfur substituent (Ph > $PhCH_2$ > allyl) as well as on ring size. Stable sulfoxonium ylides have also been formed in $Rh_2(OAc)_4$-catalyzed reactions.[51]



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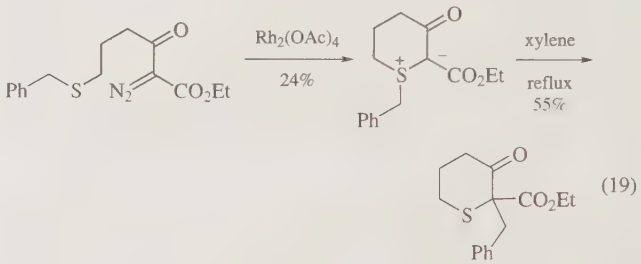
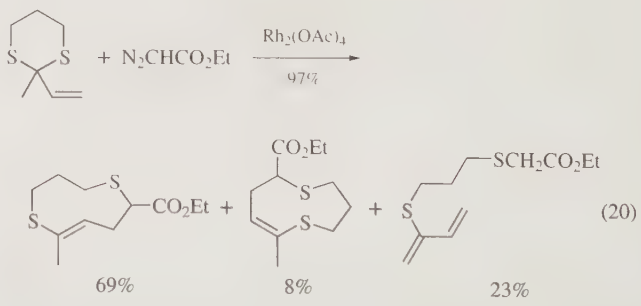


(19)

Use of the [2,3]-sigmatropic rearrangement of sulfonium ylides for ring enlargement has made possible the construction of medium ring compounds (eq 20).[47] β-Elimination is a competing process and becomes the favored transformation with the proper stereoelectronic arrangement in the reactant ylide (e.g. eq 21).[52] An intramolecular ring contraction methodology is also effectively promoted through sulfonium ylide generation with $Rh_2(OAc)_4$ catalysis (e.g. eq 22).[53] Sulfur ylides derived from $Rh_2(OAc)_4$-catalyzed reactions of diazo compounds have played important roles in β-lactam antibiotic syntheses.[54–56]



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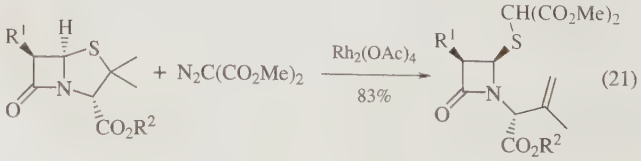

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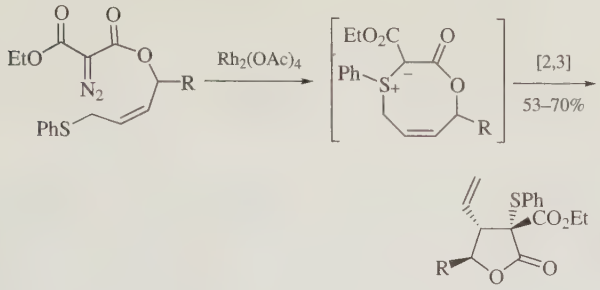
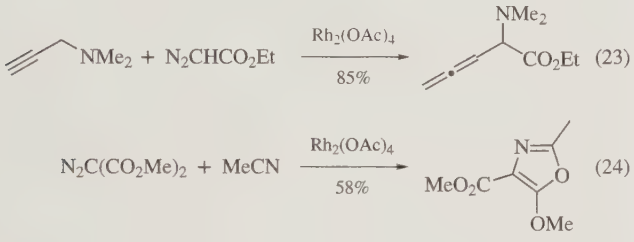
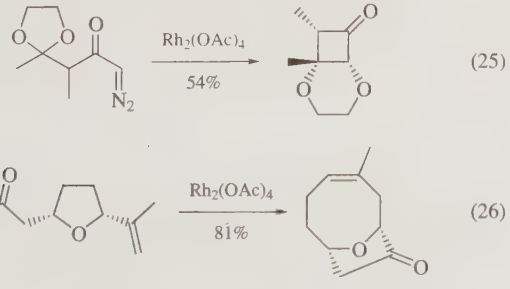


(22)

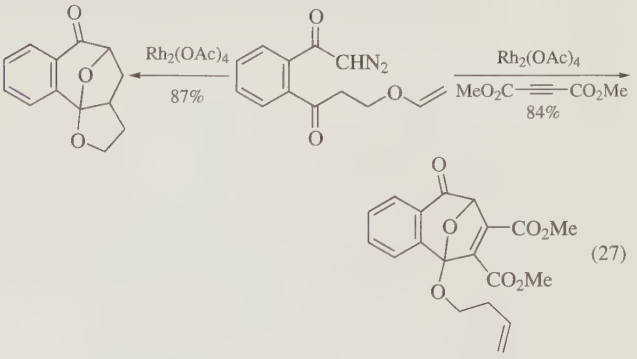
Nitrogen ylide formation is not reported as extensively as is sulfur ylide generation, but sufficient examples exist to suggest its versatility. The synthesis of allenes by [2,3]-sigmatropic rearrangement (eq 23)[57] of prop-2-yn-1-yl-dimethylammonium ylides exemplifies the potential diversity of its applications. A general methodology for oxazole synthesis has been developed through the use of nitrile ylides (eq 24).[58] Additional examples that suggest the advantages of the catalytic route to ylide generation are reported elsewhere.[11]

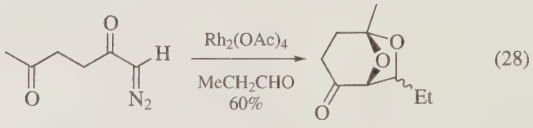


Relative to cyclopropanation (of alkenes) or cyclopropenation (of alkynes), oxonium ylide formation is generally disfavored in $Rh_2(OAc)_4$-catalyzed reactions of diazo compounds. Notable exceptions include those described in eq 17 and in intramolecular transformations. Cyclobutanone formation is the outcome of $Rh_2(OAc)_4$-catalyzed dinitrogen extrusion from 4-alkoxydiazo ketones (eq 25).[59] Allyl ethers offer a pathway to [2,3]-sigmatropic rearrangement products, including those leading to medium ring ethers (eq 26),[60,61] and tetrahydrofuran-3-ones have been prepared by a carbon–oxygen insertion methodology involving ylide intermediates,[62] but few other successful demonstrations of oxonium ylide generation have been reported.



Dirhodium(II) tetraacetate has been shown to have superior capabilities for carbonyl ylide generation with diazo ketones,[11] especially in intramolecular reactions. The carbonyl ylide, when generated in the presence of selected dipolarophiles, readily undergoes 1,3-dipolar addition (e.g. eqs 27 and 28)[63,64] either intermolecularly (***Dimethyl Acetylenedicarboxylate***, ***N-Phenylmaleimide***, diethyl fumarate, aldehydes) or intramolecularly. Regioselectivity is predictable by frontier molecular orbital interactions.[64b] Carbonyl ylide generation with carboxylate esters is rare,[30b] but with amides, carbamates, and imides, carbonyl ylide formation is well documented (e.g. eq 29).[11,65]





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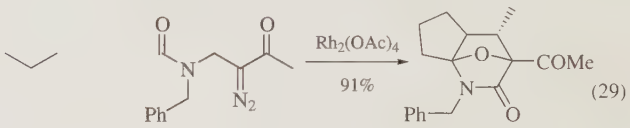
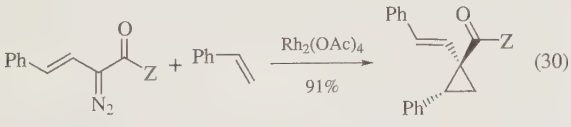


Selectivity in Metal Carbene Transformations. The high reactivity of catalytically generated metal carbenes often limits their selectivity when more than one site for addition and/or insertion exists in a molecule. In this regard, $Rh_2(OAc)_4$ is often less selective for metal carbene transformations than is either ***Dirhodium(II) Tetrakis(perfluorobutyrate)*** or rhodium(II) carboxamides (either ***Dirhodium(II) Tetraacetamide*** or ***Dirhodium(II) Tetra(caprolactam)***).[8,28,66] In addition, use of $Rh_2(OAc)_4$ can lead to lower product yields than does use of alternative dirhodium(II) catalysts. Nevertheless, for most transformations where there is one preferred site for metal carbene reaction, $Rh_2(OAc)_4$ remains the catalyst of choice.

High diastereocontrol complements exceptional stereocontrol for geometrical isomer formation in the cyclopropanation of styrene with vinyldiazocarboxylates that possess the pantolactone chiral auxiliary (eq 30).[67] However, with pantolactone diazoacetate in the cyclopropanation of styrene, a 76:24 *trans:cis* product mixture forms in only 72% yield and 28–30% diastereomeric excess (de).[68] Similarly, in competitive reactions between cyclopropanation and C–H insertion, use of $Rh_2(OAc)_4$ provides very little selectivity (eq 31),[66] but dirhodium(II) tetrakis(perfluorobutyrate) promotes exclusive C–H insertion and use of dirhodium tetra(caprolactam) leads to exclusive cyclopropanation. A variety of examples of high and low selectivities has been reported for $Rh_2(OAc)_4$-catalyzed reactions,[1] and no simple explanation has emerged that will account for all of the results. Predictions are often empirical, but changing the ligands of the catalyst often provides a dirhodium(II) compound with the desired selectivity enhancement.

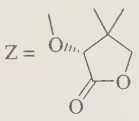
Catalytic Hydroboration of Alkenes and Alkynes. The use of $Rh_2(OAc)_4$ to catalyze the hydroboration of alkenes and alkynes with ***Catecholborane*** represents a novel application

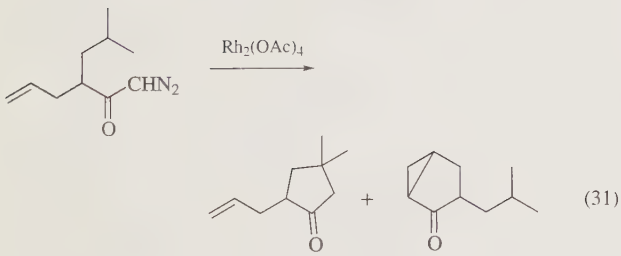
of this transition metal compound.[2] In laboratory scale reactions, 0.5 mol% $Rh_2(OAc)_4$ is effective. Selectivity is dependent on the alkene (eq 32) and often differs from that found with ***Chlorotris(triphenylphosphine)rhodium(I)*** (Wilkinson's catalyst).[69]



(30)

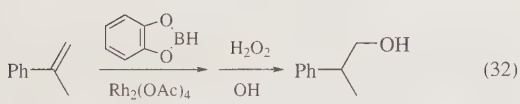
89% de (1*R*,2*R*)





(31)

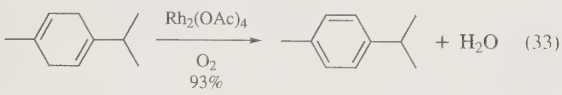
56% 44%



(32)

The hydroboration of alkynes is also promoted by rhodium acetate. However, since $Rh_2(OAc)_4$ is transformed during hydroboration, the nature of the active catalyst is at present unknown. The combination of catecholborane and $Rh_2(OAc)_4$, both in catalytic amounts, catalyzes isomerization of terminal alkenes.[2]

Autooxidation of Alkenes. In the presence of catalytic amounts of $Rh_2(OAc)_4$, cyclohexadienes undergo aromatization (eq 33), and dienes undergo oxidative cleavage (eq 34),[3a] at atmospheric pressure. *p*-Cymene is also reported to be oxidized to the tertiary alcohol. Hydroperoxide decomposition to alcohol and dioxygen, catalyzed by $Rh_2(OAc)_4$, has been demonstrated.



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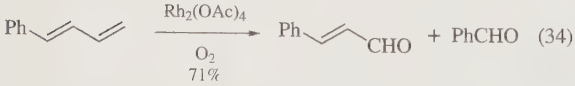

(34)

Other Catalytic Reactions. Hydrogenation activity for $Rh_2(OAc)_4$ has been reported,[70] but these results could not be repeated.[71] Hydrosilylation of alkenes is catalyzed by $Rh_2(OAc)_4$, but reactions are much less efficient than those catalyzed by dirhodium(II) tetrakis(perfluorobutyrate).[71] The same is true of silylcarbonylation reactions with alkynes,[72] and $Rh_2(OAc)_4$ is not a hydroformylation catalyst.

First Update

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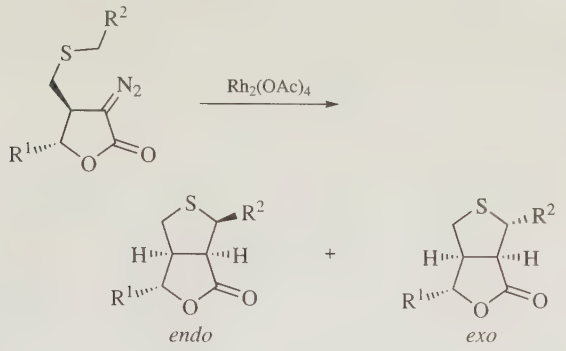
Introduction. Dirhodium tetraacetate [$Rh_2(OAc)_4$] is the prototypical catalyst for the decomposition of diazo compounds, which leads to transient rhodium-carbenoid intermediates capable of undergoing a range of synthetically useful transformations. The previous e-EROS report covered the major classes of rhodium-carbenoid reactions. These are cyclopropanation, C–H activation by C–H insertion, and ylide chemistry. Rhodium-carbenoid chemistry is a very active field and several excellent reviews have appeared in recent years. This report will highlight a few of the most interesting recent examples. The reactivity of the rhodium carbenoid is highly dependent on the catalyst structure, and so several other dirhodium complexes are covered in e-EROS. These include the more hydrocarbon soluble catalyst, dirhodium tetraoctanoate [$Rh_2(oct)_4$]; the more electron deficient catalysts, dirhodium tetrakistrifluoroacetate [$Rh_2(TFA)_4$] and dirhodium tetrakisperfluorobutyrate [$Rh_2(pfb)_4$]; the more bulky catalyst, dirhodium tetrakis(triphenylacetate) [$Rh_2(TPA)_4$]; and the chiral catalysts, tetrakis(1-[4-dodecylphenyl]sulfonyl-(2*S*)-prolinate) dirhodium [Rh_2(*S*-DOSP)$_4$], bis1,3-[*N*,*N*′-di(4-dodecyl-benzenesulfonyl)-(2S,2′S),(5R,5′R)-5,5′-prolinate]benzenedirhodium [Rh_2(*S*-biDOSP)$_2$], and tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate dirhodium [Rh_2(*S*-PTTL)$_4$]. A number of examples have appeared in recent years on the use of [$Rh_2(OAc)_4$] as a catalyst in noncarbenoid reactions and these transformations will also be highlighted.

C–H Insertion Reactions. One of the most spectacular reactions catalyzed by [$Rh_2(OAc)_4$] is intramolecular C–H activation by means of insertion of the carbenoid into a C–H bond.[73–83] C–H insertion to form five-membered rings is generally favored, but four- and six-membered rings can also be selectively formed in certain systems. The C–H bond is activated by the presence of adjacent heteroatoms such as nitrogen or oxygen. A novel recent intramolecular example is a C–H insertion adjacent to sulfur, which has been used in the diastereoselective synthesis of various thienofuranones (eq 35).[84] This is an excellent example showing the regiocontrol that is possible in intramolecular reactions because ylide formation by reaction of the carbene with the sulfide would have been anticipated to be the greatly favored transformation.

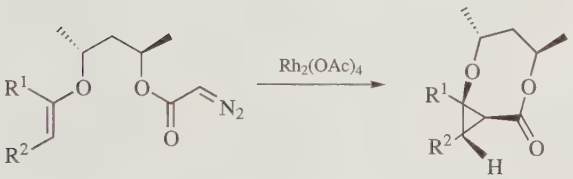
Cyclopropanations. The metal-catalyzed decomposition of diazo compounds in the presence of alkenes is a venerable method for the synthesis of cyclopropanes. The intramolecular version is particularly useful because the reactions tend to be stereospecific and have been extensively used in organic synthesis. A recent example is the highly diastereoselective cyclopropanation of an olefin tethered to the rhodium carbenoid by a 2,4-pentanediol linker (eq 36).[85]

In recent years it has become recognized that a wider array of diazo precursors are compatible with this chemistry. For example, Charette has recently shown that the reactions of nitro-substituted diazo compounds provide a very direct synthesis of cyclopropane amino acid precursors (eq 37).[86]



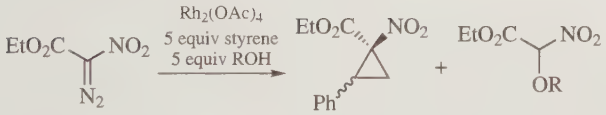
(35)

R^1	R^2	Yield (%) *endo*	Yield (%) *exo*
Ph	Ph	72	0
Ph	Et	84	0
i-Pr	Ph	27	11



(36)

R^1	R^2	Yield (%)	de (%)
Me	H	22	>98
Ph	H	39	>98
$-CH_2CH_2CH_2-$		22	>98
$-CH_2(CH_2)_3CH_2-$		64	>98
$-CH_2(CH_2)_4CH_2-$		55	>98

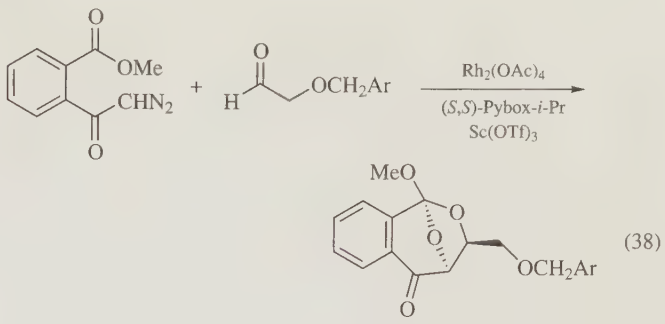


(37)

R			
t-Bu	10	:	1
i-Pr	1	:	1
$PhCH_2$	1	:	4

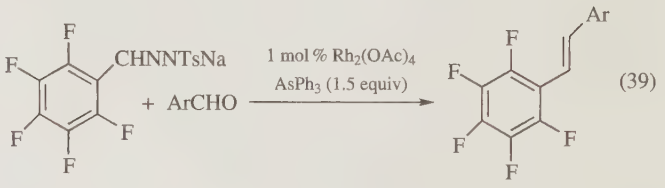
Ylide Reactions. The rhodium-carbenoid intermediates are readily trapped by nucleophiles to form ylides, which can be isolated in certain cases but will often undergo further transformations.[87–95] One of the most versatile reactions is the reaction of the carbenoid with a carbonyl group to form a carbonyl ylide, which can then initiate a cascade of cycloaddition reactions. An enantioselective variant of this chemistry is a reaction catalyzed by $Rh_2(OAc)_4$ in the presence of a chiral scandium(III) complex, which led to the formation of a tricyclic system with high asymmetric induction (eq 38).[96]

$Rh_2(OAc)_4$-catalyzed decomposition of tosyl hydrazones in the presence of triphenylarsine enables the unsymmetrical coupling of aldehydes to yield pure *trans*-alkenes (eq 39).[97] This reaction proceeds via transient arsonium ylides. The substrate scope is limited in that the aryl tosyl hydrazone must be perfluorinated.



(38)

Ar	Yield (%)	ee (%)
Ph	84	91
p-$MeOC_6H_4$	48	89
p-FC_6H_4	80	93
p-BrC_6H_4	52	83

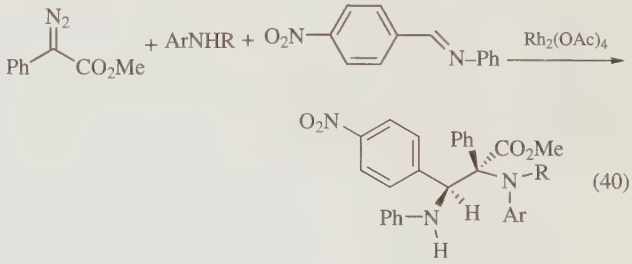


(39)

Ar	Yield (%)
Ph	70
p-BrPh	60
trans-PhCH=CH	57
o-NO_2Ph	64
p-CH_3OPh	45
p-CHOPh	35

Related examples have been reported using phosphorus[98,99] and sulfur ylides.[100,101] A similar coupling of cinnamaldehyde has been reported that gives symmetrical trienes in good yield with excellent *trans*-selectivity.[102]

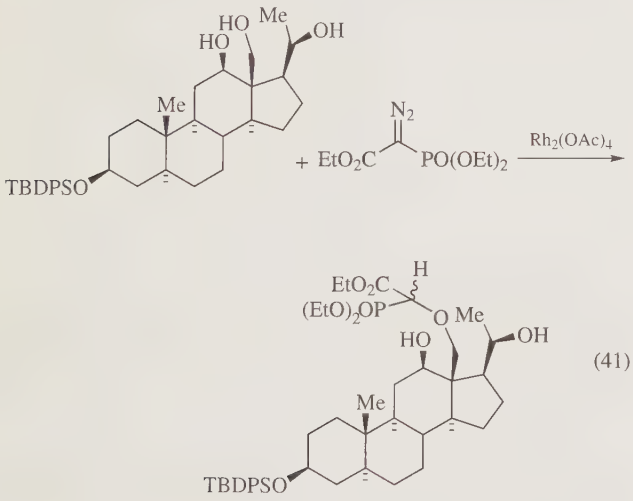
A more elaborate transformation involving ylide chemistry is the highly diastereoselective three-component reaction of phenyldiazoacetate, arylamines, and imines catalyzed by $Rh_2(OAc)_4$. This is a very novel method for the synthesis of 1,2-diamines (eq 40).[103]



(40)

Ar	R	Yield (%)	*threo*:*erythro*
Ph	H	66	12:88
p-FPh	H	61	9:91
p-ClPh	H	69	9:91
p-CF_3Ph	H	75	7:93
p-NO_2Ph	H	79	15:85
2,4-$(NO_2)_2Ph$	H	76	6:94
Ph	Me	8	<3:97

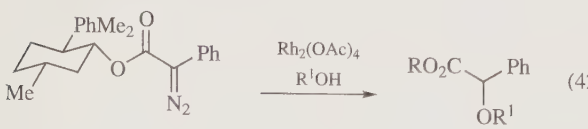
Insertions into X–H Bonds. Insertion of carbenoids into heteroatom X–H bonds generally proceeds faster than insertion into C–H bonds. These types of insertions are very important synthetic transformations and have been extensively employed. $Rh_2(OAc)_4$-catalyzed insertions into an O–H or Si–H bond have been found to be mechanistically very similar, with each displaying similar reaction constants.[104,105] Hammett studies show that insertions into O–H/Si–H bonds are relatively insensitive to steric effects in the substrates, but do show a dependence on the electronics of the X–H bond indicating a concerted mechanism with an early transition state.[105] One of the remaining challenges in carbenoid chemistry is enantioselective O–H or N–H insertion. All the reports to date report virtually no enantioselectivity using chiral catalysts for such a reaction.[106–111] An example of the regioselectivity possible in intermolecular heteroatom X–H insertion reactions is seen in the synthesis of a fragment of cephalostatin 1 by Fuchs (eq 41).[112] The phosphonate-substituted carbenoid inserted cleanly into the primary neopentyl alcohol in the presence of two secondary ring alcohols to give the product in excellent yield as a 1:1 mixture of diastereomers.



(41)

96% yield
1:1 mixture of diastereomers

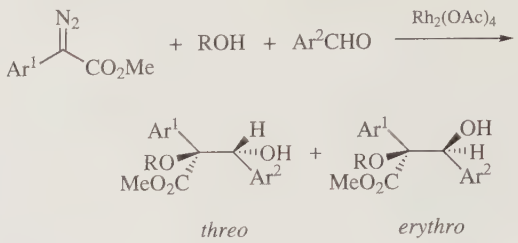
Limited diastereoselectivity has been reported in cases of alcohol O–H insertion when the diazo compound contains a bulky chiral ester (eq 42).[113]



(42)

R^1	Yield (%)	de (%)
H	79	27
Me	63	44
i-Pr	85	36
t-Bu	40	53

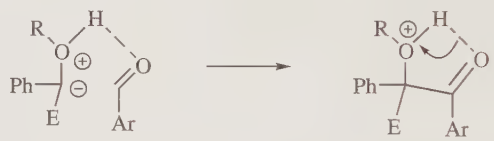
Diastereoselective O–H insertions have been observed in the three-component coupling reactions of diazo compounds, alcohols and aldehydes (eq 43).[114]



(43)

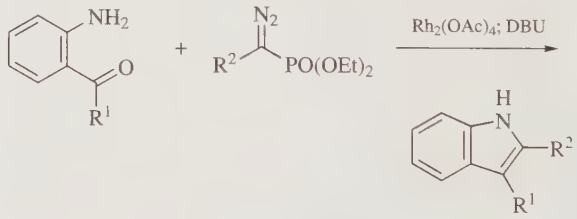
Ar^1	Ar^2	R	Yield (%)	*threo*:*erythro*
Ph	2,4-$(NO_2)_2$Ph	^{t}Bu	18	88:12
PMP	*p*-(NO_2)Ph	Bn	87	36:62
Ph	2,4-$(NO_2)_2$Ph	Bn	78	82:18
Ph	*p*-CNPh	PMB	51	29:50
Ph	2,4-$(NO_2)_2$Ph	H	65	50:50

This reaction also provides evidence for a stepwise mechanism of O–H insertion that proceeds through initial O–H oxonium ylide formation, followed by addition to the aldehyde carbonyl and proton transfer, in contrast to a previous study indicating O–H insertion proceeds via a concerted pathway (eq 44).[105]



(44)

Recently, many examples of $Rh_2(OAc)_4$-catalyzed carbenoid insertions into N–H bonds have been reported.[115–119] An interesting application of this methodology is the one-pot synthesis of substituted indoles via an intermolecular N–H insertion of a phosphonate diazo compound followed by an intramolecular Horner-Wadsworth-Emmons reaction (eq 45).[120]

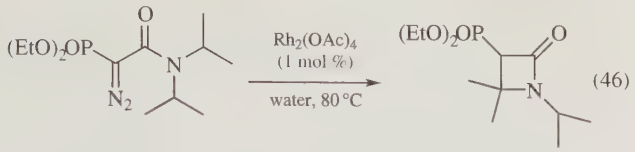


(45)

R^1	R^2	Yield (%)
H	COOEt	73
Ph	COOEt	86
Ph	CN	91
Ph	$CONMe_2$	76
Ph	Ph	14

Reactions in Nontraditional Solvents. Recently, the use of nontraditional solvents has been explored for the reactions of metal carbenoids. The ionic liquid 3-*n*-butyl-1-methyl-imidazolium ([bmim][PF_6]) has been used for both the $Rh_2(OAc)_4$-catalyzed intermolecular cyclopropanation of alkenes[121] and the

intramolecular C–H insertions of α-diazo-α-phosphono-acetamides.[122] Interestingly, water has also been shown to be a very effective solvent for $Rh_2(OAc)_4$-catalyzed intramolecular C–H insertion reactions (eq 46).[123]

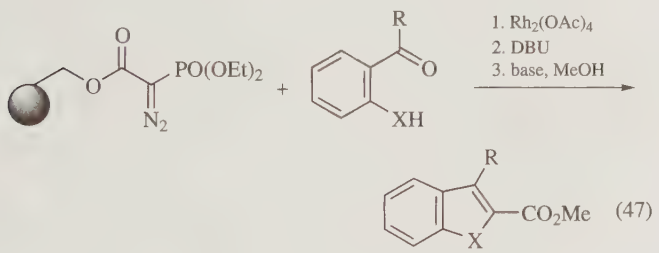


(46)

Cycle	Yield (%)
1	75
5	86
10	90

Upon completion of the reaction the product was removed by extraction with diethyl ether and the aqueous solution containing the catalyst was recycled for another run without further purification. No drop in catalyst efficiency was observed after 10 cycles and surprisingly, competition with O–H insertion into water was not observed. The selectivity for C–H insertion was attributed to the apparent hydrophobicity of the carbenoid structure that does not allow an effective approach of the water molecules.[123]

Polymer-supported Reactions. Solid-phase carbenoid chemistry has some distinct advantages over the traditional homogeneous methods. These include relatively easy separation of a solid-supported product from the reaction mixture and reuse of a solid-supported catalyst for many reaction cycles. There have been reports of carbenoid reactions catalyzed by $Rh_2(OAc)_4$ with either polymer-supported substrates[124] or polymer-supported diazo compounds (eq 47).[125,126]

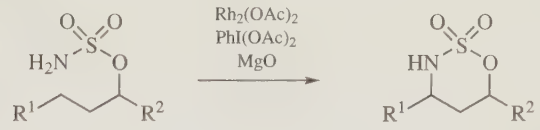


(47)

X	R	Yield (%)
N	Ph	75
N	Me	87
COO	Ph	27
COO	Me	21
COO	H	15

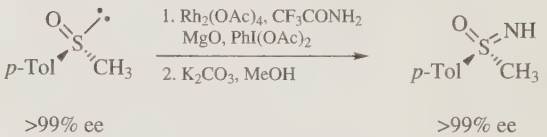
Nitrene Reactions. Nitrenes, the nitrogen equivalents of carbenes, have been used for insertions of nitrogen into C–H bonds catalyzed by $Rh_2(OAc)_4$.[127,128] Nitrenoid chemistry catalyzed by $Rh_2(OAc)_4$ has also been used for the aziridination of alkenes.[128,129] $Rh_2(OAc)_4$ catalyzes the intramolecular C–H insertion of nitrenes derived from sulfamate esters in high yield (eq 48).[130]

$Rh_2(OAc)_4$ has also been shown to be an effective immination catalyst for sulfoxides and sulfides, proceeding through a stereospecific mechanism (eq 49).[131]



(48)

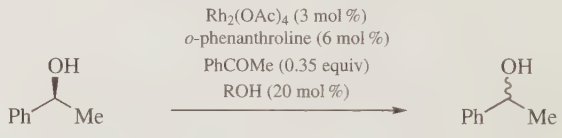
R^1	R^2	Yield (%)	*syn:anti*
Me_2	$(CH_2)_2CH_3$	90	-
Ph	CO_2Et	91	13:1
Me_2	CO_2Me	86	-
n-Pr	CO_2Bn	78	4:1



(49)

>99% ee >99% ee

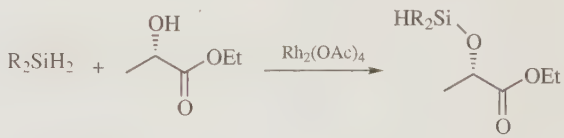
Miscellaneous Reactions. Kinetic resolutions of enantiomeric mixtures rely on the greater reactivity of one enantiomer under the reaction conditions. The maximum theoretical conversion of a racemic mixture is thus 50%. If the inactive enantiomer can be catalytically racemized under the reaction conditions, however, then the theoretical conversion becomes quantitative. $Rh_2(OAc)_4$ has been used to catalyze the racemization of enantiomerically enriched alcohols in the presence of an appropriate ketone in a reaction analogous to an Oppenhauer oxidation (eq 50).[132]



(50)

optically pure racemic

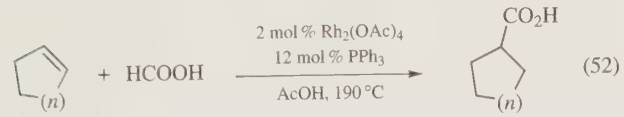
Bisalkoxy silanes have a wide variety of uses in organic chemistry including as protecting groups and linking groups for solid-support chemistry. The synthesis of unsymmetrical bisalkoxy silanes is difficult, requiring a reagent capable of selective introduction of only one alkoxy group to an appropriate silane precursor. $Rh_2(OAc)_4$ has been reported to catalyze the monoalcoholysis of silanes in quantitative yield (eq 51).[133]



(51)

R = Ph, *i*-Pr quantitative

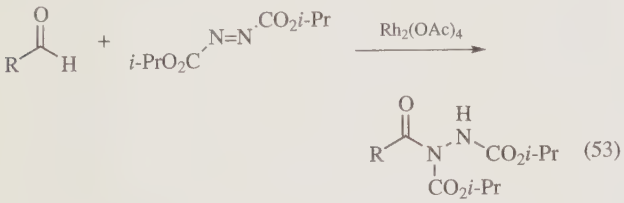
Carbon monoxide (CO) is an established one-carbon synthon but it is toxic and potentially explosive. Therefore, less hazardous materials for the introduction of one-carbon units in syntheses are of considerable interest. Formic acid has been used for the introduction of the carboxylic acid moiety to alkenes without the presence of CO gas in a $Rh_2(OAc)_4$-catalyzed reaction (eq 52).[134] The nature of the actual catalytic species is unclear, however, as both Rh(I) and Rh(III) species gave identical results.



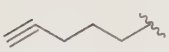
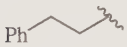
(52)

$n = 0,1,2$ 83–96% yield

$Rh_2(OAc)_4$ has also catalyzed the amidelike bond formation reaction between aldehydes and azodicarboxylates in good yield.[135] This reaction is inhibited in the presence of a radical scavenger, indicating a possible radical mechanism (eq 53).



(53)

R	Yield (%)
	97
	74
	81
	68

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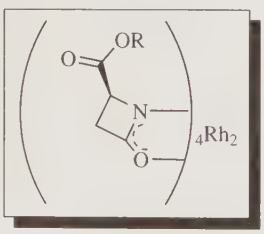
Dirhodium(II) Tetrakis[Alkyl 2-oxaazetidine-4(*S*)-carboxylate]



Dirhodium(II) tetrakis[methyl-2-oxaazetidine-4(*S*)-carboxylate], $Rh_2(4S\text{-MEAZ})_4$

[271261-55-3] $C_{20}H_{24}N_4O_{12}Rh_2$ (MW 718.22)

Dirhodium(II) tetrakis[isobutyl-2-oxaazetidine-4(*S*)-carboxylate], $Rh_2(4S\text{-IBAZ})_4$

[181628-69-3] $C_{28}H_{40}N_4O_{12}Rh_2$ (MW 830.46)

Dirhodium(II) tetrakis[menthol-2-oxaazetidine-4(*S*)-carboxylate], $Rh_2(4S\text{-MenthAZ})_4$

[417712-41-5] $C_{56}H_{88}N_4O_{12}Rh_2$ (MW 1215.14)

(reagents used for the decomposition of stablized diazo species as well as diazomalonate esters)

Physical Data: $Rh_2(4S\text{-MEAZ})_4$ $[\alpha]_D^{25} = -214$ (*c*, 0.7, CH_3CN). $Rh_2(4S\text{-IBAZ})_4$ $[\alpha]_D^{25} = -211.4$ (*c*, 0.69, CH_3CN). $Rh_2(4S\text{-MenthAZ})_4$ $[\alpha]_D^{29.6} = -184$ (*c*, 0.1, $CHCl_3$).

Form Supplied in: $Rh_2(4S\text{-MEAZ})_4$: red crystalline solid as bis-acetonitrile, purple solid after removal of nitrile ligands; $Rh_2(4S\text{-IBAZ})_4$: red crystalline solid as bis-acetonitrile, purple solid after removal of nitrile ligands; $Rh_2(4S,R\text{-MenthAZ})_4$: blue solid.

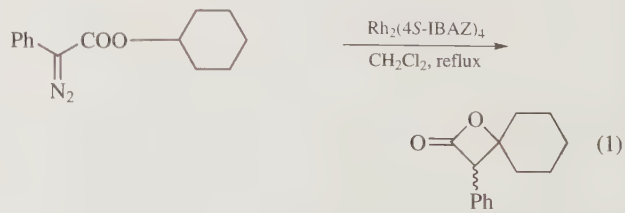
Preparative Method: ligand exchange from dirhodium(II) tetraacetate by corresponding alkyl 2-oxaazetidine-4(*S*)-carboxylate.

Handling, Storage, and Precautions: air stable, weakly hygroscopic, stored in desiccator.

Introduction. The azetidinone class of ligands for dirhodium catalysts are unique amongst the dirhodium(II) carboxamidate series for their ability to decompose such stabilized diazo species as aryl- and vinyldiazoacetates, as well as diazomalonate esters.[1] The reactive nature of the azetidinone family is derived from the extension of the Rh–Rh bond relative to dirhodium catalysts with a smaller bite angle of the NCO ligating unit. X-ray diffraction of the azetidinone compound $Rh_2(4S\text{-BNAZ})_4$ showed the Rh–Rh bond to be 2.53 Å,[2] as opposed to the Rh–Rh bond length of 2.43 ± 0.01 Å reported for five-membered ring carboxamidates.[3,4] Four ligands are bound to one dirhodium(II) nucleus; each rhodium is bound to two nitrogen and two oxygen donor atoms arranged in a *cis* configuration.

Metal Carbene Transformations. As the most reactive dirhodium(II) carboxamidate catalysts for diazo decomposition, azetidinone-based catalysts are typically used to decompose highly stable diazo compounds that are unreactive toward other dirhodium(II) carboxamidate catalysts. Intramolecular C–H insertion[5] and cyclopropanation[6] processes of these diazo species mediated by dirhodium(II) azetidinone catalysts provide enantioselectivities comparable or superior to those obtained with dirhodium(II) carboxylate catalysts.[7] As well, intermolecular cyclopropanation reactions have been found to proceed with good selectivities, predominantly forming the *cis* diastereomer in high enantiomeric excesses.[8,9]

Intramolecular C–H Insertion Reactions. The effectiveness of azetidinone-based catalysts in C–H insertions has not been explored to the extent of other dirhodium(II) carboxamidate catalysts. Dirhodium(II) azetidinone catalysts have been utilized to form β and γ-lactones; in all reported instances the insertion proceeds into the tertiary over secondary C–H bond with high levels of regioselectivity.[5] The enantioselectivities obtained are comparable to those observed with dirhodium(II) carboxylate catalysts (eqs 1 and 2).

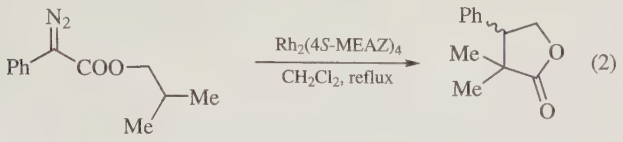


(1)

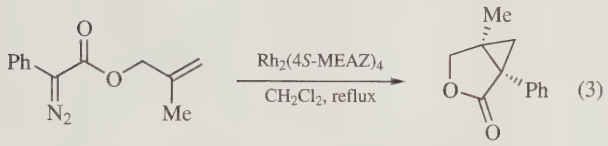
66%
51% ee

Intramolecular Cyclopropanation Reactions. Catalysts of the azetidinone family have been demonstrated to provide

intramolecular cyclopropanations with high enantiomeric excesses at low catalyst loadings (0.01 mol %).[6,7] In most reported examples, the enantioselectivity is considerably higher than that obtained with catalysts of the dirhodium(II) carboxylate series (eq 3).

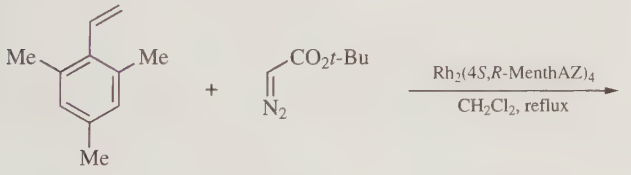


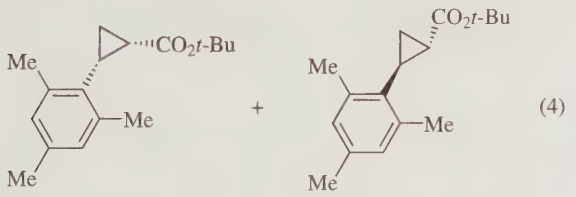
94%
90% ee



100%
94% ee

Intermolecular Cyclopropanation Reactions. Intermolecular cyclopropanations mediated by dirhodium(II) catalysts typically proceed with poor diastereoselectivity, despite providing good levels of enantiocontrol.[1,10] Dirhodium(II) azetidinone catalysts have shown a marked preference for formation of the *cis*-cyclopropanes with high enantioselectivity (eq 4).[8,9] The stereoselectivity of cyclopropanation has been noted to vary significantly with modification of the ester moiety upon the azetidinone ligand, providing a convenient manner in which to optimize the catalyst for specific substrates. Few other catalysts are capable of selectively providing *cis*-cyclopropanes in high enantiomeric excess.[11]



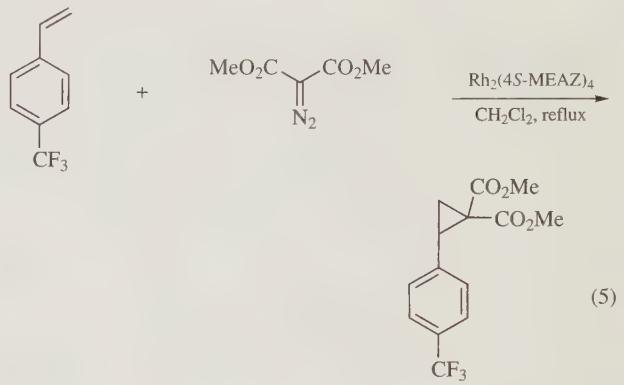


40%
97% ee

4%
76% ee

Cyclopropanation of diazomalonates proceeds with negligible enantioselectivity when catalyzed by dirhodium(II) carboxylate catalysts. The stability of diazomalonate prevents decomposition using less active dirhodium(II) carboxamidates. However Rh_2(4*S*-MEAZ)$_4$ has been shown to provide significant levels of enantioselectivity in these reactions.[6] Enantiomeric excesses of up to 50% are obtained upon cyclopropanation of styryl derivatives (eq 5).

Immobilized, Recoverable 2-Oxaazetidine-4(*S*)-carboxylate, and Mixed Ligand Catalysts. Dirhodium (II) catalysts have been immobilized on NovaSyn Tentagel hydroxy resin or Merrifield resin through the ester of an azetidinone.[12] 2-Oxaazetidine-4(*S*)-carboxylate is coupled through the carboxylate to the resin linker and exposed to a dirhodium(II) carboxamidate catalyst under ligand-exchange conditions, providing catalysts with one azetidinone ligand bound to the resin and three parent carboxamidate ligands. The three parent ligands may be azetidinones or other carboxamidate ligands, allowing the synthesis of mixed ligand catalyst species. The incorporation of a single azetidinone ligand has been found to sufficiently activate the dirhodium(II) catalyst as to allow decomposition of highly stabilized diazo species, regardless of the identity of the other three carboxamidate ligands. The selectivity of immobilized mixed ligand catalysts has been shown to differ from that exhibited by either homogenous dirhodium(II) tetrakis[alkyl 2-oxaazetidine-4(*S*)-carboxylate] or the precursor dirhodium(II) carboxamidate catalysts in cyclopropanation and C–H insertion reactions, indicating that this may provide a useful strategy for catalyst development.



73%
50% ee

Related Catalysts. Several catalysts related to Rh_2(4*S*-MEAZ)$_4$, Rh_2(4*S*-IBAZ)$_4$, and Rh_2(4*S*,*R*-MenthAZ)$_4$ have been made by variation of the alkyl group upon the ester; these variants include Rh_2(4*S*-BNAZ)$_4$ [181759-04-6],[2] Rh_2(4*S*-CHAZ)$_4$ [288614-94-8],[5] and Rh_2(4*S*,*S*-MenthAZ)$_4$ [417711-12-7].[8] Modification of the ester moiety has a substantial effect upon the stereoselectivity of the catalyzed process, allowing considerable optimization for individual transformations. Substitution of fluorine for the methylene hydrogens alpha to the carboxamide carbonyl provides the most reactive catalyst of this family, Rh_2(4*S*-dFIBAZ)$_4$.[13]

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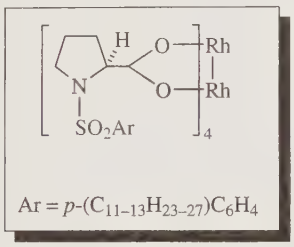
Dirhodium(II) Tetrakis[1-[[(4-dodecylphenyl]sulfonyl]-prolinate]



[179162-34-6] $C_{90}H_{140}N_4O_{16}Rh_2S_4$ (MW 1866)
(*R*)-enantiomer
[178879-60-2]

(chiral catalyst for asymmetric reactions of diazo compounds, especially aryldiazoacetates and vinyldiazoacetates[1])

Physical Data: mp 195–200 °C $[\alpha]^{22}_D$ −165° (*c* = 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.74 (d, 8 H, *J* = 9.2 Hz), 7.53 (d, 8 H, *J* = 9.2 Hz), 4.32 (m, 4 H), 3.25 (m, 4 H), 3.05 (m, 4 H), 2.07 (m, 4 H), 1.85 (m, 4 H), 1.57 (m, 8 H), 1.25 (bs, 36 H), 0.85 (m, 10 H).

Solubility: very soluble in most organic solvents including hydrocarbons.

Form Supplied in: green solid; available from Aldrich Chemical Co. The linear alkylbenzene side chains consist of a mixture of 1% C_{10}, 40% C_{11}, 28% C_{12} and 31% C_{13}.

Preparative Methods: from dirhodium tetraacetate by ligand exchange with *N*-[1-(dodecylphenyl)sulfonyl]-(2*S*)-prolinate.[2]

Purification: further purification is generally not necessary. May be dried by heating under vacuum at 100 °C. May be purified by column chromatography on silica with ether/petroleum ether as solvent. If contaminated with the free ligand, can be purified by dissolving in diethyl ether and extracting the organic layer with aqueous sodium bicarbonate, followed by drying the organic layer over $MgSO_4$, then filtering and evaporation of the solvent.

Handling, Storage, and Precautions: the catalyst is moisture, air, and thermally stable. It may be stored at room temperature for extended periods of time without any apparent decomposition. The toxicity of the title reagent, Rh_2(*S*-DOSP)$_4$, is unknown. Strong nucleophiles such as nitriles, phosphines, amines, pyridines, and sulfides will tend to coordinate to the axial site of the catalyst. This may cause partial poisoning of the catalyst or catalyst decomposition, depending on the coordinating ligand. Reactions carried out under non-anhydrous conditions tend to result in lower enantioselectivity.[3]

Original Commentary

Huw M. L. Davies
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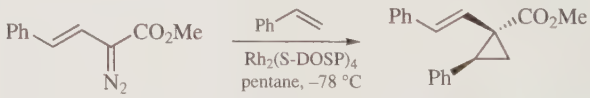
Introduction. The title reagent Rh_2(*S*-DOSP)$_4$ and its *R*-enantiomer have been shown to be exceptional chiral catalysts for transformations of carbenes derived from aryldiazoacetates and vinyldiazoacetates. The related *p-tert*-butylphenyl prolinate derivative Rh_2(TBSP)$_4$ is also commercially available. All of these catalysts display higher levels of asymmetric induction in reactions that are carried out in hydrocarbon solvents and Rh_2(DOSP)$_4$ is generally favored over Rh_2(TBSP)$_4$ because it is soluble in hydrocarbon solvents even at −78 °C. All of these catalysts are considered to be conformationally flexible but preferentially adopt a D_2-symmetric arrangement in solution.[1,2] This is a critical component for their effectiveness as chiral catalysts. Conformationally rigid analogs of Rh_2(*S*-DOSP)$_4$ have been reported[4] and these are also promising chiral catalysts.

Asymmetric Cyclopropanations. Rh_2(*S*-DOSP)$_4$ has been shown to be an exceptional chiral catalyst for asymmetric cyclopropanations of vinyldiazoacetates,[2,5] aryldiazoacetates,[6] and alkynyldiazoacetates.[7] Enantioselectivities of greater than 90% ee are very common with this catalyst. The decomposition of a vinyldiazoacetate by Rh_2(*S*-DOSP)$_4$ in the presence of styrene generates a vinylcyclopropane in 98% de and 98% ee (eq 1). This product has been applied to the asymmetric synthesis of (+)-sertraline[8] and the cyclopropane analogs of phenylalanine.[2]



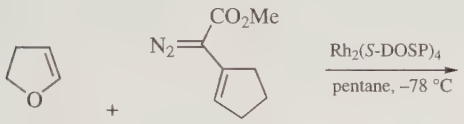
(1)

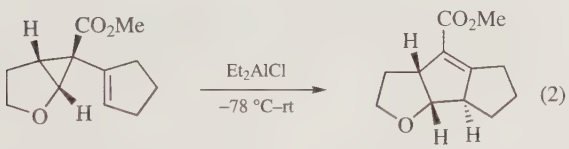
(69% yield, 98% ee, 98% de)

A special feature of Rh_2(*S*-DOSP)$_4$ is that it is designed for asymmetric transformations of donor/acceptor substituted carbenoids, unlike most of the chiral catalysts for diazo decomposition which are optimized for the cyclopropanation chemistry of unsubstituted diazoacetates.[9] Indeed, the rhodium prolinates rarely induce good asymmetric induction in the reactions of other classes of carbenoids.[2,10] The highest levels of enantioselectivity are obtained when the reactions are carried out in hydrocarbon solvents, and Rh_2(*S*-DOSP)$_4$ is ideally suited because it is soluble in hydrocarbon solvents even at −78 °C.[2] Typically, 1 mol% of catalyst is used and the reactions are virtually instantaneous at room temperature, while at −78 °C, the reaction times are 12–48 h. Several comparison studies with various other chiral rhodium and copper catalysts have been reported in recent years,[6b,c,11] but so far none have outperformed Rh_2(*S*-DOSP)$_4$ on a regular basis.

Cyclopropanations with $Rh_2(S\text{-TBSP})_4$ carried out under non-anhydrous reaction conditions result in considerable lowering of the enantioselectivity.[3] Using trioctylphosphine oxide as an additive can minimize this effect.[3] Asymmetric cyclopropanations have also been carried out with $Rh_2(S\text{-TBSP})_4$ in supercritical fluids.[3]

$Rh_2(S\text{-DOSP})_4$ catalyzed decomposition of vinyldiazoacetates in the presence of vinyl ethers leads to donor/acceptor substituted vinylcyclopropanes.[12] On treatment with diethylaluminum chloride these vinylcyclopropanes undergo a stereoselective rearrangement to cyclopentanes. An illustrative example is shown in eq 2, whereby the tricyclic system is formed in 86% ee.[12] The extent of retention of the asymmetric induction during the vinylcyclopropane rearrangement is very dependent on the cyclopropane substitution pattern.



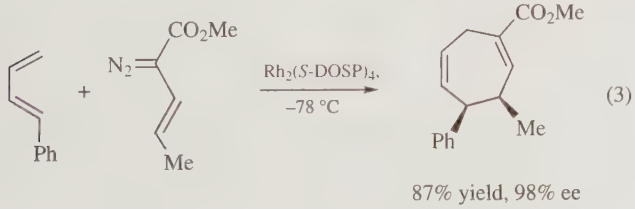


(2)

53% yield, 88% ee

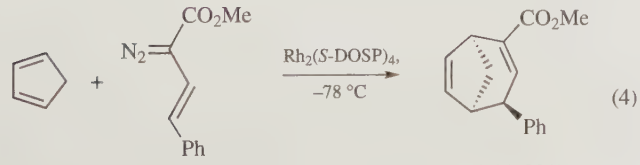
79% yield, 86% ee

Rhodium(II) carboxylate-catalyzed decomposition of vinyldiazoacetates in the presence of dienes is a very effective stereoselective method for the construction of highly functionalized cycloheptadienes.[13] The [3 + 4] cycloaddition proceeds via a divinylcyclopropane, which undergoes a Cope rearrangement in a stereodefined manner, leading to cycloheptadienes with stereocontrol at up to three stereogenic centers. When these reactions are catalyzed by $Rh_2(S\text{-DOSP})_4$ highly enantioselective reactions are obtained.[14] The reactions with phenylbutadiene and cyclopentadiene illustrate the synthetic potential of this chemistry (eqs 3 and 4).[14] Asymmetric [3 + 4] cycloadditions are also possible between vinylcarbenoids and furans[15] or *N*-BOC-pyrroles[16] leading to the synthesis of 8-oxabicyclo[3.2.1]octadienes or tropanes.



(3)

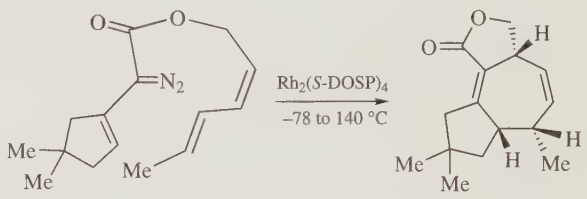
87% yield, 98% ee



(4)

77% yield, 93% ee

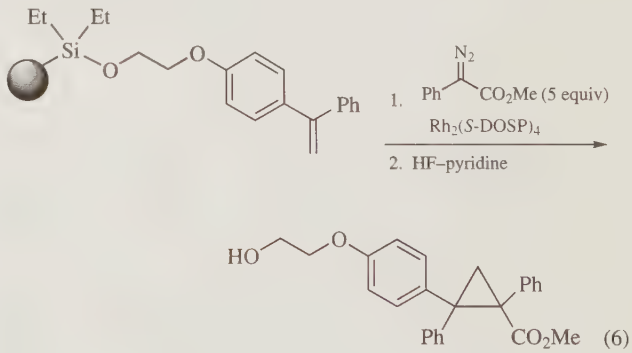
Reasonably high asymmetric induction can be obtained in intramolecular cyclopropanations.[17] $Rh_2(S\text{-DOSP})_4$-catalyzed decomposition of a *Z,E*-diene generated a tricyclic system in 93% ee with full control of relative stereochemistry (eq 5). As this reaction initially forms a *trans*-divinylcyclopropane, heating to 140 °C is required to induce equilibration to the *cis*-divinylcyclopropane followed by the Cope rearrangement. In general, the intramolecular cyclopropanations are not as highly enantioselective as the intermolecular cyclopropanations, and with certain substrates, other chiral catalysts can result in higher enantioselectivity than $Rh_2(S\text{-DOSP})_4$.[18]



(5)

56% yield, 93% ee

Aryldiazoacetates are capable of being used in solid-phase synthesis.[19] The traditional diazoacetates do not react effectively with substrates on solid support because the carbenoid intermediates are highly reactive and prone to dimerization.[20] The carbenoids derived from aryldiazoacetates are considerably more chemoselective,[21] and when $Rh_2(S\text{-DOSP})_4$ is used as catalyst, effective asymmeric cyclopropanation of an alkene on a solid support is possible (eq 6).[19] This protocol can be used to achieve asymmetric cyclopropanation of elaborate alkenes because the alkene is used as the limiting reagent.



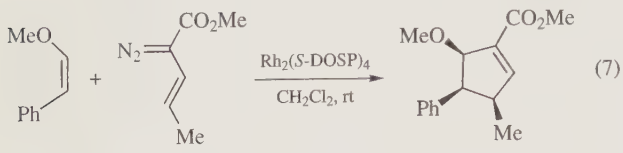
(6)

83% yield, 91% ee, 85:15 *E/Z*

[3 + 2] Cycloaddition. The $Rh_2(S\text{-DOSP})_4$ catalyzed reaction of certain vinyldiazoacetates with styryl ethers results in a very unusual transformation.[22] As illustrated in eq 7, instead of the normal cyclopropanation, a [3 + 2] cycloaddition product is formed. Remarkably, this product is formed as the all *cis* diastereomer in 98% ee. Selective cuprate additions to these [3 + 2] cycloaddition products can generate, stereoselectively, cyclopentanes with five contiguous stereocenters.

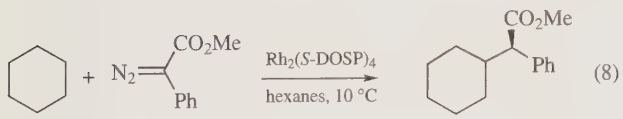
Asymmetric C–H Insertion. A major advantage with the use of aryldiazoacetates is that effective intermolecular C–H insertions can be achieved.[23] $Rh_2(S\text{-DOSP})_4$-catalyzed decomposition of methyl phenyldiazoacetate in the presence of cyclohexane

results in the formation of the C–H insertion product in 95% ee (eq 8).[24] The reaction has been extended to a range of alkanes and the selectivity of competing insertions between secondary and tertiary C–H sites depends on a delicate balance between steric and electronic effects.[24]



(7)

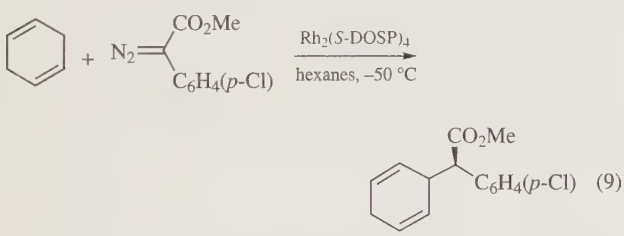
79% yield, 98% ee



(8)

80% yield, 95% ee

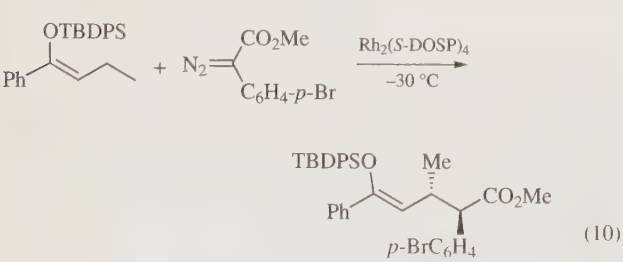
Highly efficient C–H insertion into allylic C–H positions is possible as illustrated in the example with 1,4-cyclohexadiene shown in eq 9.[25] Similar highly enantioselective C–H insertions are possible with cycloheptatriene,[26] while the reaction with cyclohexene proceeded with moderate enantioselectivity but poor diastereoselectivity.[27]



(9)

84% yield, 94% ee

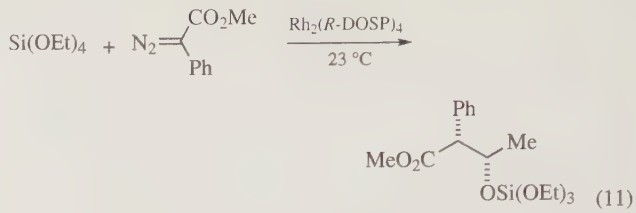
The intermolecular C–H insertion is a very general method for C–H functionalization and represents a surrogate to many classic synthetic transformations. The allylic C–H insertion of trisubstituted vinyl silyl ethers shown in eq 10 represents the equivalent of an asymmetric Michael addition.[28] Remarkably, the C–H insertion product in this case is formed with very high diastereoselectivity. In general, high diastereoselectivity is observed for C–H insertions at methylene sites in which there is considerable size differential between the two substituents.[23]



(10)

65% yield, 84% ee, >90% de

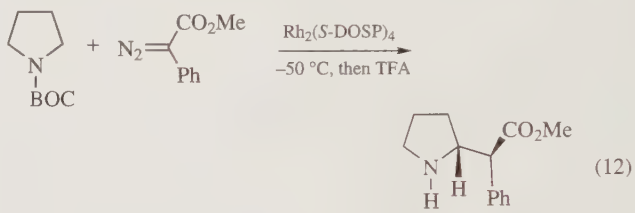
Another spectacular example of a highly diastereoselective intermolecular C–H insertion is the reaction between aryldiazoacetates and tetralkoxysilanes, which generate silyl-protected β-hydroxy esters,[29] products that would be typically prepared by an aldol reaction. The utility of this reaction is illustrated in the example with tetraethoxysilane, in which the C–H insertion product is formed in 95% ee and >90% de (eq 11). Highly diastereoselective C–H insertions are also possible with allyl silyl ethers.[30]



(11)

70% yield, 95% ee, >90% de

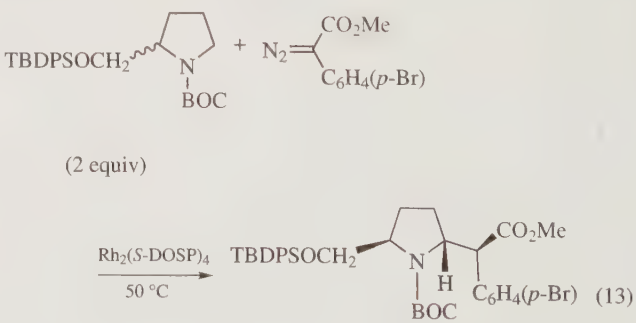
C–H insertions adjacent to nitrogen results in the formation of products that would be typically formed by a Mannich reaction. *N*-BOC-pyrrolidine is another substrate that undergoes highly diastereoselective C–H insertions, as illustrated in eq 12.[31] The related reaction with *N*-BOC-piperidine[31,32] is also a very important transformation because it represents a very direct synthesis of ritalin.



(12)

72% yield, 94% ee, 92% de

The chemoselectivity of the C–H insertion is sufficiently great that these reactions can display very impressive levels of kinetic resolution.[33] An illustrative example is the C–H insertion with the racemic 2-substituted pyrrolidine derivative shown in eq 13.[33] The C–H insertion product is formed in 98% ee with excellent control of stereochemistry at three stereogenic centers. By appropriate control of reaction conditions, a double C–H insertion on *N*-BOC-pyrrolidine is possible, generating a 2,5-disubstituted pyrrolidine with excellent control of stereochemistry at four stereogenic centers.[31]

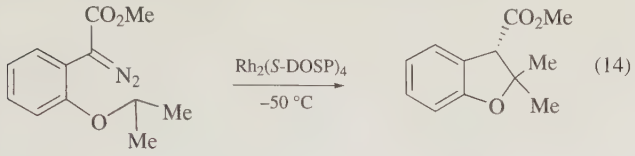


(13)

85% yield, 98% ee, >94% de

Highly asymmetric intramolecular C–H insertions are also possible in Rh_2(*S*-DOSP)$_4$-catalyzed reactions, as illustrated in eq 14.[34] The level of asymmetric induction is very dependent on the substitution pattern at the C–H insertion site, with the highest

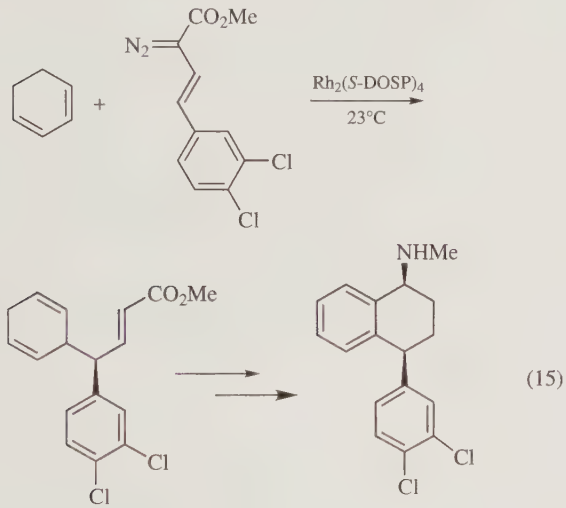
level of C–H insertion obtained for reactions at tertiary C–H sites.[34,35]



(14)

98% yield, 94% ee

Combined C–H Insertion Cope Rearrangement. The reaction of vinyldiazoacetates at allylic C–H sites does not result in the predominant formation of the products of a simple C–H insertion.[25] Instead, combined C–H insertion/Cope rearrangement products with very high enantioselectivity are formed, as illustrated in the example shown in eq 15.[25] This process has been applied to a very short asymmetric synthesis of (+)-sertraline.

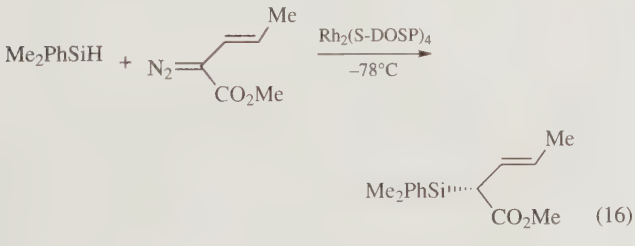


(15)

60% yield, 99% ee

(+)-sertraline

Si–H Insertions. Vinyldiazoacetates and aryldiazoacetates are capable of undergoing effective asymmetric Si-H insertions when the reaction is catalyzed by Rh_2(*S*-DOSP)$_4$. An illustrative example is shown in the reaction of a vinyldiazoacetate that results in the formation of an allylsilane in 95% ee (eq 16).[36]



(16)

64% yield, 95% ee

In summary, the Rh_2(*S*-DOSP)$_4$-catalyzed reactions of aryldiazoacetates and vinyldiazoacetates offer a wide range of applications in organic synthesis. The carbenoids derived from these diazo systems are highly chemoselective and the reactions catalyzed by Rh_2(*S*-DOSP)$_4$ are often highly enantioselective.

First Update

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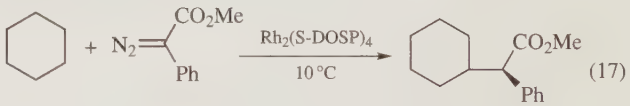
Introduction. Dirhodium(II) Tetrakis[1-[(4-dodecylphenyl)-sulfonyl]-(2*S*)-prolinate] [Rh_2(*S*-DOSP)$_4$] was described in the previous e-EROS report in 2001 as the most widely used chiral catalyst for the reactions of donor/acceptor-substituted carbenoids and this continues to be the case. The most extensive application of this catalyst in the last three years has been in the area of C–H activation by means of carbenoid induced C–H insertions and a new emerging reaction, the combined C–H activation/Cope rearrangement. Several general reviews on various aspects of this chemistry have been published in recent years.[37–39]

Intermolecular C–H Activation. Rhodium carbenoid intermediates, functionalized with both donor and acceptor groups, display a very different reactivity profile compared to the more conventional rhodium carbenoids lacking the stabilizing donor group.[37–39] Most notably, these carbenoids display exquisite selectivity in intermolecular C–H insertions, and this reaction has resulted in arguably the most general process to date for functionalization of unactivated C–H bonds. Furthermore, Rh_2(*S*-DOSP)$_4$ is an effective chiral catalyst for the reactions of the donor/acceptor-substituted carbenoids, leading to a practical enantioselective strategy for C–H activation.

The previous report described the selective C–H functionalization of alkanes as illustrated in the reaction of methyl phenyldiazoacetate with cyclohexane (eq 17). The regioselectivity of the C–H activation is governed by a delicate balance between steric and electronic effects. More highly substituted sites are electronically favored because they stabilize build-up of positive charge on the carbon of the C–H bond, but crowded sites become sterically inaccessible.



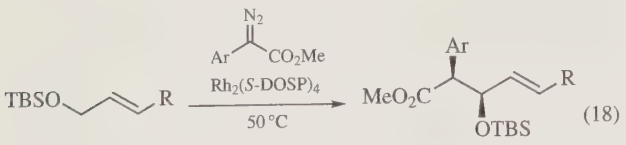
(17)

80% yield, 95% ee

Since the previous report, considerable advances have been made in the C–H activation chemistry, especially in the development of stereoselective transformations occurring at more activated C–H bonds. The scope of the C–H activation is so broad that it can be considered as a surrogate replacement of some of the classic reactions in organic synthesis. C–H activation α to oxygen leads to β-hydroxy esters and can be considered as a surrogate to the aldol reaction.[29–41] C–H activation α to nitrogen leads to β-amino esters and can be considered as a surrogate to the Mannich reaction.[42–44] The γ,δ-unsaturated esters obtained from allylic C–H activation are the typical products from a Claisen rearrangement,[45] while the 1,5-dicarbonyls formed from the allylic C–H activation of vinyl ethers are equivalent products to a Michael addition.[28] Examples of each of these reactions are given in eqs 18–21. The majority of the reactions proceed in >90% ee and are highly regioselective.

A very attractive feature of the C–H activation chemistry is that in certain substrates the reaction can also be highly diastereoselective.[40,44] A requirement for high diastereoselectivity is

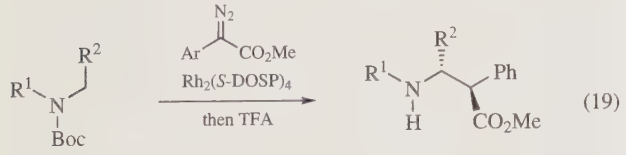
insertion occurring at a methylene C–H bond where there is considerable size differentiation between the other two substituents.



(18)

R = phenyl, alkyl, vinyl

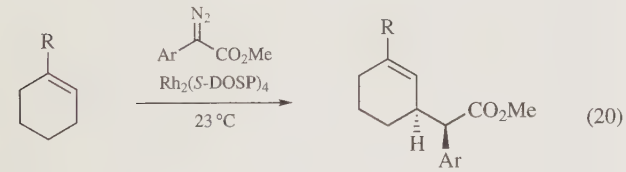
up to 98% de
up to 82% ee



(19)

R^1 = alkyl, R^2 = H, alkyl

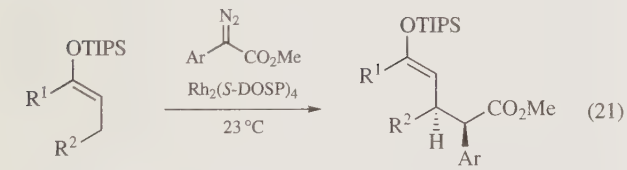
up to 92% de
up to 94% ee



(20)

R = alkyl, silyl, siloxy

up to 88% de
up to 95% ee



(21)

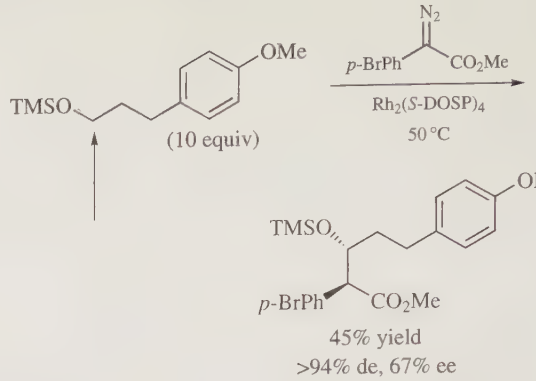
R^1 = phenyl, R^2 = alkyl

up to 90% de
up to 95% ee

The regioselectivity displayed by the donor/acceptor-substituted carbenoids in these more elaborate examples is due to a combination of steric and electronic effects. The stabilizing influence of the donor group makes these carbenoids much more selective than the more conventional carbenoid systems. The importance of stabilization of positive charge during the C–H activation step is a key controlling element as illustrated in the comparison of the reactions of siloxy-protected versus acetoxy-protected *p*-methoxyphenylpropanol.[40] C–H activation α to oxygen occurs in the siloxy derivative (eq 22), while benzylic C–H activation occurs in the acetoxy derivative (eq 23).

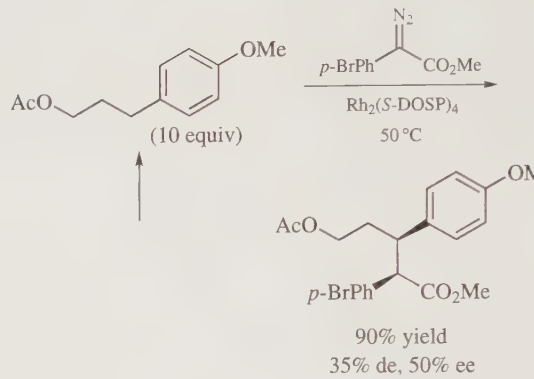
A further example of the electronic influence is seen in the regioselectivity of the C–H activation of 1,2-dimethoxyethane (eq 24).[41] C–H functionalization of the methyl C–H bond occurs in preference to C–H functionalization of the methylene C–H bond presumably because the methylene site is inductively deactivated by the β-oxygen.

A Hammett study on benzylic C–H activation confirmed that positive charge build-up on carbon occurs during the C–H activation process.[46] An interesting example of the C–H activation is the reaction shown in eq 25, which leads to a very direct synthesis of (−)-α-conidendrin.



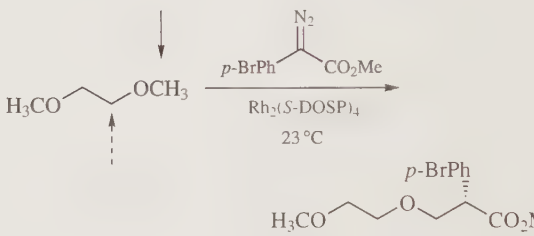
(22)

45% yield
>94% de, 67% ee



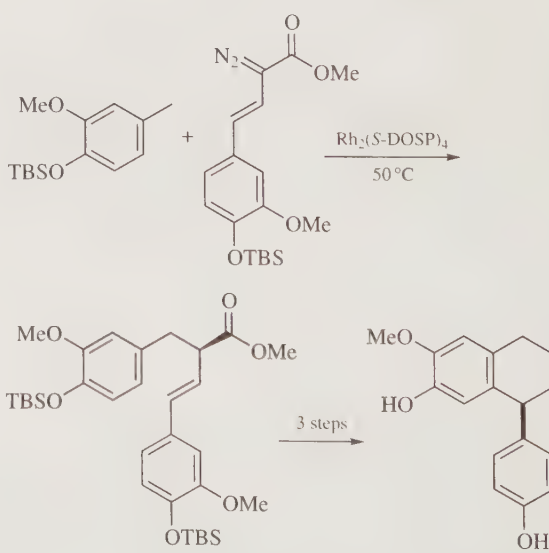
(23)

90% yield
35% de, 50% ee



(24)

72% yield
76% ee



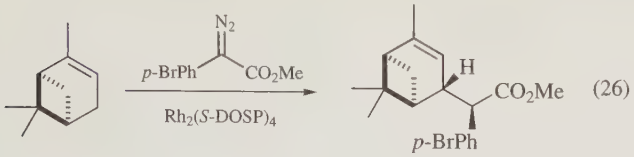
(25)

44% yield
92% ee

(−)-α-Conidendrin

The stereochemical demand of the Rh_2(*S*-DOSP)$_4$-catalyzed C–H activation is so severe that kinetic resolution can be achieved, leading to the enantioselective synthesis of elaborate structures.

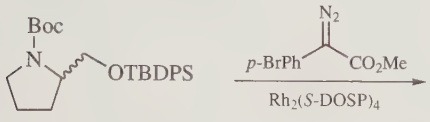
Examples have been reported showing kinetic resolution in allylic C–H activation (eq 26)[45] and in C–H activation α to nitrogen (eq 27).[44]



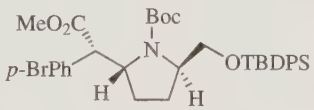
(26)

(10 equiv)

46% yield
99% ee



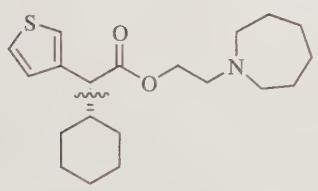
(2 equiv)



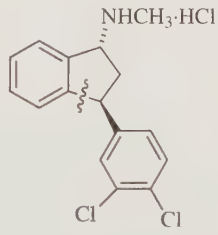
(27)

85% yield
98% ee, >94% de

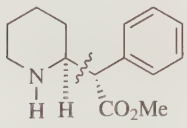
The C–H activation of aryldiazoacetates offers a very efficient approach for the construction of pharmaceutical targets. This has been demonstrated in the enantioselective synthesis of (+)-cetiedil,[47] (+)-indatraline,[48] and methylphenidate.[32,43] The bond formed in the C–H activation step is marked in each case.



(+)-cetiedil
88% ee



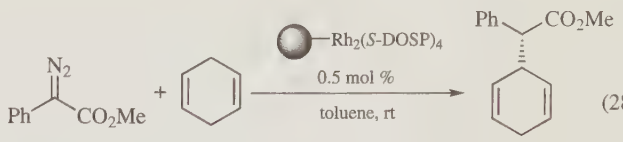
(+)-indatraline
93% ee



methylphenidate
86% ee

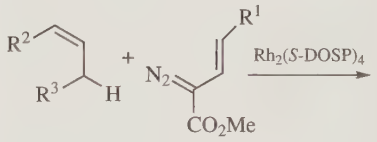
$Rh_2(S\text{-DOSP})_4$ has been effectively immobilized by a pyridine-functionalized polystyrene polymer.[49,50] The pyridine coordinates to the axial position of the dirhodium catalyst, but the catalyst is still efficient at decomposition of the diazo compound. Highly effective cyclopropanation[49] and C–H activation[50] can be achieved. The catalyst can be recycled many times as illustrated in the C–H activation of 1,4-cyclohexadiene (eq 28).[50]

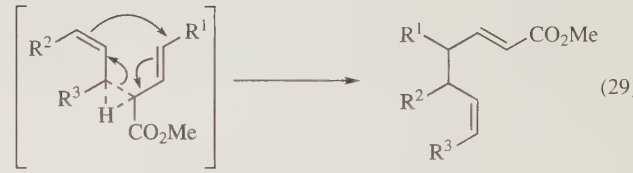
Combined C–H Activation/Cope Rearrangement. Allylic C–H activation with vinyldiazoacetates results in a most unusual outcome. Instead of the expected C–H activation, an isomeric product is formed with very high enantioselectivity (eq 29).[25] The reaction is formally a C–H activation followed by a Cope rearrangement, although this is not the actual mechanism because the C–H activation product is thermodynamically the most favorable product. Thus the transformation has been called a "combined C–H activation/Cope rearrangement."



(28)

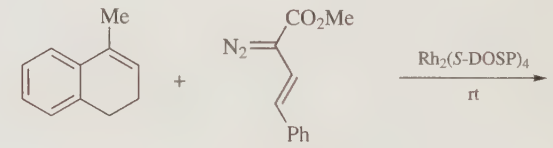
Cycle	Yield (%)	ee (%)
1	79	88
10	84	84

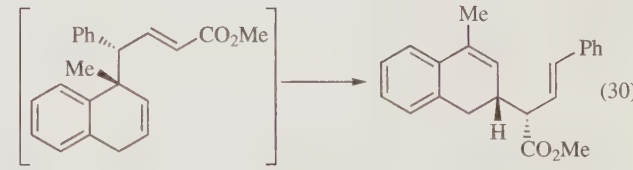




(29)

A variety of allylic substrates are amenable to the combined C–H activation/Cope rearrangement.[25,51–54] The reaction with dihydronaphthalenes is intriguing because this results in formal C–H activation with very high enantioselectivity and diastereoselectivity (eq 30).[51] The actual mechanism of this reaction is a combined C–H activation/Cope rearrangement followed by a retro-Cope rearrangement.

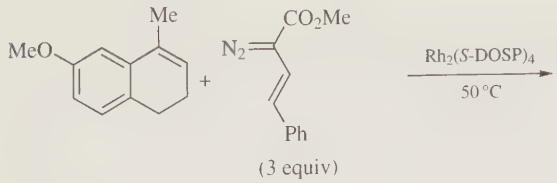




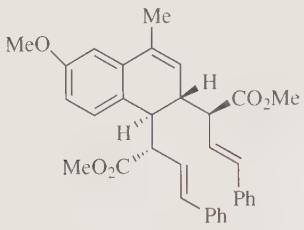
(30)

92% yield
>98% de, 98.9% ee

The reaction can also be extended to a double C–H activation protocol as illustrated in eq 31.[55] In this case, four new stereocenters are generated with excellent control of stereochemistry.



(3 equiv)

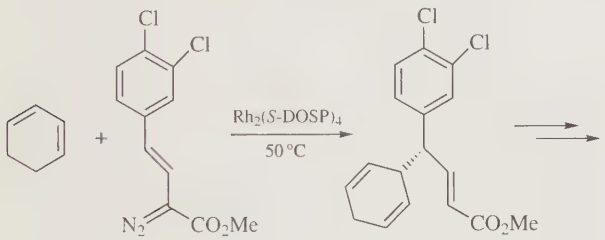


(31)

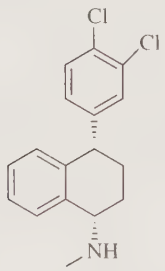
92% yield

>98% de, 99% ee

The combined C–H activation/Cope rearrangement has been used in the synthesis of pharmaceutical targets and natural products. A direct synthesis of the antidepressant (+)-sertraline is described in eq 32.[25] Rh_2(*S*-DOSP)$_4$ is capable of effecting enantiomer differentiation as illustrated in the total synthesis of erogorgiaene (eq 33).[53] One enantiomer of the dihydronaphthalene undergoes the combined C–H activation/Cope rearrangement (the other enantiomer undergoes cyclopropanation) and this becomes the key stereodetermining step in the total synthesis of erogorgiaene.

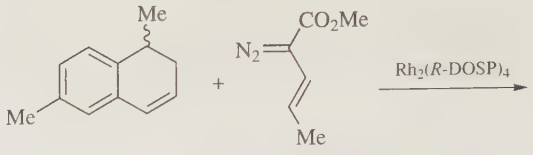


99%

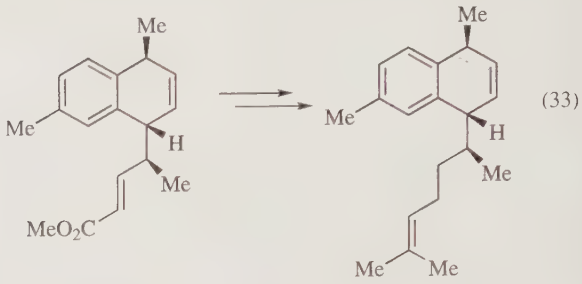


(32)

(+)-sertraline



(±) (3 equiv)

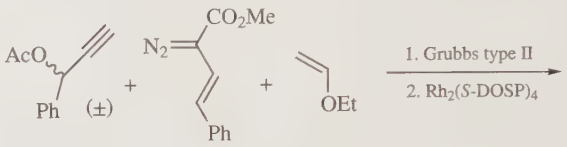


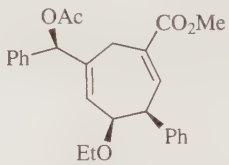
(33)

32% yield

>98% de, 90% ee

(+)-erogorgiaene

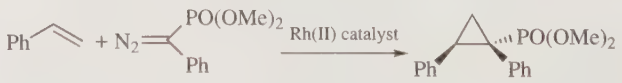




(34)

95% ee

Rh_2(*S*-DOSP)$_4$ has been broadly used because it is generally effective with a range of methyl aryldiazoacetate and vinyldiazoacetates. The nature of the donor group rarely has a major impact on the level of enantioselectivity exhibited by this catalyst. In contrast, the acceptor group can have a profound effect on the enantioselectivity. Changing a methyl ester to a *tert*-butyl ester causes a drastic drop in enantioselectivity.[2] Similarly, Rh_2(*S*-DOSP)$_4$ is not the ideal catalyst for a phosphonate as the acceptor group because Rh_2(*S*-DOSP)$_4$-catalyzed cyclopropanation of such substrates occurs in only 34% ee (eq 35).[57]

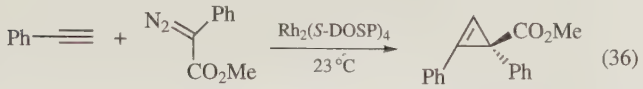


(35)

Cyclopropanation. The Rh_2(*S*-DOSP)$_4$-catalyzed cyclopropanation of donor/acceptor-substituted carbenoids is a highly stereoselective process.[2] This reaction was covered in detail in the previous e-EROS report, but some significant advances have been accomplished over the last three years. An interesting example featuring kinetic resolution is the combination of metathesis chemistry with rhodium-catalyzed tandem cyclopropanation/Cope rearrangement (eq 34).[56] This results in the formation of cycloheptadienes with high enantioselectivity.

Catalyst	Yield (%)	de (%)	ee (%)
Rh_2(*S*-DOSP)$_4$	69	95	34
Rh_2(*S*-biTISP)$_2$	89	98	88

The Rh_2(*S*-DOSP)$_4$-catalyzed reactions of aryldiazoacetates can be extended to alkynes (eq 36). This leads to a very effective enantioselective synthesis of cyclopropenes with quaternary stereogenic centers.[58]



(36)

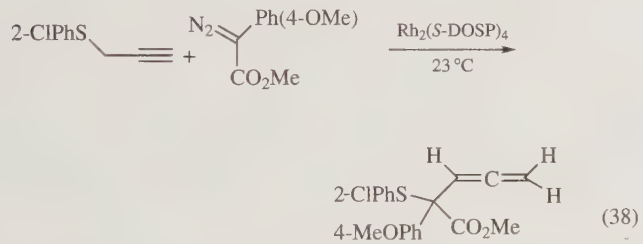
62% yield
90% ee

A wide variety of other chiral catalysts have been explored in this standard reaction, but $Rh_2(S\text{-DOSP})_4$ still appears to be the best catalyst to date (eq 37).[59]

(37)

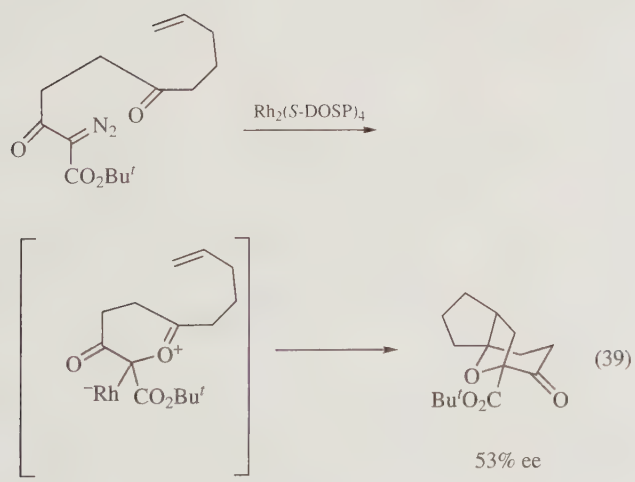
50% yield
85% ee

$Rh_2(S\text{-DOSP})_4$ has been used in many carbenoid reactions involving the initial formation of ylides which undergo a subsequent rearrangement.[60–63] Many of these reactions are not enantioselective, presumably because the catalyst is released at the ylide stage prior to rearrangement and any asymmetric induction is lost. A few examples are known where reasonably high levels of asymmetric induction can be achieved. Reactions involving sulfur ylides can be achieved with good enantioselectivity (eq 38)[64] as well as carbonyl ylides undergoing subsequent 1,3-dipolar cycloadditions (eq 39).[61,62] Other chiral catalysts perform equally well and often better than $Rh_2(S\text{-DOSP})_4$ in these cycloadditions.



(38)

92% yield
73% ee



(39)

53% ee

In summary, $Rh_2(S\text{-DOSP})_4$ has become a broadly useful chiral catalyst for the transformations of donor/acceptor-substituted carbenoids. High enantioselectivity can be achieved in a range of reactions such as C–H activation, combined C–H activation/Cope rearrangement, cyclopropanation, tandem cyclopropanation/Cope rearrangement, and several other miscellaneous reactions. A methyl ester is the ideal acceptor group on the carbenoid for high asymmetric induction, but considerable range of functionality is possible in the donor group.

1. (a) Davies, H. M. L., *Aldrichimica Acta* **1997**, *30*, 105. (b) Davies, H. M. L., *Eur. J. Org. Chem.* **1999**, 2459.
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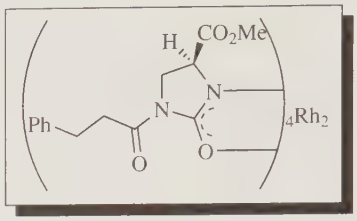
Dirhodium(II) Tetrakis[methyl 1-(3-phenylpropanoyl)-2-oxaimidazolinidine-carboxylate]

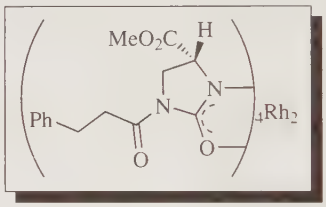


Dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(*S*)-carboxylate] $Rh_2(4S\text{-MPPIM})_4 \cdot 2\ CH_3CN$

[185437-81-4] $C_{60}H_{66}N_{10}O_{16}Rh_2$ (MW 1389.05)

Dirhodium tetrakis[μ-[methyl(4*S*-2-(oxo-κO)-1-(1-oxo-3-phenylpropyl)-4-imidazolidinecarboxylato-κN_3]$Rh_2(4S\text{-MPPIM})_4$

[184089-41-6] $C_{56}H_{60}N_8O_{16}Rh_2$



Dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(*R*)-carboxylate] $Rh_2(4R\text{-MPPIM})_4 \cdot 2\ CH_3CN$

[171230-55-0] $C_{60}H_{66}N_{10}O_{16}Rh_2$ (MW 1389.05)

Dirhodium tetrakis[μ-[methyl(4*R*-2-(oxo-κO)-1-(1-oxo-3-phenylpropyl)-4-imidazolidinecarboxylato-κN_3]$Rh_2(4R\text{-MPPIM})_4$

[171007-74-2] $C_{56}H_{60}N_8O_{16}Rh_2$

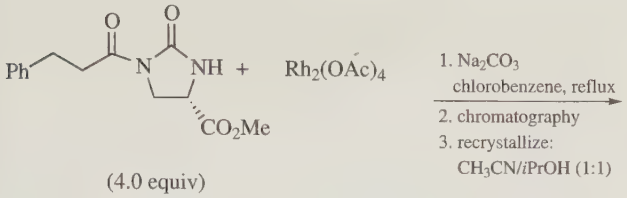
(catalyst used for intramolecular C–H insertion reactions of diazoacetates and hetero-Diels-Alder reactions)

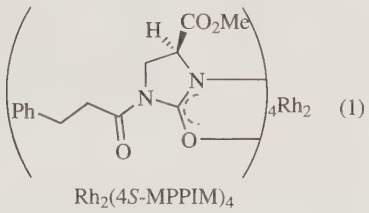
Spectral Data: for $Rh_2(4S\text{-MPPIM})_4$: ^{1}H NMR ($CDCl_3$): $(CH_3CN)_2$ δ 7.28–7.11 (comp, 20 H), 4.08 (dd, J =10.1, 5.0 Hz, 2H), 4.00–3.70 (comp, 10 H), 3.72 (s, 6 H), 3.46 (s, 6 H), 3.32–3.10 (comp, 4 H), 2.98–2.78 (comp, 12 H), 1.84 (s, 6 H, CH_3CN).[1]

Physical Data: $[\alpha]_D^{23} = -311$ (CH_3CN, $c = 0.10$).

Form Supplied in: red-orange prisms as the bis-acetonitrile complex; blue solid after removal of the axial nitrile ligands.

Preparative Method: ligand exchange between dirhodium(II) tetraacetate by methyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(*S*)-carboxylate. $Rh_2(4R\text{-MPPIM})_4$ is synthesized by using the (*R*)-enantiomer of the ligand (eq 1).





(1)

$Rh_2(4S\text{-MPPIM})_4$

Handling, Storage, and Precautions: air stable, stored in a desiccator, weakly hygroscopic

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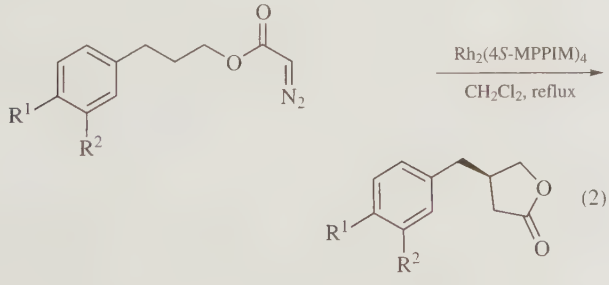
Preparation. Dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(*S*)-carboxylate], $Rh_2(4S\text{-MPPIM})_4$, was prepared from dirhodium(II) tetraacetate. The preferred procedure is to effect ligand exchange with dirhodium tetraacetate and 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(*S*)-carboxylate in refluxing chlorobenzene; liberated acetic acid is trapped by sodium carbonate in a Soxhlet extraction apparatus. Four methyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(*S*)-carboxylate molecules ligate one dirhodium(II) nucleus. The two nitrogen and two oxygen atoms are arranged in a *cis* configuration. Under the reaction conditions the (2,2-*cis*)- and (3,1)-isomers reach equilibrium at 85:15. A third isomer (4,0)-$Rh_2(MPPIM)_4$, in which each rhodium has all nitrogen or all oxygen atom attachments, is also formed; however, the amount of the (4,0)-isomer does not exceed 5% of the total.[1,2]

Asymmetric Intramolecular C–H Insertion. Enantiomerically pure β-substituted γ-butyrolactones are synthesized via intramolecular insertion into nonactivated C–H bonds promoted by dirhodium(II) carboxamidates. $Rh_2(4S\text{-MPPIM})_4$ or its enantiomer, $Rh_2(4R\text{-MPPIM})_4$ is the preferred catalyst for intramolecular C–H insertion reactions of 3-aryl-1-propyl diazoacetates which lead to lignan lactones (eq 2, Table 1).[3,4] $Rh_2(4S\text{-MPPIM})_4$ is also employed for the synthesis of enterolactone, hinokinin, isodeoxypodophyllotoxin, isolauricerisinol, and arctigenin via γ-lactone products with enantioselectivities up to 96% ee. β-Lactone by-products are formed in <5%, which demonstrates the exceptional regiocontrol provided by the catalyst.

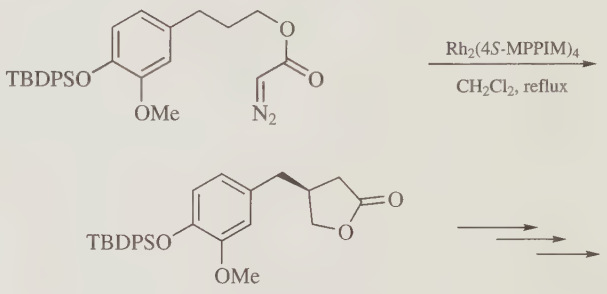


(2)

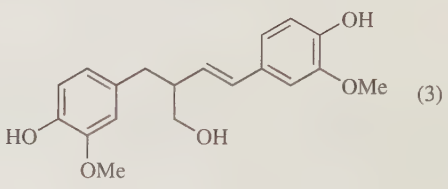
Another application of this methodology is seen in the total synthesis of (*S*)-(+)-imperanene,[5] which involves an enantioselective carbon-hydrogen insertion reaction from a diazoacetate derived from 4-hydroxy-3-methoxycinnamic acid.[6] The catalytic C–H insertion reaction occurred in 93% ee (eq 3, TBDPS = *tert*-butyldiphenylsilane).

Table 1 $Rh_2(4S\text{-MPPIM})_4$-catalyzed intramolecular C–H insertion

R^1	R^2	Yield (%)	ee (%)
OMe	OMe	62	94
OCH_2O	OCH_2O	67	97
H	H	56	91



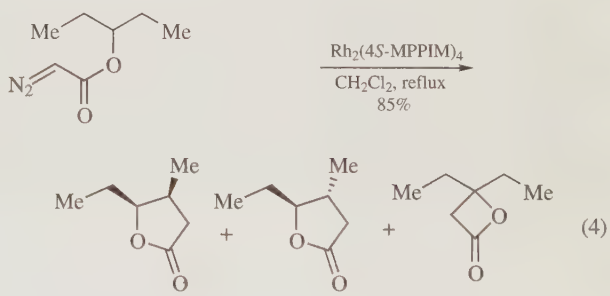
68%, 93% ee



(3)

Imperanene

Further synthetic advantages of the $Rh_2(4S\text{-MPPIM})_4$ catalyst are evident in the highly enantio-, diastereo-, and regioselective catalytic C–H insertion reaction of 3-pentyl diazoacetate (eq 4).[7] While three products are possible, one is formed preferentially in high enantiomeric excess and yield.



(4)

1 **2** **3**

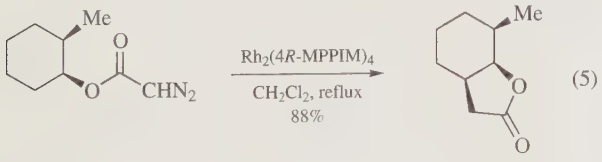
Ratio **1:2:3** = 92:3:5

1 = 99% ee

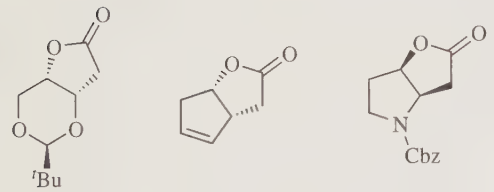
$Rh_2(4R\text{-MPPIM})_4$ has also been employed in the diastereoselective and regioselective C–H insertion reaction of chiral *cis*-2-methylcyclohexyl diazoacetate (eq 5).[8] Using only 0.1 mol % of $Rh_2(4R\text{-MPPIM})_4$, the C–H insertion of the diazoacetate occurs in 88% yield with a high diastereomeric ratio and with only 2% of the β-lactone by-product present (eq 5). However, when the configurationally mismatched catalyst is used, a mixture of products is observed.

The C–H insertion methodology has also been employed for the formation of lactones **4–6** with high levels of enantio-, regio-,

and diastereocontrol from the corresponding diazoacetate in the presence of $Rh_2(MPPIM)_4$ catalysts. The diazoacetate precursor used to produce **4** fixes the conformation of the reactant carbene providing **4** in 91% ee and 59% yield.[9] Lactone **5** was generated in high enantiomeric excess (91% ee) via an intramolecular insertion into an allylic C–H bond.[10] Insertion to form the *cis*-bicyclic lactone **6** (78% yield) is preferred over dimer formation due to activation of the C–H bond by the adjacent carbamoyl nitrogen atom.[11]

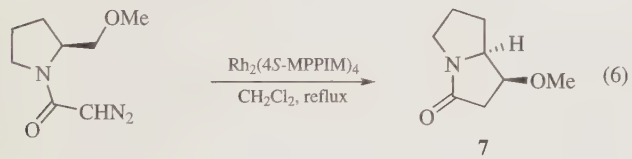


(5)



4 **5** **6**

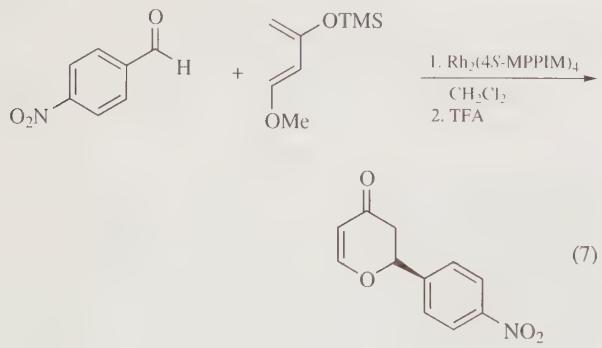
(1*S*,7a*S*)-1-Methoxyhexahydro-3*H*-pyrrolizin-3-one (**7**) has been prepared with high regio- and diastereocontrol from the diazoacetamide in 97% yield with a diastereomeric ratio of 97:3 (eq 6).[12]



(6)

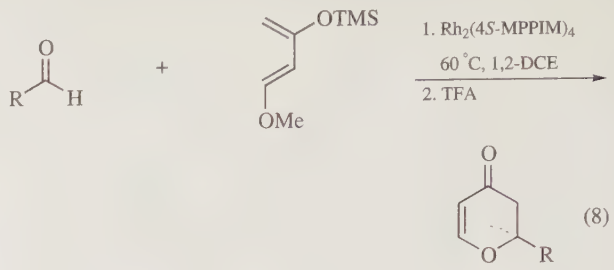
7

Asymmetric Hetero-Diels-Alder Reaction. $Rh_2(4S\text{-}MPPIM)_4$ is an effective Lewis acid for the hetero-Diels-Alder reaction.[13] Even with substrate-to-catalyst ratios as high as 10,000:1, the $Rh_2(4S\text{-}MPPIM)_4$-catalyzed hetero-Diels-Alder reaction between *p*-nitrobenzaldehyde and the Danishefsky diene was carried out efficiently in good yields and excellent enantioselectivities (eq 7).



(7)

The amount of dihydropyran formed increased at temperatures up to 60 °C without markedly affecting the enantioselectivity.[14] Enantioselectivities as high as 98% ee were routinely achieved with various substituted aromatic aldehydes and Danishefsky's diene catalyzed by 1.0 mol % $Rh_2(4S\text{-}MPPIM)_4$ under solvent free and desiccant free reaction conditions (eq 8, Table 2).



(8)

Table 2 $Rh_2(4S\text{-}MPPIM)_4$-catalyzed asymmetric hetero-Diels-Alder reaction at 60 °C

R	Yield (%)	ee (%)
p-FC_6H_4	82	96
C_6H_5	91	93
2-Naphthyl	90	98
m-$NO_2C_6H_4$	66	95

A kinetic analysis revealed the electronic influence on the rate of the reaction where the electron withdrawing *para*-nitrobenzaldehyde reacts 722 times faster than the electron rich *para*-methoxybenzaldehyde giving a Hammett ρ value of +1.9.[14] The measured association constants reveal that *para*-methoxybenzaldehyde (74 M^{-1}) is bound to the $Rh_2(4S\text{-}MPPIM)_4$ catalyst more tightly than *para*-nitrobenzaldehyde (6 M^{-1}) leading to inhibition by the reacting aldehyde. Neither reactant diene nor product show evidence for coordination with $Rh_2(4S\text{-}MPPIM)_4$.

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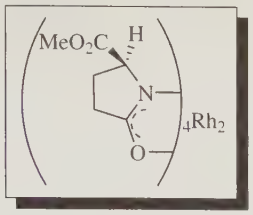
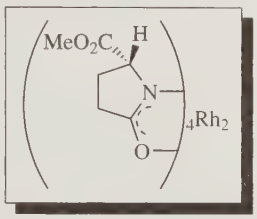
Dirhodium(II) Tetrakis[methyl 2-oxapyrrolidine-carboxylate]



Dirhodium(II) tetrakis[methyl 2-oxapyrrolidine-5(*R*)-carboxylate] $Rh_2(5R\text{-MEPY})_4 \bullet 2\ CH_3CN$

[131796-58-2] $C_{28}H_{38}N_6O_{12}Rh_2$ (MW 856.45)



Dirhodium(II) tetrakis[methyl 2-oxapyrrolidine-5(*S*)-carboxylate] $Rh_2(5S\text{-MEPY})_4 \bullet 2\ CH_3CN$

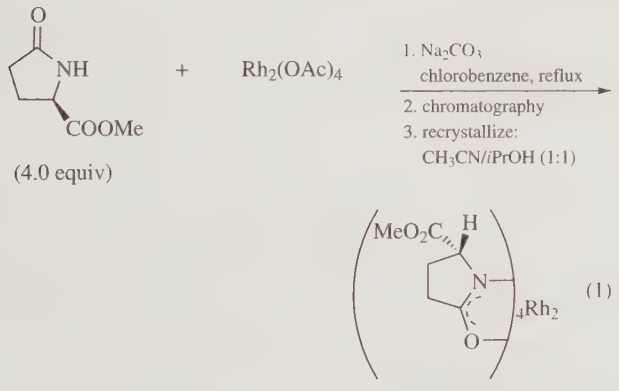
[132435-65-5] $C_{28}H_{38}N_6O_{12}Rh_2$ (MW 856.45)

(catalyst used for the decomposition of diazoacetates and diazoacetamides)

Spectral Data: for $Rh_2(5R\text{-MEPY})_4$: ^1H NMR ($CDCl_3$, 300 MHz): δ 4.32 (dd, $J = 8.8, 3.0$ Hz, 2H), 4.08–3.96 (m, 1H), 3.95 (dd, $J = 8.6, 2.1$ Hz, 2H), 3.70 (s, 6H), 3.68 (s, 6H), 2.70–2.55 (m, 4H), 2.26 (s, 6H), 1.8–2.4 (m, 12H), 1.35 (d, $J = 4.4$ Hz, 1H), 1.21 (d, $J = 6.1$ Hz, 6H).[1]

Physical Data: $[\alpha]_D^{23} = +259.5$ (CH_3CN, c = 0.098).

Preparative Methods: ligand exchange between dirhodium(II) tetraacetate by methyl 2-oxapyrrolidine-5(*R*)-carboxylate (eq 1).[2,3]



(1)

$Rh_2(5R\text{-MEPY})_4$

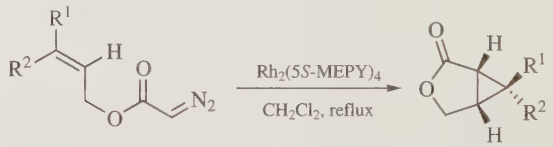
Form Supplied in: red crystalline solid as bis-acetonitrile complex, purple solid after removal of nitrile ligands.

Handling, Storage, and Precautions: air stable, weakly hygroscopic, store in a desiccator. The bis-acetonitrile complex is stable indefinitely.[2]

Preparation. Dirhodium(II) tetrakis[methyl 2-oxapyrrolidine-5(*R*)-carboxylate], $Rh_2(5R\text{-MEPY})_4$, was prepared from dirhodium(II) tetraacetate. The preferred procedure is to effect ligand substitution on $Rh_2(OAc)_4$ with methyl 2-oxapyrrolidine-5(*R*)-carboxylate in refluxing chlorobenzene; liberated acetic acid is trapped by sodium carbonate in a Soxhlet extraction apparatus. Four methyl 2-oxopyrrolidine-5(*R*)-carboxylate molecules ligate one dirhodium(II) nucleus; each rhodium is bound to two nitrogen and two oxygen donor atoms arranged in a *cis* geometry.[2,3] $Rh_2(5S\text{-MEPY})_4$ is synthesized by using the (*S*)-enantiomer of the ligand.

Asymmetric Cyclopropanation. $Rh_2(MEPY)_4$ was first synthesized by the Doyle group in the early nineties.[4] Its initial use was as a catalyst for asymmetric intermolecular cyclopropanation in which modest asymmetric induction was achieved with *d*-menthyl diazoacetate and styrene.[4]

The $Rh_2(MEPY)_4$ catalysts are most beneficial for intramolecular asymmetric cyclopropanation of substituted allylic and homoallylic diazoacetates.[5] Cyclic lactones obtained from $Rh_2(5S\text{-MEPY})_4$-catalyzed cyclopropanation were generated in high yields and excellent enantioselectivities (eq 2, Table 1).

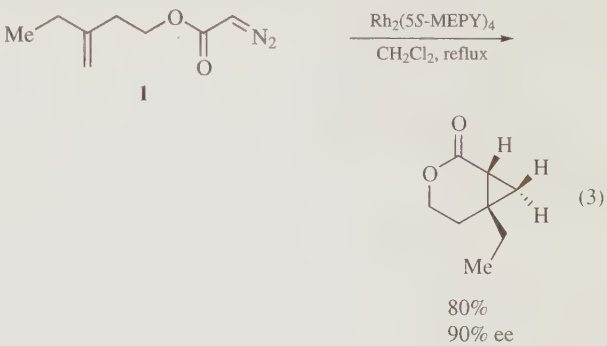


(2)

Table 1 $Rh_2(5S\text{-MEPY})_4$ catalyzed intramolecular cyclopropanation of allylic diazoacetates

R^1	R^2	Yield (%)	ee (%)
H	H	75	95
$(CH_3)_2C{=}CH(CH_2)_2$	CH_3	88	95
CH_3	CH_3	89	98
H	Bn	80	≥94
H	Ph	70	≥94

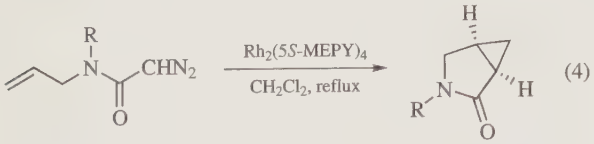
$Rh_2(MEPY)_4$catalysts were also employed for enantioselective intramolecular cyclopropanation of homoallylic diazoacetates, initially by Martin (eq 3).[6] For example, the intramolecular cyclopropanation product from catalytic diazo decomposition of 3-ethylbut-3-enyl-diazoacetate (**1**) was generated with high enantiocontrol. More extensive results were reported by Doyle and Martin.[5]



(3)

Highly enantioselective intramolecular cyclopropanation has also been realized for *N*-allylic diazoacetamides (eq 4).[5,7] Reactions of *N*-allyl-*N*-methyldiazoacetamide (R = Me) under $Rh_2(5S\text{-MEPY})_4$ catalysis provided the highest level of enantiocontrol, but

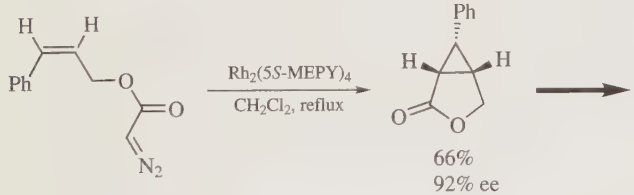
other dirhodium(II) carboxamidate catalysts were more chemoselective. Competitive intramolecular dipolar cycloaddition led to diminished yields when R = H.



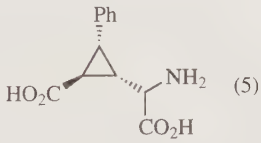
(4)

62%
93% ee
when R = Me

Pellicciari has utilized $Rh_2(5S\text{-MEPY})_4$ for the synthesis of enantiomerically pure (2*S*,1′S,2′*S*,3′*R*)-phenylcarboxycyclopropylglycine (PCCG-4).[8] The cyclopropyl derivative was generated in 66% yield and 92% ee (eq 5).



66%
92% ee

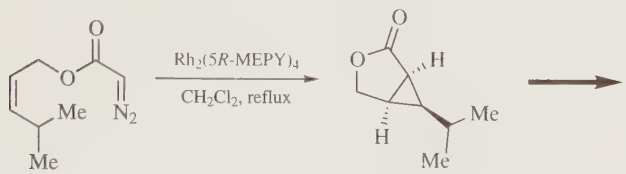


(5)

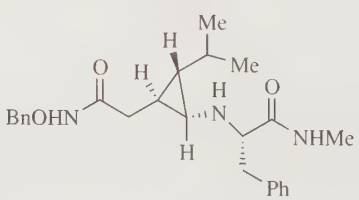
PCCG-4

$Rh_2(5S\text{-MEPY})_4$ has been compared to copper *tert*-butyl-box (box = 2,2′-isopropylidinebis[(4*S*)-4-*tert*-butyl-2-oxazoline]) and ruthenium isopropyl-pybox (pybox = 2,6-bis[4(*S*)-isopropyl-2-oxazolin-2-yl]pyridine) catalysts for the intramolecular cyclopropanation of allylic diazoacetates.[9] The dirhodium carboxamidate catalyst outperformed both ruthenium and copper catalysts for all cases examined.

The synthesis of peptidomimetic precursors has been achieved using $Rh_2(5R\text{-MEPY})_4$.[10] The synthesis of (1*S*,5*R*,6*S*)-6-isopropyl-3-oxabicyclo[3.1.0]hexan-2-one (**2**) via intramolecular cyclopropanation was carried out in 90% yield and 92% ee. The cyclopropane adduct was later used to introduce conformational strain into the backbone and side chain of a dipeptide array (eq 6).

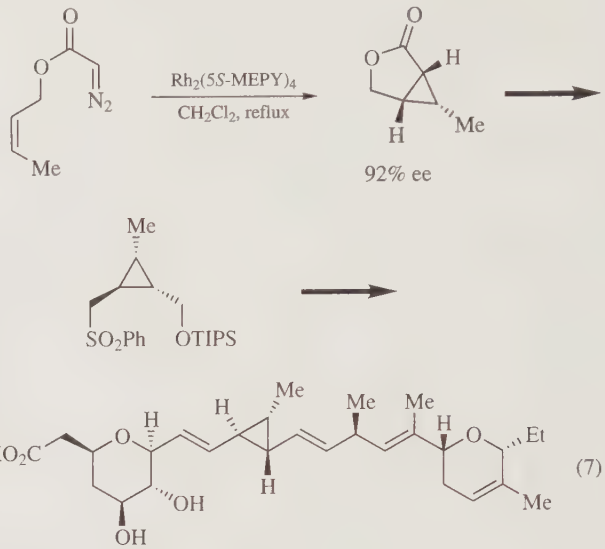


2
92% ee



(6)

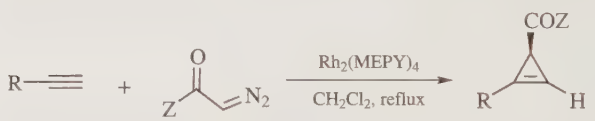
$Rh_2(5S\text{-MEPY})_4$ has been utilized in the total synthesis of (+)-ambruticin S, an antifungal antibiotic.[11] As one of three key steps in the synthesis, Martin employed $Rh_2(5S\text{-MEPY})_4$-catalyzed enantioselective cyclopropanation. The cyclopropanation proceeded in 80% yield and 92% ee (eq 7).



(7)

(+)-Ambruticin S

Asymmetric Cyclopropenation. Catalytic, asymmetric *intermolecular* cyclopropenation of substituted alkynes has been demonstrated (eq 8, Table 2).[12] Using diazoacetate esters and *N,N*-dimethyldiazoacetamide as diazo carbonyl sources, moderate to high enantioselectivities were attained with catalytic amounts of $Rh_2(MEPY)_4$. Enantioselectivities of up to 98% were achieved.



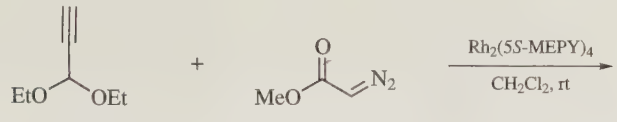
(8)

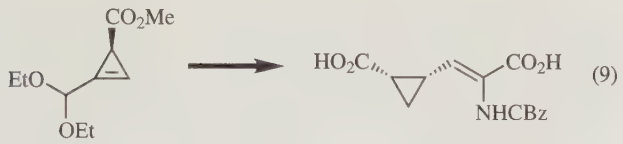
Table 2 $Rh_2(MEPY)_4$-catalyzed intermolecular cyclopropenation of acetylenes

Catalyst	Z	R	Yield (%)	ee (%)
$Rh_2(5S\text{-MEPY})_4$	OMe	$CH(OEt)_2$	42	>98
$Rh_2(5R\text{-MEPY})_4$	NMe_2	CH_2OMe	22	>98
$Rh_2(5R\text{-MEPY})_4$	NMe_2	*t*-Bu	47	89

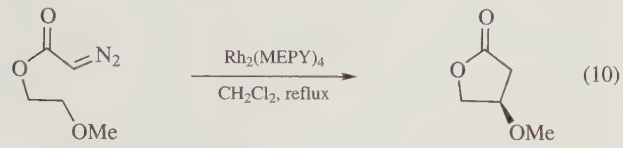
Müller and co-workers have realized intermolecular cyclopropenation of 1,1-diethoxy-2-propyne (**3**) for the synthesis of cyclopropyl-dehydroamino acids.[13] When diethoxypropyne was reacted with methyl diazoacetate in the presence of $Rh_2(5S\text{-MEPY})_4$, the cyclopropene adduct was obtained in >95% ee (eq 9). The reaction was carried out at room temperature.

Asymmetric C–H Insertion. Five-membered cyclic lactones have been synthesized via intramolecular C–H insertion.[14] With 2-methoxyethyl diazoacetate (**4**), both enantiomers of $Rh_2(MEPY)_4$ catalyzed intramolecular C–H insertion with high enantioselectivity (eq 10). Competing dimerization and azine formation, which often occurred with $Rh_2(OAc)_4$, were suppressed in the presence of the $Rh_2(MEPY)_4$ catalysts.



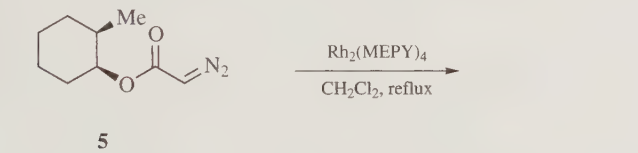


85%, >95% ee



$Rh_2(5S\text{-MEPY})_4$: 40%, 91% ee
$Rh_2(5R\text{-MEPY})_4$: 56%, 91% ee

$Rh_2(5S\text{-MEPY})_4$and $Rh_2(5R\text{-MEPY})_4$ have been investigated for the synthesis of bicyclic lactones via intramolecular C–H insertion.[1] When enantiomeric diazoacetates **5** and **5a** were reacted in the presence of $Rh_2(MEPY)_4$, outstanding chemo- and regioselectivities were observed (eq 11). Product distribution differed according to the enantiomer of $Rh_2(MEPY)_4$ utilized (Table 3).



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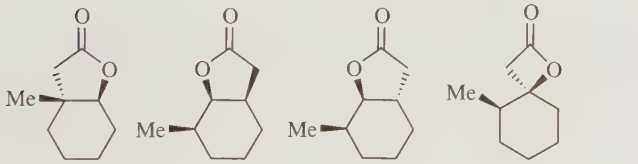
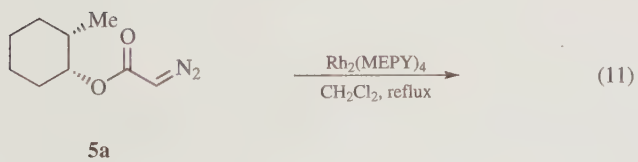
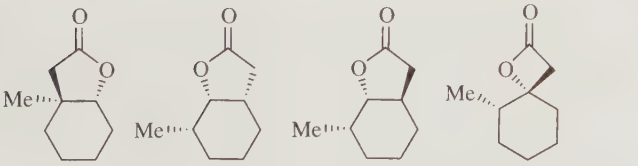


6 **7** **8** **9**



5a

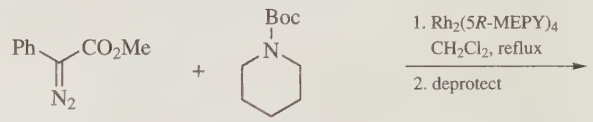


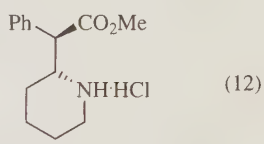
6a **7a** **8a** **9a**

Winkler and co-workers have used $Rh_2(5R\text{-MEPY})_4$ for the intermolecular C–H insertion of phenyldiazoacetate into substituted pyrrolidones.[15] The synthesis of Ritalin® was achieved in two steps using this methodology (eq 12). $Rh_2(5R\text{-MEPY})_4$ outperformed all other chiral dirhodium(II) carboxamidate catalysts screened, including azetidinone and imidazolidinone catalysts, generating the C–H insertion product in 95% ee and 94% de.

Table 3 $Rh_2(5S\text{-MEPY})_4$-catalyzed intramolecular C–H insertion of 2-methylcyclohexyl diazoacetate

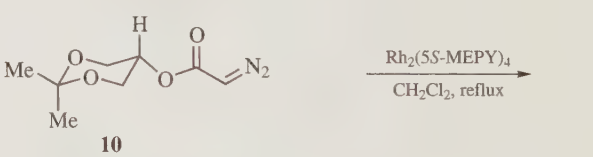
		Isolated yield	Relative yield			
			6	**7**	**8**	**9**
5	$Rh_2(5S\text{-MEPY})_4$	95	94	1	trace	5
	$Rh_2(5R\text{-MEPY})_4$	79	4	91	3	2
			6a	**7a**	**8a**	**9a**
5a	$Rh_2(5S\text{-MEPY})_4$	86	5	90	3	2
	$Rh_2(5R\text{-MEPY})_4$	74	92	3	0	5





95% ee after two recrystallizations

Stevens Rearrangement. Symmetrical 1,3-dioxan-5-yl (**10**) diazoacetates undergo conformation dependent oxonium ylide formation, competitive with C–H insertion, eventually leading to Stevens rearrangement products (eq 13).[16] $Rh_2(5S\text{-MEPY})_4$-catalyzed Stevens rearrangement occurred in 12% yield and 55% ee. The observed ratio of C–H insertion to [1,2] rearrangement was 22:78 in favor of C–H insertion. Diastereotopic association of the metal carbene at one of the two dioxolane oxygens is suggested to be the source of enantiocontrol.



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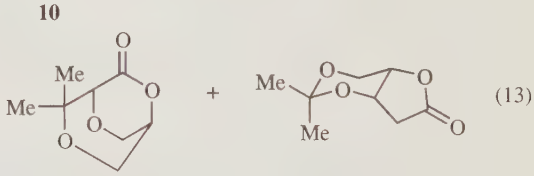

[1,2] rearrangement
12%, 55% ee

C–H insertion
41%, 85% ee

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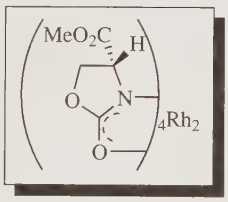
Dirhodium(II) Tetrakis[methyl 2-oxo-oxazolidine-4(*S*)-carboxylate]

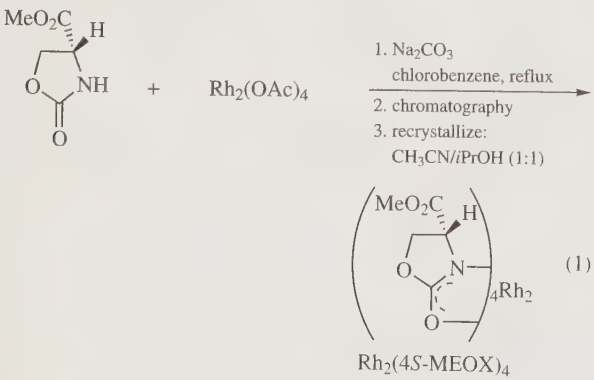


[167693-36-9] $C_{24}H_{30}N_6O_{16}Rh_2$ (MW 864.35)

(catalyst used for the decomposition of stablized diazo species and diazomalonate esters)

Physical Data: mp 293 °C, $[\alpha]_D^{25} = -222°$ (c 0.120, CH_3CN).

Preparative Methods: ligand exchange between dirhodium(II) tetraacetate by methyl (4*S*)-2-oxo-1,3-oxazolidine-4-carboxylate.[1,2] Rh_2(4*R*-MEOX)$_4$ is synthesized by using the *R*-enantiomer of the ligand (eq 1).[1]



(1)

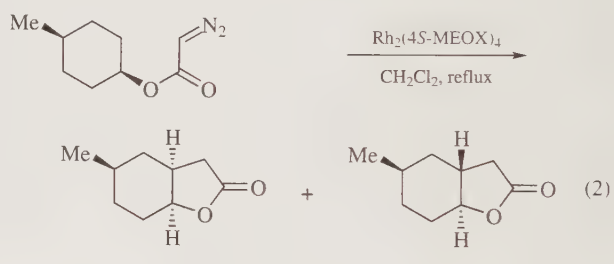
Rh_2(4*S*-MEOX)$_4$

Form Supplied in: red crystalline solid as bis-acetonitrile complex, purple solid after removal of nitrile ligands.

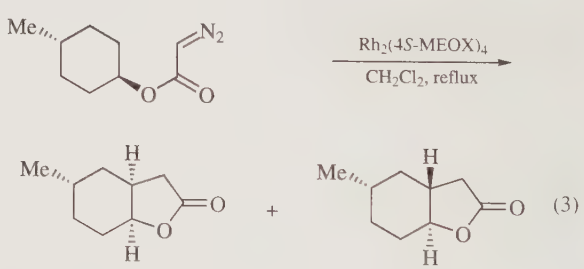
Handling, Storage, and Precautions: air stable, weakly hygroscopic, stored in desiccator.

Preparation. Dirhodium(II) tetrakis[methyl-2-oxooxazolidine-4(*S*)-carboxylate], Rh_2(4*S*-MEOX)$_4$, was prepared from dirhodium(II) tetraacetate. The preferred procedure is to effect ligand substitution on $Rh_2(OAc)_4$ with methyl (4*S*)-2-oxooxazolidine-4-carboxylate in refluxing chlorobenzene; liberated acetic acid is trapped by sodium carbonate in a Soxhlet extraction apparatus. Four methyl (4*S*)-2-oxooxazolidine-4-carboxylate molecules ligate one dirhodium(II) nucleus; each rhodium is bound to two nitrogen and two oxygen donor atoms arranged in a *cis* geometry.[1,2] Rh_2(4*R*-MEOX)$_4$ is synthesized by using the (*R*)-enantiomer of the ligand.

Intramolecular C–H Insertion. Rh_2(4*S*-MEOX)$_4$ is an effective catalyst for intramolecular C–H insertion with diazoesters.[3] Along with very high asymmetric induction, the catalyst also influences regioselectivity and diastereoselectivity (eqs 2 and 3).[4]

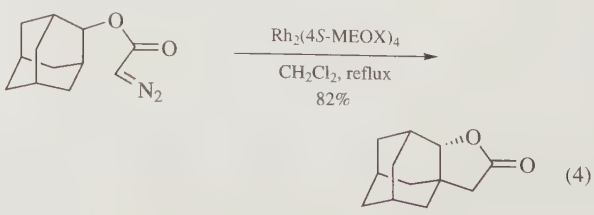


>99 (98% ee) < 1

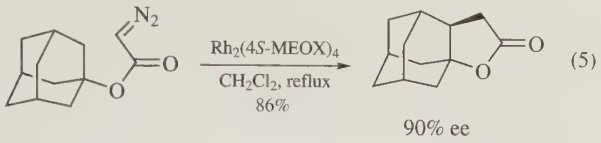


10 (68% ee) 90 (95% ee)

The open framework of the Rh_2(MEOX)$_4$ catalysts is found to be ideal for the intramolecular C–H insertion of sterically hindered substrates [1,5] (eqs 4 and 5).

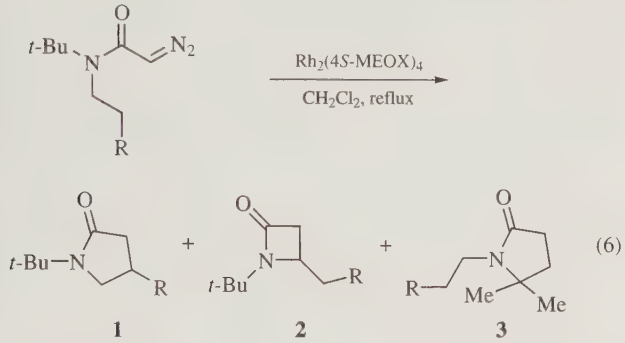


98% ee



(5)

The intramolecular C–H insertion of metal carbenes derived from diazoacetamides gives lactams. Although C–H insertion is activated by the amide nitrogen, β-lacam formation is generally preferred if access to the γ-C–H bond is sterically impeded (eq 6, Table 1).[6]

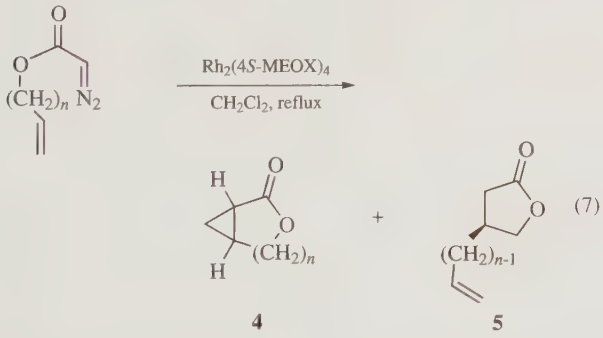


(6)

Table 1 $Rh_2(4S\text{-MEOX})_4$-catalyzed intramolecular C–H insertion of diazoacetamides

		Ratio		
		1Yield	**2**Yield	**3**Yield
R	Yield(%)	ee(%)	ee(%)	ee(%)
OEt	97	100,78	0	0
Et	82	91,71	9,80	0
COOEt	97	2	25, 46	73

As seen in eq 7, $Rh_2(4S\text{-MEOX})_4$-catalysis favors C–H insertion over cyclopropanation when rings larger than five are formed by cyclopropanation (eq 7). Compared to other dirhodium (II) catalysts, $Rh_2(4S\text{-MEOX})_4$ displays a remarkable proclivity for C–H insertion when there is an opportunity for other processes to occur (Table 2).[7]

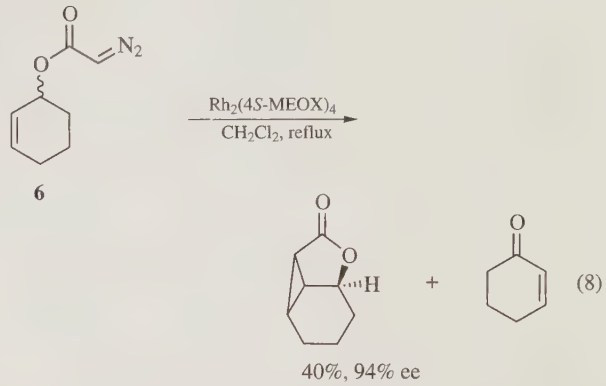


(7)

Table 2 $Rh_2(4S\text{-MEOX})_4$-catalyzed intramolecular C–H insertion versus cyclopropanation

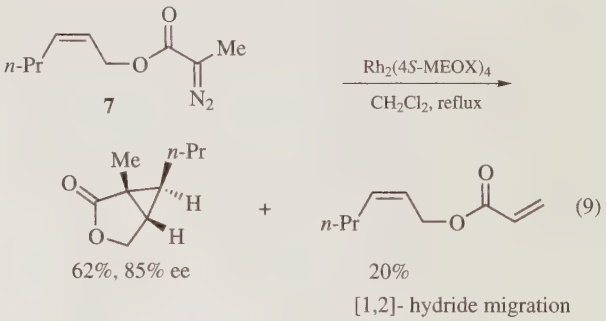
n	**4** Yield(%)	**5** Yield, ee(%)
3	19	81, 98
2	9	91, 97

Intramolecular Cyclopropanation. $Rh_2(4S\text{-MEOX})_4$ has been used for product resolution in the intramolecular cyclopropanation of racemic 2-cyclohexen-1-yl diazoacetate (**6**) (eq 8).[8] In this case, one enantiomer of the diazocarbonyl moiety was matched with $Rh_2(4S\text{-MEOX})_4$ and formed the cyclopropanation product predominantly while the other enantiomer underwent hydride abstraction. Müller has recently employed this methodology for the synthesis of optically active (*1S,5R*)-(+)-3-azabicyclo[3.3.2]non-6-en-2-one from racemic cyclohexen-3-yl diazoacetate.[9]



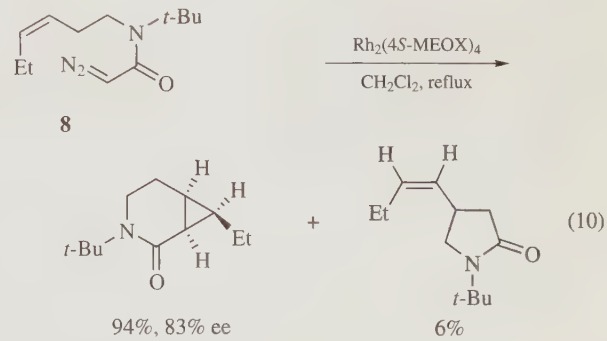
(8)

Excellent enantiocontrol has been achieved for intramolecular cyclopropanation of *cis*-disubstituted allylic α-diazopropionates (**7**) using $Rh_2(4S\text{-MEOX})_4$ (eq 9). The high enantiocontrol observed with $Rh_2(4S\text{-MEOX})_4$ is reported to be due, at least in part, to the openness of the volume segment of the catalyst that can accommodate the methyl substituent of the carbene. Relative to other dirhodium(II) carboxamidate catalysts, competing 1,2-hydride migration was higher in reactions with $Rh_2(4S\text{-MEOX})_4$.[10]



(9)

$Rh_2(4S\text{-MEOX})_4$ has also been employed for the intramolecular cyclopropanation of homoallylic diazoacetamides (**8**) (eq 10).[11] C–H insertion was minor when *N*-(*tert*-butyl)-2-diazo-*N*-[(3*Z*)-hept-3-enyl]acetamide was exposed to $Rh_2(4S\text{-MEOX})_4$ at 1.0 mol % catalyst loading (94:6 in favor of cyclopropanation).



(10)

Ylide Formation and Reactions. Allylic oxonium ylides, generated in situ by the $Rh_2(4S\text{-MEOX})_4$-catalyzed decomposition of ethyl diazoacetate (EDA), in the presence of cinnamyl methyl ether undergo highly diastereoselective [2,3] sigmatropic rearrangement with phenomenal enantiocontrol.[12] The ratio of products derived from ylide rearrangement (**9** and **10**) to cyclopropanation (**11**) was found to be 89:11 with the *threo* isomer (**10**) being predominant (eq 11). Both the diastereomers were formed with high enantioselectivity (Table 3). Involvement of metal-associated ylide in the [2,3] sigmatropic rearrangement was invoked to explain extraordinary enantiocontrol. This was the initial report of a highly catalytic enantioselective transformation of an oxonium ylide generated from a metal carbene.

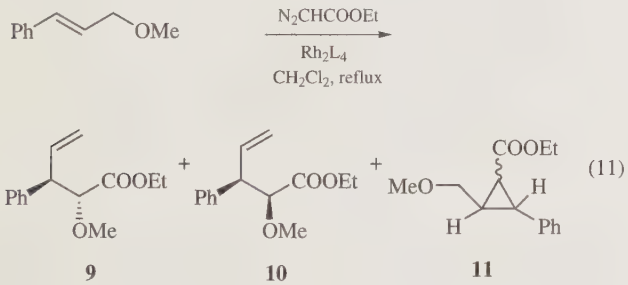


Table 3 Dirhodium(II)-catalyzed ylide transformations

Rh_2L_4	**9** Yield(%)	**10** Yield(%)
$Rh_2(OAc)_4$	83	17
$Rh_2(4S\text{-MEOX})_4$	15 (94% ee)	85 (98%ee)

Hetero-Diels-Alder Reaction. $Rh_2(4S\text{-MEOX})_4$ has been shown to be an efficient Lewis acid for the catalysis of the asymmetric hetero-Diels-Alder (HDA) reaction. Superb yields and enantioselectivities were achieved using catalyst loadings as low as 0.01% with *p*-nitrobenzaldehyde (90% yield and 96% ee), 5-nitrothiophenecarboxaldehyde (96% yield, 97% ee), (Table 4) and the Danishefsky diene (eq 12 Table4).[13]

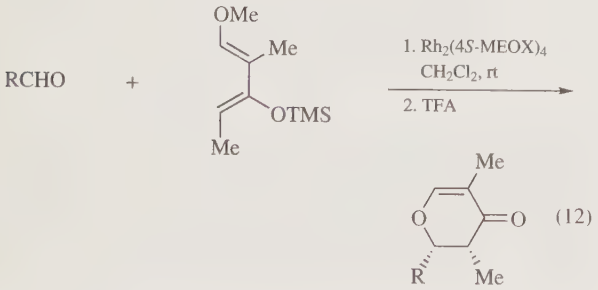


Table 4 $Rh_2(4S\text{-}MEOX)_4$-catalyzed hetero-Diels-Alder reaction

RCHO	Yield(%)	ee(%)
5-nitrothiophenecarboxaldehyde	96	97
p-nitrobenzaldehyde	90	96

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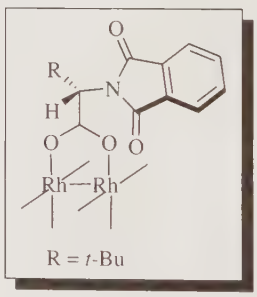
Dirhodium(II) Tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate]



(*S*)-enantiomer
[154090-43-4]
(*R*)-enantiomer
[380375-05-3]

$C_{56}H_{56}N_4O_{16}Rh_2$ (MW 1246)

(chiral catalyst for enantioselective intramolecular C–H insertion reactions, enantioselective intermolecular 1,3-dipolar cycloadditions and enantioselective [2,3] sigmatropic rearrangement)

Alternate Name: $Rh_2[(S)\text{-PTTL}]_4$

Solubility: soluble in dichloromethane, toluene and sparingly soluble in hydrocarbons.

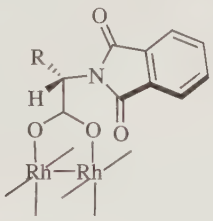
Form Supplied in: green solid.

Preparative Methods: from dirhodium tetraacetate by ligand exchange with *N*-phthaloyl-(*S*)-*t*-leucine according to the method of Callot.[1]

Purification: the title compound can be readily purified by column chromatography on silica gel with a hexanes/EtOAc solvent system (3:2) to give a green solid.

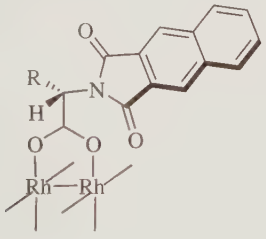
Handling, Storage, and Precautions: air stable but hygroscopic.

Introduction. The title reagent Rh_2[(*S*)-PTTL]$_4$ is a member of a family of dirhodium carboxylate catalysts which incorporate *N*-phthaloyl-(*S*)-amino acids as bridging ligands. These catalysts mediate intramolecular C–H insertions of a structurally diverse array of diazo carbonyl compounds,[2–6] intermolecular Si–H insertions,[7] intermolecular 1,3-dipolar cycloadditions,[8,9] and [2,3] sigmatropic rearrangements[10–13] with high enantioselectivities. Of these catalysts, the *tert*-butyl derivative, Rh_2[(*S*)-PTTL]$_4$ in most instances results in the highest enantioselectivities.

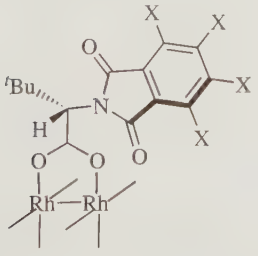


R = *t*-Bu: Rh_2[(*S*)-PTTL]$_4$
R = $C_6H_5CH_2$: Rh_2[(*S*)-PTPA]$_4$ [*131219-55-1*]/[*154171-38-7*]
R = Me: Rh_2[(*S*)-PTA]$_4$ [*131219-56-2*]/[*572890-18-7*]
R = *i*-Pr: Rh_2[(*S*)-PTV]$_4$ [*154090-42-3*]

A second generation of the above Hashimoto catalyst family has been developed by modifying the sterics and electronics of the phthalimido wall. Rh_2[(*S*)-BPTV]$_4$ and Rh_2[(*S*)-BPTTL]$_4$ feature an extension of the phthalimido group with an additional benzene ring. Rh_2[(*S*)-TFPTTL]$_4$ and Rh_2[(*S*)-TCTTL]$_4$ are more electron-deficient catalysts in which the phthalimido hydrogen atoms have been replaced with fluorine and chlorine, respectively.[9]

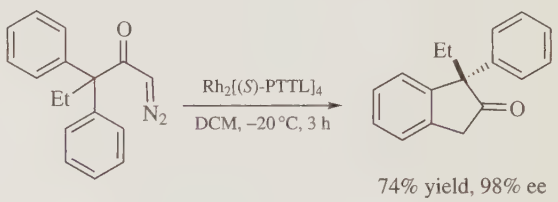


R = ^{i}Pr: Rh_2[(*S*)-BPTV]$_4$ [*221328-00-3*]
R = ^{t}Bu: Rh_2[(*S*)-BPTTL]$_4$ [*221328-03-6*]



X = F: Rh_2[(*S*)-TFPTTL]$_4$ [*564450-56-2*]
X = Cl: Rh_2[(*S*)-TCPTTL]$_4$ [*515876-71-8*]

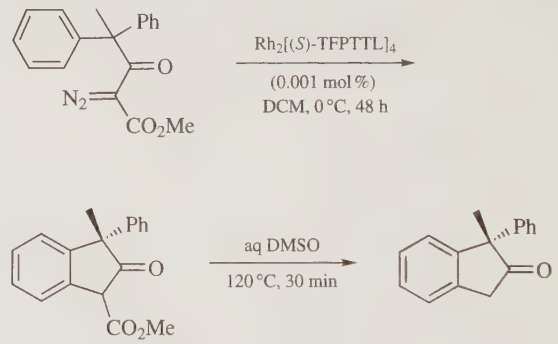
Intramolecular Aromatic C–H Functionalization. Rh_2[(*S*)-PTTL]$_4$ has been shown to be an exceptional chiral catalyst for asymmetric intramolecular C–H insertion reactions.[2–6] It emerged as a catalyst of choice, allowing a generally high order of differentiation of enantiotopic benzene rings via intramolecular aromatic substitution. It catalyzes aromatic substitution reactions of α-diazocarbonyl compounds to give products containing a chiral quaternary carbon in up to 98% ee (eq 1). The effectiveness of this reaction has been demonstrated by the first enantioselective synthesis of FR115427 [(*S*)-(+)-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquininoline hydrochloride], a noncompetitive *N*-methyl-D-aspartate receptor antagonist.[2]



(1)

74% yield, 98% ee

Dirhodium(II) tetrakis[*N*-tetrafluorophthaloyl-(*S*)-*tert*-leucinate] Rh_2[(*S*)-TFPTTL]$_4$ in which the phthalimido hydrogen atoms of the parent dirhodium(II) complex are substituted by fluorine atoms, dramatically enhances the reactivity of the catalyst in intramolecular aromatic C–H insertion reactions of α-diazo-β-keto esters (eq 2). Reactions with catalyst loading as low as 0.001 mol % of Rh_2[(*S*)-TFPTTL]$_4$ have been achieved with turnover numbers up to 98 000.[14]



(2)

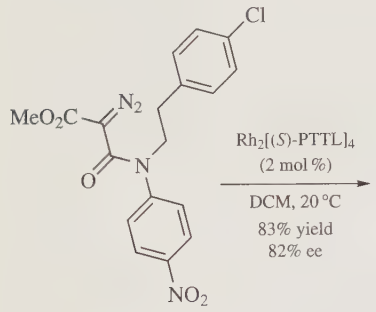
98% yield

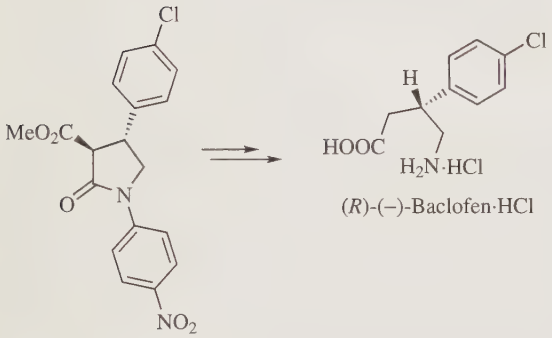
96% yield
97% ee

Intramolecular sp^3 C–H Functionalization. Rh_2[(*S*)-PTTL]$_4$-catalyzed decomposition of α-methoxycarbonyl-α-diazoacetamide leads to 4-substituted 2-pyrrolidinones in up to 82% ee via a site-selective C–H insertion process. The efficiency of this protocol has been verified by a rapid synthesis of (*R*)-(−)-baclofen (eq 3).[3]

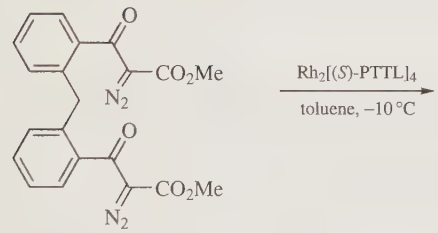
Bifunctional chiral spirans with C_2-symmetry are considered as a promising scaffold for chiral ligands, as they contain a totally rigid spiro backbone which creates an effective chiral environment.[15,16] A highly efficient one-pot construction of optically active 1,1′-spirobi[indan-3,3′-dione]derivative (up to 80% ee) has been achieved by exploiting the double intramolecular C–H insertion reaction under the influence of these dirhodium(II) carboxylates (eq 4).[17] Rh_2[(*S*)-PTTL]$_4$ proved to be the catalyst

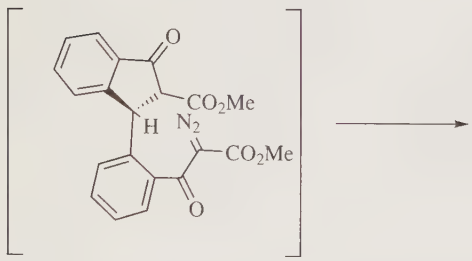
of choice for creating a reasonable degree of enantioselectivity in toluene. This protocol has the advantage of operational simplicity as well as facile entry to optically pure spirans via a single recrystallization, thus providing great potential for their large scale preparation.

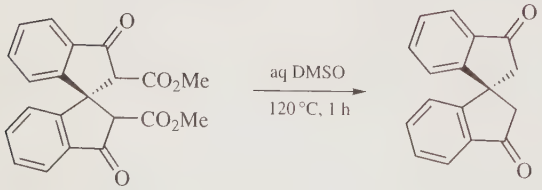




(*R*)-(−)-Baclofen·HCl (3)

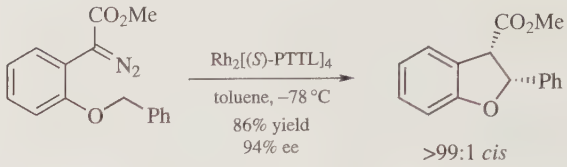






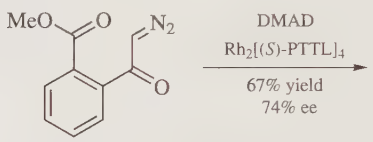
78% overall yield
80% ee (4)

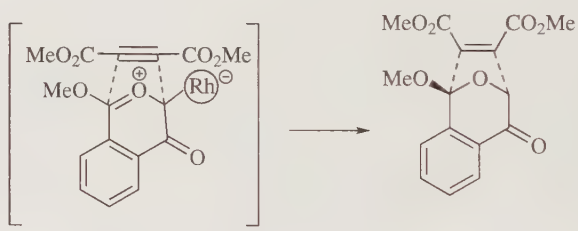
The Rh_2(*S*-PTTL)$_4$-catalyzed intramolecular C–H activation reaction of aryldiazoacetates provides exclusively *cis*-2-aryl-3-methoxycarbonyl-2,3-dihydrobenzofurans in up to 94% ee (eq 5).[4] Aside from exclusive *cis*-selectivity, high enantioselectivity was maintained with either electron-donating or -withdrawing substituents at the *para*-position of the aryl ring. Insertion into a methine C–H bond or a methyl group resulted in much lower enantioselectivity (22% and 44%, respectively).



>99:1 *cis* (5)

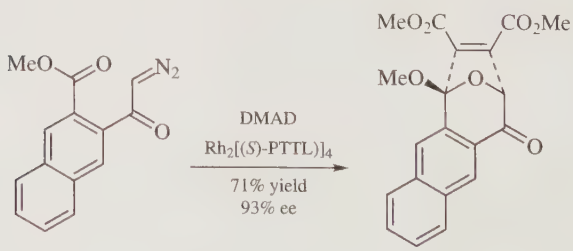
Enantioselective Intermolecular 1,3-Dipolar Cycloadditions. Copper or dirhodium(II)-catalyzed decomposition of α-diazo ketones tethered to a carbonyl group represents one of the important methods for the generation of cyclic carbonyl ylides.[10,11] Hashimoto developed a protocol for 1,3-dipolar cycloadditions via ester-derived carbonyl ylide formation from selected α-diazo ketones in which Rh_2[(*S*)-PTTL]$_4$ has proven to be the catalyst of choice for achieving high enantioselectivity (eq 6).[8,9]





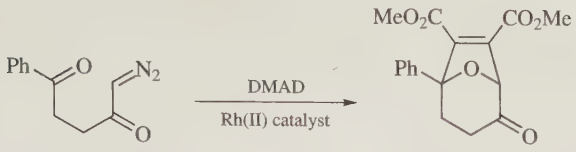
(6)

It is noteworthy that the enantioselectivity is influenced by the sterics of the alkyl group of the amino acid ligands. Rh_2[(*S*)-PTTL]$_4$ containing a bulky *tert*-butyl group proved to be the optimal catalyst. The reaction of methyl 3-diazoacetyl-2-naphthoate with DMAD in the presence of Rh_2[(*S*)-PTTL]$_4$ proceeds smoothly to afford the product in 71% yield and 93% ee (eq 7).



(7)

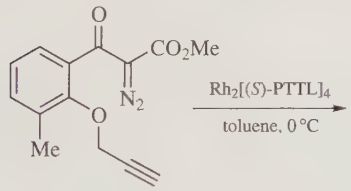
While the mechanistic profile is not clear, the steric nature of the dipolarophile and the shape of the aromatic backbone influence both the enantioselectivity as well as the efficiency of the cycloaddition. In 1,3-dipolar cycloadditions from selected α-diazo ketones Rh_2[(*S*)-BPTV]$_4$ (phthalimido group with an additional benzene ring) proves superior to Rh_2[(*S*)-PTTL]$_4$ (eq 8).[9]

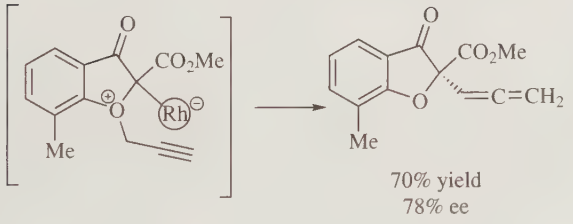


(8)

Entry	Catalyst	Yield (%)	ee (%)
1	$Rh_2[(S)\text{-PTTL}]_4$	80	69
2	$Rh_2[(S)\text{-BPTV}]_4$	79	90

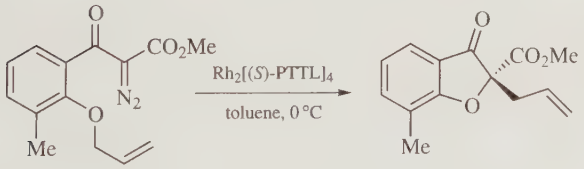
Enantioselective Oxonium Ylide Formation/[2,3] Sigmatropic Rearrangement. The formation of cyclic oxonium ylides from a dirhodium(II) or copper(I)-catalyzed decomposition of diazocarbonyl compounds followed by a [2,3] sigmatropic or [1,2] Stevens rearrangement is a powerful method for the construction of substituted cyclic ethers and carbocycles.[12,15] Hashimoto demonstrated that this reaction can be performed enantioselectively using $Rh_2[(S)\text{-PTTL}]_4$ as catalyst. With this catalyst the ylide formation and [2,3] sigmatropic rearrangement of cyclic allylic and propargylic oxonium ylide from α-diazo-β-keto esters delivered benzofuran-3-ones in high yield and enantioselectivity (eqs 9 and 10).[13]





(9)

70% yield
78% ee

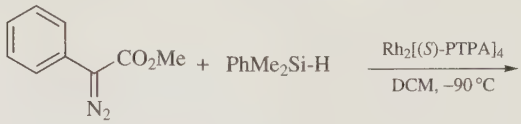


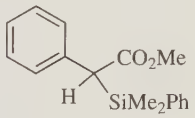
(10)

70% yield
74% ee

Si–H Insertion. Enantioselective insertion reactions of methyl phenyldiazoacetate into the Si–H bond of silanes catalyzed by $Rh_2[(S)\text{-PTPA}]_4$ occur in up to 74% ee (eq 11).[7] $Rh_2[(S)\text{-PTPA}]_4$ catalyzed Si–H insertions of methyl phenyldiazoacetate with Et_3SiH, $PhMe_2SiH$, and Ph_3SiH yielded similar enantioselectivities (65–72% ee).

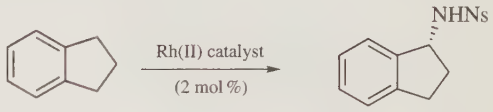
Enantioselective Amidation. $Rh_2[(S)\text{-TCPTTL}]_4$ (in which the phthalimido hydrogen atoms of the parent dirhodium(II) complex are substituted by chlorine atoms) is effective for enantioselective amidation of C–H bonds (eq 12), where this new catalyst exhibits higher reactivity and enantioselectivity (up to 84% ee) than the parent catalyst.[18]





(11)

85% yield
74% ee



(12)

Entry	Rh(II) catalyst	Solvent	Temp. (°C)	Yield (%)	ee (%)
1	$Rh_2[(S)\text{-PTTL}]_4$	CH_2Cl_2	−23	53	27
2	$Rh_2[(S)\text{-TCPTTL}]_4$	CH_2Cl_2	−23	82	70

In summary, the family of $Rh_2[(S)\text{-PTTL}]_4$ reagents have become useful chiral catalysts for a wide variety of carbenoid transformations. High enantioselectivities can be achieved in intramolecular C–H insertions, intermolecular 1,3-dipolar cycloadditions, Si–H insertions, and tandem formation and [2,3] sigmatropic rearrangement of oxonium ylides. An attractive feature of these catalysts is that they are relatively easy to synthesize.[19]

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Dirhodium(II) Tetraoctanoate

$Rh_2(O_2CC_7H_{15})_4$

[73482-96-9] $C_{32}H_{60}O_8Rh_2$ (MW 778.74)

(nonpolar solvent-soluble catalyst for carbenoid reactions of diazo compounds)

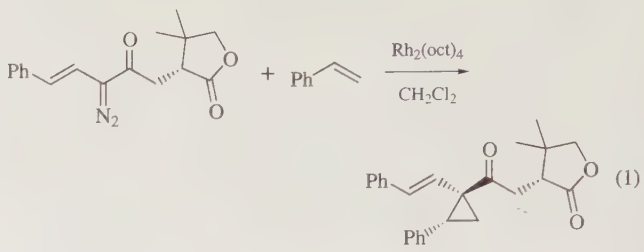
Solubility: sol MeOH, MeCN, Et_2O, CH_2Cl_2, toluene, hexane, pentane.
Form Supplied in: green solid; commercially available.
Preparative Method: prepared by ligand substitution from $Rh_2(OAc)_4$.[1]
Handling, Storage, and Precautions: air stable, weakly hygroscopic; stored in desiccator.

Original Commentary

Michael P. Doyle
University of Maryland, College Park, MD, USA

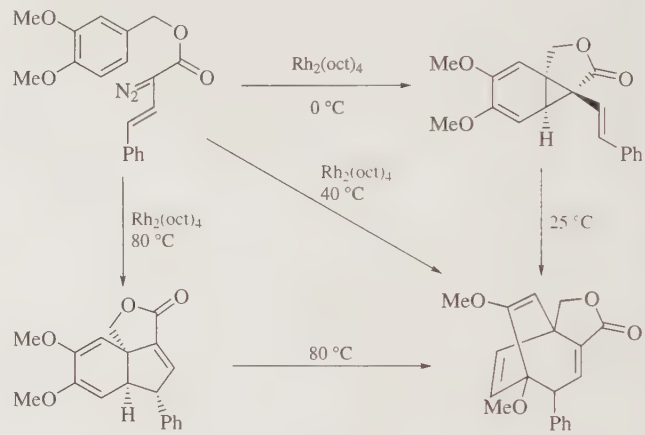
Metal Carbene Transformations. Because of its solubility in organic solvents, dirhodium(II) tetraoctanoate, $Rh_2(oct)_4$, has seen wide use as an alternative for ***Dirhodium(II) Tetraacetate*** as a catalyst for reactions of diazo compounds. However, although $Rh_2(oct)_4$ is initially soluble in relatively nonpolar organic solvents, whereas $Rh_2(OAc)_4$ is not, there are few other advantages to its use as a laboratory scale catalyst. Thus $Rh_2(OAc)_4$ can be chromatographically separated on silica or alumina from reaction products, but $Rh_2(oct)_4$ is often resistant to chromatographic separation.

Temperature Effects. Uses of $Rh_2(oct)_4$ for catalytic reactions with diazo compounds parallel those of $Rh_2(OAc)_4$.[2,3] Although product yields are higher with $Rh_2(OAc)_4$, use of $Rh_2(oct)_4$ at 0 °C in dichloromethane causes exceptionally high diastereocontrol (97% de) for the intermolecular cyclopropanation of styrene by the (*R*)-(−)-pantolactone ester of *trans*-2-diazo-4-phenyl-3-butenoate (eq 1).[4] Here temperature seems to be important since in refluxing dichloromethane both $Rh_2(OAc)_4$ and $Rh_2(oct)_4$ gave this cyclopropane product with a diastereomeric excess of 88 ± 1%.



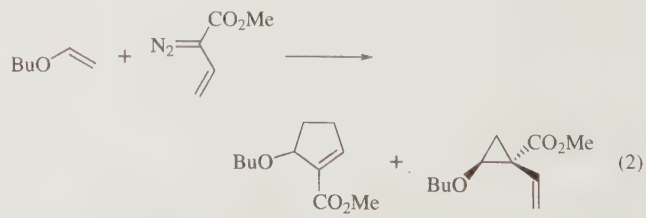
(1)

Temperature control in $Rh_2(oct)_4$-catalyzed reactions of a vinyldiazomethane (Scheme 1) in CH_2Cl_2 (0 and 40 °C) or benzene (80 °C) affords selective entry to intramolecular aromatic cycloaddition (0 °C), [3+4] annulation (40 °C), and [3+2] annulation (80 °C).[5]



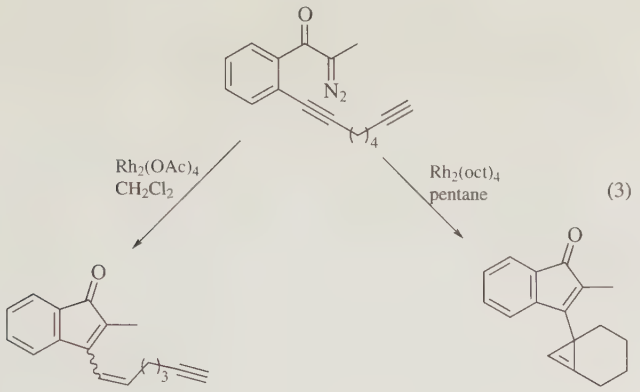
Scheme 1

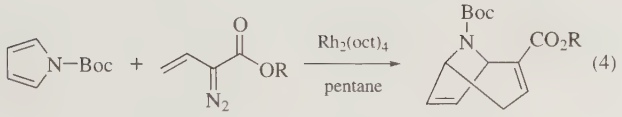
Solvent Effects. Use of $Rh_2(oct)_4$ in pentane significantly influences product control in catalytic carbenoid reactions. Cyclopropanation occurs to the exclusion of [3+2] annulation in reactions of vinyldiazomethanes with vinyl ethers (eq 2); with $Rh_2(OAc)_4$ in dichloromethane, both products are formed.[6] Intramolecular reactions of diazo ketones show a similar solvent dependence with systems designed for tandem cyclopropenation/vinylcarbene formation/cyclopropenation versus hydrogen migration (eq 3).[7] In other cases the influence of solvent on selectivity is not as great,[8,9] but for the synthesis of tropanes the use of $Rh_2(oct)_4$ in pentane has advantages not demonstrated by $Rh_2(OAc)_4$ in dichloromethane (eq 4).[10] Solvent control of the reaction pathway is associated with the degree of charge development in the transition state for the carbenoid reaction.



(2)

$Rh_2(oct)_4$, pentane	0%	91%
$Rh_2(OAc)_4$, CH_2Cl_2	24%	37%





First Update

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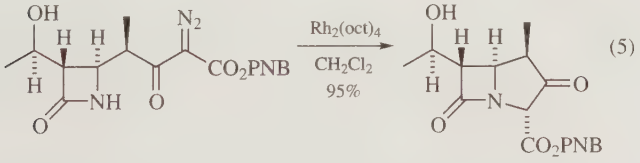
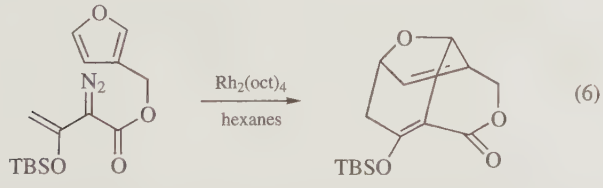
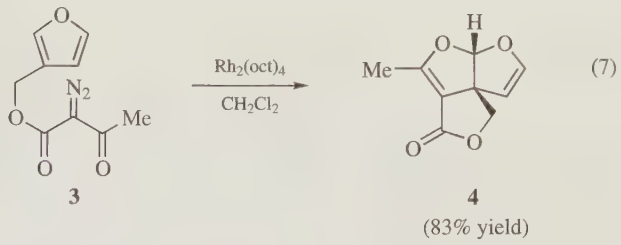
The most widely used catalyst for carbenoid reactions is dirhodium tetraacetate, but in certain cases, dirhodium tetraoctanoate ($Rh_2(oct)_4$) is preferable due to its greater solubility, especially in hydrocarbon solvents. The most significant example of $Rh_2(oct)_4$-catalyzed reactions is the intramolecular NH insertion process for the synthesis of penem antibiotics (eq 5).[11]



Since the previous e-EROS report, a number of examples have been described of novel $Rh_2(oct)_4$-catalyzed reactions.[12–36] In many cases, the use of $Rh_2(oct)_4$ was desirable because the reaction was sensitive to solvent effects and a hydrocarbon solvent was optimal. The intramolecular [4 + 3] cycloaddition of the vinyldiazoacetate (**1**) to form **2** is an impressive transformation, proceeding by a tandem cyclopropanation/Cope rearrangement (eq 6).[37] Another example involving furans is the intramolecular [3 + 2] cycloaddition of the diazoacetoacetate (**3**) to form the tricycle **4** (eq 7).[38]

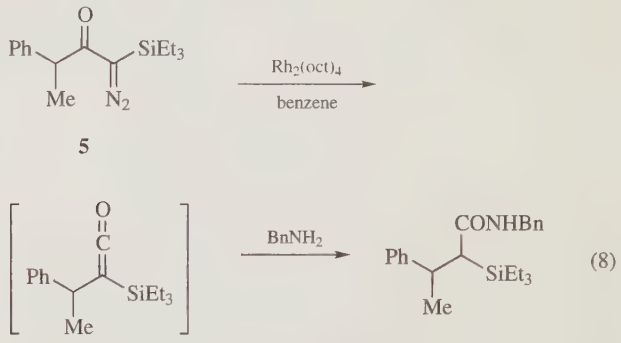


1 **2**
(83% yield)



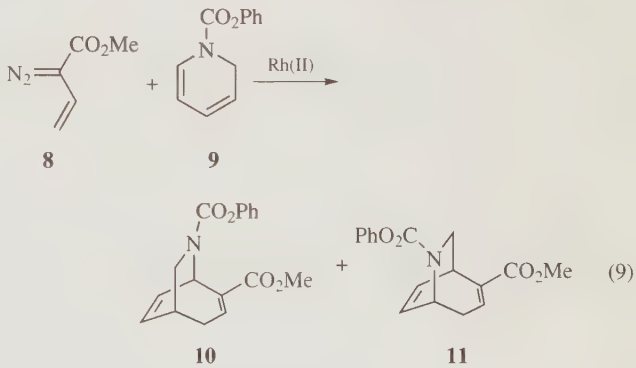
3 **4**
(83% yield)

$Rh_2(oct)_4$ has also been used as a catalyst for the conversion of the silyldiazoketone (**5**) to silylketene (**6**) by means of a Wolff rearrangement (eq 8).[35] Capture of the ketene by benzylamine readily occurs to form the α-silylamide (**7**).



5 **6** **7**
(80% yield)

$Rh_2(oct)_4$ and dirhodium tetrapivalate ($Rh_2(piv)_4$) are generally considered as interchangeable hydrocarbon-soluble catalysts but $Rh_2(oct)_4$ is less sterically crowded than $Rh_2(piv)_4$ and this can impact the chemoselectivity of the process. An interesting example of this effect is the [4 + 3] cycloaddition between vinyldiazoacetate (**8**) and the dihydropyridine (**9**) (eq 9).[22,39] Two azabicyclic regioisomers **10** and **11** are formed, the ratio of which is dependent on which of the two double bonds in **9** undergoes the initial cyclopropanation. The chemoselectivity of the initial cyclopropanation is very dependent on the steric influence of the catalysts. While $Rh_2(oct)_4$ gives close to a 1:1 mixture of **10** and **11**, the $Rh_2(piv)_4$-catalyzed reaction strongly favors the formation of **10**.

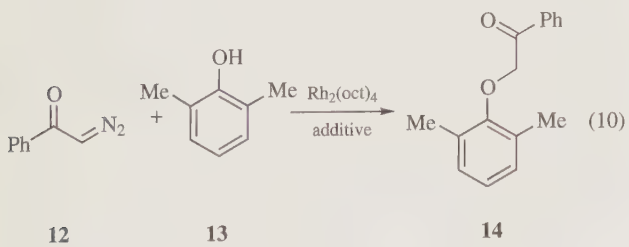


8 **9** **10** **11**

$Rh_2(oct)_4$	(**10**: 30% yield, **11**: 29% yield)
$Rh_2(piv)_4$	(**10**: 56% yield, **11**: 12% yield)

The coordination state of the second axial site during rhodium-catalyzed carbenoid reactions has not been extensively studied.

It is possible, however, that there could be some interesting effects due to this coordination as can be seen in using diisopropylethylamine as an additive on $Rh_2(oct)_4$-catalyzed O–H insertion between **12** and **13** to form **14** (eq 10).[31] The yield was greatly improved in the presence of the additive and this approach was used for the selective functionalization of asomycin, a complex macrolide natural product.



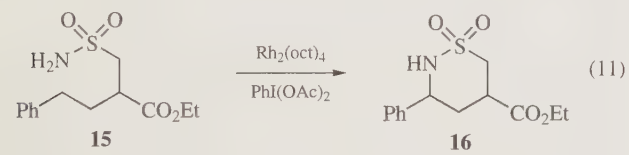
(10)

12 **13** **14**

(no additive: 35% yield)

(EtN(*i*-Pr)$_2$: 68% yield)

$Rh_2(oct)_4$ has also been used as an effective catalyst for intramolecular C–H insertions of rhodium nitrenes as illustrated in the conversion of the sulfonamide (**15**) to oxathiazinane (**16**) (eq 11).[40] This represents a novel method of C–H functionalization and it can be conducted in a one-pot procedure, in which the phenyliodinane, the nitrene precursor, is generated in situ.

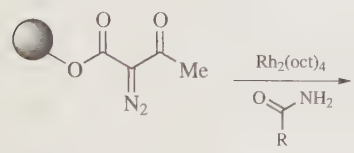


(11)

15 **16**

(91% yield, 13:1 *syn*/*anti*)

Solid-phase carbenoid reactions can be effectively exploited using $Rh_2(oct)_4$ as catalyst.[17,29] The immobilized diazoacetoacetate (**17**) was readily decomposed by $Rh_2(oct)_4$ and underwent N–H insertions into amides to form **18**, which was then cyclized to the oxazole (**19**) (eq 12).[29] Using this strategy a library of oxazole derivatives were formed.

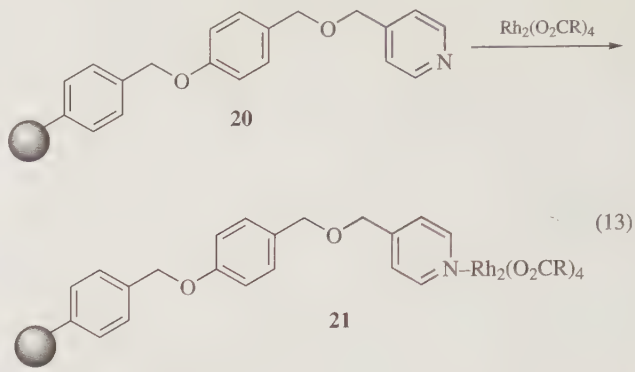


17

(12)

18 **19**

A general method for the immobilization of dirhodium teracarboxylates has been achieved through coordination to pyridine functionalized polymers. This immobilization strategy works best with high molecular weight catalysts because an encapsulation effect is involved in addition to ligand coordination. Consequently, $Rh_2(oct)_4$ is much more effectively immobilized than the standard catalyst $Rh_2(OAc)_4$ (eq 13).[41]



20 **21**

(13)

Catalyst	Immobilization (%)
$Rh_2(OAc)_4$	37
$Rh_2(oct)_4$	82

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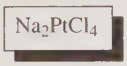
Disodium Tetrachloroplatinate(II)[1]



[10026-00-3] Cl_4Na_2Pt (MW 382.86)

(homogeneous hydrogen isotope exchange catalyst;[2] selective oxidative functionalization of alkane C–H bonds;[3] isomerization of alkenes[4])

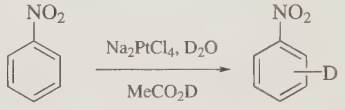
Solubility: sol H_2O (8 g/100 mL); slightly sol alcohol, acetone, acetic acid.

Form Supplied in: red-brown solid; available as a tetrahydrate $Na_2PtCl_4 \cdot 4H_2O$.

Drying: at 120 °C/0.1 mmHg for 24 h.

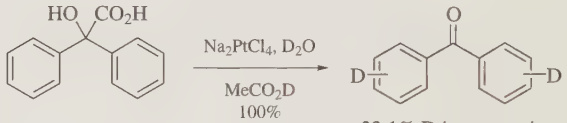
Handling, Storage, and Precautions: should be stored in the absence of moisture; irritating to skin, eyes, and respiratory organs; corrosive.

Hydrogen Isotope Exchange Catalyst. Aromatic and aliphatic compounds undergo exchange of isotopic hydrogen with a catalytic amount of this reagent (see also ***Dipotassium Tetrachloroplatinate(II)***). This system is valuable for labeling compounds with deuterium and/or tritium in one step and constitutes the homogeneous equivalent of the well-known heterogeneous platinum technique. A wide range of compounds, including benzene and substituted benzenes,[5] polyphenyls,[6] polycyclic hydrocarbons,[7] and some steroids[8] undergo D and/or T exchange. Deuteration in the side chain of long-chain alkylbenzenes occurs predominately at the benzylic and the terminal carbons.[9] Aromatics are generally quite reactive, whereas aliphatics such as cyclohexane exchange very slowly.[10] Nitrobenzene has similar reactivity to toluene[11] and bromobenzene.[12] Exchange usually occurs only in the sterically unhindered *meta* and *para* positions (eq 1).[11] Aromatic α-hydroxy acids undergo oxidative decarboxylation during the Na_2PtCl_4-catalyzed homogeneous deuteration (eq 2).[13]



(1)

deuterium distribution (% per H) *ortho*, 12.5; *meta*, *para*, 82.7

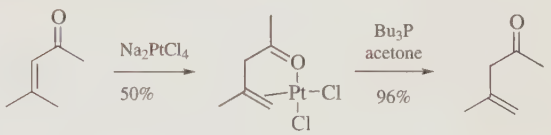


(2)

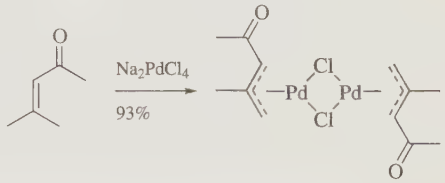
23.1% D incorporation

Functionalization of Saturated Hydrocarbons. Na_2PtCl_4 or the combination Na_2PtCl_4/Na_2PtCl_6 in aqueous solution can be used to functionalize saturated hydrocarbons (see also ***Dipotassium Tetrachloroplatinate(II)***). Unusual and often very high selectivity is observed for oxidation at what are more commonly the least reactive positions. The products from oxidation of alkanes are mainly alcohols together with chloroalkanes, ethers, and acids. Ethanol can be selectively converted to ethylene glycol.[14] The methyl group of *p*-toluenesulfonic acid is selectively oxidized to the corresponding alcohol and aldehyde.[15] In spite of the simplicity of these systems, there is little recent work on them that shows promise for the development of preparative-scale processes.

Alkene Isomerization. α,β-Unsaturated ketones can be isomerized to β,γ-unsaturated ketones through the formation of a π-complex with Na_2PtCl_4 (eq 3).[4] Analogous reaction with Na_2PdCl_4 gives a stable π-allyl complex (eq 4) (see ***Disodium Tetrachloropalladate(II)***).[16]



(3)



(4)

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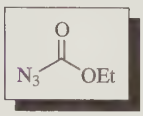
Valeri Martichonok
University of Toronto, Ontario, Canada

E

Ethyl Azidoformate[1]



[817-87-8] $C_3H_5N_3O_2$ (MW 115.09)

(electron-deficient azide; can undergo cycloadditions with alkenes to yield triazolines;[1] generates ethoxycarbonylnitrenes on thermolysis and photolysis[1])

Physical Data: bp 40 °C/30.5 mmHg; $\eta_D^{24.8}$ 1.4180;[27] bp 28 °C (20 mmHg);[28] density (20 °C) 1.1353;[28] η_D^{20} 1.4221;[28] ethyl azidoformate exhibits a level of shock sensitivity similar to nitroglycerine, igniting at 5 kg-cm on a drop-weight tester.[29]

Solubility: sol ether, methylene chloride.

Preparative Methods: as reported by Lwowski and Mattingly.[27]

Handling, Storage, and Precautions: is potentially explosive and care should be taken when distilling or heating solutions of this compound. It has been stored in the cold, protected from light, for up to 3 months without any apparent deterioration. However, ethyl azidoformate is eventually hydrolyzed in the presence of moisture, leading to the formation of HN_3. Such long-stored samples can explode on handling (due to the HN_3) and it is therefore recommended that ethyl azidoformate be used immediately after preparation. The vapors of this compound are also toxic. The original literature should be consulted before preparation and use of this compound.[27] This reagent should only be handled in a fume hood.

Original Commentary

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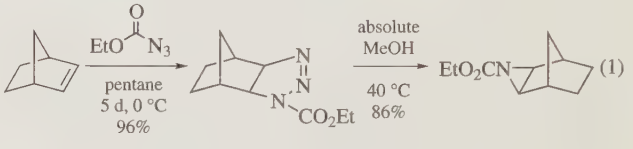
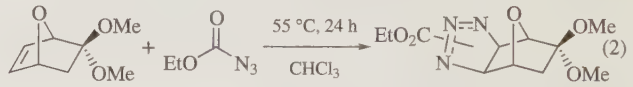
University of Michigan, Ann Arbor, MI, USA

Introduction. Ethyl azidoformate is usually prepared by the reaction of ***Ethyl Chloroformate*** with ***Sodium Azide***. It is principally used for two broad classes of reactions: (a) the cycloaddition of the azide moiety to an unsaturated functionality, and (b) as a source of ethoxycarbonylnitrene. This reagent has limited synthetic utility primarily because of its thermal instability. Ethyl azidoformate and other azidoformates begin to decompose above 60 °C.[1b] The related methyl azidoformate also displays similar reactivity and will also be discussed wherever relevant.

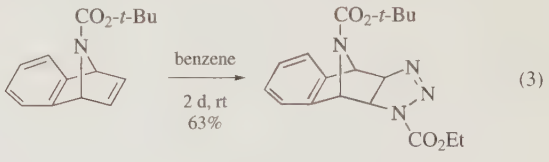
Cycloaddition Reactions. The cycloaddition reactions of azides to alkenes are generally believed to be concerted. Ethyl azidoformate is considered an electron-poor azide and reacts readily with electron-rich alkenes. The product of these reactions are Δ^2-triazolines. The triazolines derived from electron-poor azides are usually not stable and can lose nitrogen readily to give the aziridines and/or imines even at room temperature.[1c] However, many triazolines have been isolated in good yields. If the desired products are the triazolines themselves, the cycloaddition reactions are synthetically useful only if they proceed readily well below the decomposition temperature of the parent azide. At higher temperatures, ethyl azidoformate decomposes to give the corresponding nitrene which can react in a variety of pathways. Also, at higher temperatures, triazoline decomposition occurs readily. Strained and/or electron-rich alkenes undergo cycloaddition readily at room temperature or below. Norbornene,[2] substituted norbornenes,[3] and other strained bicyclic systems give triazolines in high yields (eqs 1 and 2). The presence of functional groups such as primary amines on the alkene are known to interfere with the cycloaddition reaction.[4]

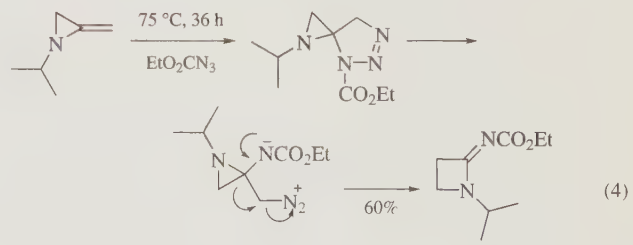


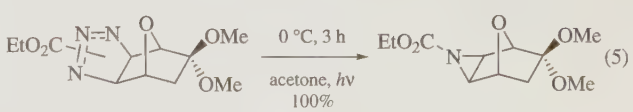


80% overall
mixture of regioisomers

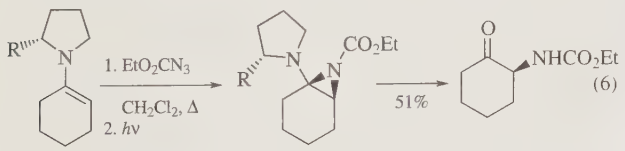
Cycloadditions with norbornenes usually proceed from the *exo* face, even in the case of a 7-substituted azanorbornene (eq 3),[5] although exceptions have been reported.[6] Unsymmetrical norbornenes exhibit poor regioselectivity (eq 2). The products of triazoline fragmentation under thermal conditions are not always predictable and both aziridines and imines can result, although there are occasional examples of good product selectivity. Other rearrangement products have also been observed (eq 4).[7] However, photolysis of triazolines generally gives the aziridines in good yields, which are free of other side-products (eq 5).[3] In many cases this thermolysis/photolysis route to aziridines is superior to the direct photolysis of ethyl azidoformate in the presence of an alkene. If aziridines are the desired products, the poor regioselectivity in the cycloaddition step is not a drawback since both regioisomeric triazolines lead to the same aziridine.



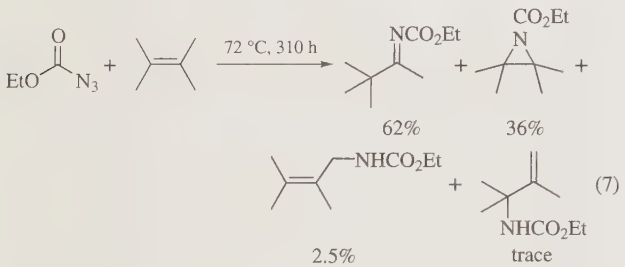




Cycloadditions of ethyl azidoformate with electron-rich alkenes are also expected to proceed readily, although few examples are known. The cycloadducts from the reaction of ethyl azidoformate with optically active enamines were subject to photolysis.[8a] α-Amino ketones were isolated in moderate yields, presumably derived from the ring opening of the initially formed aziridine (eq 6). Reaction of enol silanes with ethyl azidoformate has also been reported to give *N*-substituted α-amino ketones.[8b] However, under these conditions it is possible that the reaction may proceed through a nitrene intermediate.

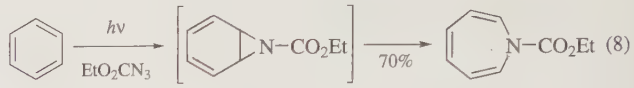


Cycloaddition of ethyl azidoformate to unactivated, unstrained alkenes usually requires elevated temperatures (70–120 °C). Under such conditions, nitrenes may be generated, leading to products derived from the fragmentation of triazolines. For example, reaction of ethyl azidoformate with tetramethylethylene (solvent) at 72 °C gave four products (eq 7).[9] The authors estimate that at least 60% of the aziridine was produced via the nitrene pathway.

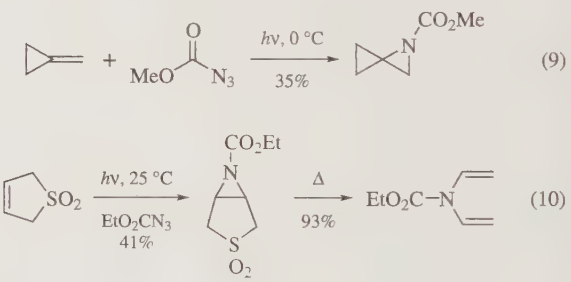


Cycloadditions of ethyl azidoformate with alkynes and other triple bonds have also been attempted. The reaction with *N,N*-diaminopropyne, a ynamine, and ***Ethoxyacetylene*** has been reported to proceed at room temperature to give triazoles, although no yields were given.[10] Reaction of ethyl azidoformate with tetramethylallene at 130 °C gave a 38% yield of the triazoline along with the oxazoline.[11] The latter is probably derived from a nitrene intermediate. The reaction of ethyl azidoformate with stabilized phosphorus ylides has also been reported to give the corresponding triazoles in excellent yields.[12]

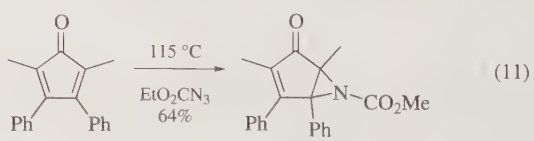
Generation and Reactions of Nitrenes. Photolysis of ethyl azidoformate gives rise to ethoxycarbonylnitrene. Curtius rearrangement of azidoformates to give isocyanates under photolytic conditions (the photo-Curtius rearrangement) is a minor pathway. Depending on the conditions of photolysis, the nitrenes generated can react from either the singlet or the triplet state and the reactivity of the two species can be different. Nitrenes undergo two major reactions, insertion into single bonds and addition across double bonds. In many cases, both reactions occur, limiting the utility. Other side products can also be formed. The synthetic application of intermolecular C–H insertion of nitrenes is severely limited because of the poor selectivity of the nitrenes for different types of C–H bonds.[13] Even intramolecular insertions of substituted azidoformates usually give a mixture of the possible insertion products and have hence found only rare application in synthesis.[14] Insertion of nitrenes into aromatic and heteroaromatic rings has found some preparative value. Irradiation of ethyl azidoformate in benzene with UV light gives good yields of the azepine (eq 8),[15] in contrast to the thermal process which gives a 40% yield.[16]



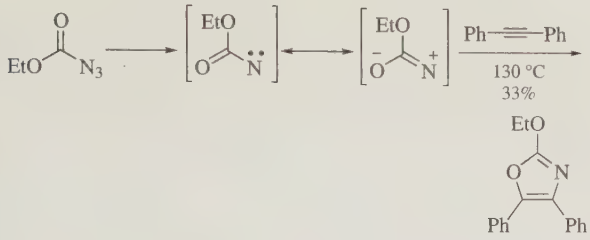
The addition of nitrenes to double bonds under photolytic conditions has found wider use. Singlet nitrenes add across alkenes stereospecifically. This reaction is applicable to many types of alkenes. Thus methoxycarbonylnitrene reacts with a strained alkene, ***Methylenecyclopropane***, to give the azaspiropentane (eq 9).[17] Reaction of ethoxycarbonylnitrene with an unactivated alkene, ***3-Sulfolene***, gives the aziridine which on thermal decomposition yields a divinyl carbamate (eq 10).[18] Ethoxycarbonylnitrene has also been added to activated alkenes such as dihydropyrans[19] and optically active silyl ketene acetals.[20] In the latter case, the isolated products were *N*-carbonylethoxy α-amino esters, presumably formed by ring opening of the initial aziridine. Modest levels of asymmetric induction were obtained. In many cases the photolysis can be done below room temperature to minimize undesirable side reactions.



Ethoxycarbonylnitrene can also be generated from ethyl azidoformate by thermolysis, producing singlet nitrenes. Reaction of ethoxycarbonylnitrene with an electron-deficient alkene gives the aziridine in good yield (eq 11).[21]



The reaction of ethoxycarbonylnitrene with ***Diphenylacetylene*** gives the corresponding oxazole in 33% yield (eq 12).[22] The mechanism of this reaction may proceed via a 1,3-dipole as shown or by a stepwise mechanism involving initial attack of the nitrene to produce a 1*H*-azirine. Aliphatic nitriles react in a similar manner under photolytic conditions to give the corresponding 5-ethoxyoxadiazoles.[23] The reaction of ethyl azidoformate with 1,1-dimethylallene under photolytic conditions has been reported to occur regioselectively at the more substituted double bond to give the the oxazoline.[11]



(12)

Photochemical addition of ethoxycarbonylnitrene to isocyanides leads to the corresponding carbodiimides in moderate yields, which on hydrolysis give ureas.[24] Addition of ethoxycarbonylnitrene to cobalt cyclopentadiene complexes has also been reported to give pyrroles, albeit in low yields.[25]

Other reagents such as ***p-Nitrobenzenesulfonyloxyurethane*** and *N*-ethoxycarbonyl-*N,O*-bis(trimethylsilyl)hydroxylamine[26] have also been used as a source of ethoxycarbonylnitrene. The article on the urethane reagent should be consulted for further applications of ethoxycarbonylnitrene in organic syntheses.

First Update

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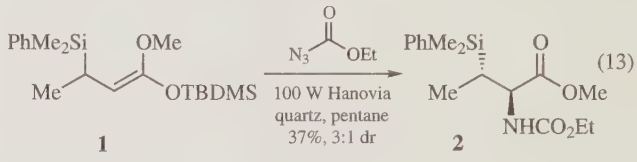
Introduction. The reactions and properties of azidoformates (N_3CO_2R; also called alkoxycarbonyl azides) continue to engage synthetic- and physical organic chemists as well as materials- and surface scientists. This update, organized by reaction type, focuses on recent applications of ethyl azidoformate as a reagent for transforming a wide range of organic substrates. Described first is direct alkene aziridination with ethyl azidoformate, usually proceeding via the acyl nitrene and often leading to in situ aziridine opening. Cycloaddition of ethyl azidoformate with alkenes, affording triazolines, is another common reaction, and these heterocyclic products can undergo further conversion upon loss of molecular nitrogen. Because it has generated considerable study in recent years, the use of ethyl azidoformate for functionalizing fullerenes is treated separately, though these processes also occur via acyl nitrene additions or [3 + 2] pathways. Additionally, ethyl azidoformate has proved useful in various syntheses of metallacycles, other heterocycles, and aza-Wittig reagents. Radical reactions and electrophilic aromatic substitution using ethyl azidoformate are also described. Finally, this update summarizes recent spectroscopic and computational studies on ethyl azidoformate.

As perhaps the archetype of its structural class, ethyl azidoformate has served as a key model for efforts to extend the chemistry of azidoformates. Such studies have explored other low-molecular weight azidoformates for imidation of sulfides and sulfoxides, including an asymmetric variant of the former process. In addition, the azidoformate unit can be embedded within complex molecular frameworks, leading to intramolecular C=C and C–H insertions as well as *N*-centered radical cyclizations. Long-chain azidoformates have been incorporated into self-assembled monolayers for light-induced surface patterning. These applications of azidoformate reactivity, closely related to the transformations of ethyl azidoformate itself, are covered briefly at the end of this update.

Direct Alkene Aziridination. Azidoformate photolysis or thermolysis generates acyl nitrenes, which can react with olefins to give aziridines. Aziridination of heteroatom-substituted alkenes with ethyl azidoformate provides synthetic versatility due to subsequent ring opening of the aziridines. Early work showed, for example, that the photochemical aziridination of enol acetates with ethyl azidoformate provided either rearrangement to an oxazoline or conversion to α-amido ketones upon deacetylation.[30]

Other enol ether substrates provided similar ring opening after aziridination. Diastereocontrol due to allylic-1,3 strain was possible in the amidation of silyl ketene acetal (**1**) (eq 13).[31] The intrinsic facial bias in a related enol ether, meanwhile, was overridden using a silyl ketene acetal bearing one of Oppolzer's chiral sulfamidoisoborneol auxiliaries.[32] A chiral auxiliary was also used in enol ether (**3**) to provide face-selective amidation, with in situ cyclization to ketal (**4**) (eq 14).[33]



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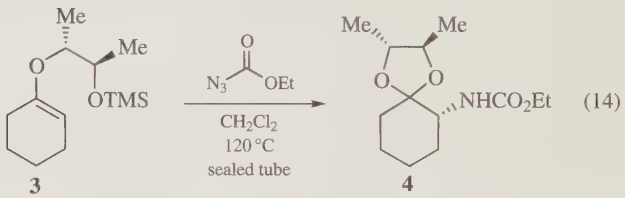
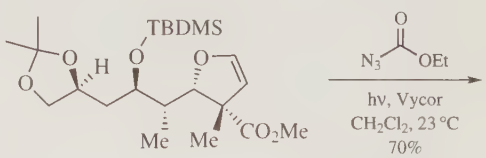
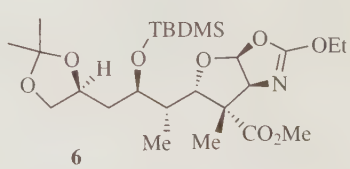


(14)

14% yield, 2.3:1 dr

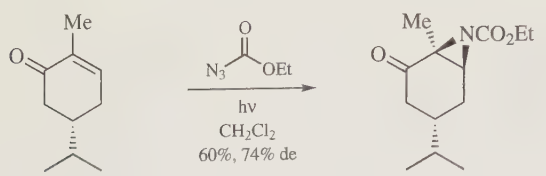
With complex dihydrofuran (**5**) (eq 15), photolytic acyl nitrene insertion provided a single diastereomer of 2-alkoxy oxazoline (**6**), via rearrangement of the initially formed aziridine. The oxazoline was readily hydrolyzed to the corresponding lactol in studies toward the synthesis of the macrocylic antibiotic lankacidin C.[34]





(15)

Aziridines were obtained upon irradiation of ethyl azidoformate with various α,β-unsaturated ketones. With chiral substrates such as (*R*)-dihydrocarvone (**7**), diastereoselective azirdination was possible (eq 16).[35] Diastereoselectivity was also observed using chiral ketals of 3-cyclohexen-1-one as substrates for photochemical carboethoxy nitrene insertion.[36] Another class of electron-deficient substrates, nitro alkenes, was also amenable to direct thermal aziridination with ethyl azidoformate.[37]

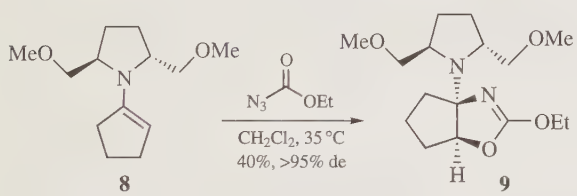


7 (16)

The photochemical reaction of ethyl azidoformate with vinyl silanes, meanwhile, provided a stereospecific synthesis of *N*-carboethoxy-2-trimethylsilyl aziridines, which were readily converted to the N–H aziridines upon reductive deacylation.[38]

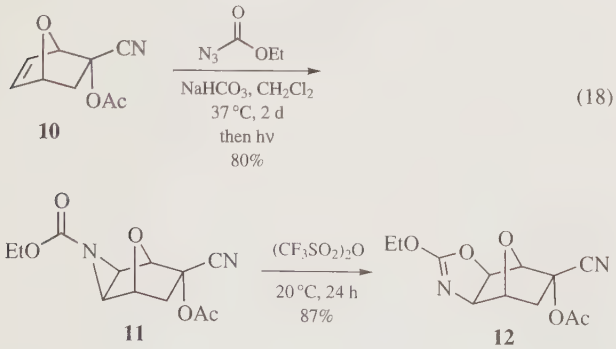
[3 + 2] Cycloadditions. Besides acyl nitrene-mediated reactivity, thermal reactions of ethyl azidoformate with alkenes at lower temperature lead to triazolines via [3 + 2] cycloaddition. The triazolines convert to aziridines upon further heating or photolysis, and they have also been utilized in acid-promoted rearrangements.

Chiral enamines served as substrates for diastereoselective reactions with ethyl azidoformate. With enamine (**8**), the alkoxy oxazoline (**9**) was isolated upon mild heating with the azidoformate (eq 17).[39] While the transformation to **9** occurred in a single operation, the regio outcome, demonstrated using 2D NMR experiments, suggested that this reaction occurred by regioselective [3 + 2] cycloaddition, followed by triazoline opening and recyclization with loss of N_2.



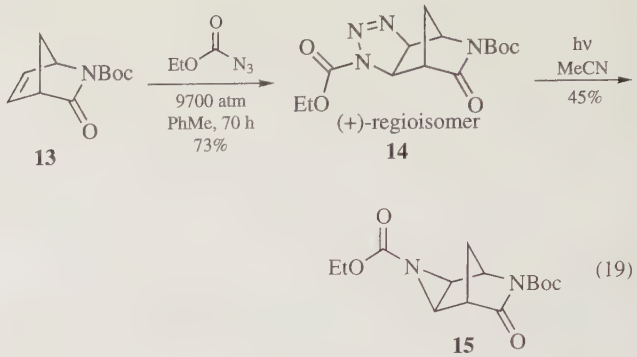
8 9 (17)

Dipolar cycloaddition of ethyl azidoformate to oxabicyclic alkene (**10**) provided aziridine (**11**) after photochemical decomposition of the regioisomeric triazolines (eq 18). The *endo*-face C2-acetoxy group assisted in the regioselective rearrangement of the aziridine to alkoxy oxazoline (**12**).[40] In a related system, 7-oxa-5-norbornen-2-one acetals reacted with ethyl azidoformate, providing a regioisomeric mixture of *exo*-face triazolines. Subsequent photolysis yielded the aziridine, which underwent alkoxy migration across the *endo*-face upon treatment with acid.[41]



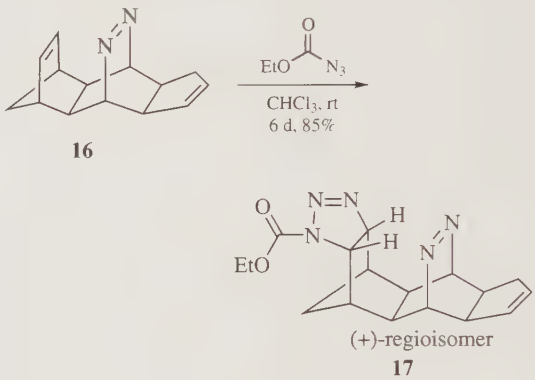
(18)

High-pressure conditions succeeded in the cycloaddition of ethyl azidoformate with azabicycloheptenone (**13**) (eq 19), whereas thermal attempts (PhMe, reflux, or PhMe, 100 °C, sealed tube) did not give the desired triazolines.[42] The regioisomeric mixture (**14**) yielded the tricyclic aziridine (**15**) upon photolysis.



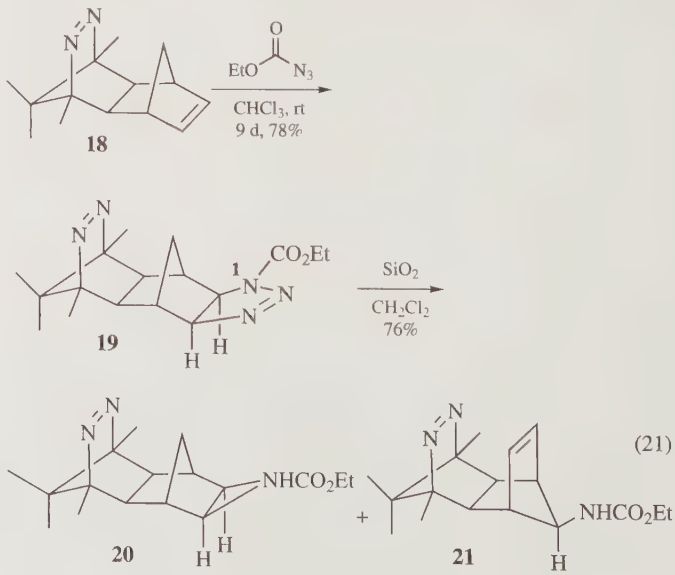
(19)

Selective aziridination in the presence of azo groups was achieved using the triazoline decomposition strategy. Slow thermal dipolar cycloaddition of ethyl azidoformate to the more reactive alkene in diene (**16**) provided triazolines (**17**) (eq 20), which were then converted to the corresponding aziridine either thermally or photochemically, using wavelengths that did not perturb the azo linkage.[43]



(20)

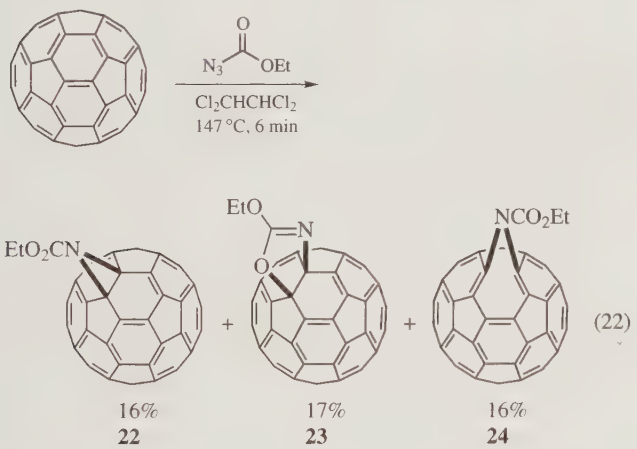
In related studies, triazolines such as **19** (eq 21), prepared by dipolar cycloaddition of ethyl azidoformate with norbornene (**18**), were used as substrates for acid-promoted rearrangements. These processes occurred via protonation of the saturated triazoline nitrogen (N1), heterocycle opening, and loss of nitrogen with concomitant bond reorganization, as in the rearrangement to **21**. Formation of aziridine (**20**) also occurred under these conditions.[44]



(21)

Fullerene Derivatives. In recent years, a prominent use of ethyl azidoformate has been as a reagent for functionalizing fullerene surfaces, including nanotubes as well as C_{60} and C_{70}. When a solution of ethyl azidoformate was added dropwise to a suspension of single-walled carbon nanotubes (SWCNTs) in hot *o*-dichlorobenzene, *N*-carboethoxy aziridino units were incorporated. A variety of other azidoformates were also effective in this process, which improved the solubility characteristics of the SWCNTs without disrupting their electronic properties.[45] At the elevated temperatures used, the reaction likely proceeded via acyl nitrene addition. Attempts to use alkyl azides in [3 + 2] reactions with the SWCNT surface failed.

In thermal reactions with C_{60}, ethyl azidoformate provided three products: the [6,6]-aziridine (**22**), the corresponding rearranged oxazoline (**23**), and the cage-opened [6,5]-aza-bridged annulene (**24**) (eq 22).[46] The cage-opened material was previously misassigned as the closed [6,5]-aziridine.[47] The reactions with ethyl azidoformate were conducted at elevated temperatures, consistent with carboethoxy nitrene generation. Interestingly, *tert*-butyl azidoformate ($BocN_3$) reacted with C_{60} at lower temperature, presumably via a triazoline intermediate. Those conditions led to a reversal in the relative amounts of [6,6]-aziridine and the cage-opened [6,5] isomer.[46a]



(22)

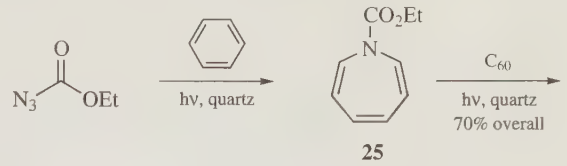
22 **23** **24**

In studying the fluorescence properties of C_{60} derivatives, Luh and co-workers used boron tribromide to convert the [6,6]-*N*-carboethoxy aziridine adduct (**22**) into the corresponding [6,6]-oxazolidinofullerene.[48]

A triazoline intermediate was implicated in the lower-temperature reactions of ethyl azidoformate with C_{60} and C_{70}. More vigorous heating of the initial adducts led to cage-opened bisazafulleroids that fragmented upon FAB-MS to $(C_{59}N)^+$ or $(C_{69}N)^+$, isoelectronic heteroanalogs of the all-carbon starting materials.[49]

In benzene solution, photoreaction of ethyl azidoformate with C_{60} gave products incorporating the carboethoxy nitrene fragment and a C_6H_6 unit. Initial addition of the nitrene to benzene had provided the *N*-carboethoxy azepine (**25**), which underwent further [2 + 4] or [2 + 6] photoreaction with the buckminsterfullerene at a [6,6] junction (eq 23).[50] Treatment of C_{60} with **25** in the absence of light did not provide the cycloadducts.

Other Heterocycle and Metallacycle Synthesis. Various thiones (e.g., **26**, eq 24) provided the corresponding imines when heated with ethyl azidoformate. The suggested mechanism involved 1,3-dipolar cycloaddition to the C=S unit, loss of nitrogen to the thiaziridine, and final sulfur extrusion.[51]



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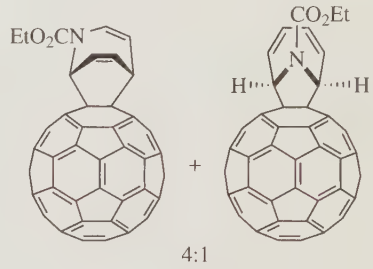

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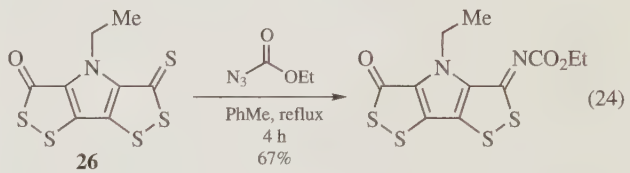
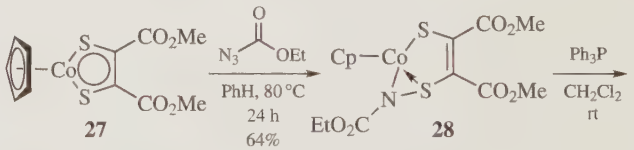


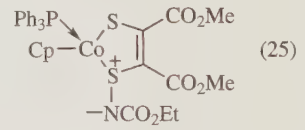
(24)

26

A cobaltathiaziridine, meanwhile, formed in the thermal reaction of ethyl azidoformate with (1,2-ethenedithiolato)cobalt(III) complex (**27**) (eq 25).[52] The metallacycle (**28**) underwent various ring-opening processes, including cleavage of the Co–N bond with triphenylphosphine, leading to ylide **29**.



27 **28**



(25)

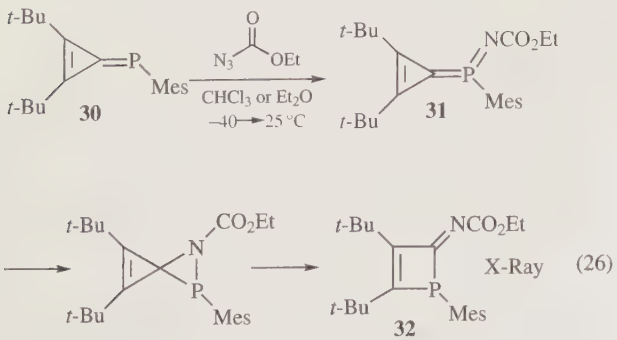
29

Thermal or photochemical reactions of azidoformates with tetraphosphorus hexaoxide provided the first examples of O → N replacement with preservation of the heteroadamantyl cage structure. With ethyl azidoformate, the *N*-carboethoxy derivative was obtained.[53]

Formation of Iminophosphorus Compounds. Aza-ylide-type intermediates were involved in reactions of other phosphorus-containing compounds with azidoformates. With mesitylphosphatriafulvene (**30**) (eq 26), the Staudinger process (attack of phosphorus on the azido group, leading ultimately to loss of N_2), provided intermediate (**31**) which underwent a ring closure–ring expansion sequence, leading to the 1*H*-2-iminophosphete (**32**).[54]

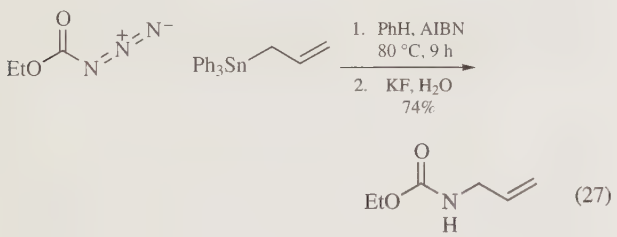
Treatment of various azidoformates with triphenylphosphine, meanwhile, provided aza-Wittig species, and these were used in

imine-forming reactions with aldehydes as part of a scheme to prepare *cis*-disubstituted β-lactams.[55]



(26)

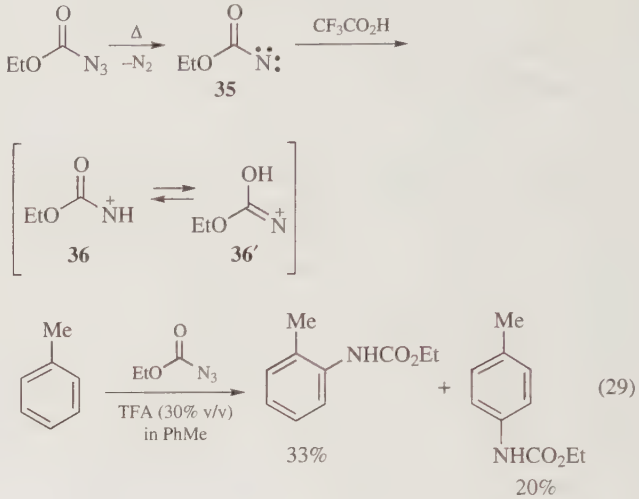
Radical Reactions. Azidoformates react via radical chain processes upon treatment with initiators.[56] Using this mode of reactivity, Dang and Roberts reported the allylation of an ethyl azidoformate-derived *N*-centered radical (eq 27).[57] The authors proposed that in the chain propagation steps triphenyltin radical adds to N1 of the azido group, leading to loss of N_2 and generating a tin-bound, *N*-centered radical. This radical then adds to the allyl stannane, affording both product and a chain-carrying triphenyltin radical. *N*-Protodestannylation with aqueous potassium fluoride during workup provided the tin-free, *N*-allylated products.



(27)

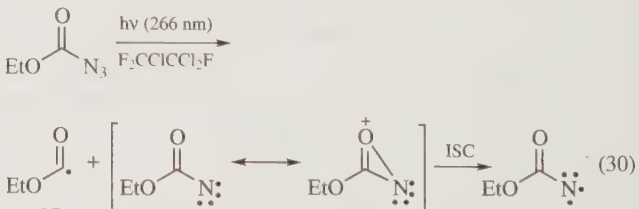
Ethyl azidoformate mediated the α-alkoxylation of amides using silyl ethers (eq 28).[58] In this case, the azidoformate did not appear to generate a radical directly, as neither triplet sensitizers nor radical initiators facilitated the reaction. However, an alkoxy radical produced by homolytic N–O bond cleavage of *N*-alkoxy urethane (**33**) may be involved. The urethane (**33**) was isolated upon thermolysis of ethyl azidoformate in 1-(trimethylsilyloxy) pentane and gave α-alkoxylation product (**34**) when heated at 120 °C in DMF solution. The authors proposed that the *N*-trimethylsilyl, *N*-alkoxy urethane **33** formed via capture of the singlet nitrene, followed by O → N silyl migration.

Electrophilic Aromatic Substitution. In strongly acidic solution, thermolysis of ethyl azidoformate provided the tautomeric nitrenium ions (**36**/**36′**), which participated in electrophilic aromatic substitution (eq 29).[59] A range of experiments indicated that the nitrenium ion resulted from protonation of the thermally generated acyl nitrene (**35**) rather than via initial protonation of ethyl azidoformate. For example, activation parameters for the decomposition of ethyl azidoformate were the same in the presence or absence of trifluoroacetic acid.



(29)

Spectroscopic and Computational Studies. A recent laser flash photolysis study utilized ethyl azidoformate to generate carboethoxy nitrene in Freon-113 ($F_2ClCCFCl_2$) solution.[60] Two transient species were generated in the photolysis, one of which was scavenged by O_2 and was assigned as the acyl radical (**37**) (eq 30). On the basis of time-dependent density functional theory calculations, the other species was determined to be the triplet carboethoxy nitrene (**39**). The spectroscopic measurements indicated a lifetime of 2–10 ns for the singlet species (**38**), which underwent intersystem crossing to the triplet nitrene (**39**). Interestingly, k_{ISC} was 100 times greater for carboethoxy nitrene (**38**) than for singlet phenyl nitrene. Apparently, participation by the carbonyl oxygen gives singlet carboethoxy nitrene a closed-shell electron configuration (cf. **38**), allowing spin–orbit intersystem crossing.



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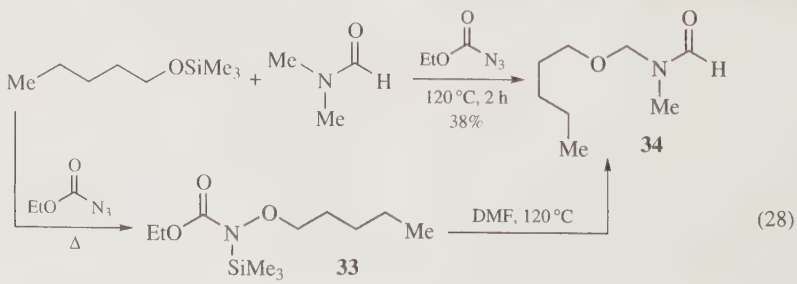
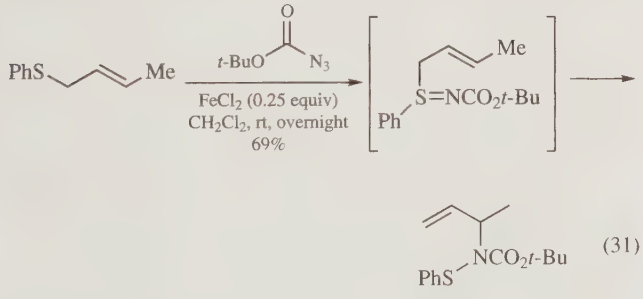


(28)

The computation of ethyl azidoformate conformation, geometry, vibrational frequencies, and ionization energies was accomplished using ab initio methods.[61] The conformations having the azido group in-plane with the carbonyl are energy minima, with the anti arrangement of the azido and ethoxy groups slightly favored (1 kcal mol^{-1}). This conclusion was consistent with a later calculation on methyl azidoformate.[62] The latter study also contained a wealth of data, obtained computationally and via laser flash photolysis experiments, on azidoformate-derived acyl nitrenes. For example, activation barriers for both intramolecular and bimolecular insertion reactions of singlet carboalkoxy nitrenes are purely entropic ($\Delta H^{\dagger} \leq 0$), and even the bimolecular processes typically occur considerably faster than the Curtius rearrangement to alkoxy isocynates, especially at low temperature.

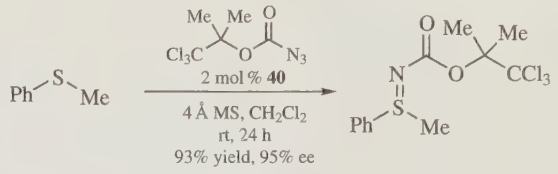
Sulfide and Sulfoxide Imidation. Low-molecular weight azidoformates, principally *tert*-butyl azidoformate ($BocN_3$), have been used in transition metal-mediated sulfur imidation reactions. Upon screening a wide range of metal salts, Bach identified $FeCl_2$ as an effective promoter for both sulfoximidation and sulfimidation.[63] With the sulfoxide substrates, stoichiometric iron(II) chloride was required for best yields, and imidation occurred with retention of configuration at sulfur. Sulfides underwent efficient imidation with only 0.25 equiv $FeCl_2$, and the reactions showed ligand acceleration with added acetylacetone or dimethylformamide. With allyl phenyl sulfides, sulfimidation led to room temperature [2,3] sigmatropic rearrangement (eq 31), providing Boc-protected *N*-allylamines after N–S bond cleavage.[64]



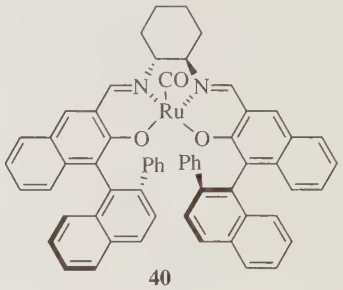
(31)

Enantioselective sulfimidation of aryl alkyl sulfides occurred using azidoformates and chiral Ru(salen)(CO) catalyst (**40**).[65] There was a strong dependence of enantioselectivity on azidoformate structure, with (2,2,2-trichloro-1,1-dimethyl)ethyl azidoformate providing sulfoxides with impressive enantioselectivities and yields (eq 32). This system did not effect alkene aziridination, suggesting that a metal nitrene was not involved in sulfimidation.[66] Instead, the authors proposed the metal-bound azidoformate as the direct *N*-carboalkoxy donor, with concerted departure of N_2 rather than prior nitrogen loss to the metal nitrenoid.

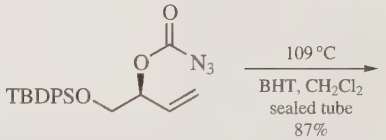
Azidoformates within Complex Frameworks. Selective intramolecular C=C and C–H insertions, both photochemical and thermal, can occur when an azidoformate is tethered within a suitable molecular architecture. Bergmeier demonstrated that thermolysis of allylic azidoformates in 1,1,2,2-tetrachloroethane (TCE) resulted in diastereoselective alkene amidochlorination.[67] With methylene chloride as the solvent and in the presence of a radical inhibitor, the intermediate bicyclic aziridines (e.g., **41**, eq 33) could be isolated in crude form and reacted with organocopper nucleophiles,[67b] a strategy that played a key role in the synthesis of (−)-bestatin, an aminopeptidase inhibitor.[68]

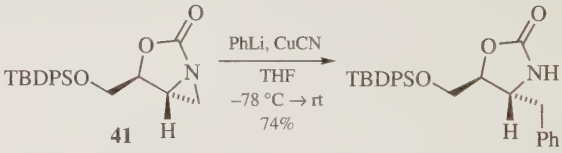


(32)



40

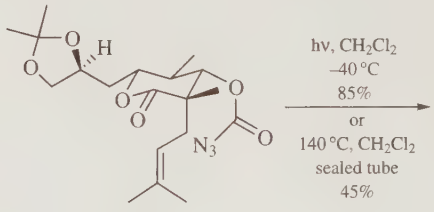




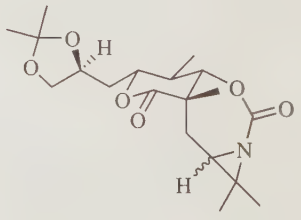
41

(33)

Aziridination occurred in preference to allylic C–H insertion in α-prenyl lactone (**42**) (eq 34) with the photolysis providing a higher yield than the thermal conditions.[34] Intramolecular aziridination also occurred upon irradiation of farnesyl azidoformate, and the product was readily hydrolyzed to the N–H aziridine in a study of aziridine derivatives of isoprenoid polyenes.[69]



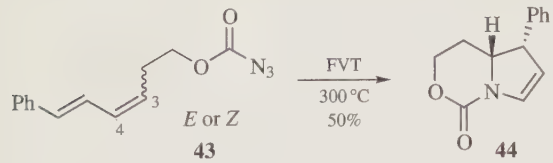
42



(34)

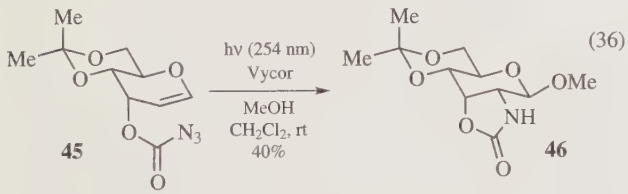
Flash vacuum thermolysis (FVT) of 3,5-hexadienyl azidoformates provided 2-pyrrolidines with both 3,4-alkene isomers (**43**) yielding the same diastereomer of product **44** (eq 35).[70] The proposed mechanism involved a triplet nitrene in nonstereospecific aziridination of the 3,4-alkene, with both the *cis*- and *trans*-aziridines converging to a single product via 4π conrotatory

opening to the azomethine ylide and subsequent disrotatory 6π electrocyclization.



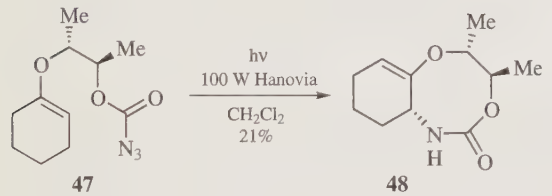
(35)

β-Linked 2-allosamine derivatives formed when allal azidoformate (**45**) was irradiated in the presence of alcohols (eq 36).[71] A reactive glycosyl aziridine may be an intermediate, given the high selectivity for the β-anomers (e.g., **46**)



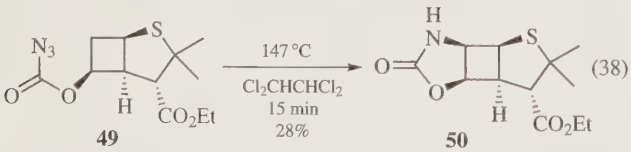
(36)

Another enol ether substrate for intramolecular C=C insertion (**47**) contained two stereocenters in the linker between the alkene and azidoformate units (eq 37). Photolysis provided a single diastereomer (**48**), which could arise via initial aziridination or from direct allylic C–H insertion.[72]



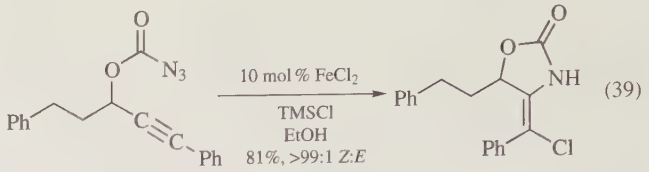
(37)

Intramolecular C–H insertion reactions of azidoformates have also been used recently in synthesis. Oxazoline (**50**) from thermolysis of azidoformate (**49**) (eq 38) was an intermediate in the synthesis of a penicillin N analog.[73] The 3-*O*-carbonyl azide derivative of diacetone-D-glucose provided C2–H insertion in a study of carbene and nitrene insertions within that sugar structure.[74]



(38)

In studies related to the previously discussed sulfur imidation chemistry (cf. eq 31), Bach discovered that allylic azidoformates underwent intramolecular amidochlorination when treated with $FeCl_2$.[75] The cyclization proceeded via an iron-complexed, *N*-centered radical, with further intramolecular delivery of a chlorine atom from the metal center. Propargyl azidoformates reacted analogously, providing (*Z*)-chloroalkenes (eq 39). The iron(II)-mediated conditions were applicable to azidoformate (**45**) (see eq 36), leading to either glycosyl chloride formation or one-pot amidoglycosylation in the presence of alcohol acceptors.[76]



(39)

Finally, patterned electrophilic surfaces have been created by functionalizing self-assembled monolayers with azidoformate residues.[77] Irradiation through a mask converted the exposed azidoformate groups to the urethanes, leaving the remaining carbonyl azides as electrophilic sites for further reaction.

Related Reagents. *t*-Butyl Azidoformate; *p*-nitrobenzenesulfonyloxyurethane

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G

Gallium Trichloride

[13450-90-3] $GaCl_3$ *(MW 179.03)*

(used as a Lewis acid or a precursor of organogallium reagents)

Physical Data: mp 77.9 °C; bp 201.3 °C; *d* 2.47 g cm^{-3}.

Solubility: soluble in hexane, benzene, diethyl ether, ethanol, and other organic solvents as well as water.

Form Supplied in: colorless solid.

Purification: high-purity (99.999%) gallium trichloride is available.

Handling, Storage, and Precautions: moisture sensitive. A convenient way of handling this compound is to prepare a methylcyclohexane stock solution. The solvent is liquid over a wide range of temperature from −126 °C to 101 °C. Toxicity of gallium nitrate (i.v.) rat LD_{50}: 46 mg kg^{-1}.

Original Commentary

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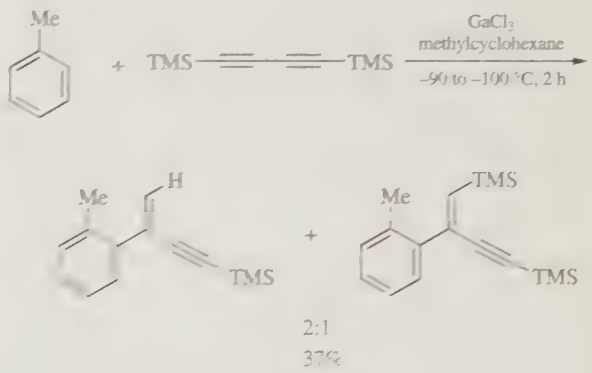
Lewis Acid. Gallium trichloride has been used in Friedel–Crafts alkylation and acylation reactions as a Lewis acid.[1] Although its acidity is generally considered to be lower than that of aluminum trichloride, another group 13 Lewis acid, its high solubility in organic solvents makes it useful for kinetic studies. Recent studies, however, have revealed novel aspects of this compound in electrophilic aromatic substitution reactions. Spectroscopy revealed that gallium trichloride interacts with π-acids such as silylethyne[2] or silylallene.[3] The complexes are strongly electrophilic compared with conventional alkenylating reagents, and react with aromatic hydrocarbons even at −78 °C to give β-silylalkenylated arenes. *Ipso*-substitution takes place with 1,2,3-trimethoxybenzene at the 2-position, and treatment of the arenium cation thus formed with organomagnesium compounds gives the 2,5-dihydrobenzene alkylated at the 5-position. The silylethyne–gallium trichloride complex, in the absence of an aromatic hydrocarbon, spontaneously trimerizes to a conjugated trienyl cation which, on treatment with organolithium or magnesium compounds, gives alkylated trienes.[4] In the presence of gallium trichloride, cationic species appear to gain a lifetime sufficient to allow attack by organometallic reagents. Some unusual orientations have also been observed in aromatic substitutions using gallium trichloride. The reaction of toluene and bis-silylated buta-1,3-diyne gives an *ortho*-substituted product exclusively,[5] and even isopropylbenzene reacts at the *ortho*-position predominantly. The tendency of the reaction to occur at the vicinity of the alkyl substituent, however, is restricted to diyne-based electrophiles. Other closely related electrophiles derived from silylethyne, silylallene, or bis-silylated 1,3,5,7-octatetrayne and gallium trichloride exhibit normal orientation. Gallium trichloride is also used in catalytic aromatic acylation reactions.[6] Aliphatic and aromatic acid anhydrides react with anisole derivatives in the presence of 10 mol % gallium trichloride and 10–20 mol % silver perchlorate to give the *para*-acylated products.

The interaction of gallium trichloride with a π-acid results in regioselective reduction of an aldehyde group located in the vicinity of an ethynyl group.[7]

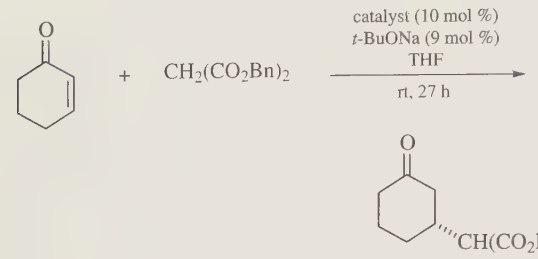
Gallium trichloride shows strong affinity toward halogens.[8] *ortho*-Acylation of anilines with nitriles has been known to take place in the presence of boron trichloride. When gallium trichloride is added, the reaction is accelerated; this is ascribed to the abstraction of chlorine from the organoboron intermediate with concomitant formation of the stable gallium tetrachloride anion. It turns out that gallium trichloride is more effective than aluminum trichloride in this transformation.

The soft nature of gallium is effectively utilized in the activation of dithioacetals. In the presence of gallium trichloride and water, thioacetals are hydrolyzed to aldehydes and ketones.[9] Allylstannanes react with thioacetals to give allylated products (eq 1).[10]



(1)

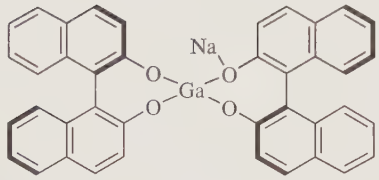
Asymmetric Catalysis. Gallium–sodium–bis(binaphthoxide) (GaSB) prepared from gallium trichloride, sodium *tert*-butoxide (four equiv) and BINOL (two equiv) is an excellent catalyst for the asymmetric Michael addition of malonate to cyclopentenone and cyclohexenone.[11] Use of 10 mol % of the catalyst gives the adducts in high yields and high enantiomeric excesses up to 98% ee (eq 2). The reaction can be accelerated by the presence of one more equivalent of sodium *tert*-butoxide, indicating the rapid complex formation between sodium malonate and GaSB. Gallium–lithium–bis(binaphthoxide) (GaLB) catalyst is prepared from gallium trichloride and lithiated binaphthol, and is used in the asymmetric ring-opening reaction of *meso*-epoxides with 1,1-dimethylethanethiol.[12] The reaction, being accelerated by the presence of MS 4A, is conducted with 10 mol % of the complex giving the thioalcohol of 98% ee from cyclohexene oxide. The asymmetric ring-opening of the same epoxide oxide with *para*-methoxyphenol is catalyzed by 20 mol % of the GaLB catalyst to give the alkoxycyclohexanol in 93% ee.[13]



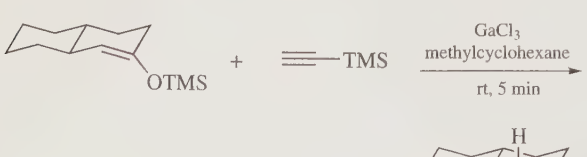
(2)

87%, 98% ee

Catalyst =



Carbometalation. Carbometalation (carbogallation) with a carbon–carbon triple bond has become an important reaction of organogallium compounds. Carbogallation was first found in the dimerization of alkynylgallium reagents;[14] reaction of silylated 1-alkynes with gallium trichloride gave enynes. Alkynyldichlorogalliums generated by transmetalation turn out to be unstable in hydrocarbon solvents and spontaneously dimerize to give bisgallated enynes. Such carbogallation reactions also take place between allylgallium and 1-alkynes to give gallated 1,3-dienes.[15] The alkyne should either be 1-gallated or 1-silylated for the carbogallation to occur. Gallium enolate and ethynylgallium, which are generated from silyl enol ethers and silylethyne by treatment with gallium trichloride undergo carbogallation (eq 3).[16] After acid work-up, α-ethenylated ketones are obtained. This is a novel and convenient method to ethenylate enolate derivatives. Equatorial preferences are observed in the ethenylation of cyclohexanone enolates.[17] These results are in contrast to the stereochemistry observed in enolate alkylation, which takes place from the axial surface of the enolate plane. In general, isomerization to the thermodynamically stable conjugated enone is not observed. The ethenylation also occurs with silylated 1,3-dicarbonyl compounds,[18] and ethenylmalonate possessing an acidic proton can be synthesized by this method. The ethenylmalonate is relatively insensitive to acid, while it rapidly isomerizes to the conjugated product in the presence of triethylamine. Analogously, gallium phenoxide reacts with silylethyne to give *ortho*-(β-silylethenyl)phenols.[19] These studies revealed that organogallium compounds undergo carbometalation reactions similar to organotin compounds. The enolate and phenoxide of both organometallic reagents carbometalate with carbon–carbon triple bonds. The above serves as an interesting example of the fact that organometallic reagents of elements arranged diagonally in the periodic table exhibit similar reactivities.



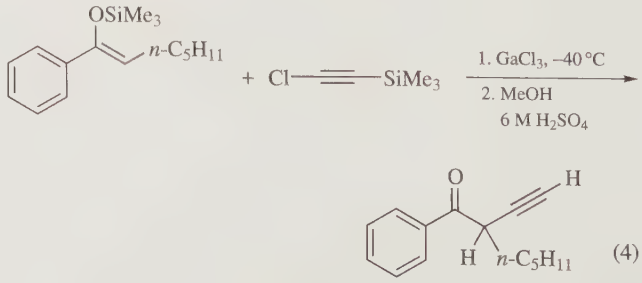
(3)

52%

First Update

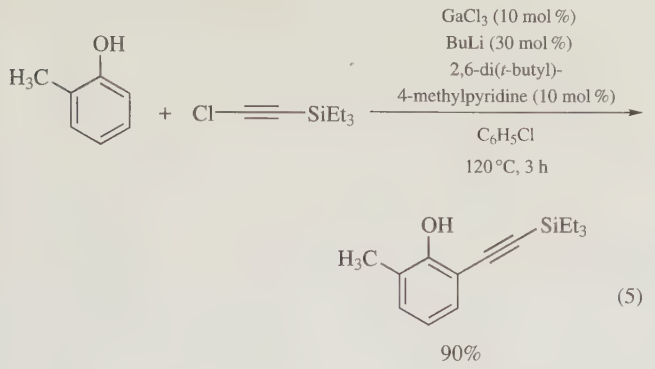
Shigeki Matsunaga & Masakatsu Shibasaki
University of Tokyo, Tokyo, Japan

Carbometallation. Gallium lies in the middle of the XIII group (B, Al, Ga, In, and Tl). In addition to the vertical relationship, a diagonal relationship to Sn was also noted.[19] Recently, many reactions utilizing gallium-specific behavior were reported.[20] In the reaction style of carbometallation (carbogallation) with a carbon-carbon triple bond, notable advances were achieved to broaden substrate scope and to enable catalytic use of gallium trichloride. In the one-step ethenylation reaction using stoichiometric gallium trichloride, the reaction was extended to thioester silyl enolate and dienolate donors.[21] By using trimethylsilylchloroethyne instead of trimethylsilylethyne, one-step α-ethynylation of enol silyl ethers was realized at −40 °C within 5 min,[22] although stoichiometric gallium trichloride was essential. Acidic work-up with 6 M sulfuric acid is employed. α-Ethynylation of α-monosubstituted enol silyl ethers was also successful to afford products in good yield (eq 4). To avoid undesired isomerization of α-ethynyl ketones, the products were purified by flash column chromatography at −78 °C. The sequential carbometallation/elimination reaction was demonstrated to afford conjugated polyenes in one-pot.[23] Important progress in the carbometallation reaction is the use of catalytic gallium trichloride. By using triethylsilylchloroethyne instead of trimethylsilylchloroethyne, and by raising the reaction temperature, catalytic α-ethynylation was realized. It has been found that 10 mol % of gallium trichloride, 30 mol % of BuLi, and 10 mol % of 2,6-di(*t*-butyl)-4-methylpyridine were effective for one-step *ortho*-ethynylation of phenols.[24] The reaction proceeded at 120–160 °C within 3 h, and the products were obtained in 68–90% yield (eq 5). To effect the catalytic process, the reaction is performed at over 120 °C. When using 1 equiv of gallium trichloride, the reaction proceeds at 80 °C. The reaction system was also applicable to one-step *ortho*-ethynylation of *N*-benzylanilines, although 100 mol % of BuLi and 20 mol % of gallium trichloride were required.[25] A similar strategy was also successfully applied to catalytic α-ethynylation reaction of enol silyl ethers.[26] The reaction proceeded smoothly at 130 °C in methylcyclohexane with 10 mol % of gallium trichloride. In the α-ethenylation reaction, direct use of ketones instead of enol silyl ethers was realized using catalytic gallium trichloride and amine base.[27] The coupling of cyclic ketones and triethylsilylethyne was promoted by 10 mol % of gallium trichloride and 10 mol % 2,6-di(*t*-butyl)-4-methylpyridine at 180 °C in *o*-dichlorobenzene.



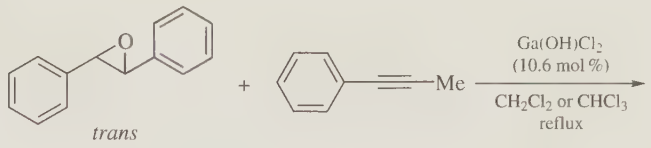
(4)

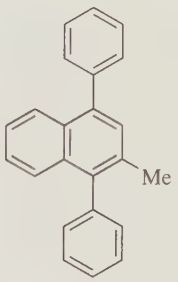
93%



(5)

90%

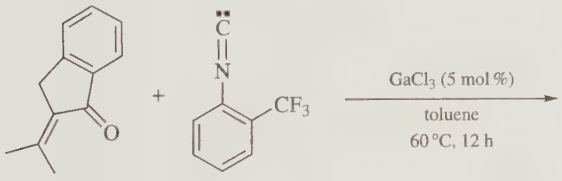


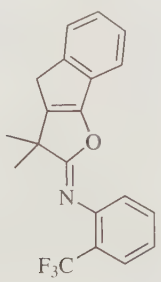


(7)

93%

Lewis Acid. The π-acidic nature of gallium trichloride was utilized in cycloisomerization reactions. Gallium trichloride activated alkynes effectively, thus promoting the skeletal reorganization of enynes[28] and ω-aryl-1-alkynes.[29] This example is the first use of a main-group metal halide as catalyst for skeletal reorganization of enynes. The reactivity of gallium trichloride in this reaction is ascribed to the relative softness of gallium(III). Gallium trichloride compared favorably with aluminum halides in a [4 + 1] cycloaddition of α, β-unsaturated carbonyl compounds and isocyanides, affording unsaturated γ-lactone derivatives (eq 6).[30] Gallium trichloride gave better results than Et_2AlCl, $ZrCl_4$, $Yb(OTf)_3$, $Y(OTf)_3$, and $In(OTf)_3$. The relatively low affinity of gallium trichloride towards oxygen or nitrogen atoms enabled catalytic use of gallium trichloride. Gallium trichloride was also an effective promoter in a [3 + 2] cycloaddition of alkenyl Fisher carbene complexes with imines. The yield of 3-pyrroline derivatives was enhanced by 10 mol % of gallium trichloride from 55% (without gallium trichloride) to 82%, although the exact role of gallium trichloride is not clear.[31] $Ga(OH)Cl_2$ generated from gallium trichloride was effective for activation of aldehydes[32] and epoxides[33] towards nucleophilic attack of alkynes. Sequential ring opening of epoxides, and cyclization with alkynes proceeded with complete regioselectivity using 10 mol % of gallium trichloride in chloroform (eq 7). Gallium trichloride gave better results than indium trichloride and $In(OTf)_3$. In the Mannich-type reaction of trifluoromethylated *N,O*-hemiacetal with silyl enolates, the strong protic acid ($H^+GaCl_3Cl^-$) generated from gallium trichloride was a suitable promoter.[34]



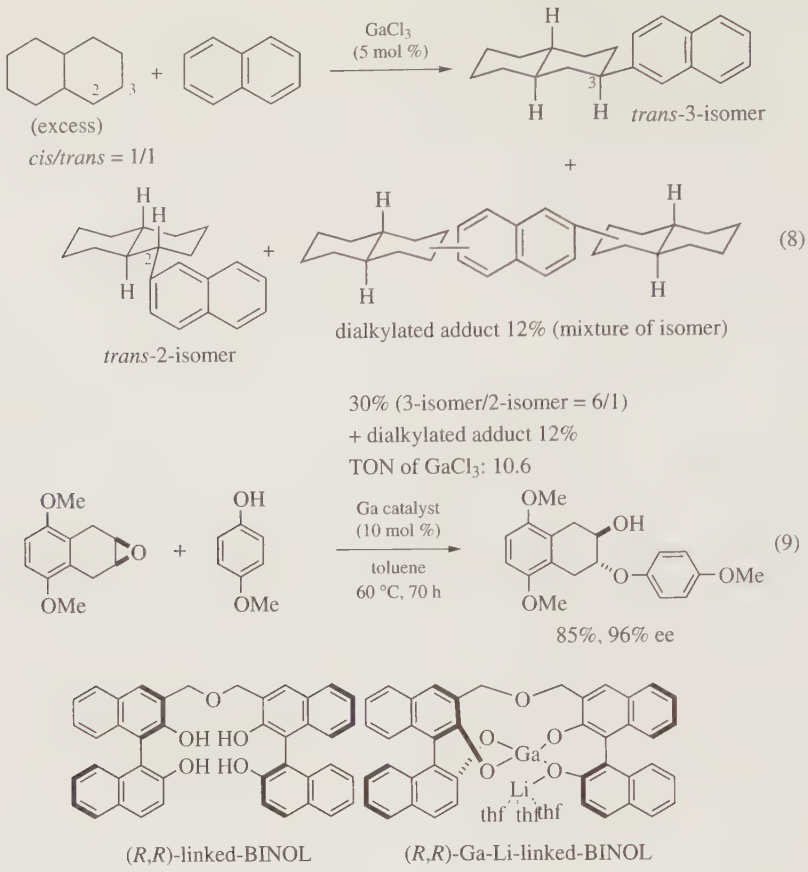


(6)

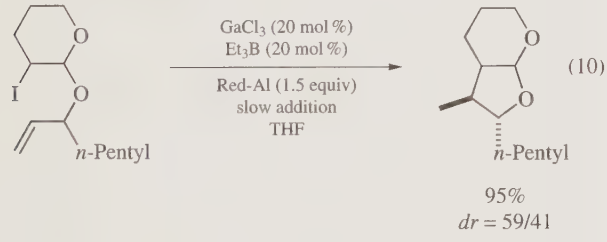
C–H Activation. Gallium trichloride catalyzes the aromatic alkylation of naphthalene or phenanthrene using cycloalkanes.[35] The reaction proceeded preferably at equatorial position of cycloalkanes (eq 8).[36] Although the substrate scope is rather limited, the reaction is mechanistically quite interesting. Catalytic gallium trichloride promoted a carbon-carbon bond formation between aromatic hydrocarbons and aliphatic hydrocarbons without added oxidizing agent. The turnover number of the reaction based on gallium trichloride was 10.6, counting dialkylation twice. When the reaction was performed with pure *cis*-bicyclo[4.4.0]decane, the reaction rate was higher than that with pure *trans*-bicyclo[4.4.0] decane. From both *cis*- and *trans*- bicyclo[4.4.0]decane, the *trans*-product was obtained predominantly. These results suggested that a tertiary C–H bond is activated initially, followed by migration of carbocation and trapping with aromatic hydrocarbons. The higher reaction rate of *cis*-isomer indicates equatorial selective activation of the tertiary C–H bond in cycloalkanes and would be the most probable mechanism.

Asymmetric Catalysis. The instability problem of GaLibis-(binaphthoxide),[12,13] prepared from gallium trichloride, BuLi, and BINOL, was improved by a novel chiral ligand, linked-BINOL.[37] Ga-Li-linked-BINOL complex was effective for the catalytic asymmetric ring-opening of epoxides with *para*-methoxyphenol. Epoxide opening proceeded with 10 mol % the linked-BINOL catalyst, and the diol mono aryl ether was obtained in 85% yield and 96% ee (eq 9).

Other Reagents Prepared from Gallium Trichloride. The gallium hydride reagent $HGaCl_2$ was found to promote radical reactions like organotin hydrides. $HGaCl_2$ was prepared from gallium trichloride (2 equiv) and sodium bis(2-methoxyethoxy) aluminum hydride (Red-Al, 1.0 equiv) in THF at 0 °C for 30 min. Stoichiometric amounts of $HGaCl_2$ were effective in radical reductions of various halides and in radical cyclizations of halo acetals.[38] Considering the price of gallium trichloride, catalytic use of gallium trichloride is desirable. Radical cyclization proceeded smoothly with 20 mol % of gallium trichloride, 20 mol % of Et_3B, and 1.5 equiv of Red-Al to afford cyclized adducts in 64–95% yield (eq 10).[38] Red-Al is added slowly to avoid the formation of undesired species such as GaH_3. Water tolerant allylic and allenyl gallium reagents were prepared from organomagnesium reagents and gallium trichloride.[39] Alkenyl gallium reagents can be prepared from alkenyl magnesium reagents[40] and by



radical hydrogallation of alkynes using $HGaCl_2$ and Et_3B. Alkenyl gallium reagents are used in palladium-catalyzed cross-coupling reaction with aryl halides.[40]



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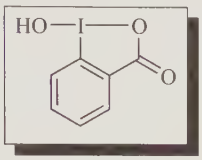
H

1-Hydroxy-1,2-benziodoxol-3(1*H*)-one[1]



[131-62-4] $C_7H_5IO_3$ (MW 264.02)

(cleavage of phosphates,[2] oxygenation of α,β-unsaturated carbonyl compounds,[3] α-hydroxylation of ketones,[4] methoxylation of steroids,[5] oxidation of sulfides,[6] chemical cleavage of proteins,[7] palladium-catalyzed coupling with arylboronic acids,[8] preparation of iodonium salts,[9] synthesis of benziodoxole derivatives[10])

Alternate Name: 2-iodosobenzoic acid; 2-iodosylbenzoic acid; *o*-iodosobenzoic acid; *o*-iodosylbenzoic acid; IBA [304-91-6].

Physical Data: mp 231–232 °C (dec).

Solubility: soluble in H_2O, DMSO, alcohol; insoluble in ether, CH_2Cl_2, MeCN, and nonpolar organic solvents.

Form Supplied in: white microcrystalline solid; commercially available; typical impurities: 2-iodobenzoic acid and 2-iodoxybenzoic acid.

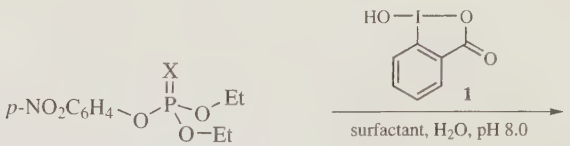
Analysis of Reagent Purity: iodometric titration,[11] elemental analysis, ^{1}H NMR.

Preparative Methods: oxidation of 2-iodobenzoic acid with fuming nitric acid at 50 °C;[12] chlorination of 2-iodobenzoic acid followed by hydrolysis with aq NaOH;[13] oxidation of 2-iodobenzoic acid with $NaIO_4$ in boiling 30% aq acetic acid;[14] oxidation of 2-iodobenzoic acid with potassium persulfate in H_2SO_4 at 0 °C.[15]

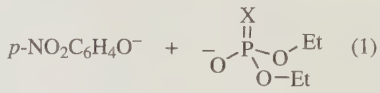
Purification: dissolution in aq NaOH followed by acidification to pH 3 by addition of 5% aq acetic acid.[11]

Handling, Storage, and Precautions: can be stored indefinitely long in the dark; refrigeration should be used for long-term storage.

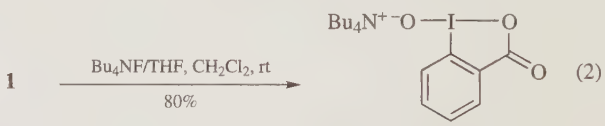
Catalyst in the Cleavage of Phosphate Esters. Since the mid-1980s 1-hydroxy-1,2-benziodoxol-3(1*H*)-one and its derivatives have attracted considerable research interest due to their excellent catalytic activity in the hydrolytic cleavage of reactive phosphates, phosphonates, and carboxylates.[2] This activity is explained by a pronounced *O*-nucleophilicity of the benziodoxole anion due to the α-effect.[2] Typical reaction conditions include micellar aq cetyltrimethylammonium chloride (CTACl) at pH 7.5–8.0 (phosphate buffer); a representative hydrolytic cleavage of insecticides paraoxone and parathione with benziodoxole (**1**) is shown in eq 1.[2a] It has been demonstrated that under similar conditions dilute solutions of benziodoxole (**1**) can efficiently cleave numerous phosphates and phosphonates, including the fluorophosphonate nerve agents sarin and soman.[2b]

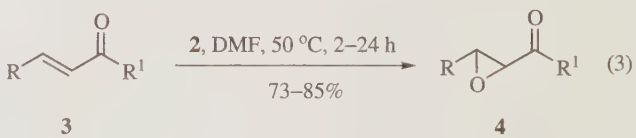


X = O, paraoxone
X = S, parathione



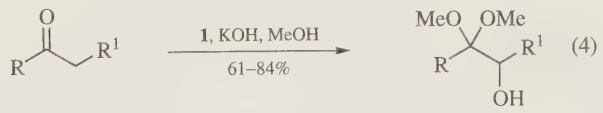
Oxygenation of α,β-Unsaturated Carbonyl Compounds. The treatment of benziodoxole (**1**) with tetrabutylammonium fluoride affords tetrabutylammonium salt (**2**) (eq 2), which can be used without isolation as an efficient nucleophilic oxygen atom transfer reagent.[3] Reagent **2** reacts with α,β-unsaturated carbonyl compounds (**3**) yielding *trans*-epoxides (**4**) with high stereoselectivity (eq 3). This reaction probably involves a nucleophilic attack of the oxyanion of **2** on the electron-deficient double bond followed by reductive elimination of *o*-iodobenzoate anion.[3] The sodium salt of benziodoxole (**1**) can also effect epoxidation of α,β-unsaturated carbonyl compounds, but the yields of products (**4**) in this case are much lower.[3]





R = PhC(O), R^1 = Ph; R = Me, R^1 = Ph; R = Ph, R^1 = Ph; etc.

α-Hydroxylation of Ketones. 1-Hydroxy-1,2-benziodoxol-3(1*H*)-one (**1**) in methanolic KOH at room temperature converts various ketones (**5**) to α-hydroxydimethylacetals (**6**) in high yield (eq 4).[4] The mechanism of this reaction (eq 4) involves nucleophilic addition of the enolate anion to the hypervalent iodine atom in **1** followed by reductive elimination of *o*-iodobenzoic acid and acetal formation. Reagent **1** is particularly convenient because the reduction product *o*-iodobenzoic acid is soluble under the basic reaction conditions thus allowing isolation of the oxidation product (**6**) by simple extraction with dichloromethane. α-Hydroxydimethylacetals (**6**) can be hydrolyzed to the respective α-hydroxyketones by treatment with 5% H_2SO_4 in chloroform. α-Hydroxylation of ketones using the alternative reagent, (diacetoxyiodo)benzene, gives lower yields and the reaction work-up is not as convenient.

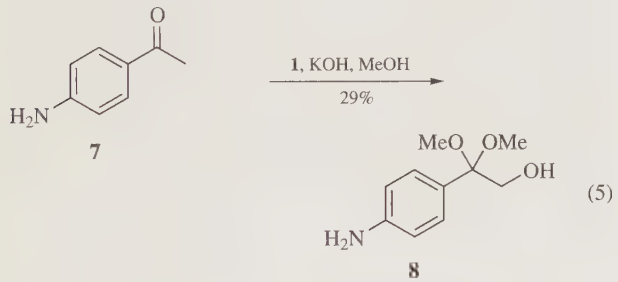


(4)

5 **6**

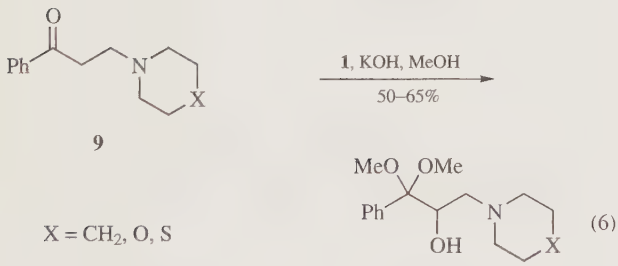
R = Ph, R^1 = Me; R = Ph, R^1 = Et; R = Et, R^1 = Et;
R + R^1 = $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_{10}$, etc.

This reaction (eq 4) has been successfully applied to a series of para-substituted acetophenones, 1-phenyl-1-propanone, 3-pentanone, cyclopentanone, cyclohexanone, cycloheptanone, cyclododecanone, 2-methylcyclohexanone, 2-norbornanone, and benzalacetone.[4] The α-hydroxylation procedure is compatible with the presence of the amino or thioether groups in substrate. For example, various aminoketones (**7**, **9**, **11**) can be selectively converted into the respective α-hydroxydimethylacetals (**8**, **10**, **12**) using reagent **1** without oxidation at primary, secondary, and tertiary amino groups, or at the sulfur atom in the case of a morpholino group (eqs 5, 6, and 7).[16]



(5)

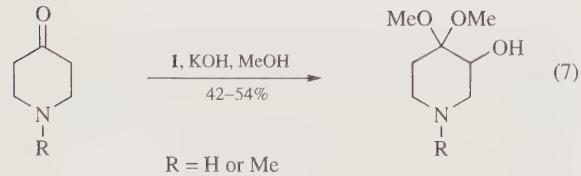
7 **8**



(6)

X = CH_2, O, S

9 **10**

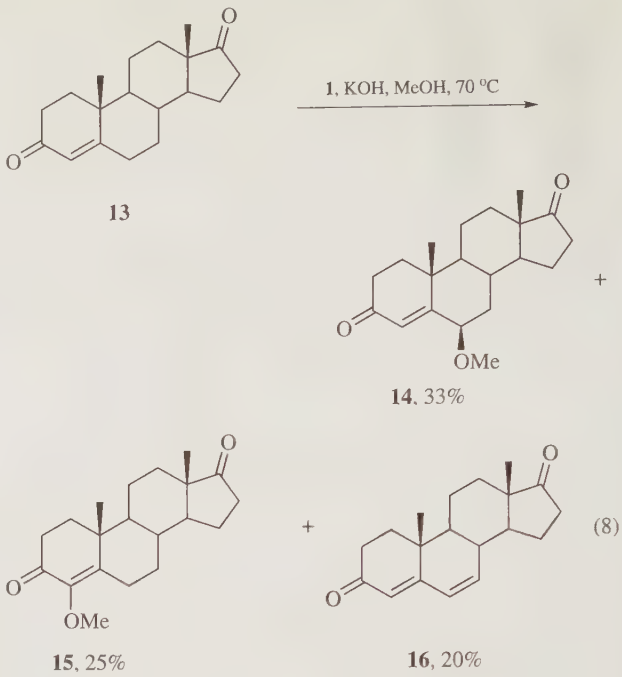


(7)

R = H or Me

11 **12**

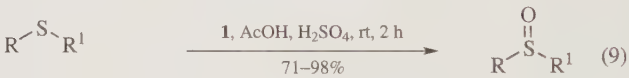
Methoxylation of Steroids. The reaction of 1-hydroxy-1,2-benziodoxol-3(1*H*)-one (**1**) with enolizable steroidal 4-en-3-ones and 17-ones in methanolic KOH affords products of methoxylation along with products of dehydrogenation.[5] For example, treatment of 4-androstene-3,17-dione (**13**) with reagent **1** and KOH in methanol gave methyl ethers **14** and **15** and the dehydrogenated product, the 4,6-dienone (**16**) (eq 8).[5a]



(8)

13 **14**, 33% **15**, 25% **16**, 20%

Oxidation of Sulfides. Organic sulfides are oxidized by 1-hydroxy-1,2-benziodoxol-3(1*H*)-one (**1**) in a mixture of acetic and sulfuric acids at room temperature to produce sulfone-free sulfoxides (eq 9).[6] The oxidation of sulfides can also be performed by using hydrogen peroxide as the oxidizer and 0.1 equiv of benziodoxole (**1**) as a catalyst in methanol.[17] The alternative reagents for oxidation of sulfides, (diacetoxyiodo)benzene or iodosylbenzene, are generally less selective oxidizers and may require the presence of a bromide salt, montmorillonite, or alumina as a catalyst.[1]



(9)

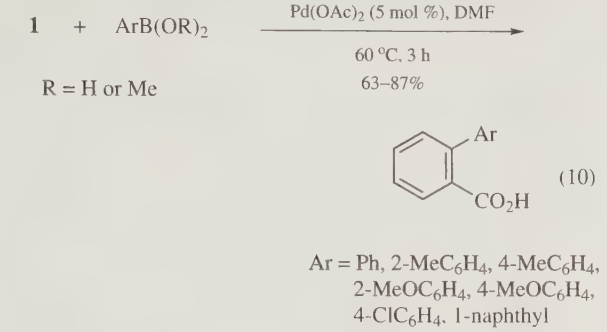
R, R^1 = alkyl, aryl

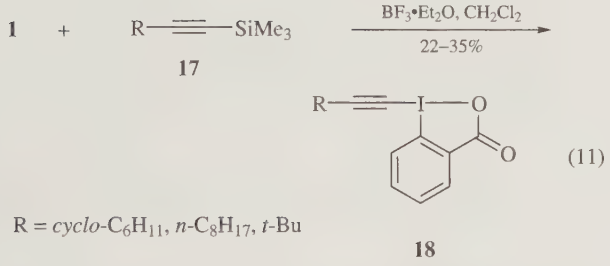
Chemical Cleavage of Proteins. 1-Hydroxy-1,2-benziodoxol-3(1*H*)-one (**1**) in acetic acid in the presence of guanidinium hydrochloride is used as a reagent for the cleavage of proteins at tryptophan and tyrosine residues.[11] The mechanism of this cleavage reaction involves oxidative halogenation of the indole nucleus of tryptophan and the phenol ring of tyrosine. Addition of *p*-cresol as a scavenger for tyrosine modification allows selective cleavage at tryptophan.[7]

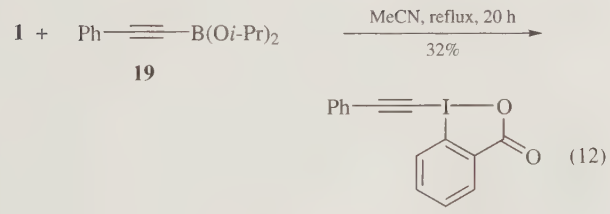
Palladium-catalyzed Coupling Reaction with Arylboronic Acids and Aryl Borates. Biaryl-2-carboxylic acids can be prepared by palladium-catalyzed coupling reaction of 1-hydroxy-1,2-benziodoxol-3(1*H*)-one (**1**) with arylboronic acids or arylborates with good yields under mild conditions (eq 10).[8]

Preparation of Aryl and Alkynyl Iodonium Salts. 1-Hydroxy-1,2-benziodoxol-3(1*H*)-one (**1**) is used as starting material for the preparation of various iodonium salts. Diphenyliodonium-2-carboxylate, which is commonly used as a convenient benzyne precursor, is prepared by the reaction of compound **1** with benzene in sulfuric acid followed by neutralization with aq sodium

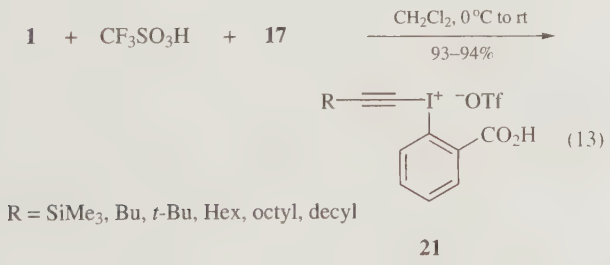
hydroxide or ammonium hydroxide.[9] Alkynylbenziodoxoles (**18**) are prepared by treatment of alkynyltrimethylsilanes (**17**) with reagent **1** in the presence of BF_3-etherate followed by heating with methanol and column chromatography (eq 11).[18] An alternative synthesis of alkynylbenziodoxole (**20**) consists in the reaction of reagent **1** with alkynylboronate (**19**) in refluxing acetonitrile (eq 12).[19]



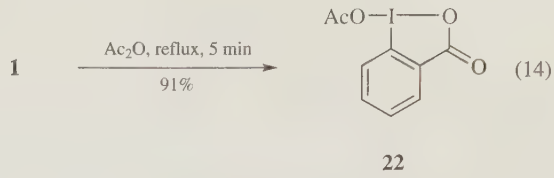




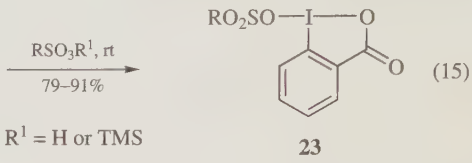
Alkynyl(*o*-carboxyphenyl)iodonium triflates (**21**) are prepared by the reaction of reagent (**1**) with trifluoromethanesulfonic acid and alkynyltrimethylsilanes (**17**) (eq 13).[20]



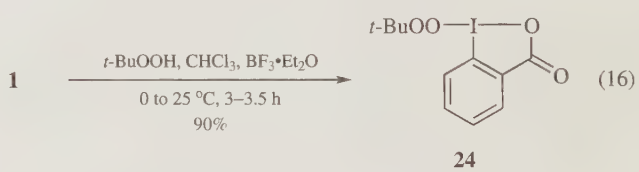
Preparation of 1-Acetoxy-1,2-benziodoxol-3(1*H*)-one. 1-Hydroxy-1,2-benziodoxol-3(1*H*)-one (**1**) can be converted to the acetoxy derivative (**22**) by heating with acetic anhydride (eq 14).[13] Acetate (**22**) is commonly used for the preparation of other iodine substituted benziodoxoles, such as, phosphoranyl-derived benziodoxoles,[21] azido-, and cyanobenziodoxoles.[22]



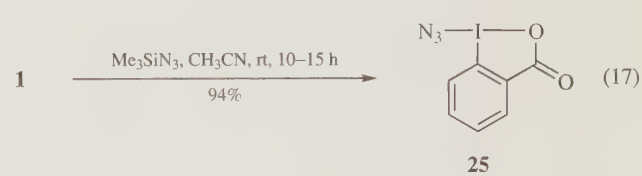
Preparation of Benziodoxole Sulfonates. The sulfonate derivatives (**23**) can be conveniently prepared in a simple, one-step procedure by the treatment of hydroxybenziodoxole (**1**) with the corresponding sulfonic acids or trimethylsilyltriflate (eq 15).[20c,23] Sulfonates (**23**) are isolated as moderately hygroscopic, but thermally stable, crystalline solids.



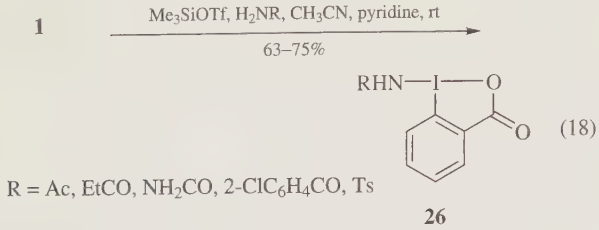
Preparation of 1-(*tert*-Butylperoxy)-1,2-benziodoxol-3(1*H*)-one. A useful oxidizing reagent, 1-(*tert*-butylperoxy)-1,2-benziodoxol-3(1*H*)-one (**24**), is prepared by treatment of hydroxybenziodoxole (**1**) with *tert*-butyl hydroperoxide in the presence of BF_3-etherate (eq 16).[10] Peroxide (**24**) is a stable, crystalline product which can be safely stored at room temperature for an indefinite period of time.



Preparation of 1-Azido-1,2-benziodoxol-3(1*H*)-one. The stable hypervalent iodine azide, 1-azido-1,2-benziodoxol-3(1*H*)-one (**25**), can be synthesized in one step by the reaction of hydroxybenziodoxole (**1**) with trimethylsilyl azide in acetonitrile (eq 17).[24] Azide (**25**) is a thermally stable, nonexplosive crystalline solid, and a useful azidating reagent.



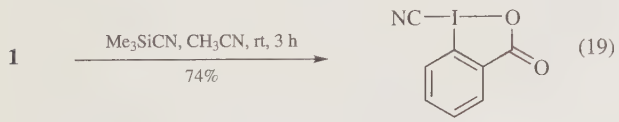
Preparation of Amidobenziodoxoles. Amidobenziodoxoles (**26**) can be conveniently prepared in one step from hydroxybenziodoxole (**1**), trimethylsilyltriflate, and the appropriate amide, RNH_2 (eq 18).[25] Amides (**26**) are thermally stable, white, nonhygroscopic, microcrystalline solids, and useful amidating reagents.



(18)

26

Preparation of 1-Cyano-1,2-benziodoxol-3(1*H*)-one. The stable hypervalent iodine cyanide, 1-cyano-1,2-benziodoxol-3(1*H*)-one (**27**), can be synthesized in one step by the reaction of hydroxybenziodoxole (**1**) with cyanotrimethylsilane (eq 19).[26] Cyanide (**27**) is a thermally stable, nonexplosive crystalline solid, and a useful cyanating reagent.



(19)

27

Related Reagents. 1,2-Benziodoxol-3(1*H*)-one derivatives; iodosylbenzene; (diacetoxyiodo)benzene; IBX; DMP.

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Hypofluorous Acid[1]

(HOF)		
[14034-79-8]	FHO	(MW 36.01)
(HOF·MeCN)		
[147583-45-7]	C_2H_4FNO	(MW 77.07)

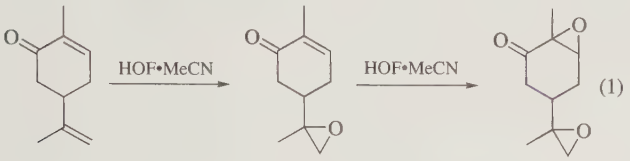
(the HOF·MeCN complex is used for tertiary hydroxylations,[2] epoxidations,[3] and oxidation of amines,[4] alcohols and ketones,[5] aromatics,[6] and sulfides[7])

Physical Data: mp −117 °C; bp −79 °C/1 mmHg; ^{19}F NMR δ +27.5 ppm (of the MeCN complex, −8.5 ppm).

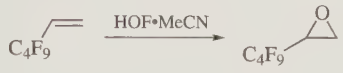
Handling, Storage, and Precautions: HOF is a very unstable substance and of little use in synthetic chemistry. Neat liquid HOF can be unpredictably explosive at temperatures above −40 °C. Its acetonitrile complex is much more stable but nevertheless has to be prepared in situ and, for all practical purposes, has to be reacted soon after its formation. The concentration of the reagent is determined iodometrically (HOF + 2KI → I_2 + KF + KOH). Both forms of the hypofluorous acid may be toxic and should be treated accordingly. Use in a fume hood.

Epoxidation. HOF was synthesized originally by Appelman,[8] but it was hardly a useful synthetic reagent since it was difficult

to make and could be generated only in very minute amounts. Still, it was demonstrated that it can react with a few unsaturated compounds.[9] Recently, it was discovered that HOF can be prepared simply by passing ***Fluorine*** through aqueous ***Acetonitrile***, thus forming a stabilized complex HOF·MeCN.[3,10] Possessing a strong electrophilic oxygen, it is an excellent oxygen transfer agent which epoxidizes a wide variety of alkenes (eq 1),[3a,c] including very deactivated ones which cannot be directly epoxidized by any other method (eq 2).[3b]



(1)

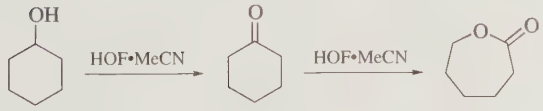


(2)

Other Oxidations. The electrophilic properties of the oxygen have been put to use for attacking the deactivated, relatively electron-rich, tertiary C–H bond, resulting in tertiary hydroxylation as demonstrated, for example, by 4-*t*-butylcyclohexanol acetate (eq 3).[2] Being a strong oxidizer, HOF·MeCN can oxidize amines to the corresponding nitro derivatives (eq 4),[4] alcohols to ketones (eq 5),[5] and sulfides to sulfones.[7] The reactions proceed at 0 °C, in a few minutes and usually in very good yields. On prolonging the reaction time and using an excess of reagent, ketones are also oxidized to the corresponding esters much faster than with the peroxy acids used in the conventional Baeyer–Villiger oxidation (eq 5).[5] The reagent can also hydroxylate and otherwise oxidize many aromatic compounds (eq 6), although yields are moderate.[6] It should be mentioned that ***Xenon(II) Fluoride***/H_2O form in situ HOXeF, which adds the elements of H and OF across some alkenes (eq 7).[11]

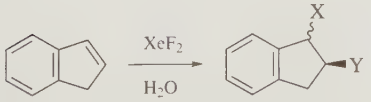
(3)

(4)



(5)

(6)



(7)

X = OH, Y = F (*cis* and *trans*)
X = F, Y = OH (*cis* and *trans*)

1. Appelman, E. H., *Acc. Chem. Res.* **1973**, *6*, 113.
2. Rozen, S.; Brand, M.; Kol, M., *J. Am. Chem. Soc.* **1989**, *111*, 8325.
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10. Appelman, E. H.; Dunkelberg, O.; Kol, M., *J. Fluorine Chem.* **1992**, *56*, 199.
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Hypofluorous Acid, Acetonitrile Complex[1]

HOF·MeCN

[147583-45-7] C_2H_4FNO (MW 77.07)

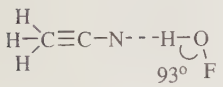
(the HOF · CH_3CN complex is used for tertiary hydroxylations,[2] epoxidations,[3] oxidation of amines,[4] alcohols and ketones,[5] aromatics,[6] sulfides and thiophenes,[7] amino acids,[8], ethers,[9] and acetylenes.[10] It is also useful in other oxygen transfer reactions such as hydroxylations α to carbonyls[11] and the preparation of tertiary *N*-oxides[12])

Physical Data: (for the non-complexed HOF): mp −117 °C; bp −79 °C (1 Torr); ^{19}F NMR +27.5 ppm. ^{19}F NMR for the HOF · MeCN complex: −8.5 ppm. Enthalpy of formation of the complex: 14.3 kJ mol^{-1}.[13]

Handling, Storage, and Precautions: while HOF is a very unstable substance and of little use in synthetic chemistry, its acetonitrile complex is much more stable. Nevertheless, it has to be prepared in situ and for all practical purposes reacted soon after its formation. The concentration of the reagent is determined iodometrically (HOF + 2KI → I_2 + KF + KOH). The reagent may be toxic and should be treated accordingly. Still, since it is an heavy metal-free agent, and its only side product is aqueous HF which may be easily neutralized, it is considered to be an ecologically friendly reagent.[5a] Free HOF was originally synthesized by Appelman,[14] but it was hardly a useful synthetic reagent since it was difficult to make, could be generated only in very minute amounts and has a very short half-life time at temperatures above −100 °C. Even so, it was demonstrated that it can react with a few unsaturated compounds.[15] Some years ago it was discovered that a much more stable form of HOF can be prepared simply by passing commercially available prediluted

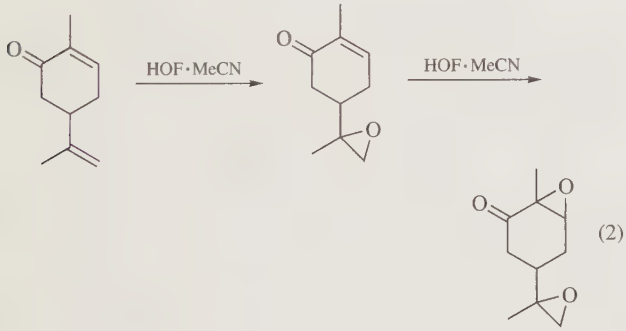
F_2 through aqueous acetonitrile thus forming a stabilized complex HOF · MeCN.[1] It should be noted that it is also possible to prepare any desirable F_2/N_2 mixtures from 95% fluorine and nitrogen using a vacuum line system.[12] The X-ray structure of the complex[16] reveals that the acetonitrile nitrogen atom is coordinatively bonded to the hydrogen atom of the HOF forming almost a straight chain with the OF bond forming an angle of 93° (eq 1). The reagent possesses a strongly electrophilic hydroxylium moiety (HO^+) turning the reagent into an excellent oxygen transfer agent.

$$F_2 + MeCN + H_2O \longrightarrow HOF{\bullet}MeCN \qquad (1)$$



from the X-ray structure of the HOF•MeCN complex

Epoxidations. The reagent is able to epoxidize practically any type of olefin (eq 2) including very deactivated ones which cannot be directly epoxidized by any other method (eqs 3 and 4).[3]



(2)

$$C_4F_9CH{=}CH_2 \xrightarrow{HOF{\cdot}MeCN} C_4F_9CH(O)CH_2 \qquad (3)$$

(4)

X = COOR; Y = H
X = H; Y = COOR

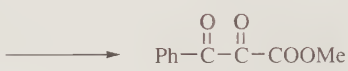
cis (from maleates)
trans (from fumarates)

Since it is a very powerful oxygen transfer agent, short reaction times and low temperatures are sufficient for most epoxidations. As a result, sensitive substrates such as polyaromatics could also be epoxidized with much higher yield compared to other routes. Thus, for example, pyrene was allowed to react with HOF · MeCN for 5 s at −15 °C, forming pyrene-4,5-oxide in 80% yield (eq 5).[17] Unlike other epoxidation reagents, HOF · MeCN was also able to epoxidize unsaturated free carboxylic acids in excellent yields (eq 6).[18]

Reaction with Acetylenes. HOF · MeCN reacts with most acetylenic compounds via the corresponding *gem*-diepoxides (eqs 7 and 8). The products are similar to the ones obtained with other oxidants although the yields are usually much higher, the reaction times considerably shorter and the whole process takes place at room temperature. Internal acetylenes are usually oxidized to vicinal diketones while external ones lose a CO fragment forming aldehydes.[19]

(5)

$$Me(CH_2)_7CH{=}CH(CH_2)_7COOH \xrightarrow{HOF{\bullet}MeCN} Me(CH_2)_7CH(O)CH(CH_2)_7COOH \qquad (6)$$



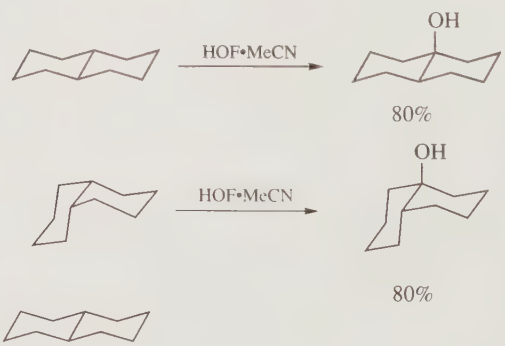
(7)

95%

$$Ar{-}C{\equiv}C{-}H \xrightarrow{HOF{\cdot}MeCN} ArCHO + ArCOOH \qquad (8)$$

>80% 5–10%

Hydroxylations of Deactivated sp^3 and sp^2 Carbon Centers. The electrophilic properties of the oxygen in the HOF · MeCN complex were mobilized for attacking deactivated, relatively electron rich, tertiary sp^3 C–H bonds. The reaction results in tertiary hydroxylation as demonstrated, for example, for *cis*- and *trans*-decalins (eq 9).[2] The reaction proceeds relatively slowly (2–3 h), but with a full retention of configuration, resembling the parallel reactions with F_2.[20] This emphasizes the electrophilic nature of the active hydroxylium species HO^+ of the reagent.



80%

(9)

80%

Several aromatic compounds were also reacted with HOF · MeCN to give either quinones or phenol derivatives. The results of these reactions vary considerably with the substrate (eqs 10 and 11).[21]

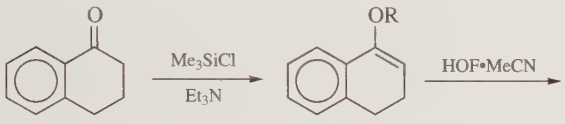
(10)

45%

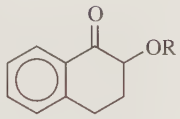
(11)

45%

Hydroxylation α to a Carbonyl Group. With HOF · MeCN it is easy to introduce an hydroxyl group α to any enolizable carbonyl, being a ketone, ester or an acid. Since the α position of any enol derivative is relatively electron rich, the electrophilic hydroxylium moiety in HOF · MeCN quickly reacts with it forming the corresponding α-hydroxy derivative in very good yields. Both, enol acetates and silyl enol ethers can be used, although the latter are preferred for esters and acids (eqs 12–14).[11]

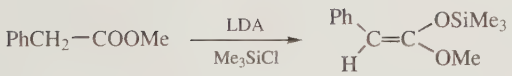


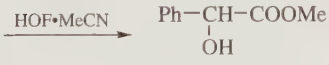
R = $SiMe_3$
R = Ac



(12)

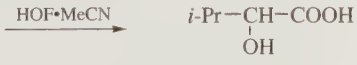
R = H > 90%
R = Ac > 80%





(13)

95%

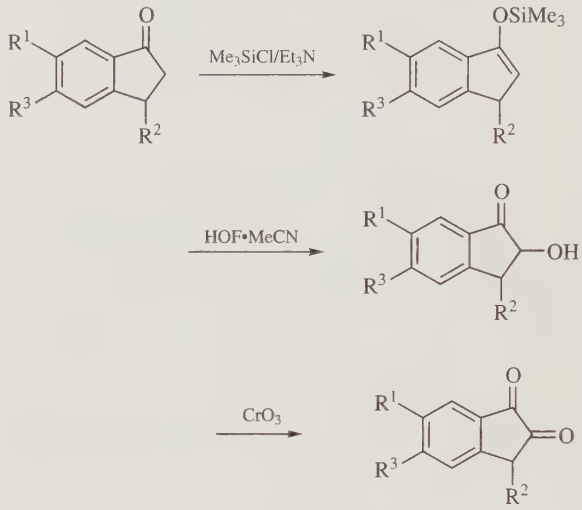


(14)

75%

This reaction was used to prepare several previously unknown indan-1,2-diones, usually in yields exceeding 80% (eq 15).[22] These compounds are very promising agents for latent fingerprint visualization.[23]

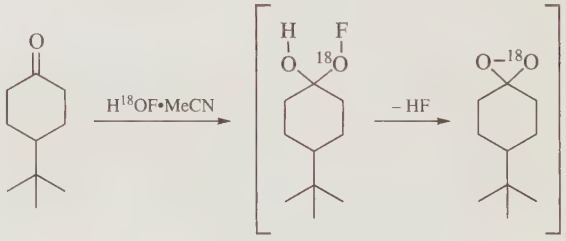
Oxidation and Oxygen Transfer Reactions with Alcohols, Ketones and Ethers. Being a strong oxidizer, HOF · MeCN can oxidize alcohols to ketones by absorbing the hydride-like hydrogen α to the hydroxyl group. This mechanism, proven by labeling the reagent with the ^{18}O isotope, is responsible for the fact that secondary alcohols are easier to oxidize with HOF · MeCN than primary ones (eq 16).[5a] The reaction of HOF · MeCN with ketones (Baeyer–Villiger reaction), on the other hand, proceeds with a different mechanism. By conducting the reaction with labeled $H^{18}O$ · MeCN, it was proven that the original mechanism of a formation of a dioxirane intermediate suggested by Baeyer more than a century ago, is correct for the reaction with HOF · MeCN. The result is a relatively fast rearrangement of ketones to esters as demonstrated by 4-*tert*-butylcyclohexanone which was converted to the corresponding lactone in 95% yield (eq 17). It should be noted that a different mechanism takes place when the Baeyer–Villiger oxidation is carried orthodoxly with peracids or hydrogen peroxide.[24]

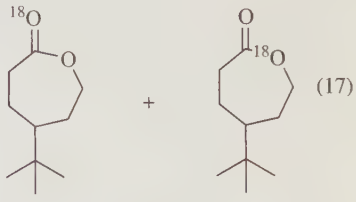


(15)

$R^1 = R^2 = R^3 = H$; $R^1 = R^3 = OMe$, $R^2 = H$; $R^1 = R^2 = H$, $R^3 = OMe$; $R^1 = R^3 = H$, $R^2 = Me$; $R^1 = R^3 = benzo$, $R^2 = H$

(16)

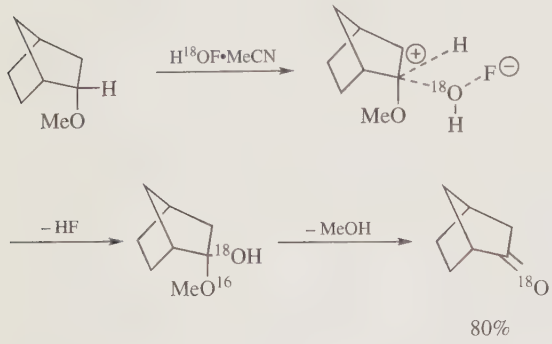




(17)

Oxidation of ethers to the corresponding ketones is a difficult reaction rarely described in the literature. HOF · MeCN can complete such a transformation in good yields although sometimes

more than 10-fold excess of the reagent is needed and the reaction in general is relatively slow. As with elemental fluorine,[20] the reaction mechanism involves a pentacoordinated non-classical carbonium ion absorbing the hydride-like hydrogen α to the ether moiety. As a result, the oxygen atom in the product originates from the reagent, demonstrating its oxygen transfer capabilities (eq 18).[9]



(18)

Sulfur-Containing Substrates.[7] HOF · MeCN is able to transfer its oxygen atom to sulfides and form sulfones at room temperature, usually in nearly quantitative yields with reaction times of seconds or minutes. Unhindered (such as dibutyl-) or very hindered (di-*tert*-butyl-) sulfides behave alike and produce the corresponding sulfones. Sulfones are easily also obtained from sulfoxides.[7b] When a low temperature (−78 °C) is maintained, and methanol is added, the oxidation of sulfides could be stopped at the sulfoxide stage as demonstrated for dibenzylsulfide, but in general the reaction favors the formation of sulfones (eqs 19 and 20).

(19)

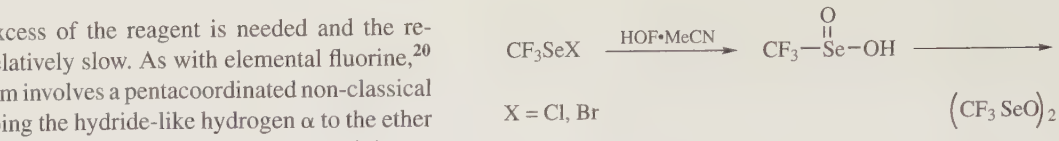
R = Bu;
R = *t*-Bu

(20)

While there are many reagents which can oxidize common sulfides to sulfones, all fail with very electron-poor sulfides. Arylperfluoroalkyl sulfides, for example, cannot be oxidized cleanly to their sulfones by any conventional reagent. For such compounds HOF · MeCN requires relatively long reaction times of up to 20 min and a 4–5-fold excess of the reagent, but eventually it produces the corresponding previously unknown sulfones in excellent yields. Trifluoromethylhaloselenides were also oxidized with HOF · MeCN to trifluoroselenic acid and finally dehydrated to the corresponding anhydride (eqs 21 and 22).[16]

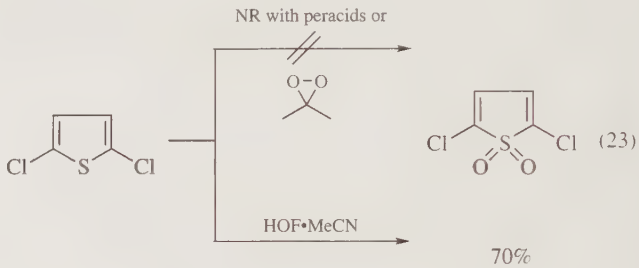
(21)

Ar = *p*-MeC_6H_4; R_f = *n*-C_8F_{17}
Ar = 3,4-$Cl_2C_6H_3$; R_f = *n*-C_4F_9
Ar = R_f = C_6F_5



(22)

The high potency of the reagent along with its ability to react under very mild conditions and short reaction times proved to be valuable in reactions where the initial transformation is difficult and at the same time the formed products are prone to a potential cascade of secondary reactions. Such a situation is found in the oxidation of thiophenes. The reaction has to overcome a substantial aromatic stabilization, requiring relatively harsh conditions. On the other hand, the non-aromatic *S,S*-dioxide products are sensitive to Diels–Alder and other ene and diene reactions which are strongly facilitated by high temperatures and prolonged reaction times. Thus, for example 2,5-dichlorothiophene or ethyl 2-methyl-5-thiophenecarboxylate could not be converted to the corresponding dioxides by any oxidizing agent save HOF · MeCN, which completed the transformation at room temperature in 20 min (eqs 23 and 24).[7]



(23)

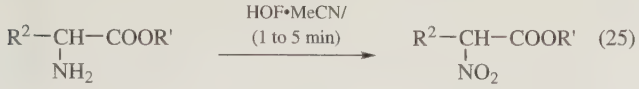
(24)

R^1 = COOEt; R^2 = R^3 = H; R^4 = Me 90%
R^1 = R^4 = Me; R^2 = COMe; R^3 = H 80%

Transferring Oxygen Atom(s) to Nitrogen-Containing Compounds.[4,8,12] The combination of potency and mildness which characterizes HOF · MeCN and which was responsible for the successful transformation of thiophenes to their *S,S*-dioxide derivatives (see above) was also the basis for the preparation of α-nitro acids from the corresponding amino acids. In the past when amino acids were directly oxidized, the products were ammonia or its salts and a nitrogen-free organic residue. HOF · MeCN was allowed to react for 1–5 min with α-amino acids such as glycine and alanine or with the dicarboxylic acids aspartate and glutamate. In these cases, and in many other, the corresponding α-nitro carboxylates were obtained in yields of 80% or higher. The peptide aspartame was also converted to the α-nitro derivative without affecting the amide link (eqs 25 and 26).

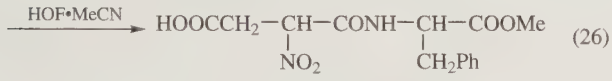
Primary aromatic, and the more difficult to oxidize aliphatic amines, can be converted to their respective nitro derivatives,[4] although NaF has to be added to the more basic aliphatic substrates in order to absorb some of the HF present in the reagent solution. Polyamines such as 2-aminoaniline and other similar derivatives,[25] and sensitive ones such as the bicyclic mirtanyl

amine, were also converted to the corresponding nitro derivatives in high yields (eqs 27–29).



(25)

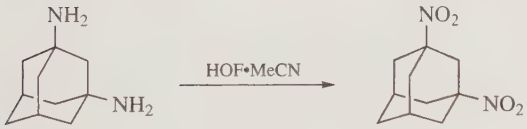
R' = Et, R^2 = H
R' = CH_2Ph, R^2 = Me
R' = Me, R^2 = $MeOOCCH_2$
R' = Me, R^2 = $MeOOC(CH_2)_2$



(26)

(27)

(28)

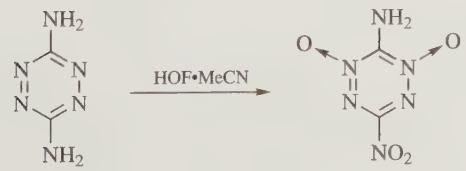


(29)

Tertiary amines were reacted with HOF · MeCN to form *N*-oxides in good yields.[12] The reaction works well with pyridine derivatives containing electron-donating or -withdrawing groups. Other aromatic amines such as quinoline and diazine derivatives react as well. An interesting case is the oxidation of 3-amino-1,2,4,5-tetrazine derivatives which are precursors to thermally stable strong explosives.[26] Both the tertiary and the primary nitrogen atoms were subjected to oxidation. The usual reaction conditions (0 °C, 5–10 min) were also applied to tertiary aliphatic amines. They responded as expected and produced the corresponding *N*-oxides, again in 85–95% yield (eqs 30–32).[12]

(30)

R = H 95%
R = 2-OMe 70%
R = 2-CN 98%

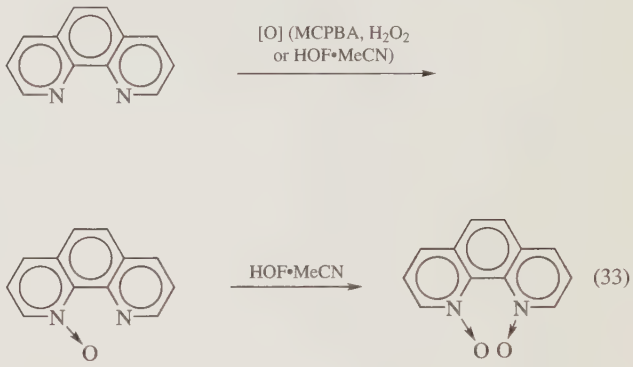


(31)

(32)

$R^1 = R^3 = C_8H_{17}$; R^2 = Me 95%
R^1 = Bz; R^2 = Et; R^3 = Ph 85%

These results were a prelude to the synthesis of *N,N'*-phenanthroline-dioxide.[27] Despite many attempts, this compound eluded chemists for more than 50 years. No oxygen transfer agent was able to take out of planarity the three rings of the parent phenanthroline to accommodate the two oxygen atoms in the crowded bay area between the two nitrogen atoms. The relatively new HOF · MeCN was the right tool for this task and the desired dioxide, which constitutes the smallest helicene made so far, was obtained in higher than 60% yield (eq 33).



(33)

The Introduction of ^{18}O Isotope. Since HOF · MeCN is easily made from water and diluted fluorine, and since $H_2{}^{18}O$ is the most convenient source for this isotope, it is very easy to prepare epoxides, sulfones, nitro compounds, etc., labeled with the ^{18}O isotope. Such examples can be found in most of the references listed below.

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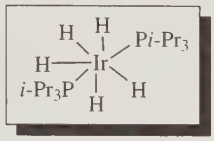
Iridium(V) Pentahydrobis(isopropylphosphine)



[53470-70-5] $C_{18}H_{47}P_2Ir$ (MW 517.73)

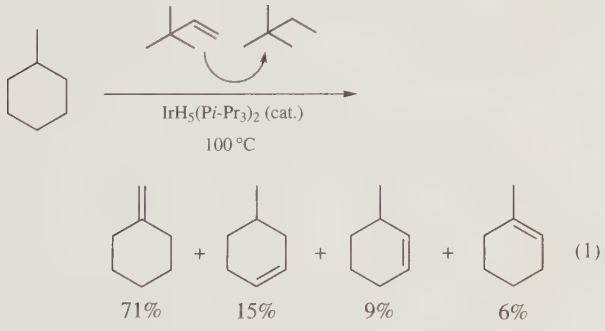
(used in the C–H activation of nitriles,[1–8] isomerization of unsaturated compounds,[9–12] and dehydrogenation of alcohols[13–15])

Solubility: soluble in hexane, methylene chloride, poorly soluble in methanol.

Appearance: white powder.

Preparation: reduction of $[(PH\text{-}i\text{-}Pr_3)]^+[IrCl_4(P\text{-}i\text{-}Pr_3)_2]^-$ with $LiAlH_4$ according to the procedure described.[16]

C–H Activation. $IrH_5(i\text{-}Pr_3P)_2$ (**1**) can catalyze dehydrogenation of cyclooctane into cyclooctene at 150 °C in the presence of an olefin as an hydrogen acceptor.[1] $IrH_5(i\text{-}Pr_3P)_2$ can promote the transformation of methylcyclohexane to methylenecyclohexane at 100 °C (eq 1).[2]



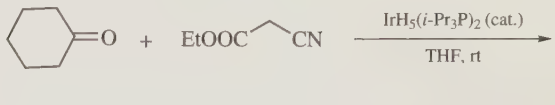
(1)

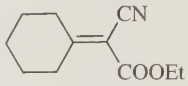
Deuterium-hydrogen exchange between benzene-d_6 and neohexene is catalyzed by $IrH_5(i\text{-}Pr_3P)_2$.[3] Similar exchange between CH_4 and benzene is catalyzed by $IrH_5(i\text{-}Pr_3P)_2$.[4]

$IrH_5(i\text{-}Pr_3P)_2$ (**1**) can promote the Knoevenagel addition of cyanoacetate to aldehydes and ketones under the neutral and mild conditions (eq 2)[5] likewise to $RuH_2(PPh_3)_4$-catalyzed reactions, which proceed highly efficiently.[6]

This catalyst can activate both the α-C–H bond and the C–N triple bond of nitrile, therefore catalytic cross-coupling reactions of nitriles occur without using extremely strong bases (Thorpe-Ziegler reaction) to afford cyanoenamines in high yields (eq 3).[7]

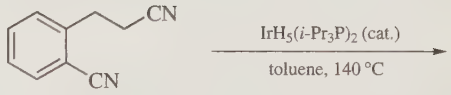
Furthermore, $IrH_5(i\text{-}Pr_3P)_2$ can be used as an acid/base ambiphilic catalyst. Mutual destruction of reagents in acid- and base-promoted reactions in the same container is now avoidable with the use of $IrH_5(i\text{-}Pr_3P)_2$ catalyst, a Lewis acid and base ambiphilic catalyst. The catalyst can be used in the three-component reaction of nitriles, olefins, and water, which proceeds efficiently to give glutarimides that are important intermediates in the manufacture of pharmacological compounds (eq 4).[8]

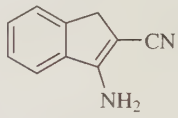




(2)

75%





(3)

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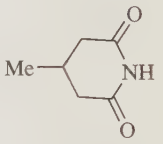
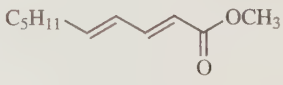


(4)

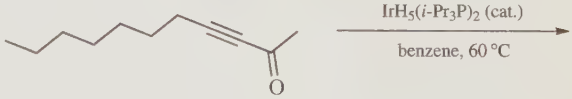
91%

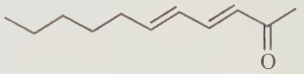
Isomerization. $IrH_5(i\text{-}Pr_3P)_2$ can isomerize 2-ynoic esters or amides to the corresponding (2*E*,4*E*)-dienoic esters or amides (eq 5).[9] The methodology could be used in the synthesis of polyene compounds.[10] α,β-Ynones can be transformed to α,β,γ,δ-unsaturated dienones in the presence of the catalyst **1** (eq 6).[11] The methodology was successfully applied to the synthesis of γ-keto aldehydes.[12]



(5)

92%

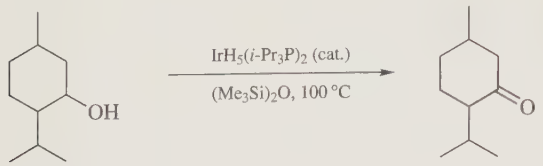




(6)

99%

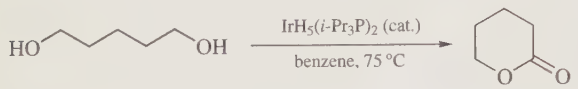
Dehydrogenation. Dehydrogenation of alcohols occurs with $IrH_5(i\text{-}Pr_3P)_2$ catalyst to give the corresponding ketones (eq 7).[13]



(7)

90%

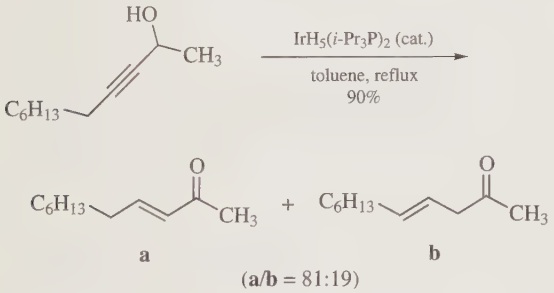
Diols can be dehydrogenated twice to give lactone. 1,5-Pentandiol can be transformed to δ-lactone in high yield (eq 8).[14]



(8)

88%

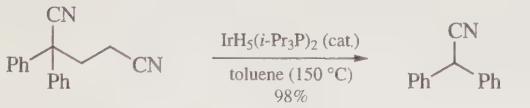
Propargylic alcohols could be isomerized (presumably via the allenol) in the presence of the catalyst **1** to afford the enones (eq 9).[15]



(9)

(**a**/**b** = 81:19)

Carbon-Carbon Bond Cleavage. In the presence of the catalyst **1** the β-selective C–C bond cleavage of nitriles and ketones proceeds to give the corresponding products. Indeed, 2,2-diphenylpentanedinitrile undergoes reaction with the catalyst **1** in toluene at 150°C gave 2,2-diphenylacetonitrile in over 98% yield (eq 10).[16]



(10)

Related Reagents. Iridium, pentahydrobis(trimethylphosphine) 53470-69-2 and iridium, pentahydrobis(tripheneylphosphine) 29497-68-5.

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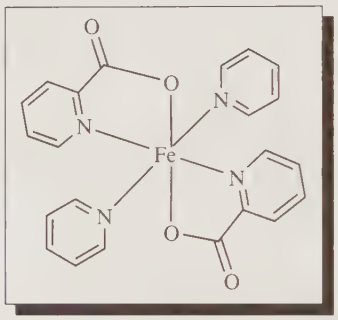
Iron(II) Bis(pyridine)bis(2-pyridinecarboxylato-N1,O_2)



[128391-66-2] $C_{22}H_{18}N_4Fe_1O_4$ (MW 458.26)
[183183-14-4]

(catalyst for Gif-type oxygenation and functionalization of C–H bonds; aliphatic C–H bonds, α–heteroatom functionalized sp^3 C–H bonds)

Physical Data: mp 157 °C.
Solubility: soluble in polar organic solvents.
Form Supplied in: brick-red microcrystalline solid.
Analysis of Reagent Purity: ^1H, ^{13}C NMR, IR, UV-vis, and elemental analysis.
Handling, Storage, and Precautions: store under inert atmosphere. Avoid skin contact and inhalation.

Gif Reagents. A series of reagents for the oxygenation of hydrocarbons were developed by Derek Barton and co-workers[1] in the period between 1983 and 1998, and named after a small research-oriented town (Gif-sur-Yvette) at the outskirts of Paris where the first phase of the work was undertaken. The reagents are composed of a redox-active metal (usually iron) and an oxo-donor system (O_2/reducing agent, H_2O_2, *t*-BuOOH). The most practical Gif reagents (Table 1) are the Gif^{IV} ($Fe_{cat}/O_2/Zn$ in pyridine/AcOH; $[Fe_3O(OAc)_6(py)_3]$ is frequently used as precatalyst) and the $GoAgg^{III}$ branches (named in honor of Barton's subsequent research headquarters at Texas A&M University and composed of $FeCl_3$/picolinic acid (1:3)/H_2O_2 (aq 30%) in py or

Table 1 Barton's Gif oxygenation systems

System	Precatalyst	Oxidant	Reductant	Solvent[c]	Ref.
Gif^{I}	none added[a]	O_2	Fe^0/Na_2S	py/AcOH (10:1 v/v)	3
Gif^{II}	none added[a]	O_2	Fe^0/H_2S	py/AcOH/H_2O (6.6%)	3, 4
Gif^{III}	none added[a]	O_2	Fe^0	py/AcOH/H_2O (6.6%)	5
Gif^{IV}	$Fe^{II/III}$[b]	O_2	Zn	py/AcOH/H_2O[d] (6.6%)	5
GO	$Fe^{II/III}$[b]	O_2	Hg cathode	py/CF_3COOH	6
$GoAgg^{I}$	Fe^{II}	KO_2[e]		py/AcOH	7
$GoAgg^{II}$	Fe^{III}[f]	H_2O_2(30%)[g]		py/AcOH	7, 8
$GoAgg^{III}$	Fe^{III}[f]/PicH (1:3)	H_2O_2 (30%)[g]		py/AcOH (or py)	9
$GoChAgg^{I}$	Cu^{II}	H_2O_2 (30%)[g]		py/AcOH (or py)	10
$GoChAgg^{II}$	none added[a]	O_2	Cu^0	py/AcOH	11
$GoAgg^{IV}$[h]	Fe^{III}[i]	*t*-BuOOH (90%)[g]		py/AcOH, 60 °C	12
$GoAgg^{V}$[h]	Fe^{III}[d]/PicH (1:3)	t-BuOOH (90%)[g]		py/AcOH, 60 °C	12

[a] Although no compound is added, the zero-valent metal partially dissolves in solution.
[b] Usually $[Fe_3O(OAc)_6(py)_3]\cdot 0.5py$.
[c] At room temperature, unless otherwise noted.
[d] Addition of H_2O is optional.
[e] Under inert gas (Ar, N_2).
[f] Usually $FeCl_3\cdot 6H_2O$.
[g] Under inert gas or O_2.
[h] Later expelled from the GoAgg family.[12]
[i] Usually $Fe(NO_3)_3\cdot 9H_2O$.

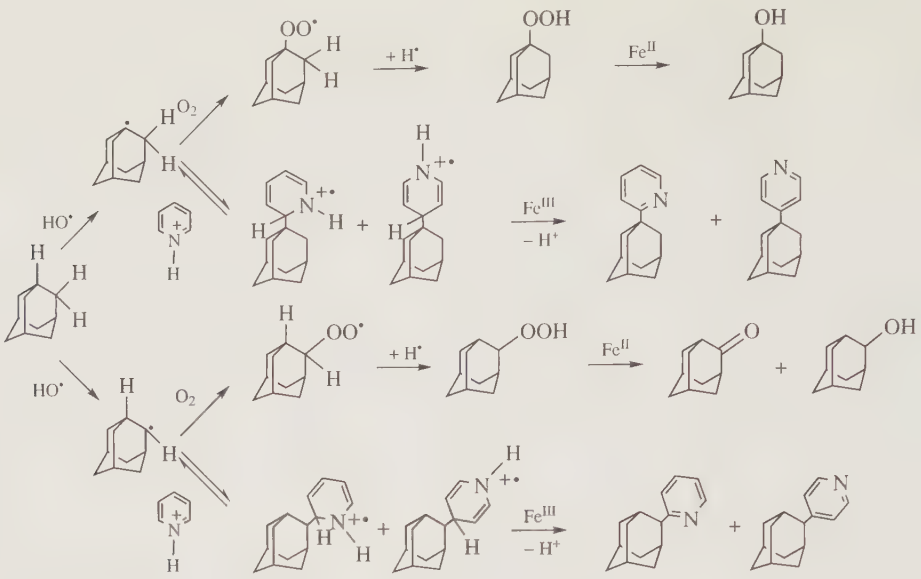
py/AcOH). The latter system is distinguished by a fifty-fold acceleration of the rate of the Gif reaction in the presence of picolinic acid as an iron chelator. Subsequent work[2] has indicated that the employment of Fe(II) vs. Fe(III) precursors is of little consequence with respect to the product profile obtained, whereas the use of metal chlorides may have a detrimental effect as it could lead to generation of chlorinated substrates. The $GoAgg^{III}$-type reagent $[Fe(py)_2(Pic)_2]$ is an isolable product that can be used as an alternative precatalyst. This moderately air-stable reagent can be synthesized by the reaction of metallic iron with picolinic acid in pyridine, or can be generated in situ by simply dissolving $[Fe(OAc)_2]$ and picolinic acid in py/AcOH (10:1 v/v). At the Fe(III) level, useful chloride-free $GoAgg^{III}$-type reagents are the readily available species $[Fe(Pic)_3]$ and $[Fe_2O(Pic)_4(py)_2]$. Because the reaction of these Fe(III) precursors with H_2O_2 generates dioxygen, an elevated concentration of products of substrate oxygenation is obtained by comparison to that realized by Fe(II) reagents, unless dioxygen is vigorously swept away by a stream of inert gas.

Gif Reactions. $GoAgg^{III}$ reagents, such as $[Fe(py)_2(Pic)_2]/H_2O_2$ in py/AcOH, can mediate hydrogen-atom abstraction from the C–H bonds of unfunctionalized hydrocarbons, leading to generation of diffusively free carbon-centered radicals.[13] Scheme 1 summarizes the different categories of products obtained in the presence of a typical substrate. Adamantane is activated both at the tertiary and secondary positions to afford the corresponding *tert*- and *sec*-adamantyl radicals. The product profile is dominated by the competitive capture of these adamantyl radicals by dioxygen and protonated pyridine (solvent matrix).[14]

The reaction with dioxygen generates incipient adamantylhydroperoxyl radicals ($Ad^{\cdot} + O_2 \rightarrow AdOO^{\cdot}$), which, by virtue of H-atom abstraction largely from H_2O_2, are the precursors of the intermediate adamantyl hydroperoxides (AdOOH). Occasionally these alkylhydroperoxides have been detected in the product profile in low concentrations,[15] but are otherwise rapidly decomposed by means of Fe(II)/ROOH Haber-Weiss chemistry to afford the final oxo products, alcohols, and aldehyde/ketones.[16] For the secondary position of adamantane, the amount of ketone obtained supercedes that of alcohol by at least three fold, in agreement with the established function of Gif catalysts as good ketonization agents.[15] The high ketone/C–2 alcohol ratio is difficult to explain by the Haber-Weiss mechanism alone, and may be further attributed to a fast 1,2-H atom migration step operating on the precursor *sec*-$AdO^{\cdot}$ radicals (*sec*-$Ad(H)O^{\cdot} \rightarrow$ *sec*-$Ad^{\cdot}OH$) at the expense of H-atom abstraction.[13]

The alkyl radicals generated in the Gif reaction also react with the special solvent of Gif chemistry, namely protonated pyridine, to afford synthetically useful alkyl pyridines. This is a well studied transformation that involves the selective and reversible addition of nucleophilic alkyl radicals to positions 2- and 4- of the pyridinium cation.[17] In the case of adamantane, both *tert*- and *sec*-adamantyl radicals are trapped by protonated pyridine to afford the corresponding 2- and 4-adamantylpyridines. Under routine Gif conditions the amounts of *tert*-adamantylpyridines tend to be more pronounced because a significant portion of *sec*-adamantyl radicals are diverted toward formation of oxo products. This is due to the higher reversibility and the lower rate constant (by two orders of magnitude) for the addition reaction of *sec*- vs. *tert*-adamantyl radicals with the pyridinium cation.[14] However, comparable amounts of *tert*- and *sec*-adamantylpyridines can be obtained if a vigorous stream of inert gas is employed.[2] All four products can be readily separated by column chromatography.

Several lines of evidence have recently confirmed[13] that the major oxidant in Gif solutions is the hydroxyl radicals rather than the originally proposed Fe^{V}=O species.[18] Hydroxyl radicals are generated via Fenton-like interactions[19] between Fe(II) sites and hydrogen peroxide in GoAgg systems. Gif^{IV}-type chemistry relies on Fe(II)/O_2 interactions and reducing equivalents provided by Zn dust to afford hydroxyl radicals. As the substrate-derived



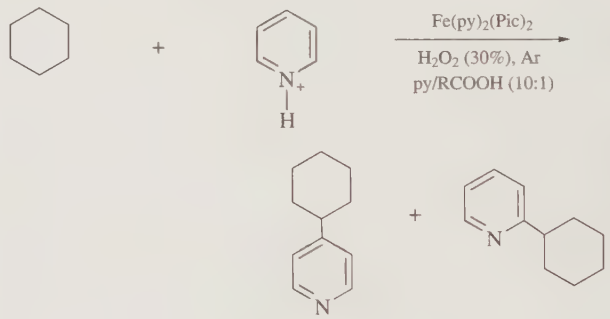
Scheme 1

alkylhydroperoxide builds up, especially under dioxygen-rich conditions, a secondary oxidant becomes apparent by means of its enhanced selectivity for the activation of tertiary C–H bonds.[13] The interaction of Fe(II) and ROOH generates these more selective alkoxyl radicals,[20] with the caveat that, as suggested above, only *tert*-RO· radicals contribute to H-atom abstractions in Gif chemistry. Hydroxyl radicals, but not alkoxyl radicals, would also attack the solvent matrix by virtue of addition to pyridine to afford bipyridines and hydroxypyridines[16] (the latter with increasing partial pressures of dioxygen). By adjusting the ratio of substrate vs. pyridine, the oxidizing power can be proportionally directed toward the substrate, although a minimum amount of pyridine (about 10 equiv with respect to the catalyst) is always needed for catalytic turnover.[21]

Among the C–H activation reactions discussed above, those leading to formation of alkylpyridines are the most useful ones for synthetic purposes.[22] Efforts to render Gif chemistry competitive for the synthetic production of oxo products, with particular emphasis placed on the industrially important mixture of cyclohexanone/cyclohexanol,[23] have been undertaken by Schuchardt et al.[24] and met with moderate success. The scope and limitations of the Gif procedures for generating 2- and 4- functionalized pyridines are discussed below.

Synthesis of Alkylpyridines. The indiscriminate nature of hydroxyl radicals precludes the attainment of high regioselectivities in C–H functionalization processes, hence the utility of Gif chemistry in the synthesis of alkylpyridines depends on the employment of substrates possessing equivalent or highly preferred C–H bonds for activation purposes. In other cases, as for instance with adamantane noted above, the success of the process relies on the ease of purifying the resulting mixture of alkylpyridine isomers.

A typical substrate such as cyclohexane (6 mmol) can be functionalized by the system $Fe(py)_2(Pic)_2$ (0.4 mmol)/H_2O_2 (30% aq, 2 mmol) in pyridine/acetic acid (or TFA) (15.0/1.5 mL) to afford 2-cyclohexylpyridine (0.49 mmol, 49% vs. H_2O_2), and 4-cyclohexylpyridine (0.27 mmol, 27%) (Scheme 2). Hydrogen peroxide is added slowly over a period of 30 min under a stream of argon to minimize accumulation of dioxygen and thus formation of oxo products. Hydrogen peroxide is also used in substoichiometric amounts to prevent overoxidation and detrimental cross reactions with hydroxyl radicals. After allowing the reaction to stir for an additional period of 2 h, most of the H_2O_2 is consumed and the products are purified by silica gel chromatography (ether/hexane) in good efficiencies with respect to hydrogen peroxide, assuming a 1:2 stoichiometry of substrate/H_2O_2 (established for many Gif reactions).

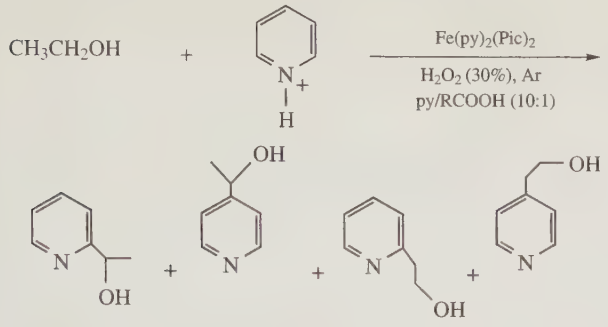


Scheme 2

Substrates with C–H bonds at positions adjacent to heteroatoms are readily activated by Gif reagents. For instance, hydrogen-atom abstraction from the α- and β-carbon atoms of ethanol produces the corresponding α- and β-hydroxyethyl radicals, which add exclusively to positions 2- and 4- of pyridine under a stream of argon (Scheme 3). The resulting 2- and 4-hydroxyethylpyridines demonstrate a seven-fold selectivity in favor of the products derived from α-hydroxyethyl radicals, in agreement with the known kinetics of hydrogen-atom abstraction from ethanol by hydroxyl radicals.[25] All four hydroxyethyl-pyridines can be separated by column chromatography, but synthetically useful yields can only be obtained for the 2- (30% vs. H_2O_2) and 4-(α-hydroxyethyl)pyridine (20%). Gif reagents based on Fe(II) precursors are preferably applied in these reactions, because Fe(III) sites can readily oxidize hydroxyalkyl radicals to the corresponding aldehydes (eq 1).[26]

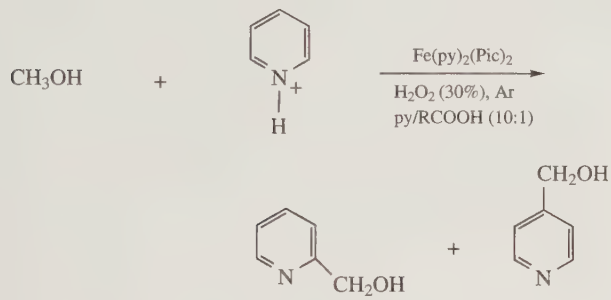
A more straightforward case is that of methanol, for which both the 2- and 4-pyridylcarbinol are formed under the general reaction

conditions noted above, but only 2-pyridylcarbinol can be purified in moderate yields (20%) by column chromatography (Scheme 4).



Scheme 3

$$Fe(III) + CH_3^{\bullet}CHOH \longrightarrow Fe(II) + H^+ + CH_3CHO \quad (1)$$



Scheme 4

An indirect approach can also be implemented in order to obtain the desired regioselectivity and improve on the yields of the alkylpyridines. For this purpose, two substrates are used simultaneously: dimethylsulfoxide (DMSO) and the iodo-substituted hydrocarbon of interest (R–I). This procedure has been pioneered by Minisci and co-workers.[27] For instance, 2- and 4-*tert*-adamantylpyridine can be selectively obtained by first allowing the hydroxyl radicals generated by the Gif system $Fe(py)_2(Pic)_2/H_2O_2$ (0.4 mmol/15 mmol) to react, almost exclusively, with DMSO (8.0 mL). The resulting methyl radicals (eq 2) will then perform iodine-atom abstraction from *tert*-iodoadamantane (4.0 mmol) in a thermodynamically driven reaction (eq 3). The generated *tert*-adamantyl radicals will, in turn, add to protonated pyridine (py/AcOH: 15.0/1.5 mL) as indicated above (Scheme 1) to afford 2- (45% based on 1-Ad-I) and 4-adamantylpyridine (35%). The two products are easily separated by column chromatography along with minor amounts of 1-adamantanol (16%) and trace amounts of unreacted 1-Ad-I.

$$HO^{\bullet} + Me_2S{=}O \longrightarrow MeS(=O)OH + Me^{\bullet} \quad (2)$$

$$Me^{\bullet} + \text{1-Ad-I} \longrightarrow MeI + \text{1-Ad}^{\bullet} \quad (3)$$

Acknowledgments. This work has been generously supported by grants from the NIH/NIEHS (ES07381) and the Division of Chemical Sciences, Office of Science, U.S. Department of Energy (DE-FG02-99ER14978).

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Iron(II) Perchlorate

$Fe(ClO_4)_2$

$(Fe(ClO_4)_2 \cdot 6H_2O)$
[13520-69-9] $H_{12}Cl_2FeO_{14}$ (MW 362.87)

(aromatic and aliphatic hydroxylation; reductive decarboxylation of peracids; dehydration and monooxygenation of organic compounds)

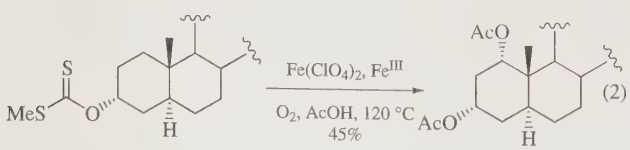
Alternate Name: ferrous perchlorate.
Physical Data: dec >100 °C.
Solubility: ~98 g/100 mL H_2O at 0 °C; sol alcohol, $HClO_4$.
Form Supplied in: light green crystalline powder.
Handling, Storage, and Precautions: eye irritant; hygroscopic; contact with combustible material may cause fire. **Warning**: conversion to lower hydrates by unintentional dehydration may cause explosion. Use due caution in handling, as for all perchlorates. Use in a fume hood.

Aromatic Hydroxylation (Fenton Oxidation).[1] Aromatic substrates are hydroxylated under mild conditions when treated with iron(II) salts, such as iron(II) perchlorate or ***Iron(II) Sulfate***, ***Hydrogen Peroxide***, and an appropriate oxidant (eg Fe^{3+}, Cu^{2+}, O_2) in aqueous acetonitrile (eq 1). Yields are generally less than 50%. The rate-determining step in the reaction was shown to be the production of a hydroxyl radical which reacts directly with the aromatic substrate, generating a phenolic radical intermediate. This is ultimately converted to the corresponding phenol. An interesting rearrangement of a hydrogen atom during the oxidation (NIH shift),[2] as observed during enzymatic hydroxylation, also takes place during the reaction.

(1)

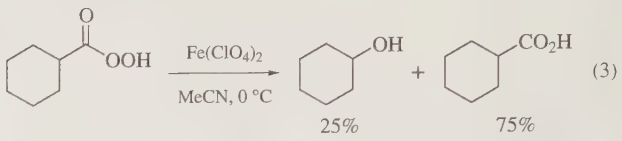
R = Me, Cl, OMe, H

Aliphatic Hydroxylation. C–H bond activation by metal complexes is of fundamental importance in hydrocarbon functionalization.[3] The regio- and stereospecific conversion of *O*-cholestan-3α-yl *S*-methyl dithiocarbonate to cholestane-1α, 3α-diyl diacetate demonstrates the coordination of iron–dioxygen complexes, formed by the reaction of iron(II) perchlorate and oxygen, with electron-rich *S*-alkyl xanthates to lead to the oxidation of neighboring C–H bonds (eq 2).[4] In the absence of Fe^{II}, no reaction takes place.



(2)

Reductive Decarboxylation of Peracids. Peroxycyclohexanecarboxylic acid is converted to cyclohexanol (25%) and cyclohexanecarboxylic acid (75%) when treated with iron(II) perchlorate at 0 °C in acetonitrile (eq 3).[5] Treating *cis*- or *trans*-3-hydroxyperoxycyclohexanecarboxylic acid in a similar manner leads to nearly pure *cis*-1,3-cyclohexanediol (85:15 *cis*:*trans*), indicating participation by the hydroxyl group.



(3)

Dehydration and Monooxygenation of Organic Compounds. Iron(II) perchlorate hexahydrate is used to prepare $Fe(MeCN)_4(ClO_4)_2$, a catalyst used in combination with H_2O_2 to dehydrogenate and monooxygenate organic substrates in dry acetonitrile.[6] No products resulting from ·OH radical chemistry are observed, which suggests that classical Fenton-type chemistry[1,7] does not occur under these conditions. With alcohols, aldehydes, methylstyrene, thioethers, sulfoxides, and phosphines, the active catalyst, $Fe(H_2O_2)^{2+}$, promotes the monooxygenation to aldehydes, carboxylic acids, epoxide, sulfoxides, sulfones, and phosphine oxides, respectively.

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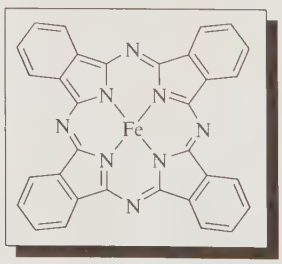
Iron(II) Phthalocyanine

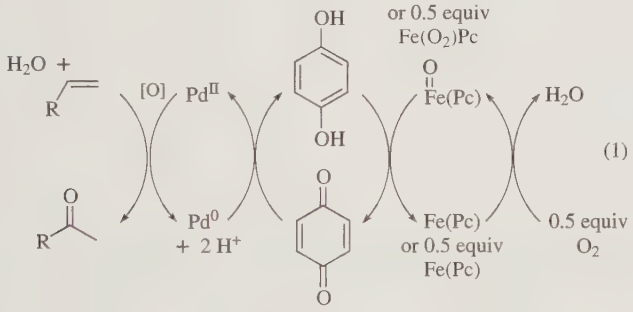


[132-16-1] $C_{32}H_{16}FeN_8$ (MW 568.41)

(oxidation of terminal alkenes to methyl ketones; 1,4-oxidation of 1,3-dienes; allylic oxidation of cyclic alkenes; siloxane elimination from silylamides to form nitriles)

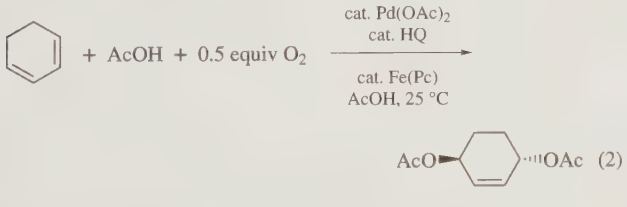
Physical Data: mp >300 °C.
Form Supplied in: black powder.
Handling, Storage, and Precautions: store tightly sealed in a cool, dry place.

Preparation of Methyl Ketones from Alkenes (Wacker Oxidation). Methyl ketones are conveniently prepared from terminal alkenes by Wacker oxygenation using a catalytic amount of ***Palladium(II) Chloride*** and ***Copper(II) Chloride***.[1] The reaction can be slow and chlorinated byproducts are usually observed. Iron phthalocyanine (Fe(Pc)) serves as the oxygen-activating complex in a multicatalyst system used to perform Wacker-type[2] oxidation reactions (eq 1).[2b] This catalyst system offers a chloride-free environment in which alkenes are smoothly converted to methyl ketones with molecular oxygen, under mild conditions, in moderate to high yield. Unlike typical Wacker oxidations using $CuCl_2$, no chlorinated byproducts are formed.[1a,3] In addition, the removal of chloride from the system increases the rate of reaction.[4] In the catalyst system, Fe(Pc) reoxidizes hydroquinone to benzoquinone, which serves to reoxidize Pd^0 to Pd^{II} after Pd^{II} catalyzes the oxidation of the alkene to the ketone (eq 1). In the present catalyst system, acid ($HClO_4$) is added to prevent the rapid precipitation of Pd from the aqueous DMF reaction mixture. The reoxidation of hydroquinone by other means,[5] including electrochemical reoxidation,[6] has been reported.

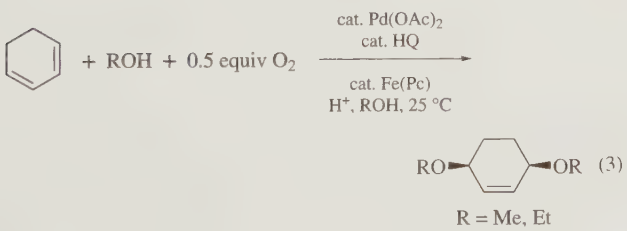


(1)

1,4-Oxidation of Conjugated Dienes.[7] Conjugated dienes can be oxidized to *trans*-1,4-diacetates and *cis*-1,4-diolethers when treated with the above catalyst system in acetic acid or alcohol (eqs 2 and 3).



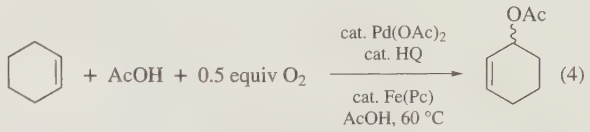
(2)



(3)

R = Me, Et

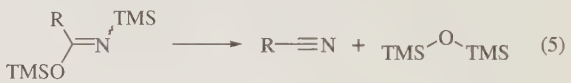
Aerobic Allylic Oxidation of Alkenes.[6c] Exposure of cyclohexene to the above described catalyst system in acetic acid gives the desired allylic oxidation product (eq 4). Again, Fe(Pc) and molecular oxygen take the place of less convenient oxygen sources such as MnO_2.[8]



(4)

Epoxidation of Alkenes. In a comparison of transition metal phthalocyanines, iron(II) phthalocyanine most effectively catalyzes the epoxidation of alkenes when ***Iodosylbenzene*** is the oxygen donor.[9] It is less effective than other metal–phthalocyanine catalysts when NaOCl is used as the oxygen donor. A mixture of *cis*- and *trans*-epoxides are produced from *cis*-alkenes. In the presence of 2,6-di-*t*-butyl-*p*-cresol, highly stereoselective epoxidation of the *cis*-alkene is observed.

Preparation of Nitriles from Amides.[10] Iron phthalocyanine readily catalyzes the decomposition of bis(trimethylsilyl)amides to give nitriles under relatively mild conditions (75 °C, 6 h, 100%, eq 5). This serves as a useful alternative to the less general thermal decomposition of bis(silylamides)[11] or the thermal decomposition of monosilylamides in the presence of stoichiometric amounts of an acidic reagent.[12] Catalytic amounts of fluoride ion or simple Lewis acids such as $FeCl_3$, $ZnCl_2$, or $AlCl_3$, are also effective reagents for this transformation.



(5)

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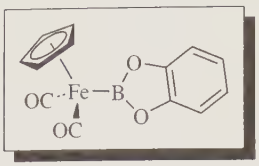
Iron(II) 1,3,2-Benzodioxaborol-2-yldicarbonyl(η^5-2,4-cyclopentadien-1-yl)



[148607-89-0] $C_{13}H_9BO_4Fe$ (MW 295.87)

(transition metal boron reagent[1–3] for stoichiometric borylation of arenes and alkenes under photochemical conditions)

Physical Data: $d = 1.567$ g cm^{-3}.

Solubility: soluble in hydrocarbon solvents and halogenated solvents.

Form Supplied in: pale yellow crystal.

Analysis of Reagent Purity: ^{1}H NMR (C_6D_6) δ 7.13 (m, 2H), 6.81 (m, 2H), 4.20(s, 5H); ^{11}B NMR (C_6D_6,$BF_3 \cdot OEt_2$) δ 51.8.

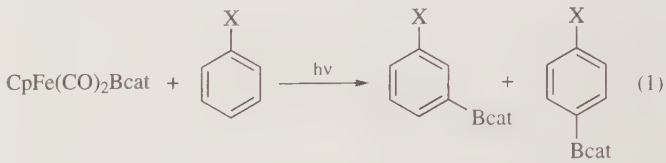
Preparative Methods: addition of ClBcat in toluene to a toluene suspension of Na[CpFe(CO)$_2$] at ambient temperature followed by filtration, concentration, extraction with pentane, and crystallization at −30 °C from pentane solution.[4]

Purification: recrystallization at −30 °C from pentane solution.

Handling, Storage, and Precautions: air and moisture sensitive, not compatible with donor solvents like H_2O, alcohol, and THF, but thermally stable in solution at 120 °C. Should be stored and handled under an inert atmosphere or by using standard Schlenk techniques.

General Aspects. CpFe(CO)$_2$Bcat is one of the first three transition metal boryl complexes reported to functionalize unsaturated hydrocarbons via C–H activation under photochemical conditions.[5] It is readily prepared by the salt elimination method. It can also be prepared by ligand-exchange reaction of less stable complex $CpFe(CO)_2BPh_2$ with catecholborane.[4] Because of its unusual but useful reactivity, the bonding in the structure of CpFe(CO)$_2$Bcat was analyzed by crystallographic, spectroscopic,[6] and computational methods.[7] It has also been used as a model complex for mechanistic study on the photochemical borylation of unsaturated hydrocarbons.[8] In those reactions, cleavage of C–H bond and Fe–B bond occurs with concomitant formation of a strong B–C bond. Among the transition metal boryl complexes of group 6–9, CpFe(CO)$_2$Bcat is one of the most reactive, and activates C(sp^2)–H bonds in arenes and alkenes under photochemical conditions. However, CpFe(CO)$_2$Bcat is unreactive toward alkane C–H bonds under the same conditions. CpFe(CO)$_2$Bcat also reacts with protic HY reagents (Y: OH, OR, NHR, Cl), borane, and nonpolar reagents (e.g., H_2, Br_2). In addition to those reactions involving cleavage of Fe–B bonds, CpFe(CO)$_2$Bcat undergoes ligand substitution at the iron center with phosphines under photochemical conditions.

Photochemical, Stoichiometric Borylation of Arenes via Direct C–H Activation. Photolysis of CpFe(CO)$_2$Bcat in benzene results in the formation of PhBcat in quantitative yield. Irradiation of CpFe(CO)$_2$Bcat in a variety of monosubstituted arenes leads to the formation of arylboronic ester isomers in lower yields as shown in eq 1.[6] The by-product $[CpFe(CO)_2]_2$ in those reactions is presumably generated by the decomposition of the initially formed $CpFe(CO)_2H$. The *ortho, meta*, and *para* ratio of products and yields are shown in Table 1. The similarity of the product ratio for arenes with electron-withdrawing substituents and arenes with electron-donating substituents is strong evidence against an electrophilic aromatic substitution pathway. In-depth mechanistic studies, including the measurement of kinetic isotope effects, and CO dissociation suggests a photochemically induced CO dissociation/C–H activation pathway.



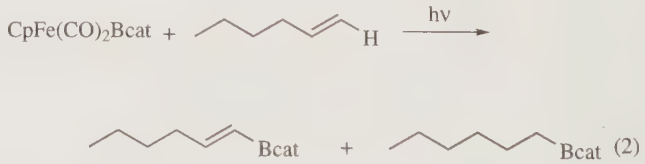
(1)

X = H, Me, OMe, Cl, CF_3, NMe_2

Table 1 Ratio of product isomers from reaction of CpFe(CO)$_2$Bcat with C_6H_5X

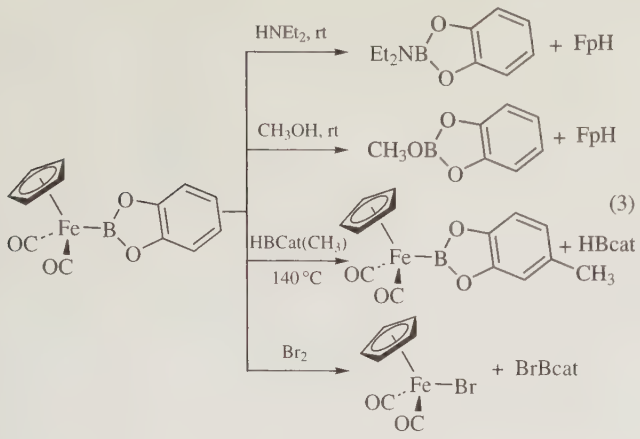
		Product Isomer Ratio		
X	Yield (%)	*o*	*m*	*p*
H	100	-	-	-
Me	70	-	1.1	1.0
OMe	55	1.0	1.6	1.1
Cl	52	-	1.5	1.0
CF_3	33	-	1.5	1.0
NMe_2	30	-	1.0	8.0

Photochemical, Stoichiometric Borylation of Alkenes via Direct C–H Activation. Photolysis of CpFe(CO)$_2$Bcat in terminal alkenes (e.g., 1-hexene) forms terminal alkenylboronate esters as the major product in high yield.[6] Small amounts of 1-alkyl boronic esters are also produced (eq 2). The reaction of CpFe(CO)$_2$Bcat with 4-octene results in at least three isomeric alkenylboronate esters in addition to octylboronate ester, which demonstrates poor selectivity for internal olefins.



(2)

Other Reactions Involving Cleavage of Fe–B Bond. Protic HY reagents such as water, alcohol, amines, or mineral acids (Y: OH, OR, NHR, Cl) undergo Fe–B bond metathesis with CpFe(CO)$_2$Bcat to generate hydroxyl, alkoxy, or chloroboronic CatBY esters and the by-product $CpFe(CO)_2H$ under thermal conditions. Nonpolar reagents like bromine also cleave the Fe–B bond to form CpFe(CO)$_2$Br and CatBBr products under thermal conditions. Hydridic reagents such as boranes undergo boryl exchange with CpFe(CO)$_2$Bcat to generate a new iron-boryl complex.[9] In this reaction, the original boryl group accepts the hydride of the new borane (eq 3).



Dative-Ligand Substitution at Iron Centers. The bisphosphine complex $CpFe(PMe_3)_2Bcat$ was conveniently prepared by irradiation of $CpFe(CO)_2Bcat$ with excess PMe_3 in pentane.[6] $CpFe(CO)(PMe_3)Bcat$ is an intermediate in the formation of the bisphosphine complex. High purity $CpFe(PMe_3)_2Bcat$ is obtained in 52% yield by recrystallization (eq 4).

$$CpFe(CO)_2Bcat \xrightarrow[PMe_3]{h\nu} CpFe(CO)(PMe_3)Bcat \xrightarrow[PMe_3]{h\nu} CpFe(PMe_3)_2Bcat \quad (4)$$

Related Reagents. Tungsten, tricarbonyl(4,6-dimethyl-1,3,2-benzodioxaborol-2-yl)[(1,2,3,4,5,-η)-1,2,3,4,5-pentamethyl-2,4-cyclopentadien-1-yl); iron, 1,3,2-benzodioxaborol-yl(η^5-2,4-cyclopentadien-1-yl)bis(trimethylphosphine); manganese, 1,3,2-benzodioxaborol-2-ylpentacarbonyl; rhenium, 1,3,2-benzodioxaborol-2-ylpentacarbonyl.

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M

Mercury(0)

Hg

[7439-97-6] Hg (MW 200.59)

(photosensitizer for C–H bond cleavage reactions;[1–6] solvent for metals to give amalgams which can act as selective reducing agents;[8–19] heterogeneous catalyst poison, especially for Group 10 metal catalysts;[22] electrode material in electrosynthesis[24])

Physical Data: mp −38.87 °C; bp 356.6 °C; *d* 13.6 g cm^{-3}.

Solubility: sparingly soluble in organic solvents and water.

Form Supplied in: silvery liquid; widely available; electronic grade (foreign metals ≤1 ppm) and ACS grade (99.9995%) are available, normally making purification unnecessary.

Handling, Storage, and Precautions: as a volatile heavy metal, care must be taken to prevent long term inhalation of the vapor. Carrying out reactions in a fume hood, cleaning up spills, and assuring that the air handling system of the laboratory is operating normally is generally sufficient.

Original Commentary

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Mercury Photosensitization. This allows the dehydrodimerization of a variety of volatile organic molecules on a 1 to 50 g scale without a solvent in a simple apparatus which can be put together from standard laboratory photochemical equipment.[1–5] A 254 nm low-pressure mercury lamp is used, together with quartz glassware. The reactive triplet excited state of mercury is usually designated Hg*. The reaction happens in the vapor phase at rt and pressure, but no special precautions have to be taken; the normal vapor pressure of the substrate is usually enough to replenish the vapor above the substrate when reaction has taken place. Mercury is supplied in the form of a small mercury drop in the substrate. Normal laboratory glassware can contain sufficient adsorbed mercury so that Hg photosensitized reactions can occur. To obtain a valid control experiment in the absence of mercury, it is sometimes necessary to anneal the glassware in a glassblower's oven. This implies that care needs to be taken in interpreting the results of what are ostensibly normal or nonmercury photosensitized reactions where special care to remove trace mercury may not have been taken.

The liquid phase is unreactive and this has important effects on the selectivity of the reaction. Dehydrodimerization or functionalization always leads to the condensation of the product, which protects it from further reaction and so the substrate only undergoes one homolysis even if there are several C–H bonds of similar strength. To take a simple example, cyclohexane dimerizes to bicyclohexyl with no further oligomerization. The origin of the nonreactivity of the liquid phase is probably that the very narrow atomic absorption line for vapor-phase mercury is broadened and shifted when the mercury is dissolved. Perfect matching of the emitter and absorber in the vapor phase, where both are vapor-phase mercury atoms, leads to efficient energy transfer in the vapor; energy transfer is probably poor for dissolved Hg. The use of a high-pressure mercury lamp (or even allowing the temperature of the lamp to become abnormally high) causes the selectivity of the reaction to change sharply for the worse, presumably because absorption can now take place in the liquid phase and so condensation no longer protects the condensate from further reaction.

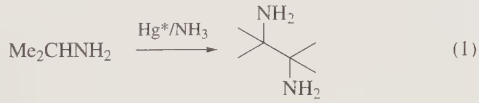
The absorption coefficient for mercury vapor is so large that all the light is absorbed within a few micrometers of the inside surface of the reactor and so the bulk of the vapor is protected from irradiation. This means that 'normal' organic photochemistry is severely suppressed; essentially all the energy is absorbed by the mercury atoms, leaving none to excite the much more weakly absorbing organic species. Absorption of the 254 nm line is responsible for the chemistry described here, and so the excited state responsible is the $^3P_1$ state of mercury. The quartz glassware is transparent to the 254 nm line, allowing for efficient transmission to the reaction zone.

A useful modification for certain substrates is the use of a reactive atmosphere. In this case, the temperature is typically adjusted so that the vapor pressure of the substrate is 100 Torr. This is necessary so that the reactive gas has a substantial partial pressure (*P*) in the reaction zone; in the case where the substrate has a *P*(substrate) of 100 Torr, the *P*(reactive gas) would be 660 Torr. The two most useful reactive gases are H_2 (Hg*/H_2 conditions)[4] and NH_3 (Hg*/NH_3 conditions).[5] The reason for moving to these reactive gases is that the standard conditions, with reflux under N_2 (Hg* conditions), completely fail when the Hg* attacks a functional group in the substrate. This typically happens for substrates having multiple bonds or N lone pairs. Under Hg*/H_2 or Hg*/NH_3 conditions, H atoms take over from Hg* as the active species, and a much wider range of substrates are reactive. For example, NEt_3 fails to react at all under Hg* conditions, presumably because Hg* attacks the N lone pair, and energy transfer leads to thermal excitation of the substrate but not to productive chemistry. Under Hg*/H_2 conditions the compound undergoes dehydrodimerization at the C–H bond α to N. Arenes seem to work best under Hg* conditions, probably because H atom addition leads to undesired and unselective partial saturation of the aromatic ring. In practice there is little point in attempting to predict what will happen with a given substrate because it is easy to try Hg* conditions first and then move to Hg*/H_2 conditions if the results are unsatisfactory.

In each case, the crude product is collected by removing the volatile starting material by rotary evaporation after the reaction is over. The main limitation is that the substrate be volatile, but compounds with up to 16 nonhydrogen atoms have been successfully dimerized. The reaction proceeds under reduced pressure if this is useful to vaporize the substrate. Another useful modification is to use steam distillation to bring the substrate into the vapor phase; in this variant, water is added to the substrate and the mixture is refluxed. The weakest C–H (or X–H) bond in the

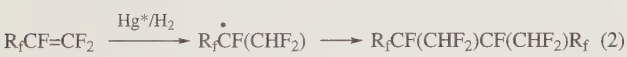
molecule is homolyzed and the resulting C-centered (or, in general, X-centered) radicals recombine. That part of the radical pool which disproportionates instead of recombining does not in general lead to lower chemical yield because the H atoms present add to the alkene disproportionation product and re-form the initial radical. Quantum yields of 0.04–0.8 are usual and the majority of substrates have values in the range 0.2–0.6. Chemical yields are good to excellent (40–98%). Conversions depend on photolysis time.

The great advantage of the method is that it allows a number of difficult synthetic transformations to be carried out in one step. The synthesis of a few simple compounds that are otherwise very difficult to make is shown below. In the diamine synthesis, Hg*/NH_3 conditions gave the best results (eq 1).



(1)

A variant, hydrodimerization of alkenes, takes place under Hg*/H_2 conditions (eq 2). The H atoms add to the terminal carbon of the alkene to give the intermediate radical shown.

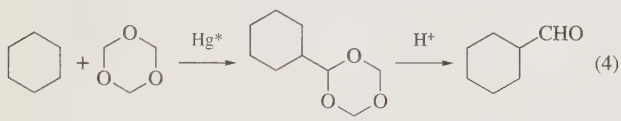


(2)

Another useful feature is the facility with which two different substrates cross dimerize (eq 3).

(3)

In suitable cases, the volatility or polarity differences among the three allow easy separation by distillation or chromatography (eq 4).



(4)

The intermediate radicals can undergo rearrangement in special cases, as in the case of hexenyl radicals which cyclize. Trapping the intermediate radicals with CO, SO_2, and O_2 has proved possible, giving aldehydes, ketones, sulfonic acids, and hydroperoxides.[6]

Since methane has strong C–H bonds, it only reacts well under Hg*/NH_3 conditions to give CH_2=NH as product.[5a] Arenes do not undergo cleavage of the strong aryl C–H bonds but benzylic C–H bonds of side chain alkyl groups can be cleaved under Hg* conditions; neither Hg*/H_2 nor Hg*/NH_3 conditions seem to be useful for arenes, however, probably because H atoms readily add to arene rings to give a complex mixture of products.

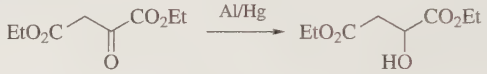
Reduction. Ultrasonically dispersed mercury reduces α,α′-dibromo ketones to an intermediate that is believed to be a mercurated 2-oxyallyl species which gives a 4-methylene-1,3-dioxolane with acetone.[7]

Amalgams. This is a traditional and well-established application of Hg^0. Metallic mercury readily forms amalgams with most metals but Na/Hg, Al/Hg, and Zn/Hg are the most useful in organic chemistry. The mercury serves both to keep the surface of the metal clean (because inorganic salts adhere poorly to the amalgam) and to dilute the active metal (and so moderate its thermodynamic reducing potential), which can improve the selectivity of the reduction.

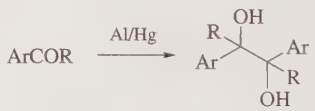
Sodium Amalgam. ***Sodium Amalgam*** is a liquid up to 1%, semisolid at 1.2%, and a pulverizable solid at higher concentrations, except in a narrow range around 40% Na, where the material is a low melting (< 30 °C) solid. These materials can be made from elemental Na and Hg (*caution*: much heat is evolved) and analyzed by titration with acid.[8] Na/Hg is useful for the reduction of α,β-unsaturated carboxylic acids to the saturated forms, and for the Emde degradation of a quaternary amine (eq 5).[9] The reduction of aldonolactones to aldoses with Na/Hg is a key transformation in sugar chemistry.[10] Oximes are readily reduced to amines.[11]

(5)

Aluminum Amalgam. ***Aluminum Amalgam***, readily prepared[12] by treating base-etched elemental aluminum with aqueous mercury(II) salts, is a useful replacement for Na/Hg when the compound to be reduced is base sensitive. Diethyl oxaloacetate can be reduced to diethyl malate (70–80% yield) (eq 6) and aryl ketones can be reduced to the corresponding pinacols (30–60% yield) (eq 7) in this way.[12] Desulfurization of disulfides is also possible.[13]

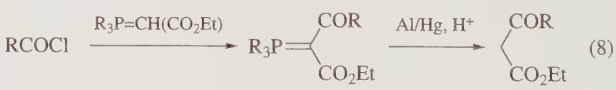


(6)



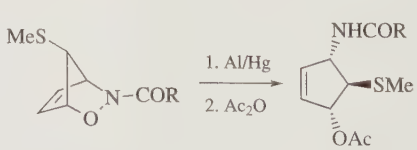
(7)

Dienes undergo what is effectively a 1,4-addition of H_2 to give the monoenes, and cumulenes undergo a 1,2-reduction.[14] The C–S bond in α,β-unsaturated phenyl sulfones can be hydrogenolyzed stereospecifically to give the alkene in excellent yield.[15] Net hydrogenolysis of a P=C bond is involved in the sequence shown in eq 8, in which an acyl halide is converted to a keto ester.[16a]



(8)

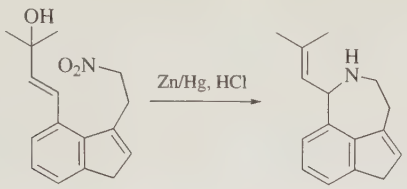
In a recent synthesis of mannostatin A, King and Ganem have shown how the N–O bond of a cyclic acyl-nitroso compound can be hydrogenolyzed by Al/Hg (eq 9).[16b]



(9)

Zinc Amalgam. The classic use of ***Zinc Amalgam*** is the Clemmensen reduction of ArCOR to $ArCH_2R$.[17] Variants of this method

have proved successful for specific substrates.[18] The nitroalkene closure shown in eq 10 is a more recent application of Zn/Hg.[19]



(10)

Ultrasound[20] and Rieke[21] methods are increasingly being used as an alternative to Hg amalgamation for activating metals, a trend encouraged by disposal problems of mercury-contaminated wastes.

Catalyst Poison. Mercury selectively poisons heterogeneous catalysts, particularly of the platinum group metals (PGM). This can be useful when a homogeneous PGM catalyst decomposes with time to give the free metal; in such a case, Hg^0 can suppress the heterogeneous component of the reaction.[22] This can improve selectivity or give mechanistic information about which products are attributable to which pathway.

Potential Route to Organomercury Compounds from Hg^0. Organomercury compounds are synthetically accessible[23] from metallic mercury by a number of routes, including reaction of elemental mercury with alkenes in acid medium and with acyl and alkyl halides (under thermal or photochemical conditions). Organic synthetic applications of this chemistry seem to be very rare, however.

Electrolysis at Mercury Cathodes. The high overvoltage of a mercury surface in several electrochemical processes is often used to advantage; for example, proton reduction to H_2 is kinetically disfavored relative to electron transfer to an organic substrate. An example of an organic electrochemical application is provided by reduction of a number of alkyl halides, RX, to the radical, R•, which dimerizes to R_2, disproportionates to RH and the corresponding alkene, and also leads to the formation of R_2Hg.[24]

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First Update

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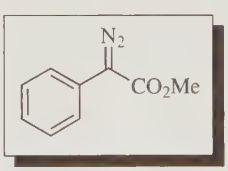
The rise of Green Chemistry has seen a decline in the use of heavy metals, especially mercury. Alternative reductants to amalgams are now readily available for most purposes (e.g., ultrasound[20] and Rieke[21] metals), although mercury photosensitization has few alternatives.

Hg(0) helps distinguish homogeneous from heterogeneous catalysis.[25] Mercury electrodes are common inert electrodes in electrochemical reductions.[26]

In thioglycosides protected as the *O*-sulfonate ester, the sulfonyl group is easily removed with sodium amalgam in 2-propanol.[27]

Methyl Phenyldiazoacetate



[22979-35-7] $C_9H_8N_2O_2$ (MW 176)

(precursor to highly chemoselective metal carbenoids)

Physical Data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (m, 2 H), 7.37 (m, 2 H), 7.17 (m, 1 H), 3.85 (s, 3 H); IR (neat): 3061, 3026, 3003, 2954, 2089, 1709, 1598, 1498, 1438 cm^{-1}.

Solubility: soluble in most organic solvents including hydrocarbons.

Form Supplied in: not commercially available.

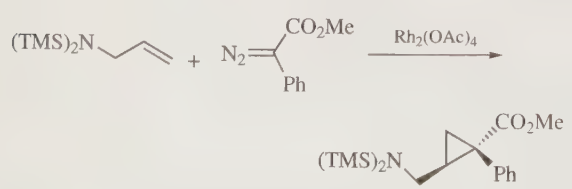
Preparative Methods: [1] DBU (32.0 mL, 214 mmol) was added in one portion to a stirred solution of methyl phenylacetate (26.7 g, 178 mmol) and *p*-acetamidobenzenesulfonyl azide (51.4 g, 214 mmol) in acetonitrile (200 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight and then quenched with saturated ammonium chloride (200 mL). The aqueous layer was extracted with diethyl ether (3 × 100 mL) and the combined organic layers were dried ($MgSO_4$). The residue was purified by flash chromatography (SiO_2, diethyl ether/pentane = 5:95) to give methyl phenyldiazoacetate (23.3 g, 132 mmol, 75% yield) as an orange oil.

Purification: readily purified by silica gel chromatography using diethyl ether/pentane (5:95) as solvent to give the title compound as an orange oil.

Handling, Storage, and Precautions: the title compound appears stable to storage at room temperature (23 °C) or below. No difficulty in handling this compound was experienced over several years of study. As with any diazo compounds, however, caution should be exercised in handling this compound and especially, excessive heating should be avoided. As a precaution, it is recommended that all procedures using this compound should be conducted behind a blast shield.

Introduction. The title compound represents a member of a class of diazo compounds which on metal catalyzed decomposition generate donor/acceptor-substituted metal-carbenoid intermediates. These intermediates are much more chemoselective than the more conventional metal carbenoids which contain only acceptor group(s), such as the carbenoids derived from ethyl diazoacetate or dimethyl malonate.[2] Other diazo compounds of this class are substituted phenyldiazoacetates,[3] heteroaryldiazoacetates,[4] vinyldiazoacetates,[5] and alkynyl diazoacetates.[6] The donor/acceptor-substituted carbenoids display remarkable chemoselectivity and have greatly expanded the application of metal-carbenoid intermediates in organic synthesis.

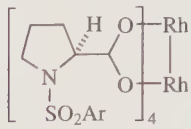
Intermolecular Cyclopropanation. Even though the metal catalyzed decomposition of diazo compounds in the presence of alkenes is a very useful method for the synthesis of cyclopropanes, the reaction has been plagued by poor diastereocontrol especially in the classic reaction where unsubstituted diazoacetates are used as the carbenoid source.[7] In contrast, the cyclopropanation chemistry of methyl aryldiazoacetates is routinely highly diastereoselective (eq 1).[3,8] Hammett studies,[9] kinetic isotope, and modeling studies[10] indicate that the donor group stabilizes the highly electrophilic carbenoids. Consequently, these carbenoids are much more chemoselective than the conventional carbenoids.



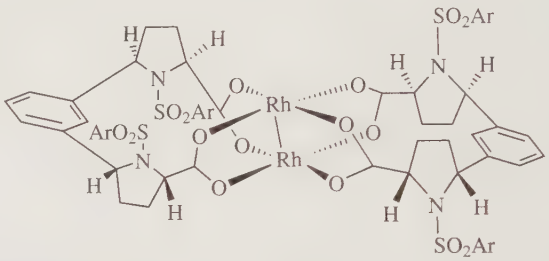
(1)

74% yield
92% de

The synthetic utility of aryldiazoacetates has been greatly enhanced by the discovery of dirhodium tetraprolinates as spectacular chiral catalysts for their transformations.[11] A number of prolinate derivatives have been evaluated,[3,8,12] but the most notable are the hydrocarbon soluble catalysts Rh_2(*S*-DOSP)$_4$ (**1a**)[3b] and Rh_2(*S*-TBSP)$_4$ (**1b**)[3b,c] and the bridged prolinate catalyst Rh_2(*S*-biTISP)$_2$ (**2a**) and Rh_2(*S*-biDOSP)$_2$ (**2b**).[12b]

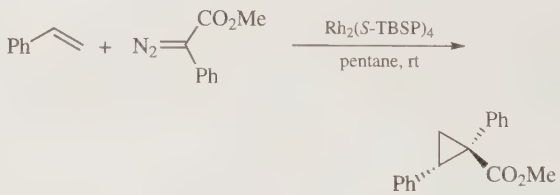


1a, Rh_2(*S*-DOSP)$_4$: Ar = *p*-$C_{12}H_{25}C_6H_4$
1b, Rh_2(*S*-TBSP)$_4$: Ar = *p*-^{t}BuC_6H_4



2a, Rh_2(*S*-biTISP)$_2$: Ar = 2,4,6-tri-^{i}PrC_6H_2
2b, Rh_2(*S*-biDOSP)$_2$: Ar = *p*-$C_{12}H_{25}C_6H_4$

The Rh_2(*S*-TBSP)$_4$ catalyzed asymmetric cyclopropanation of aryldiazoacetates is a very efficient process (eq 2).[3b] A variety of other catalysts have been explored with moderate success for the asymmetric cyclopropanation with methyl phenyldiazoacetate,[3,8,11] but none compete effectively with the *N*-(arylsulfonyl)prolinate catalysts.



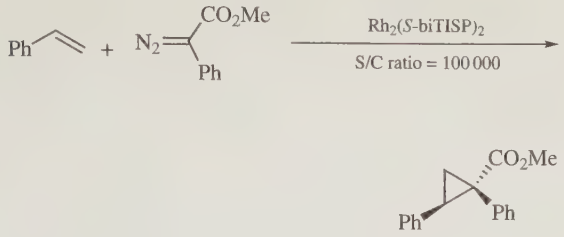
(2)

90% yield
96% de, 87% ee

A major advantage of the enhanced stability of the donor/acceptor-substituted carbenoids is that they allow the chemistry to occur with very high-turnover numbers. The most impressive example of this to date is the high-turnover reaction achieved with the bridged prolinate catalyst Rh_2(*S*-biTISP)$_2$, whereby the cyclopropanation can be conducted with 0.001% of catalyst and the product is obtained in 75% yield and 99.3% ee after recrystallization (eq 3).[13]

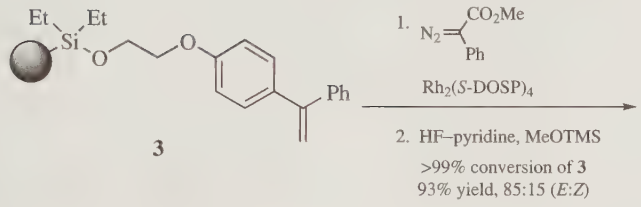
The utilization of carbenoid transformations in solid phase chemistry has been rather limited,[14] presumably because the carbenoids are too reactive for routinely effective solid phase reactions. In contrast, solid phase reactions are very effective with the donor/acceptor-substituted carbenoids. Very high conversions have been achieved with immobilized trapping agent **3** (eq 4) and

the stereoselectivity is very much comparable to the corresponding homogeneous reaction.[15]

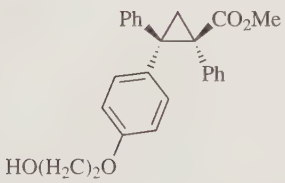


(3)

crude: 92% yield, 85% ee
recrystallized: 75% yield, 99.3% ee

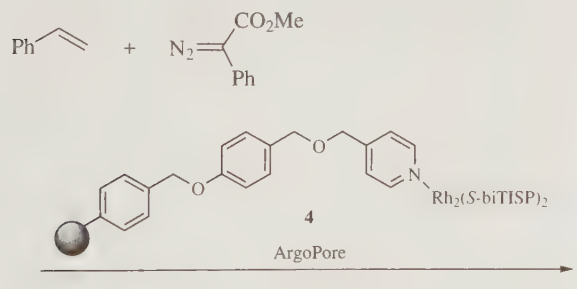


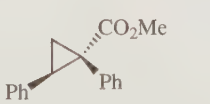
>99% conversion of **3**
93% yield, 85:15 (*E*:*Z*)



(4)

A pyridine linked argopore resin was found to be very effective for immobilization of dirhodium tetraprolinates.[16] In the case of Rh_2(*S*-biTISP)$_2$ on solid support (**4**), asymmetric cyclopropanation is very effective and the catalyst can be recycled up to 15 times without loss in yield or enantioselectivity (eq 5).[15a]



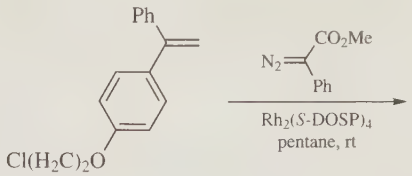


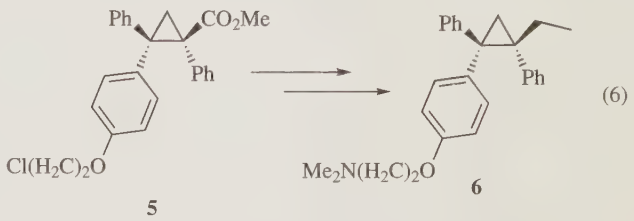
(5)

87–91% yield, 85–88% ee
>94% de over 15 cycles

The synthetic potential of this chemistry has been demonstrated by a short asymmetric synthesis of the cyclopropane analog of tamoxifen (eq 6).[17] In addition to the spectacular enantioselectivity of this reaction (98% ee), the diastereoselectivity (75% de) is remarkable especially when one considers that the only difference between the two aromatic rings is a *p*-methoxy substituent.

Further conversion of **5** to the tamoxifen analog **6** is readily achieved using conventional chemistry.

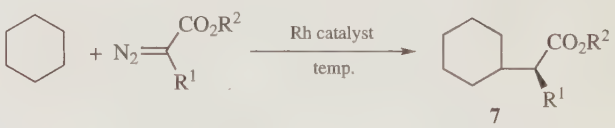




(6)

75% yield
98% ee, 76% de

Intermolecular C–H Activation. A very attractive method for functionalizing unactivated C–H bonds is carbenoid induced C–H insertion. Some very successful examples of intramolecular C–H activation have been achieved using the conventional carbenoid systems lacking donor groups.[18] The intermolecular version, however, was relatively undeveloped until very recently because the conventional carbenoids were too reactive.[17] Carbene dimerization and poor regioselectivity in the C–H activation were difficult to control. This situation has now totally changed with the development of the donor/acceptor-substituted carbenoids.[19] The difference in reactivity between the carbenoid systems is shown in eq 7.[20] Rhodium(II) pivalate catalyzed decomposition of ethyl diazoacetate in cyclohexane gave only 10% yield of the C–H insertion product **7a**. The major products were diethyl fumarate and diethyl maleate formed by carbene dimerization. In contrast, the same reaction using methyl phenyldiazoacetate gave the C–H insertion product **7b** in 94% yield. When the reaction of methyl phenyldiazoacetate was catalyzed by Rh_2(*S*-DOSP)$_4$ at 10 °C, **7b** was formed in 80% yield and 95% ee.[21]

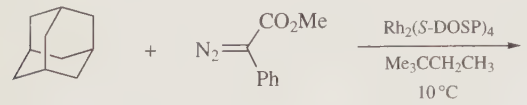


(7)

Product	R^1	R^2	Rh catalyst	Temp. (°C)	Yield, % (ee, %)
7a	H	Et	$Rh_2(OAc)_4$	23	10
7b	Ph	Me	$Rh_2(OAc)_4$	23	94
7b	Ph	Me	Rh_2(*S*-DOSP)$_4$	10	80 (95)

The Rh_2(*S*-DOSP)$_4$ catalyzed C–H activation chemistry of aryldiazoacetates is generally highly enantioselective.[19] Furthermore, the reaction displays impressive regiocontrol, governed by a subtle balance of steric and electronic effects. The C–H activation occurs with build-up of positive charge on carbon and, consequently, C–H activation of alkanes can occur at methine or methylene sites but

not on methyl. A good example of the chemoselectivity displayed in these reactions is the reaction with adamantane (**8**), which results in exclusive C–H insertion into the methine C–H bond to form **9** in 90% ee (eq 8).[1] 2,2-Dimethylbutane is a good inert solvent but for more activated systems, a hydrocarbon solvent such as hexane is adequate.



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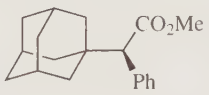
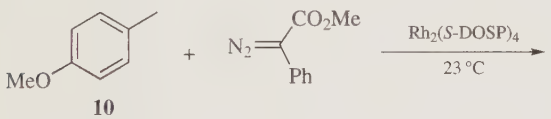


(8)

9

66% yield, 90% ee

The C–H activation is strongly favored at benzylic sites.[21] In general, a methylene C–H bond is more reactive than either a methyl or a methane C–H bond, but if the aromatic ring is sterically protected by being at least *p*-disubstituted as in *p*-methylanisole (**10**), effective C–H activation at the benzylic methyl position is feasible to form **11** (eq 9).[21b]



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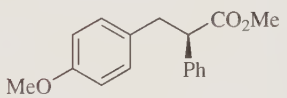
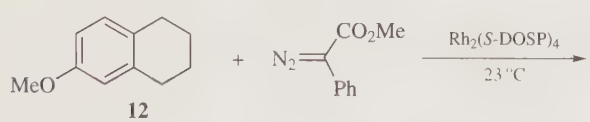


(9)

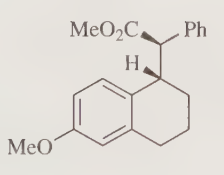
11

67% yield, 79% ee

The reaction can display very high chemoselectivity as illustrated in the reaction with tetrahydronaphthalene **12** (eq 10).[21a] The *p*-methoxy substituent in **12** stabilizes the transition state for the C–H activation, leading to a strong preference for the formation of the C–H activation product **13**.



12

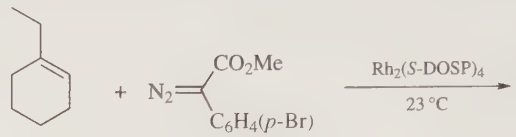


(10)

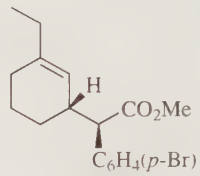
13

72% yield, 94% ee, 59% de
99:1 regioselectivity

Impressive regiocontrol is also seen in C–H activation of allylic C–H bonds. Even though 1-ethylcyclohexene (**14**) has three methylene allylic sites, due to primarily steric effects, the C–H activation by *p*-bromophenyldiazoacetate (**15**) strongly favors the formation of **16** (eq 11).[22] The products from the allylic C–H activation are γ,δ-unsaturated esters, compounds which would be classically derived from a Claisen rearrangement.[22] The allylic C-H activation has been used for the asymmetric synthesis of several pharmaceutical agents such as sertraline, indatraline, and ceitedil.[23]



14 **15**

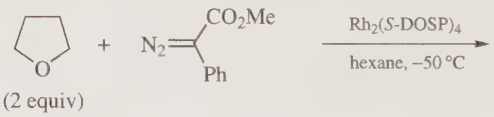


(11)

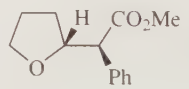
16

46% yield, 94% ee, 50% de
96:4 regioselectivity

C-H Activation at a position α to the oxygen is strongly preferred as seen in the reaction with tetrahydrofuran, in which the C–H activation product **17** was formed in 66% yield despite the fact that the reaction was conducted in hexane as solvent (eq 12).[1] When the reaction was conducted at −50 °C, the major diastereomer was formed in 97% ee. C–H Activation at a position α to the oxygen is also effective with tetraalkoxysilanes,[24] silyl ethers,[25] and methyl ethers.[26]



(2 equiv)



(12)

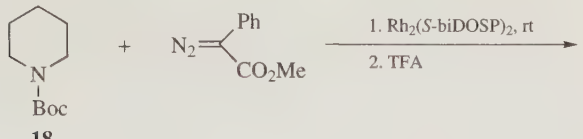
17

97% ee, 2.8:1 dr
66% yield

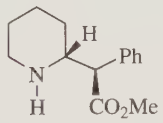
The C–H activation of *N*-Boc-piperidine (**18**) is a very impressive example because it represents a very direct synthesis of the pharmaceutical agent, *threo*-methylphenidate (**19**).[27] The highest levels of asymmetric induction were obtained when Rh_2(*S*-biDOSP)$_2$ was used as catalyst, which gave a 3:1 mixture of diastereomers from which **19** was isolated in 52% overall yield in 86% ee (eq 13).[27a,c]

When the C–H activation is conducted in systems with considerable size differentiation between the two substituents, the reactions can be highly diastereo- and enantioselective. For example, the reaction of **15** with allyl silyl ether **20** generates the protected β-hydroxy ester **21** (eq 14) in >94% de, a compound that would be typically obtained by an aldol reaction.[25b] This example further illustrates the chemoselectivity associated with this chemistry

because the diene is not cyclopropanated, while C–H activation adjacent to the acetoxy group is not observed. Highly diastereoselective C–H insertions are also observed when tetraalkoxysilanes,[24] silylated alcohols,[25b] *N*-Boc-pyrrolidine,[26a,c] and certain cyclic and acyclic alkenes[22] and acyclic vinyl ethers[28] are used as substrates.



18

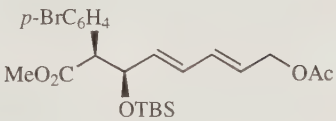


(13)

19

86% ee, 52% yield

20

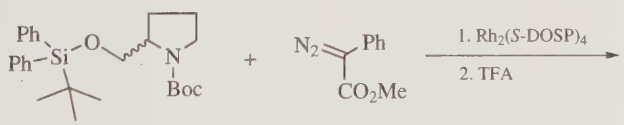


(14)

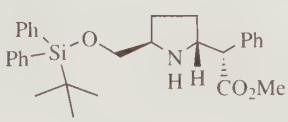
21

92% yield
>94% de, 72% ee

Another striking example of the chemoselectivity of this process is the kinetic resolution shown in eq 15.[26a,c] Substrate **22** contains three sites that are electronically activated yet only one is susceptible to C–H activation because the other two are too crowded. This example also illustrates the remarkable stereoselectivity that is possible in this chemistry because **23** is formed essentially as a single diastereomer in 98% ee.



22
(±) (2 equiv)

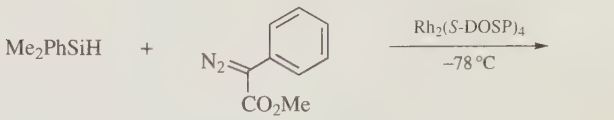


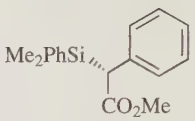
(15)

23

85% yield
98% ee, >94% de

Miscellaneous Reactions. Methyl phenyldiazoacetate is capable of undergoing effective asymmetric Si–H insertions when the reaction is catalyzed by Rh_2(*S*-DOSP)$_4$. An illustrative example is shown in the reaction of a phenyldiazoacetate that results in the formation of the benzylsilane **24** in 85% ee (eq 16).[29] A wide variety of other chiral catalysts have also been explored in this standard reaction,[30] but Rh_2(*S*-DOSP)$_4$ still appears to be the best catalyst to date.



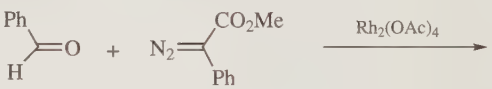


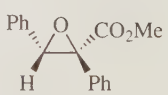
(16)

24

50% yield
85% ee

Rhodium catalyzed reaction of methyl phenyldiazoacetate with aldehydes results in the stereoselective formation of epoxides (eq 17).[31] A similar reaction with imines generates aziridines.[31a] This method of epoxide formation is unique to donor/acceptor-substituted carbenoids because very different products are formed in the reaction of ethyl diazoacetate with aldehydes.[32] These reactions presumably proceed via oxonium or iminium ylides because chiral catalysts do not induce asymmetric induction in these processes.[31]





(17)

76% yield
>95% de

Other intermolecular reactions of methyl phenyldiazoacetate which have been described include O-H insertion,[33] sulfur ylide formation,[34] and electrophilic substitution of pyrroles.[35] Substituted aryldiazoacetates have been shown to be capable of various intramolecular reactions, such as cyclopropanation,[36] C–H insertion,[37] and ylide formation.[38] Although the intramolecular reactions are generally effective, in general comparable reactions using the more conventional carbenoids are known.

In summary, the rhodium catalyzed reactions of methyl aryldiazoacetates offer a wide range of applications in organic synthesis. As the carbenoids derived from these diazo systems contain both donor and acceptor groups, they display high reactivity but are remarkably chemo- and stereoselective. The unusual reactivity profiles of these carbenoids offer exciting new opportunities for developing new strategic reactions for synthesis.

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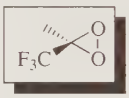
Methyl(trifluoromethyl)dioxirane[1]



[115464-59-0] $C_3H_3F_3O_2$ (MW 128.06)

(selective, reactive oxidizing agent capable of epoxidation of unreactive alkenes[5] and arenes,[7] oxyfunctionalization of alkanes,[3] oxidation of alcohols[16] and ethers[19])

Alternate Name: TFDO.

Physical Data: known only as a dilute solution.

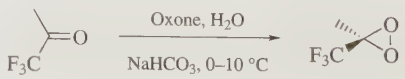
Solubility: sol in acetone and CH_2Cl_2; sol in most other organic solvents, but reacts slowly with many of these.

Form Supplied in: dilute solutions of the reagent in 1,1,1-trifluoro-2-propanone are prepared from Oxone (***Potassium Monoperoxysulfate***) and this ketone as described below.

Drying: initial drying of reagent solutions is accomplished with reagent grade anhyd $MgSO_4$ in the cold. After filtration, solutions are typically stored over molecular sieves.

Analysis of Reagent Purity: concentrations of the reagent can be determined by classical iodometric titration or by reaction with an excess of an organosulfide and determination of the amount of sulfoxide formed by NMR or gas chromatography.

Preparative Methods: TFDO solutions are prepared by mixing 1,1,1-trifluoro-2-propanone (TFP) and aqueous buffered Oxone in the cold and collecting the volatile TFDO–TFP mixture by transfer into a cold trap in a stream of inert gas under reduced pressure (eq 1).[3]



(1)

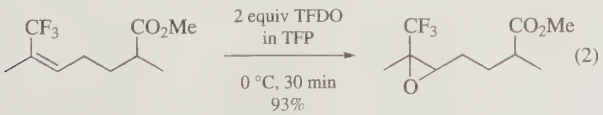
Handling, Storage, and Precautions: solutions of the reagent can be kept in the freezer of a refrigerator at −20 °C for as long as a week. The concentration of the reagent decreases relatively slowly (ca. 6–8% in 48 h), provided solutions are properly stored. It is particularly important that solutions be kept from light and traces of heavy metals, since the reagent is particularly susceptible to their influence. These dilute solutions are not known to decompose explosively, but the usual precautions for handling peroxides should be applied, including the use of a shield. All reactions should be performed in a hood to avoid exposure to the powerful, volatile oxidant.

Original Commentary

Jack K. Crandall
Indiana University, Bloomington, IN, USA

Introduction. Methyl(trifluoromethyl)dioxirane is a fluorinated derivative of the extremely useful oxidant ***Dimethyldioxirane*** (DDO), over which it has several advantages as a reagent. However, it is more expensive and difficult to prepare, since it is obtained from the volatile (bp 22 °C) ketone TFP.[2] Nonetheless, the much greater reactivity of TFDO can be of major advantage for less reactive substrates. Furthermore, the concentration of TFDO (ca. 0.8 M) normally obtained is several times greater than that of DDO. Solutions of TFDO in halocarbon solvents free of starting ketone can be obtained by extraction of the TFP into water, owing to the water solubility of the ketone hydrate.[4] Oxidations with TFDO are performed by adding the reagent to the reactant, often in CH_2Cl_2 solution, and then simply removing the volatile solvents when reaction is complete (usually minutes).

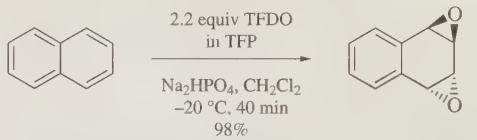
Alkenes and Arenes. Like DDO, TFDO performs rapid epoxidations of alkenes with retention of alkene stereochemistry.[1,2] Since DDO is adequately reactive towards most double bonds, there is ordinarily no reason to employ TFDO in reactions of this type. One important exception is the epoxidation of trifluoromethyl-substituted alkenes, which are resistant to classic epoxidizing reagents and which require a large excess of DDO during two weeks to complete epoxidation.[5] TFDO rapidly converts such alkenes to epoxides (eq 2). Another example of the beneficial effect of TFDO is in the preparation of the sensitive epoxides of enol ethers, where the short reaction times and facile product isolation are crucial.[6]



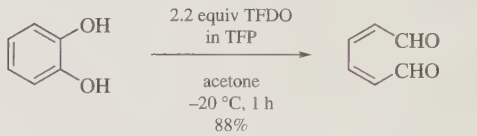
(2)

Polycyclic aromatic hydrocarbons like phenanthrene are converted to epoxides by TFDO.[7] This reactive reagent even permits the epoxidation of naphthalene, which undergoes fast sequential diepoxidation as shown in eq 3. Interestingly, the second epoxidation shows high *anti* stereoselectivity. Catechol is oxidatively cleaved by TFDO into (*Z,Z*)-muconic acid in good yield (eq 4).[8] This reagent also oxidizes 2,6-di-*t*-butylphenol to the corresponding quinone and a hydroxyquinone derivative (eq 5).[8]

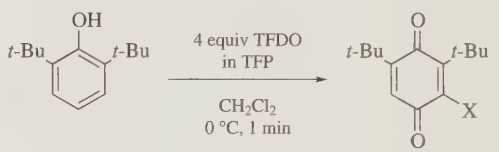
Alkynes are oxidized by TFDO to give a variety of different products, depending on the nature of the alkynic substituents.[9] Reaction is thought to proceed via an oxirene intermediate. This highly unstable, anti-aromatic heterocycle quickly rearranges to the isomeric α-ketocarbene, which then leads to the observed products by typical carbenoid transformations. For example, cyclodecyne gives bicyclic ketones by transannular insertion processes common to this medium-ring system (eq 6).



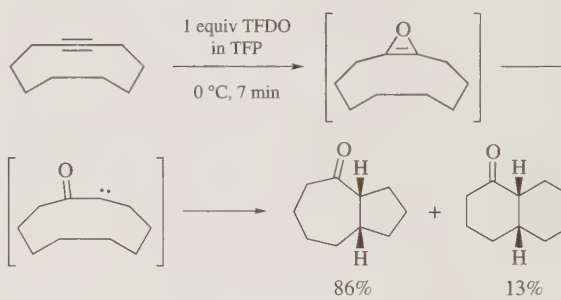
(3)



(4)

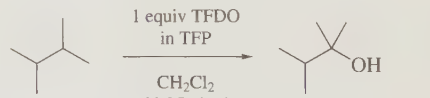


(5)

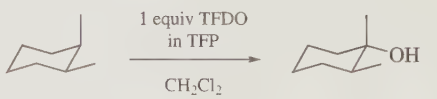


(6)

Alkanes. The most impressive applications of TFDO to date have involved the hydroxylation of unactivated C–H bonds.[1,3] While dimethyldioxirane performs similar reactions, the much greater reactivity of TFDO permits higher conversions of alkanes with less oxidant and in minutes rather than hours. Despite its more reactive nature, TFDO displays selectivity for attack at tertiary > secondary > primary C–H bonds almost as advantageous as that for DDO.[3] Examples include the exclusive formation of the tertiary alcohol from 2,3-dimethylbutane (eq 7) and the stereospecific oxidation of *cis*-1,2-dimethylcyclohexane (eq 8). Cyclohexane is oxidized to cyclohexanone by TFDO in a slower process that involves a fast second oxidation of the initially formed cyclohexanol. Heptane generates a 41:41:18 mixture of 2-, 3-, and 4-heptanone.

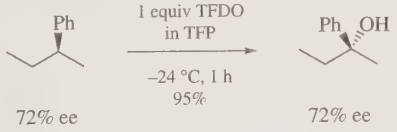


(7)



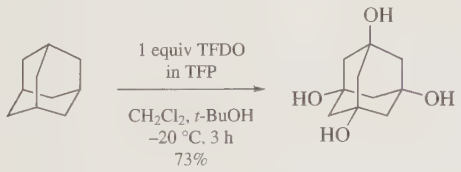
(8)

The stereospecificity of these C–H oxidations is illustrated in eq 9 by the benzylic oxidation of optically active (*S*)-(−)-2-phenylbutane, which gives only the tertiary alcohol with total retention of configuration.[10] Interestingly, ketone-free TFDO in CH_2Cl_2 is three times more reactive than TFDO–TFP.



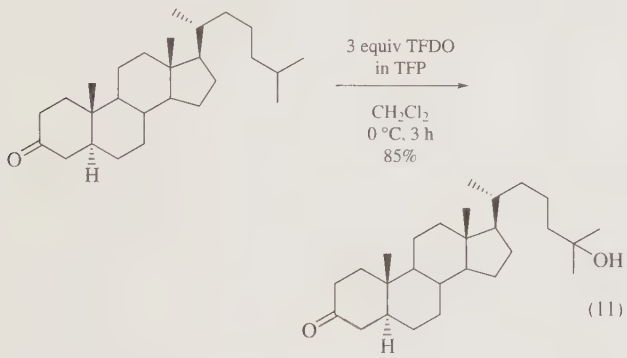
(9)

Adamantane is an informative substrate for oxidation by TFDO; it not only shows very high bridgehead selectivity, but can be converted to mono-, di-, tri-, and even tetrahydroxylated adamantane (eq 10) in good yields by varying the ratio of oxidant to hydrocarbon.[11]



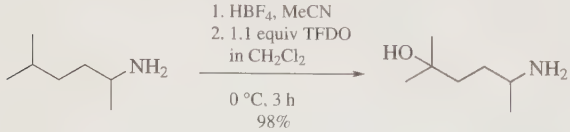
(10)

Several impressive oxyfunctionalization reactions on steroid substrates illustrate the enormous potential of this process. Not only is there a preference for tertiary C–H oxidation, but there is also significant site selectivity, presumably governed by steric features. For example, the cholestane derivative in eq 11 gives rapid, selective C-25 side-chain oxidation without appreciable reaction at other tertiary carbons.[12] Coprostane[13] and estrone[14] derivatives undergo C-5 and C-10 hydroxylation, respectively.



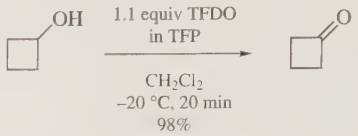
(11)

The stability of TFDO to strong acid adds a further dimension to its chemistry, as illustrated by the reactions of amines in the form of their fluoroborate salts with ketone-free solutions of TFDO.[15] The amino group is deactivated under these conditions and remote C–H hydroxylation takes place (eq 12).

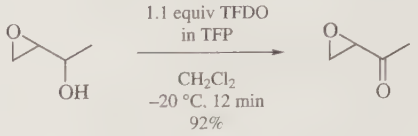


(12)

Alcohols. Secondary alcohols are smoothly oxidized to the corresponding ketones by TFDO, whereas primary alcohols are converted to acids in a slower process.[16] In view of the many methods for alcohol oxidations, this reagent will be advantageous for such conversions only in special situations. However, TFDO does perform sensitive oxidations under favorable experimental conditions that may be useful with problem cases. Cyclobutanol is oxidized by TFDO without the ring cleavage that is often problematic (eq 13). Other reactive functions can be accommodated as shown for the epoxy alcohol in eq 14.

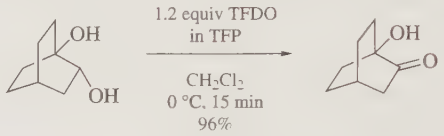


(13)



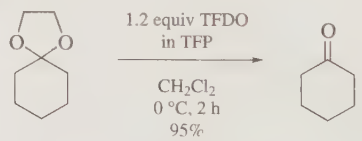
(14)

Vicinal diols are oxidized to α-hydroxy ketones by TFDO without cleavage between the two functional groups. Thus, tertiary–secondary *vic*-diols are usefully oxidized by TFDO (eq 15).[17] Optically active secondary–secondary diols have been converted to α-hydroxy ketones without racemization.[18]

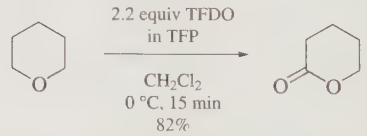


(15)

Ethers and Acetals. TFDO selectively oxidizes adjacent to an oxygen atom in compounds of these types.[19] The initially generated hemiacetals decompose to carbonyl compounds and alcohols, which may be subject to further oxidation. Ethylene glycol acetals are attacked at the dioxolane ring, leading to an interesting deprotection of the carbonyl unit under nonacid conditions (eq 16). Cyclic ethers like tetrahydropyran yield lactones by subsequent oxidation of a stable cyclic hemiacetal intermediate (eq 17). Even methyl *t*-butyl ether is oxidatively liberated to *t*-butanol upon reaction with TFDO.



(16)



(17)

First Update

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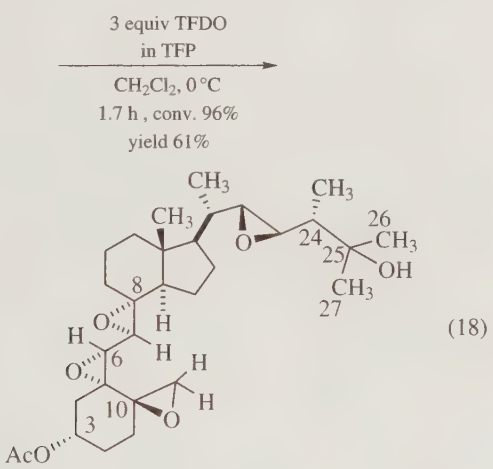
Direct Functionalization of C–H Bonds by Methyl(trifluoromethyl)dioxirane. With most existing methods of direct oxyfunctionalization of saturated hydrocarbons, the major

problem is not mainly low reactivity of the alkane molecules, but rather the difficulty of achieving selective oxidations. Indeed, selective oxidations of nonactivated alkane C–H bonds are limited to a few biological processes, which are hard to imitate.

Thus, it is remarkable that methyl(trifluoromethyl)dioxirane (TFDO) has proven to be an outstanding reagent for the selective oxidation of a variety of alkanes, including polycyclic saturated hydrocarbons, even at subambient temperatures.[1,20] Reaction kinetics and the careful application of radical-clock probes[20,21] have shown that the facile *O*-insertion into unactivated C–H bonds is likely to occur by a substantially concerted oxenoid-type mechanism. Despite the high reactivity, TFDO oxidations of alkanes can be remarkably selective.[1,20] In the alkane functionalizations by TFDO, the energetic and mechanistic characteristics differ significantly from radical oxidations more common with traditional reagents.[3] Careful theoretical studies are in accord with the finding that tertiary C–H bonds are considerably more prone to *O*-insertion by dioxiranes than their secondary and primary counterparts.[22]

A FMO model for dioxirane tertiary C–H *O*-insertion[20,22d] is suited for explaining the stringent steric and stereoelectronic alignment factors, which result in the observed astounding selectivity. An example is reaction of the tetraepoxide of 3β-acetyl vitamin D_2 with TFDO to afford its 25-hydroxy derivative in good isolated yield (eq 18).[23a] The tetraepoxide starting material (having the *R* configuration at all of the seven newly generated stereocenters) was obtained in high yield as a single diastereoisomer upon reaction of 3β-acetyl vitamin D_2 with TFDO at −40 °C.[23a]

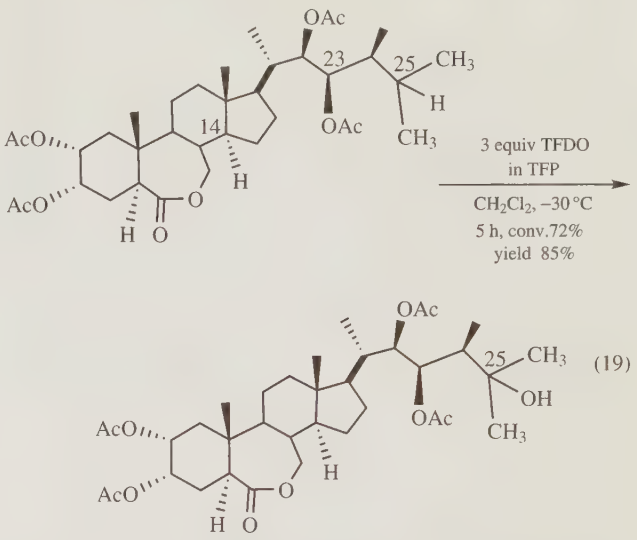


(18)

This surprisingly high site-selectivity for dioxirane *O*-insertion at the tertiary C25–H parallels that already recorded for the analogous triepoxide of vitamin D_3.[23b] Analogous to the case reported for some cholestane derivatives,[12–14] the site-selectivity is likely to derive from a distinct preference displayed by dioxiranes in attacking tertiary C–H centers bearing *geminal* methyl groups; in fact, these offer less steric opposition to optimal stereoalignment as compared to the other tertiary C–H positions available in these target molecules.

Along the same lines, treatment of the 2,3,22,23-tetraacetyl derivative of brassinolide — a plant hormone with a steroidal skeleton — with TFDO using the conditions given in eq 19 led to the nearly exclusive formation of its C25–OH analog.[24]

Treatment of the same starting material with a larger excess of TFDO (6 equiv) at room temperature and prolonged reaction time (24 h) gave the 14,25-dihydroxy tetraacetyl brassinolide as the major product (78% yield).[24]



(19)

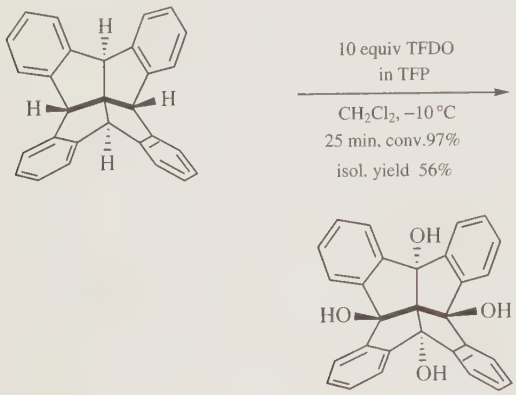
The examples above illustrate the facile hydroxylation of unactivated methine carbons of several 5β- and 5α-steroids achieved by TFDO. This reagent uses simple procedures and mild conditions to selectively yield the corresponding mono- and/or dioxygenated derivatives in reasonable isolated yields. The method that enables site-selective oxyfunctionalization in side chain and ring D in bile acids and sterols from natural sources is a key transformation into bioactive products such as 25-hydroxyvitamin D derivatives, brassinolides, ecdysonic compounds, and cardiotonic steroids.[24] TFDO is the reagent of choice because of its reactivity and high selectivity. Concerns about the cost of the reagent are chiefly linked to that of its parent ketone, i.e., 1,1,1-trifluoropropanone (TFP) (industrial price: ca. $150/100 mL). However, this concern fades considering that the expensive TFP is volatile (bp 22 °C) and it is easily recovered from spent solutions by careful low-temperature fractional distillation over granular P_2O_5.[25]

The regioselective functionalization of complex compounds is an important goal in organic synthesis; in particular, the bridgehead functionalization of polycyclic compounds can provide an access to derivatives bearing quaternary carbon centers or strained bridgehead double bonds. Controlled functionalization of centropolyindans[26] at their benzylic and/or benzhydrylic bridgehead positions is of particular interest since it allows the synthesis of complex three-dimensionally fused polyquinane carbon skeletons. Representative centropolyindanes undergo selective oxygen atom insertion into their bridgehead C–H bonds by dioxiranes.[27] Varying the excess of the TFDO reagent, allows conversion of tetrabenzo[5.5.5.5]fenestrane (fenestrindane) into either the monoalcohol or the all-bridgehead tetraalcohol (eq 20).[27a]

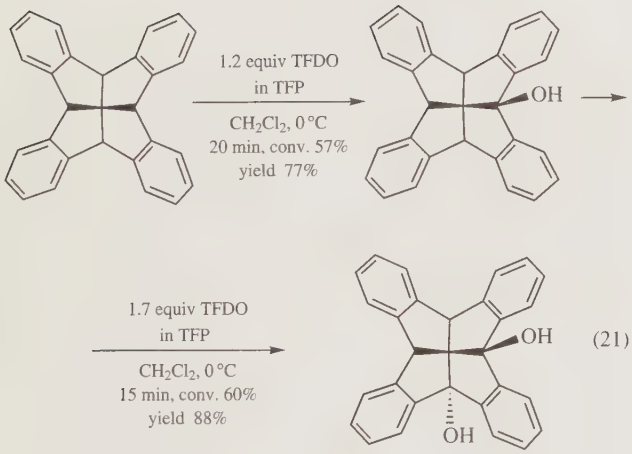
The versatile use of TFDO is demonstrated by the step-wise hydroxylation of the centropolyindane with regio- and stereocontrol. Treatment of fenestrindan with nearly stoichiometric TFDO at the conditions given in eq 21 rapidly afforded the monoalcohol as the only product. Under similar conditions, the monoalcohol gave a single dialcohol regioisomer bearing both hydroxyl groups on the same indane unit, i.e., 4b,8b-dihydroxyfenestrindane (eq 21).[27b]

The second hydroxylation occurs preferentially at the proximal 8b position with *anti* stereochemistry, perhaps because the

orientation of the initial -OH moiety disfavors dioxirane *O*-insertion at the benzhydrylic C–H from the same concave *syn* face by electrostatic dipole-dipole repulsion.[27b]



(20)

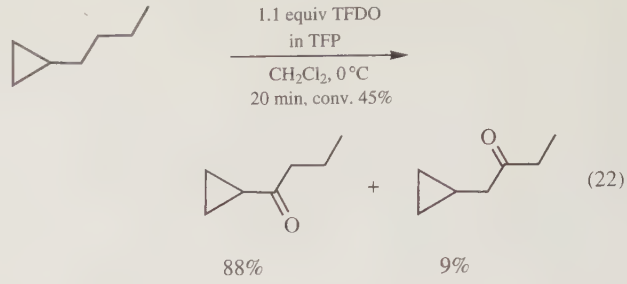


(21)

The efficiency of *O*-atom transfer by TFDO is demonstrated by its ability to oxidize a variety of saturated hydrocarbons into alcohols. Examples are provided by the transformation of *trans*- and *cis*-1,2-dimethylcyclohexanes into the corresponding 1,2-dimethylcyclohexan-1-ols (eq 8) stereospecifically, by the conversion of *trans*- and *cis*-decalin into the corresponding 1-decalol with no epimerization at the reaction center,[3] and by the oxidation of optically active 2-phenylbutane to 2-phenyl-2-butanol in over 90% yield and with *complete retention* of configuration (eq 9),[10] all serve well to illustrate the efficiency and selectivities attainable with TFDO. With stoichiometric or a modest excess of TFDO, these oxidations entail reaction times of minutes rather than hours, and avoid excess oxidant, as is required when using the milder DDO (dimethyldioxirane).

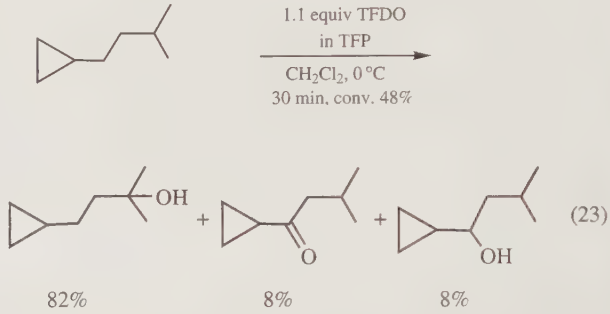
All the reactions above are characterized by high tertiary vs. secondary selectivities. The selective bridgehead hydroxylation of adamantane by *excess* (6 equiv) TFDO affords adamantan-1,3,5,7-tetraol along with the 1,3,5-triol, in 73% and 24% yield, respectively (eq 10). In these oxidations, kinetic data have shown that TFDO is more reactive than DDO by a factor of ca. 10^3, with no loss of selectivity.[11]

Data reported on oxidation of hydrocarbons bearing cyclopropyl moieties suggest that alkane C–H bonds positioned "alpha" to a cyclopropane ring are "activated" toward dioxirane *O*-insertion.[28] Product distributions indicate that usually cyclopropyl activation of α-C–H bonds dominates when no tertiary C–H is present (eq 22).



(22)

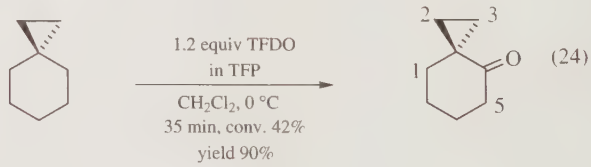
In the absence of serious steric constrains, the cyclopropane moiety is free to adopt orientations with angles between the extremes of 0 and 90 degrees with respect to the p-orbital component of the proximal C–H bonds.[29] However, oxidation of (3-methyl-butyl)-cyclopropane (eq 23) clearly demonstrates that cyclopropyl activation competes poorly with oxidation at the tertiary C–H.[28]



(23)

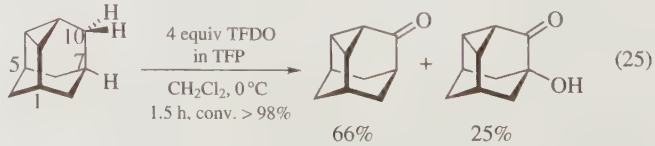
Thus, in the absence of steric constraints which prevent the cyclopropane moiety from adopting the specific favorable orientations, the normal order of dioxirane reactivity toward alkane C–H bonds may be established as: tertiary C–H ≅ benzhydrylic C–H > α-cyclopropyl C–H > benzylic C–H > secondary-C–H > primary C–H.

Cyclopropyl activation can again be invoked to rationalize the preferential oxyfunctionalization at the α-CH_2 of spirooctane (eq 24).[28]



(24)

The cyclopropyl moiety — if suitably oriented — can exert a marked activating effect on dioxirane oxidation at alpha C–H bonds as seen in the hydroxylation of 2,4-didehydroadamantane (eq 25).[28]

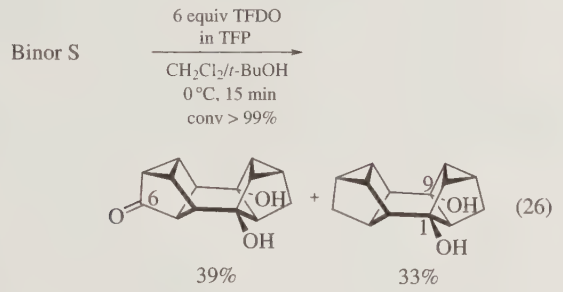


(25)

For this substrate, Murray et al. have reported that reaction with 2.2 equiv of dimethyldioxirane (DDO) proceeds at room tempera-

ture with 82% conversion, yielding 2,4-didehydroadamantan-10-one and 2,4-didehydroadamantan-7-ol in 29% and 21% yield, respectively, during 12 h.[30] Comparable selectivity is obtained with the more powerful TFDO, although the oxidation is considerably faster, giving 80% conversion in 1.5 h at 0 °C. Alternatively, treatment with TFDO excess (4 equiv) using the conditions in eq 25 results in practically complete conversion into ketone and the valuable 7-hydroxy-2,4-didehydroadamantan-10-one. Control experiments show that the latter is generated by the oxidation of the initially formed 7-hydroxy-2,4-didehydroadamantane.[28]

Similarly, in the TFDO oxyfunctionalization of Binor S, the valuable ketone resulting from the oxidation of methylene CH_2 alpha to the cyclopropyl moiety is obtained, along with the product expected from hydroxylation at tertiary bridgehead C–H bonds (eq 26).[31]

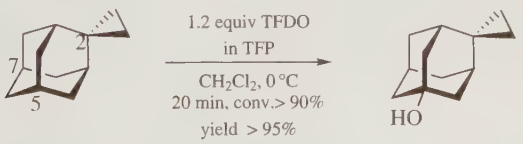


(26)

Reaction monitoring, and control experiments using the isolated diol, show that oxyfunctionalization at the C-6 methylene only takes place in the facing nortricyclane subunit after hydroxylation at the bridgehead C(1)–H and C(9)–H.[31]

In both cases above, the effective competition with the preferential dioxirane *O*-insertion at tertiary bridgehead C–H's stems from the favorable "bisected" orientation of the methylene C–H bonds relative to the neighboring cyclopropyl ring.

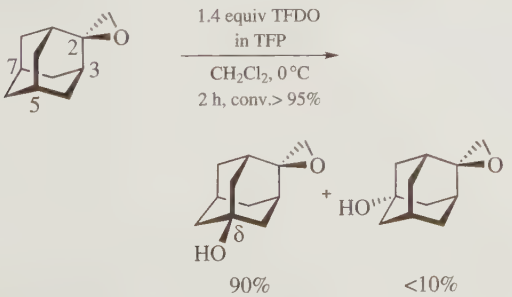
The "deactivating" arrangement of the cyclopropyl moiety in spiro adamantanylcyclopropane makes this compound an informative probe; in this substrate TFDO hydroxylation occurs at C-5 exclusively, yielding the bridgehead alcohol shown in eq 27.[28]



(27)

In this case, the proximal tertiary C–H's at C-3 and C-1 become deactivated since their p-orbital component is constrained in the unfavorable "eclipsed" arrangement with respect to the cyclopropane ring.[28]

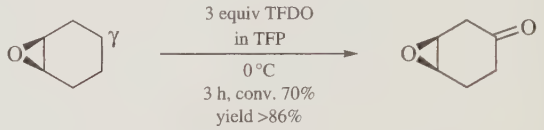
A similar regioselectivity is observed for methyleneadamentane oxide bearing a spiro fused oxiranyl ring (eq 28).[32]



(28)

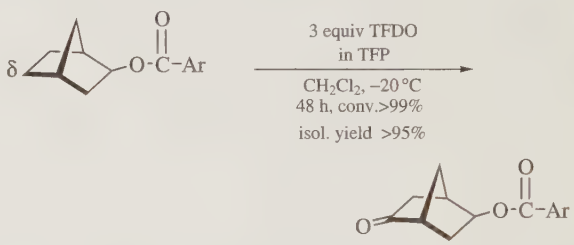
Here it is apparent that the oxiranyl ring has a marked deactivating effect on the proximal C–H bonds, leading to exclusive hydroxylation at bridgehead C5–H and C7–H with surprisingly high *Z/E* diastereoselectivity. This is parallel to the stereodiscrimination observed for the TFDO oxidation of adamantanes carrying electron-withdrawing substituents at C-2.[33]

In the transformation presented in eq 28, the epoxide ring remains untouched; thus, the reaction is also earmarked by valuable chemoselectivity. This feature of TFDO oxidation is confirmed by the finding that a variety of epoxy alcohols can be cleanly converted into the corresponding epoxy ketones in high yields. Epoxy ketones could also be obtained by the *direct* oxidation of bicyclic epoxides using TFDO. The oxyfunctionalization usually occurs at the remote γ and/or δ C–H bonds with respect to the epoxide ring. An example is given by the transformation in eq 29.[34]



(29)

Other interesting examples of remote oxyfunctionalization using TFDO are provided by the oxidation of several open-chain, cyclic, and bicyclic esters.[35] One clear-cut case is represented by the transformation of *exo*-2-[(*p*-chlorobenzoyl)oxy]norbornane into its 6-norbornanone with high regioselectivity (eq 30).



(30)

The collection of the examples reported herein convincingly suggest that TFDO should be considered the reagent of choice for the direct oxidation of C–H bonds because of its efficiency, remarkable selectivity, and simplicity of operations.

Related Reagents. Potassium monoperoxysulfate oxone; potassium monoperoxosulfate (oxone)/1,1,1-trifluoropropanone (TFDO in situ); dimethyldioxirane (DDO).

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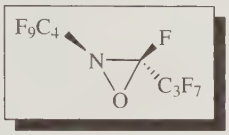
Oxaziridine, 3-Fluoro-3-(heptafluoropropyl)-2-(nonafluorobutyl)[1]



[143813-70-1, 145733-84-2] $C_8F_{17}NO$ (MW 449.06)

(strong but selective oxidizing agent for the oxyfunctionalization of alkanes[2,3] and silanes,[4] the epoxidation of alkene,[5] the ketone formation from alcohols[6] and ethers,[7] the oxygenation of sulfides, sulfoxides,[8] amines,[9,10] and selenides[11])

Alternate Name: perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine.

Physical Data: 68–69 °C/190 mm Hg.[2]

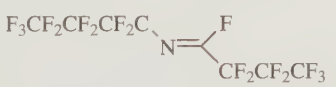
Solubility: soluble in chloroform, methylene chloride, trifluoroethanol, trifluoroacetic acid and most other organic solvents, but reacts slowly with many of them.

Form Supplied in: colorless liquid from synthesis, as described below.[12,13]

Analysis of Reagent Purity: IR (film): 1414 cm^{-1}. ^{19}F NMR ($CDCl_3$, 188 MHz) $CF_3{}^ACF_2{}^GCF_2{}^FCF^CF^DN(O)CF^ECF_2{}^ICF_2{}^K$ $CF_3{}^B$ A,B −81.4(6 F); C,D −99.2 (ddt) and −106.5 (ddt) (2 F, AB pattern); E −139.7 (1F, m); F, G, I, K −125.0 to −127.1 (8 F); $J_{CD} = 208$ Hz.[2]

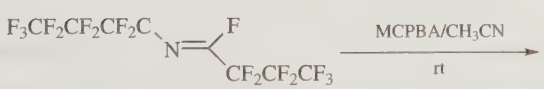
Preparative Methods: perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) is easily prepared in sizable quantities and good yields from commercially available perfluorotributylamine in two steps: Conversion of perfluorotributylamine to perfluoro-(*Z*)-4-aza-4-octene by SbF_5 (eq 1)[12] followed by oxidation with acid free *m*-chloroperbenzoic acid (eq 2).[13]

$$(CF_3CF_2CF_2CF_2)_3N \xrightarrow[120\text{–}130\,^\circ C]{SbF_5}$$

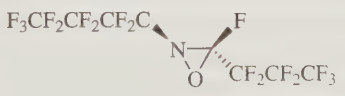


(1)

perfluoro-(*Z*)-4-aza-4-octene



perfluoro-(*Z*)-4-aza-4-octene



(2)

1

Purification: distillation in vacuum at 68–69 °C/190 mm Hg.[2]

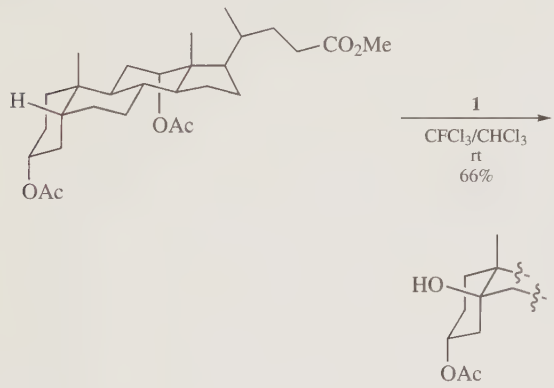
Handling, Storage, and Precautions: perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) is indefinitely stable at room temperature when humidity is avoided. Since there are no toxicological data in the literature on perfluorooxaziridines, usual precautions for handling chemicals whose properties are not fully known should be taken. The reagent should be handled only in a fume hood to avoid exposure. Since it is a potent oxidizing agent, reactions with strong reducing compounds can be quite energetic.

Introduction. Perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) is a neutral, aprotic oxidizing agent able to transfer oxygen to several different organic substrates. It can perform a selective oxidation of alkenes to epoxides,[5] alcohols and ethers to ketones,[6,7] sulfides to sulfoxides or sulfones,[8] silanes to silanols,[4] heteroaromatic nitrogen compounds and tertiary amines to corresponding *N*-oxide,[9,10] thio- and selenophosphoryl derivates to phosphoryl products,[14] selenides to selenoxides,[11] and it is able to effect the regio-, diastereo-, and enantioselective hydroxylation of unactivated aliphatic tertiary C–H bonds.[2,3] Perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) is a powerful oxidizing agent as shown by its ability to perform the oxyfunctionalization of unactivated hydrocarbon sites. At the same time, it behaves as a mild reagent as proven by its ability to perform the quantitative oxidation of thioethers into sulfoxides without overoxidation to sulfones. Being a powerful oxidizing agent, particularly mild reaction conditions can be employed so that higher yields and selectivities than those given by other reagents could be obtained. A particularly useful aspect of the reagent is its indefinite storage stability. Oxidation can be performed in both aprotic and protic solvents, in most cases halogenated hydrocarbons (CFC-11, CFC-113, chloroform, methylene chloride) are employed but other solvents, namely *tert*-butyl alcohol and trifluoroethanol, have also been used. Usually, the only "coproduct" formed in the reactions is the perfluoro-(*Z*)-4-aza-4-octene.[12,13] As both the oxaziridine **1** and perfluoro-(*Z*)-4-aza-4-octene are quite volatile compounds,[12,13] in many cases the reactions workup is particularly simple. In fact, the final products can be isolated by simply removing the solvent, the coproduct, and the excess of the oxaziridine **1**, if any, under reduced pressure.

Hydroxylation of Unactivated Hydrocarbons. Perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) is able to perform the hydroxylation of unactivated tertiary aliphatic C–H bonds with high regio- and stereoselectivities, at room temperature, in the condensed phase, and in good yields.[2] Reaction times range from several hours to a few minutes. A remarkable selectivity for the attack at tertiary C–H bond is noted in most cases. Oxidation of primary C–H bonds or dioxyfuntionalization of the substrate with several oxidizable sites have never been observed. Minor amounts of ketones are formed, probably through further oxidation of initially produced secondary alcohols and the amounts of these by-products is larger when longer reaction times are needed. Alicyclic hydrocarbons carrying equatorial tertiary C–H bond react faster than isomers having axial C–H bonds. For instance, oxidation of *cis*-dimethylcyclohexane and *cis*-decalin is faster than the reaction of the corresponding *trans* isomers.[2] A high retention of configuration (>98%) occurred in all cases.

Only few reagents are able to perform the selective oxyfunctionalization of unactivated hydrocarbon sites. A common characteristic of most of them, for instance ozone, peracids, hydrogen peroxide, dioxiranes, hydroperoxides, is their intrinsic instability, which is related to the looseness of the bond between the electrophilic oxygen, delivered in the oxidation process, and the rest of the molecule. For this reason they decompose at room temperature with oxygen liberation. Oxaziridine **1**, instead, is indefinitely stable at room temperature and decomposes only at 150–170 °C without oxygen loss. From this point of view, its ability to work as strong oxidizing agent is quite surprising.

The hydroxylation can be extended to complex, polyfunctional molecules of biological interest as 5β-steroids.[3a] These substrates react with perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) to give the corresponding 5β-hydroxy derivatives in good yields and with complete site-selectivity and stereoselectivity (eq 3). The reaction has been performed with androstanes, cholestanes, pregnanes, and cholanic acids. In all cases 5β-hydrogen is abstracted in preference to the others in the substrate also when various functional groups are present just as if the functional group in this reaction is the unactivated 5β-hydrogen. Probably the site-selectivity is strictly related to the *cis* junction of the A/B rings of steroids but further studies are required before the relative relevance of steric and electronic effects can be assessed.



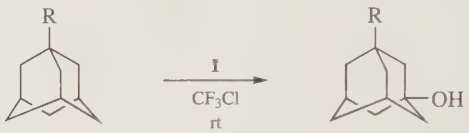
(3)

Several different functional groups, as halide, ketone, carboxylic acid, and ester, can be present on different sites of the steroid framework (at C-3, C-11, C-12, C-17, C-20, C-21, C-24) without changing the course of the reaction. The only observed effect is an increase of reaction times when the functional group is near the reactive site. The same effect is observed when dioxiranes are used.[15] This can be justified on the basis of the electrophilic nature of oxaziridine **1**.

In general, oxidative properties of oxaziridine **1** recall those of dioxiranes,[16] which have been successfully employed in the oxyfunctionalization of various steroids.[15,17] However, low site-selectivity[15b] or double oxyfunctionalization[18] have been observed in some cases when these reagents have been employed on 5β-steroids having structures identical or similar to those treated with oxaziridine **1**.

All the reactions have been performed by adding an excess of the oxaziridine **1** to a ca. 1 M solution of the steroid substrate and stirring the mixture at room temperature. The process of the reaction has been monitored by TLC and, when a fair conversion was obtained, excess chloroform and perfluorotributylamine were added, the chlorinated phase was separated and evaporated to give a residue, which was purified by flash-chromatography. $CFCl_3$ has been the solvent employed for substrates of low polarity, with more polar starting materials $CFCl_3/CHCl_3$ or $CFCl_3/CH_2Cl_2$ have been preferred, and the cholanic acid was reacted in 2-methyl-2-propanol/$CHCl_3$. The oxaziridine **1** has a low solubility in this last mixture, but the hydroxylation process occurs nicely despite the fact that a two-phase system is used. Reaction times range from 2 to 60 h.

Perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) can afford, in preparative yields, 3-substituted adamantan-1-ols,[3b] which are good precursors of biologically and industrially important adamantanes (eq 4).[19] When other oxidizing agents are used the major problem is the difficulty to achieve a selective oxidation. For example, variable amounts of adamantan-1,2-ol and adamantan-1,3-diol are obtained with ozone[20] and peracids.[21] Perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) instead reacts with excellent regioselectivity, and good yields also with bridgehead adamantane derivatives containing various functional groups such as halogen, hydroxyl, carbonyl, and carboalkoxyl. Mild reaction conditions, high regioselectivity, and chemical yields render this process an immediately useful and generalized approach to synthetically challenging polyfunctional adamantane derivatives.



(4)

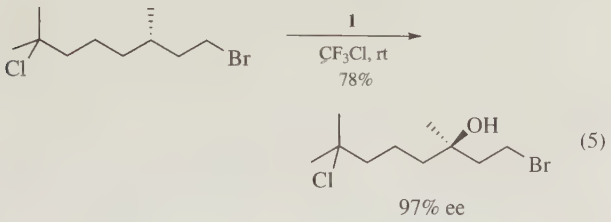
R = CH_2Br, F, Cl, Br, OH, CH_2CO_2H, CO_2H, CO_2CH_3

R	Yield (%)
CH_2Br	94
F	82
Cl	85
Br	89
OH	85
CH_2COOH	90
COOH	82
$COOCH_3$	85

It is really interesting that perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) is able to perform the enantiospecific oxyfunctionalization of unactivated hydrocarbons under remarkably mild reaction conditions (eq 5).[3c] The reaction occurs with retention of configuration at the oxidized stereogenic center and the enantiospecificity is highly independent from both the framework of the substrate and the presence of functional groups (carbalkoxy, chloro, bromo, hydroxyl residues).

Room temperature treatment of (*R*)-2,6-dimethyloctane with oxaziridine **1**, cleanly affords 3-octanol having the (*S*)-configuration. The enatiospecificity of the oxyfunctionalization changes from high to moderate on prolonging the reaction time. By performing the reaction in the presence of metal fluorides, well-known scavengers of HF, the decrease of optical purity at long reaction times is definitively depressed. This behavior proves that the change in the enantiospecificity is due to in situ racemization of the formed alcohol under catalysis by traces of hydrofluoric acid (generated by the hydrolytic decomposition of perfluoro-(*Z*)-4-aza-4-octene or present in oxaziridine **1**).

When structurally different halogen substituted citronellyl derivatives are treated with oxaziridine **1** (eq 5), almost complete retention of configuration occurred, thus confirming the enantiospecific character of the oxyfunctionalization.

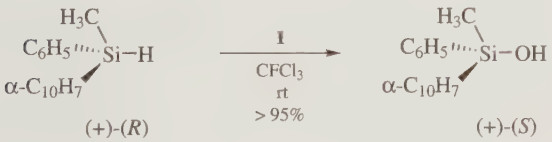


(5)

Also the oxyfunctionalization of some derivatives of 3-methyladipic acid and isoamyl alcohol occurred with very high retention of configuration.

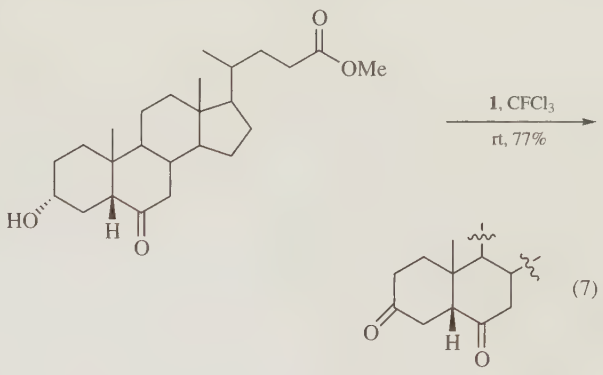
The selective oxyfunctionalization of nonactivated C–H bonds under mild and homogeneous conditions is an important objective. In fact, different approaches have been employed including catalytic methods (microorganisms,[22] enzymes,[23] and transition metals[24]) stoichiometric reagents (ozone,[20,25] fluorine,[26] peroxides and peroxy acids[27]). However, very limited examples of stereospecific oxyfunctionalization at nonactivated sites have been described. A single example of oxidation at purely aliphatic sites with 70–85% retention of configuration has been reported by action of chromic acid.[28]

Oxyfunctionalization of Silanes. Syntheses of silanols requires neutral conditions because of possible rapid condensation of silanols with formation of siloxanes. As a potent yet selective oxidizing agent under neutral and aprotic conditions, perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) is effective in this reaction. Silanols are formed with nearly quantitative yields and complete enantiospecificity regardless the nature of the residues at silicon (alkyl, aryl, alkenyl, alkynyl groups).[4] Also geminal dihydroxylation of a SiH_2 group can be performed and the yield of corresponding silanediol is nearly quantitative. Apolar ($CFCl_3$, $CHCl_3$, CH_2Cl_2, $CFCl_2CF_2Cl$) or protic (CF_3CH_2OH, $(CF_3)_2CHOH$) solvents can be used. The oxidations occur nearly instantaneously at room temperature and require 1 to 2 h at −78 °C. The oxyfunctionalization of (+)-(*R*)-methylnaphtylphenylsilane affords the corresponding silanol having the (+)-(*S*)-configuration. In $CFCl_3$ and at room temperature, the reaction occurs with complete retention of configuration (eq 6).



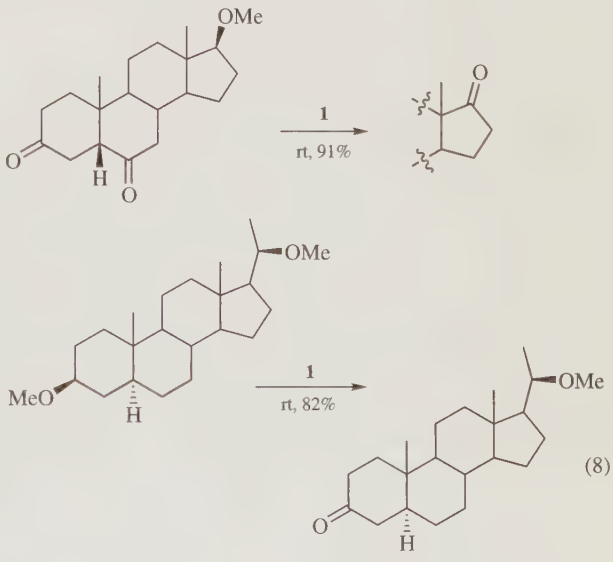
(6)

Oxidation of Alcohols. Perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) oxidizes secondary alcohols to corresponding ketones at room temperature.[6] The presence of a phenyl or a carbethoxy group does not interfere with the oxidation. The same holds when a tertiary alcoholic function or some steric hindrance is present. Interestingly, the reaction occurs in high yields also with some steroids. For instance, 6-keto-lithocholic acid methyl ester affords the 3,6-diketo product in 77% yield (eq 7). Epimerization at C-5 to give 5α-cholanic products, which can take place through enolization of the keto group at C-6, is not observed due to the neutral conditions of the reaction.



(7)

Oxidation of Ethers. Perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) is able to perform the oxidation of ethers of secondary alcohols to corresponding ketones.[7] The methyl ethers appears to be the substrates of choice, while the oxidation of alkyl ethers of secondary alcohols $R^1R^2CHOCH_2R$ is much less selective and leads to a mixture of products. The mechanism of the process could be rationalized through the formation of hemiketal, spontaneously producing the ketone by loss of a molecule of methanol. The reaction is highly selective with tertiary C–H bond being oxidized exclusively. Several steroids with a keto group on C-3, C-12, C-17, and C-20 have been obtained starting from the corresponding methoxy precursors having androstane, pregnane or cholanic acid skeletons and belonging to either the 5α or the 5β series (eq 8). In all cases good yields were obtained and the presence of a ketone or a carboxylic acid or ester did not interfere with the oxidation. The reaction conditions were quite substrate dependent because oxidation of ethers is sensitive to steric hindrance. A synthetically useful exploitation of this effect is the selective oxidation of only one methoxy group in dimethoxylated compound. The attack at the more hindered and less favored site can nevertheless be performed by changing the ether functionality at the preferential oxidation site to an ester.

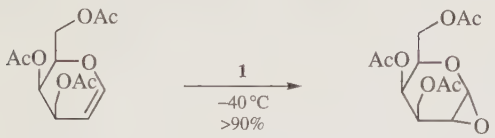


(8)

Epoxidation of Alkenes. Several and structurally different olefins have been obtained from corresponding olefins.[5a] Alkyl-substituted double bonds react under particularly smooth conditions (−40 °C, 30 min). Mildly and strongly electron deficient

substrates can also be oxidized, and the more electron poor the double bond is, the more severe the reaction conditions become. The reaction can be successfully performed not only on simple, model compounds but also on complex, polyfunctional substrates of biological interest as terpenes and steroids. The transformation occurs stereoselectively with *cis*- and *trans*-olefins affording corresponding *cis*- and *trans*-epoxides, respectively. The diastereoselectivity of the process can vary depending on the conformational and configurational constrains of the substrate. When the stereogenic center is far away from the double bond and free rotation is possible, the two possible epimers are formed in equimolar amounts. When access to the double bond is biased by the rigidity of the system, complete diastereoselection can be obtained. Both aprotic and protic solvents can be used, and this allows a wide range of substrates to be oxidized in homogeneous conditions. The presence of some functional groups which are known to be oxidized by the reagent, for instance secondary alcohols[6] and their ethers,[7] does not interfere with epoxide formation as this last reaction occurs usually at substantially lower temperature. In contrast, the reagent transforms vinyl and allyl sulfides into corresponding alkenyl sulfoxides,[8a] and alkenyl-substituted nitrogen heteroaromatics and tertiary amines give alkenyl *N*-oxides.[9,10] In these cases oxidation at the heteroatomic site is preferred over epoxidation. The selective epoxidation of a single double bond in a di-unsaturated substrate is also possible.

Perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) is also able to perform the direct epoxidation of glycals to 1,2-anhydrosugars[5b] in a nonreactive medium. These latter labile products can thus be reacted with a defined nucleophile at a later stage. On epoxidation of tri-*O*-acetyl-D-galactal the process occurs with complete stereoselection and 1,2-anhydro-3,4,6-tri-*O*-acetyl-α-D-galactopyranose is obtained exclusively (eq 9).



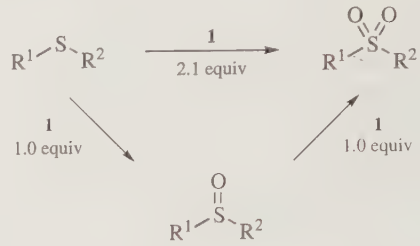
(9)

de >98%

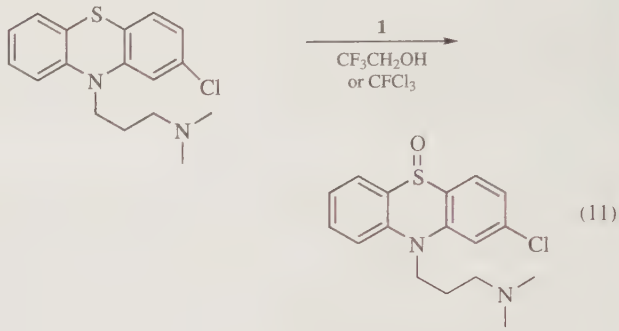
Oxidation of Organosulfur Substrates. The oxidation of sulfides to sulfoxides has been explored with many different oxidizing agents, however, very few of these reagents are generally applicable because they overoxidize sulfoxides to sulfones. A quite interesting feature of perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) is an unusual combination of high selectivity along with high oxidizing power. The reagent is able to selectively oxidize thioethers to corresponding sulfoxides in nearly quantitative yields when 1 equiv is used and the reaction is performed at −40 °C in an inert solvent to mediate the exothermicity of the reaction.[8a] The sulfones are formed when 2 equiv of the oxaziridine are employed for the transformation. Alternatively, the sulfones can be obtained by reacting sulfoxides with an equimolecular amount of the oxaziridine **1** (eq 10). Both routes afford sulfones in high yields when the reaction is carried out at −20 to 0 °C.

Both aprotic (halogenated hydrocarbons) and protic (trifluoroethanol) solvents can be employed. The typical reaction conditions are notably mild.

The presence of various nitrogen functionalities such as an amide group, an azido residue, or a tertiary amine,[10] does not interfere with the oxidation of sulfur. The same holds for the presence of various oxygen functionalities (ketone, carboxylic acid, or ester), halogens, and even olefinic double bond.[5] The sulfinyl and sulfonyl derivatives of several polyfunctional compounds of biological interest have been prepared in high yields. Tricyclic neuroleptic drugs such as chlorpromazine hydrochloride and free base give the corresponding sulfoxides in 90–93% isolated yields (eq 11).



(10)



(11)

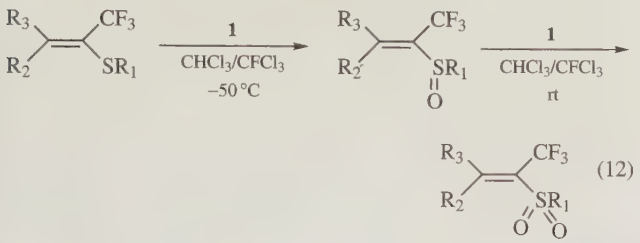
93% hydrochloride
90% free base

Oxidation of several organophosphorus agrochemicals containing the thioether function yields either sulfoxides or sulfones.[8c] Phosphoric, phosphoramidic, and phosphorothioic moieties do not interfere with the oxidation. The phosphorothionic function remains unaffected in the oxidation of the thioether, but undergoes oxidative desulfuration prior to oxidation of sulfoxides to sulfones. The high chemical yields and the very mild conditions make the oxaziridine **1**, particularly, interesting for the preparation of metabolites and analytical standards of biochemical, toxicological, and environmental compounds.

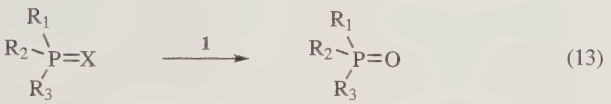
Several trifluoromethyl-substituted vinyl sulfoxides, which are not readily available by other methods can be obtained in nearly quantitative yields, at low temperature (eq 12).[8b] After removal of the sulphur residue, these products may serve as versatile synthons for the preparation of polyfunctional trifluoromethyl-substituted compounds of biological interest.

Conversion of Thio- and Selenophosphoryl into Phosphoryl Group. As mentioned before, perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) is able to perform the transformation of phosphorothioates into corresponding phosphates.[14] This behavior of the oxaziridine **1** is quite general and allows to transform thiophosphoryl into phosphoryl group on many structurally different phosphorus(V) derivatives (eq 13).

High yields of phosphoryl products are obtained under mild reaction conditions with a wide variety of derivatives (R_1, R_2, R_3 = alkyl, aryl, *O*-alkyl, *O*-aryl, NH-alkyl, *N*-alkyl$_2$). Similarly, triphenylphosphine selenide affords quantitatively the corresponding oxide.



R_1	R_2	R_3	Sulfoxides Yield (%)	Sulfones Yield (%)
Et	Ph	H	87	96
Et	3,4-Cl_2-C_6H_3	H	95	83
Et	$(CH_2)_2$Ph	H	>98	90
Et	cyclohexyl	H	87	97
Et	H	cyclohexyl	87	95
Et	H	Ph	87	
Et	H	3,4-Cl_2-C_6H_3	95	
Hexyl	$(CH_2)_2$Ph	H	82	
Et	CH_2 cyclohexyl	H		87
Et	COOEt	H		94
Et	(*E*)-CH=CHPh	H		90

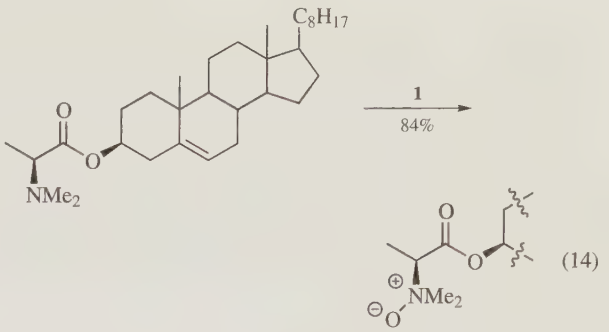


(13)

X = S, Se

R_1	R_2	R_3	Yield (%)
Et	Et	Et	93
i-Bu	*i*-Bu	*i*-Bu	95
Ph	Ph	Ph	95
4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	97
EtO	EtO	Me	93
EtO	EtO	CF_2Br	94
MeO	MeO	4-NO_2-C_6H_4O	94
EtO	EtO	4-NO_2-C_6H_4O	90
MeO	MeO	3-Ch_3-4-NO_2-C_6H_3O	91
MeO	MeO	2,5-Cl_2-4-Br-C_6H_2O	90
MeO	MeO	EtS(O)CH_2CH_2O	97
EtO	EtO	EtS(O)CH_2CH_2O	90
Et_2N	4-NO_2-C_6H_4O	4-NO_2-C_6H_4O	88
Ph	Ph	Ph	97

Oxidation of Tertiary Amines. Tertiary amines are converted into corresponding *N*-oxides in high yields, under very mild conditions.[10] When performed on complex and polyfunctional compounds, the reaction occurs with noteworthy chemo- and diastereoselectivity. For instance, when the L-*N*,*N*-dimethylalaninyl ester of cholesterol reacts with oxaziridine **1** under standard conditions the corresponding *N*-oxide is obtained in nearly pure form after the work-up of the reaction mixture (eq 14). By comparison, when the same compound is treated with *m*-chloroperbenzoic acid, the attack occurs at both nitrogen and olefinic sites and when reacted with hydrogen peroxide the *N*-oxide could never be detected, as the acrylic ester of the cholesterol is the main product. Clearly, the *N*-oxide is formed but undergoes in situ Cope elimination.



(14)

The oxidation is totally chemoselective. For example, olefinic double bonds, those of cholesteryl esters included, are oxidized by perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**),[5a] but this functionality remains unchanged under the reaction conditions employed for tertiary amine oxidation. Also the presence of other functional groups (*e.g.*, tertiary amide, urea, carbamate moiety or an ether of secondary alcohol)[7] does not interfere with the *N*-oxide formation. Other reactive sites (olefinic double bonds, electron rich aromatic rings) remain unattacked and decomposition processes of the formed *N*-oxides (Cope reaction) are avoided. Yields given by the oxaziridine **1** are higher than those of other standard oxidizing reagents, such as *m*-chloroperbenzoic acid and hydrogen peroxide.

As to the diastereoselectivity, it is worth noting that a single *N*-oxide is often obtained starting from complex tertiary amines such as dextromethorphan, brucine, haloperidol, pimozide and fenspiride. This selectivity can be rationalized as a result of the conformational preferences of the amines.

Reaction with Heteroaromatic Nitrogen Compounds. When perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**1**) reacts with pyridines bearing a substituent at the 2-position, the corresponding *N*-oxides are formed under particularly mild conditions.[9] Starting from pyridines substituted at the 3- and 4-positions, *N*-perfluoroacylpyridiniumaminides are also produced and isolated as solid, stable compounds (eq 15).[9b] Formation of *N*-oxides and *N*-aminides is the result of the nucleophilic attack of pyridines at the oxygen or nitrogen of the oxaziridine ring, respectively. The regioselectivity of the reaction is controlled by the steric hindrance of the substituent in the pyridine ring and it is not sensitive to electronic factors. Since steric hindrance at reaction center makes the attack at nitrogen more difficult, it is reasonable that *ortho*-substitution in pyridines favors the formation of *N*-oxides.

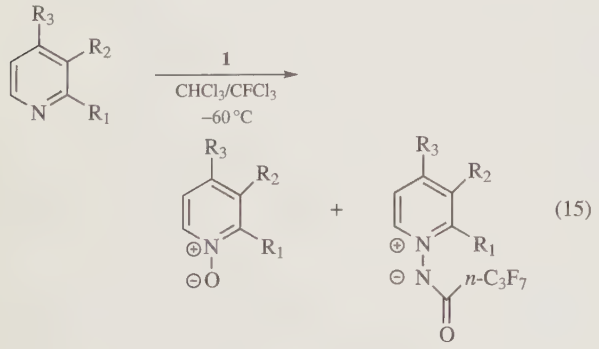
Polycyclic nitrogen heteroaromatics, such as quinoline, isoquinoline, and acridine, afford the corresponding *N*-oxides in medium to high yields under particularly mild conditions.[9a]

When di-*O*-acetylpyridoxine is treated with oxaziridine **1** the corresponding *N*-oxide is isolated in good yield (eq 16) and a selective formation of *N*-oxide is obtained also starting from papaverine.

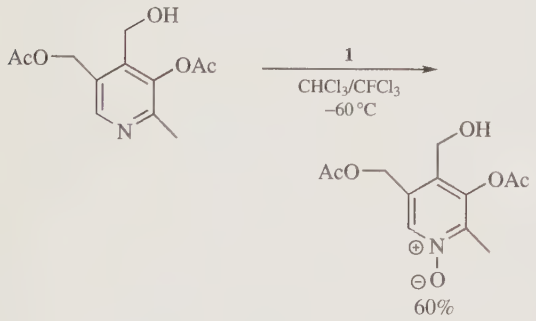
Alcohol[6] and ether[7] moieties are oxidized by oxaziridine **1**, but these groups remain unaffected in the reaction of di-*O*-acetylpyridoxine, probably due to the very mild reaction conditions. Also the presence of other functional groups such as alkenyl and oxycarbonyl groups does not interfere with the *N*-oxide formation.

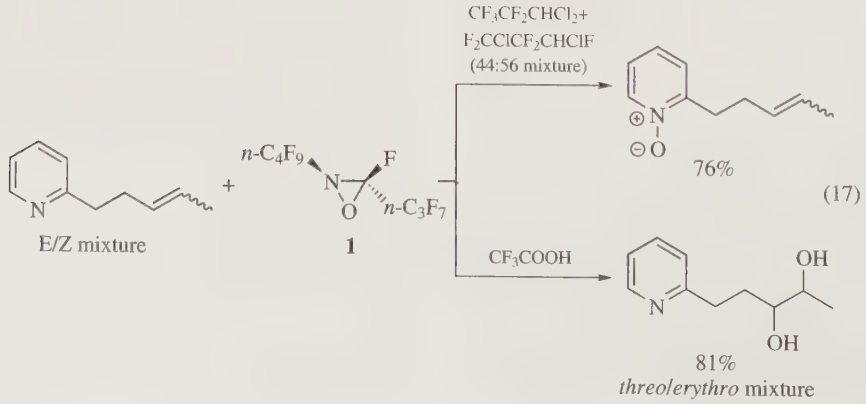
The chemoselectivity of the oxidation of alkenyl-pyridines can be controlled by simply choosing the reaction solvent (eq 17).[10]

Specifically, when pyridines are treated with oxaziridine **1** in halogenated solvent, the corresponding alkenyl *N*-oxides are exclusively formed. The oxidative attack can be diverted to the olefinic double bond by protonating the nitrogen with trifluoroacetic acid. In this case dihydroxyalkylpyridines are exclusively obtained due to the fact that the acidic medium leads to in situ opening of initially formed epoxides. Lower selectivity is shown by standard reagents such as hydrogen peroxide and *m*-chloroperbenzoic acid.



R_1	R_2	R_3	*N*-oxide yield (%)	*N*-aminide yield (%)
H	H	H	44	33
H	H	CH_3	35	35
H	H	$(CH_3)_2CH$	40	24
H	H	CH_2CH_2-4-pyridyl	35	40
H	H	(*E*)-CH=CH-4-pyridyl	30	25
H	H	4-pyridyl	30	25
H	H	CN	50	35
H	CH_3	H	52	20
H	(*S*)-1-metyl-2-oxopyrrolidin-3-yl	H	30	45
H	$COOC_6H_{13}$	H	25	45
CH_3	H	H	70	
$(CH_2)_2CH_3$	H	H	68	
2-pyridyl	H	H	20	
2-pyridylcarbonyl	H	H	59	





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Palladium(II) Acetate[1]

$Pd(OAc)_2$

[3375-31-3] $C_4H_6O_4Pd$ (MW 224.52)
(trimer)
[53189-26-7]

(homogenous oxidation catalyst[3] that, in the presence of suitable co-reagents, will effect the activation of alkenic and aromatic compounds towards oxidative inter- and intramolecular nucleophilic attack by carbon, heteroatom, and hydride nucleophiles[1,3,4,5])

Alternate Names: bis(acetato)palladium; diacetatopalladium(II); palladium diacetate.

Physical Data: mp 205 °C (dec).

Solubility: sol organic solvents such as chloroform, methylene chloride, acetone, acetonitrile, diethyl ether. Dissolves with decomposition in aq HCl and aq KI solutions. Insol water and aqueous solutions of NaCl, NaOAc, $NaNO_3$ as well as in alcohols and petroleum ether. Decomposes when heated with alcohols.

Form Supplied in: orange-brown crystals; generally available.

Preparative Method: preparation of palladium diacetate from palladium sponge was developed by Wilkinson et al.[2]

Purification: palladium nitrate impurities can be removed by recrystallization from glacial acetic acid in the presence of palladium sponge.

Handling, Storage, and Precautions: can be stored in air. Low toxicity.

Original Commentary

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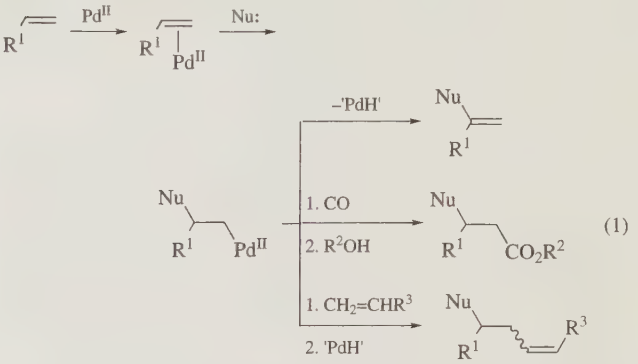
University of Uppsala, Uppsala, Sweden

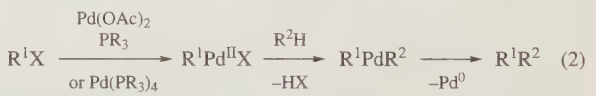
General Considerations. Salts of palladium that are soluble in organic media, for example $Pd(OAc)_2$, ***Dilithium Tetrachloropalladate(II)***, and $PdCl_2(RCN)_2$, are among the most extensively used transition metal complexes in metal-mediated organic synthesis. Palladium acetate participates in several reaction types, the most important being: (i) Pd^{II}-mediated activation of alkenes towards nucleophilic attack by (reversible) formation of Pd^{II}–alkene complexes, (ii) activation of aromatic, benzylic, and allylic C–H bonds, and (iii) as a precursor for Pd^0 in Pd^0-mediated activation of aryl, vinyl, or allyl halides or acetates by oxidative addition to form palladium(II)–aryl, –vinyl and –(π)-allyl species, respectively.[1b] All reactions proceed via organopalladium(II) species which can undergo a number of synthetically useful transformations.

Alkenes complexed to Pd^{II} are readily attacked by nucleophiles such as water, alcohols, carboxylates, amines, and stabilized carbon nucleophiles (eq 1). Attack occurs predominantly from the face opposite to that of the metal (*trans* attack), thus forming a new carbon–nucleophile bond and a carbon–metal σ-bond.



(1)

The σ-complex obtained is usually quite reactive and unstable, and can undergo a number of synthetically useful transformations such as β-hydrogen elimination (eq 1) to give a vinyl substituted alkene and insertion of CO (eq 1) or alkenes (eq 1) into the carbon–palladium bond, which permit further functionalization of the original alkene. The same general chemistry is observed for complexes generated from Pd^0 (eq 2). Heck vinyl couplings and carbonylations together with allylic nucleophilic substitution reactions are among the synthetically most interesting reactions employing palladium acetate.[5]

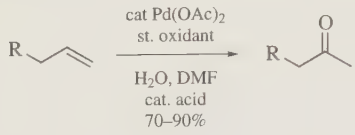


(2)

The transformations in eqs 1 and 2 ultimately produce palladium(0), while palladium(II) is required to activate alkenes (eq 1). Thus, if such a process is to be run using catalytic amounts of the noble metal, a way to rapidly regenerate palladium(II) in the presence of both substrate and product is required. Often this reoxidation step is problematic in palladium(II)-catalyzed nucleophilic addition processes, and reaction conditions have to be tailored to fit a particular type of transformation. A number of very useful catalytic processes, supplementing the processes that employ stoichiometric amounts of the metal, have been developed.[1,3–5]

Oxidative Functionalization of Alkenes with Heteroatom Nucleophiles.

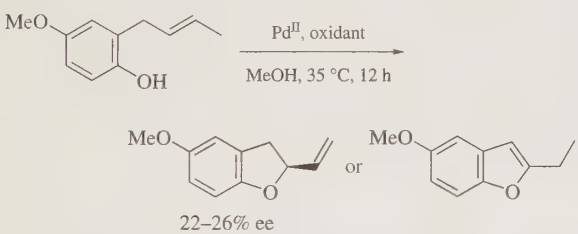
Oxidation of Terminal Alkenes to Methyl Ketones. The oxidation of ethylene to acetaldehyde with water acting as the nucleophile using a $Pd^{II}Cl_2$–$Cu^{II}Cl_2$ catalyst (see ***Palladium(II) Chloride*** and ***Palladium(II) Chloride–Copper(II) Chloride***) under an oxygen atmosphere is known as the Wacker process. On a laboratory scale the reaction conveniently allows the transformation of a wide variety of terminal alkenes to methyl ketones.[6] Some synthetic procedures that employ $Pd(OAc)_2$ in chloride-free media have been developed (eq 3).



(3)

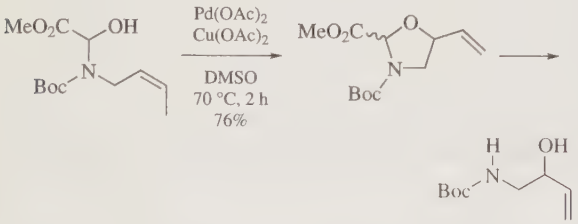
By this, both the use of the highly corrosive reagent combination $PdCl_2$–$CuCl_2$ and the occurrence of chlorinated byproducts are avoided. The stoichiometric oxidant used in these reactions can be a peroxide,[7] ***1,4-Benzoquinone***,[8] or molecular ***Oxygen***.[8a,9] An electrode-mediated process has also been described.[10]

Other Heteroatom Nucleophiles. Alcohols and carboxylic acids also add to metal-activated alkenes,[1a] and processes for the industrial conversion of ethylene to vinyl acetate and acetals are well established.[1c] However, these processes have not been extensively used with more complex alkenes. In contrast, a number of intramolecular versions of the processes have been developed, a few examples of which are given here. Allylphenols cyclize readily in the presence of palladium(II) to form benzofurans (eq 4). Catalytic amounts of palladium acetate can be used if the reaction is carried out under 1 atm of molecular oxygen with copper diacetate as cooxidant, or in the presence of ***t-Butyl Hydroperoxide***. If instead of palladium acetate a chiral π-allylpalladium acetate complex is used, the cyclization proceeds to yield 2-vinyl-2,3-dihydrobenzofuran with up to 26% ee.[11]



(4)

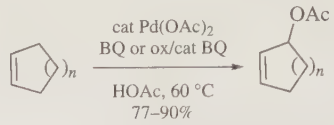
Methyl glyoxylate adducts of *N*-Boc-protected allylic amines cyclize in the presence of a catalytic amount of palladium acetate and excess ***Copper(II) Acetate*** to 5-(1-alkenyl)-2-(methoxycarbonyl)oxazolidines (eq 5).[12] These heterocycles are easily converted to unsaturated *N*-Boc protected β-amino alcohols through anodic oxidation and mild hydrolysis.



(5)

Nitrogen nucleophiles such as amines, and in intramolecular reactions amides and tosylamides, readily add to alkenes complexed to Pd^{II} derived from $PdCl_2(RCN)_2$ (see ***Palladium(II) Chloride***) with reactivity and regiochemical features paralleling those observed for oxygen nucleophiles.[3,4] Intramolecular nucleophilic attack by heteroatom nucleophiles also occurs in conjunction with other palladium-catalyzed processes presented in the following sections.

Allylic C–H Bond Activation. Internal alkenes, in particular cyclic ones, can be transformed into allylic acetates in a palladium-catalyzed oxidation (eq 6).[13] With benzoquinone as stoichiometric oxidant or electron transfer mediator,[9a] the allylic acetoxylation proceeds with high selectivity for the allylic product and usually in excellent yield.

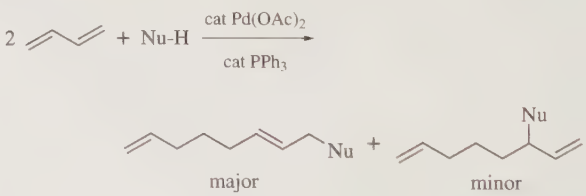


(6)

This one-step transformation of an alkene to an allylic acetate compares well with other methods of preparation such as hydride reduction of α,β-unsaturated carbonyl compounds followed by esterification. The scope and limitations of the reaction have been investigated.[14] The allylic acetoxylation proceeds via a π-allylpalladium intermediate,[15] and as a result, substituted and linear alkenes generally give several isomeric allylic acetates. With oxygen nucleophiles the reaction is quite general, and reactants and products are stable towards the reaction conditions. This is normally not yet the case with nitrogen nucleophiles, although one intramolecular palladium-catalyzed allylic amination mechanistically related to allylic acetoxylation has been reported.[16]

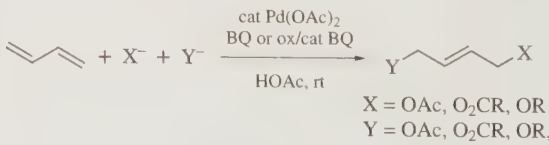
Functionalization of Conjugated Dienes. Electrophilic transition metals, particularly palladium(II) salts which do not form stable complexes with 1,3-dienes, do activate these substrates to undergo a variety of synthetically useful reactions with heteroatom nucleophiles.[17] Some examples are presented below.

Telomerization. Conjugated dienes combine with nucleophiles such as water, amines, alcohols, enamines and stabilized carbanions in the presence of palladium acetate and ***Triphenylphosphine*** to produce dimers with incorporation of one equivalent of the nucleophile.[1,18] Telomerization of butadiene (eq 7) yields linear 1,6- and 1,7-dienes and has been used for the synthesis of a variety of naturally occurring materials.[19]



(7)

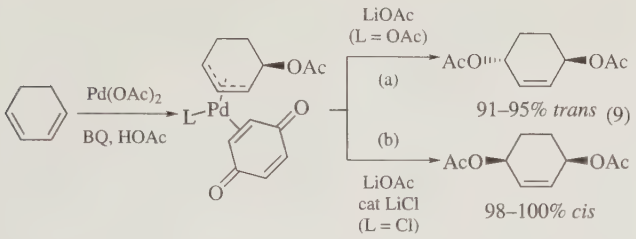
Oxidative 1,4-Functionalization. The regio- and stereoselective palladium-catalyzed oxidative 1,4-functionalization of 1,3-dienes (eq 8) constitutes a synthetically useful process.[20–23]



(8)

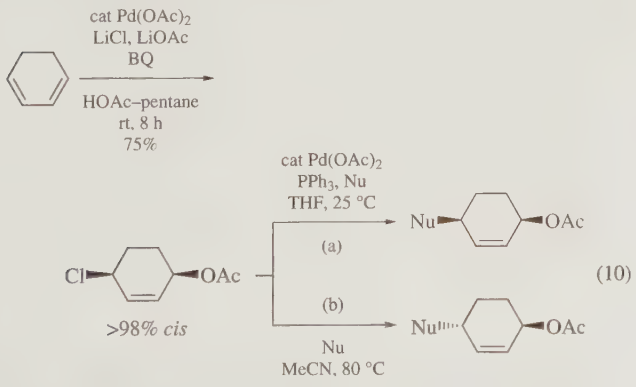
A selective catalytic reaction that gives high yields of 1,4-diacetoxy-2-alkenes occurs in acetic acid in the presence of a lithium carboxylate and benzoquinone. The latter reagents act as the activating ligand and reoxidant for palladium(0).[24] The reaction can be made catalytic also in benzoquinone by the use of ***Manganese Dioxide***,[20] electrochemistry,[25] or metal-activated molecular oxygen[9a] as stoichiometric oxidant. If the reaction is carried

out in alcoholic solvent in the presence of a catalytic amount of a nonnucleophilic acid, *cis*-1,4-dialkoxides can be obtained.[23] An important feature of the 1,4-diacetoxylation reaction is the ease by which the relative sterochemistry of the two acetoxy substituents can be controlled (eq 9).



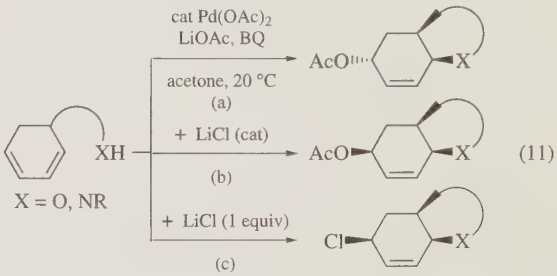
The first step in the reaction sequence is a regioselective and stereoselective *trans*-acetoxypalladation of one of the double bonds, thus forming a π-allylpalladium(II) intermediate, which is then attacked by a second nucleophile. By variation of the concentration of chloride ions, reactions selective for either the *trans*-diacetate or the *cis*-diacetate (eq 9) can be accomplished. The use of other chloride salts resulted in poor selectivity. The selectivity for the *trans* product at chloride-free conditions is further enhanced if the reaction is carried out in the presence of a sulfoxide co-catalyst.[26] Enzymatic hydrolysis of the *cis-meso*-diacetate yields *cis*-1-acetoxy-4-hydroxy-2-cyclohexene in more than 98% ee,[27] thus giving access to a useful starting material for enantioselective synthesis.[28]

In a related catalytic procedure, run in the presence of a stoichiometric amount of ***Lithium Chloride*** (eq 10), it is possible to obtain *cis*-1-acetoxy-4-chloro-2-alkenes with high 1,4-selectivity and in high chemical yield.[21] A selective nucleophilic substitution of the chloro group in the chloroacetate, either by palladium catalysis or by classical methods (eq 10), and subsequent elaboration of the acetoxy group, offer a number of useful transformations.[22] The methodology has been applied to, for example, a synthesis of a naturally occurring 2,5-disubstituted pyrrolidine, some tropane alkaloids, and perhydrohistrionicotoxin.[29]

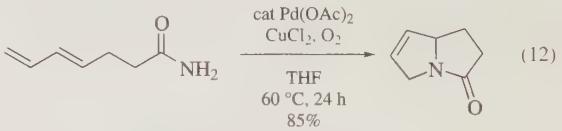


The use of two different nucleophiles can lead to unsymmetrical dicarboxylates.[30] Palladium-catalyzed oxidation of 1,3-cyclohexadiene in acetic acid in the presence of CF_3CO_2H/LiO_2CCF_3, with MnO_2 and catalytic benzoquinone, yielded 70% of *trans*-1-acetoxy-4-trifluoroacetoxy-2-cyclohexene (more than 92% *trans*), with a selectivity for the unsymmetrical product of more than 92%. 1,3-Cycloheptadiene afforded the *cis* addition product in 58% yield with a selectivity for the unsymmetrical product of more than 95%. Since the two carboxylato groups have different reactivity, for example toward hydrolysis, further transformations can be carried out at one allylic position without affecting the other.

Intramolecular versions of the 1,4-oxidations have been developed.[31] In these reactions the internal nucleophile can be a carboxylate, an alkoxide, or nitrogen functionality, and the result of the first nucleophilic attack is the regioselective and stereoselective formation of a *cis*-fused heterocycle (eq 11).



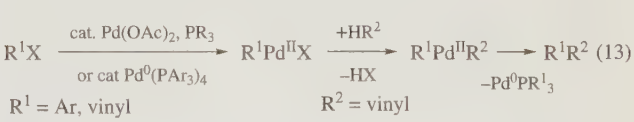
The second attack can be directed as described above to yield either an overall *trans* or *cis* product in >70% yield. With internal nucleophiles linked to the 1-position of the 1,3-diene, spirocyclization occurs. The synthetic power of the method has been demonstrated in the total syntheses of heterocyclic natural products,[32] and further developed into a tandem cyclization of linear diene amides (eq 12) to yield bicyclic compounds with trisubstituted nitrogen centers.[33]



Functionalization of Alkenes with Palladium-Activated Carbon Nucleophiles.

Heck Coupling.[5] The 'Heck reaction' is the common name for the coupling of an organopalladium species with an alkene and includes both inter- and intramolecular reaction types. However, no general reaction conditions exist and the multitude of variations can sometimes seem confusing.

The original version of the Heck reaction involved the coupling of an alkene with an organomercury(II) salt in the presence of stoichiometric amounts of palladium(II),[34] a method still used in nucleoside chemistry.[35] The finding that the organomercury reagent can be replaced by an organic halide, however, greatly increased the versatility of the process.[36] The modified process is catalyzed by zerovalent palladium, either in the form of preformed tertiary phosphine complexes or, preferentially, formed in situ from palladium acetate (eq 13).



To keep the active catalyst in solution, reactions are often carried out in the presence of tertiary phosphines such as ***Triphenylphosphine***,[37] or rather tri(*o*-tolyl)phosphine,[38] which is now the phosphine most widely employed in Heck coupling

reactions.[5] Other ligands successfully employed include tris(2,6-dimethoxyphenyl)phosphine and the bidentate ligands ***1,2-Bis(diphenylphosphino)ethane*** (dppe), ***1,3-Bis(diphenylphosphino)propane*** (dppp), ***1,4-Bis(diphenylphosphino)butane*** (dppb), and ***1,1′-Bis(diphenylphosphino)ferrocene 1*** (dppf). Coupling reactions can occur in homogenous aqueous media if a water-soluble palladium ligand, trisodium 3,3′,3′-(phosphinetriyl)tribenzenesulfonate, is employed. This greatly facilitates workup procedures, and good yields of coupled products were obtained from reacting aryl and alkyl iodides with alkenes, alkynes, and allylic acetates.[39] In all cases, an inert atmosphere and the presence of a base, normally ***Triethylamine***, is required.

Phase-Transfer Conditions. The Heck conditions described above are not useful, however, for a large number of alkenic substrates.[40] A sometimes serious drawback is the high temperature (ca. 100 °C) often required. Upon addition of tetrabutylammonium chloride ('phase-transfer conditions' or 'Jeffery conditions'), aromatic halides or enol triflates react under mild conditions with vinylic substrates or allylic alcohols.[5,41] Variations of these conditions include the optional or additional presence of silver or thallium salts. The effect of using different salts, bases, catalysts, solvents, and protecting groups in the coupling of aminoacrylates with iodobenzene has been studied.[42]

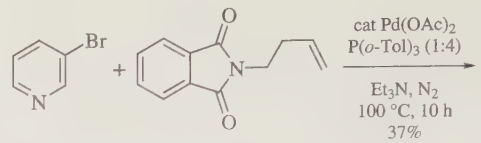
Cross Coupling. In cross-coupling reactions, an aryl, vinyl, or acyl halide or triflate undergoes a palladium-catalyzed Heck-type coupling to an aryl-, vinyl-, or alkyl-metal reagent (eq 14) to give a new carbon–carbon bond.[5]

$$R^1X \xrightarrow{+Pd^0} R^1Pd^{II}X \xrightarrow[-MX]{+R^2M} R^1PdR^2 \xrightarrow{-Pd^0} R^1R^2 \quad (14)$$

Mg, Zn, and Zr are examples of metals used in cross-coupling reactions,[43] but, in particular, organostannanes have been employed in mild and selective palladium acetate-catalyzed couplings with organic halides and triflates.[44] Aryl arenesulfonates undergo a cross-coupling reaction with various organostannanes in the presence of palladium diacetate, dppp, and LiCl in DMF.[45] An advantage of the arylsulfonates over triflates is that the former are solids whereas the latter are liquids. Also, arylboranes and boronic acids also undergo a palladium-catalyzed cross-coupling with alkyl halides, although the catalysts of choice are ***Tetrakis(triphenylphosphine)palladium(0) 1***, ***Dichloro[1,4-bis(diphenylphosphino) butane]palladium(II)***, or ***Dichloro[1,1′-bis(diphenylphosphino) ferrocene]palladium(II)***[46]

Arylation of Alkenes by Coupling and Cross Coupling. Alkenes can be functionalized with palladium-activated arenes, yielding styrene derivatives in a process applicable to a wide range of substrate combinations. An early demonstration of the possibilities of the Heck arylation was the coupling of 3-bromopyridine with *N*-3-butenylphthalimide (eq 15), the first step of four in a total synthesis of nornicotine.[47]

N-Vinylimides readily undergo palladium-catalyzed vinylic substitution with aryl bromides to yield 2-styryl- and 2-phenylethylimines. With aryl iodides (eq 16), the reaction proceeds even in the absence of added phosphine,[48] which opens the possibility of a sequential disubstitution of bromoiodoarenes.



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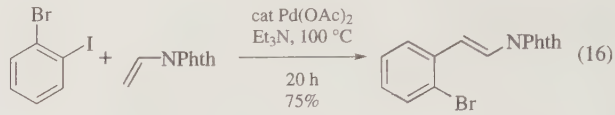
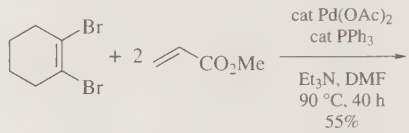
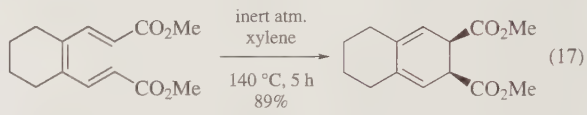


(16)

Vicinal dibromides undergo a twofold coupling reaction with monosubstituted alkenes to yield 1,3,5-trienes (eq 17). The reaction, catalyzed by palladium acetate in the presence of triphenylphosphine and triethylamine, can also be applied to aromatic tri-and tetrabromides.[49]

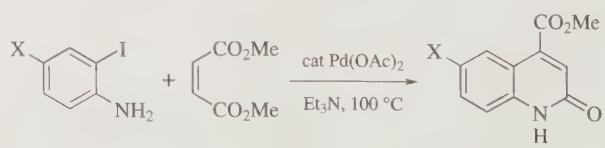




(17)

A double coupling of 2-amidoacrylates with 3,3′-diiodobiphenyl constitutes a key step in a short preparation of a biphenomycin B analog.[50] Palladium acetate-catalyzed double coupling reactions of 1,8-diiodonaphthalene with substituted alkenes and alkynes under phase-transfer conditions are useful also for the synthesis of various acenaphthene and acenaphthylene derivatives.[51]

1,2-Disubstituted alkenes are generally less reactive towards coupling than are monosubstituted alkenes. However, the use of the more reactive aryl iodides can result in reasonable yields of the coupled product, usually as a mixture of (*E*) and (*Z*) isomers.[52] The reaction has been applied to a coupling of 2-iodoaniline derivatives with ***Dimethyl Maleate*** (eq 18), the product of which spontaneously cyclizes to form quinolone derivatives in 30–70% yield. If, instead, the 2-iodoaniline is coupled with ***Isoprene*** or cyclohexadiene in the presence of palladium acetate, triphenylphosphine, and triethylamine, indole and carbazole derivatives are obtained by a coupling followed by intramolecular nucleophilic attack by the heteroatom.[53]

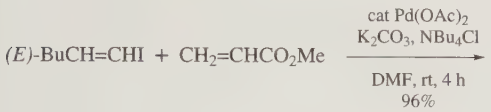


(18)

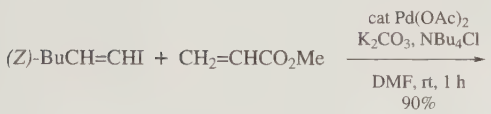
X = H (71%), OH (55%), Br (30%)

2-Alkylidenetetrahydrofurans can be prepared via intramolecular oxypalladation and subsequent coupling by treatment of aryl or alkyl alkynic alcohols with ***n-Butyllithium*** followed by palladium acetate and triphenylphosphine. The reaction proceeds to yield furans in moderate yields.[54]

Formation of Dienes and Enynes by Coupling and Cross Coupling. The vinylation of methyl acrylate, methyl vinyl ketone, or acrolein with (*E*) or (*Z*) vinylic halides under phase-transfer conditions gives high yields of (*E,E*) (eq 19) or (*E,Z*) (eq 20) conjugated dienoates, dienones, and dienals, respectively.[55] Coupling of vinyl halides or triflates with α,β- or β,γ-unsaturated acids under phase-transfer conditions yields vinyl lactones.[56]



(*E,E*)-BuCH=CHCH=CHCO$_2$Me (19)
99% (*E,E*)

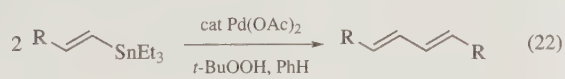


(*E,Z*)-BuCH=CHCH=CHCO$_2$Me (20)
95% (*E,Z*)

Commercially available trimethylvinylsilanes can be vinylated using either vinyl triflates or vinyl iodides in the presence of silver salts, in a reaction catalyzed by palladium acetate in the presence of triethylamine. The resulting 3-substituted 1-trimethylsilyl-1,3-dienes are obtained in reasonable to good yields.[57]

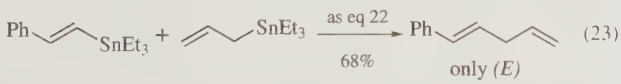
Alkenylpentafluorosilicates derived from terminal alkynes react readily with allylic substrates in a palladium-catalyzed cross-coupling reaction to yield (*E*)-1,4-dienes (eq 21).[58] Treatment of 1-alkenylstannanes with t-BuOOH in the presence of 10% of palladium acetate gives 1,3-dienes (eq 22), whereas coupling between 1- and 2-alkenylstannanes provides 1,4-dienes in good yields (eq 23).[59]

(21)



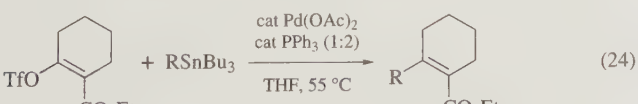
(22)

R = Ph, 80%, (*E*):(*Z*) = 4:1
R = C_6H_{13}, 76%, only (*E*)



(23)

Cross coupling of enol triflates under neutral conditions with allyl-, vinyl-, or alkynylstannanes in the presence of palladium diacetate and triphenylphosphine proceeds to give high yields of 1,4- and 1,3-dienes and 1,3-enynes, respectively (eq 24).[60]



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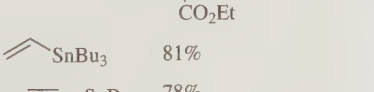
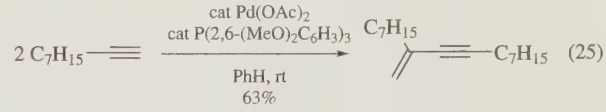
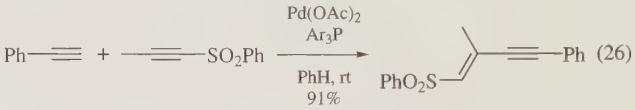


Terminal alkynes react to form 1-en-3-ynes in a process catalyzed by palladium acetate and tris(2,6-dimethoxyphenyl)phosphine. A number of functional groups such as internal alkenes, esters, and alcohols are tolerated, and good yields of homo- (eq 25) as well as hetero-coupled enynes (eq 26) are obtained.[61]

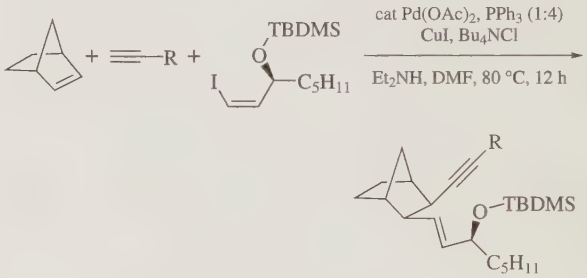


(25)



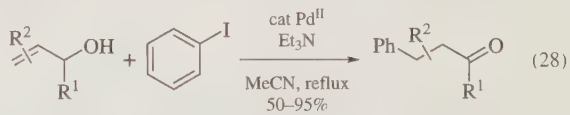
(26)

An interesting approach to 1-en-5-ynes is the palladium-catalyzed tandem coupling of a *cis*-alkenyl iodide, a cyclic alkene, and a terminal alkyne (eq 27). With norbornene as the alkene, the coupling occurs in a stereodefined manner, and the enyne products are obtained in good yields.[62] ***Potassium Cyanide*** can be used instead of an alkyne to yield the corresponding cyanoalkene.[63]



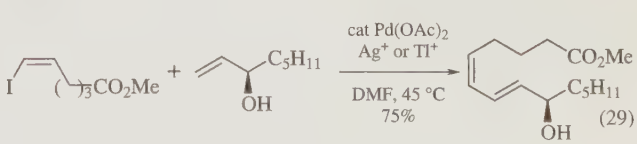
(27)

Formation of Aldehydes, Ketones, and Allylic Dienols by Coupling to Allylic Alcohols. Allylic alcohols can be coupled with aryl or vinyl halides or triflates. The outcome of the reaction depends on the coupling agent and the reaction conditions. Thus arylation of allylic alcohols under Heck conditions constitutes a convenient route to 3-aryl aldehydes and 3-aryl ketones (eq 28).[64]



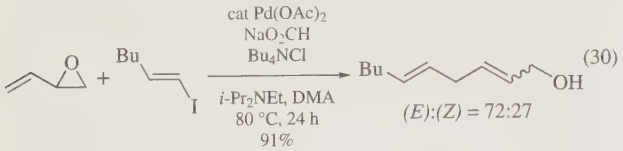
(28)

Coupling of primary allylic alcohols with vinyl halides carried out under phase-transfer conditions (cat $Pd(OAc)_2$ in the presence of Ag_2CO_3 and *n*-Bu_4NHSO_4 in acetonitrile) gave 4-enals,[65] whereas secondary allylic alcohols, when treated with a vinyl halide or enol triflate, afforded conjugated dienols with good chemoselectivity, regiochemistry, and stereoselectivity.[66] Since the coupling reaction under these conditions proceeds without touching the carbon bearing the alcohol functional group, it was possible to prepare optically active dienols from vinyl iodides and optically active allylic alcohols (eq 29).[67]

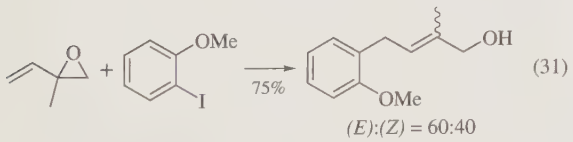


(29)

Formation of Allyl and Aryl Primary Allylic and Homoallylic Alcohols from Vinyl Epoxides and Oxetanes. Vinylic epoxides can be coupled with aryl (eq 30) or vinyl (eq 31) iodides or triflates to form allylic alcohols in 40–90% yield.[68] When employing palladium acetate as the catalyst, a reducing agent such as sodium formate is required in addition to the salts normally present under phase transfer conditions.

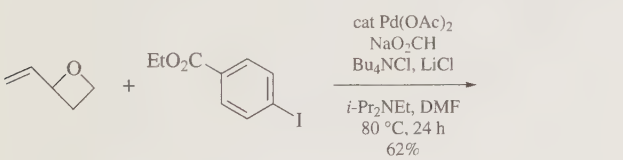


(30)



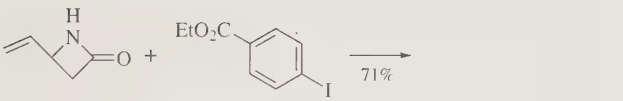
(31)

Vinyloxetane couples with aryl or vinyl iodides or triflates to form homoallylic alcohols under essentially the same reaction conditions (eq 32).[69] The process has also been applied to the preparation of aryl-substituted 3-alkenamides from 4-alkenyl-2-azetidinones (eq 33).[70]



(32)

(E):(Z) = 88:12

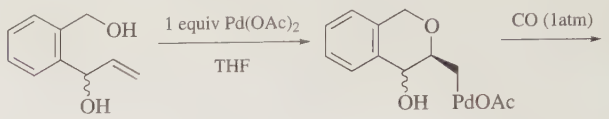


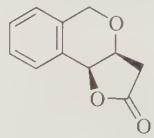
(33)

(E):(Z) = 85:15

Homoallylic alcohols can also be prepared using a one-pot transformation of homopropargyl alcohols. Intramolecular hydrosilylation followed by a palladium-catalyzed coupling of the in situ generated alkenoxysilane with an aryl or alkenyl halide, in the presence of fluoride ions, affords the alcohol product.[71] This process has also been applied to the preparation of 1,3-dienes.

Carbonylation. Carbon monoxide readily inserts into Pd–C σ-bonds. The resulting acylpalladium intermediate can react intermolecularly or intramolecularly with amines or alcohols to form ketones, amides, or esters, respectively, or with alkenes to yield unsaturated ketones.[1a,5] Thus treatment of vinyl triflates with $Pd(OAc)_2$, PPh_3, and MeOH in DMF results in one-carbon homologation of the original ketone to α,β-unsaturated esters.[72] Benzopyrans with a *cis*-fused γ-lactone can be prepared in high yield from *o*-disubstituted arenes by carbonylation of the intermediate formed upon intramolecular attack of the phenol on the terminal alkene (eq 34). The sequence affords the *cis*-fused lactone, regardless of the relative stereochemistry of the hydroxide and the methylenepalladium in the intermediate.[73]

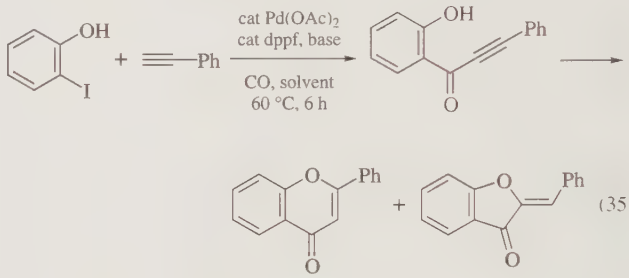




(34)

68%; one isomer

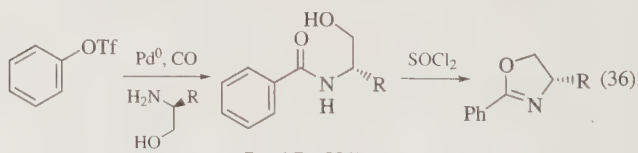
Vinyl triflates undergo carbonylative coupling with terminal alkynes to yield alkenyl alkynyl ketones in a reaction catalyzed by palladium acetate and dppp in the presence of triethylamine.[74] When applied to 2-hydroxyaryl iodides (eq 35), subsequent attack by the hydroxyl group on the alkyne yielded flavones and aurones. The cyclization result depends on the reaction conditions. ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** as base in DMF yields mainly the six-membered ring flavone, whereas the only product observed when employing potassium acetate in anisole was the five-membered ring aurone.[75]



(35)

base	sol	
AcOK	anisole	0:100
DBU	DMF	92:8

Chiral α,β-unsaturated oxazolines can be obtained by a carbonylation–amidation of enol triflates or aryl halides with chiral amino alcohols (eq 36).[76] The palladium catalyst can be either $Pd(PPh_3)_4$, ***Bis(dibenzylideneacetone)palladium(0)*** and PPh_3, or $Pd(OAc)_2$ and dppp in the presence of triethylamine.

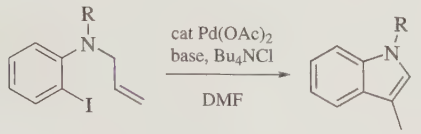


(36)

N-Substituted phthalimides are obtained from coupling *o*-dihalo aromatics with carbon monoxide and primary amines. The best catalysts for this reaction, however, were $PdCl_2L_2$ species.[77]

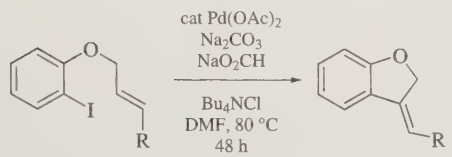
Formation of Heterocyclic Compounds. Coupling reactions of 2-halophenols or anilines with molecules containing functionalities that allow the heteroatom nucleophile to form a heterocycle either by intramolecular oxy- or amino-palladation of an alkene, or by lactone or lactam formation, has already been mentioned in the preceding sections.[78] In addition to these powerful techniques, carbon–heteroatom bonds can be constructed in

steps prior to the cyclization. For example, the enamine 3-((2-bromoaryl)amino)cyclohex-2-en-1-one undergoes a palladium-catalyzed intramolecular coupling to yield 1,2-dihydrocarbazoles in moderate yields.[79] Intramolecular coupling of 2-iodoaryl allyl amines gave high yields of indoles under phase-transfer conditions (eq 37).[80] The corresponding aryl allyl ethers require the additional presence of sodium formate in order to give benzofurans in good yields (eq 38).



(37)

R	Base	Time	Temp.	Yield
H	Na_2CO_3	24 h	25 °C	97%
Me	Et_3N	48 h	25 °C	81%
MeCO	NaOAc	24 h	80 °C	90%



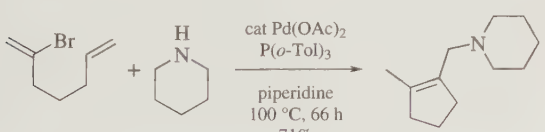
(38)

R = H (47%), Me (83%), C_5H_{11} (83%), Ph (81%)

The principle has been applied to the preparation of pharmaceutically interesting heterocyclic compounds,[81] and to the assembly of fused or bridged polycyclic systems containing quaternary centers.[82]

Formation of Carbocycles.

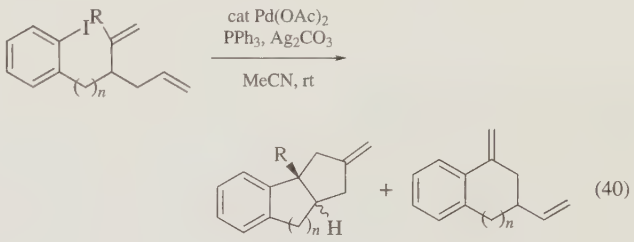
By Intramolecular Heck Coupling. 1-Bromo-1,5-dienes and 2-bromo-1,6-dienes cyclize in the presence of ***Piperidine*** and a palladium acetate–tri-*o*-tolylphosphine catalyst to produce cyclopentene derivatives (eq 39).[83] 2-Bromo-1,7-octadiene, when subjected to the same reaction conditions, cyclized to yield a mixture of six and five-membered ring products, whereas competing dimerization and polymerization was observed for the more reactive 2-bromo-1,5 dienes.



(39)

The influence of phosphine ligands, added salts, and the type of metal catalyst on the selectivity of the cyclization have been studied.[84] With K_2CO_3 as base, Wilkinson's catalyst (***Chlorotris-(triphenylphosphine) rhodium(I)***) showed higher selectivity for the formation of 1,2-dimethylenecyclopentanes over 1-methylene-2-cyclohexenes than the palladium acetate–triphenylphosphine catalyst.

The palladium-catalyzed cyclization of acyclic polyenes to form polycyclic systems (eq 40) constitutes a very powerful further development of the above method. σ-Alkylpalladium intermediates, produced in an intramolecular Heck reaction, can be efficiently trapped by neighboring alkenes to give bis-cyclization products of either spiro or fused geometry. The second cyclization also produces a σ-alkylpalladium intermediate which can also be trapped.

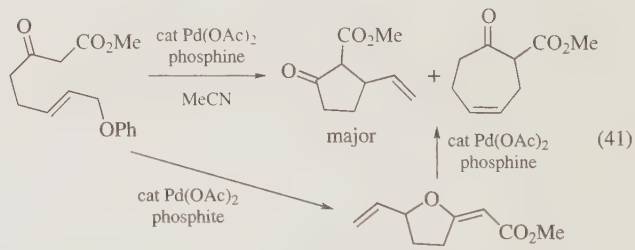


(40)

R	*n*	Ratio
Me	1	1:1.5
Me	2	100:0 (1:1 H_α:H_β)
H	1	0:100

1-Iodo-1,4- and -1,5-dienes can be transformed into α-methylenecyclopentenones and -hexenones, respectively, by palladium-catalyzed carbonylation and subsequent intramolecular coupling.[85] Better results, however, were obtained using ***Tetrakis-(triphenylphosphine) palladium(0)***.

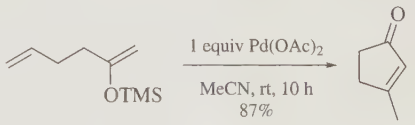
Via (π-Allyl)palladium Intermediates. Allylic substitution, by nucleophilic attack on (π-allyl)palladium complexes generated from allylic substrates, are most often catalyzed by Pd^0–phosphine complexes.[86,87] There are, however, a few examples of intramolecular reactions where the active catalyst is generated in situ from palladium acetate. For example, ethyl 3-oxo-8-phenoxy-6-octenoate reacts to yield cyclic ketones in the presence of catalytic amounts of palladium diacetate and a phosphine or phosphite ligand (eq 41).[88] The product distribution between five- or seven-membered rings depends on the ligand employed and the solvent used. With a chiral phosphine, (*E*)-methyl 3-oxo-9-methoxycarbonyloxy-7-nonenoate was cyclized to give (*R*)-3-vinylcyclohexane with 41–48% ee.[89]



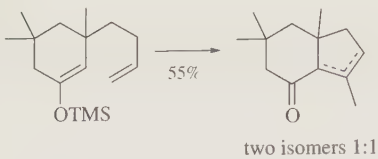
(41)

Another example is based on the palladium-catalyzed 1,4-chloroacetoxylation methodology,[21,22,29] where a common intermediate, by proper choice of reaction conditions, can be transformed into *cis*- or *trans*-annulated products.[89]

By Cyclization of Alkenyl Silyl Enol Ethers. Treatment of alkenyl silyl enol ethers with stoichiometric amounts of palladium acetate induces an intramolecular attack to form carbacycles (eqs 42 and 43). Good to high yields of α,β-unsaturated ketones were obtained.[90]



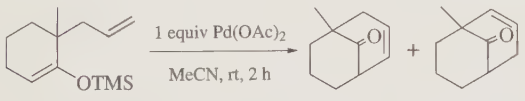
(42)



(43)

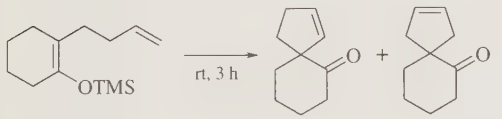
two isomers 1:1

With slightly different substrates, the observed products were not α,β-unsaturated ketones but nonconjugated bicycloalkenones.[91] The method, which affords bridged (eq 44) as well as spirocyclic (eq 45) bicycloalkenones in acceptable to good yields, has been applied to the preparation of bicyclo[3.3.1]nonadienones[92] and to a total synthesis of quadrone.[93]



(44)

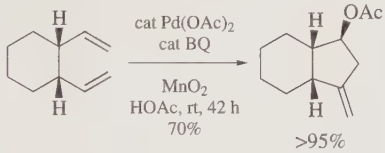
58% 14%



(45)

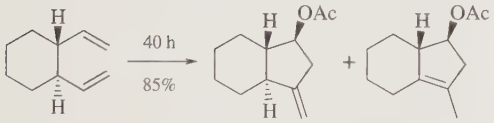
58% 36%

By Cyclization of Simple Dienes. Treatment of 1,5-dienes with catalytic amounts of $Pd(OAc)_2$ and benzoquinone with MnO_2 as stoichiometric oxidant in acetic acid leads to an oxidative cyclization reaction (eqs 46–47).[94] The reaction normally yield cyclopentanes with acetate and exomethylene groups in a 1,3-configurational relationship.[95]



(46)

>95%

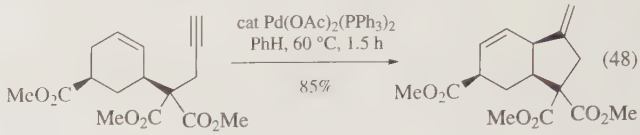


(47)

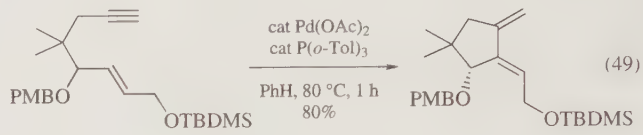
87:13

The selectivity of the reaction depends strongly upon the structure of the starting alkene. Substituents in the 1,3- and/or 4-positions of the diene are tolerated, but not in the 2- and 5-positions; thus the reaction most likely proceeds via an acetoxypalladation of the 1,2-double bond followed by insertion of the 5,6-alkene into the palladium–carbon σ-bond and subsequent reductive elimination.[96] The cyclization is compatible with the presence of several types of functional groups such as alcohols, acetate (even in the allylic position), ethers, nitriles, and carboxylic acids. An improved diastereoselectivity was observed in reactions carried out with chiral nucleophiles in the presence of water-containing molecular sieves.[97] The synthetic utility of the reaction was demonstrated by a synthesis of diquinanes.[98]

By Cycloisomerization of Enynes. When 1,6-enynes, prepared by a $Pd(PPh_3)_4$-catalyzed coupling of an allylic carboxylate with dimethyl propargylmalonate anion, is treated with a catalytic amount of a palladium(II) species, a carbocyclization leading to cyclopentanes carrying an exocyclic double bond occurs (eq 48).[99] Yields of 1,4-dienes ranging from 50% to 85% are observed. If the enyne has oxygen substituents in the allylic positions, the reaction instead yields a 1,3-diene (eq 49).[100] Cycloisomerization could also be induced for internal enynes carrying alkynic electron-withdrawing substituents.[101]

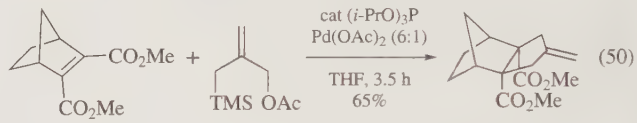


(48)

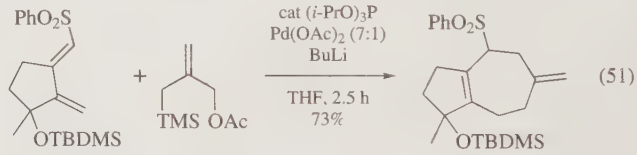


(49)

By Cycloaddition. Palladium acetate, combined with $(i\text{-PrO})_3P$, catalyzes the [2 + 3] cycloaddition of trimethylenemethane to alkenes carrying electron-withdrawing substituents (eq 50). The yields of five-membered carbocycle varied from 35–89%.[102] With 1,3-dienes, a [4 + 3] cycloaddition gave seven-membered ring products in good yield (eq 51), and in some cases excellent diastereomeric ratios were observed.[102]



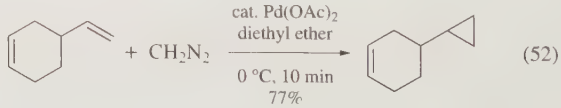
(50)



(51)

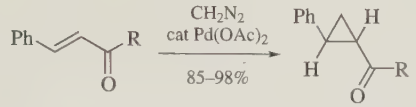
>97% selective

By Cyclopropanation. Alkenes undergo a cyclopropanation reaction with diazo compounds (caution)[103] such as ***Diazomethane*** or ***Ethyl Diazoacetate*** in the presence of a catalytic amount of palladium acetate.[104] With diazomethane, a selective cyclopropanation of terminal double bonds can be obtained (eq 52).[105]

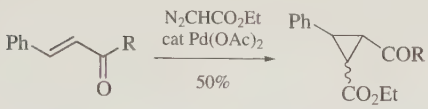


(52)

With diazo esters, the regioselectivity in transition metal-catalyzed cyclopropanation of dienes and trienes was generally not as good with palladium acetate as with a rhodium carboxylate catalyst,[106] although both palladium and rhodium carboxylates were better catalysts for the reaction than ***Copper(II) Trifluoromethanesulfonate***. α,β-Unsaturated carbonyl compounds also undergo palladium-catalyzed cyclopropanation, yielding the corresponding cyclopropyl ketones (eq 53) and esters (eq 54).[107]

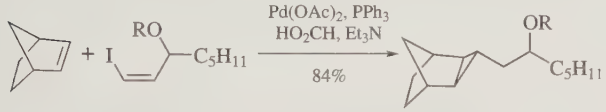


(53)



(54)

Asymmetric cyclopropanations of α,β-unsaturated carboxylic acid derivatives with CH_2N_2 proceeds in greater than 97.6% diastereomeric excess when Oppolzer's sultam is used as a chiral handle.[108] The stereoselectivity of the reaction was found to be temperature dependent, with the best results obtained at higher temperatures. A coupling of norbornene and a *cis*-alkenyl iodide in the presence of a hydride donor resulted in a cyclopropanation of the norbornene (eq 55).[65]

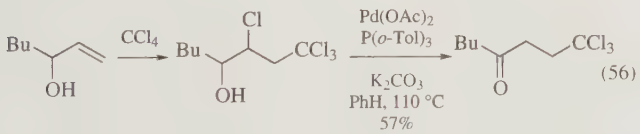


(55)

Other examples of palladium-catalyzed cyclopropanation are intramolecular processes catalyzed by, for example, ***Dichloro[1,2-bis(diphenylphosphino) ethane]palladium(II)***,[109] ***Tetrakis(triphenylphosphine) palladium(0)***,[110] or ***Bis(allyl)di-μ-chlorodipalladium***.[111]

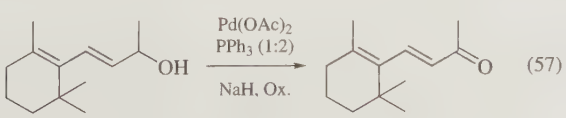
Oxidations.

Carbonyl Compounds by Oxidation of Alcohols and Aldehydes. Salts of palladium, in particular $PdCl_2$ in the presence of a base, catalyze the CCl_4 oxidation of alcohols to aldehydes and ketones. Allylic alcohols carrying a terminal double bond are transformed to 4,4,4-trichloro ketones at 110 °C, but yield halohydrins at 40 °C. These can be transformed to the corresponding trichloro ketones under catalysis of palladium acetate (eq 56).[112] The latter transformation could be useful for the formation of ketones from internal alkenes provided the halohydrin formation is regioselective.



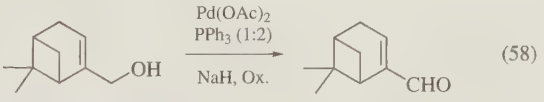
(56)

Secondary alcohols can be oxidized in high yield to the corresponding ketones by bromobenzene in a reaction catalyzed by palladium acetate in the presence of a base and a phosphine ligand. These reaction conditions, when applied to Δ^2-, Δ^3-, and Δ^4-unsaturated secondary alcohols, yielded product mixtures. When the stoichiometric oxidant was bromomesitylene and a $Pd(OAc)_2$:PPh_3 ratio of 1:2 was used, the oxidation proceeded smoothly for a wide variety of alcohols (eqs 57 and 58).[113]



(57)

Ox = PhBr, 48%, MesBr, 77%

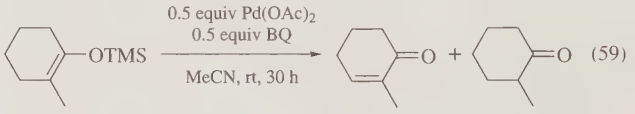


(58)

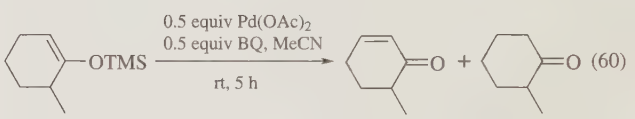
Ox = PhBr, 100%

Oxidation of aldehydes in the presence of ***Morpholine*** proceeded effectively to yield 50–100% of the corresponding morpholine amides.[114]

α,β-Unsaturated Ketones and Aldehydes by Oxidation of Enolates. Palladium diacetate-mediated dehydrosilylation of silyl enol ethers proceeds to yield unsaturated ketones in high chemical yield and with good selectivity for the formation of (*E*)-alkenes (eqs 59 and 60).[115] Although stoichiometric amounts of $Pd(OAc)_2$ are employed, this method for dehydrogenation has been employed in key steps in the total synthesis of some polycyclic natural products.[116]

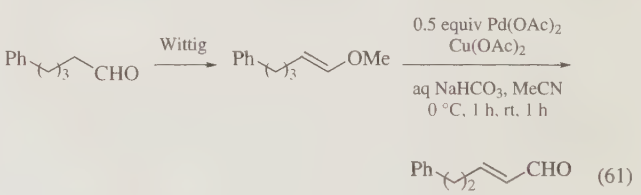


(59)



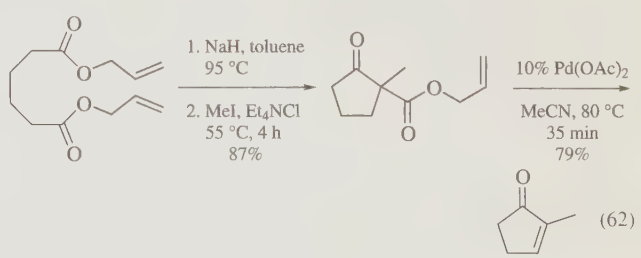
(60)

Oxidation of primary vinyl methyl ethers yields α,β-unsaturated aldehydes. The method has been applied to a transformation of saturated aldehydes to one-carbon homologated unsaturated aldehydes (eq 61) by a Wittig reaction and subsequent palladium acetate-mediated oxidation.[117] The oxidations, which were carried out in $NaHCO_3$-containing aqueous acetonitrile, yielded 50–96% of the unsaturated aldehydes.



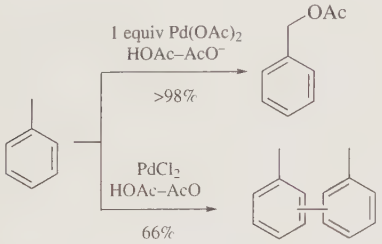
(61)

Allyl β-keto carboxylates and allyl enol carbonates undergo a palladium-catalyzed decarboxylation–dehydrogenation to yield α,β-unsaturated ketones in usually high chemical yield and with good selectivity.[118] Following this approach, it was possible to obtain 2-methyl-2-cyclopentenone in two steps from diallyl adipate in a procedure that could be convenient for large-scale preparations (eq 62).[119]



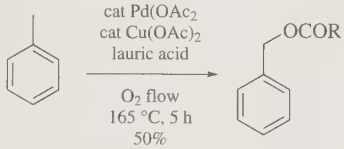
(62)

Activation of Phenyl and Benzyl C–H bonds: Oxidation of Aromatics. If palladium diacetate is heated in an aromatic solvent, oxidation of the solvent by cleavage–substitution of a C–H bond occurs, resulting in a mixture of products.[120] Depending on the reaction conditions, biaryls and phenyl or benzyl acetates are isolated. Seemingly small changes can result in large changes in product distribution (eq 63). For example, the oxidation of toluene by a palladium(II) salt yields benzyl acetate in reactions mediated by palladium acetate, whereas bitolyls are the major products in reactions carried out in the presence of chloride ions (eq 63).[121]



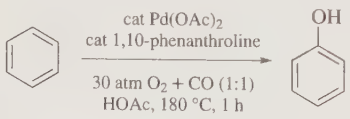
(63)

Oxygen Nucleophiles. A reagent such as permanganate oxidizes toluene to benzoic acid,[122] whereas benzylic oxidation by palladium acetate results in benzyl alcohol derivatives. The oxidation is favored by electron-releasing substituents in the phenyl ring.[123] Catalytic amounts of palladium acetate and tin diacetate, in combination with air, effects an efficient palladium-catalyzed benzylic oxidation of toluene and xylenes. For the latter substrates, the α,α′-diacetate is the main product.[124] A mixed palladium diacetate–copper diacetate catalyst has also been found to selectively catalyze the benzylic acyloxylation of toluene (eq 64).[125]



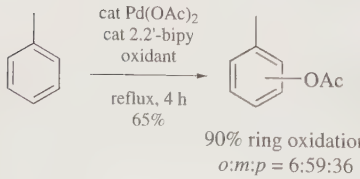
(64)

Benzene can be oxidized to phenol by molecular oxygen in the presence of catalytic amounts of palladium diacetate and 1,10-phenanthroline (eq 65).[126] If potassium peroxydisulfate is used as a stoichiometric oxidant with 2,2′-bipyridyl as a ligand, a process yielding mainly *m*-acetoxylated aromatics results (eq 66).[127]



(65)

12–13 turnovers/Pd



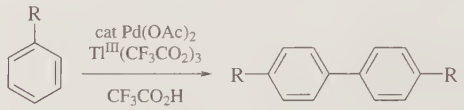
(66)

90% ring oxidation
o:*m*:*p* = 6:59:36

Palladium diacetate in ***Trifluoroacetic Acid*** ($Pd(O_2CCF_3)_2$) gives a mixture of *o*- and *p*-trifluoroacetoxylated products.[128] The reagent is also capable of oxidizing saturated hydrocarbons such as adamantane and methane. In the presence of carbon monoxide and with sodium acetate as co-catalyst, carbonylation of aromatic C–H bonds occurs, eventually yielding acid anhydrides.[129]

Naphthalenes and methylbenzenes can be oxidized to *p*-quinones by aqueous H_2O_2 in acetic acid catalyzed by a Pd^{II}–DOWEX polystyrene resin. Yields and selectivities are generally higher for the methylnaphthalenes (50–65% *p*-quinone) than for methylbenzenes (3–8%).[130]

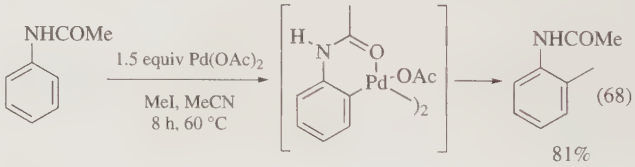
Carbon Nucleophiles. Palladium-mediated homocoupling of substituted arenes generally yields mixtures of all possible coupling products. If the reaction is carried out with a catalytic amount of palladium diacetate and with ***Thallium(III) Trifluoroacetate*** as stoichiometric oxidant (eq 67), aryls carrying substituents such as alkyl or halide afford mainly the 4,4′-biaryls in yields ranging from 60% (R = ethyl) to 98% (R = H).[131] Biaryls can also be formed without the palladium catalyst.[132]



(67)

R = Me, 40 h, 95% (74% 4,4')

Oxidative substitution of aromatics with a heteroatom substituent in a benzylic position generally yields *o*-substituted products.[1b,5] The reaction probably proceeds via a cyclopalladated phenylpalladium species (eq 68), which decomposes to form substituted products. For example, the alkylation of a number of acetanilides proceeds with high selectivity for the *o*-alkylated product.[133]

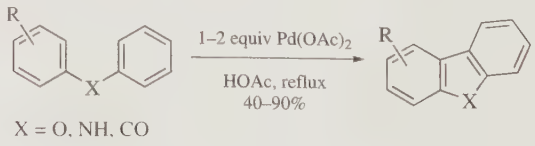


(68)

81%

With *t*-butyl perbenzoate as hydrogen acceptor, it is possible to couple benzene or furans with alkenes. In the absence of alkene, benzoxylation of the aromatic compound is observed.[134]

When heated in palladium acetate-containing acetic acid, diphenyl ether, diphenylamine, benzophenone, and benzanilide gave high yields of cyclized products (eq 69). A large number of ring substituents were tolerated in the cyclization.[135]

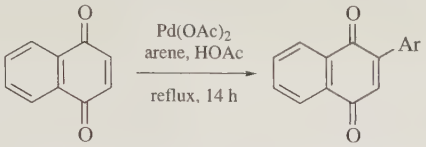


(69)

X = O, NH, CO

Oxidation of benzoquinones and naphthoquinones by palladium diacetate in arene-containing acetic acid gave the corresponding aryl-substituted quinones (eq 70).[136] Treatment of 1,4-naphthoquinone with aromatic heterocycles, for example furfural,

2-acetylfuran, 2-acetylthiophene, and 4-pyrone, yielded the corresponding 2-heteroaryl-substituted 1,4-naphthoquinones.



(70)

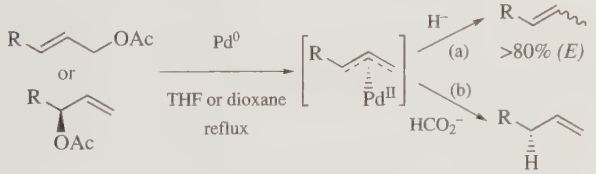
arene = C_6H_6 (85%), 2,5-$Me_2C_6H_4$ (78%), 2,5-$Cl_2C_6H_4$ (70%)

Palladium-Catalyzed Reductions.

Reduction of Alkynes. Alkynes are selectively reduced to (*Z*)-alkenes by a reduction catalyst prepared from NaH, *t*-$C_5H_{11}OH$, and $Pd(OAc)_2$ (6:2:1) in THF. The reactions, carried out in the presence of quinoline under near atmospheric pressure of H_2, are self-terminating at the semihydrogenated stage, and are more selective than the corresponding reductions catalyzed by Lindlar's catalyst. Omitting the *t*-$C_5H_{11}OH$ gave a catalyst that effected complete reduction.[137]

Alkenyldialkylboranes from internal alkynes undergo palladium acetate-catalyzed protonolysis to yield (*Z*)-alkenes under neutral conditions and (*E*)-alkenes in the presence of Et_3N.[138]

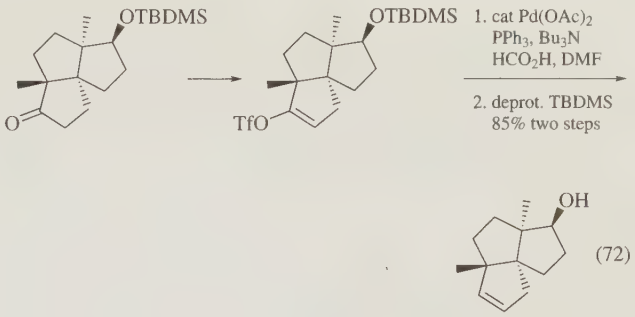
Hydrogenolysis of Allylic Heterosubstituents. Chemoselective removal of an allylic heterosubstituent in the presence of sensitive functional groups is a sometimes difficult transformation since nucleophilic displacement with hydride donors is efficient only if the heterosubstituent is a good leaving group or the hydride donor is powerful. However, removal of an allylic heterosubstituent is a reaction readily performed by Pd^0.[87] The resulting (π-allyl)palladium complexes are readily attacked by hydride nucleophiles (eq 71). Thus, mild hydride donors such as ***Sodium Borohydride*** or ***Sodium Cyanoborohydride*** can be employed.[139] Treatment of allylic oxygen, sulfur, and selenium functional groups with a combination of $Pd(PPh_3)_4$ and ***Lithium Triethylborohydride*** yielded the corresponding hydride-substituted compounds with good regio- and stereoselectivity, with the more highly substituted (*E*)-alkene as the predominant product (eq 71).[140] Similar results are observed for all hydride donor systems but one: that derived from formic acid yields predominantly or exclusively the less substituted alkene (eq 71).[142]



(71)

The regio- and stereoselective hydride attack on the more substituted terminus of (π-allyl)palladium complexes derived from allylic formates has been applied to the palladium acetate–*n*-Bu_3P-catalyzed formation of ring junctions in hydrindane, decalin, and steroid systems, and to stereospecific generation of steroidal side-chain epimers.[141]

Deoxygenation of Carbonyls. Carbonyl compounds can be deoxygenated to form alkenes in a palladium-catalyzed reduction of enol triflates (eq 72). The reaction is quite general, and has been applied to aryl as well as alkyl enol triflates.[142]



(72)

First Update

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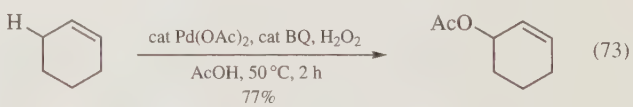
General Considerations. The format of this first update is based on that used in the original article. As such, the same or similar headings and subheadings have been employed here. Of necessity, however, additional headings have been introduced to allow for the best categorization of the many new processes that have been reported since the original publication.

Oxidative and Non-oxidative Functionalization of Alkenes and Other π-Systems with Heteroatom Nucleophiles.

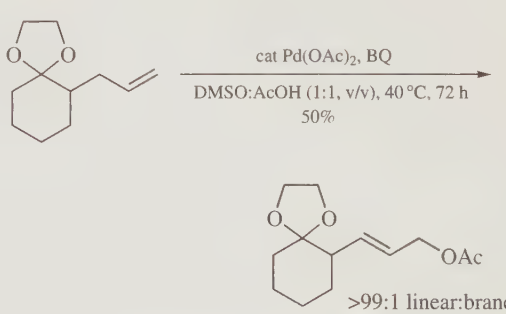
Oxidation of Terminal Alkenes to Methyl Ketones. An aerobic variant of the classic Wacker oxidation reaction has been described and is believed to involve a palladium(II) hydroperoxide as the key intermediate.[143]

Allylic C–H Bond Activation and Allylic Oxidations. A new system has been developed for the allylic acetoxylation of alkenes. This uses $Pd(OAc)_2$ as catalyst, 1,4-benzoquinone (BQ) as a co-catalyst/electron-transfer mediator, hydrogen peroxide as the stoichiometric oxidant and acetic acid as the solvent (eq 73).[144]



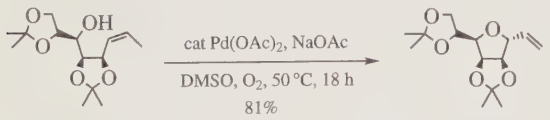
(73)

Terminal alkenes can be transformed into predominately linear and *E*-configured allylic acetates using 1,4-benzoquinone in the presence of catalytic quantities of $Pd(OAc)_2$ and a mixture of DMSO and acetic acid as solvent (eq 74). Wacker-type oxidation products are not observed, perhaps as a result of the stabilization, by DMSO, of a charged intermediate in the catalytic cycle.[145]



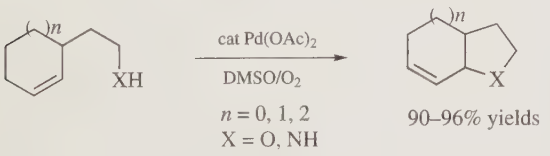
(74)

Sugar-derived γ,δ-unsaturated alcohols can be efficiently transformed into *C*-vinyl furanosides using an oxidative cyclization procedure (eq 75). Thus, treatment of a DMSO solution of the relevant substrate with catalytic quantities of $Pd(OAc)_2$, sodium acetate and oxygen provides the expected cyclization products which serve as precursors to *C*-linked amino acids and glycosides.[146]



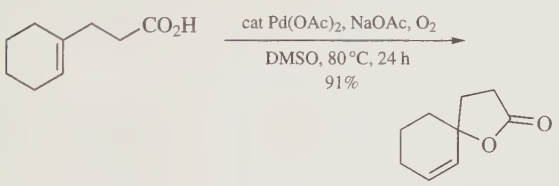
(75)

A palladium-catalyzed and intramolecular allylic oxidation reaction using tethered *O*- or *N*-nucleophiles in conjunction with molecular oxygen (as a reoxidant) has been described. This process provides a range of ring-fused heterocycles in good to excellent yield (eq 76).[147] Related intermolecular amination reactions have also been described.[148]



(76)

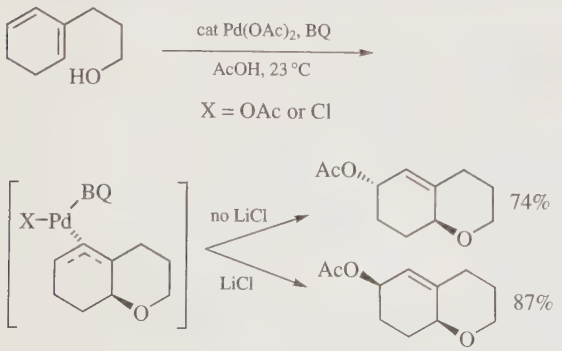
Exposure of a range of unsaturated carboxylic acids to catalytic quantities of $Pd(OAc)_2$ in the presence of oxygen leads to the efficient formation of unsaturated five- and six-membered lactones (eq 77).[149]



(77)

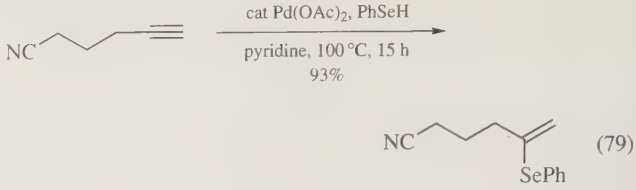
Functionalization of Conjugated Dienes.

Oxidative 1,4-Functionalization. 2-(3′-Hydroxypropyl)-substituted 1,3-cyclohexadienes have been shown to engage in stereoselective cyclization reactions to form annulated tetrahydropyrans. By appropriate adjustment of the reaction conditions, either the *cis*- or *trans*-fused products can be obtained in an essentially exclusive manner (eq 78). The reaction results in the 1,4-functionalization of the conjugated diene unit and involves a (π-allyl)palladium intermediate.[150]



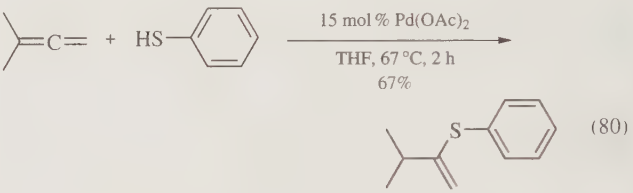
(78)

Addition Reactions. Treating terminal alkynes with benzeneselenol in the presence of $Pd(OAc)_2$ and pyridine results in highly regioselective hydroselenation of the triple bond and provides the corresponding terminal alkenes as the exclusive products of reaction (eq 79).[151]



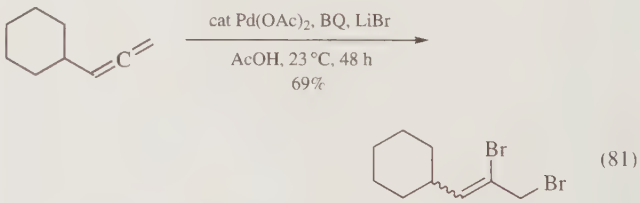
(79)

A palladium-promoted and regioselective addition of thiophenol to allenes has been developed. For example, reaction of this thiol with 1,1-dimethylallene in the presence of 15 mol % of $Pd(OAc)_2$ gave only the one adduct and thereby avoided the production of regioisomers usually associated with this transformation (eq 80). The active species is thought to be a thiol adduct of palladium, namely $[Pd(SPh)_2]_n$.[152]



(80)

2,3-Dibromoalkenes can be formed in a regioselective manner from allenes using $Pd(OAc)_2$ and 1,4-benzoquinone in the presence of lithium bromide (eq 81). The corresponding dichlorides are also available via this procedure but stoichiometric quantities of a palladium(II) species are required in this case.[153]

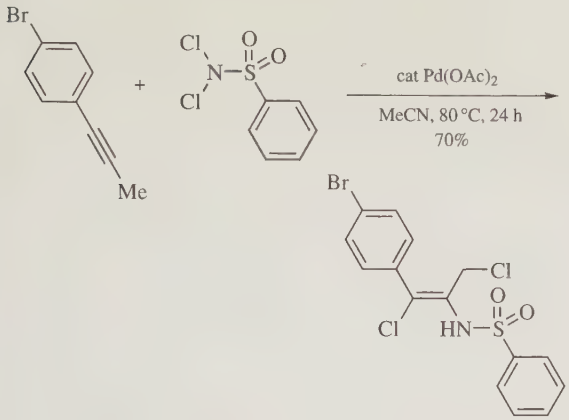


(81)

A regio- and stereo-selective reaction that is catalytic in palladium and results in the activation of multiple sites within internal alkynes has been discovered and this allows for the surprisingly efficient generation of functionalized β-haloenamines (eq 82).[154]

Exocyclic bis-silylated olefins have been constructed through the $Pd(OAc)_2$-catalyzed reaction of alkynes with a tethered disilanyl group. The reactions are carried out in the presence of *tert*-alkyl isocyanide, although the precise role of this ligand is unclear. Diimide reduction of the disilylated alkene so-formed followed by Fleming–Tamao-type oxidation of the two C–Si bonds in the saturated product then affords 1,2,4-triols in a stereoselective manner (eq 83).[155]

The palladium-catalyzed annulation of oxygenated 1,3-dienes by *ortho*-iodinated phenols or aniline derivatives proceeds under mild conditions to give 2-substituted dihydrobenzofurans or indolines, respectively (eq 84).[156] By using malonate residues in place of the heteroatom substituent on the arene it is also possible to form the corresponding indanes by this sort of process.



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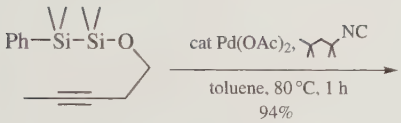

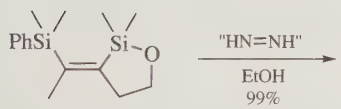

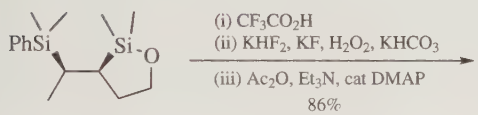

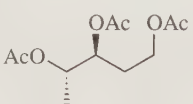

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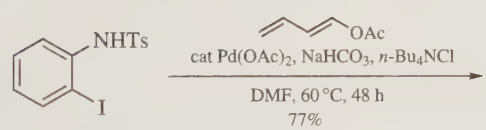
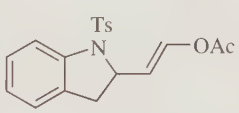
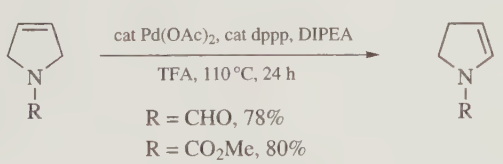




(84)

Isomerization Reactions. It has been shown that *N*-formyl- and *N*-carbomethoxy-2,5-dihydropyrroles undergo an efficient Pd-catalyzed double bond isomerization reaction to give *N*-formyl- and *N*-carbomethoxy-2,3-dihydropyrroles, respectively (eq 85).[157]

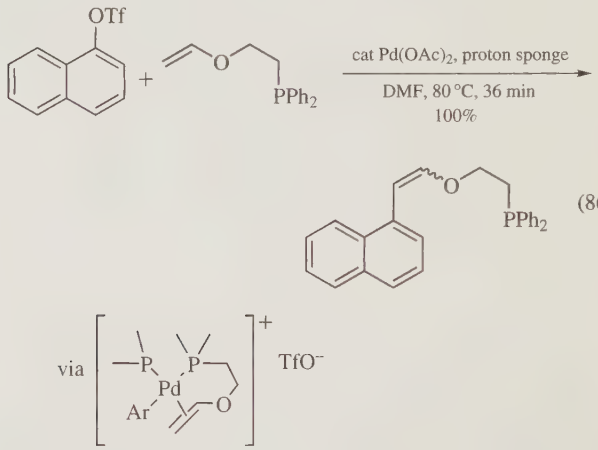


(85)

Functionalization of Alkenes and Other π-Systems with Palladium-Activated Carbon Nucleophiles.

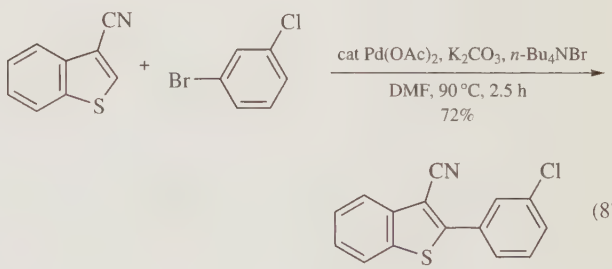
Heck Coupling. Detailed investigations of various reaction conditions used to effect the Heck reaction have led to the discovery of several new and versatile protocols. Thus, experiments with ligand-free systems have shown that a combination of $Pd(OAc)_2$, K_3PO_4 and *N,N*-dimethyl acetamide (as catalyst, base and solvent, respectively) is highly effective in promoting the Heck coupling of aryl bromides.[158] Studies involving microwave irradiation under solvent-free conditions or using water as the solvent have also proved fruitful.[159,160]

Arylation of Alkenes by Coupling and Cross-coupling. The cross-coupling of aryl triflates with vinyl ethers incorporating a β-diphenylphosphine moiety proceeds in remarkably high yield and such outcomes are attributed to the complexation of the pendant phosphorus to the pivotal palladium-centered intermediate (eq 86).[161]



(86)

A series of 3-cyano-substituted benzo[*b*]thiophenes has been shown to undergo Heck-type coupling, at C2, with various aryl halides (eq 87).[162]

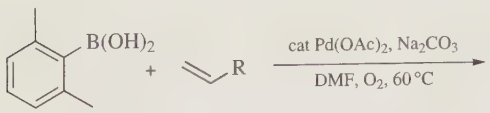


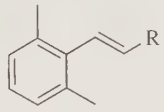
(87)

Arylboronic acids engage in Heck reactions with vinyl sulfones and phosphonates to give the corresponding β-arylated α,β-unsaturated sulfones and phosphonates, respectively (eq 88).[163,164]

Phenyltributyltin reacts in a similar manner with a variety of α,β-unsaturated esters and related compounds to give the corresponding β-arylated systems in good to excellent yields (eq 89).[165]

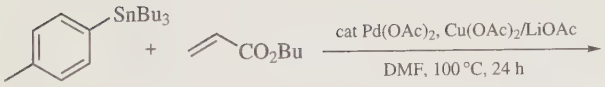
Certain trialkylbenzyl ammonium halides can participate in Heck reactions with both electron-deficient and electron-rich alkenes to give β-substituted styrenes. A radical-based pathway has been invoked to account for the formation of the observed products (eq 90).[166]

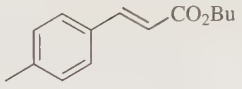




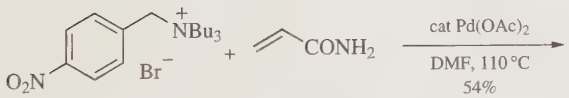
(88)

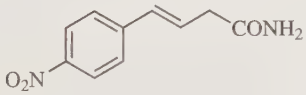
R = SO_2Ph, 74%
R = $PO(OEt)_2$, 86%





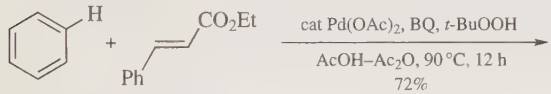
(89)

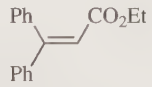




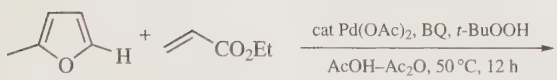
(90)

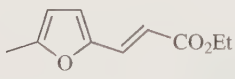
Related products are accessible from the corresponding unfunctionalized arene and via a process that involves palladium insertion into the relevant C–H bond. Oxidative turnover is effected by the added *t*-BuOOH (eqs 91 and 92).[167]





(91)

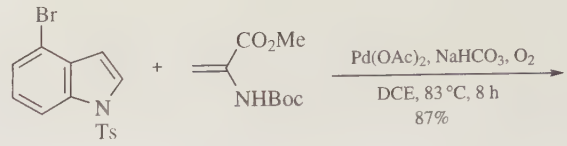


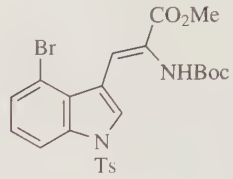


(92)

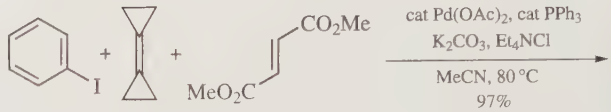
Stoichiometric quantities of $Pd(OAc)_2$ have been used to effect the incorporation of the elements of dehydroalanine at the 3-position of an *N*-protected form of 4-bromoindole and so providing a useful precursor to clavicipitic acid (eq 93). The reaction is carried out under an oxygen atmosphere.[168]

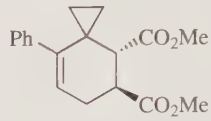
A reaction sequence involving Heck then Diels–Alder processes and that exploits the propensity of bicyclopropylidene to undergo carbopalladation with aryl- or alkenyl-palladium species has been developed. This ultimately affords spiro[2,5]oct-4-ene derivatives in excellent yield (eq 94).[169]





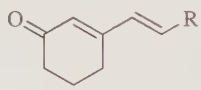
(93)





(94)

Formation of Dienes and Enynes by Coupling and Cross-coupling. The reaction of β-tosyloxyenones with terminal alkenes under Heck-type conditions has been investigated. By using as little as 1 mol % $Pd(OAc)_2$ and 0.9 mol % PPh_3, good to excellent yields of various β-vinylated enones have been obtained (eq 95).[170]



(95)

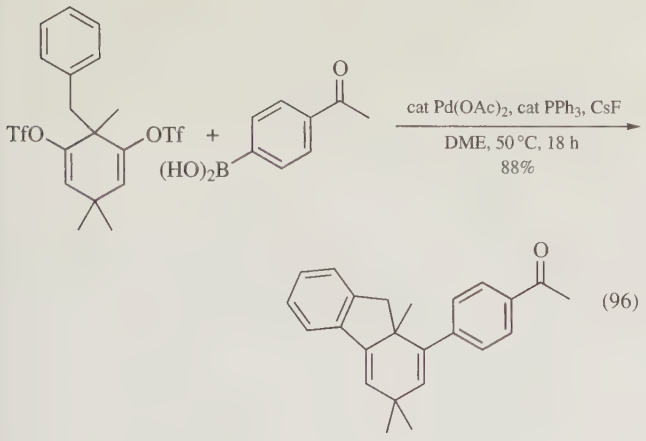
R = Ph, CN, CO_2Me
$CONH_2$, CO_2H, COMe

This protocol has been extended to the generation of a range of β-alkynylated enones.[171]

$Pd(OAc)_2$ has proven to be a remarkably effective catalyst and precatalyst for the Suzuki reaction.[172] Although a full listing of its uses in this area are beyond the scope of this article, it is important to note that $Pd(OAc)_2$ has been exploited in numerous such aryl-aryl coupling reactions, including in several instances where water is the solvent or co-solvent,[173–177] or where ***tetra-n-butylammonium bromide*** (TBAB) is used as a surfactant/additive,[174,175,177–180] or where microwave-accelerated conditions have been employed.[173,176]

Polyurea microcapsules containing $Pd(OAc)_2$ (Pd EnCat™) have been used in Suzuki cross-coupling processes conducted in either batch or continuous-flow mode.[178]

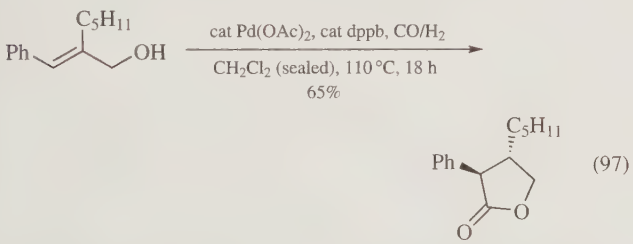
Treatment of a benzyl-substituted and symmetrical bis-enol triflate with various aryl boronic acids in the presence of $Pd(OAc)_2$ results in a Suzuki–Miyaura cross-coupling reaction, then an intramolecular Heck reaction between the remaining triflate residue and the benzyl group and so as to give the illustrated product (eq 96).[181]



(96)

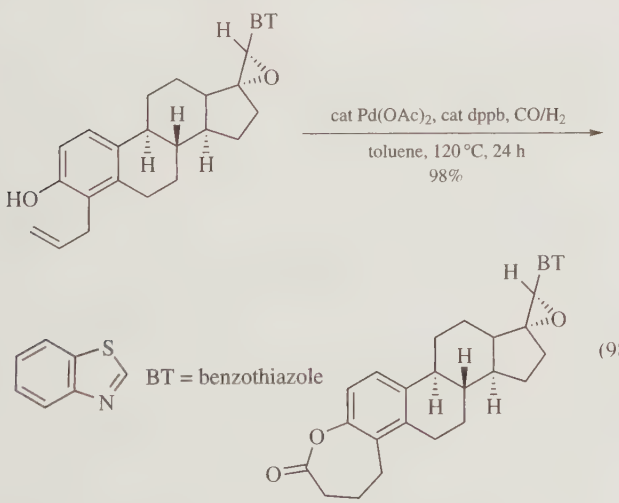
Formation of Aldehydes, Ketones and Allylic Dienols by Coupling to Allylic Alcohols. The palladium-catalyzed reaction of allylic alcohols with aryl iodides has been shown to occur in water when $NaHCO_3$ and *n*-Bu_4NCl are present. Such reactions afford β-arylketones and aldehydes in good yield.[182]

Carbonylation and Related Reactions. The first stereoselective, palladium-catalyzed and reductive cyclocarbonylation of β,γ-substituted allylic alcohols has been reported. Thus, *E*-allylic alcohols are converted, with high diastereoselectivity, into *trans*-2,3-disubstituted γ-lactones (eq 97).[183]



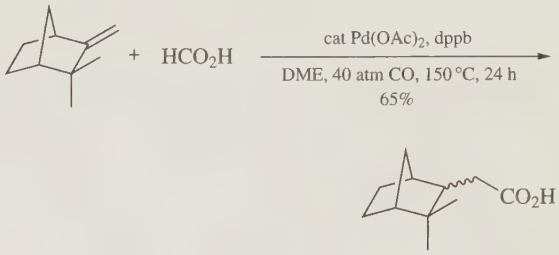
(97)

Related and regioselective processes have been exploited in the preparation of novel lactone-annulated steroids (eq 98).[184]



(98)

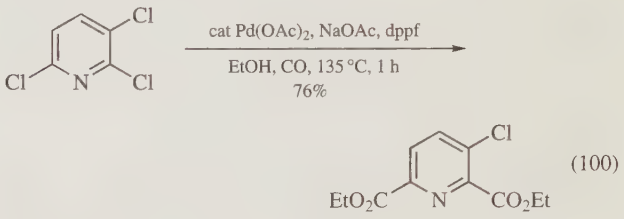
Methylenecycloalkanes have been found to undergo a regioselective, palladium-catalyzed hydrocarboxylation reaction with formic acid and carbon monoxide to give cycloalkylacetic acids in good yield. In the case of camphene, carbon monoxide pressures of 40 atm are required to achieve satisfactory conversions (eq 99).[185]



(99)

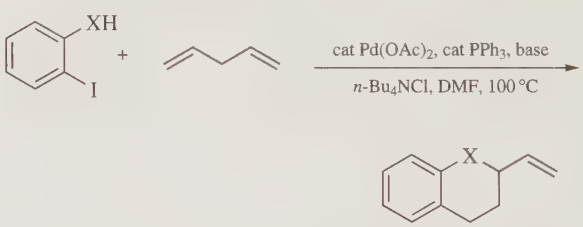
2:1 exo:endo

Carboalkoxylation of variously substituted chloropyridines has been achieved using dppf and carbon monoxide in the presence of $Pd(OAc)_2$ (eq 100).[186]



(100)

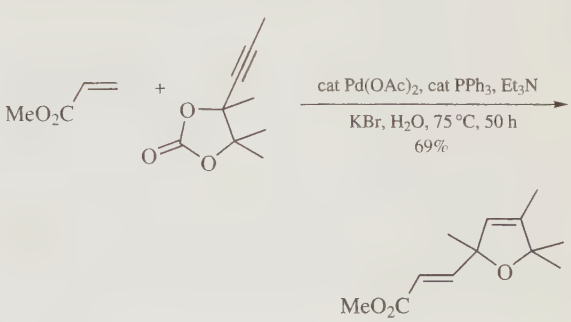
Formation of Heterocyclic Compounds. Many new applications of $Pd(OAc)_2$ in heteroannulation processes have been reported. A method for forming six-membered *O*- and *N*-heterocycles from *ortho*-halogenated phenols or anilines and 1,4-dienes has been described. This can be extended to the preparation of carbocycles through the use of a diethyl malonate group in place of the heteroatom residue (eq 101).[187]



(101)

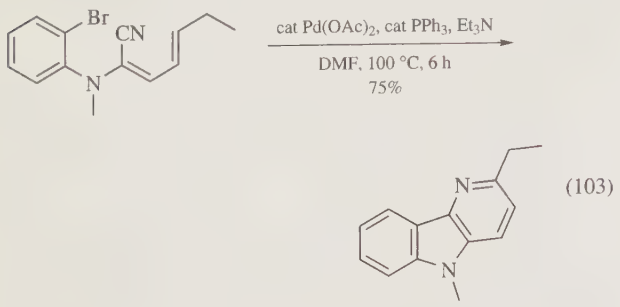
X = O, 70%
X = NH, 65%

2-Alkenyl-substituted 2,5-dihydrofurans can be prepared by reaction of alkynyl-substituted cyclic carbonates with electron-deficient alkenes in the presence of $Pd(OAc)_2$ and via processes involving successive C–C and C–O bond formations as well as accompanying loss of carbon dioxide (eq 102).[188]



(102)

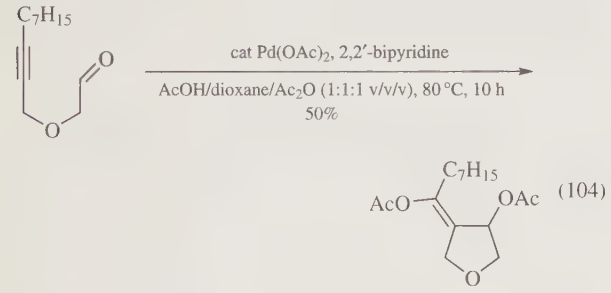
α-(*ortho*-Bromo-*N*-methylanilino)-α,β-unsaturated and α,β,γ,δ-doubly unsaturated nitriles cyclize to form indoles and aza-carbazoles, respectively, upon exposure to catalytic quantities of $Pd(OAc)_2$ in DMF at elevated temperatures (eq 103).[189]



(103)

Related heteroannulation chemistry has been conducted on the solid-phase and provided new routes to hydrobenzofurans, hydrobenzopyrans, indolines and tetrahydro-quinolines.[190] Using alkenyl-based substrates in solution-phase variations of such processes has led to (*E*)-2-alkyl(aryl)idene-1,2,3,4-tetrahydroquinoxalines and pyrido[2,3-*d*]pyrimidines.[191,192]

The capacity to effect direct insertion of a C–O or C–N multiple bond into a carbon–palladium bond has been exploited in a $Pd(OAc)_2$-mediated cyclization reaction of alkynes containing tethered aldehyde, ketone or nitrile groups. Such processes can result in the formation of tetrahydrofurans incorporating a tetra-substituted and exocyclic double bond of defined geometry (eq 104).[193]



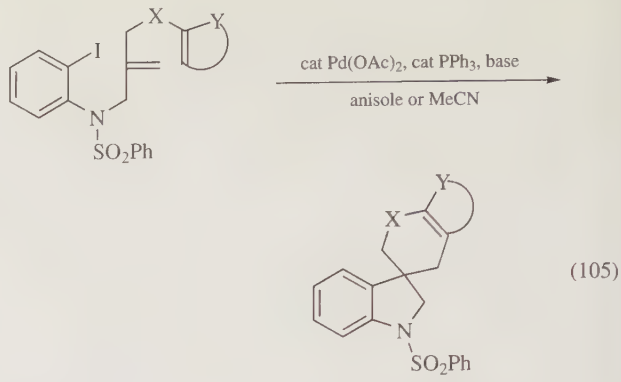
(104)

The reaction of heterocumulenes or alkynes with *ortho*-iodo-anilines under a carbon monoxide atmosphere has been shown to give 4(3*H*)-quinazolinones or 2-quinolones, respectively.[194,195] A related cyclocarbonylation reaction has been used to synthesize new cardanol and cardol derivatives in a regioselective manner.[196]

Versatile and efficient routes to various spirocyclic compounds, including [5,5]-, [5,6]- and [5,7]-spiroindolines, have been established by exploiting a sequence of palladium-catalyzed cyclization processes (eq 105).[197]

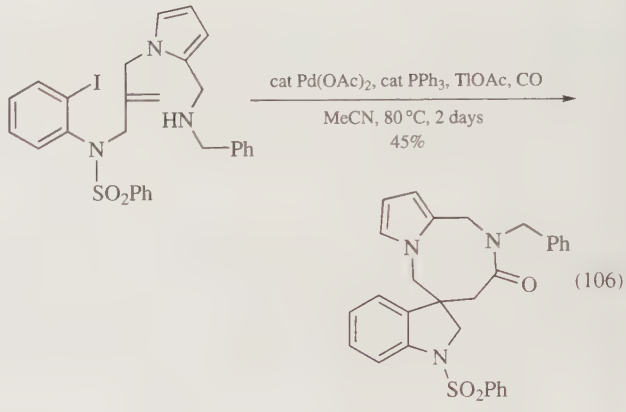
Related cascades involving a carbonylation step, and leading to spirocyclic ketones, lactones and lactams have also been described (eq 106).[198,199]

Electron-rich aryl isonitriles and 6-iodo-*N*-propargylpyridones undergo a palladium-catalyzed cascade reaction at ambient temperature to afford 11*H*-indolizino[1,2-*b*]quinolin-9-ones in good yield (eq 107). The value of this protocol has been demonstrated through its use in the synthesis of several compounds displaying anti-cancer properties.[200]

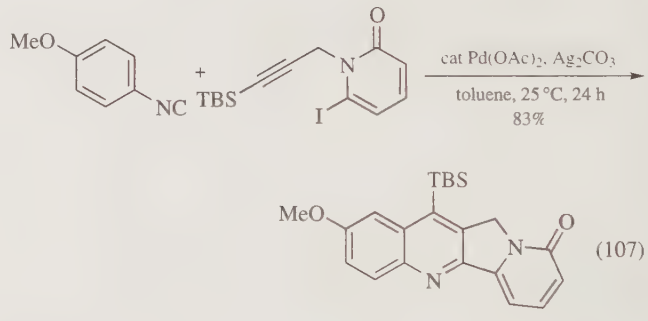


(105)

X = O, $N(SO_2Ph)CH_2$
Y = CH, N, O, S



(106)

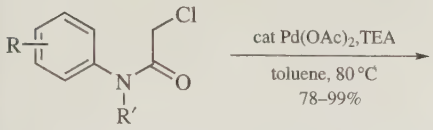


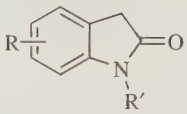
(107)

Miscellaneous Processes. A versatile synthetic route to the pyrrolophenanthridone alkaloids has been developed that involves a palladium-mediated cyclization of *N*-benzoyl indolines, then 2,3-***dichloro-5,6-dicyano-1,4-benzoquinone*** (DDQ)-promoted oxidation of the resulting dihydropyrrolophenanthridones.[201] Related processes have been exploited in an elegant total synthesis of the marine alkaloid (+)-dragmacidin F and in the preparation of biologically relevant indoles.[202,203]

The palladium-catalyzed arylation of carbonyl compounds is proving to be a very important process.[204] Both inter- and intramolecular variants are known. For example, the synthesis of the pharmaceutically important oxindole framework has been accomplished via the palladium-catalyzed cyclization of α-chloroacetanilides that involves C–C bond formation at an *ortho*-position on the aromatic ring (eq 108).[205]

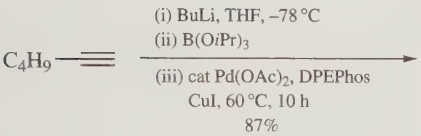
In situ generated lithium alkynyltriisopropoxyborates have been homocoupled in the presence of $Pd(OAc)_2$ and bis[(2-diphenylphosphino)phenyl]ether (DPEPhos) and thus providing a mild and efficient route to 1,3-diynes (eq 109).[206]





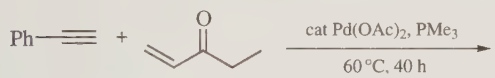
(108)

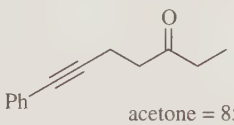
R = H, Me, OMe, Cl, CF_3, NO_2, TMS, OTBS
(in various, and multiple substitution patterns)
R′ = Bn, PMB, Me, Et, Ph, $CHPh_2$



(109)

The first palladium-catalyzed conjugate addition of terminal alkynes to α,β-unsaturated enones has been reported. The reaction, which can be carried out in either water or acetone, affords β-alkynyl ketones in high yields (eq 110).[207]

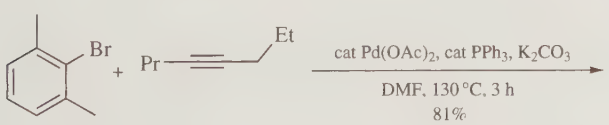


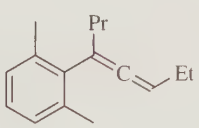


(110)

acetone = 85%
water = 91%

2,6-Disubstituted aryl bromides react with dialkylacetylenes, in the presence of catalytic quantities of both $Pd(OAc)_2$ and PPh_3, to give the corresponding aryl-substituted allenes in good yield (eq 111).[208]

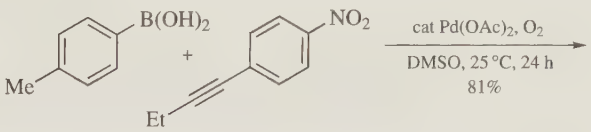


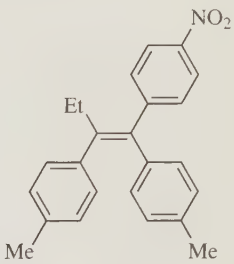


(111)

Tetrasubstituted olefins are readily formed through the Pd-catalyzed *cis*-addition of two aryl groups, one from each of 2 equiv of an added aryl boronic acid, to the opposing ends of an internal alkyne (eq 112).[209]

Oxidative C–C bond scission of certain tertiary-alcohols has been observed in the presence of $Pd(OAc)_2$ and oxygen. Such processes have been exploited in the formation of enynes, β,γ-unsubstituted ketones and annulated tetralones.[210–212]

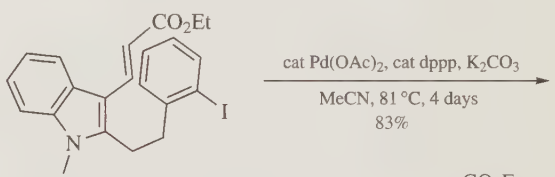


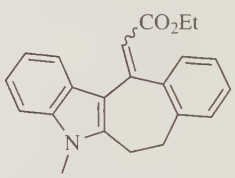


(112)

Formation of Carbocycles.

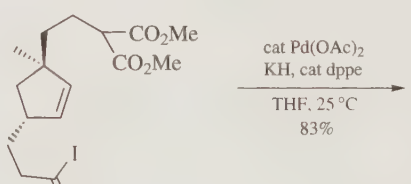
By Intramolecular Heck Coupling. The intramolecular Heck reaction has been used to prepare tetracyclic ethylenic esters required for testing as anti-inflammatory agents (eq 113).[213]

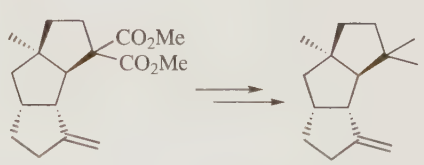




(113)

A palladium-catalyzed cyclization sequence involving a malonate anion-based termination step and leading to linear triquinanes has been reported and employed in the synthesis of the sesquiterpene-type natural product (±)-$\Delta^{9(12)}$-capnellene (eq 114).[214]



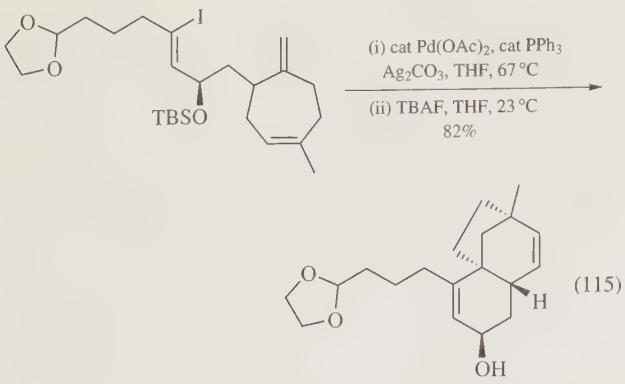


major isomer

(±)-$\Delta^{9(12)}$-capanellene

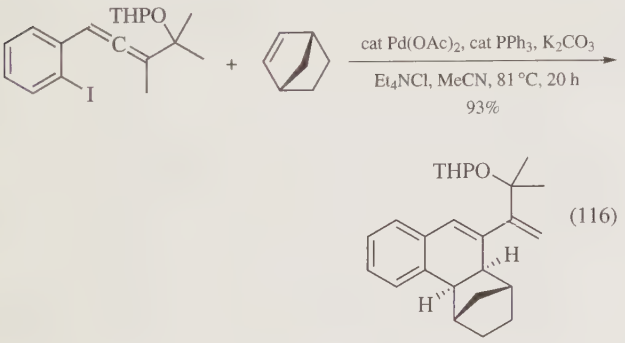
(114)

The first total synthesis of (±)-scopadulcic acid was achieved using a reaction sequence that involved, as the pivotal step, a two-fold Heck cyclization process. This delivered, with full stereocontrol, the BCD-ring system of the target tetracyclic diterpene (eq 115).[215]



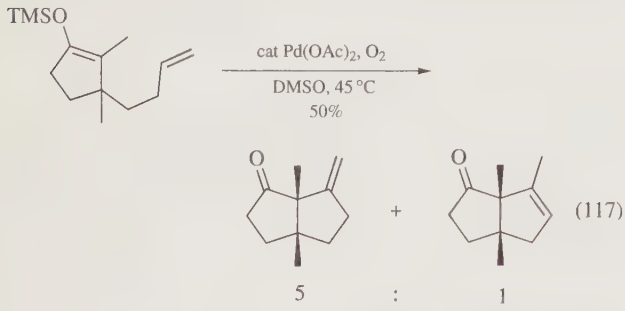
(115)

(*ortho*-Iodoaryl)allenes have proven to be versatile four-carbon synthons that can participate in palladium-catalyzed [4 + 2] "cycloaddition" reactions with simple (unactivated) alkenes such as norbornene (eq 116).[216]



(116)

By Cyclization of Alkenyl Silyl Enol Ethers. A simple method for the construction of bicyclo[4.3.0]nonanes and bicyclo[3.3.0] octanes has been developed and this involves a palladium-catalyzed cycloalkenylation reaction as the pivotal step. The selective formation of products incorporating an exocyclic double-bond was observed in a number of cases (eq 117).[217]

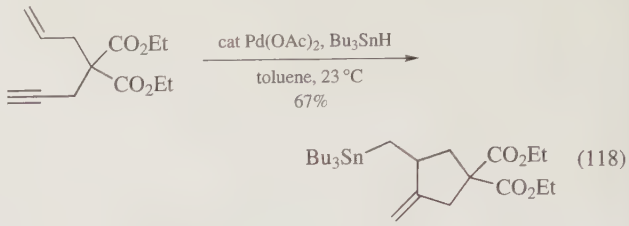


(117)

The value of such processes in natural product synthesis has been clearly demonstrated.[218]

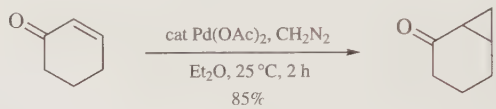
By Cycloisomerization of Enynes. Two pivotal papers have been published in this area and these cover the scope and limitations of the title reaction, as well as detailing the use of alternative catalyst systems.[219,220] In certain instances $Pd(OAc)_2$ is quite clearly the catalyst of choice.

The participation of enynes in a palladium-catalyzed hydrostannylation reaction has been investigated. For example, treatment of 1,6-enynes with ***tri-n-butylstannane*** in the presence of $Pd(OAc)_2$ affords good yields of cyclopentylidene-based homoallylic stannanes (eq 118).[221]

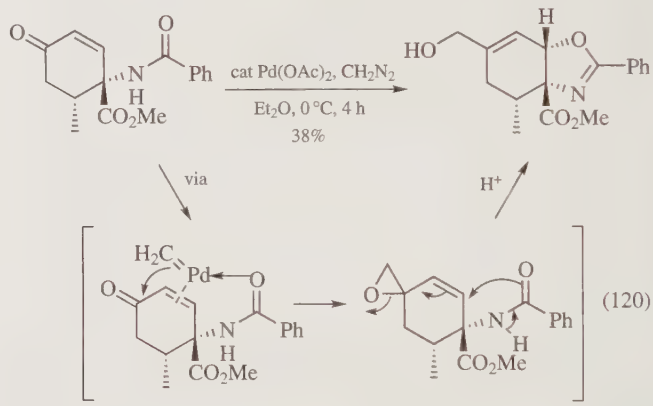


(118)

By Cyclopropanation. 2-Cyclohexenone reacts with diazomethane in the presence of catalytic $Pd(OAc)_2$ to give the expected cyclopropyl ketone (eq 119) and this process represents an especially useful way of preparing such systems. However, when the enone carries an amide unit at the γ-carbon, a competing pathway, commencing with diazomethane addition to the carbonyl group, is observed. Under acidic conditions, tetrahydrobenzoxazoles are the observed products of reaction (eq 120).[222]



(119)



(120)

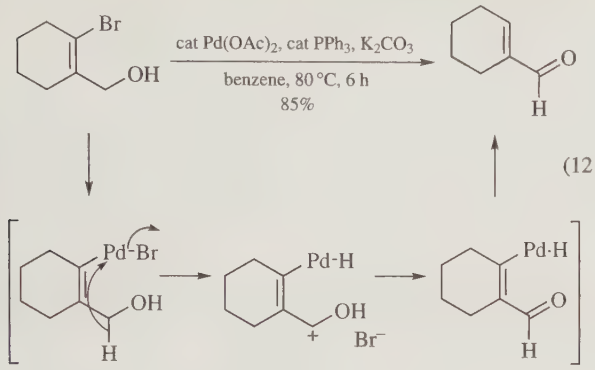
Oxidations.

Carbonyl Compounds by Oxidation of Alcohols and Aldehydes. A critical assessment of the use of palladium catalysts in the aerobic oxidation of alcohols has concluded that $Pd(OAc)_2$–Et_3N is the most versatile and convenient catalyst system and that this often functions under especially mild conditions.[223] There have been many other recent advances in this field and such that there is now a wealth of methods available for effecting the palladium-catalyzed oxidation of alcohols. A procedure using pyridine under an oxygen atmosphere has been shown to convert benzylic and aliphatic alcohols into the corresponding aldehydes or ketones. The yields of product are frequently over 90%.[224,225] Replacing pyridine with (−)-sparteine in such processes allows for the oxidative kinetic resolution of chiral secondary alcohols.[226]

Both primary and secondary alcohols can be converted into the corresponding aldehyde or ketone by a method using allyl diethyl phosphate, as hydrogen acceptor, in combination with either potassium or sodium carbonate and $Pd(OAc)_2$ as catalyst.

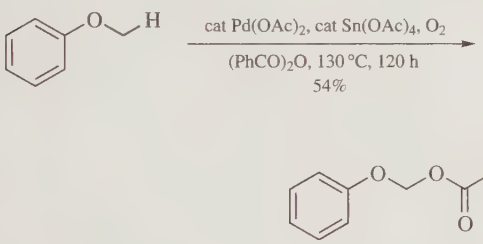
For example, 2-octanone and cinnamaldehyde have each been synthesized by this route, and in yields of 85 and 90%, respectively.[227]

Certain brominated allylic alcohols suffer loss of the elements of HBr when exposed to Heck-type reaction conditions and so affording the corresponding α,β-unsaturated aldehydes or ketones (eq 121).[228]



(121)

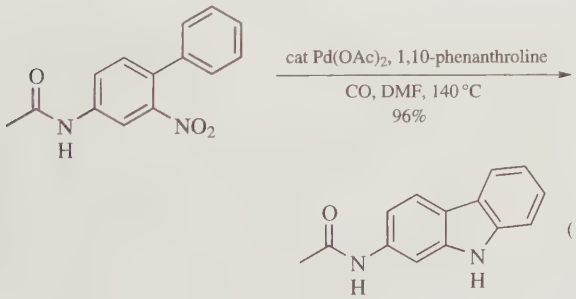
Functionalization at Carbon Bearing Non-allylic C–H Bonds. C–H activation at the methoxy group of anisole has been achieved using a combination of catalytic quantities of both $Pd(OAc)_2$ and $Sn(OAc)_4$ together with oxygen and benzoic anhydride (as a trapping reagent). By such means phenoxymethyl benzoate is obtained in 54% yield (eq 122).[229]



(122)

Carboxylation of aromatic Ar–H bonds has been achieved using TFA solutions of potassium persulfate ($K_2S_2O_8$) in the presence of catalytic quantities of $Pd(OAc)_2$.[230]

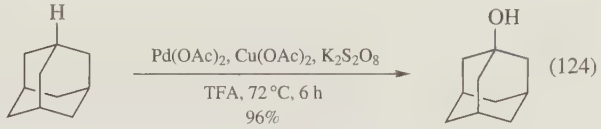
A simple method for the construction of carbazole rings that exploits carbon monoxide as the reagent for effecting the reduction of nitro groups has been developed (eq 123).[231]



(123)

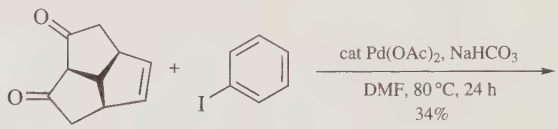
A related protocol has been utilized in the synthesis of substituted indoles.[232]

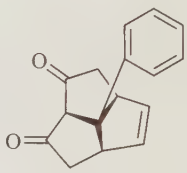
The high yielding conversion of adamantane into 1-adamantanol has been achieved using a combination of stoichiometric quantities of each of $Pd(OAc)_2$, ***Copper Acetate*** and $K_2S_2O_8$ (eq 124).[233]



(124)

Upon exposure to Heck-type reaction conditions, a triquinacene derivative was shown to react with iodobenzene in a process that led to the introduction of a phenyl group at the central (and sp^3-hybridized) carbon of the tricyclic ring system (eq 125).[234]



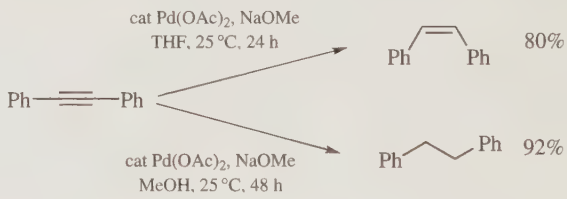


(125)

The saturated analogue of the illustrated substrate underwent the same novel arylation reaction in a more efficient manner.

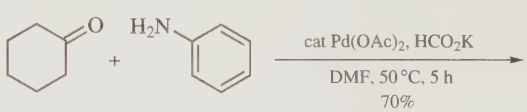
Reductions. Pd EnCat™ has been found to effect a wide range of hydrogenation reactions at catalytic loadings. This catalyst, which can be easily recovered and reused, displays none of the pyrophoric properties associated with the reduced form of the free palladium salt.[235]

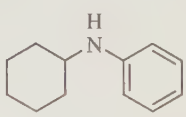
Reduction of Alkynes. Internal alkynes have been found to undergo either partial or full reduction upon treatment with sodium methoxide in the presence of $Pd(OAc)_2$. The extent of reduction can be controlled by altering the solvent used and the partial reduction process affords the *Z*-alkene as the major reaction product (eq 126).[236]



(126)

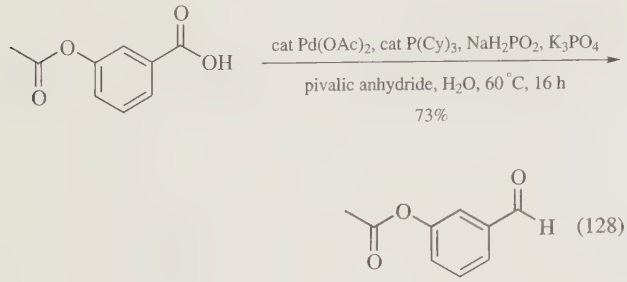
Other Reduction Processes. A simple method for the reductive amination of aldehydes and ketones has been developed. Using potassium formate as the reductant and $Pd(OAc)_2$ as catalyst, a variety of primary and secondary aliphatic amines as well as certain aromatic amines have been synthesized (eq 127).[237]





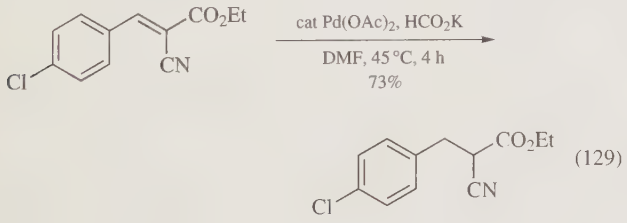
(127)

The $Pd(OAc)_2$-catalyzed reduction of carboxylic acids with a combination of sodium hypophosphite and pivalic anhydride provides a mild and general route to aldehydes that avoids the use of metal hydride reagents or high pressure hydrogenation conditions (eq 128).[238]



(128)

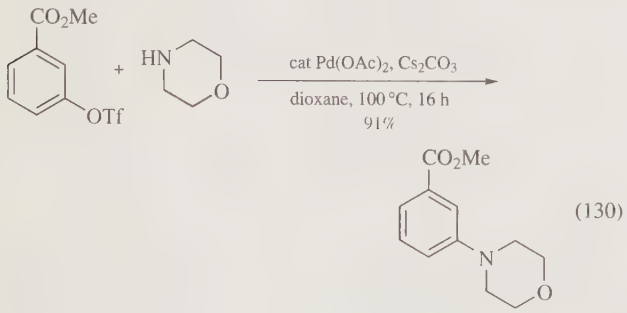
A variety of α,β-unsaturated α-cyanoesters have been chemoselectively reduced with potassium formate in the presence of catalytic quantities of $Pd(OAc)_2$. No reduction of cyano, carboxylate and halogen groups is observed under these conditions (eq 129).[239]



(129)

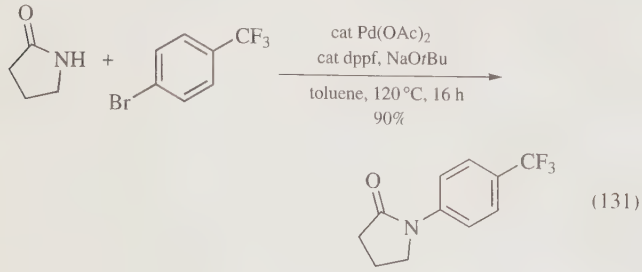
Palladium-Catalyzed Reductions.

Buchwald–Hartwig and Related Reactions. The $Pd(OAc)_2$-catalyzed Buchwald–Hartwig-type couplings of both electron-poor and electron-rich aryl triflates have been shown to proceed efficiently with various amines provided the appropriate base is used. NaO*t*Bu is usually employed for electron-rich systems while Cs_2CO_3 is preferred for electron-deficient and "neutral" species (eq 130).[240,241]



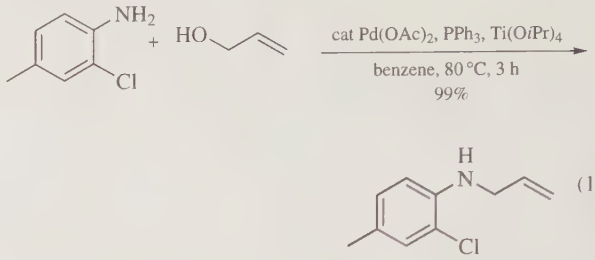
(130)

The direct lactamination of aryl halides has been accomplished under related conditions (eq 131).[242]



(131)

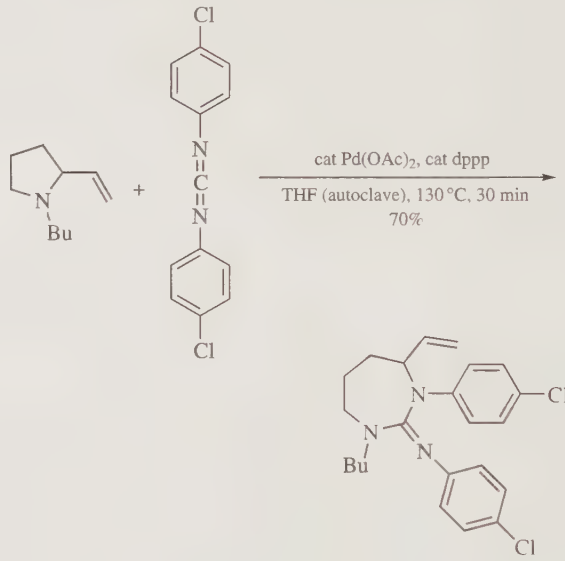
Tsuji–Trost and Related Reactions. By using $Pd(OAc)_2$, triphenylphosphine and *Titanium Tetraisopropoxide* in combination with allylic alcohols, the mono *N*-allylation of anilines can be achieved in almost quantitative yield (eq 132).



(132)

When *cis*-2-butene-1,4-diol is "coupled" with 2-aminophenol under such conditions, the corresponding 3,4-dihydro-2-vinyl-2*H*-1,4-benzoxazines are formed.[243]

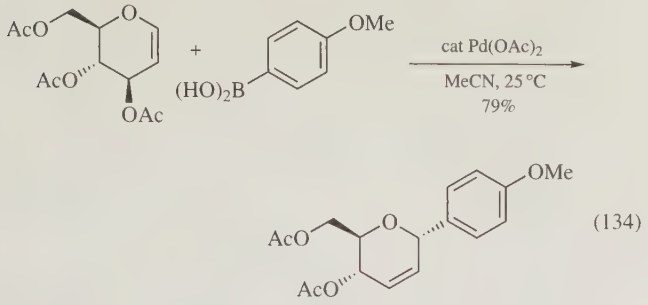
Seven-membered cyclic arylguanidines have been prepared, in good yield, through the "substitution" of the allylic C–N bond within 2-vinylpyrrolidines by carbodiimides (eq 133).[244]



(133)

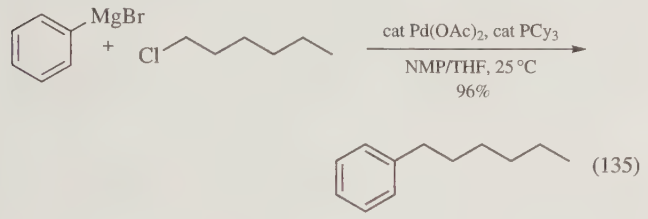
Miscellaneous Processes. A convenient procedure for the palladium-catalyzed conversion of aryl halides into the corresponding nitrile has been devised. Previously observed catalyst deactivation by the cyanide ion is avoided through slow release of (soluble) cyanide in the form of acetone cyanohydrin that is introduced into the reaction mixture by syringe-pump.[245] This procedure has been refined through the development of a ligand-free catalyst system and by utilizing ***potassium ferricyanide*** as the source of cyanide.[246] Another procedure involving the use of polymer-supported PPh_3 under microwave conditions has been reported.[247]

The $Pd(OAc)_2$-catalyzed addition of arylboronic acids to peracetylated glycals has been investigated.[248] The reaction proceeds via *syn*-addition of the relevant aryl–Pd complex to the glycal double bond and this is followed by an *anti*-elimination process that then delivers the illustrated S_N1-type product (eq 134).



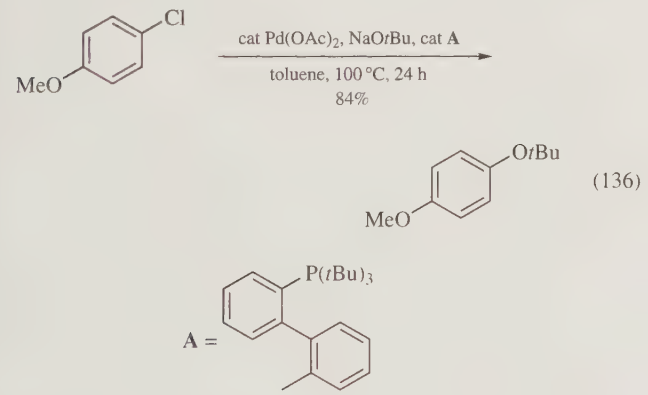
(134)

Otherwise sluggish Kumada-type cross-coupling reactions can be accelerated by using a $Pd(OAc)_2$–PCy_3 catalyst system and so allowing such processes to take place at room temperature and in excellent yield (eq 135).[249]



(135)

The $Pd(OAc)_2$-catalyzed synthesis of aryl *tert*-butyl ethers from aryl halides and sodium *tert*-butoxide has been described (eq 136). When aryl chlorides incorporating electron-donating substituents are used as substrates the reactions still proceed efficiently and under mild conditions.[250]

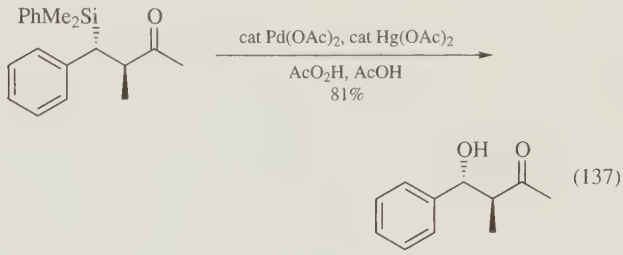


(136)

Palladium-catalyzed Deprotection Processes. Several palladium-catalyzed and mild methods for the deprotection of various functional groups have been developed. For example, a system for the conversion of hydrazones into the corresponding carbonyl compounds that is catalytic in both $Pd(OAc)_2$ and $SnCl_2$ has been reported,[251,252] as has a procedure for the $Pd(OAc)_2$-catalyzed cleavage of allyloxycarbonyl (Alloc) protected alcohols.[253]

During efforts directed towards the synthesis of carbapenem antibiotics, an efficient method for the $Pd(OAc)_2$-catalyzed cleavage of allyl esters was developed. Sodium 2-ethylhexanoate was used as the allyl group scavenger.[254]

Work by Tamao and Fleming has shown that the phenyldimethylsilyl moiety can serve as useful precursor to a hydroxy group. Several new and mild methods for effecting such conversions have been reported, one of which utilizes a catalytic Pd(II)/Hg(II) system (eq 137). These reactions proceed with retention of configuration at the carbon originally bearing silicon while potentially epimerizable centers remain unaffected.[255]



(137)

Related Reagents. Sodium Hydride–Palladium(II) Acetate–Sodium *t*-Pentoxide; thallium(III) trifluoroacetate–palladium(II) acetate.

1. (a) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer: Berlin, 1980. (b) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, *CA*, 1987. (c) Tsuji, J., *Synthesis* **1990**, 739.
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5. Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic: London, 1985.
6. For example, see: Tsuji, J., *Synthesis* **1984**, 369.
7. (a) Roussel, M.; Mimoun, H., *J. Org. Chem.* **1980**, *45*, 5387. (b) Mimoun, H.; Charpentier, R.; Mitschler, A.; Fischer, J.; Weiss, R., *J. Am. Chem. Soc.* **1980**, *102*, 1047.
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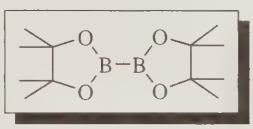
Pinacol Diborane



[73183-34-3] $C_{12}H_{24}B_2O_4$ (MW 253.94)

(versatile reagent for syntheses of organoboron compounds)

Alternate Names: bis(pinacolato)diboron; B_2pin_2; diborane pinacol ester; pinacol diborane.

Physical Data: mp 135–140 °C.

Solubility: soluble in most organic solvents.

Form Supplied in: colorless, stable crystalline solid; commercially available.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 24 H); ^{13}C NMR ($CDCl_3$) δ 24.9, 83.4; ^{11}B NMR (toluene, $BF_3{\cdot}OEt_2$) δ 30.6.

Preparative Methods: commercially available but expensive; prepared from boron tribromide.[2]

Purification: can be purified by recrystallization from pentane.

Handling, Storage, and Precautions: easy to handle in air without special precautions; nevertheless, storage in a tightly closed bottle and in a refrigerator is recommended; causes eye, skin, and respiratory tract irritation.

Original Commentary

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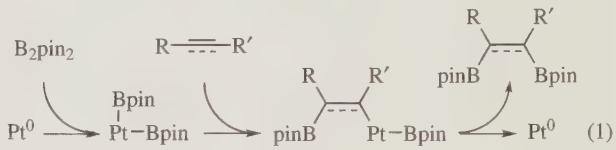
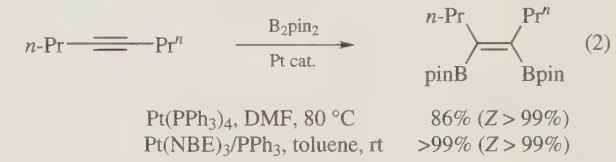
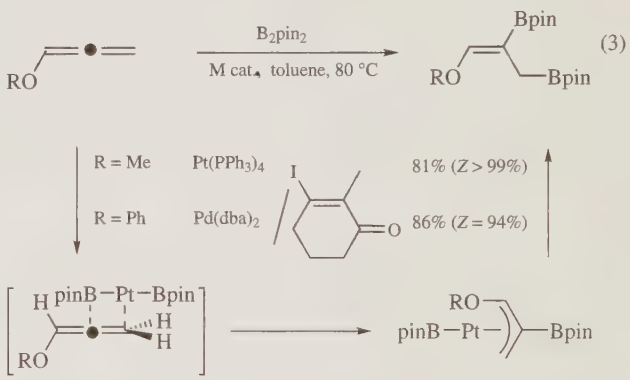
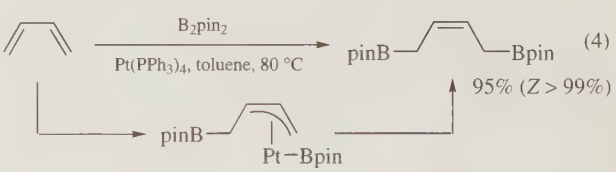
Hokkaido University, Sapporo, Japan

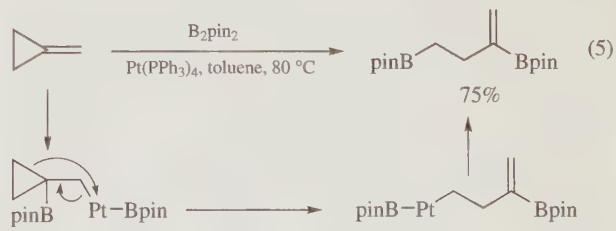
Diboration of Unsaturated Hydrocarbons. B_2pin_2 adds to unsaturated hydrocarbons in the presence of a catalytic amount of a Pt^0 complex to afford diborated products in high yield with excellent regio- and stereoselectivity. The reaction is recognized to proceed through a catalytic cycle, which involves (a) oxidative addition of the B–B bond to Pt^0, (b) insertion of the unsaturated hydrocarbon into the B–Pt bond, and (c) reductive elimination of the product to regenerate Pt^0 (eq 1). The diboration of alkynes,[3] allenes,[4] conjugated dienes,[5] methylenecyclopropanes,[6] and α,β-unsaturated carbonyl compounds[7] is efficiently catalyzed by phosphine-based Pt^0 complexes (eqs 2–6), whereas phosphine-free Pt^0 complexes are favorable for the reaction of simple alkenes because of the low coordination ability of the alkene over phosphine (eq 7).[8] Although Pd complexes also catalyze the diboration of allenes in the presence of a vinyl iodide (eq 3),[4b] the mechanism may be different from that of the Pt-catalyzed reaction. Since the reagent and reaction conditions are sufficiently mild, the method is readily applicable to the synthesis of functionalized bis(boryl) compounds containing carbonyl, cyano, and epoxy groups, which are not obtainable by conventional diboration using diboron tetrahalides.

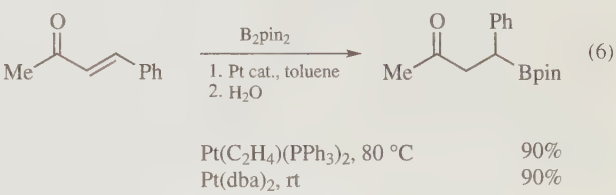


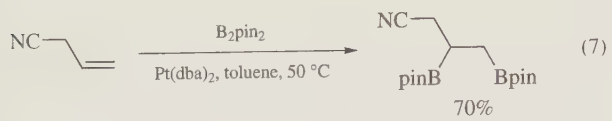






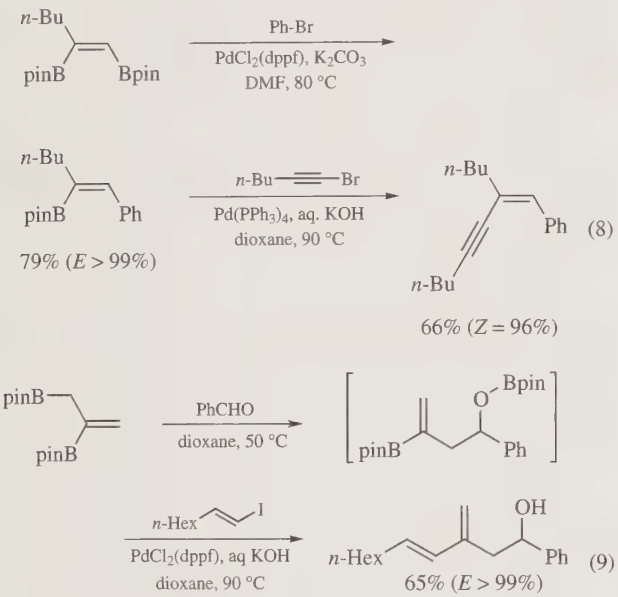






(7)

The diborated products undergo stepwise transformation at the two B–C bonds because of their potential reactivity difference. The 1,2-bis(boryl)-1-alkenes can cross-couple with two different organic halides giving regio- and stereodefined polysubstituted alkenes (eq 8).[9] The utility of the protocol is demonstrated in the synthesis of Tamoxifen, which is used to treat breast cancer.[10] The 2,3-bis(boryl)-1-alkenes participate in a sequential reaction involving allylboration of aldehydes and cross-coupling with organic halides to produce substituted homoallyl alcohols (eq 9).[4a]

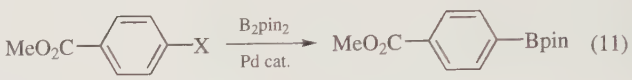


(8)

(9)

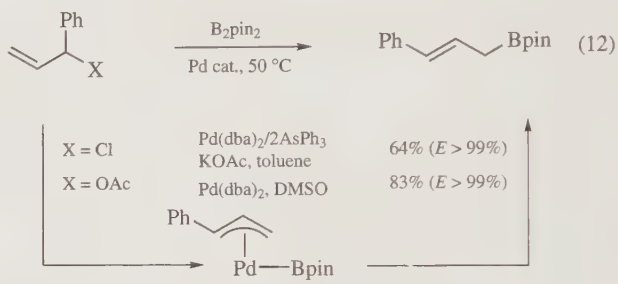
Cross-Coupling with Organic Halides. B_2pin_2 cross-couples with organic halides or pseudo-halides in the presence of a Pd^0 catalyst and a base, providing organoboronates in excellent yields. The reaction may proceed through (a) oxidative addition of the organic halide to Pd^0, (b) displacement of the X ligand with the base, (c) transmetalation with B_2pin_2, and (d) reductive elimination of the product to regenerate Pd^0 (eq 10). The choice of an appropriate base is essential for the successful borylation, because stronger bases prompt a further coupling of the borylated products with organic halides, resulting in the competitive formation of homo-coupling products. Selective synthesis of aryl-,[11] allyl-,[1c,d,12] and benzylboronates[1c,d] can be achieved by using KOAc as base (eqs 11–13); however, the reaction of vinyl electrophiles requires a much stronger base, KOPh, to avoid the formation of homo- and Heck-coupling products arising from insertion of the vinylboronates into the C–Pd bond (eq 14).[13] The borylation of allyl acetates proceeds without a base because this oxidative addition directly yields $R'CO_2$-Pd-R active for transmetalation with B_2pin_2 (eq 12).[12] The coupling is feasible with various functional groups, e. g., CO_2Me, COMe, NO_2, and CN, which need protection-deprotection in the two-step procedure for preparing organoboronates from magnesium or lithium reagents. The method has been applied to a concise synthesis of L-BPA (4-borono-L-phenylalanine), which is used for the treatment of malignant melanoma and brain tumors in neutron-capture therapy.[14]

(10)

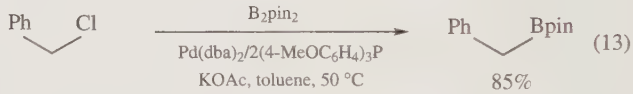


(11)

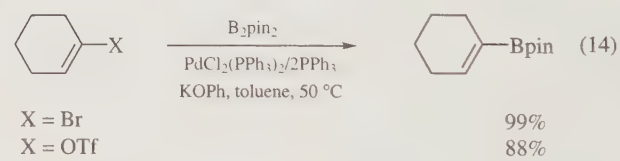
X = Br	$PdCl_2$(dppf), KOAc, DMSO, 80 °C	86%
X = OTf	$PdCl_2$(dppf)/dppf, KOAc, dioxane, 80 °C	80%
X = Cl	$Pd(dba)_2/2P(c\text{-}C_6H_{11})_3$, KOAc, dioxane, 80 °C	87%
X = N_2BF_4	$PdCl_2$(dppf), MeOH, rt ~40 °C	81%



(12)

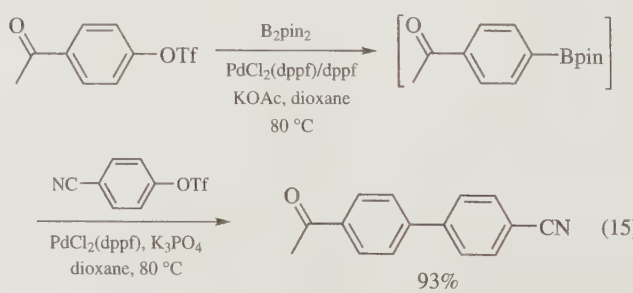


(13)

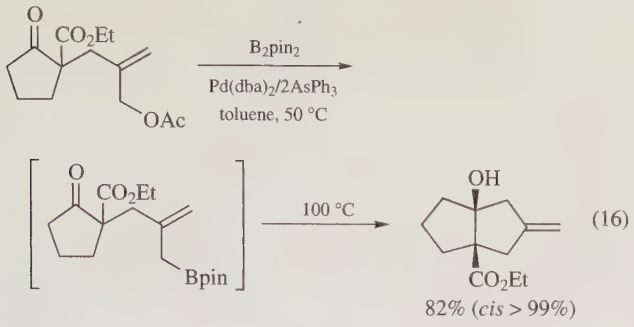


(14)

The direct preparation of aryl- and allylboronates from aryl and allyl electrophiles now allows a one-pot, two-step procedure to access unsymmetrical biaryls[11b,15] and cyclic homoallyl alcohols[16] (eqs 15 and 16), the utility of which is amply demonstrated in the synthesis of natural products, biologically active compounds, and functional materials.

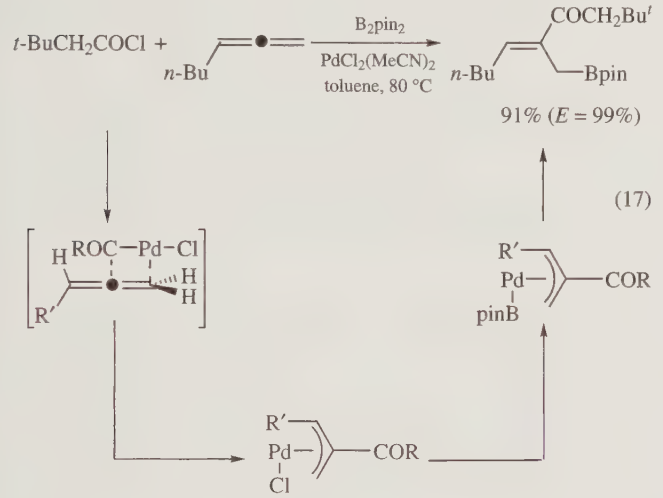


(15)



(16)

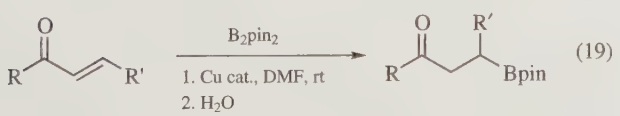
Three-Component Reaction with Acyl Halides and Allenes. B_2pin_2 reacts with acyl halides and allenes in the presence of a Pd catalyst without a base to give 2-acylallylboronates (eq 17).[17]



(17)

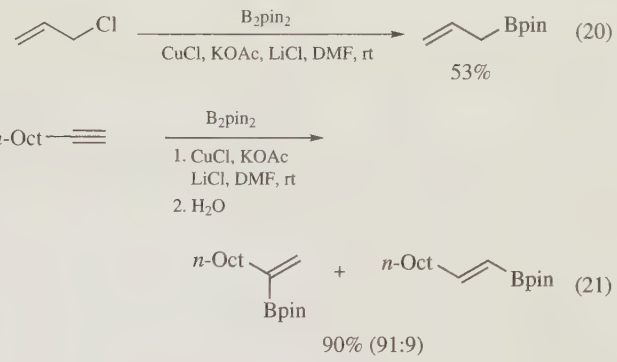
Borylation through Borylcopper Species. B_2pin_2 undergoes transmetalation with oxocopper(I) to form a borylcopper(I) species that reacts with organic electrophiles (eq 18). The addition of B_2pin_2 to α,β-unsaturated carbonyl compounds catalyzed by CuCl/KOAc or CuOTf/P(*n*-Bu)$_3$ is followed by treatment of the mixture with H_2O, resulting in high yields of β-boryl carbonyl compounds (eq 19).[18] The CuCl/KOAc-catalyzed reaction may proceed through 1,4-addition of a B-Cu species to give a copper enolate, which participates in transmetalation with B_2pin_2 to regenerate the B-Cu species. The method is efficiently utilized in the synthesis of boron-containing cyclic amino acids, potential boron carriers in neutron-capture therapy.[19] B_2pin_2 also reacts with allyl halides and alkynes in the presence of a stoichiometric amount of CuCl and KOAc, yielding allyl- and vinylboronates, respectively (eqs 20 and 21).[18a,c]

(18)



(19)

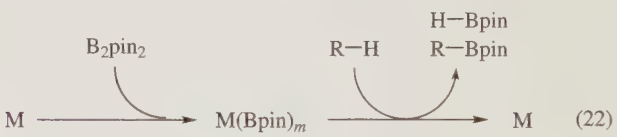
R = Me, R′ = H	CuCl/KOAc	90%
R = Ph, R′ = Ph	CuOTf/P(*n*-Bu)$_3$	96%



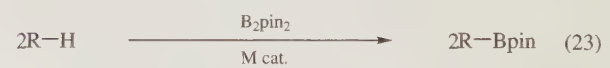
(20)

(21)

Direct C–H Borylation of Hydrocarbons. B_2pin_2 reacts with hydrocarbons in the presence of a transition-metal catalyst via C–H bond activation to produce organoboronates in good yields. The mechanism may involve reactions of B_2pin_2 with metal complexes to form (boryl)metal intermediates which react with the hydrocarbon, giving the borylated product and H–Bpin (pinacolborane) (eq 22). The aliphatic and aromatic C–H borylations are catalyzed by Cp*Re(CO)$_3$ under photochemical conditions[20] or by Cp*Rh(η^4-C_6Me_6) under thermal conditions (eqs 23 and 24).[21] A catalyst generated from [IrCl(COE)$_2$]$_2$ and dtbpy (4,4′-di-*tert*-butyl-2,2′-bipyridine) exhibits high activity toward aromatic C–H borylation, allowing room temperature reactions (eq 24).[22] The selective benzylic C–H borylation is achieved by using a Pd/C catalyst (eq 25).[23] Since H–Bpin also participates in the C–H borylation, 2 mol of the organoboronates are formed from 1 mol of B_2pin_2.



(22)

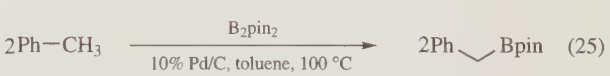


(23)

R = *n*-Pent	Cp*Re(CO)$_3$, *h*ν, CO, pentane, rt	48%
R = *n*-Oct	Cp*Rh(η^4-C_6Me_6), octane, 150 °C	88%

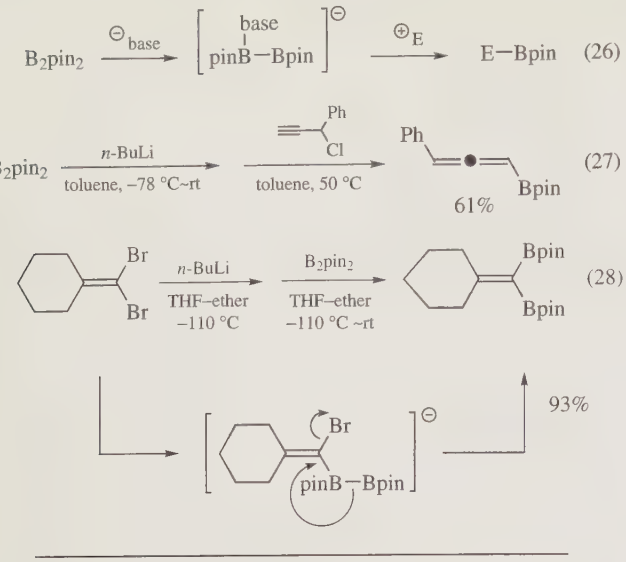
(24)

Cp*Re(CO)$_3$, *h*ν, CO, benzene, rt	38%
Cp*Rh(η^4-C_6Me_6), benzene, 150 °C	92%
[IrCl(COE)$_2$]$_2$/2dtbpy, benzene, rt	83%



(25)

Borylation through Four-Coordinated Species. B_2pin_2 reacts with a strong base such as organolithiums to generate a four-coordinated diboron species, which participates in borylation of organic electrophiles (eq 26). The intermolecular reaction of the propargyl halide proceeds in an S_N2' manner giving the allenylboronate (eq 27).[18a] B_2pin_2 coordinated with 1-halo-1-lithioalkenes undergoes intramolecular 1,2-transfer of the boryl group to afford 1,1-bis(boryl)-1-alkenes (eq 28).[24]



First Update

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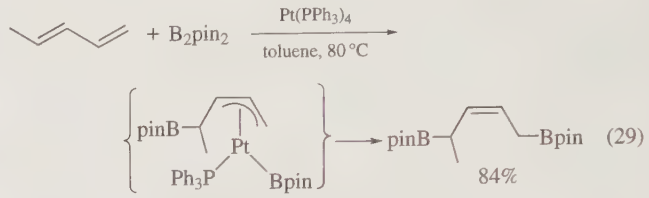
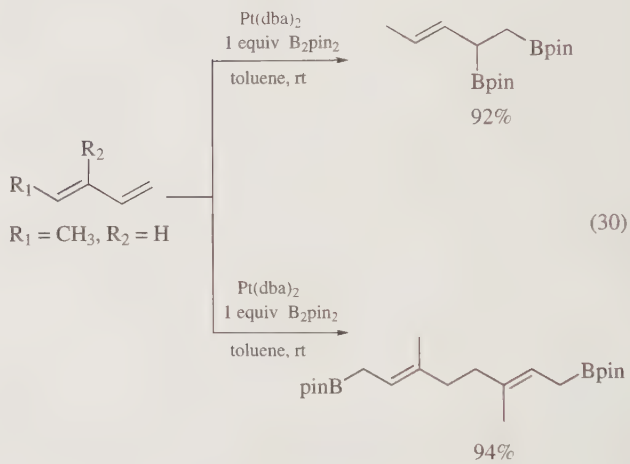
Diboron compounds are becoming an important class of boron reagents for the synthesis of organoboron compounds.[25–28] B_2pin_2 is used preferentially over other diboron(IV) compounds because both B_2pin_2 and pinacol boronic ester derivatives can be handled in air and exhibit high stability towards hydrolysis and thermolysis.[25] Among a wide range of organic and organometallic transformations of B_2pin_2, transition metal-catalyzed B_2pin_2 addition to unsaturated hydrocarbons,[1] cross-coupling with organic electrophiles,[1c] and direct borylation of hydrocarbons via C–H bond activation[29] are the most well studied reactions. These methods apply to a wide range of organic substrates, and enable access to many classes of boron compounds that are essentially unavailable through conventional methods such as transmetalation or hydroboration.[30] Although requiring a transition metal to activate the B–B bond that is stabilized by π-donor pinacolato groups in B_2pin_2, these metal-catalyzed reactions have the advantage of high selectivity, high compatibility with pendant functional groups, and mild reaction conditions. Since metal boryl species are putative reaction intermediates in those transformations, the synthesis of transition metal mono-, bis-, or/and trisboryl complexes via B_2pin_2 oxidative addition or transmetalation also received considerable attention.[31,32] Study on uncatalyzed organic reactions of B_2pin_2 is limited, but the reaction of alkylidene-type carbenoids with B_2pin_2 is well studied, and provides a new class of organoboron compounds: 1,1-diborylated alkenes.[33] Pinacol esters of alkyl, alkenyl, allyl, benzyl, aryl, heteroarylboronic acids, and bisboronic acids derived from the above transformations can be easily converted in a single step to alcohols, amines, olefins, and other classes of functionalized molecules.[34,35] More importantly, they are extremely useful synthetic intermediates for carbon-carbon bond forming reactions that allow further elaboration of the carbon framework.[36]

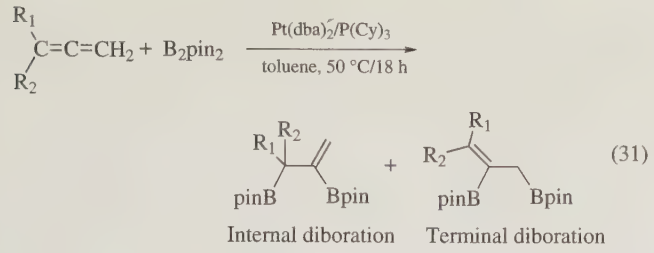
Diboration of 1,3-Dienes, Allenes, Enones, and Other Unsaturated Molecules. As described previously in the original article, the Pt[0] catalyzed addition of 1,3-dienes with B_2pin_2 affords various allylboronic esters (eq 4). Reactions using phosphine-based catalysts such as $Pt(PPh_3)_4$ stereoselectively produce *cis*-1,4-addition products with *Z*-configuration for aliphatic and cyclic dienes.[8] The reaction mechanism suggests that an *anti*-π-allylborylplatinum^{II} intermediate bound to a single phosphine ligand undergoes reductive elimination at the less-substituted terminal carbon before isomerization to a thermally more stable *syn*-π-allylborylplatinum^{II} intermediate (eq 29).[5] Interestingly, the change to catalyst $Pt(dba)_2$ results in 1,2-addition or dimerization (eq 30).[5,8]



anti-π-allylborylplatinum^{II}



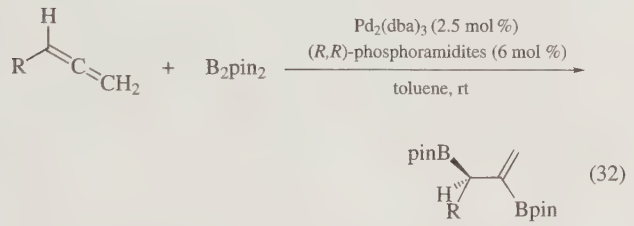
Diboration of allenes with B_2pin_2 becomes a general and useful method for synthesizing allylboronic ester compounds. The $Pt(dba)_2/P(Cy)_3$-catalyzed addition of B_2pin_2 to monosubstituted allenes occurs predominantly at the internal double bond, whereas terminal diboration products were regioselectively obtained from 1,1-disubstituted allenes (eq 31, Table 1).[4a] Morken's group reported that $Pd_2(dba)_3$ catalyzed room temperature diboration of monosubstituted allenes in the presence of bulky phosphine ligands. The same group achieved enantioselective diboration of prochiral allenes in >90% ee and good yield by using $Pd_2(dba)_3$ and TADDOL-derived phosphoramidites as chiral ligands (eq 32).[37] Cheng's group demonstrated that phosphine-free Pd complexes, promoted by the cocatalysts of alkenyl iodides or aryl iodides, regioselectively catalyzed 1,2-diboration of monosubstituted and 1,1-disubstituted allenes at the terminal double bond. The reaction is also highly stereoselective, providing 1,2-bisboryl products with *Z*-stereochemistry.[4b] An extension of diboration methodology is the acylboration of allenes.[17] This method provides an efficient route to a new class of 2-acylallylboronates (eq 33, Table 2). The addition of B_2pin_2 to a number of other double bonds has extended diboration to functionalization of organic molecules.[38]



(31)

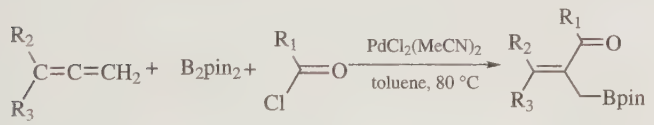
Table 1 Diboration of allenes

R_1	R_2	Yield (%)	Internal:Terminal
H	H	99	-
n-C_4H_9	H	90	84:16
CH_3	CH_3	99	2:98
CH_3O	H	85	0:100



(32)

R = CH_3, decyl, cyclohexyl, *tert*-Bu, Ph, Bn, $PhCH_2CH_2$, $BnOCH_2CH_2$ — 42–75% yield, 87–92% ee



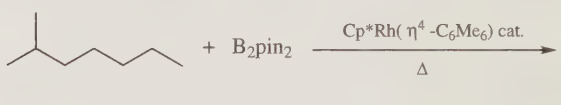
(33)

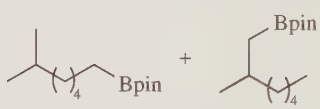
Table 2 Acylboration of allenes

R_1	R_2	R_3	Yield (%)	*E*/*Z*
C_6H_5	Me	Me	68	-
p-MeC_6H_4	Me	Me	72	-
p-$NO_2C_6H_4$	Me	Me	77	-
p-$MeOC_6H_4$	Me	Me	61	-
m-$MeOC_6H_4$	Me	Me	75	-
o-$MeOC_6H_4$	Me	Me	57	-
1-$C_{10}H_7$	Me	Me	92	-
t-$BuCH_2$	Me	Me	80	-
t-$BuCH_2$	H	n-Butyl	91	99:1
t-$BuCH_2$	H	Ph	77	93:7
t-$BuCH_2$	H	cyclohexyl	88	93:7
p-MeC_6H_4	H	t-Butyl	50	98:2

Borylation via C–H Bond Activation.

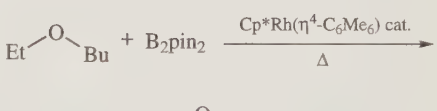
Catalytic Borylation of the Saturated C–H Bond. Hartwig and Chen et al. demonstrated that simple alkanes regiospecifically react at terminal carbon-hydrogen bond with B_2pin_2, yielding pinacol 1-alkylboronic esters (eq 22). Photochemical borylation can be catalyzed by $Cp^*Re(CO)_3$ (eq 23).[20] Thermal borylation can be catalyzed by Rh and Ir complexes containing Cp* and thermally labile ligands such as hydride and olefins, among this group $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ is the most active catalyst (eq 24).[21] A recent study showed that thermal, catalytic borylation tolerates certain functionalities. Alkyl groups in molecules containing nitrogen, oxygen, and fluorine functionality undergo regiospecific borylation at primary C–H bonds in the same manner as simple hydrocarbons.[39] Borylation of a substrate with more than one type of terminal methyl group occurs preferentially at the least hindered and least electron-rich methyl group (eqs 34 and 35).[21,39] Depending on the reactivity of substrate towards borylation with HBpin, 2 equiv of alkylboronic esters can be produced for each B_2pin_2, with H_2 being the corresponding by-product.[21] Compared to other tetra(alkoxo)diborons, the hydrocarbon moiety of B_2pin_2 is less susceptible toward C–H activation, and B_2pin_2 is more efficient in delivering boryl group to organic substrates than is HBpin. Thus, B_2pin_2 is the most commonly used boron reagent for borylation via C–H activation. Because of the low activity of secondary C–H bonds, cyclohexane is often used as reaction solvent for solid and valuable substrates.

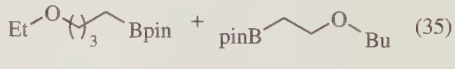




(34)

5:1





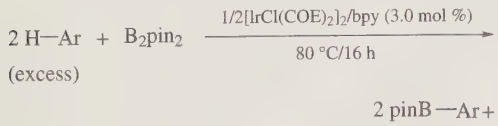
(35)

1: 4

Catalytic Borylation of Aromatic and Heteroaromatic C–H Bonds. Hartwig's group reported borylation of benzene via C–H activation using B_2pin_2 as the boron reagent.[20,21] A number of improvements have been made with respect to catalyst efficiency. A maximum turnover number (8000 TON, 80% yield) was achieved by Ishiyama and Hartwig et al. (eq 24).[22] The reactivity and selectivity of catalysts $[X\text{-}Ir(COD)_2]_2$ and 2,2′-bipyridine (bpy) derivatives was systematically investigated by varying anionic ligand X and substituents on bpy.[40,41] This study led to the discovery that combination of 1/2 $[Ir(OMe)(COD)_2]_2$ with 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) enables room temperature borylation of arenes and heteroarenes with equimolar equivalents of B_2pin_2 or HBpin. In comparison with these highly efficient Ir catalysts, the previously mentioned rhodium systems generally show far lower reactivity.

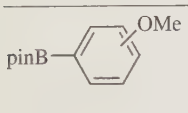
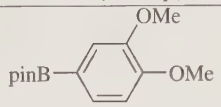
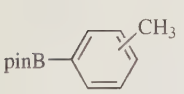
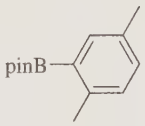
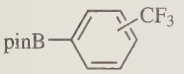
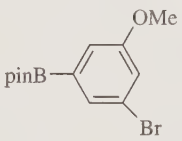
The Iridium-catalyzed borylation reaction was found to be suitable for arenes possessing various functional groups such as OMe, halides, COOMe, CN, CF_3, and benzylic C–H bonds.[22] Because the borylation reaction is not an electrophilic aromatic substitution, the electronic property of the substituents has little influence on regioselectivity. The reactions of monosubstituted arenes result in a mixture of *meta*- and *para*-products in statistical ratios

(ca. 2:1) in most cases. Regioisomerically pure products were obtained in the borylation of 1,3-disubstituted arenes and the borylation of symmetrical 1,2- and 1,4- disubstituted arenes (eq 36 Table 3).[22]

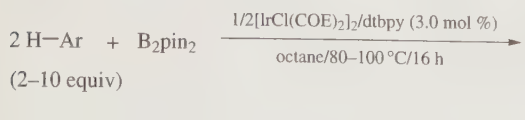


(36)

Table 3 Ir-catalyzed direct borylation of arenes with B_2pin_2

Product	Yield (*o: m: p*)
	
95% (1:74:25)	86%
	
82% (0:69:31)	58%
	
80% (0:70:30)	73%

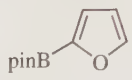
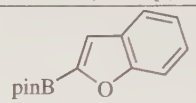
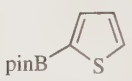
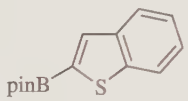
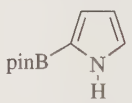
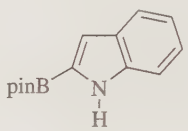
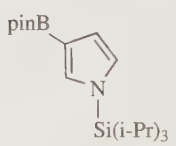
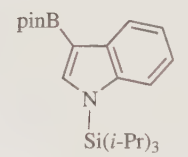
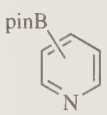
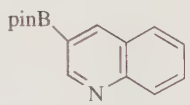
Borylation of five-membered heteroarenes such as pyrrole, furan, thiophene, and their benzo-fused derivatives can be effectively catalyzed by Ir complexes used for arene borylation if the reaction is conducted with a ratio of substrate: B_2pin_2 of less than 10.[42] Use of larger excesses of substrate results in coordination of heteroatom to the Ir metal center, retarding formation of the 16e catalytically active Ir species. Octane, hexane, and cyclohexane have been used as reaction solvents. Those reactions selectively occurred at the C–H bond α to the heteroatom unless the substituents at the heteroatom or 2-position were sterically inhibitory. By this method, not only monoborylated heteroarenes but also 2,5-bis(boryl)pyrrole, -furan, -thiophene were obtained in high yield at room temperature from equimolar equivalents of B_2pin_2 and heteroarene substrate.[41] Six-membered heteroarenes show significantly lower reactivity and different regioselectivity than those of five-membered compounds.[42] Borylation of quinoline selectively gives 3-borylquinoline as monoborylated product in 84% yield, whereas pyridine results in a mixture of 3- and 4-borylpyridine in a 2:1 ratio (eq 37 Table 4).



(37)

Catalytic Borylation of Alkenylic and Benzylic C–H Bonds. Catalytic, selective borylation of alkenes presents a bigger challenge than the borylation of other types of hydrocarbons because hydrogenation, hydroboration, and diboration are often competitive. Marder's group achieved the borylation of alkenes in excellent yields by using *trans*-$[Rh(Cl)(CO)(PPh_3)_2]$ as catalyst in an appropriately chosen solvent mixture (3:1, toluene: acetonitrile).[43] The method is suitable for monosubstituted and 1,1-disubstituted alkenes. Monosubstituted alkenes can be even converted to pinocol vinyl bis(boronate), providing an alternative method for synthesizing 1,1-diborylated alkenes (eq 38). However, an attempt at the borylation of 1,1,2-trisubstituted alkenes was unsuccessful.

Table 4 Ir-catalyzed direct borylation of heteroarenes with B_2pin_2

Product	Yield (*o: m: p*)
	
83%	91%
	
83%	89%
	
67%	92%
	
79%	83%
	
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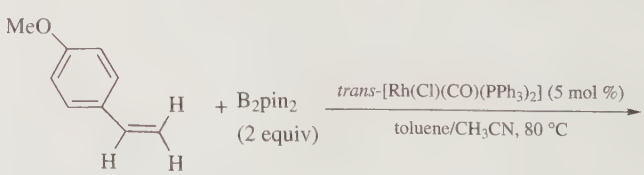
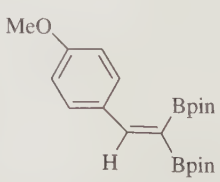




83%

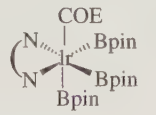
(38)

Marder's group also reported the first example of benzylic C–H borylation, using a Rh^I catalyst.[44] Later, Pd/C was reported to

catalyze borylation of toluene, xylenes, and mesitylene at the benzylic C–H bond with higher regioselectivity (eq 25).[23] However, selectivity for borylation of arenes possessing longer alkyl chains is low.

Synthesis of Pinacol Boryl Complex of Re, Rh, Ir, Pt. The synthesis of Re, Rh, Ir, Pt mono-, bis-, or trisboryl complexes via the oxidative addition or transmetallation of B_2pin_2 and other diboron(IV) compound has been reviewed.[31,32] The structure and reactivity of those isolated pinacol boryl complexes together with kinetic and theoretical studies on their roles in catalytic cycles allow elucidation of the reaction mechanisms of diboration,[1a,3b] cross-coupling reactions,[11a] and borylation via C–H activation.[45] A good example is the experimental and theoretical studies on the synthesis, structure, and reactions of (dtbpy)Ir(COE)(Bpin)$_3$ that is the probable intermediate in the iridium-catalyzed borylation of arenes (eq 39).[22,46,47]

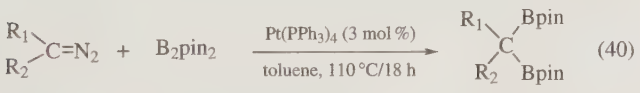
$$[Ir(COE)_2Cl]_2 + (4,4'\text{-di-}t\text{-Bu})Bpy \xrightarrow[\text{mesitylene, 50 °C}]{B_2pin_2}$$



$$\xrightarrow[\text{rt}]{C_6D_6} 3\ C_6D_5Bpin \quad (39)$$

80%

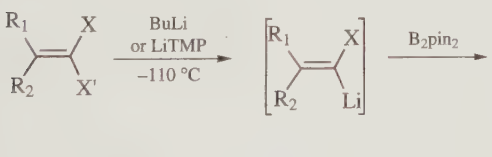
Insertion of Diazoalkane into the B–B Bond. Abu Ali et al. reported that $Pt(PPh_3)_4$ catalyzed the insertion of various diazoalkanes into B_2pin_2 (eq 40).[48] This method provides a unique synthetic route to substituted C1-bridged bisboronic esters, especially those made from diazoalkanes possessing quaternary carbon(s) because they cannot be synthesized by dihydroboration of alkynes.

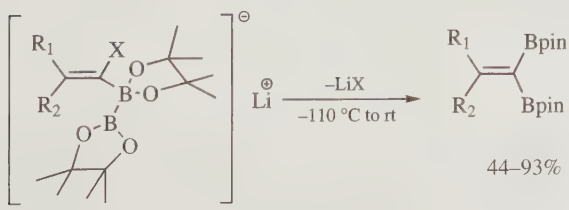


(40)

75–78%

***gem*-Diboration of Alkylidiene-type Carbenoids.** Hiyama's group reported that B_2pin_2 reacts with 1,1-dihaloalkenes and 1-haloalkenes to produce 1,1-diborylated alkenes.[33] The reaction proceeds via 1-halo-1-lithio alkenes (alkylidene-type carbenoid) and borate complexes that undergo stereospecific 1,2-migration of the boron substituent (eq 41).





(41)

44–93%

Synthetic Utility. Although pinacol esters of organoboronic acids show applications as biologically active compounds, they have been mainly utilized as intermediates for synthesizing non-boronic targets because of their ease of conversion to other functional groups.[27,39,49] A good example is the synthesis of hydroxylated polypropylene by tandem borylation and oxidation.[50] Most significantly, these organoboronic esters are valued for selective carbon-carbon bond formation.[51] A number of sequential processes[11b] or one-pot processes[52,15b] involving cross coupling or borylation with B_2pin_2 and Suzuki-Miyaura coupling have been developed for making symmetrical[52] and unsymmetrical biaryls,[15b] which are core structural units in many natural products, e. g., secalonic acids. 1,2- or 1,1-Diborylalkenes prepared by diboration of alkynes and *gem*-diborylation of alkylidene-type of carbenoids may undergo sequential cross-coupling reactions with organic electrophiles to provide stereodefined tri- or tetrasubstituted ethylenes.[3a,33] This method has been successfully applied to tamoxifen synthesis.[10a] Allylboronic esters are also valuable reagents in organic synthesis for diastereoselective addition to carbon-oxygen or carbon-nitrogen double bonds to provide homolytic alcohols or amines.[53]

Related Reagents. 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (HBpin); bis(catecholato)diboron.

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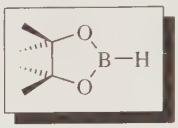
Pinacolborane



[25105-63-8] $C_6H_{13}BO_2$ (MW 127.98)

(monofunctional hydroborating agent, also used in transition metal catalyzed aryl couplings)

Alternate Name: 4,4,5,5-tetramethyl-1,3,2-dioxaborole.

Physical Data: bp 42–43 °C, 50 mm Hg; *fp* 5 °C; *d* 0.882 g cm^{-3}.

Solubility: soluble in ether, THF, CH_2Cl_2, and other organic solvents.

Form Supplied in: neat colorless liquid and also as 1.0 M solution in THF.

Analysis of Reagent Purity: ^1H NMR, ^{11}B NMR (δ 28.0, d).

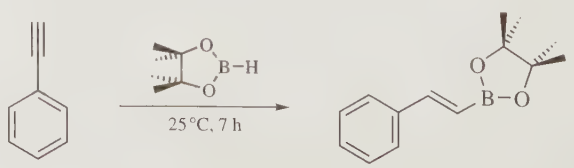
Preparative Methods: reaction of borane-methyl sulfide with pinacol at 0 °C in CH_2Cl_2 furnishes pinacolborane.[1] This solution can be used directly for further reactions or can be distilled to obtain a colorless liquid (*bp* 42–43 °C, 50 mm Hg) (eq 1).

(1)

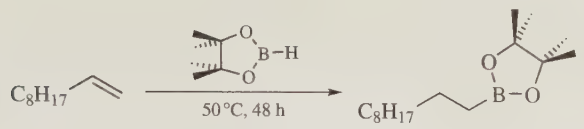
Purification: distillation.

Handling, Storage, and Precautions: packaged under nitrogen. Store and handle under a nitrogen atmosphere and refrigerate.

Hydroboration. Pinacolborane is a stable, easily prepared and stored hydroborating agent. Unlike catecholborane[2] which requires harsh reaction conditions for hydroboration of alkenes (100 °C) and alkynes (70 °C), hydroboration with pinacolborane proceeds under mild conditions furnishing the boronates. Knochel and co-workers[1] observed an excellent level of regioselectivity for hydroboration of alkynes with pinacolborane at room temperature (eq 2). Alkenes, however, react slowly with pinacolborane and often require heating for 2–3 days to furnish the terminal pinacolboronates as the major regioisomer (>98%) (eq 3).

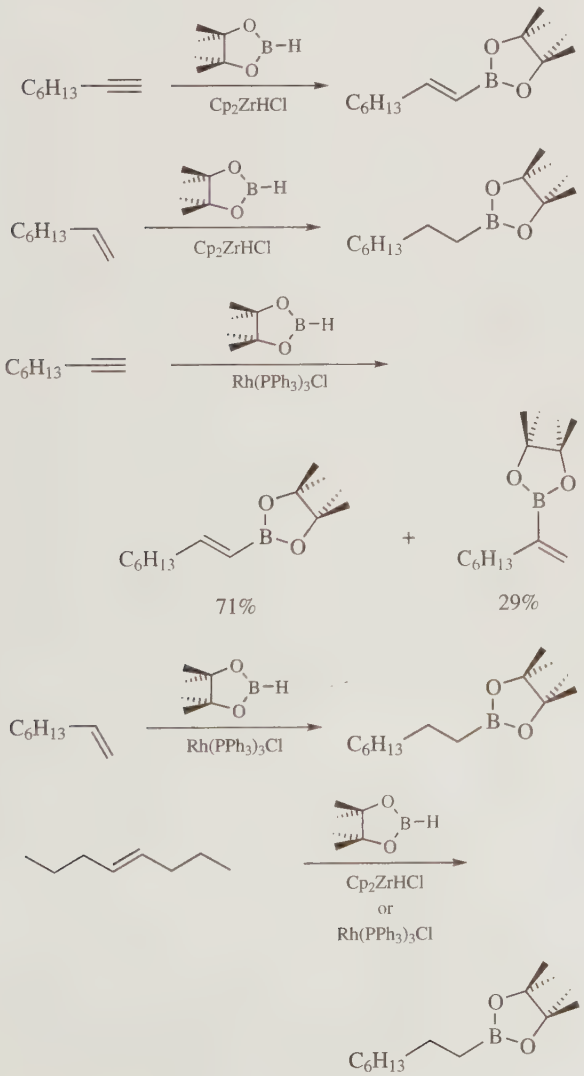


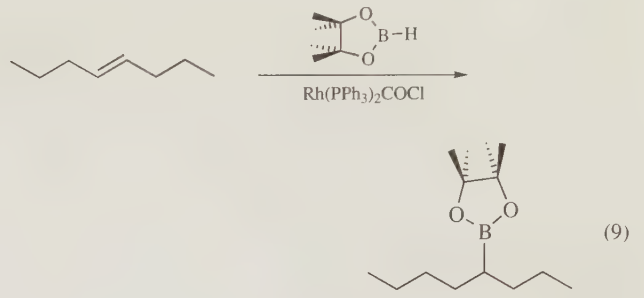
(2)

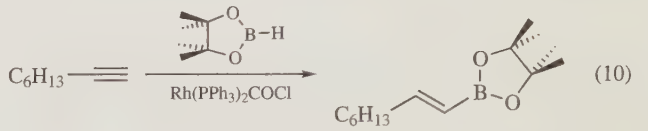


(3)

Metal-catalyzed Hydroboration. Pereira and Srebnik discovered that $HZrCp_2Cl$ is an excellent catalyst for hydroboration of alkynes[3] (eq 4) and terminal alkenes[4] (eq 5) with pinacolborane. However, $HZrCp_2Cl$ is not compatible with many functional groups and hence the effect of other catalysts, such as $Rh(PPh_3)_3Cl$ and $Rh(PPh_3)_2(CO)Cl$ was studied. Wilkinson's catalyst [$Rh(PPh_3)_3Cl$] hydroborates alkynes with very poor regioselectivity (eq 6), however, terminal alkenes undergo facile hydroboration (eq 7). Hydroboration of internal alkenes with pinacolborane in the presence of $HZrCp_2Cl$ or $Rh(PPh_3)_3Cl$ leads to isomerization furnishing the terminal pinacolboronates[4] (eq 8). Changing the catalyst system to $Rh(PPh_3)_2(CO)Cl$[4] overcomes this problem and the expected internal boronate is obtained as the major product (eq 9). This catalyst also dramatically increases the regioselectivity in the hydroboration of alkynes[5] (eq 10). Recently $Pt(dba)_2/P(2,4,6\text{-}MeO\text{-}C_6H_2)_3$ has also been reported as an efficient catalyst for hydroboration of alkynes with pinacolborane under mild reaction conditions and in good yields.[6,7]

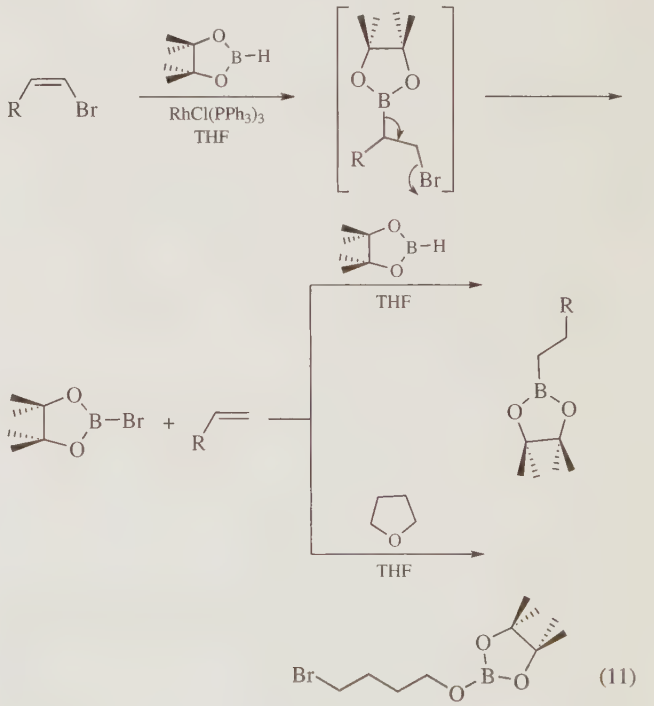






Vinylic ethers, acetals, and esters, also undergo catalytic hydroboration with pinacolborane without difficulty.

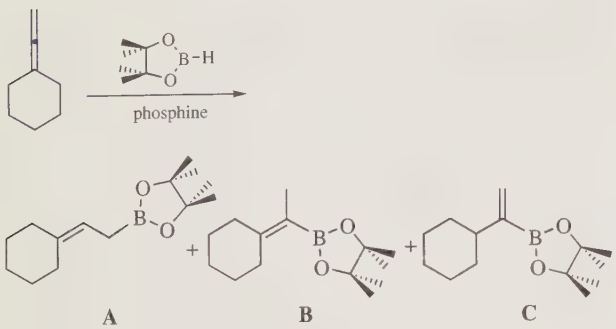
Vinyl bromides, however, do not provide the expected hydroboration product under these conditions. Instead, initial hydroboration occurs β- to the bromine atom and is followed by a fast *syn*-elimination to furnish the terminal alkene. This then undergoes hydroboration to provide the debrominated boronate. The intermediate *B*-bromopinacolborane cleaves the ether C–O bond in the solvent THF to provide 4-bromobutanol upon oxidation[4,8] (eq 11).



Hydroboration of allenes with pinacolborane provides the allylboronate or vinylboronates regioselectively depending on the bulk and basicity of the supporting phosphine ligand[6] (eq 12).

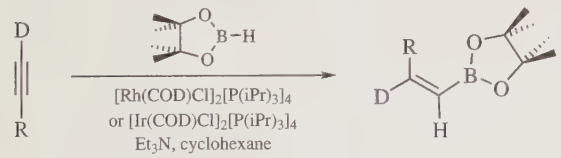
Recently Miyaura and co-workers[9] have reported a *trans*-hydroboration of terminal alkynes using $[Rh(COD)Cl]_2[P(^iPr)_3]_4$ or $[Ir(COD)Cl]_2[P(^iPr)_3]_4$ (eq 13). Mechanistic studies via deuterium labeling show that after the oxidative addition of the alkyne to the metal, the acetylenic deuterium undergoes migration to the β-carbon resulting in the formation of a vinylidene metal

complex. Oxidative addition of borane to the metal complex and 1,2-boryl migration to the α-carbon results in the stereospecific formation of thermodynamically stable alkenylmetal complex. This subsequently undergoes reductive elimination to provide the *Z*-vinylboronate as the sole product (eq 14).



(12)

	A	B	C
$Pd(C_6H_{11})_3$	56	0	44
$P[2,4,6\text{-}(OCH_3)_3C_6H_2]_3$	1	0	99
$P[C(CH_3)_3]_3$	0	100	0



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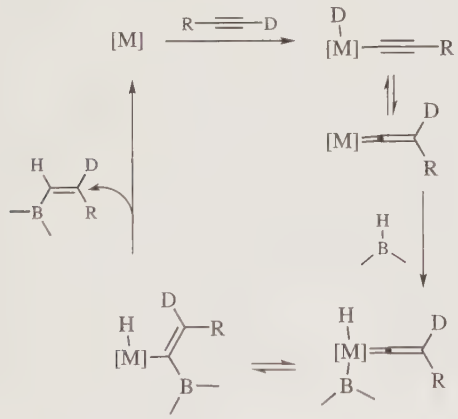
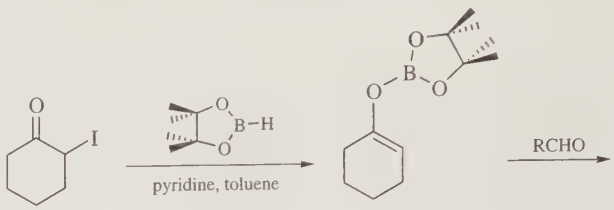
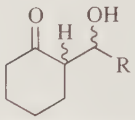


(14)

Generation of Boron Enolates. Mukaiyama and co-workers[10] have reported the formation of boron enolates from α-iodoketones by reaction with pinacolborane in the presence of a base (pyridine or Et_3N). The resulting enolborates upon reaction with aldehydes furnished the aldol products in moderate yield and diastereoselectivity (eq 15). Cyclic α-iodoketones provided higher diastereoselectivities (>98% *syn*) than the acyclic α-iodoketones (*syn:anti* 83:17). The moderate yields were ascribed to the decomposition of the highly labile boron enolates during their isolation or during their reaction with aldehydes.

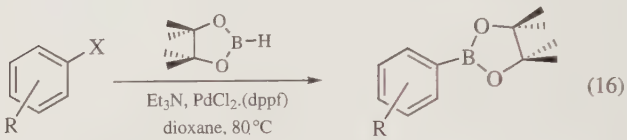
Suzuki-Miyaura Cross Coupling. Arylboronates are valuable reagents in organic synthesis owing to their widespread use in Suzuki-Miyaura cross coupling reactions.[11,12] Pinacolborane is extensively used in the borylation of aryl halides in the presence of a base (typically pyridine, Et_3N, or KOAc) and a catalytic amount of $PdCl_2$(dppf) affording arylboronates[13,14] (eq 16).





(15)

syn:anti >98:<2

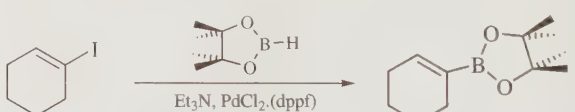


(16)

X = Br, I, OTf
R = Alkyl, Aryl, nitrile, ester, ketone, ether, amine, etc.

Pinacolborane is tolerant towards several functional groups including esters, ketones, ethers, tertiary amines, nitriles, etc. The resulting pinacolboronates are stable to air and moisture and can be purified by column chromatography. Hence the reaction has broad scope and can be used on a variety of substrates. Aryl iodides react faster than bromides or triflates. The typical solvents are dioxane, toluene, acetonitrile, and 1,2-dichloroethane. Pinacolborane reacts with polar solvents such as DMF, decomposing to pinacolatodiboron. Electron donating groups such as $-NMe_2$ increase the reactivity of the aryl halides in this reaction.

Aryl chlorides typically do not react under these conditions. However, Miyaura[15] has been able to extend the scope of this reaction to include aryl chlorides by changing the catalyst system to $Pd(dba)_2$ and PCy_3 and replacing pinacolborane with bis(pinacolato)diboron. Vinyl iodides and triflates undergo borylation with pinacolborane under similar conditions in the presence of triphenylarsine ($AsPh_3$)[16] (eq 17). Benzylic halides react with pinacolborane in the presence of $PdCl_2$, PPh_3, and *N,N*-diisopropylethyl amine[17] (eq 18). Borylation of allylic halides in the presence of $Pt(dba)_2$, $AsPh_3$, and Et_3N leads to highly regio- and stereoselective allylboronates[18] (eq 19).



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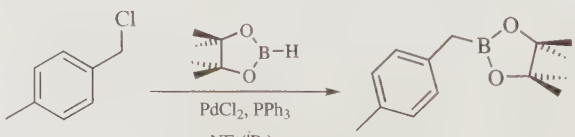
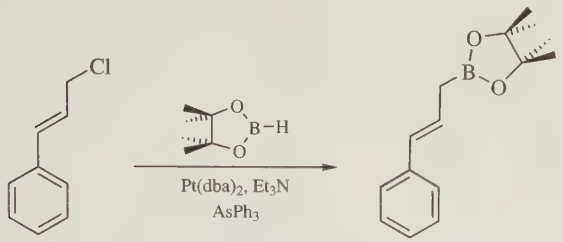
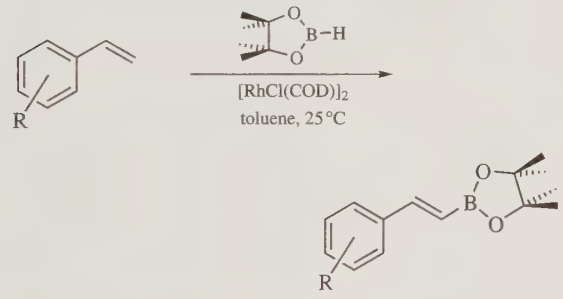


(18)

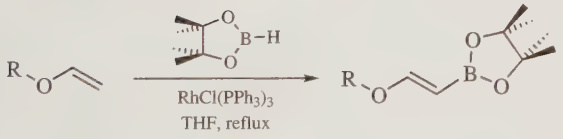


(19)

Dehydrogenative Borylation. Murata and co-workers[19,20] observed that the reaction of pinacolborane with olefins in the presence of bis(chloro-1,5-cyclooctadienylrhodium) at room temperature provides vinyl pinacolboronate. It is interesting to note that dehydrogenative borylation occurs in the presence of phosphine-free rhodium catalyst whereas olefin hydroboration is the predominant reaction with phosphine-containing rhodium catalysts such as $Rh(PPh_3)_2COCl$ and Wilkinson's catalyst (eq 20). However, Westcott and co-workers[21] were successful in achieving dehydrogenative borylation of vinyl ethers under refluxing conditions in the presence of Wilkinson's catalyst (eq 21).

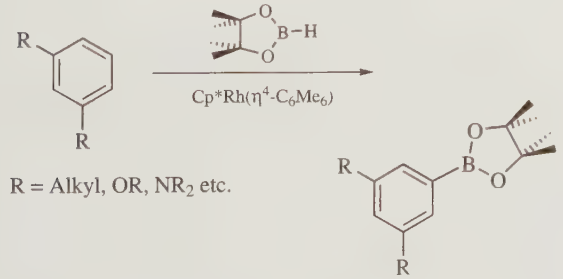


(20)



(21)

Smith and Marder reported the dehydrogenative borylation of arenes, yielding arylboronates, with pinacolborane in the presence of rhodium and iridium catalysts such as $Cp^*Rh(\eta^4\text{-}C_6Me_6)$,[22,23] $CpIrPMe_3$,[24] and $[RhClP(^iPr)_3]_2N_2$[25] (eq 22). Toluene and other methyl substituted arenes react with pinacolborane in the presence of $[RhClP(^iPr)_3]_2N_2$ and furnish benzylboronates via benzylic C–H activation and dehydrogenative borylation[25] (eq 23).



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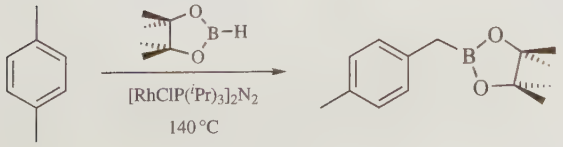

(23)

Related Reagents. Catecholborane (benzo-1,3,2-dioxaborole); bis-(pinacolato)diboron.

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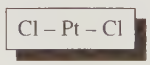
Platinum(II) Chloride[1,2]



[10025-65-7] Cl_2Pt (MW 266.00)

(catalyst used for a variety of C–X bond formations and C–C bond formations)

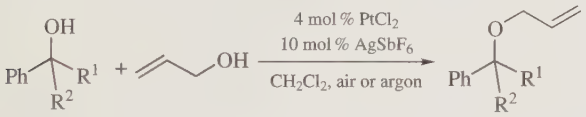
Physical Data: mp 581 °C, *d* 6.05.
Solubility: insoluble in H_2O, alcohols, toluene; soluble in CH_2Cl_2, acetone, and hot toluene (80 °C).
Form Supplied in: olive-brown powder, widely available.

Purification: $PtCl_2$ can be dried by heating at 60 °C in vacuo (0.001 atm) for 12 h.

Handling, Storage, and Precautions: keep container tightly closed under argon. Store in a cool dry, well-ventilated area. Wash thoroughly after use. Toxicological properties have not been thoroughly investigated and recorded.

Hydrosilylation. $PtCl_2$ is not a common hydrosilylation catalyst. Nevertheless, the hydrosilylation of styrene,[3] 2-phenylpropene, methyl methacrylate was studied.[4]

C–O Bond Formation. Etherification of diols is effectively achieved with cationic platinum catalysis, using a mixture of $PtCl_2$ and $AgSbF_6$.[5] Etherification of benzylic alcohols is also possible by intermolecular dehydration (eq 1). The etherification is believed to proceed via an S_N1 pathway since complete racemization with an enantiopure alcohol was observed.

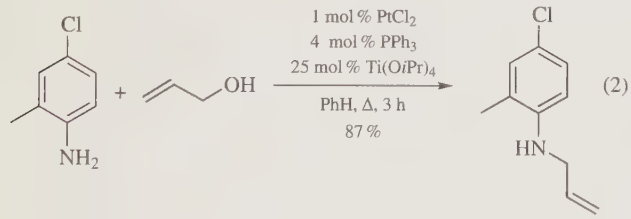


(1)

R^1 = 1° alk
R^2 = H, Me

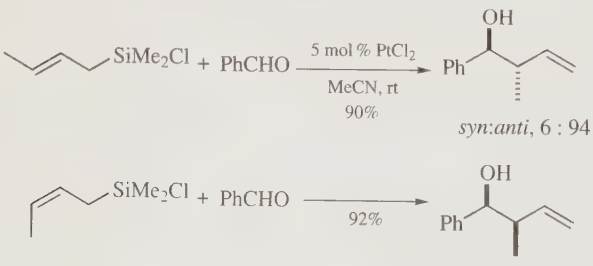
(2 equiv)

C–N Bond Formation. An isolated example of platinum-catalyzed allylation of an aniline derivative with allyl alcohol has been recently reported.[6] Presumably departure of -OTi(OiPr)$_3$ forms a Pt(0) π-allyl complex in situ, which is subsequently trapped by aniline (eq 2).



(2)

Halophilic Activation of Chlorosilanes and C–C Bond Formation via Allylation. Fürstner[7] has shown that $PtCl_2$ efficiently catalyzes addition of allyldimethylchlorosilane to aldehydes. The process is chemoselective for aldehydes since ketones, esters, nitriles, and alkenes are uneffected. Highly diastereoselective reactions can be observed with crotylsilanes as shown in (eq 3). This catalysis exploits the well-known halide affinity of Pt(II); presumably interaction of $PtCl_2$ with the chlorine atom of allyldimethylchlorosilanes increases electrophilicity at silicon.

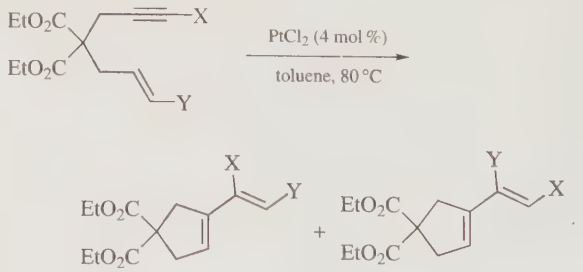


(3)

Subsequent coordination to the aldehyde carbonyl and a hetero-Cope process delivers the allyl moiety.

Activation of Alkynes. Platinum(II) salts foster electrophilic activation of alkynes, rendering the two carbon sites highly reactive toward nucleophilic attack.[8] Catalytic hydration of alkynes with $PtCl_2$ is highly effective, comparable to Zeise's dimer catalysis.[9] Compared to the Hg(II) catalysis, cleaner reaction products and higher regioselectivities, controlled by chelation, were observed. Recently, platinum(II)-catalyzed addition of alcohols to alkynes[10] and hydration of a nitrile was disclosed.[11] Applications of electrophilic activation of alkynes for C–C bond formation is shown in the following section.

Skeletal Rearrangements of Enynes. Cycloisomerization rearrangements of enynes involving carbon-carbon bond cleavage has enjoyed extensive development in the last decade, and has been recently reviewed.[12] Despite frequently similar outcomes, these transformations are distinct from enyne metathesis involving the carbene-complex-catalyzed processes pioneered by Katz[13] now employing Ru-based catalysts.[14] One of the first reports of skeletal rearrangements of an enyne partner was given by Trost in 1988[15] with a special, relatively electrophilic, palladium catalyst, tetracarbomethoxypalladacyclopentadiene (TCPC) in the presence of tri-*o*-tolylphosphite. It is noteworthy that platinum(II) complexes also trigger the skeletal rearrangement.[16] In 1994, Murai and co-workers found a highly selective skeletal reorganization of 1,6- and 1,7-enynes using $[RuCl_2(CO)_3]_2$ under an atmosphere of carbon monoxide.[17] Interestingly, this contribution mentions that other metal halides such as $[RhCl(CO)_2]$, $ReCl(CO)_5$, $[IrCl(CO)_2]_n$, $PtCl_2$, and $AuCl_3$ also effect similar rearrangements. Murai[18] introduced $PtCl_2$ as a highly versatile catalyst for various skeletal rearrangements, a finding soon confirmed by a myriad of papers describing new uses of this complex.[1,2] 1,6-Enynes or 1,7-enynes can be very efficiently transformed into vinylcyclopentenes or hexenes.[18] As illustrated in eq 4, the anomalous, metathesis product (by comparison with the expected product resulting from a carbene-complex-catalyzed process) is observed in some cases.

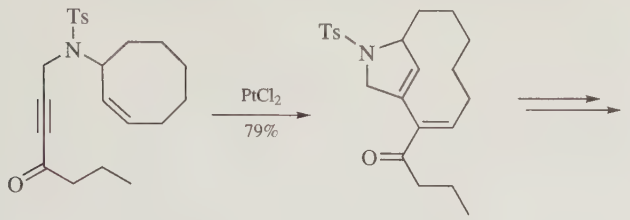


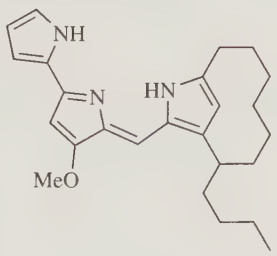
(4)

	formal metathesis product	anomalous metathesis product
X = H, Y = Ph	66%	-
X = Ph, Y = H	70%	4%
X = CO_2Et, Y = H	-	80%

This paved the way for numerous synthetic applications including notable total syntheses. Thus, the "low tech" $PtCl_2$ (and also

$PtCl_4$, $PtBr_2$, or $PtBr_4$) system as designated by Fürstner proved more versatile than Trost's electrophilic catalysts,[19] on the cyclooctene substrates of (eq 5).[20] These reactions were run on a multigram scale in the formal synthesis of streptorubine B.

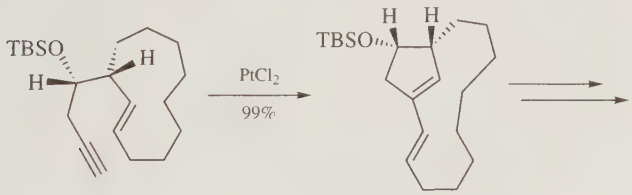


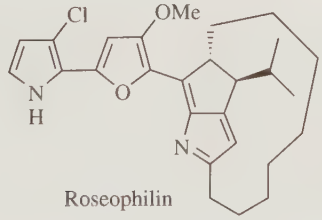


(5)

Streptorubine B

Similarly, a formal synthesis of roseophilin was devised by Trost, based on a nearly quantitative transformation of an enyne moiety into a bicyclic diene system (eq 6).[21] Recently, the related $PtBr_2$ has been shown to catalyze a sequential 1,7-enyne metathesis-aromatization reaction.[22] Rearrangement of enynes into 1-vinylcycloalkenes can be effected in ionic liquids.[23]



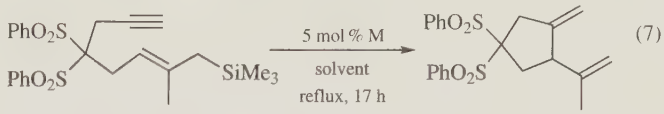


(6)

Roseophilin

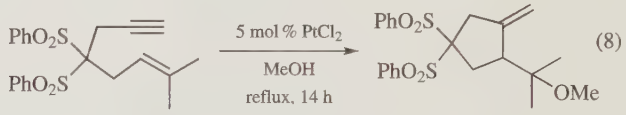
Two findings gave better insight into the mechanism of these transformations. Thus, Echavarren reported that 1,6-enynes can be converted into 1,4-dienes (Alder ene-type adducts) with a variety of metal halides (Pt(II), Pd(II), Ru(II), Ru(III), Au(III), etc.) if the alkene is part of an allylsilane (stannane) entity,[24,25] with $PtCl_2$ usually giving optimal results (eq 7).

When the TMS group is absent and the reaction carried out in methanol, platinum(II)-catalyzed alkoxycyclization takes place (eq 8).[26] This hydroxycyclization catalyzed by Pt(II) is found to be mechanistically similar to the carbohydroxypalladation reported by Genêt.[27,28] The synthetic importance of this process is that it allows simultaneous and generally stereoselective formation of both a C–O and a C–C bond from the enyne precursor.



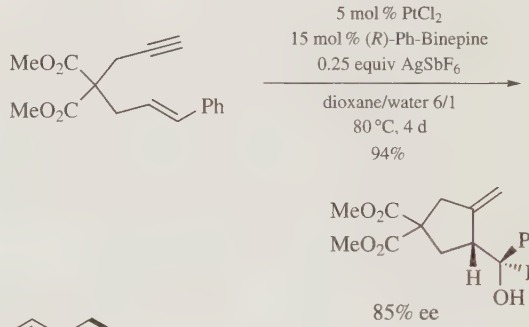
(7)

$CpRuCl(PPh_3)_2$ + 10 mol % $NaPF_6$, MeOH	92%
$RuCl_3$, MeOH	53%
$PdCl_2$, MeOH	47%
$Pd(MeCN)_4(BF_4)_2$, MeOH	82%
$PtCl_2$, acetone	94%



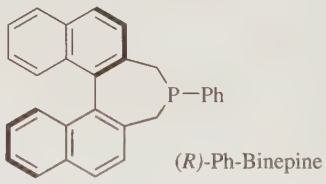
(8)

This reaction was transformed into an asymmetric process via removal of the choride ligands from the platinum-ligand coordination sphere, providing a more electrophilic metal center, thereby allowing reactions to be run at lower temperature. Currently the best ligand is the atropisomeric monophosphine (*R*)-Ph-binepine, providing ee's up to 85% (eq 9).[29] Very recently, gold(I) catalysis also appears highly versatile, with ee's up to 94% obtained using [$(AuCl)_2$(Tol-BINAP)] as precatalyst with a different enyne precursor.[30]



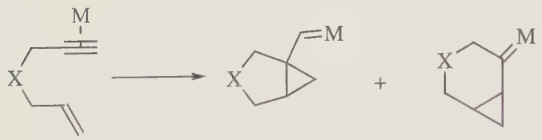
(9)

85% ee



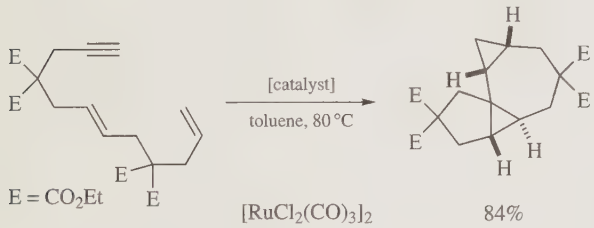
(*R*)-Ph-Binepine

These findings are consistent with cyclopropylplatina carbene intermediates originating from electrophilic activation of the alkyne by the metal. A previously postulated slipped, polarized η^1-platinum complex is not supported by DFT calculations. Instead, it is proposed that the triple bond is η^2-coordinated, triggering nucleophilic attack of the pendant olefin to give both *exo*- and *endo*-platina carbenes in a single step (eq 10).[31–35] For $X = CH_2$, the *exo*-mode is kinetically favored, in contrast to the *endo*-mode, which gives the more stable metal carbene. Closer inspection of the *exo*-intermediate reveals it to be one resonance form of a metallated "nonclassical" homoallylcyclopropylmethyl-cyclobutyl cation.[36] This enables rationalization of the mixture of classical and anomalous metathesis products.



exo-dig pathway *endo-dig* pathway (10)

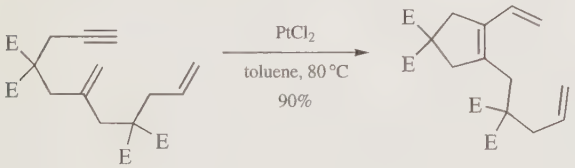
Formation of Cyclopropanes. The intermediacy of metallacarbenoid species in these skeletal rearrangements was invoked by Trost with the palladole chemistry.[37,38] Mechanistic studies by Murai employed acyclic linear dienyne systems to trap the proposed carbenoid intermediate by a pendant olefin (eq 11).[39] A remarkable tetracyclic assembly gave the unprecedented tetracyclo[6.4.0.0.^{1,9}0^{2,4}]undecane derivative as a single diastereomer. This transformation proved to be relatively general and occurred with different organometallic complexes from group eight to ten (ruthenium, rhodium, iridium) and notably $PtCl_2$. This reaction involves two cyclopropanations,[40] as if both carbon atoms of the alkyne moiety have acted as carbenes, resulting in the formation of four carbon-carbon bonds.



(11)

$[RuCl_2(CO)_3]_2$	84%
$PtCl_2$	75%
$[Rh(OCOCF_3)_2]_2$	72%
$[IrCl(CO)_3]_n$	54%

Changing the connectivity (1,1 instead of 1,2) of the central olefin provided the exocyclic diene (eq 12).

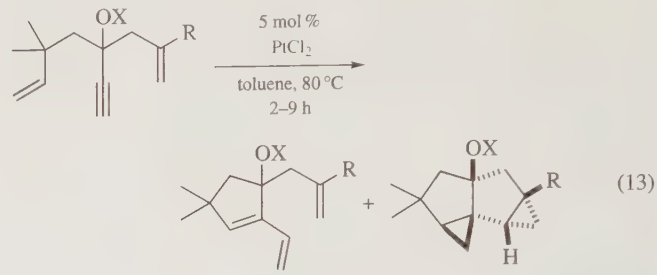


(12)

More recently, the biscyclopropanation reactivity has been observed on branched dienyne systems to diastereoselectively generate highly strained cyclopropyl-substituted diquinane frameworks (eq 13).[41] The formal metathesis product was observed as a minor product, with introduction of a methyl group on one ene segment proving detrimental to the yield.

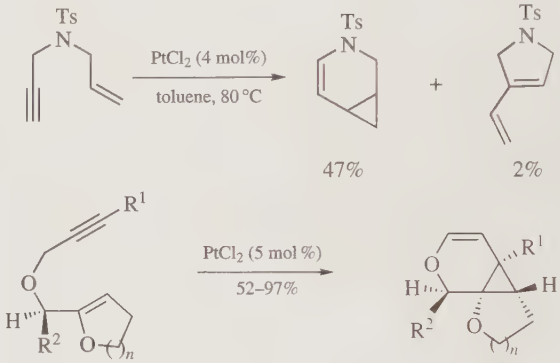
Formation of another biscyclopropane tetracyclic derivative is found in the work of Diver.[42] Cationic gold-based catalysts are also highly effective promotors of reactions resulting from an initial electrophilic activation of an alkyne, including formation of biscyclopropane tetracyclic derivatives.[43]

When X = O and likely for R = NTs (eq 10), the *endo*-mode becomes both the kinetic and the thermodynamic pathway.[33] The resulting metala carbenoid is ideally suited for a 1,2-hydride shift which installs the endocyclic double bond. Blum reported a novel $PtCl_4$-catalyzed rearrangement of allyl propargyl ethers to 3-oxabicyclo[4.1.0]heptenes along with similar transformations,[44] including propargylallylamines converted to bicyclo[4.1.0]heptenes, and polycyclic derivatives (eq 14).[32,45,46]



(13)

R = H, X = H	7%	48%
R = H, X = $SiMe_2CH_2Br$	5%	61%
R = H, X = Me		68%
R = Me, X = Me		34%



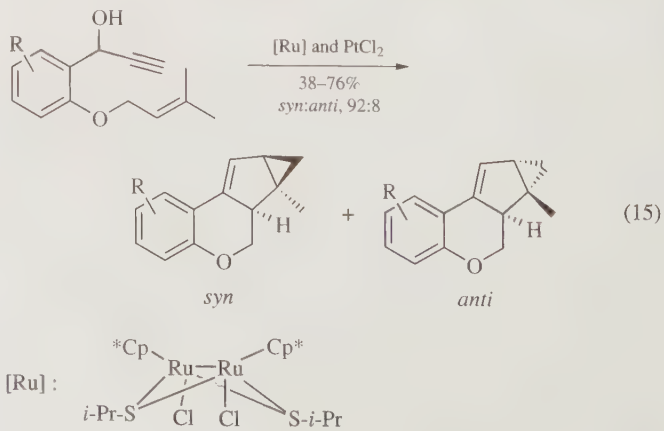
(14)

n = 1,2

R^1 = Me, Et, Ph

R^2 = Ar, cinnamyl, crotyl, i-Pr, t-Bu

The Uemura group reports intramolecular cyclization of a propargyl alcohol onto a pendant olefin gives polycyclic derivatives as a mixture of *syn* and *anti* diastereomers (eq 15).[47] An intriguing aspect of this reaction is that the catalyst is a mixture of a ruthenium and a platinum complex, each acting separately and selectively. The thiolate-bridged diruthenium complex first promotes propargylic substitution via an allenylidene intermediate,

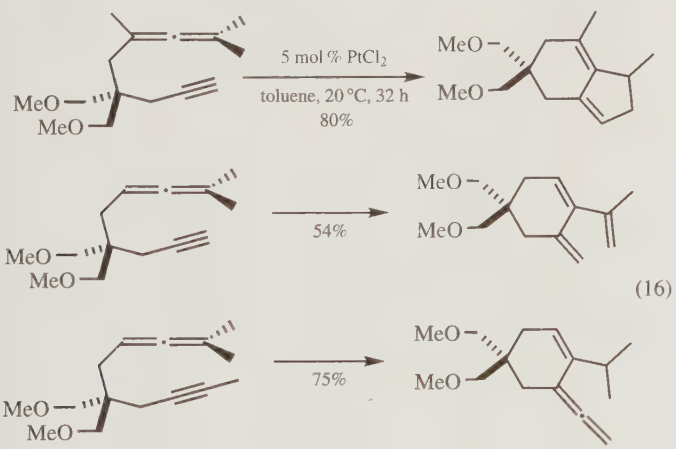


(15)

and the latter species subsequently undergoes ene reaction forming a 1,5-enyne system, followed by $PtCl_2$-catalyzed 5-*endo-dig* cyclization.

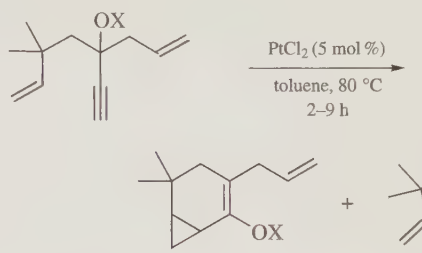
Other Nucleophiles. Nucleophiles such as enol ethers,[34] or silyl enol ethers[48] react with electrophically activated triple bonds. Dake reports synthesis of 2-azahydrindans through use of an enamine as a nucleophile.[49] The carbonyl group of 1,3-cycloalkyldiones was involved in metal-catalyzed synthesis of oxabicyclic derivatives.[50] An *ortho*-ketal[51] or amide group[52] attached to aryl alkynes can also give rearranged products. Ohe and Uemura describe catalytic cyclopropanation of alkenes via 2-furyl[53,54] or 2-pyrrolyl carbenoids[55] that originate from internal nucleophilic attack of carbonyl oxygen or imine nitrogen onto a π-alkyne complex or σ-vinyl cationic complex. Initially, group six complexes like $Cr(CO)_5$ were used. Late transition metal compounds such as $[RuCl_2(CO)_3]_2$, $[RhCl(COD)]_2$, $[Rh(OAc)]_2$, $PdCl_2$, and $PtCl_2$ also catalyze the inter- or intramolecular cyclopropanation. Related formation of furans and pyrroles from propargylic alcohols and ketones has also been achieved.[56]

Recently, Iwasawa has utilized 1,3-dienes to make diquinanes.[57] $PtCl_2$-catalyzed allene transformations have provided an intriguing panel of reactivity. Subtle modification of allenyne substitutions give contrasting results. Tetrasubstituted allenes generate the previously unknown hydrindene product, but a precursor missing a methyl at the internal position gives the classical Alder-ene product (eq 16). Introduction of a methyl on the alkyne affords an unprecedented vinylallene. This behavior compares with the work of Brummond[58] in which a cyclohexyltriene is exclusively formed from the malonate precursor with $[Rh(CO)_2Cl]_2$. Such distinct pathways between rhodium and platinum might be attributed to distinct metal geometries of the intermediate metalacyclopentenes.



(16)

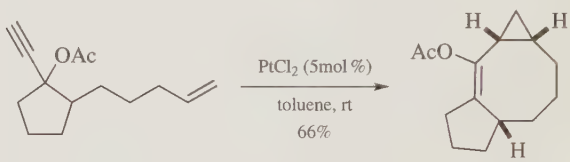
Anchimeric assistance by an *O*-acyl group followed by 1,2-migration has also been observed. This reactivity, reminiscent palladium(II)-mediated 1,3-migration of allylic acetates,[59] is a highly efficient synthesis of allylic metala-carbenoid species. First rationalized as such by Rautenstrauch in 1984,[60,61] this isomerization has served for the synthesis of cyclopentenones from 1,4-enyne systems bearing an acetate group in position 3. Access to bicyclic cyclopropyl derivatives is also revealed in the same seminal contribution. This reactivity has remained dormant for almost two decades, until it was demonstrated with simple $PtCl_2$ on the dienyne precursors of (eq 17). Worthy of note is the strikingly different behavior shown in eq 13. Recent DFT investigation of this reaction suggests two very energetically close alternatives: *endo*-cyclization followed by 1,2-migration, or 1,2-migration followed by cyclopropanation.[62]



(17)

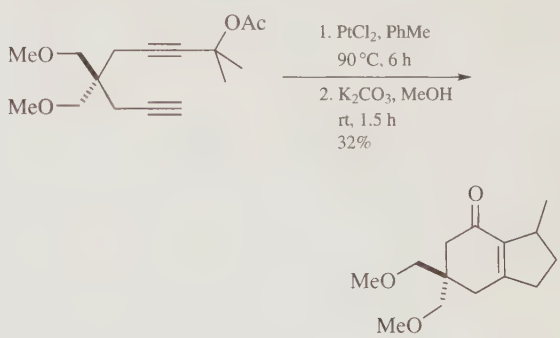
$X = COCH_3$	80%	8%
$X = p\text{-}COC_6H_4NO_2$	70%	6%

This provides access to various polycyclic derivatives, as illustrated by stereoconvergent reaction of a mixture of enyne diastereomers into a single diastereomeric tricyclic cyclooctyl ring (eq 18).[41]



(18)

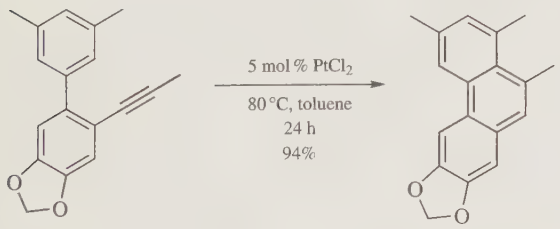
Similar access to the carane family has also been disclosed by Fürstner using $AuCl_3$[63] and Marco-Contelles with $PtCl_2$.[64] With disubstituted alkynes, 1,3-migration of the acetate gives allenylesters, which are versatile partners for [3,3] Cope rearrangements.[65] 1,5-Enynes are important precursors for preparation of perfumery agents such as sabinol[66] or sabina ketone.[67] Combining $PtCl_2$-catalyzed 1,3-*O*-acyl migration of disubstituted alkynes, with the cycloisomerization of allenynes provides bicyclic enones after methanolysis. A nice feature of concurrent tandem catalysis[68] is that it alleviates the tedious synthesis of allenyne precursors (eq 19).



(19)

Friedel-Crafts Reactions. Extension of catalysis to Friedel-Crafts alkylations has been reported.[69] A $PtCl_2$/AgOTf combination promotes intermolecular hydroarylation of ethyl propiolate.[70] An intramolecular investigation by Murai established that $PtCl_2$ or Ru(II) catalysis of electron-rich ω-aryl-1-alkynes forms dihydronaphthalenes.[71] Efficient access to phenanthrenes is shown in eq 20. Pyrroles and thiophenes are also competent substrates

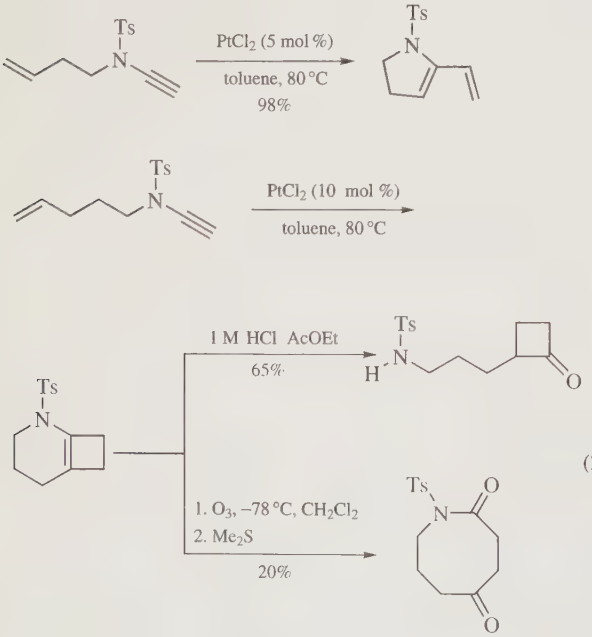
in these reactions.[72] An exhaustive study by Sames has focused on the comparison between $PtCl_2$ and $PtCl_4$ for the arene-alkyne electrophilic arylation.[73] Although $PtCl_2$ gives a satisfactory synthesis of chromenes, dihydroquinolines, and coumarins, it appears less general than $PtCl_4$, and notably more sensitive to alkyne substitution pattern. The greater reactivity of $PtCl_4$ vs. $PtCl_2$ was ascribed to a higher electrophilicity and solubility.



(20)

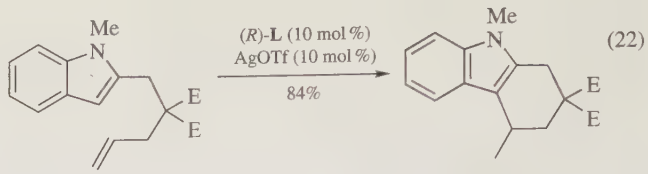
Echavarren has shown that 5-(2-furyl)-1-alkynes react with $PtCl_2$ to give phenols via a multistep mechanism involving initial nucleophilic attack of furan on the activated alkyne.[74] Based on DFT calculations, a mechanism for these transformations has been proposed.[75]

Use of Ynamides. Partners such as ynamides[76] constitute a new dimension, since the alkyne is altered in electronic and steric demands. Moreover, the direct attachment of the alkyne to a nitrogen atom provides ready accesss to nitrogen-based heterocycles. While a 1,6-enynamide gives a metathesis product, an isomerized [2 + 2] product is obtained with a longer tether. The resulting bicyclic enamide can be oxidatively cleaved to a keto-lactam or hydrolyzed to an aminocyclobutanone (eq 21). Hsung has studied intramolecular Friedel-Crafts reactions based on initial activation of an ynamide.[77]

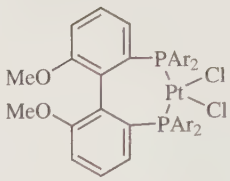


(21)

Dienes. Using $PtCl_2$ catalysis, Widenhoefer reports intramolecular alkylation of indoles with unactivated olefins, including an asymmetric version.[78]



(22)



Ar = C_6H_2 4-OMe-3,5-*t*-Bu

(*R*)-**L**

Related Reagents. $PdCl_2$; $PtBr_2$; $PtCl_4$; $AuCl_3$; $[RuCl_2(CO)_3]_2$; [IrCl(CO)$_3$]n; $AuCl(PPh_3)$.

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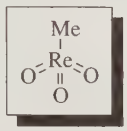
Rhenium(VII) Methyltrioxo



[70197-13-6] CH_3O_3Re (MW 250)

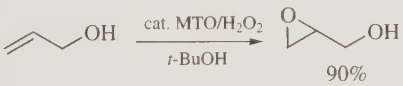
(catalyst in the hydrogen peroxide oxidation of numerous compounds, including the well-studied epoxidation of alkenes.[5] Catalyzes 1,3-allylic transpositions,[6] the metathesis of alkenes[7,8] and aldehyde olefination[9,10])

Physical Data: thermally stable white solid, mp 111°C. Hydrolyzed rapidly in basic aqueous solutions but much slower in acidic solutions. Deactivated under photolysis conditions.

Solubility: highly soluble in virtually any solvent from pentane to water.

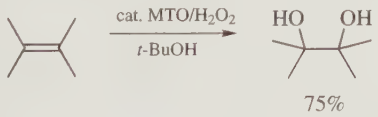
Form Supplied in: commercially available from Aldrich and Fluka.

Epoxidation of Alkenes.[5] In 1991, Hermann demonstrated that alkenes are efficiently converted to the corresponding epoxide using methyltrioxorhenium (MTO) as the catalyst and hydrogen peroxide as the co-oxidant.[11] A range of alkenes undergo epoxidation at ambient temperatures with a catalyst loading of 0.1 to 1 mol% (eq 1).



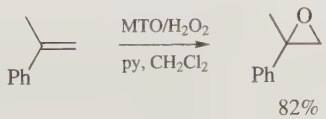
(1)

However, serious limitations of the original procedure included ring opening or oxidative cleavage of the newly formed epoxide, a consequence of the acidic nature of the rhenium catalyst (eq 2).



(2)

The addition of tertiary amines, usually pyridine, has been found to be successful in both suppressing such side reactions and substantially increasing the rate of epoxidation.[12] The reaction is remarkably general for efficient epoxidation of a number of alkenes (eq 3–6).



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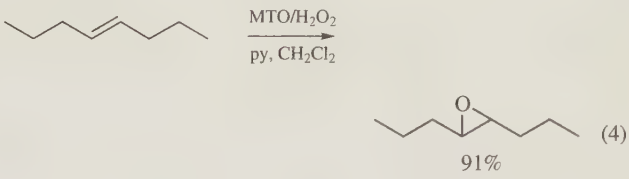

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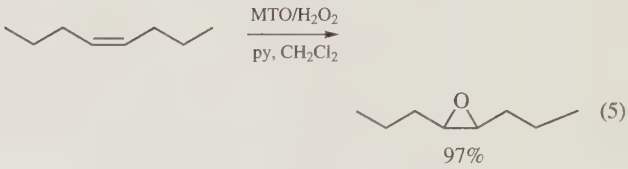
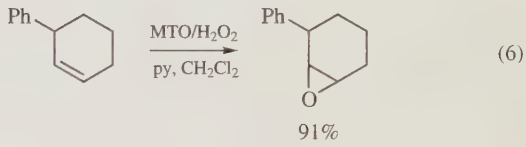
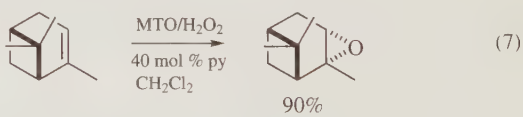


(5)



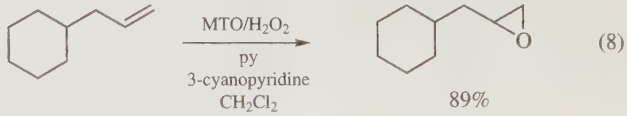
(6)

It must be stressed that the amount of amine added to the MTO-catalyzed epoxidation reaction is critical. The addition of tertiary amines was found to significantly inhibit catalyst activity at low concentrations. Studies have shown that the lifetime of the catalyst is intrinsically linked to the amount of pyridine present and concentrations of 3 mol% or more of pyridine in nitromethane or dichloromethane are required for high conversions of alkenes. An example that highlights this not well-understood phenomena is the epoxidation of monoterpenes (eq 7).[13] A relatively high mol% of pyridine had to be employed in order to produce high yields. Even higher mol% of pyridine significantly decreased the yield. The tertiary amine additives are thought to play a crucial role in preventing decomposition of the epoxide products, prolonging the lifetime of the catalyst in solution and increasing the rate of epoxidation. An extensive amount of work on the equilibria and kinetics of amine additives in MTO-catalyzed epoxidation reactions has been undertaken.[14]

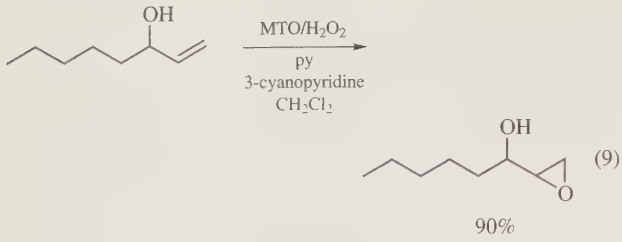


(7)

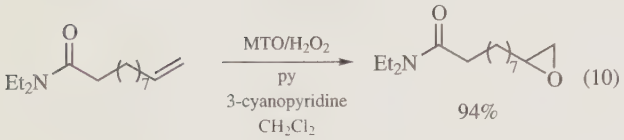
Other tertiary amines have been utilized in the MTO-catalyzed epoxidation reactions. Pyrazole was also found to be an effective additive for a variety of alkenes.[15] The use of an equimolar amount of 3-cyanopyridine and pyridine as an additive for the epoxidation of terminal alkenes has been found to be high yielding with little-to-no destruction of the resulting epoxide detected.[16,17] This system is effective for the epoxidation of a range of alkenes, in particular alkenes of relatively low reactivity (eq 8-10). Electron deficient alkenes did not perform well under such epoxidation conditions.



(8)

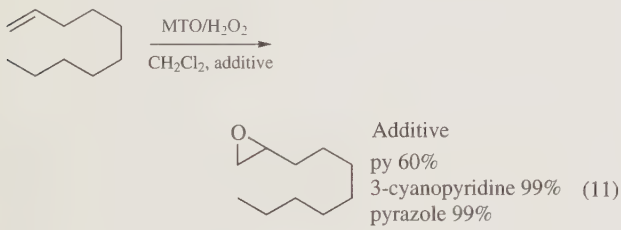


90% (9)

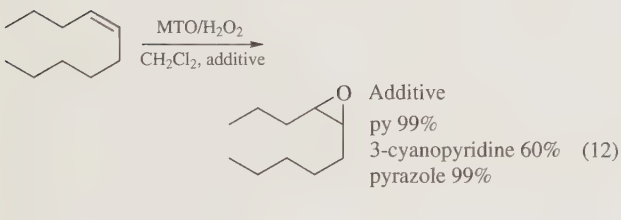


94% (10)

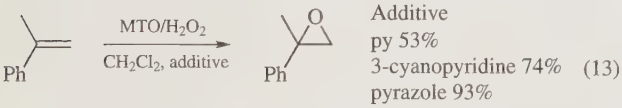
A comparative study of the effectiveness of various amine additives has been undertaken (eq 11-13).[18]



(11)



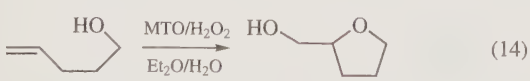
(12)



(13)

Although pyridine is less expensive than pyrazole, the latter seems to be more general. However, the choice of amine additive remains unclear when applying this methodology to new substrates and, although somewhat predictable, may be a matter of experimental trial and error.

Treatment of homo-allylic alcohols with catalytic MTO and hydrogen peroxide results in epoxidation followed by hydroxyl lactonization to yield substituted tetrahydrofurans in high yield (eq 14).[19] Alcohols, acids and esters all undergo such domino epoxidation/cyclization reactions.[20]



(14)

The epoxidation process has several distinct advantages over existing methodology. The epoxidation is carried out under neutral (non-acidic) conditions and does not suffer from unwanted side reactions. All the reagents used in the MTO-catalyzed epoxidation are easily handled and commercially available. In comparison, *meta*-chloroperbenzoic acid (*m*-CPBA) is only available as a mixture with the acid and cannot be purified safely due to its explosive nature. DMDO needs to be prepared and titrated directly prior to use.

Typical Procedure for the Epoxidation of Alkenes.[17] The alkene (10 mmol) was dissolved in dichloromethane (3 mL, 2 M concentration in alkene) to which the amine (1.2 mmol) and MTO (0.05 mmol) was added. Then 30% hydrogen peroxide (20 mmol) was added and the reaction vigorously stirred whereupon the solution turns yellow, indicative of the formation of the active catalyst. After 1h a catalytic amount of manganese oxide was added (to destroy any remaining peroxides in solution). When evolution of oxygen had stopped, the layers were separated, the aqueous layer extracted with dichloromethane (3×25 mL) and the combined organic extracts dried (Na_2SO_4) and concentrated under reduced pressure.

Other systems have been developed in the formation of acid-sensitive epoxides. Adam has developed an MTO-catalyzed epoxidation process using a urea/hydrogen peroxide (UHP) adduct.[21] Although this methodology allows for the isolation of some acid-sensitive epoxides, other alkenes, such as α-methylstyrene, gave significant amounts of the corresponding 1,2-diols and yields in many cases were only modest.

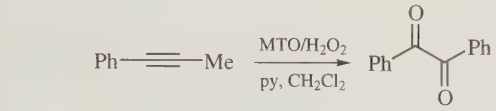
Sodium percarbonate (the so-called 'solid form' of hydrogen peroxide) has been utilized in the MTO-catalyzed epoxidation.[22] Although the use of sodium percarbonate offers no improvement in performance, it uses a safer and more easily handled co-oxidant that may prove to have application on an industrial scale. Trifluoroethanol has been used as the solvent in the MTO-catalyzed reaction of alkenes and has shown enhanced rates of epoxidation for a variety of alkenes at low catalyst loading (0.1 mol%).[23] Unfortunately the lack of solubility of non-polar alkenes in such a fluorinated solvent remains a problem. Epoxidation of alkenes in an ionic liquid has been reported and the use of no organic solvents has possible industrial applications in a more eco-friendly process.[24] A limitation of this process is once again the low solubility of certain alkenes in an ionic liquid. For example, 1-decene showed poor solubility in such a system which manifested itself in a modest yield of 46%. MTO has been supported on a silica tether allowing for epoxidation of alkenes under environmentally benign conditions.[25] Although such a system has much promise the silica supported MTO has lower reactivity in comparison to its homogeneous partner.

Regio- and Diastereoselectivity. Unlike many other transition metal-catalyzed epoxidation reactions, little-to-no diastereoselectivity is usually detected in the MTO-catalyzed epoxidation of allylic alcohols.[21,26] An extensive comparative study has been undertaken showing that metal alcoholate binding does not apply in MTO-catalyzed epoxidation reactions.[27] This observation tends to suggest that a rhenium peroxo complex is the active oxidant. Computational experiments have demonstrated that the rhenium *bis*(peroxo) complex (probably the hydrated form) is the active species in the MTO-catalyzed epoxidation of propenol.[28]

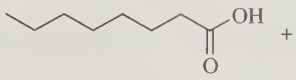
Oxidation of Alkynes. The MTO/hydrogen peroxide oxidation of alkynes has been studied.[29] Internal alkynes yield predominantly diketones (eq 15), whilst terminal alkynes yield the corresponding acid or esters, depending on the solvent employed (eq 16).

Baeyer-Villiger Oxidation. Oxidation of cyclic and acyclic ketones to the corresponding lactones and esters has been achieved. For example, cyclobutanone is converted to the

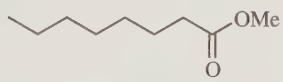
corresponding lactone under the usual MTO/hydrogen peroxide conditions in almost quantitative yield in less than 1 h.[30] The scope of this reaction has been explored.[31] γ-Butyrolactones were obtained in high yield and regioselectively by an MTO-catalyzed hydrogen peroxide Baeyer-Villiger oxidation (eq 17).



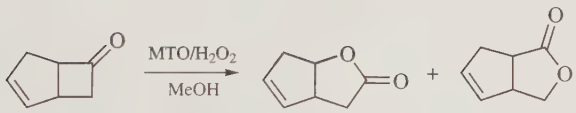
79% (15)



18%



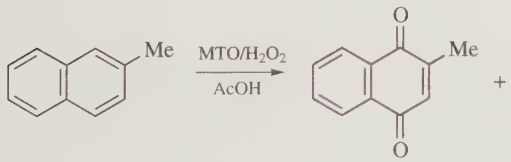
81% (16)



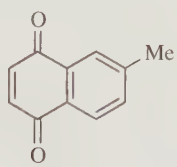
87% 13% (17)

Noteworthy is the chemoselectivity of the process - the oxidation can even be done in the presence of alkene moieties.

Aromatic Oxidation. The oxidation of aromatic groups to quinones is another facet of the MTO-catalyzed oxidation reactions with hydrogen peroxide and is of particular importance in the production of vitamin K_3 (eq 18).[32] A highly acidic solution with a high concentration of hydrogen peroxide is essential. The reaction is both remarkably high yielding and selective.

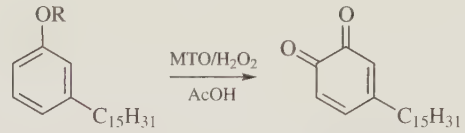


Vitamin K_3



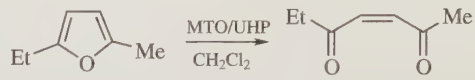
7:1; 67% (18)

An efficient synthesis of *ortho*- and *para*-benzoquinones of cardanol derivatives has been described using a similar oxidative process (eq 19).[33] Regioselectivity depends upon the nature and substitution pattern of the aromatic ring.



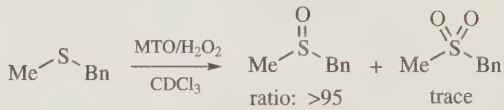
75% (19)

It has been shown that furan derivatives can be oxidized to the corresponding enediones using MTO and urea/hydrogen peroxide (eq 20).[34] Yields were high in all cases.



87% (20)

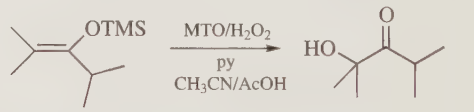
Oxidation of Sulfides. The MTO/hydrogen peroxide system effectively oxidizes sulfides to the corresponding sulfoxides (eq 21).[35,36]



ratio: >95 trace (21)

Further oxidation to the sulfone was found to be very slow in comparison to sulfide oxidation, and could be achieved on addition of a further equivalent of hydrogen peroxide. Thioketones have been oxidized in a similar fashion to yield ketones with expulsion of sulfur dioxide.[37] Symmetrical disulfides have been oxidized to the corresponding thiosulfinates, thiosulfonates, and sulfonic acids.[38]

Oxidation of Silyl Compounds. MTO-catalyzed oxidization of silyl enol ethers with hydrogen peroxide yields α-hydroxyketones in high yield.[39] The reactions were conducted with pyridine as the amine additive in acetic acid (eq 22).



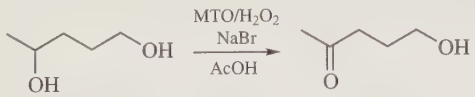
95% (22)

It is thought that the acid lowers the basicity of the solution increasing catalyst lifetime. The addition of acid alone resulted in total hydrolysis of the silyl-enol ether. Methyl trimethylsilyl ketene acetals undergo oxidation using the anhydrous MTO/UHP system,[21] yielding α-hydroxyesters in high yield for a number of substrates (eq 23).[40]

95% (23)

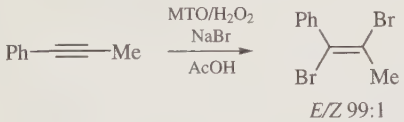
Oxidation of triorganosilanes to silanols has been achieved by treatment with MTO/UHP.[41] High conversions and excellent selectivity over disiloxane products were obtained. Of particular interest is the transformation of an optically active silane to its corresponding silanol with almost complete retention configuration via oxidative insertion.[41]

Oxidation and Bromination of Alcohols. Although the oxidation of alcohols by hydrogen peroxide alone is negligible, catalytic amounts of bromide ions greatly enhance the rate of MTO-catalyzed oxidation of alcohols with hydrogen peroxide.[42] Interestingly, a secondary alcohol has been selectively oxidized in the presence of a primary alcohol (eq 24).[42]



(24)

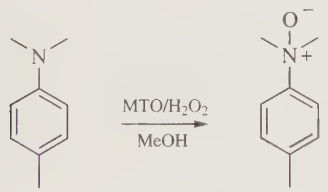
Under similar conditions, acetylene and phenols were brominated in quantitative yields (eq 25).[42] In the case of the dibromination of acetylene derivatives *E/Z* selectivity was high at high bromide ion concentrations.



(25)

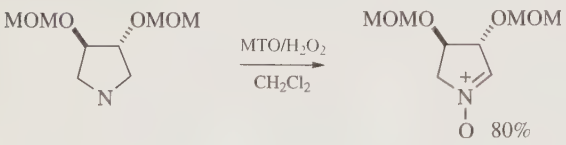
Oxidation of Phosphines, Arsenides, and Stannanes. Under standard MTO-catalyzed oxidation conditions with hydrogen peroxide, tertiary phosphines, triphenylarsine, and triphenylstibene were all efficiently oxidized.[43] A detailed account of the rates of reactions of these oxidative processes has been reported which supports a mechanism that allows for nucleophilic attack of the substrate at the rhenium peroxide species.[43]

Oxidation of Nitrogen-Containing Compounds. Various substituted aniline derivatives have been oxidized under MTO/hydrogen peroxide conditions in good yield to the corresponding *N*-oxide derivatives (eq 26).[44]



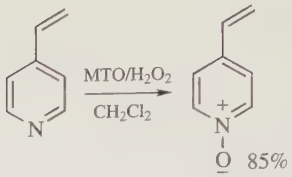
(26)

Nitrones are formed upon MTO/hydrogen peroxide oxidation of secondary amines (eq 27).[45]

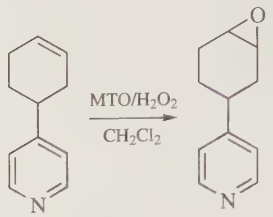


(27)

In the same manner, pyridine derivatives are oxidized to their respective *N*-oxides in good yield.[46] Noteworthy is that *N*-oxidation, and not epoxidation, was observed when treating the substrates with MTO/hydrogen peroxide (eq 28); non-conjugated systems under such oxidative systems gave epoxides in preference to *N*-oxidation (eq 29). No degradation of the MTO catalyst was seen on *N*-oxidation, an observation that is not paralleled in the MTO-catalyzed epoxidation of alkenes.

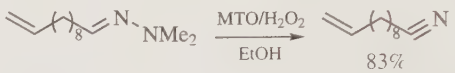


(28)



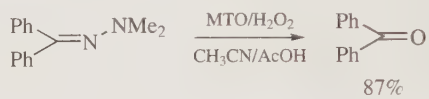
(29)

N,N-Dimethyl hydrazones, derived from aldehydes, are efficiently oxidized to the corresponding nitriles in high yield (eq 30).[47,48] A number of examples have been reported.



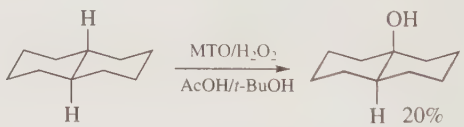
(30)

Interestingly, hydrazones derived from ketones were found to yield the corresponding ketones (eq 31).[49]

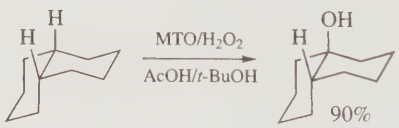


(31)

Oxidative Insertion. MTO has been found to catalyze oxidative insertion of remote C–H bonds in the presence of a large excess of hydrogen peroxide.[50] This intriguing observation has been applied to a number of different hydrocarbons. Moreover, the reactions are stereospecific, as exemplified in the case of *cis*- and *trans*-decalin (eq 32 and 33).



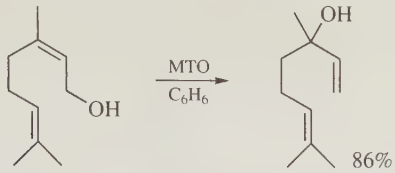
(32)



(33)

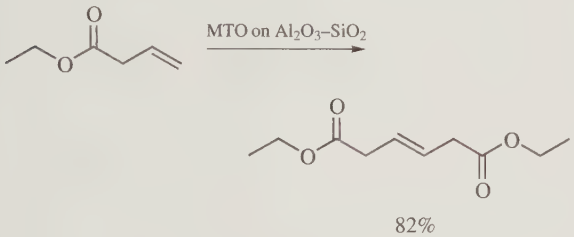
Dehydration, Amination, and Disproportionation of Alcohols. Ether formation, dehydration and disproportionation reactions catalyzed by MTO has been carried out.[51] Yields were found to vary dramatically depending upon the substrate. These reactions have limited synthetic value and at present offer no advantages to existing technologies in each of these areas.

1,3-Allylic Transpositions. MTO is an effective catalyst in the isomerization of allylic alcohols. A variety of allylic alcohols have been tried and yields were generally high (eq 34).[6] Side reactions included condensation and dehydration of the product, processes that have been reported by the same group.[6]



(34)

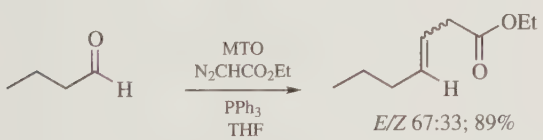
Metathesis. MTO is active in alkene metathesis when activated by a co-catalyst such as $S_4N_4/AlCl_3$, or supported on silica or alumina.[7,8] In the original communication of Hermann et al.,[7] the self-metathesis of allylic halides, silanes and unsaturated carboxylates and nitriles was achieved using MTO/Al_2O_3-SiO_2 as the catalytic system (eq 35).



(35)

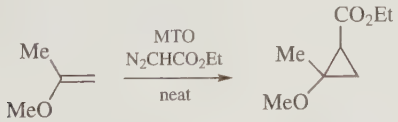
At present, the metathesis reactivity of MTO has not been developed as a synthetically viable reagent in comparison to the well established Schrock and Grubb catalysts available.

Formation of Alkenes from Aldehydes. Treatment of various aldehydes with diazoalkenes and tertiary phosphines in the presence of MTO gave the corresponding coupled product in high yield.[9,10] *E/Z* selectivity was low in most cases (eq 36). An obvious advantage over Tebbe-Grubbs-type coupling reactions is that only a catalytic amount of the organometallic coupling reagent is required.

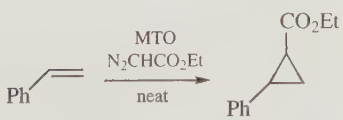


(36)

Cyclopropanation and Aziridination. MTO catalyzes both the reactions of ethyldiazoacetate and organic azides with alkenes and carbonyl compounds, respectively, to yield cyclopropanes in good yield.[52] A number of examples of the cyclopropanation of alkenes have been reported under mild conditions (eq 37 and 38). The reaction is remarkably general to differing steric and electronic environments of the alkene.

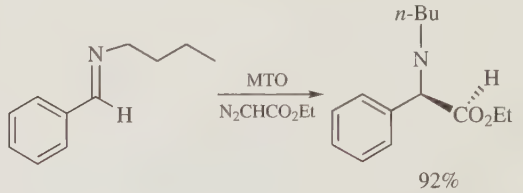


(37)



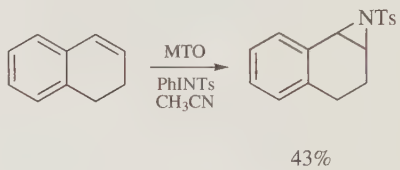
(38)

The analogous reaction with imines or carbonyl compounds results in the corresponding aziridines or epoxides respectively (eq 39).[52]



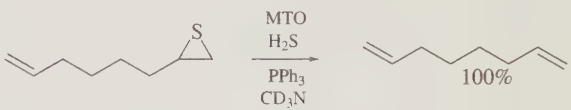
(39)

MTO-catalyzed aziridination has also been achieved from alkenes utilizing [*N*-(*p*-tolylsulfonyl)imino]iodobenzene as the nitrene transfer reagent (eq 40).[53] Although yields at present are moderate to poor the reaction holds much promise for effective aziridination of alkenes.



(40)

Miscellaneous Reactions. MTO catalyses the formation of alkenes from *epi*-sulfides with triphenylphosphine (eq 41).[54] The reaction is general and high yielding at room temperature.



(41)

MTO also catalyzes the trimerization of aldehydes - one of the three oxygen atoms in the product is derived from MTO (eq 42).[55]

(42)

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Andrew Hudson
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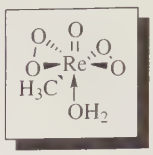
Rhenium(VII) Aquamethyloxodiperoxy



[152385-10-9] CH_5O_6Re (MW 299.25)

(reagent used as oxidation catalyst for a wide variety of substrates)

Physical Data: yellow powder; mp 56 °C; $pK_a = 3.8$.

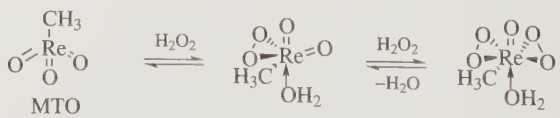
Solubility: soluble in water, alcohols, ethers, toluene, and most organic solvents.

Form Supplied in: the reagent is not available commercially, however, a solution of this reagent is readily obtained by addition of methyltrioxorhenium (MTO) to a solution of hydrogen peroxide (anhydrous or not). Both reagents can be found commercially. The mixture results in a yellow solution which is stable for weeks below ca. 0 °C and thus needs not be freshly prepared.

Purification: the isolated $CH_3ReO(O_2)_2 \cdot H_2O$ can be purified by sublimation at 25 °C under vacuum of ca. 0.001 Torr. However, a purification step is not needed as MTO/H_2O_2 is a catalytic system and this reagent is formed in the reaction mixture.

Handling, Storage, and Precautions: isolated organorhenium peroxo complexes are explosive. Solutions of H_2O_2 in flammable solvents can be considered dangerous. A general rule for safe handling is to limit the concentration of H_2O_2 to 20 wt% of the reaction mixture. There is no data about the toxicity and health risks of methyltrioxorhenium (MTO). The use of gloves, coat, and safety glasses is recommended when doing reactions with MTO/H_2O_2.

Epoxidation of Alkenes. The breakthrough in the application of rhenium compounds for synthetic organic reactions came in 1987 when Herrmann et al.[1] developed an efficient synthesis for methyltrioxorhenium (MTO), starting from dirhenium heptoxide and tetramethyltin. This synthetic pathway made it possible to conduct the synthesis of MTO on a multigram scale in few hours. This synthetic pathway is now optimized and MTO can be obtained in nearly quantitative yield by addition of perfluorinated carboxylic acid anhydrides[2] or trichloroacetic anhydride[3] to the former reaction mixture. MTO is an air and water stable colorless solid that sublimes at 65 °C/0.001 Torr.[2] MTO reacts with H_2O_2 with the formation of monoperoxo- and diperoxo-organorhenium(VII) species (eq 1).[4]

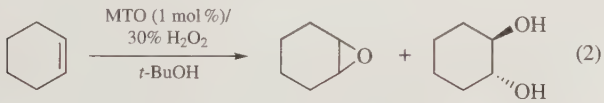


(1)

The monoperoxo-organorhenium(VII) species has never been isolated, however, density functional calculations have indicated that the monoperoxo species is also active for oxidation.[5–7] On the other hand, the diperoxo-organorhenium(VII) was isolated from a solution of MTO in an excess of H_2O_2 and its structure determined by X-ray crystallography.[8] The diperoxo-organorhenium(VII) species confers a characteristic yellow color

to the solution and is most reactive towards oxygen-accepting substrates.[6,7] This species is also the most abundant in the equilibrium, suggesting that it is the thermodynamically more stable peroxo complex.[8] One of the earlier applications of MTO in organic synthesis was to oxidize olefins to epoxides and diols using hydrogen peroxide.[9]

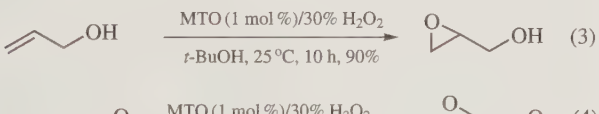
Herrmann et al.,[9] in their pioneering work, showed that the system MTO/H_2O_2/*t*-BuOH is quite active in the oxidation of alkenes to epoxides and diols. Besides *t*-BuOH, solvents such as tetrahydrofuran, ethyl acetate, toluene, and water may be used.[9] This reaction system usually operates at room temperature with 0.1 to 1 mol % MTO with respect to the alkene and generally results in high conversions into epoxide, but a significant amount of *trans*-1,2-diol is often formed via ring opening of the epoxide due to the intrinsic Lewis acidity or simply by protonation of the epoxide. Temperature control is essential for reactive olefins because of the high catalytic activity (eq 2).[9]



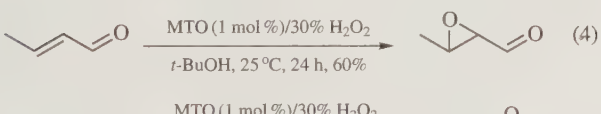
(2)

82 °C, 0.1 h	3%	97%
10 °C, 5 h	90%	10%

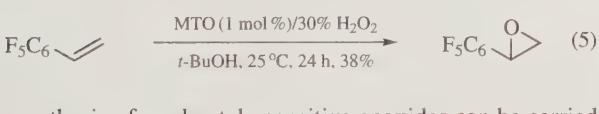
The presence of electron-withdrawing groups on the substrates makes the reaction significantly slower than when nucleophilic alkenes are used. However, good yields for epoxides can be achieved when prolonging the reaction time and adjusting the temperature (eqs 3–5).[9]



(3)

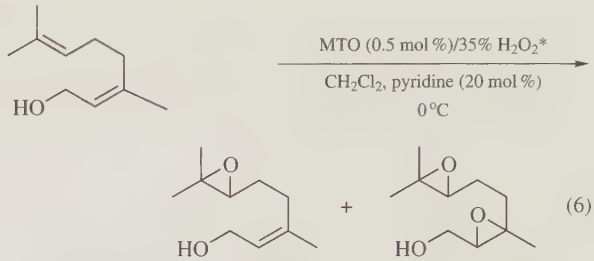


(4)



(5)

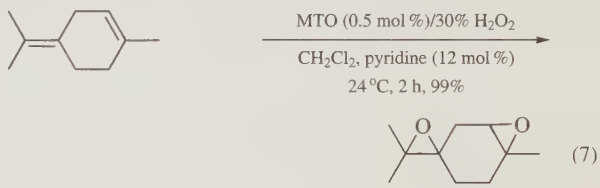
The synthesis of moderately sensitive epoxides can be carried out by using the biphasic MTO/H_2O_2-H_2O/CH_2Cl_2 system, in which the epoxides are separated from the H_2O_2-H_2O phase, reducing the formation of by-products such as *trans*-1,2-diols.[10] Sharpless and co-workers[11] discovered that it is possible to enhance the MTO/35% H_2O_2/CH_2Cl_2 system through addition of 12 mol % of pyridine, which acts both by protecting the epoxide products and through enhancing catalyst activity. The origin of the rate-improving effect is still not fully understood, but several observations of the reaction indicate that pyridine or pyridine derivatives play important roles as phase transfer catalysts, transporting the peroxo complexes of MTO from the aqueous layer to the organic phase.[12,13] Jacobs et al.[14] used the MTO/H_2O_2/aromatic amine system for the epoxidation of a variety of terpenes with high selectivity for epoxides, e.g., α-pinene, which is prone to isomerization, solvolysis, and rearrangement reactions with Lewis and Brønsted acid catalysts, is epoxidized in 90% yield using a two-phase mixture CH_2Cl_2/pyridine (12 mol %) and 35% H_2O_2. Depending on the appropriate choice of solvent, temperature, and cocatalyst, the reaction may be directed towards single or double epoxidation, or directly towards a rearranged product.[14] The primary product from nerol (eq 6) is the 6,7-epoxide, with negligible aldehyde production, proving the great preference for epoxidation.[14,15]



(6)

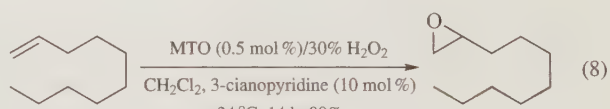
* 1.1 equiv H_2O_2	78%	12%
* 1.4 equiv H_2O_2	11%	61%

The facile bis-epoxidation of α-terpinolene (eq 7) is surprising due to its unique ability to form acid-sensitive epoxides in nearly quantitative yield.[16]



(7)

Sharpless and co-workers[16] studied additives other than pyridine, such as 3-cyanopyridine and pyrazole, and concluded that pyrazole is an effective additive for most acid-sensitive epoxides. Thus, in most cases, the addition of either pyridine (12 mol %) or pyrazole (12 mol %) will result in the same outcome; pyridine, however, is generally preferred since it is much less expensive and commonly available.[16] Terminal (eq 8) and *trans*-disubstituted alkenes (eq 9) are olefins of lower reactivity; however, they can be efficiently converted to their corresponding epoxides using either 3-cyanopyridine or pyrazole as additives (for *trans*-disubstituted alkenes only 2 mol % of additive is required). Nonaromatic nitrogen bases are found to reduce the catalytic performance.[5]



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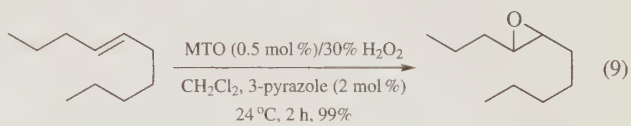
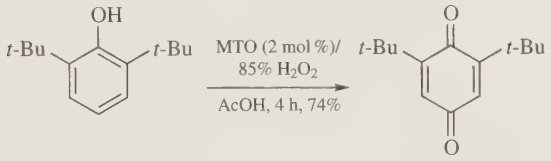


(9)

Higher selectivity for epoxide can be achieved by using of anhydrous H_2O_2 in form of the urea-H_2O_2 complex (UHP) (*see* rhenium, methyloxodiperoxo).[3,17]

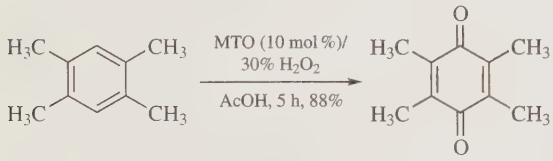
Oxidation of Phenols and Naphthols. Phenols and naphthols can be readily oxidized to quinones with high yields and easy work-up using the MTO/H_2O_2 system.[18–20] Typically the oxidation is done in acetic acid using 2 mol % of MTO. The use of concentrated hydrogen peroxide (85%) is interesting as water retards the MTO/H_2O_2/AcOH system in this reaction.[19] Alternatively, commercially available 35% H_2O_2 in acetic anhydride can be employed. As expected from the electrophilic MTO/H_2O_2/AcOH

oxidant, the more electron-rich phenol is oxidized at a higher rate, as expressed by the extent of its conversion.[18] This can be seen in the oxidation of 2,3,6-trimethylphenol compared to nonsubstituted phenol, for which under identical conditions, a reaction time of 4 h is necessary to obtain 85% conversion compared to 100% for the 2,3,6-trimethylphenol after 2 h.[18] The oxidation of 2,6-dialkyl-substituted phenols is not sensitive to steric effects of the alkyl substituents (eq 10).[18]



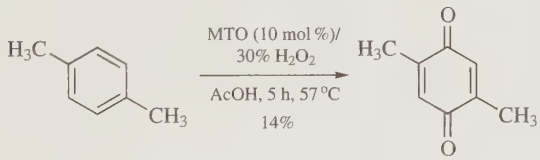
(10)

Oxidation of Alkyl Arenes. Alkyl-substituted arenes are oxidized to *p*-benzoquinones using the MTO/H_2O_2/AcOH system.[21] This oxidation is quite selective and oxidation of the methyl side chain is usually not observed (eq 11).



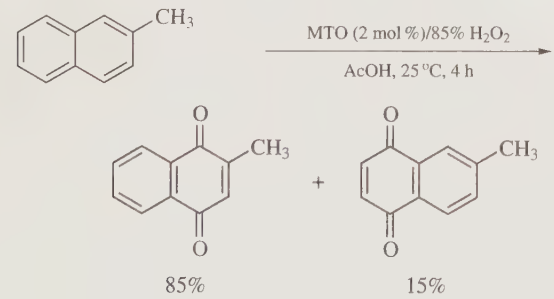
(11)

It is found that high conversions are difficult to obtain for less-substituted arenes (eq 12). The oxidation of C–H arene bonds is carried out using a large excess of H_2O_2, ca. 20-fold, and a high loading of MTO, ca. 10 mol %. These more severe conditions contrast with the ones used for hydroquinone and phenol oxidation with MTO/H_2O_2.[18–22]



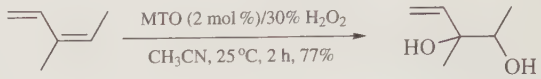
(12)

Interestingly, MTO/H_2O_2/AcOH efficiently oxidizes 2-methylnaphthalene preferentially to 2-methyl-1,4-naphthoquinone (vitamin K_3), using both a low excess of H_2O_2 and a low loading of MTO. The high regioselectivity is particularly noteworthy, since the isomeric 6-methyl-1,4-quinone is formed in only 15% yield (eq 13).[19]



(13)

Oxidation of Conjugated Dienes. Aquamethyloxodiperoxyrhenium (MTO/aq H_2O_2) oxidizes conjugated dienes to diols (eq 14).[9,22] However, it is possible to obtain epoxides in high yield when anhydrous reaction conditions are used, employing UHP (*see* rhenium, methyloxodiperoxy). Generally, electron-rich conjugated dienes react more rapidly with MTO/H_2O_2. Interesting, some substrates give rise to diols in which the two OH groups are in the relative positions 1 and 4 (eq 15).[22]



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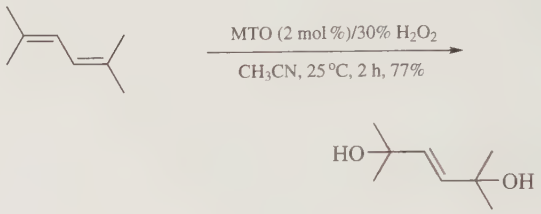
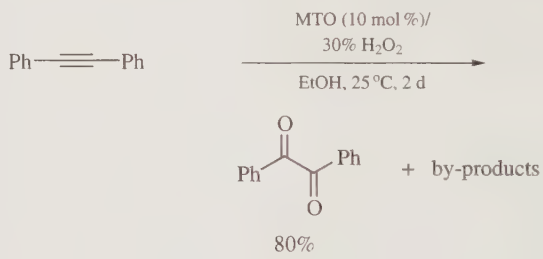


(15)

Oxidation of Alkynes. The MTO/H_2O_2 system can oxidize internal and terminal alkynes at high conversions; however, the selectivity for the products depends strongly on the choice of solvent.[23] An example of the synthetic application of MTO/H_2O_2 is the oxidation of diphenylacetylene, which is resistant to oxidation by common organic peracids and gives complex product mixtures with poor yields and low conversions. Using 10 mol % of MTO and 30% H_2O_2 (ratio alkyne:H_2O_2 of 1:3.3) with EtOH as solvent affords an 80% yield of the α-diketone (eq 16).[23]

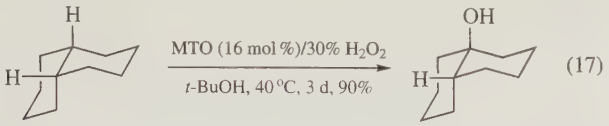


(16)

Aromatic alkynes are less reactive under these conditions than aliphatic alkynes. The aliphatic alkynes lead to more complex mixtures of products; in acetone or methylene chloride, the α-diketone, the α,β-unsaturated ketone, the α-hydroxyketone, and the α,β-epoxyketone are found, along with the carboxylic acid from rearrangement or cleavage of the triple bond. Typically, internal alkynes yield a mixture of α-diketones (major product) and carboxylic acids; terminal alkynes give carboxylic acids, their derivatives, and α-keto acids as the major products.[23]

Oxidation of Alkanes. Alkanes can be oxidized to the corresponding alcohols or ketones through insertion of oxygen into a deactivated or activated C–H bond. However, the MTO load has to be high (ca. 16 mol %) and a large excess of H_2O_2 (25-fold) is used. Even under these conditions, reaction times for deactivated C–H bonds, such as in cycloalkanes or decalins, are generally longer than those used for most epoxidations (ca. 2 to 3 d).[24] The reaction rate can be improved by adding pyrazine-2-carboxylic acid, with an increase in the total yield.[25] The reactions are stereospecific with retention of configuration, as seen in the oxidation of the stereoisomeric 1,2-dimethylcyclohexanes and decalins.[24] The yields vary from good to excellent for *cis*-decalin (eq 17)

and *cis*-1,2-dimethylcyclohexane, however, the *trans*-systems are more difficult to oxidize (eq 18).[24]



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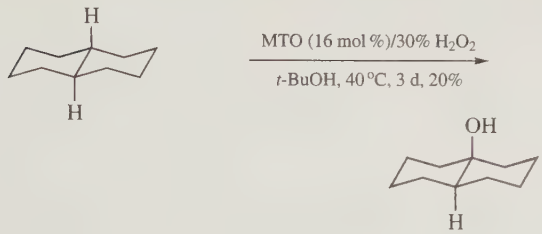
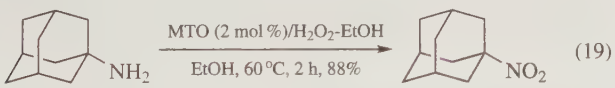
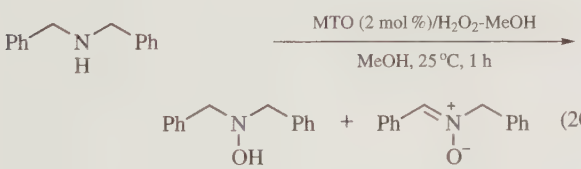


(18)

Oxidation of Amines and Anilines. MTO/H_2O_2 is efficient for the oxidation of primary amines to nitro compounds (eq 19),[26,27] secondary amines to nitrones (eq 20),[26–30] anilines to nitrobenzenes (eq 21),[26,27] benzylamines to oximes (eq 22),[26,27] and either 4-substituted *N,N*-dimethylanilines[5] or pyridines[26] to *N*-oxides (eq 23). Typically, these reactions are carried out at room temperature in MeOH or EtOH, using 2 mol % of the MTO, and an excess of 30% H_2O_2 (3 to 5-fold). Higher oxidative selectivity results when the H_2O_2-MeOH or H_2O_2-EtOH solutions have been previously dried with anhydrous $MgSO_4$.[27] The UHP complex can be also employed for these reactions, mainly to improve the yield in the oxidation of proline[29], purine,[31] and pyrimidine[31] derivatives.

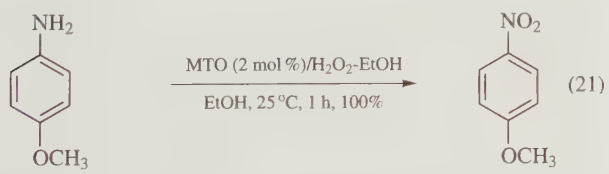


(19)



(20)

1 equiv H_2O_2	66%	6%
5 equiv H_2O_2	0%	97%



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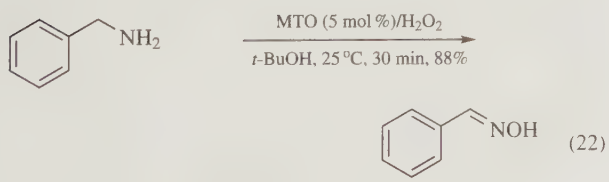
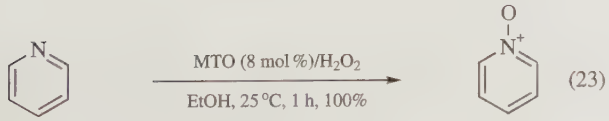


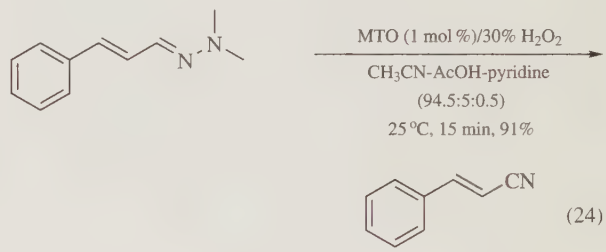
(22)



(23)

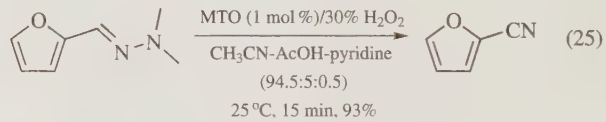
Secondary amines are first oxidized to hydroxylamines, whose formation is rate controlling, followed by conversion to the corresponding nitrones in very good yields.[26–30] High selectivity for hydroxylamine can be attained by the use of stoichiometric amounts of H_2O_2 (eq 20).[27] MeOH is the best solvent for the synthesis of nitrones because the reaction in other solvents, such as EtOH, *i*-PrOH, *t*-BuOH, CH_3CN, THF, and AcOEt, gives a significant amount of the hydroxylamines.[27]

Oxidation of *N,N*-Dimethylhydrazones to Nitriles. *N,N*-Dimethylhydrazones of aliphatic, unsaturated, aromatic, and heterocyclic aldehydes can be oxidatively transformed into nitriles using 30% aq hydrogen peroxide and MTO (ca. 1 mol %).[32,33] This reaction can be carried out either at room temperature in a CH_3CN-AcOH-pyridine mixture (94.5:5:0.5)[32] or at −50 °C in ethanol, adding an ethanolic solution of dimethylhydrazone dropwise to the oxidant solution containing MTO.[33] The nitrile yields are high using both methods, usually above 90%. Interestingly, other oxidizable functional groups, such as olefins, do not interfere, indicating the far greater reactivity of the hydrazone moiety compared to the olefin (eq 24).[32]



(24)

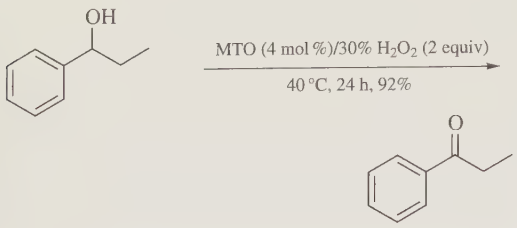
The *N,N*-dimethylhydrazone of furfuraldehyde can be efficiently transformed into the corresponding nitrile at room temperature using MTO/H_2O_2 (eq 25).



(25)

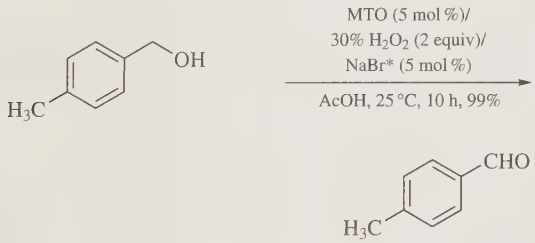
The use of acetic acid is mandatory since the hydrazones are sufficiently basic to deactivate MTO to the inactive perrhenate.[5,9,32] Hydrolysis can effectively be suppressed by a small amount of pyridine, to reduce the Lewis acidity of MTO and its peroxo adducts.[32] The reaction without pyridine is accompanied by 5–10% hydrolysis to the parent aldehyde.[32]

Oxidation of Alcohols. Primary and secondary alcohols (eq 26) can be oxidized to aldehydes and ketones, respectively, in the presence of catalytic amounts of MTO (4–16 mol %) and an excess of 30% aq H_2O_2.[15,34] Typically, the reactions are much slower than the epoxidation of alkenes, requiring 10–24 h to give good yields. Oxidation of substrates which have both alkene and alcohol groups, such as allylic alcohols, selectively yields epoxides or triols (eq 6).[14] The oxidation of alcohols is proposed to proceed via hydride abstraction.[34]



(26)

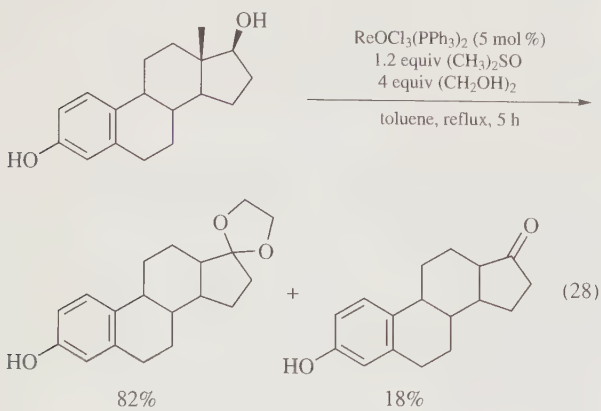
The addition of bromide ions (ca. 5 mol % of HBr or NaBr) enhances the rate of oxidation of alcohols in the MTO/H_2O_2/AcOH system, acting as a co-catalyst.[35] Several "active bromine" intermediates, including BrO^-, HOBr, and Br_2, as well as $^1O_2$, have been identified as part of the reaction sequence when bromide is oxidized by hydrogen peroxide with MTO catalyst.[35] Side reactions, such as further oxidation of the aldehydes to carboxylic acids or formation of acetate esters, can diminish the yield of the reaction. However, it is possible to obtain good to excellent yields of aldehydes (eq 27) using the MTO/H_2O_2/AcOH system at room temperature.[35] Excellent yields of methyl esters can be obtained in the oxidation of aldehydes when MeOH is used as a solvent.[35]



(27)

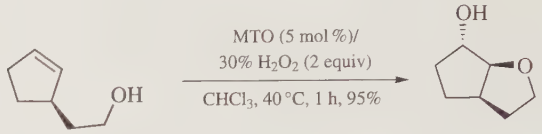
* Added in three portions during the reaction time.

The trichlorooxobis(triphenylphosphene)rhenium(V) complex, $ReOCl_3(PPh_3)_2$, can be also applied to oxidize benzylic and allylic alcohols.[36] This rhenium(V) system selectively oxidizes secondary alcohols using DMSO as oxidant and conveniently produces the corresponding ethylene ketals in the presence of ethylene glycol.[37] In contrast to MTO/H_2O_2, no oxidative cyclization occurs (*see in*: rhenium, aquamethyloxodiperoxy-).[37] The phenol group is also unaffected during the oxidative ketalization of the secondary alcohol, as observed for β-estradiol (eq 28). The selectivity for ketone formation is about 18%. However, (+)-dihydrocholesterol could be ketalized quantitatively through addition of a small amount of the mild base 2,4,6-collidine as a buffer.[37]



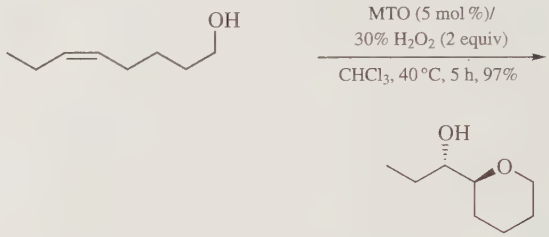
(28)

Oxidative Cyclization of Hydroxyalkenes. Diperoxoaquamethyloxorhenium works efficiently to make tetrahydrofurfuryl alcohols from 5-hydroxyalkenes.[38] This method achieves excellent regioselectivity for the formation of five-membered rings and has been used successfully for primary, secondary and, tertiary 5-hydroxyalkenes. For example, 2-(cyclopent-2-enyl)ethanol can be converted to (3a*R*,6*S*,6a*S*)-hexahydro-2*H*-cyclopenta[*b*]furan-6-ol in high yield (eq 29).[38]



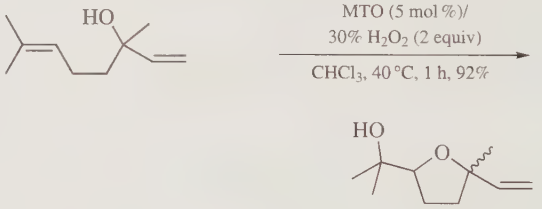
(29)

The oxidative cyclization of 6-hydroxyalkenes to six-membered rings is slower than observed for five-membered rings (eq 30). The attempt to close rings larger than six members only results in triols, which are formed by the acid-catalyzed ring opening of the epoxy-alcohols.[38]



(30)

The oxidative cyclization of secondary and tertiary alcohols is not selective for the formation of *cis* or *trans* isomers, which are usually formed in comparable yields when an alkyl group is bound to a carbon atom that becomes part of the ring (eq 31).[38]

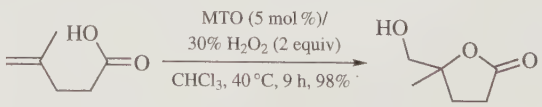


(31)

cis:*trans* (1.0:0.86)

Acyclic 1,5-nonconjugated dienes can have both double bonds oxidized, leading to hydroxytetrahydrofuran. For example, 1,5-hexadiene is oxidized to 2,5-dihydroxymethyltetrahydrofuran.[38]

Hydroxylactonization of γ,δ-Unsaturated Carboxylic Acids. γ-Lactones can be efficiently obtained from the hydroxylactonization of γ,δ-unsaturated carboxylic acids or esters with the MTO/H_2O_2/$CHCl_3$ system.[39] This method shows nearly complete regioselectivity with more than 95% yield under mild conditions (eq 32).

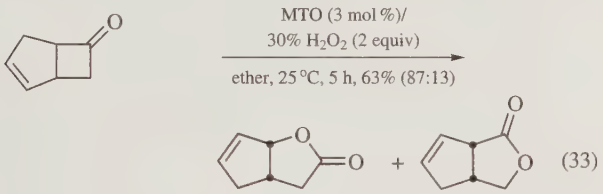


(32)

Baeyer-Villiger Oxidation. The MTO/H_2O_2 system is able to catalyze the Baeyer-Villiger rearrangement of cyclic ketones

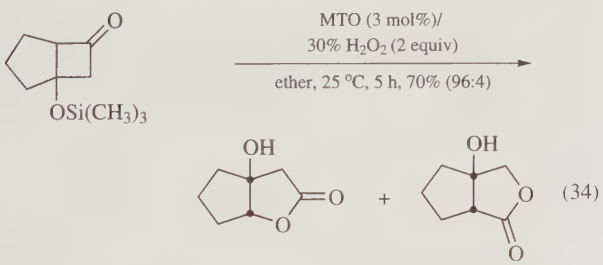
to lactones.[40] This is surprising because the d^0-peroxo complex $CH_3ReO(O_2)_2 \cdot H_2O$ behaves as a highly active electrophilic epoxidation catalyst as well as a nucleophilic Baeyer-Villiger catalyst.[40] The reason for this dualism is not yet clear,[41] however, if the keto oxygen coordinates to rhenium, there is an activation of the substrate as well as an increase of electron density on the metal center.[42] This latter fact increases the nucleophilic character of the peroxo groups. The geometry of $CH_3ReO(O_2)_2 \cdot H_2O$ presents a different chemical environment for the oxygen atoms of the peroxo groups attached to rhenium. This is revealed by the ^{17}O NMR having different chemical shifts for the peroxo oxygen atoms.[40] This may be another factor responsible for the nucleophilic behavior of MTO/H_2O_2 in Baeyer-Villiger reactions.[40]

The MTO/H_2O_2 system can convert cyclobutanone to γ-butyrolactone in high yield.[40] Functionalized cyclobutanones can also be converted γ-butyrolactone in good yields.[42] The lactonization is highly chemoselective in the presence of carbon-carbon double bonds (eq 33), aromatic rings, or chlorine substituents.[42]



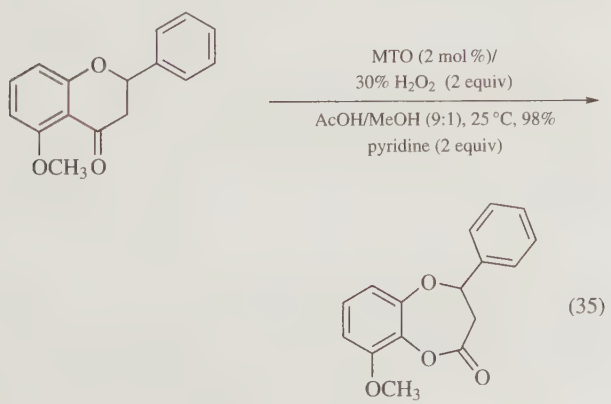
(33)

Interestingly, for the bicyclo[3.2.0]hept-2-en-6-one (eq 33) not more than 5% of epoxides are formed as by-products. This preference of lactonization to epoxidation is totally unexpected and remarkable.[9,14,42] A trimethylsiloxy-substituted ketone is converted directly into the hydroxylated lactone with high yield and regioselectively (eq 34).[42]



(34)

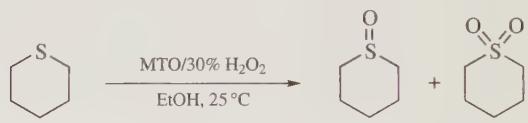
Flavanone derivatives can undergo Baeyer-Villiger rearrangements under mild conditions giving acceptable to good yields of lactones (eq 35).[43] A ring-opening of the lactone moiety can occur due to the acidity of MTO; however, the use of buffers, such as pyridinium acetate suppresses this side reaction.[43]



(35)

A great improvement of the MTO/H_2O_2 system can be obtained by replacing conventional solvents by ionic liquids, such as $[bmim]BF_4$.[44] The yield of lactone is considerably improved and ring opening of the lactone moiety is suppressed.[43] After simple extraction of the lactone with diethyl ether, the catalyst can be repeatedly recycled and efficiently reused for the lactonization process in the same reaction medium.[44]

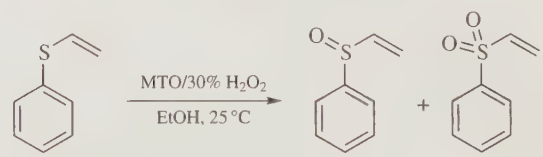
Oxidation of Sulfur Compounds. Sulfides can be selectively oxidized in high yields to sulfoxides ($R_2S:H_2O_2 = 1:1.1$) or to sulfones ($R_2S:H_2O_2 = 1:2.2$) using the MTO/H_2O_2/EtOH system.[45] Alcoholic H_2O_2 solutions are previously dried with anhydrous $MgSO_4$.[45] The UHP complex can also be used as oxidant. A wide variety of sulfides can be selectively oxidized either to sulfoxides or sulfones, such as: cyclic, acyclic dialkyl, alkyl aryl, and diaryl sulfides (eq 36). Even those sulfides bearing oxidatively sensitive groups, such as carbon-carbon double bonds, chloro substituents, ester, and alcohol groups are smoothly oxidized.[45,46] Thiophenes can be also oxidized to sulfoxides and sulfones.[47] The best solvents for this oxidation are MeOH and EtOH. The reactions do not give high yields and are slower when carried out in solvents such as $CHCl_3$, *i*-PrOH, *t*-BuOH, THF, and CH_3CN.[45] Electron-rich sulfides are more rapidly oxidized to sulfoxides at room temperature using 1 mol % of MTO. However, deactivated sulfides, such as bis(4-nitrophenyl)sulfide, need higher temperatures as well as higher amounts of MTO (50 °C and 5 mol % MTO), but good yields of sulfoxides can still be achieved (88%, 5 h).[45]



(36)

1 mol % MTO/1.1 equiv H_2O_2, 1 h	98%	0%
2 mol % MTO/2.2 equiv H_2O_2, 3 h	0%	89%

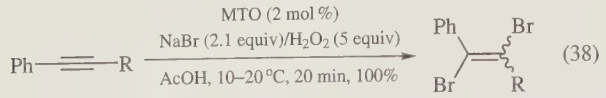
Although H_2O_2/MTO is an efficient epoxidation catalytic system, sulfides are more reactive than carbon-carbon double bonds. Therefore, it is possible to obtain a high yield of either vinylic sulfoxide or sulfone under mild conditions (eq 37).[45]



(37)

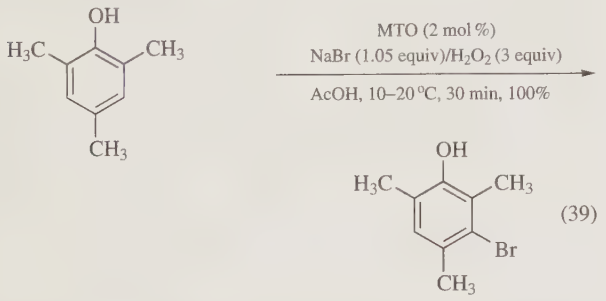
1 mol % MTO/1.1 equiv H_2O_2, 1 h	85%	0%
2 mol % MTO/2.2 equiv H_2O_2, 2 h	0%	84%

Bromination of Alkynes and Phenols. MTO catalyzes the bromination of alkynes using a combination of H_2O_2 and bromide. Substrates like diphenylacetylene, methylphenylacetylene, and phenylacetylene are brominated in quantitative yields (eq 38). The *trans*-dibromoalkene is favored when the size of the R group is increased.[35]



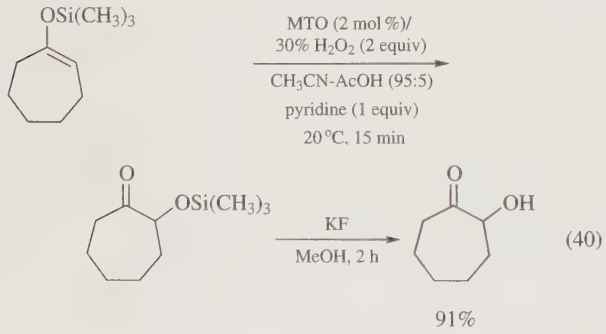
R	*cis*:*trans*
H	1:7
CH_3	~ 1:99
Ph	> 1:99

Phenols are brominated rapidly by H_2O_2, bromide, and MTO. Usually, the selectivity follows the order *para* > *ortho* > *meta*. This order is sufficiently pronounced that only one single product is obtained in each case when competing sites are available.[35]



In these reactions the hydrogen peroxide is added under strong stirring using a syringe pump. Typically, the reaction temperature is close to 10 °C in order to avoid deactivation of MTO.[35]

Oxidation of Silyl Enol Ethers. The MTO/H_2O_2 system can oxidize silyl enol ethers to α-hydroxy and α-siloxy ketones.[48] A workup with potassium fluoride gives the α-hydroxy ketones in high isolated yields. This conversion is best carried out in acetonitrile solutions containing pyridine and acetic acid.[48]



This reaction works efficiently when the silyl enol ether does not have an electron-withdrawing group conjugated with the enol ether double bond. In the case of 1-phenyl-1-(trimethylsiloxy) ethene the yield is only 60%, presumably due to its lower reactivity toward oxidation, which allows hydrolysis to compete. The even less reactive 4-(trimethylsiloxy)-3-penten-2-one gives only the hydrolysis product 2,4-pentanedione.[48]

Related Reagents. Methyltrioxorhenium; trichlorooxobis (triphenylphosphene)rhenium(V); hydrogen peroxide; urea-hydrogen peroxide complex.

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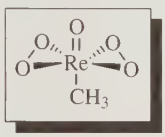
Rhenium(VII) Methyloxodiperoxy



[171078-32-3] CH_3O_5Re (MW 281.24)

(reagent used as oxidation catalyst for a wide variety of substrates under anhydrous conditions)

Physical Data: solutions have a characteristic yellow color, other properties are not available as $CH_3ReO(O_2)_2$ formed under anhydrous conditions has not been isolated.

Solubility: soluble in water, alcohol, ethers, and most organic solvents.

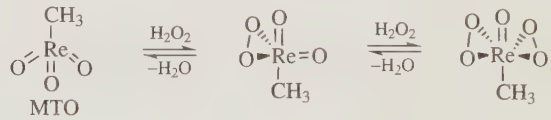
Form Supplied in: the reagent is not available commercially; however, this species is formed in the reaction mixture during oxidation employing methyltrioxorhenium (MTO) and the urea–hydrogen peroxide complex (UHP) both of which are readily available.

Purification: not applicable for this reagent.

Handling, Storage, and Precautions: UHP has a quite high H_2O_2 content (36.2%); however, it is relatively stable to impact.[1] Anhydrous UHP is hygroscopic and is best stored at low temperatures, but samples stored at room temperature do not show a considerable decrease of oxygen content over periods of up to 1 year.[1] A general rule for safe handling is to limit the concentration of H_2O_2 to 20 wt% in the reaction mixture. It is not recommended to use UHP and carboxylic anhydrides except when the oxidant is present in a large excess of chlorinated solvents such as dichloromethane.[1] There are no data available about the toxicity and health risks of MTO. The use of gloves, coat, and safety glasses is recommended when doing reactions with MTO/H_2O_2.

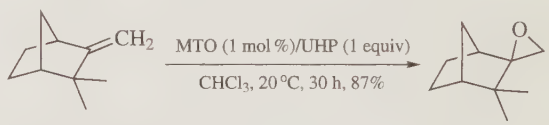
Epoxidation of Alkenes. The first application of the diperoxorhenium complex in organic synthesis was the epoxidation of olefins using MTO in combination with aq H_2O_2 as terminal oxidant.[2] However, the intrinsic acidity (Brønsted and Lewis) of the diperoxorhenium complex, $CH_3ReO(O_2)_2 \cdot H_2O$, causes ring opening of the epoxides yielding a significant amount of *trans*-1,2-diol.[2] Some optimizations of MTO/aq H_2O_2 can be done in order to increase the selectivity of the epoxides, such as addition of aromatic amines to the reaction mixture (*see also*: rhenium, aquamethyloxodiperoxy).[3–6] Another approach to avoid epoxide ring opening is to replace aq H_2O_2 solutions by the urea–hydrogen peroxide complex (UHP). This replacement significantly diminishes the amount of water in the reaction mixture; however, completely anhydrous conditions can only be achieved by using of molecular sieves (3 or 4 Å) or other drying agents together with UHP, for trapping the water that is formed as a by-product of oxidation with H_2O_2.

UHP is insoluble in nonpolar organic solvents, however, addition of UHP (2 equiv) to a methylene chloride solution of MTO (5 mol %) results in a rapid development of the yellow color characteristic of the diperoxorhenium complex (eq 1).[7,8]



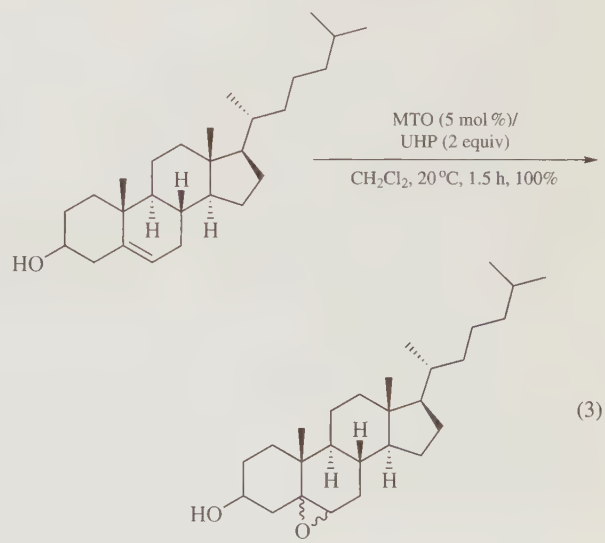
(1)

The oxidation of camphene with UHP is a good example of the success of the anhydrous MTO/UHP system in preventing ring opening of highly sensitive epoxides. This reaction gives 87% yield of the epoxide and none of the 1,2-diol (eq 2). Conversely, the reaction of camphene with 85% H_2O_2 and MTO results in the exclusive formation of the cleavage and rearrangement products and none of the epoxide.[9]



(2)

The oxidation of cholesterol at room temperature using MTO/UHP gives the epoxide in high yield and stereoselectivity (eq 3).[7] Furthermore, no ketone by-product is formed, indicating the high preference for epoxidation of the MTO/UHP system. Interestingly, the ratio of the α and β epoxides is increased from 4:1 to 5:1,

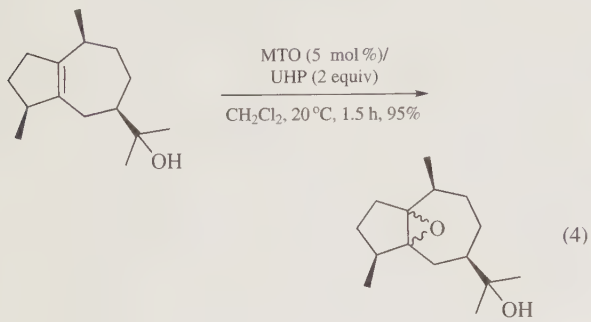


(3)

α:β = 4:1

when completely anhydrous reaction conditions are employed, by adding 3 or 4 Å molecular sieves or anhydrous Na_2SO_4 to the reaction mixture. However, the epoxidation rate is three times slower, probably due to the competitive absorption of H_2O_2 by the sieves or Na_2SO_4.[7]

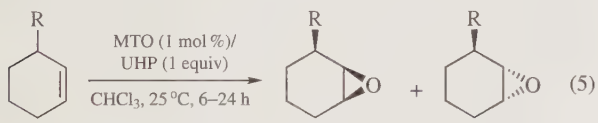
The epoxidation of guaiol gives a high yield and stereoselectivity (α:β = 9:1) using the MTO/UHP system (eq 4). This reaction, when done with *m*-CPBA as stoichiometric oxidant, gives the epoxide in high yield, but the stereoselectivity is lower (α:β = 6:4).[7]



(4)

α:β = 9:1

The epoxidation of 3-alkyl cyclohexenes gives a mixture of the respective diastereomeric epoxides in moderate to good yields (eq 5).[10] The *trans* selectivity increases with the size of the substituent due to steric effects.[10]



(5)

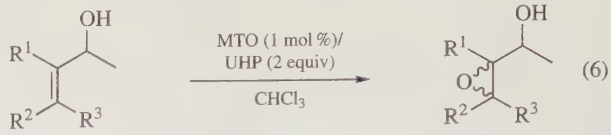
R	Conversion (%)	Diastereoselectivity (*cis*:*trans*)
Me	31	49:51
Et	62	46:54
i-Pr	53	27:73
t-Bu	88	9:91

A major drawback of the UHP/MTO system is the insolubility of the polymeric UHP complex, a fact that results in a kinetically slow heterogeneous reaction. For example, electron-poor olefins resist oxidation to the point of competing with catalyst deactivation.[5,11]

Epoxidation of Allylic Alcohols. Epoxidation of chiral allylic alcohols with MTO/UHP gives a mixture of *threo*- and *erythro*-epoxyalcohols in excellent yields; in most cases high *threo* diastereoselectivity is obtained (eq 6).[9]

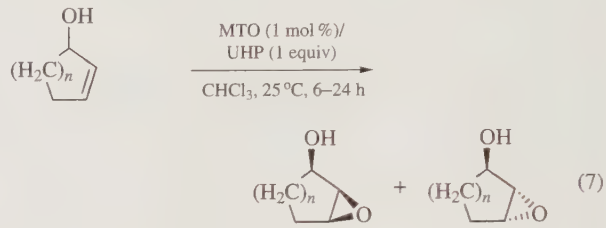
Cyclic allylic alcohols can be also epoxidized in moderate to excellent yields using the MTO/UHP system (eq 7). Good *cis* selectivity is observed for five- and six-membered rings. The diastereoselectivity is a function of competition between steric and electronic effects between substrate and the diperoxorhenium species.[10]

The MTO/UHP system has also been successfully employed for oxidation of [60]fullerene to 1,2-epoxy[60]fullerene. The MTO loading used is very high (ca. 200 mol %), however, it is possible to obtain a 35% yield in the optimized reaction.[12]



(6)

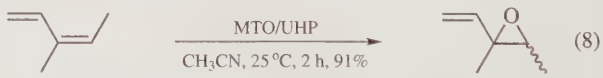
R^1	R^2	R^3	Time (h)	Conversion (%)	*threo*:*erythro*
CH_3	H	H	17	88	50:50
H	CH_3	H	20	81	67:33
H	H	CH_3	20	90	82:18
CH_3	H	CH_3	25	95	91:9
H	CH_3	CH_3	15	91	83:17
CH_3	CH_3	CH_3	17	88	95:5



(7)

Substrate *n*	Conversion (%)	Diastereoselectivity (*cis*:*trans*)
1	52	80:20
2	76	81:19
3	92	45:55
4	89	5:95

Epoxidation of Conjugated Dienes. The oxidation of conjugated dienes using the MTO/UHP system results in epoxides in good to excellent yields (eq 8).[13] However, the presence of water readily hydrolyzes the epoxide to diols (*see* rhenium, aquamethyloxodiperoxy).[13]



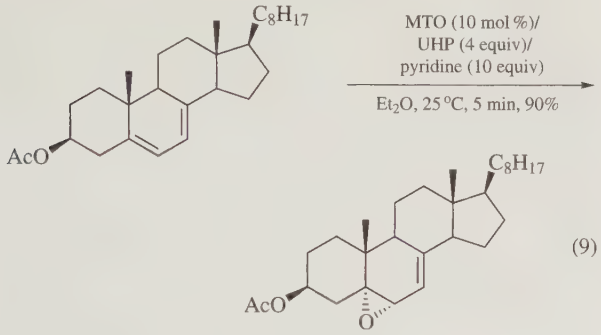
(8)

(*cis*:*trans* = 1:1.4)

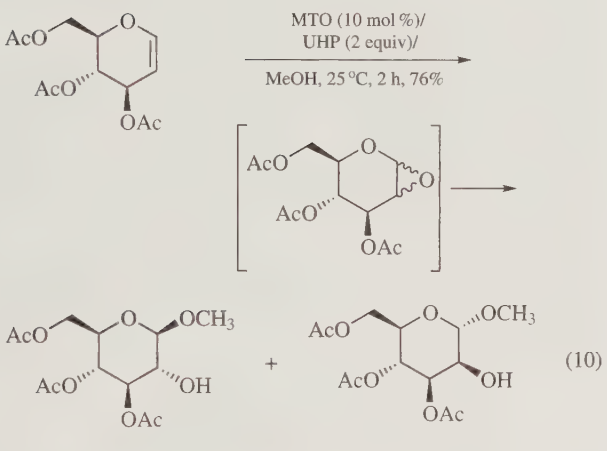
MTO/UHP can be used for the oxidation of steroidal conjugated dienes, such as cholesta-3,5-diene, resulting in a variety of oxygenated steroids depending on the reaction conditions.[14–16] For this kind of molecule, the addition of pyridine increases the selectivity for oxidation of the β side. However, even in the presence of pyridine and using UHP, the major products formed are diols.[14] The effect of the solvent on the selectivity of the oxidation of steroidal dienes with MTO/UHP is dramatic.[15] The cholesta-5,7-dien-3β-yl acetate can be selectively epoxidized using the MTO/UHP/pyridine system in Et_2O (eq 9).[15]

Oxidation of Glycals. Oxidation of glycals by MTO/UHP in methanol provides direct access to methyl glycosides.[17] The oxidation of 3,4,6-tri-*O*-acetyl-D-glucal results in a α-D-manno-pyranoside and β-D-gluco-pyranoside (1:2) in an isolated yield of 76% (eq 10).[17] Comparable results are obtained using aq H_2O_2

solutions. The diastereoselectivies observed for this class of molecules are similar to those observed in the epoxidation of cyclohex-2-enol, indicating that an allylic hydroxyl group has a modest *syn*-directing ability.[10,17]



(9)



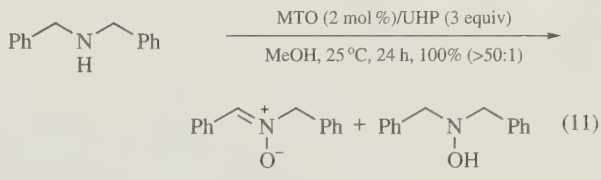
(10)

(α:β = 1:2)

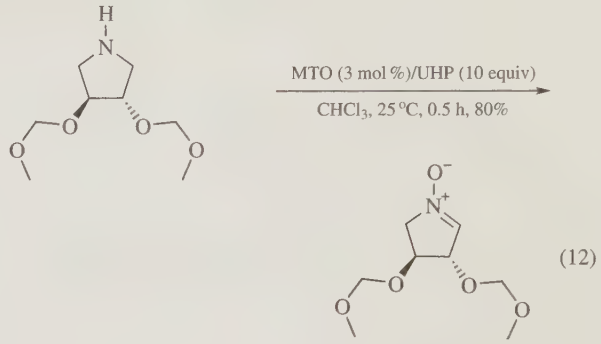
The intermediate of this transformation is an epoxide (eq 10), which readily suffers methanolysis due to its very sensitive nature.[18] The application of the MTO/UHP system for the oxidation of glycols in the presence of dibutylphosphate (DBP) yields glycosyl phosphate. The phosphate group acts as activating protector of the anomeric position affording glycosyl donors and is a powerful tool for the construction of various glycoconjugates.[18,19] The oxidation reaction carried out in an ionic liquid, such as [bmim]BF_4 leads to complete conversion and good diastereoselectivity between α- and β-glycosyl phosphate.[18]

Oxidation of Nitrogen Containing Compounds. The MTO/UHP system is efficient in oxidizing secondary amines to nitrones. For this reaction the use of an alcoholic solvent is essential for attaining good conversions and complete oxidation to nitrone. Typically, 2 mol % of MTO and 3 equiv of UHP are sufficient for the practical transformation of dibenzylamine to its nitrone (eq 11).[20] Completely anhydrous conditions were unessential. However, an excess of water appears to have an unfavorable effect on the reaction rate and on the nitrone/hydroxylamine ratio. The increase of hydrolysis products (benzaldehyde) in the absence of the drying agent was very limited.[20]

Nitrones of proline derivatives, such as (3*S*,4*S*)-3,4-bis(methoxymethoxy)-1-pyrroline, can be obtained in excellent yield using the MTO/UHP system and methylene chloride as solvent (eq 12).[21]

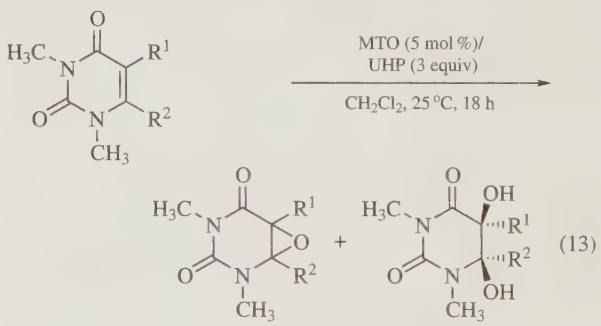


(11)



(12)

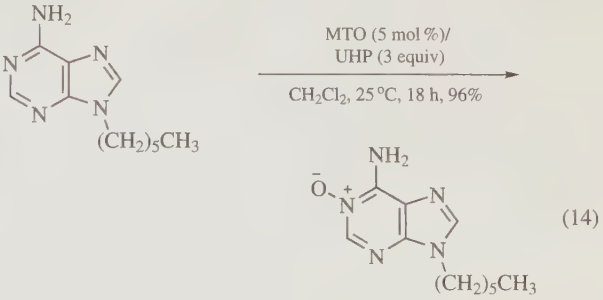
MTO/UHP is also a useful and selective catalytic system for the oxidation of pyrimidine and purine derivatives.[22] Uracil derivatives can be converted into the biologically relevant 5,6-oxiranyl-5,6-dihydrouracils in good yields (eq 13). Interestingly, *cis*-1,2-diols are obtained as ring-opened products of the uracil epoxides. This fact is remarkable as *trans*-1,2-diols are usually observed as side-products in MTO epoxidations of alkenes.[2,22]



(13)

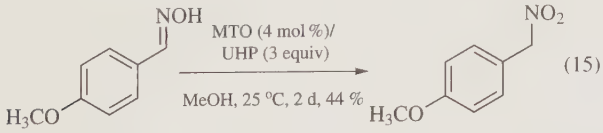
		Yield (%)	
R^1	R^2	Epoxide	Diol
H	H	82	7
CH_3	H	89	4
H	CH_3	87	7

Purine derivatives, such as adenine, are selectively oxidized to the corresponding 1-oxides using MTO/UHP (eq 14), with a simple work up. However, MTO/H_2O_2/pyrazine-2-carboxylic acid (PCA) gives slightly higher yields.[22]



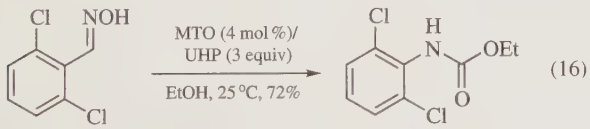
(14)

Aryl oximes can be oxidized to the corresponding aryl nitromethanes using MTO/UHP.[23] Typically, this reaction uses a loading of 2–10 mol % of MTO in the presence of 3 equiv of UHP and MeOH or CH_3CN as solvent at room temperature. The yields obtained for this transformation are poor even using prolonged reaction times.[23] However, electron-donating groups at the *ortho-* or *para-* positions favor *N*-oxidation (eq 15).[23]



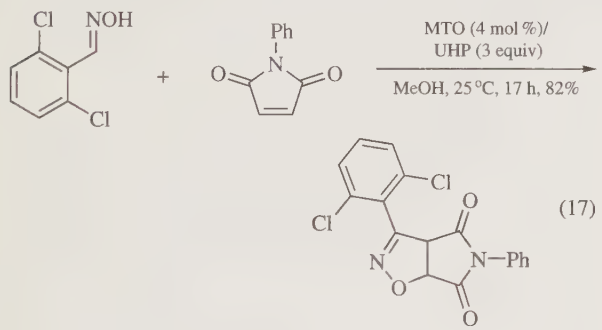
(15)

Oxidation of 2,6-disubstituted aryl oximes with MTO/UHP results in carbamates as products (eq 16).[23] This reaction does not proceed in non-nucleophilic solvents such as CH_2Cl_2, CH_3CN, or ionic liquids {[bmim]BF_4}.[23]



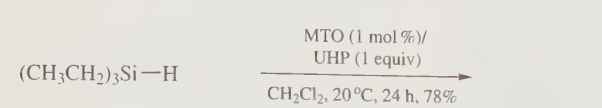
(16)

The reaction proceeds through a nitrile oxide intermediate, which can be trapped in good yield when performing the reaction in the presence of *N*-phenylmaleimide or dimethylmaleate (eq 17).



(17)

Oxidation of Silanes. MTO/UHP constitutes a convenient oxidation system to catalytically convert silanes to the corresponding silanols in good to excellent yields (eq 18).[24] This catalytic system has high chemoselectivity for silanols versus disiloxanes and, in the case of optically active silanes the oxidation occurs with retention of configuration. These favorable features of MTO/UHP are in stark contrast to those of MTO/85% H_2O_2, which exhibits lower conversions and a chemoselectivity shifted toward the disiloxane. No enantiomeric excess is obtained with optically active silanes.[24]

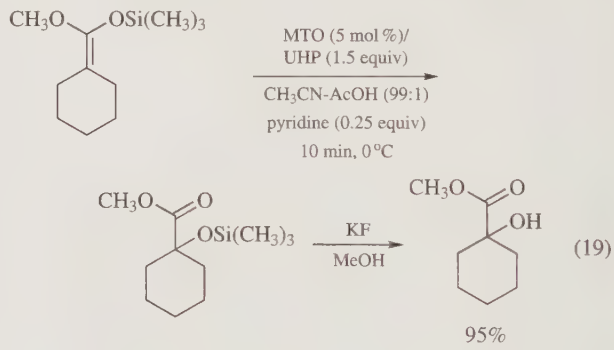


(18)

It is assumed that the Si–H oxidation takes place in the helical urea channels, which generate a confined environment where the condensation of the silanol to disiloxane is avoided for steric reasons.[24]

While the reaction conditions are acidic enough to dimerize the silanol, the reaction is believed to occur inside the channels of the urea matrix, thus avoiding the dimerization. The dependence of the reactivity and selectivity for the MTO/UHP oxidant on the catalyst/urea ratio is also indicative of host-guest chemistry. With higher amounts of the catalyst or less urea, the Si–H oxidation results in lower conversions and worse silanol/disiloxane selectivities, indicating that the reaction takes place only partially inside the urea matrix and a significant portion occurs in solution. Nevertheless, when larger amounts of urea were employed, only the extent of silane conversion was reduced, while the selectivity of silanol remained high. The excellent product ratio indicates that the oxidation takes place inside the urea channels. However, the concentrations of both the catalyst and the oxygen donor H_2O_2 inside the tubes is significantly lower (dilution effect), and consequently, the reaction rate is reduced.[24]

Oxidation of Methyl Trimethylsilyl Ketene Acetals. The MTO/UHP system oxidizes methyl trimethylsilyl ketene acetals that, after treatment with potassium fluoride, give α-hydroxy esters in high yields (eq 19).[25] The aq MTO/H_2O_2 system (*see* rhenium, aquamethyloxodiperoxo in Oxidation of silyl enol ethers) is inadequate for more hydrolytically labile ketene acetals, resulting in a significant substrate hydrolysis (70%), even in the presence of pyridine.[25] Hydrolysis can be suppressed using UHP, a lower temperature (0 °C), and dropwise addition of the substrate.[25]



(19)

Related Reagents. Methyltrioxorhenium; hydrogen peroxide.

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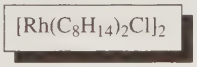
Rhodium(I) bis Cyclooctene Chloride Dimer



[12279-09-3] $C_{32}H_{56}Cl_2Rh_2$ (MW 717.50)

(convenient source of rhodium(I) and serves as an effective pre-catalyst in a variety of reactions including aryl- and vinyl-C–H bond activation, hydroiminoacylation, cycloisomerization, and C–C bond activation)

Physical Data: mp 140 °C (dec). It exists as a reddish brown solid.

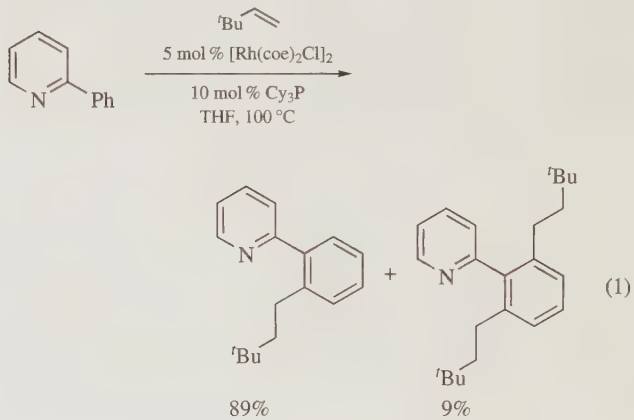
Analysis of Reagent Purity: characteristic strong bands at 1458, 1439, and 1350 cm^{-1} in the infrared spectrum.

Preparative Methods: The reagent is prepared by adding an excess of *cis*-cyclooctene to an isopropanol–water (4:1) solution of rhodium(III) chloride 3-hydrate, filtering, and washing with ethanol.[1]

Handling, Storage, and Precautions: The catalyst should be handled under an inert atmosphere, such as nitrogen or argon, and stored at reduced temperature (2–8 °C). The complex is susceptible to slow oxidation upon exposure to air, and appropriate precautions should be taken to maintain catalytic efficacy.[2] Standard good laboratory practices should be used when working with this reagent.

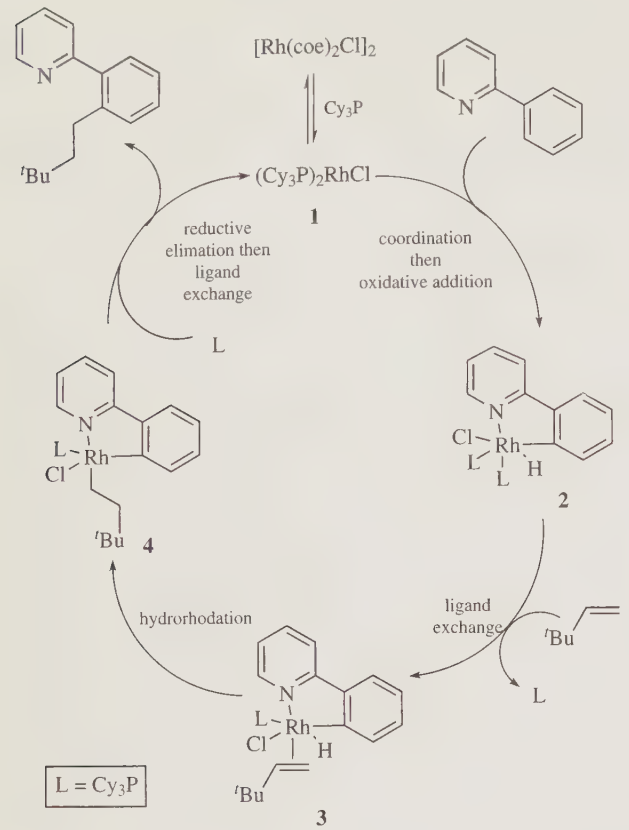
Background. In recent years $[Rh(coe)_2Cl]_2$ has gained a great deal of attention as a convenient source of rhodium(I). The mild and chemoselective nature of rhodium-catalyzed reactions has led to the rapid development of new and exciting carbon–carbon and carbon–heteroatom bond forming reactions. The *cis*-cyclooctene (coe) ligands of the $[Rh(coe)_2Cl]_2$ complex are easily displaced by a variety of nucleophiles including achiral and chiral phosphines. As a result, the activity of the catalytic system is easily modified, and $[Rh(coe)_2Cl]_2$ acts as an efficient catalyst precursor in a variety of transformations as will be described in this review.

Pyridine- and Imine-directed C–H Bond Activation. The earliest reports of rhodium-catalyzed C–H bond activation[3] followed Murai's et al.[4] seminal publication of ruthenium-catalyzed cross-coupling of aromatic C–H bonds to olefins. The first examples of rhodium-catalyzed C–H bond activation described regioselectively cross-couples of alkenes to 2-phenylpyridines, wherein the pyridyl nitrogen functions as the directing element.[5] For example, the thermal reaction of 2-phenylpyridine and 3,3-dimethylbutene in the presence of 5 mol% $[RhCl(coe)_2]_2$ and 30 mol% Cy_3P gave an 89% yield of the 2-(2′-alkylphenyl)pyridine along with 9% of the 2-(2′,6′-dialkylphenyl)pyridine (eq 1). However, the reactions of alkenes capable of double bond isomerization, such as 1-hexene and its homologs, give yields in the 25–40% range. Interestingly, reactions conducted with the $[RhCl(coe)_2]_2/Cy_3P$ system were shown to proceed under milder conditions in half the time than those catalyzed by Wilkinson's catalyst, $(Ph_3P)_3RhCl$. The results of ligand screening suggest that the increased reactivity of the Cy_3P system may be a function of the phosphine's cone angle and not its electron-donating capacity.[6] $[RhCl(coe)_2]_2$ in the absence of phosphine ligands fails to catalyze the reaction.



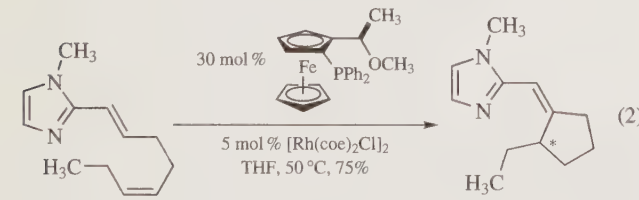
(1)

The regioselective cross-coupling is thought to proceed as shown in Scheme 1. Thus, $[RhCl(coe)_2]_2$ and Cy_3P react by ligand exchange to presumably generate $(Cy_3P)_3RhCl$. Loss of a phosphine ligand leads to a transient 14-electron rhodium(I) species **1** that may ligate the pyridine nitrogen of the bi-aryl substrate. Oxidative addition to the proximal phenyl C–H bond gives a rhodium metallacycle **2** that can exchange an olefin for a phosphine ligand. Hydrorhodation of the alkene occurs to give the less hindered alkylrhodium(III) intermediate **4**. Sequential reductive elimination and ligand exchange events release the mono-alkylated product, regenerating **1** in the process. A second iteration yields the bis-alkylated by-product.



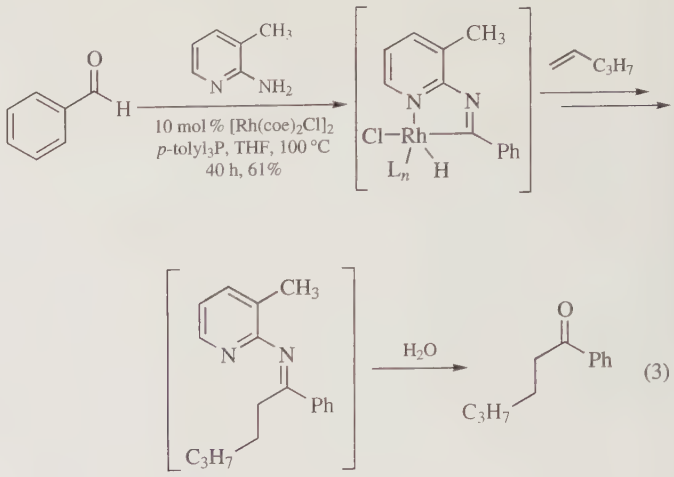
Scheme 1 A possible mechanism for the regioselective alkylation of 2-phenylpyridine

The scope of pyridine-directed rhodium-catalyzed C–H bond/olefin couplings has been expanded to inter-[7] and intramolecular[8] variants involving 2-vinylpyridines[9] and 2-vinylquinolines.[10] Attempts to render the intramolecular process highly enantioselective have currently been thwarted, although the reaction of an imidazole substrate proceeded with good ee (eq 2).[11]



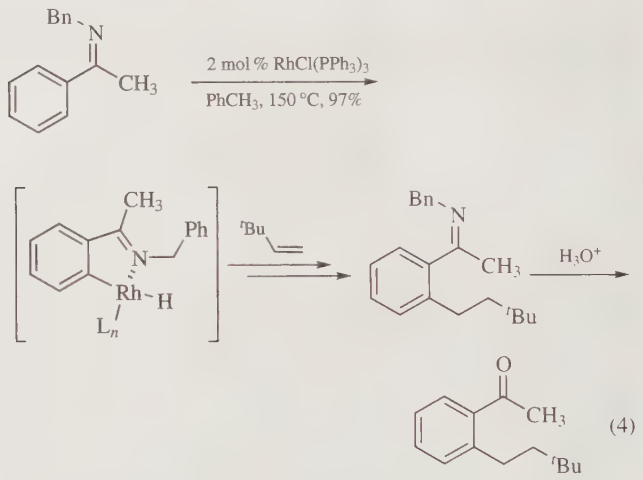
(2)

The pyridyl moiety has been used to activate the iminyl C–H bond of 2-amino-3-picoline-derived aldimines.[12] Cross-coupling reactions of the metallated intermediates with alkenes provide ketones after hydrolysis of the ketimine intermediates. Hence, the transformation serves as a hydroacylation equivalent that circumvents the untoward acylmetal decarbonylation events (and the high CO pressures sometimes used to combat those events) that often plague the traditional process. The aldimines are formed conveniently, in situ, and the reaction can be performed with catalytic amounts of 2-amino-3-picoline. A variety of aromatic and aliphatic aldehydes react efficiently with terminal alkenes, while $(Ph_3P)_3RhCl$ and $[RhCl(coe)_2]_2$/(*p*-tolyl)$_3$P proved to be the preferred catalyst systems. The proposed mechanism for the reaction is similar to that previously described for the alkylation of 2-phenylpyridine with alkenes (eq 3).



(3)

The $(Ph_3P)_3RhCl$-catalyzed inter-[13] and intramolecular[14] coupling of aryl C–H bonds to alkenes via imine-directed C–H bond activation provides rapid and efficient access to *ortho*-alkylated aryl ketones and aldehydes after acidic work-up of the reaction mixtures (eq 4).

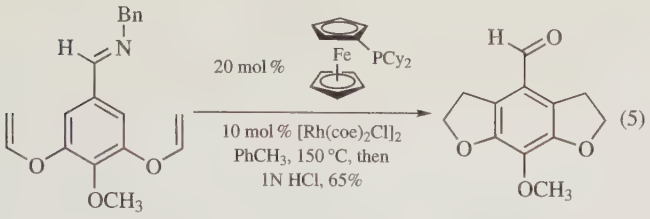


(4)

Despite the power of the transformation, the $(Ph_3P)_3RhCl$-catalyzed process has certain limitations. For example, aldimines do not intermolecularly *ortho*-alkylate without hydroiminoacylation, and some elaborate systems manufactured within the context of target-directed synthesis fail to efficiently alkylate under $(Ph_3P)_3RhCl$ catalysis. The ability of $[RhCl(coe)_2]_2$ to function as a rhodium(I) source in a ligand screening has enjoyed some success. It has been shown that aryl aldimines will *ortho*-alkylate under the influence of $[RhCl(coe)_2]_2$ and Cy_3P, although bis-alkylated products are preferentially formed.[15] Also, $[RhCl(coe)_2]_2$ and the electron-rich dicyclohexyl ferrocenyl phosphine ($FcPCy_2$) ligand proved efficient in a tandem cyclization en route to a mescaline analog (eq 5).[16] The equivalent transformation under $(Ph_3P)_3RhCl$ catalysis proceeded to only 10% conversion.

The ferrocenyl-PCy_2/$[RhCl(coe)_2]_2$ system was effectively employed in the total synthesis of (+)-lithospermic acid.[17] In the key bond-forming event, a chiral imine derived from (*R*)-aminoindane underwent smooth cyclization to give a dihydrobenzofuran in 88%

yield and 73% ee after hydrolysis of the auxiliary (eq 6). A reagent-controlled asymmetric variant of the reaction is also known.[18]



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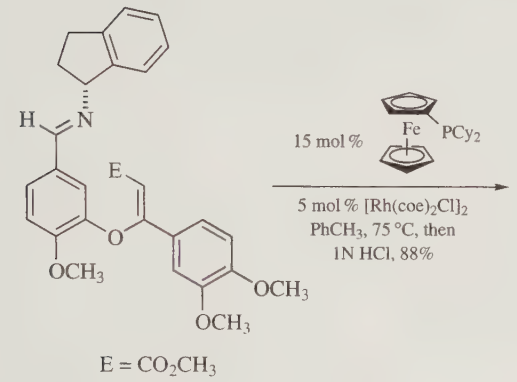
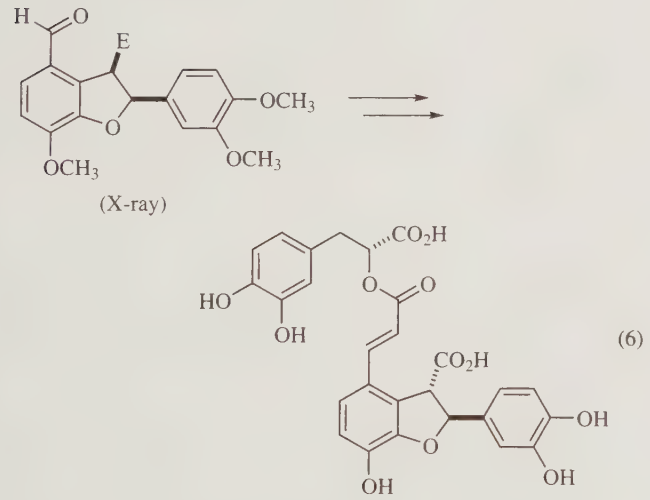
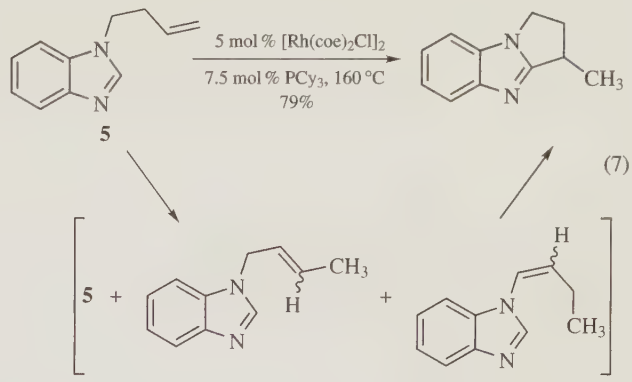


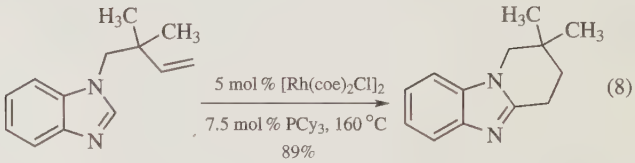
E = CO_2CH_3

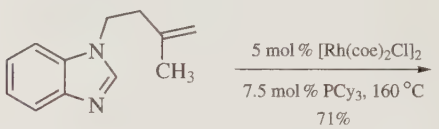


(6)

(+)-lithospermic acid







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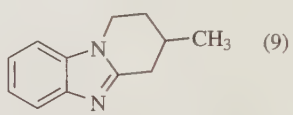
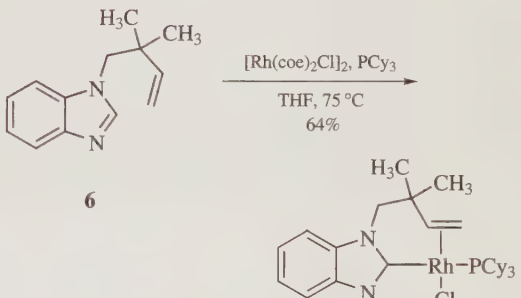


(9)



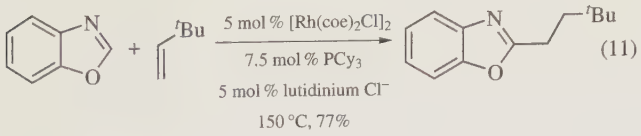
(10)

NHC, isolable

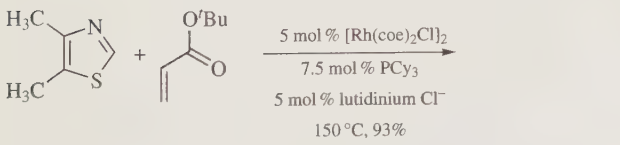
C–H Bond Activation of Heterocycles. The benzimidazole C(2)–H bond is readily coupled to *N*(1)-tethered alkenes under rhodium catalysis to yield five- and six-membered ring-annulated products in good yield (eq 7).[19] Interestingly, the substrate **5** isomerizes to a mixture of alkene isomers prior to cyclization. The regioselectivity of cyclization seems to be a function of sterics and/or proclivity for alkene isomerization, as substrates **6** and **8** apparently undergo 6-*endo* cyclization (eqs 8 and 9).

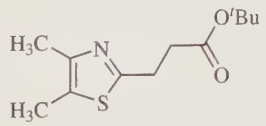
The optimal catalyst system for this transformation is formed in situ from $[RhCl(coe)_2]_2$ and PCy_3, and has proven better than either Wilkinson's catalyst, which gives reduced yields, or $[RhCl(coe)_2]_2$ alone, which completely fails. The mechanism of the reaction was partially elucidated and found to involve the intermediacy of an isolable *N*-heterocyclic carbene (NHC) (eq 10).[20]

This mechanistic insight guided the expansion of the substrate scope to include a variety of heterocycles capable of forming an NHC. Indeed, the thermal[21] and microwave-assisted[22] *intermolecular* cross-coupling of various alkenes to heterocycles including benzthiazole, benzoxazole, 4,5-dimethylthiazole, and purine are possible in the presence of a rate-enhancing weak acid such as lutidinium chloride (eqs 11 and 12, for example). In accord with the proposed mechanism, indole and pyrimidine, which are not known to form *N*-heterocyclic carbenes, do not react. However, C–H bond activation of 4,4-dimethyl-2-oxazoline, a synthetically useful formate equivalent, leads to intermediates that couple with a variety of functionalized alkenes (eq 13).[23]



(11)





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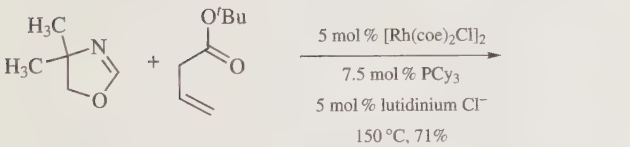
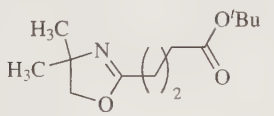
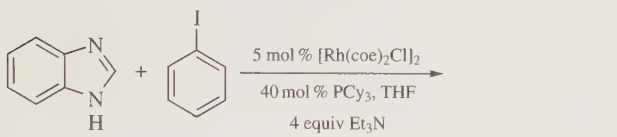
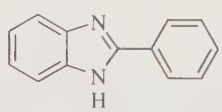




(13)

In addition to the cross-coupling of alkenes, the C(2)-carbon of benzoxazoles, benzthiazoles, and oxazolines can be directly cross-coupled with aryl iodides to give 2-arylazoles in moderate to good yield via rhodium(I) catsalysis (eqs 14–16).[24] Electron-rich aryl iodides seem to react best, while aryl chlorides do not participate in the reaction. The mechanism of the reactions is not fully elucidated, although it is suggested to proceed, in part, by oxidative addition of the aryl iodide to an NHC-rhodium intermediate.





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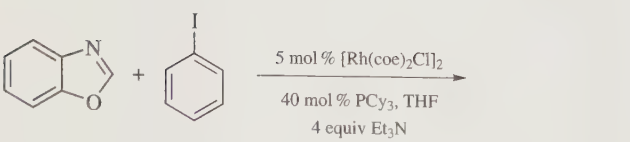

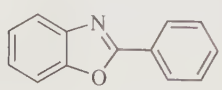

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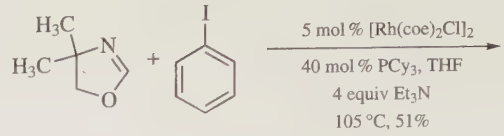
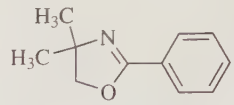
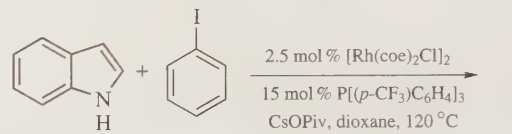
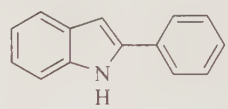




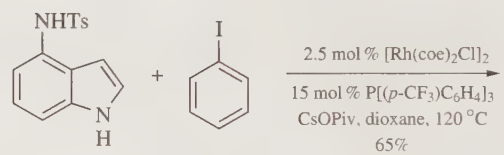
(16)

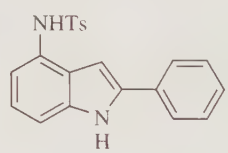
In a related process, the cross-coupling of indole and iodobenzene is accomplished in the presence of $[RhCl(coe)_2]_2$, $[p\text{-}(CF_3)C_6H_4]_3P$, and CsOPiv to regioselectively yield 2-phenylindole in excellent yield (eq 17).[25] Remarkably, the chemoselective functionalization of C–H bonds is achieved even in the presence of acidic carbamate and sulfonamide N–H bonds (eq 18, for example).





(17)



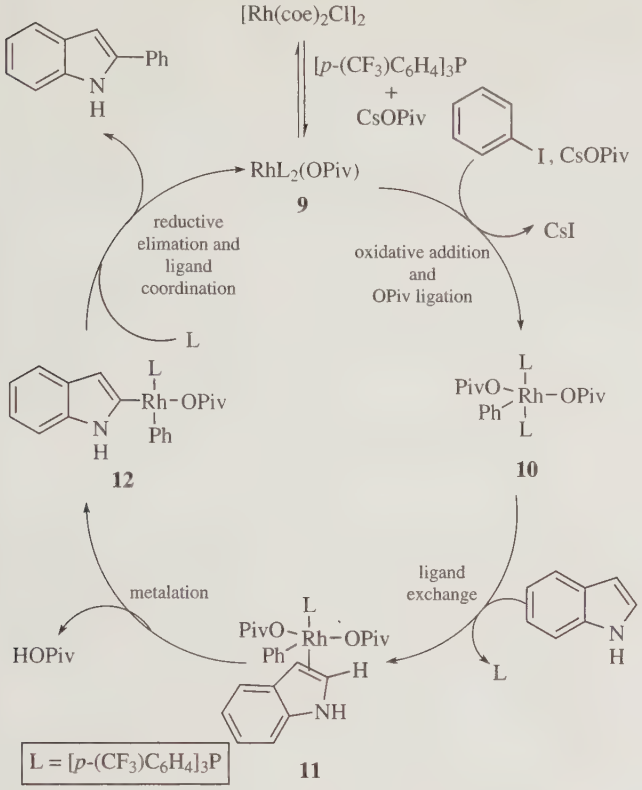


(18)

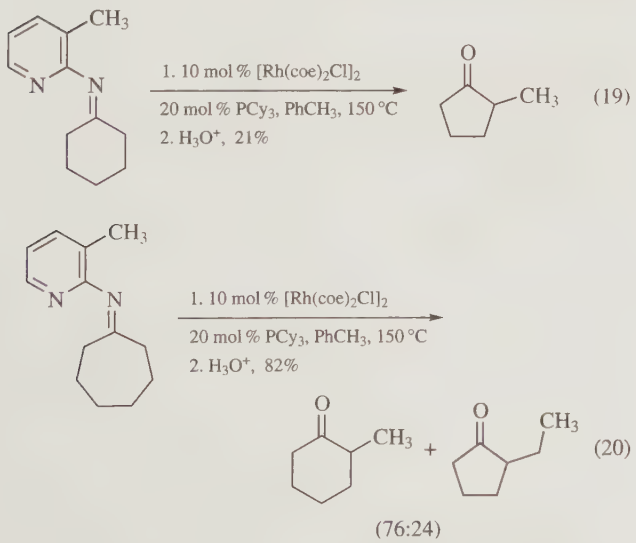
In contrast to the aforementioned reactions of benzoxazoles and benzimidazoles, which ostensibly proceed by oxidative addition of aryl iodides to NHC intermediates, the authors propose that oxidative addition of the haloarene to a rhodium(I) complex precedes the C–H bond activation step, without the intermediacy of a NHC. Hence, as outlined in Scheme 2, oxidative addition of iodobenzene to a catalytic species **9** gives the Rh(III)-aryl species **10** after pivalate-iodide exchange. Indole ligation followed by pivalate-assisted metalation gives an intermediate that can reductively eliminate the product and regenerate a catalytic Rh(I) species.

C–C Bond Activation and Sequenced C–H/C–C Bond Activation. A $[RhCl(coe)_2]_2/PCy_3$ system was used to induce the skeletal reorganization of 2-amino-3-picoline-derived cycloalkanoketimines[26] by C–C bond activation.[27] For example, reaction of the cyclohexanoketimine gives a 21% yield of 2-methylcyclopentanone after hydrolysis, while the isomerization of the cycloheptanoketimine derivative yielded a 76:24 mixture of 2-methylcyclohexanone and 2-ethylcyclopentanone in 82% yield (eqs 19 and 20). Likewise, the reaction of the cyclooctanoketimine

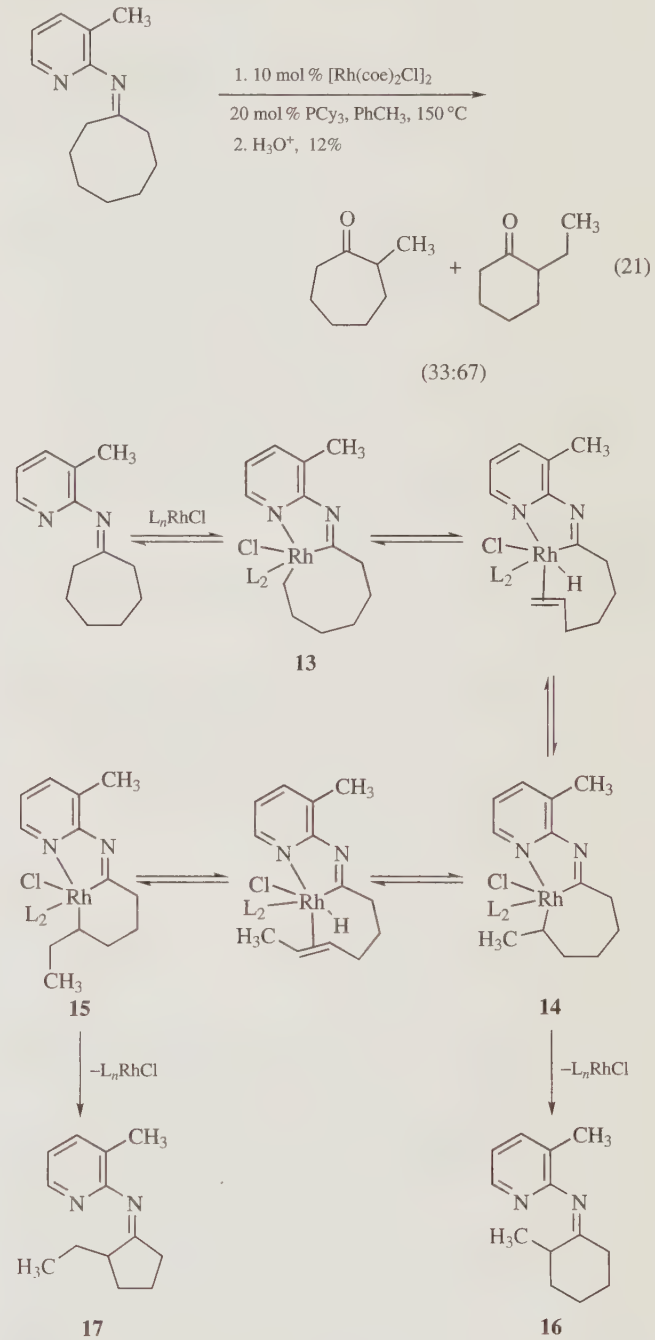
gave the ring-contracted products 2-methylcycloheptanone and 2-ethylcyclohexanone as a 33:67 mixture, respectively, in 12% yield (eq 21).



Scheme 2 A mechanism for the direct 2-arylation of indole



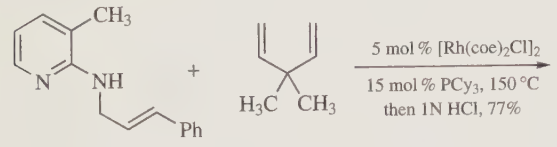
As shown in Scheme 3 for the case of the cycloheptanoketimine, the authors propose that pyridyl-directed C–C bond activation gives an (iminoacyl)Rh(III) metallacycle **13**, which then enters an equilibrium of isomeric complexes that interconvert by a series of β-hydride elimination and hydrometalation events. Hence, reductive elimination from the metallacycles **14** and **15** yields 2-methylcyclohexanoketimine **16** and 2-ethylcyclopentanoketimine **17**, respectively. Interestingly, the final ketone product partition (see eq 20) seems to parallel the thermodynamic stabilities of the penultimate ketimine intermediates, although it is not clear whether **16** and **17** re-enter the equilibrium. It is noteworthy that the cyclopentanoketimine failed to isomerize as did the cyclononanone analog and its higher homologs.



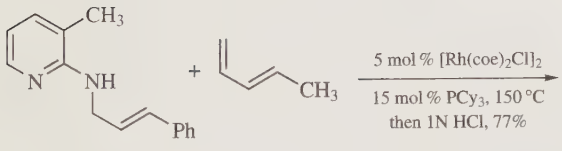
Scheme 3 A mechanism for isomerization initiated by C–C bond activation

An exciting area of research has recently emerged as the discovery of metal-catalyzed C–C bond activation has been combined with C–H bond activation to provide a new method for carbocycle synthesis. Specifically, the allylamine **18** functions as a formaldehyde equivalent in a process that yields products of formal tandem hydroacylation of dienes.[28] For example, thermal reaction of 3,3-dimethyl-1,4-pentadiene with **18** in the presence of $[RhCl(coe)_2]_2$ and PCy_3 gives the cyclohexanone product in 77% yield (eq 22).

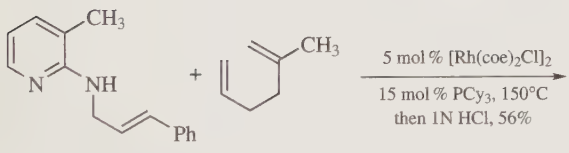
The reactions of 1,3-pentadiene (piperylene) and 2-methyl-1,5-hexadiene give the cyclopentanone and cycloheptanone products respectively (eqs 23 and 24). Also, symmetrical acyclic ketones can be made under analogous conditions by reacting allylamine **18** with an excess of a terminal mono-alkene such as 1-hexene.[29]



(22)



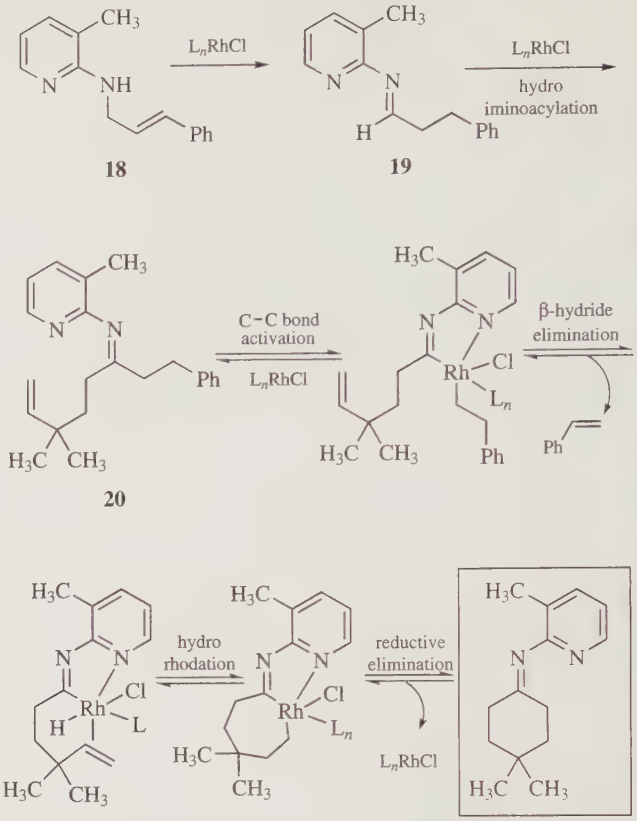
(23)



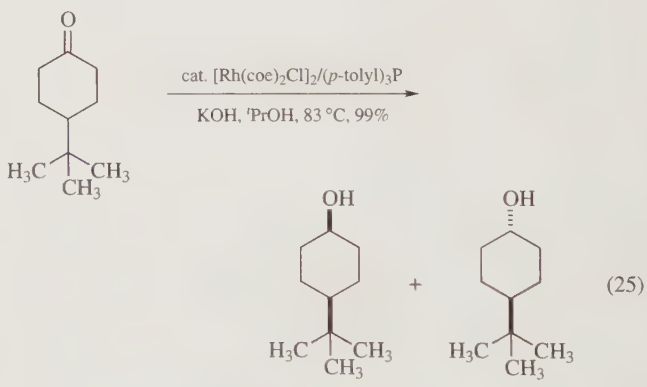
(24)

The reactions are postulated to proceed by the complicated sequence of events as summarized in Scheme 4 for the reaction of 3,3-dimethyl-1,4-pentadiene with **18**. Thus, rhodium-catalyzed alkene isomerization of **18** gives the aldimine **19**, which reacts by directed hydroiminoacylation (as outlined in eq 3) to produce the ketimine **20**. Subsequent pyridyl-directed activation of the homobenzylic C–C bond and loss of styrene leads to the imino-acylrhodium(III) hydride **21**. Hydrometallation and reductive elimination regenerates a rhodium(I) species and releases the penultimate ketimine intermediate, which, interestingly, may re-enter the reaction manifold by C–C bond activation. To this point, the reaction of 1,5-hexadiene produces a 38:40:22 mixture of cycloheptanone, 2-methylcyclohexanone, and 2-ethylcyclopentanone that likely arises as a result of cycloalkanoketimine isomerization as illustrated in Scheme 3.

Hydrogenation. The use of $[RhCl(coe)_2]_2$ modified by a variety of ligands has been reported for the hydrogenation of alkenes.[30] The hydrogenation of cyclohexene with $[RhCl(coe)_2]_2$ in the presence of 2-aminopyridine occurs one order of magnitude faster than that with Wilkinson's catalyst alone.[31] The moderately diastereoselective transfer hydrogenation of 4-*tert*-butylcyclohexanone with isopropanol in the presence of KOH is catalyzed by a $[RhCl(coe)_2]_2$/(*p*-tolyl)$_3$P system (eq 25).[32]



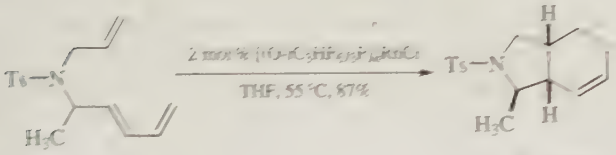
Scheme 4 A mechanism for the formal tandem hydroacylation of 3,3-dimethyl-1,4-pentadiene



(25)

(3:1)

[4 + 2] Cycloadditions. The intramolecular [4 + 2] cycloadditions of non-activated enedienes and dieneynes are catalyzed by 1,1,1,3,3,3-hexafluoroisopropyl phosphite-modified $[RhCl(coe)_2]_2$.[33] Diastereoselective substrate-controlled formation of hexahydroisoindoles under very mild conditions with this catalyst system and stands in sharp contrast conditions to the thermal non-catalyzed equivalents (>140 °C), which yield mixtures of diastereomers in moderate yield (eq 26).[34] An asymmetric variant[35] of the reaction, catalyzed by (+)-DIOP-modified $[RhCl(coe)_2]_2$, delivers hexahydroisoindoles with moderate enantiomeric excess (eq 27).[36]



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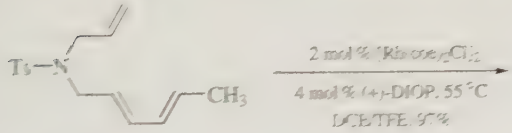

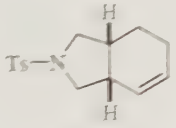

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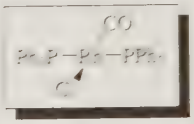
Rhodium(I) Carbonyl(chloro)bis (triphenylphosphine)



(trans/cis)
[13938-94-8] $C_{37}H_{30}ClOP_2Rh$ (MW 690.96)
(trans)
[15318-33-9]
(cis)
[16353-77-8]

(catalyst for carbonylation,[2] decarbonylation,[3] carbonyl exchange,[4] reduction,[5] hydrometalation,[6] and C–H activation reactions;[7] reagent for alkylation of acid chlorides[8])

Physical Data: mp 209–210 °C (*trans* isomer), 204–205 °C (*cis* isomer), 195–197 °C (*trans/cis* mixture); IR carbonyl stretching 1970 cm^{-1} (nujol mull), 1977 cm^{-1} ($CHCl_3$).

Solubility: sol chloroform and dichloromethane; moderately sol aromatic hydrocarbons and CCl_4; insol ether, alcohols, and aliphatic hydrocarbons.

Form Supplied in: bright yellow crystalline solid, widely available.

Preparative Method: to a solution of $RhCl_3 \cdot 3H_2O$ (2 g, 7.6 mmol) in 70 mL of absolute ethanol is slowly added triphenylphosphine (7.2 g, 2.75 mmol) in 300 mL of boiling absolute ethanol. The solution becomes clear within 5 min, at which point sufficient (10–20 mL) 37% formaldehyde solution is added, causing the red solution to become pale yellow.

After several minutes, yellow microcrystals precipitate. Upon cooling, the resulting crystals are washed with ethanol and diethyl ether, dried (4.5 g, 85%) and recrystallized from hot toluene.[1c]

Handling, Storage, and Precautions: the complex is air-stable as a crystalline solid and can be stored without special precautions. In solution it readily reacts with oxygen, which therefore must be excluded during preparation and use of this reagent.

Original Commentary

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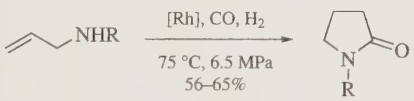
Carbonylation Reactions. Rhodium is the most widely used catalyst for the carbonylation of alkenes with CO and H_2.[1,2] Although $RhH(CO)_2L_2$ (L = PPh_3, PBu_3, etc.) is recognized as the actual species that reacts with alkenes in the ligand modified rhodium catalyst system, many other rhodium complexes can be utilized as precursors in the presence of suitable ligands (L), CO, and H_2. $RhCl(CO)(PPh_3)_2$ has been used as a catalyst precursor in the hydroformylation of alkenes and formaldehyde.[1b,2b]

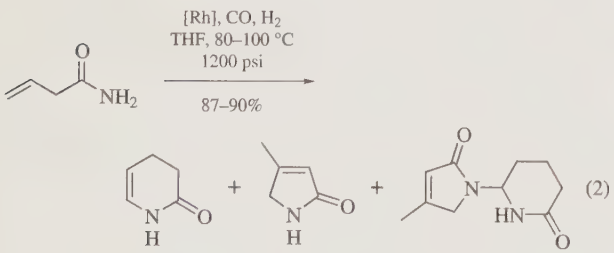
Hydroformylation of terminal alkenes produces a mixture of regioisomeric linear and branched aldehydes. Triphenylphosphine-stabilized rhodium catalysts can be used to form linear, unbranched aldehydes from simple alkenes such as propene. The presence of triphenylphosphine, however, gives poor results in the hydroformylation of $R_fCH{=}CH_2$ (R_f = perfluoroalkyl group), which with ***Dodecacarbonyltetrarhodium*** or ***Hexadecacarbonylhexarhodium*** produces the branched aldehydes $R_fCH(CHO)Me$ regioselectively and in good yields.[9]

Heterocyclic compounds have been obtained through rhodium-catalyzed hydroformylation of functionalized alkenes such as allylamines (eq 1),[10] 3-butenamides (eq 2)[11] and allyl alcohols.[12]



(1)

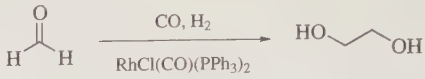
[Rh] = $RhCl(CO)(PPh_3)_2$ or $Rh(acac)CO(PPh_3)_2$



(2)

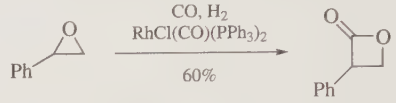
[Rh]	
$RhCl(CO)(PPh_3)_2$	53:47: 0
$RhH(CO)PPh_3)_3$–dppb	98: 2: 0
$RhCl(PPh_3)_3$	53:41: 6
$RhCl(PPh_3)_3$–10 $P(OPh)_3$	3: 3:94

Hydroformylation of formaldehyde has been extensively investigated because of its importance to the commercial production of ethylene glycol (eq 3).[1b,13] The $RhCl(CO)(PPh_3)_2$–***Triethylamine*** catalyst system produced a mixture of straight chain carbohydrates, from trioses to hexoses.[14] The hydroformylation in the presence of 3-ethylbenzothiazolinium bromide gives trioses selectively.



(3)

$RhCl(CO)(PPh_3)_2$ catalyzes the reaction of CO with epoxides (eq 4),[15] amines (eqs 5 and 6),[16,17] and azides (eq 7).[17]



(4)

(5)

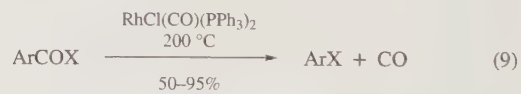
(6)

(7)

[Rh] = $RhCl(CO)(PPh_3)_2$, $[RhCl(CO)(dppe)]_2$, $[Rh(dppp)_2Cl]_2$

Decarbonylation Reactions. $RhCl(CO)(PPh_3)_2$ is a product of the stoichiometric decarbonylation of aldehydes with ***Chlorotris(triphenylphosphine)rhodium(I)*** (eq 8).[3b,18] However, at elevated temperatures $RhCl(CO)(PPh_3)_2$ is an effective catalyst for the decarbonylation of aroyl chlorides and aroyl cyanides (eq 9).[3a,19]

(8)



(9)

Carbonyl Exchange (Isotope Labelling). The carbonyl carbon of aroyl chlorides can be ^{13}C or ^{14}C labelled through acyl carbonyl exchange reactions with CO catalyzed by $RhCl(CO)(PPh_3)_2$ without formation of aryl chloride (ArCl) decarbonylation products (eqs 10 and 11).[4] Statistical distribution of ^{13}C is easily attained. The carbonyl group of aliphatic acid chlorides is also easily exchanged, but small amounts of decarbonylated products are formed.[4] Alkene migration or isomerization does not occur in the carbonyl exchange reactions of 3-butenoyl chlorides, although 1,3-scrambling of chlorine has been observed in the $RhCl(PPh_3)_3$-catalyzed decarbonylation of 3-butenoyl chlorides to allyl chlorides.[20]

(10)

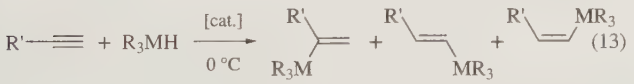
(11)

Reduction Reactions. The most widely studied homogeneous hydrogenation catalysts are all rhodium complexes. $RhCl(CO)(PPh_3)_2$ has been rarely used because of its low reactivity as a hydrogenation catalyst. The low reactivity, however, allows it to be a potentially useful catalyst for selective hydrogenation of terminal alkenes.[21] $RhCl(CO)(PPh_3)_2$-catalyzed reduction of diphenylacetylene with ***Sodium Borohydride*** gives (*Z*)-stilbene, whereas (*E*)-stilbene is formed with $RhCl(PPh_3)_3$ as the catalyst.[22]

Aromatic nitro compounds are reduced in good yields to aromatic amines with secondary alcohols as the reducing agent using the $RhCl(CO)(PPh_3)_2$–KOAc catalyst system (eq 12).[23]

$$ArNO_2 \xrightarrow[120\text{–}150\ ^\circ C]{RhCl(CO)(PPh_3)_2,\ R_2CHOH} ArNH_2 \qquad (12)$$

Hydrometalation Reactions. For the catalytic hydrometalation of alkenes, $RhCl(CO)(PPh_3)_2$ has no advantages over $RhCl(PPh_3)_3$ and its congeners, chloroplatinic acid (***Hydrogen Hexachloroplatinate(IV)***),[24] or radical catalysts.[25] The regioselectivity of hydrometalation of terminal alkynes depends on the ligands. For example, the hydrosilation and hydrogermylation of phenylacetylene in the presence of $RhCl(CO)(PPh_3)_2$ gives (*E*)-1-silyl- or 1-germyl-substituted 2-phenylethylene, whereas with $Rh[(CF_3CO)_2CH](C_2H_4)_2$ the isomeric 2-metalated 2-phenylethylenes are produced (eq 13).[26] In the hydrostannation of terminal alkynes, $RhCl(CO)(PPh_3)_2$ gives 2-stannyl-1-alkenes as the major product.[6]



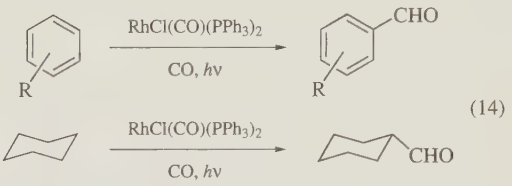
(13)

M	R'	R	[Cat]	Yield (%)	Isomer ratio
Si	Ph	Et	$RhCl(CO)(PPh_3)_2$	97	6:72:22
Si	Ph	Et	$Rh[(CF_3CO)_2CH](C_2H_4)_2$	93	96:4:trace
Ge	Ph	Bu	$RhCl(CO)(PPh_3)_2$	65	7:70:23
Ge	Ph	Bu	$Rh[(CF_3CO)_2CH](C_2H_4)_2$	85	95:4:1
Sn	Ph	Bu	AIBN, 80 °C	81	0:67:33
Sn	Ph	Bu	$RhCl(CO)(PPh_3)_2$	99	78:20:2
Sn	Ph	Bu	$RhCl(CO)(PPh_3)_2$, RI[a]	90	100:0:0
Sn	$AcOCH_2$	Bu	$RhCl(CO)(PPh_3)_2$	71	73:27:trace
Sn	$SiMe_3$	Bu	$RhCl(CO)(PPh_3)_2$	91	76:24:0

[a] RI = radical inhibitor, galvinoxyl

Hydrosilanes easily react with acylmetal complexes (metal = Fe, Mo, Mn) to form silyloxyalkyl metal complexes by using $RhCl(CO)(PPh_3)_2$ or $Rh(CO)(PPh_3)_3$ as catalysts.[27]

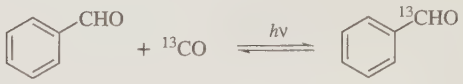
Hydrocarbon C–H Activation. Under photochemical conditions, $RhCl(CO)(PPh_3)_2$ activates C–H bonds of aromatic and aliphatic hydrocarbons, leading to carbonylated products (eq 14)[7,28] and/or dehydrogenated products (eq 15).[29] UV irradiation of a solution of $RhCl(CO)(PPh_3)_2$ leads to the extrusion of CO to form a coordinatively unsaturated complex, $RhCl(PPh_3)_2$ (eq 16), which then inserts into the C–H bond of the hydrocarbon.[30] This photochemical reaction can be used for isotope labelling of aldehydes with ^{13}CO (eq 17).[28]



(14)

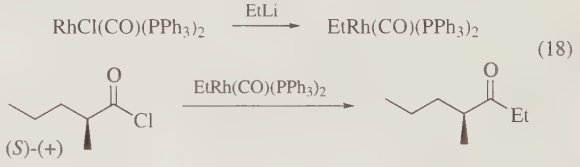
$$C_nH_{2n+2} \xrightarrow{RhCl(CO)(PPh_3)_2} C_nH_{2n} + H_2 \qquad (15)$$

$$RhCl(CO)(PPh_3)_2 \underset{\Delta}{\overset{h\nu}{\rightleftharpoons}} RhCl(PPh_3)_2 + CO \qquad (16)$$

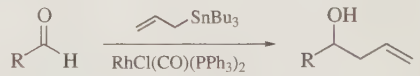


(17)

Alkylation of Acid Chlorides. A number of rhodium complexes, including *trans*-$RhCl(CO)(PPh_3)_2$, facilitate the alkylation of acid chlorides, affording ketones in moderate to high yields.[8] This reaction proceeds by initial pretreatment of the catalyst precursor with an appropriate Grignard, organolithium, or organoytterbium[31] reagent to give an active alkylrhodium(I) species (eq 18). This reaction is specific for acid chlorides. Alkylation of ketones[32] and amines[33] can also be effected by *trans*-$RhCl(CO)(PPh_3)_2$ in a carbon monoxide–water system. In a more recent study,[34] nucleophilic addition of allylic stannanes to aromatic aldehydes has been accomplished by using derivatives of *trans*-$RhCl(CO)(PPh_3)_2$ in high yields (eq 19).



(18)

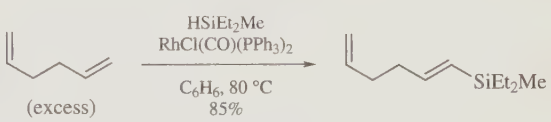


(19)

Oxidation Reactions. The liquid phase oxidation of benzaldehyde to benzoic acid proceeds readily in the presence of a catalytic amount of *trans*-$RhCl(CO)(PPh_3)_2$ in benzene and under an atmosphere of oxygen (conversion is 78%).[35] Oxidation of terminal alkenes to methyl ketones also employs the use of a rhodium catalyst.[36]

Miscellaneous. *trans*-$RhCl(CO)(PPh_3)_2$ is a moderately active catalyst precursor for the hydrosilation[37] and transfer hydrogenation[38] of imines. This rhodium complex is also used in the photochemical dehydrogenation of hydrocarbons,[39] and the thermal carbonylation of alkyl halides.[40]

The reaction of 1,5-dienes with hydrosilanes using *trans*-$RhCl(CO)(PPh_3)_2$ gives dehydrogenative silylation products, 1-silyl-1,5-dienes, in high yields (eq 20).[41]

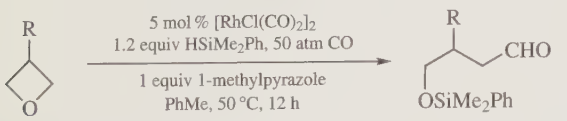


(20)

First Update

Mitchell P. Croatt, Travis J. Williams & Paul A. Wender
Stanford University, Stanford, CA, USA

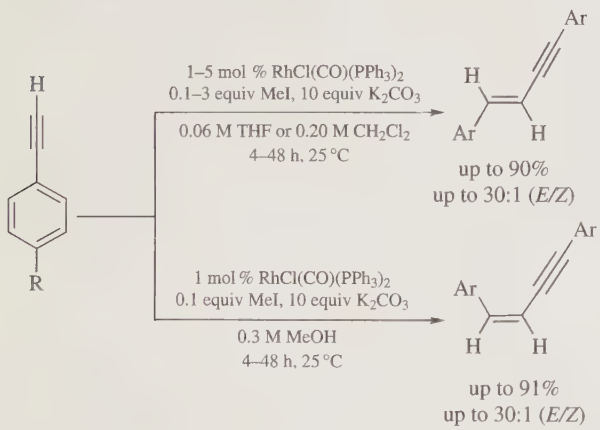
Oxetane Opening. Murai and co-workers have reported that when $[RhCl(CO)_2]_2$ is modified with 1-methylpyrazole, silylformylations of oxetanes are possible (eq 21).[42] While requiring a high pressure of CO (50 atm), the products can be prepared in up to 83% yield.



(21)

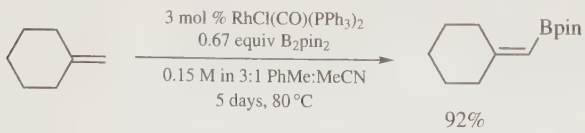
R = H: 83%
R = Me: 80%
R = Ph: 42%

Alkyne Coupling. Stang and Crittell have reported the C–H activation of terminal alkynes with $RhCl(CO)(PPh_3)_2$.[43] The resulting alkynylrhodium species are known to add to alkynes, thus affording a net rhodium-catalyzed alkyne pseudodimerization to form enynes (eq 22).[44]Interestingly, the configuration of the resulting enyne is a function of the solvent. In methanol the reaction exhibits selectivity for the formation of *Z*-enynes, but *E*-enynes are formed in reactions run in tetrahydrofuran or dichloromethane.



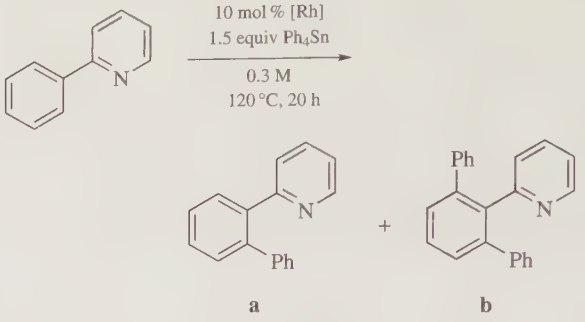
(22)

Alkene Dehydrogenative Borylation. In addition to silylation of alkene C–H groups mentioned previously (eq 20),[41] $RhCl(CO)(PPh_3)_2$ will catalyze the borylation of alkene C–H groups.[45] Although the products of some of these reactions (e.g., reactions of styrenes) are accessible by alkyne hydroboration, this method is applicable to 1,1-disubstituted alkenes, which leads to products that are difficult to prepare in other ways (eq 23).



(23)

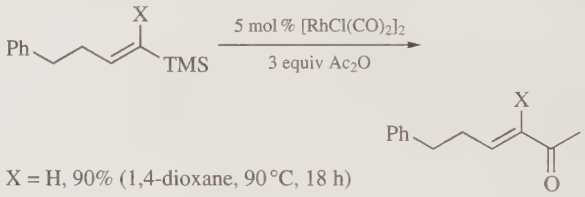
Oxidative Aryl Coupling. While pyridine-directed C–H activation/arylation is catalyzed by $RhCl(CO)(PPh_3)_2$ or $RhCl(PPh_3)_3$ in the presence of tetraaryl tin reagents, Wilkinson's catalyst is preferred (eq 24).[46]



(24)

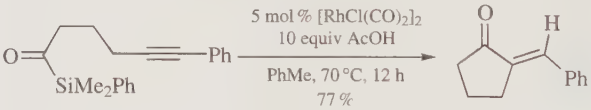
[Rh] = $[RhCl(CO)(PPh_3)_2]$ in THF: 5% **a**
[Rh] = $[RhCl(PPh_3)_3]$ in PhMe: 56% **a**, 20 % **b**

Vinyl- and Acylsilane Activation. In the presence of $[RhCl(CO)_2]_2$, vinylsilanes can be acylated by anhydrides to give α,β-unsaturated ketones (eq 25).[47] Oxygenated vinylsilanes (eq 25, X = O(CO)Ph) participate efficiently, and $[RhCl(CO)_2]_2$ can catalytically effect intramolecular hydroformylation reactions of acylsilanes (eq 26).[48]



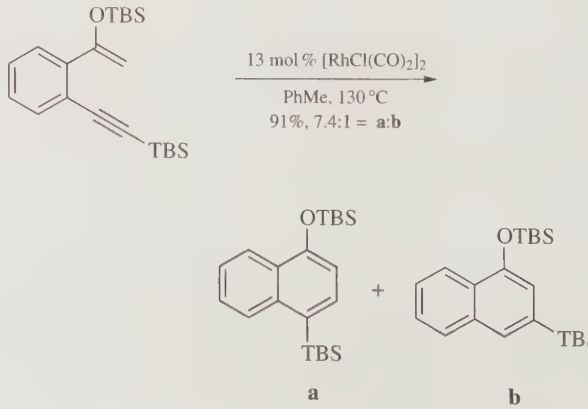
(25)

X = H, 90% (1,4-dioxane, 90 °C, 18 h)
X = OC(O)Ph, 98% (PhMe, 80 °C, 4 h)

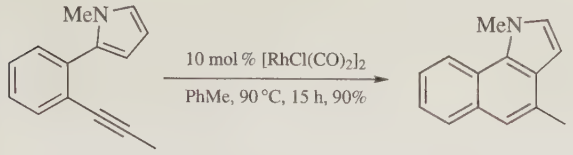


(26)

1,6-Enyne Cyclization Reactions. Among other late-metal sources, $[RhCl(CO)_2]_2$ catalyzes the cyclization of 2-alkynyl styrenes to give substituted naphthalenes (eqs 27 and 28).[49] The reaction tolerates a wide range of substituents on both the olefin and the alkyne. In addition to $[RhCl(CO)_2]_2$, the most useful catalysts were found to be $PdCl_2$ and $PtCl_2$. When the starting alkyne is a silylacetylene, migration of the silyl group is observed (eq 27).



(27)



(28)

[5 + 2] Cycloaddition Reactions. The [5 + 2] cycloaddition reactions[50] of tethered alkyne-vinylcyclopropanes (VCPs)[51–54] (eqs 29 and 30) and allene-VCPs[55] (eq 31) are efficiently catalyzed by $[RhCl(CO)_2]_2$. Tethered alkene-VCPs react more efficiently in the presence of modified Wilkinson's catalyst or $[(C_{10}H_8)Rh(cod)]SbF_6$ (eq 32).[54,56]

(29)

10 mol % $RhCl(PPh_3)_3$	2.0 M PhMe	110 °C	3 h	89%
1 mol % $[RhCl(CO)_2]_2$	0.01 M TFE	55 °C	19 h	90–95%
2 mol % $[(C_{10}H_8)Rh(cod)]SbF_6$	0.15 M DCE	rt	15 min	>99%

3.3:1 *E*:*Z*

(30)

10 mol % $RhCl(PPh_3)_3$/AgOTf	PhMe	110 °C		0
5 mol % $[RhCl(CO)_2]_2$	PhMe	110 °C	20 min	80%

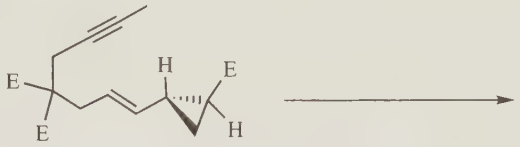
(31)

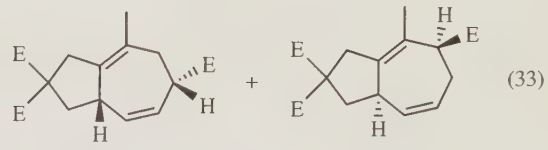
0.2 mol % $RhCl(PPh_3)_3$	1.0 M PhMe	100 °C	6 h	90%
1 mol % $[RhCl(CO)_2]_2$	0.1 M DCE	80 °C	6 h	89%

(32)

0.1 mol % $RhCl(PPh_3)_3$/AgOTf	0.01 M PhMe	110 °C	15 h	90%
5 mol % $[(C_{10}H_8)Rh(cod)]SbF_6$	0.05 M DCE	60 °C	6 h	96%

In reactions of a tethered alkyne-VCP containing a cyclopropane substituted in the 2-position, $[RhCl(CO)_2]_2$ offers regioselectivity which is opposite of bulkier Rh(I) sources. In the systems studied, the Rh(I) catalysts are generally more selective than Ru(II) catalysts (eq 33) and applicable to a wider range of substrates.[57–59]





a b

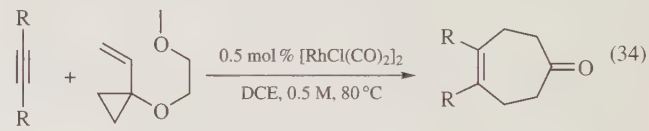
(33)

10 mol % $RhCl(PPh_3)_3$/AgOTf
10 mM in PhMe, 1 h, 110 °C — 81% (20:1 **a**:**b**)

5 mol % $[RhCl(CO)_2]_2$
10 mM in PhMe, 1 h, 110 °C — 93% (1:11 **a**:**b**)

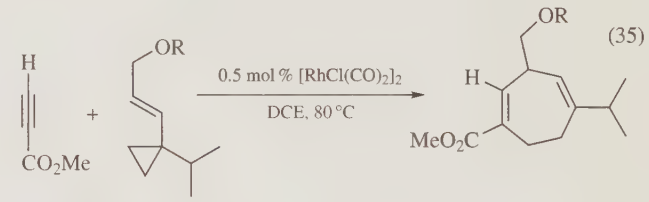
10 mol % $[CpRu(NCMe)_3)_3]^+ PF_6^-$
200 mM in acetone, rt — 88% (1:2.5 **a**:**b**)

Intermolecular [5 + 2] cycloaddition reactions are readily achieved with a variety of alkynes and VCPs. Although oxygenation of the VCP in the 1-position is beneficial to reactivity (eq 34),[60,61] it is not essential (eq 35).[62] Allenes will also react in the [5 + 2] process, thus giving *exo*-alkylidene cycloheptanones (eq 36).[63]



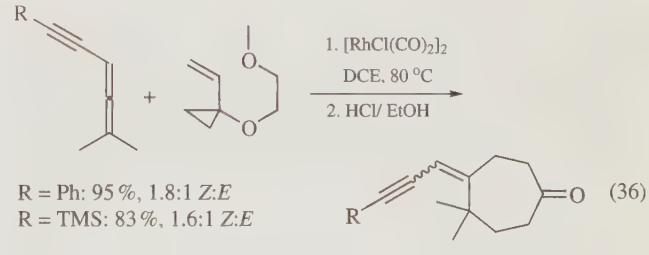
(34)

R = CO_2Et, CO_2Et	96%
R = $CH_2N(H)Ts$, H	87%
R = $(CH_2)_3CO_2H$, H	87%
R = H, H	75%



(35)

R = H 82%
R = TBS 93%

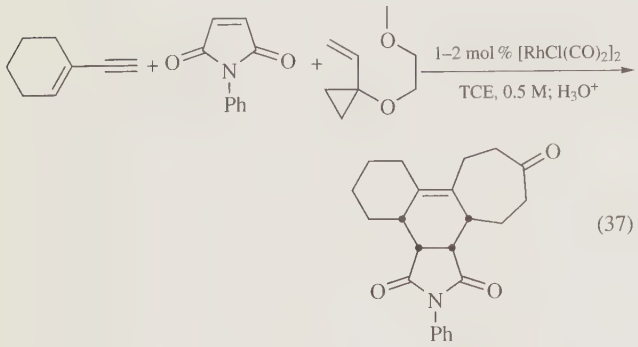


R = Ph: 95 %, 1.8:1 *Z*:*E*
R = TMS: 83 %, 1.6:1 *Z*:*E*

(36)

Since the intermolecular [5 + 2] reaction is completely chemoselective for alkynes over alkenes, a serial [5 + 2]/[4 + 2] reaction in which a VCP is reacted with a conjugated enyne and dienophile is possible (eq 37).[64] Mechanistically, this reaction proceeds with

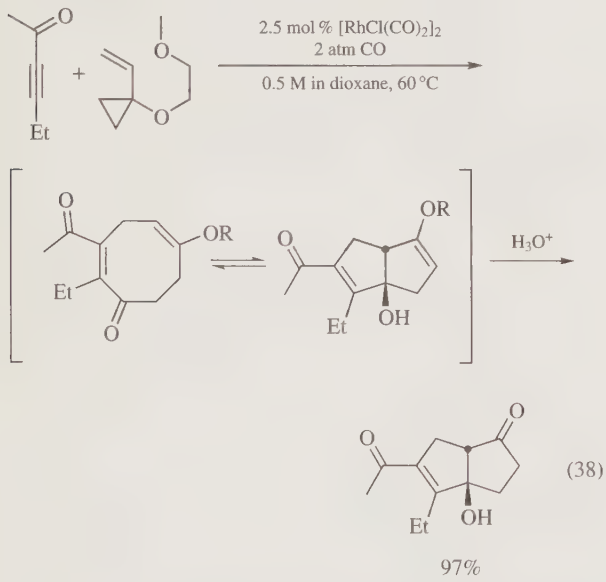
initial [5 + 2] reaction of the alkyne and VCP to give an intermediate diene, which reacts with the dienophile in situ, forming four consecutive stereocenters. This reaction is readily scalable, with reactions of up to 100 mmol producing excellent yields.



(37)

91%

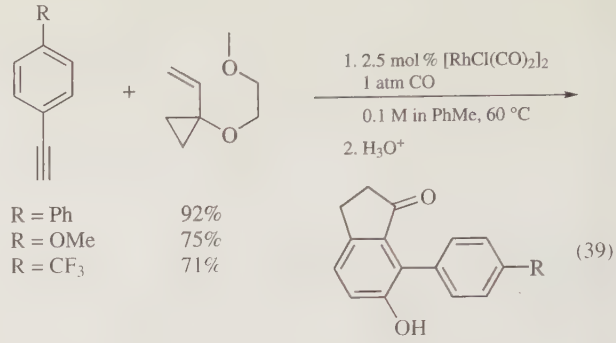
[5 + 2 + 1] and [5 + 1 + 2 + 1] Cycloadditions. In the presence of 1 or 2 atm of CO [5 + 2 + 1] cycloadditions of a VCP, alkyne, and CO can be realized. These reactions proceed in high yield and with high regioselectivity with a variety of alkynes. The initially formed eight-membered ring products undergo transannular closure to give, after hydrolysis, bicyclo[3.3.0]octenone adducts (eq 38).[65] This reaction has also been accomplished with an allene as the two-carbon component.[63]



(38)

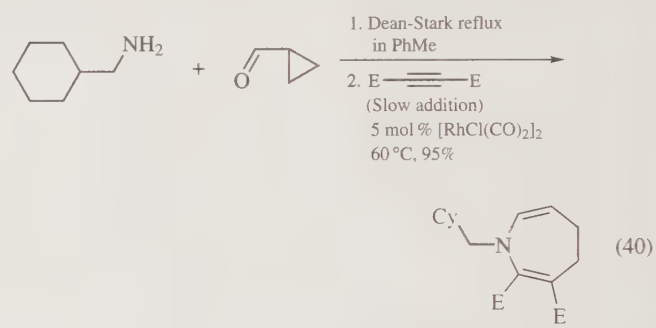
97%

Reaction of a VCP and terminal alkynes with $[RhCl(CO)_2]_2$ under 1 atm of CO produced an unexpected [5 + 1 + 2 + 1] adduct (eq 39).[66] The mechanism of this reaction involves incorporation of two molecules of CO, a VCP, and an alkyne to initially produce a nine-membered ring, which undergoes ring closure to give the observed biaryl product. *para*-Substituted aryl alkynes generally give good yields, and aryl alkynes bearing groups at the *meta*- or *ortho*-positions react successfully. Halogen groups are tolerated, enabling further elaboration of the biaryl core. This reaction can be run bidirectionally, impressively combining seven components in a single flask!



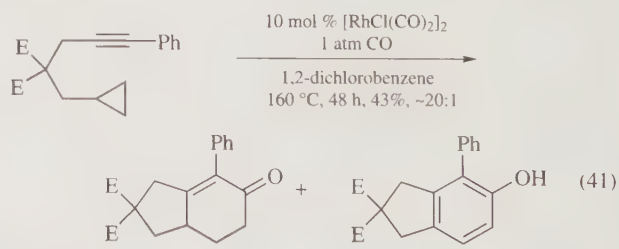
(39)

Hetero-[5 + 2] Cycloadditions. In addition to VCPs, cyclopropyl imines can be used in [5 + 2] reactions, affording access to dihydroazepines (eq 40).[67] The reaction is very efficient with a variety of aldimines and ketimines, either preformed or synthesized in situ in a serial imine formation/aza-[5 + 2] cycloaddition procedure, in up to multigram quantities. Substitution of the cyclopropane is also well-tolerated, leading to single regioisomeric products via cleavage of the less substituted cyclopropyl bond. Moreover, Murai reports that $[RhCl(CO)_2]_2$ will convert a cyclopropyl imine to the corresponding pyrrole.[68]



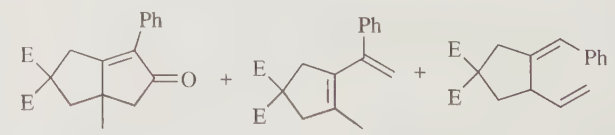
(40)

[3 + 2 + 1] Cycloadditions of 4-Pentynylcyclopropanes and CO. $[RhCl(CO)_2]_2$ converts 4-pentynylcyclopropanes and CO to bicyclo[4.3.0]nonenones in up to 60% yield.[69] Oxidation accompanies cycloaddition in most cases, generating a small amount of phenol adduct (eq 41).



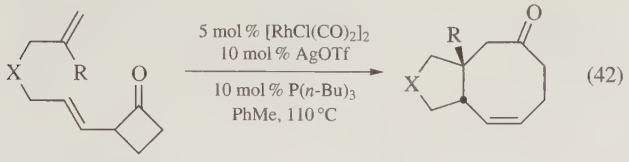
(41)

Also observed in trace quantities:



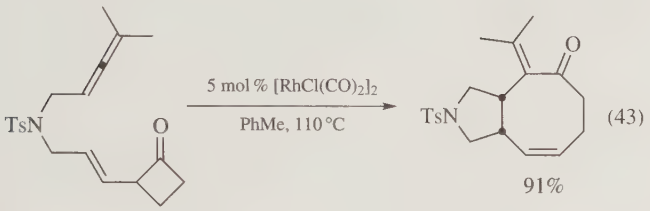
[6 + 2] Cycloadditions. A number of Rh(I) sources, $RhCl(CO)(PPh_3)_2$, $RhCl(PPh_3)_3$, and $[RhCl(CO)_2]_2$ are competent catalysts for [6 + 2] cycloaddition reactions of tethered alkene

and allene-vinylcyclobutanones (eqs 42 and 43). A variety of functional groups and substitution patterns are tolerated in this reaction and quaternary centers can be set.[70]



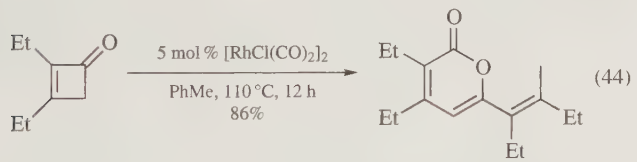
(42)

X = O; R = H: 80%
X = $C(CO_2Me)_2$; R = Me: 78%

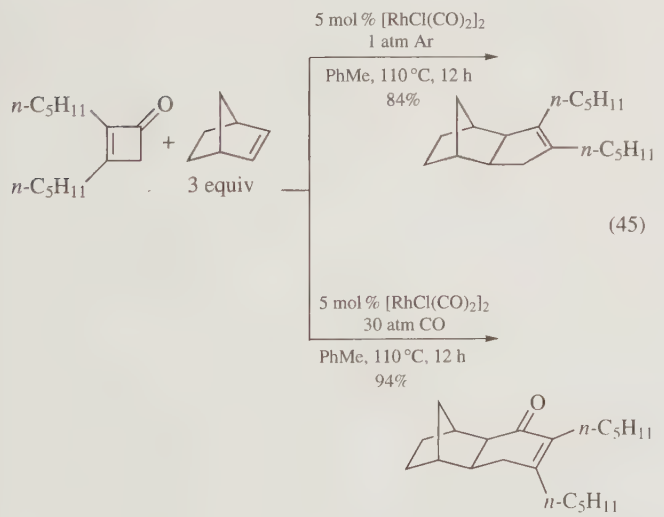


(43)

[4 + 2] and [3 + 2] Cycloadditions of Cyclobutenones and Norbornene. Both $[RhCl(CO)_2]_2$ and $[RuCl_2(CO)_2]_2$ will dimerize cyclobutenones to give 2-pyranones (eq 44). $[RhCl(CO)_2]_2$ will also catalyze the decarbonylative [3 + 2] reaction of cyclobutenones with norbornene. Under 30 atm of CO, a [4 + 2] product is observed (eq 45).[71]

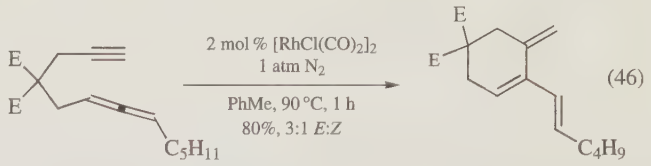


(44)

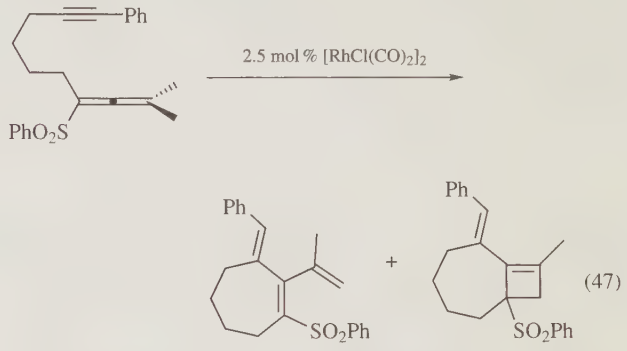


(45)

Cycloisomerization Reactions. Ene reactions of tethered alkyne-allenes have been realized using a catalytic amount of $[RhCl(CO)_2]_2$ (eq 46).[72] This reaction has also been reported to produce cyclobutene systems (eq 47).[73] When tethered alkyne-allenes are treated with $AgBF_4$ and 1 atm of CO, efficient [2 + 2 + 1] reactions ensue (eq 48, further described under Allenic Pauson-Khand reactions).[74] This example illustrates two of the structurally diverse heterocycles possible from the same starting material.

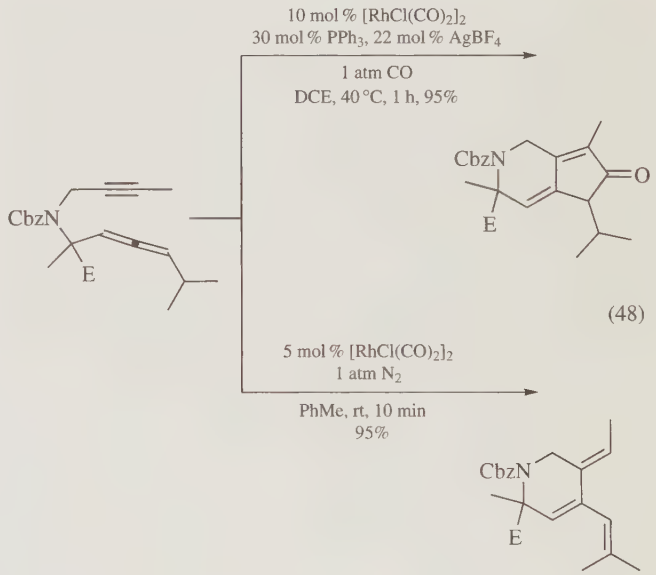


(46)



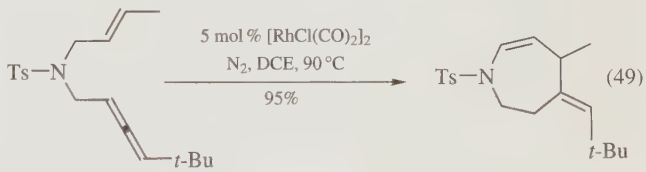
(47)

PhMe, 80 °C, 20 h	62%	0%
xylenes, reflux, 13 h	10%	80%

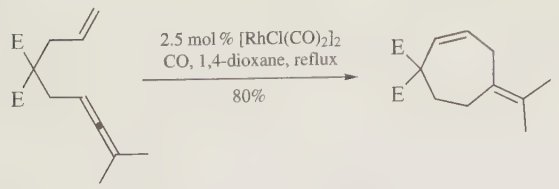


(48)

When a tethered alkene-allene was treated with $[RhCl(CO)_2]_2$, ene-type products resulted. This reaction, reported by both the Brummond[75] and Itoh[76] groups, has been used to produce seven-membered carbo- and heterocycles (eqs 49 and 50). Surprisingly, this reaction is preferred to carbonylative pathways, even under 1 atm of carbon monoxide.

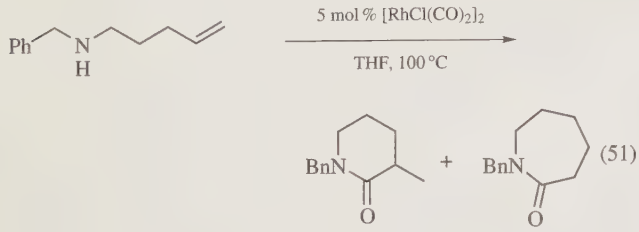


(49)



(50)

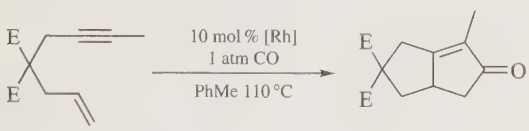
Cyclocarbonylation of 4- and 5-Amino Alkenes. In the presence of HCl and high pressures of CO, 4- and 5-amino alkenes can be cyclocarbonylated by $[RhCl(CO)_2]_2$ (eq 51). Other rhodium and cobalt catalysts were also applicable in forming the six- and seven-membered lactams.[77]



(51)

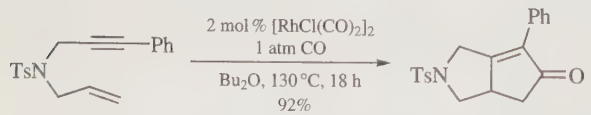
10 mol % HCl, 69 bar CO, 87% 57 : 43
5 mol % HCl, 35 bar CO, 79% 78 : 22

Pauson-Khand Reactions. Intramolecular Pauson-Khand-like reactions are possible using rhodium(I) catalysts when used with tethered 1,6-enynes.[78] Some rhodium species $(RhCl(CO)(PPh_3)_2$ and $RhCl(PPh_3)_3)$ need to be activated by the use of silver salts (eq 52) while others ($[RhCl(CO)(dppe)]_2$ and $[RhCl(CO)_2]_2$) are active without dechlorination of the rhodium precursor (eq 53).[79,80] Presently, the intermolecular Pauson-Khand reaction can only be accomplished with very reactive alkenes such as norbornene or ethylene. These alkenes typically afford a mixture of cyclopentenone products in only moderate yields (eq 54). Modification of $[RhCl(CO)_2]_2$ with BINAP affords asymmetric induction in the intramolecular Pauson-Khand reaction (eq 55).[81] Desymmetrization reactions of 1,4-dienes tethered to alkynes are also possible with this catalyst.[82]



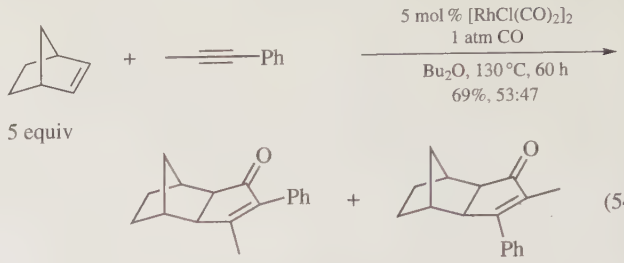
(52)

[Rh] = $RhCl(CO)(PPh_3)_2$/AgOH: 90%
[Rh] = $RhCl(PPh_3)_3$/AgOH: 89%
[Rh] = $[RhCl(CO)(dppe)]_2$: 96%

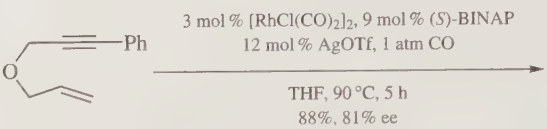


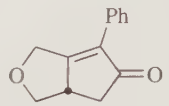
(53)

Compared to the intramolecular Pauson-Khand reactions of tethered enynes, a tethered diene-yne is more reactive. Under certain conditions a mixture of [2+2+1], [4+2+1], and [4+2] products were formed (eq 56).[83] The dienyl Pauson-Khand reaction has also been performed with cyclic dienes tethered to alkynes to produce tricyclic products (eq 57).[84] Intermolecular [2+2+1] reactions of CO, alkynes, and butadienes also react efficiently in the presence of $[RhCl(CO)_2]_2$ (eq 58).[85]

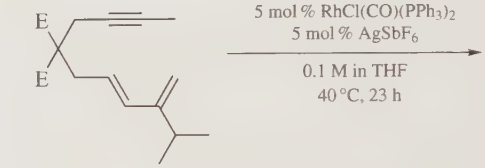


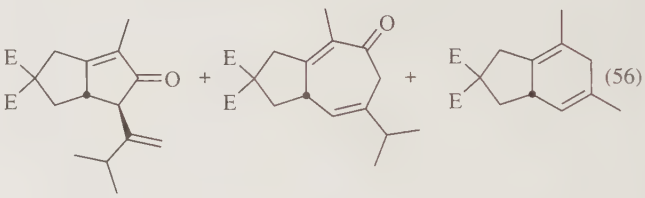
(54)





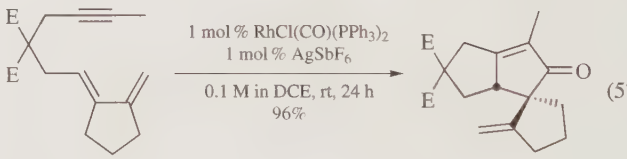
(55)





(56)

25% 18% 45%



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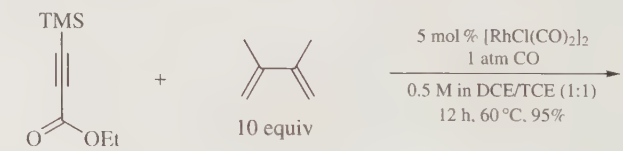
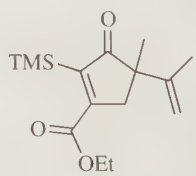
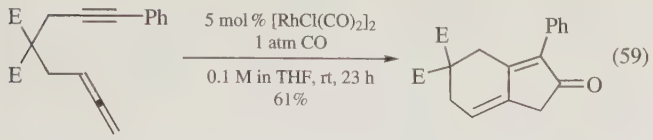




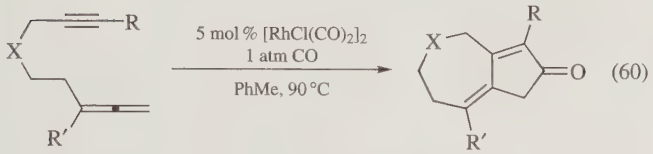
(58)

Allenic Pauson-Khand Reactions. The rhodium(I)-catalyzed [2+2+1] reaction of tethered alkyne-allenes, the allenic Pauson-Khand reaction, was first reported in 2001. Initially reported yields were moderate, but selective reaction of the distal double bond of the allene was observed (eq 59).[80] Studies by the Brummond and Mukai groups revealed that $[RhCl(CO)_2]_2$ is an excellent catalyst, accepting a wide variety of substrates. Both

groups report selectivity for cycloaddition across the distal olefin of the allene: a seven-membered ring is formed in preference to reaction of the proximal allene double bond (eq 60).[86–88]



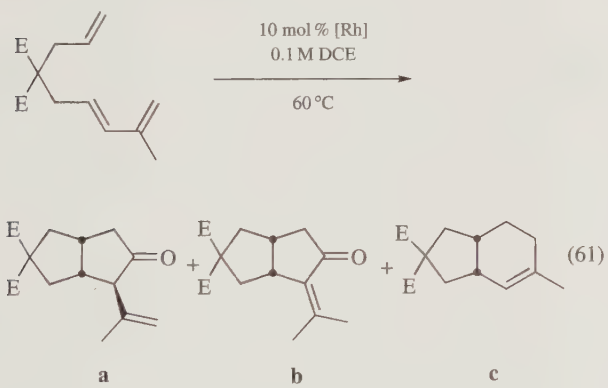
(59)



(60)

$X = CH_2$	R = H	$R' = SO_2Ph$	84%
$X = C(CO_2Me)_2$	R = *i*-Pr	R′ = H	76%
$X = C(CO_2Me)_2$	R = Ph	R′ = H	77%

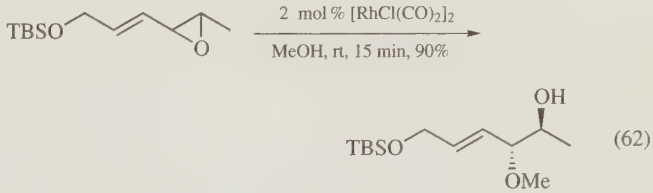
Diene-Ene [2+2+1] Cycloadditions. Tethered diene-enes also readily react with rhodium(I) sources in a [2+2+1] fashion. Although the reaction is faster with a catalyst formed from $RhCl(CO)(PPh_3)_2$ and $AgSbF_6$, reactions with $[RhCl(CO)_2]_2$ are higher yielding and afford less isomerization (eq 61).[89] When $[(C_{10}H_8)Rh(cod)]SbF_6$[54] was used, a [4+2] cycloaddition occurred selectively. An intermolecular diene-ene [2+2+1] reaction is possible when norbornene is used as the alkene.



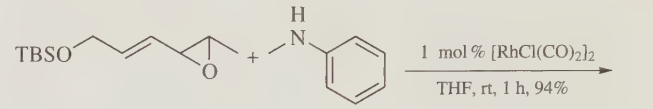
(61)

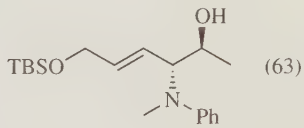
[Rh] = $RhCl(CO)(PPh_3)_2/AgSbF_6$, 2.5 h: 75% **a**, 7% **b**
[Rh] = $[RhCl(CO)_2]_2$, 5.5 h: 90% **a**, 5% **b** (5% SM recovered)
[Rh] = $[(C_{10}H_8)Rh(cod)]SbF_6$, 3 h: 76% **c**

Allylic Substitution Reactions. Vinyl epoxides undergo ring opening with an alcohol or aniline using $[RhCl(CO)_2]_2$ (eqs 62 and 63).[90] The reaction is diastereo- and regioselective, and can be conducted intramolecularly.[91] In a related reaction, oxabenzonorbornadienes can be desymmeterized by allylic substitution catalyzed by a chiral rhodium species (eq 64).[92] Although $[RhCl(CO)_2]_2$ is effective in some examples, $[RhCl(cod)]_2$ is more generally applicable. Optimal results are observed with JOSIPHOS (1-phosphino-2-(1-phosphinoethyl)-ferrocene)-based ligands.



(62)





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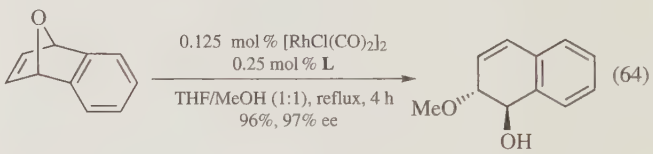

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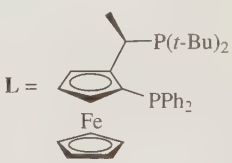
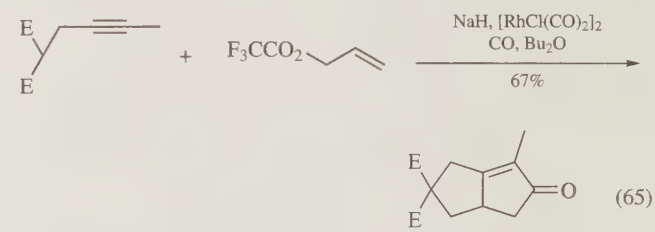
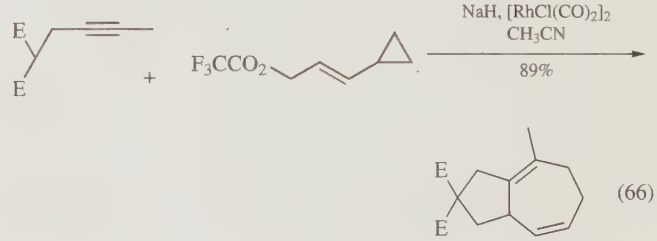


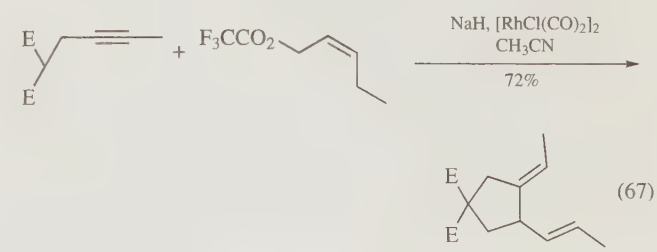
Martin and co-workers have reported applications of $[RhCl(CO)_2]_2$ in serial reaction catalysis.[93] By using an allylic alkylation/cycloaddition strategy,[94] an initially formed 1,6-enyne or alkyne-VCP can be further reacted in situ to afford more complex products. By varying the precursors Pauson-Khand cycloaddition, [5+2] cycloaddition, or cycloisomerization adducts are formed (eqs 65–67).



(65)



(66)



(67)

Related Reagents. Carbonylhydridotris(triphenylphosphine)-rhodium(I); chlorotris(triphenylphosphine)rhodium(I); tetracarbonyl(di-μ-chloro)dirhodium.

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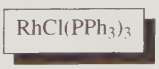
Rhodium(I) Chlorotris(triphenylphosphine)



[14694-95-2] $C_{54}H_{45}ClRh$ (MW 925.24)

(catalyst precursor for many reactions involving alkenes, alkynes, halogenated organics, and organometallic reagents; notably hydrogenations, hydrosilylations, hydroformylations, hydroborations, isomerizations, oxidations, and cross-coupling processes)

Alternate Name: Wilkinson's catalyst.

Physical Data: mp 157 °C. It exists in burgundy-red and orange polymeric forms, which have identical chemical properties (as far as is known).

Solubility: about 20 g L^{-1} in $CHCl_3$ or CH_2Cl_2, about 2 g L^{-1} in benzene or toluene; much less in acetic acid, acetone, methanol, and other aliphatic alcohols. Virtually insol in alkanes and cyclohexane. Reacts with donor solvents like DMSO, pyridine, and acetonitrile.

Form Supplied in: burgundy-red powder, possibly containing excess triphenylphosphine, triphenylphosphine oxide, and traces of rhodium(II) and -(III) complexes.

Analysis of Reagent Purity: ^{31}P NMR displays resonances for the complex in equilibrium with dissociated triphenylphosphine (CH_2Cl_2, approximate δ ppm: 31.5 and 48.0 {J values: Rh–P^1 −142 Hz; Rh–P^2 −189 Hz; P^1–P^2 −38 Hz} shifted in the presence of excess PPh_3).[3] Triphenylphosphine oxide contaminant can also be observed (CH_2Cl_2, δ ppm: 29.2) but paramagnetic impurities are generally not evident. In rhodium NMR a signal is observed at −1291 ppm.

Preparative Method: good quality material can be obtained using the latest *Inorganic Syntheses* procedure,[4] with careful exclusion of air. Recrystallization is *not* recommended.

Handling, Storage, and Precautions: the complex should be stored at reduced temperature under dinitrogen or argon. It oxidizes slowly when exposed to air in the solid state, and faster in solution. Such partial oxidation can influence the catalytic efficacy. Consequently, the necessary precautions are governed by the reaction in question. For mechanistic and kinetic studies, reproducible results may only be obtained if the catalyst is freshly prepared and manipulated in an inert atmosphere; even the substrate should be treated to remove peroxides. For hydrogenations of alkenes on a preparative scale, complex that has been handled in the air for very brief periods should be active, but competing isomerization processes may be enhanced as a result of partial oxidation of the catalyst. At the other extreme, exposure to air just before use is clearly acceptable for oxidations in the presence of O_2 and *t*-BuOOH.

Original Commentary

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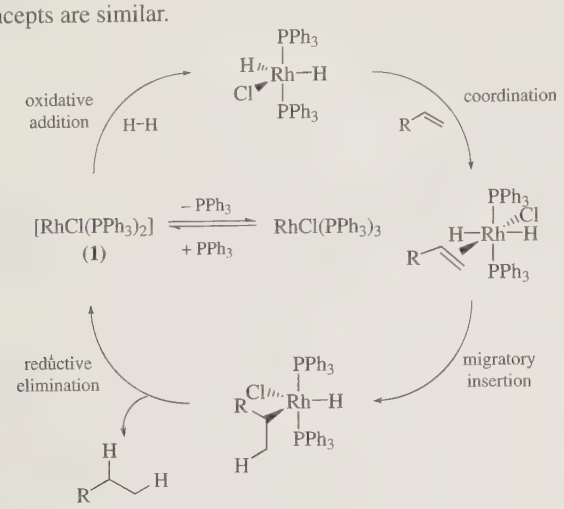
Background.[1] In solution, Wilkinson's catalyst is in equilibrium with the 14e species $RhCl(PPh_3)_2$ (**1**) and triphenylphosphine. The 14e complex is far more reactive than the parent material; consequently it is the reactive entity most likely to coordinate with the substrate and/or the reagents. Generally, the catalytic cycles involving this material then proceed via a cascade of oxidative addition, migratory insertion, and reductive elimination reactions. The postulated mechanism for the hydrogenation of alkenes illustrates these features (Scheme 1), and is typical of the rationales frequently applied to comprehend the reactivity of $RhCl(PPh_3)_3$. Other types of transformations may be important (e.g. transmetalations), and the actual mechanisms are certainly

more complicated in many cases; nevertheless, the underlying concepts are similar.

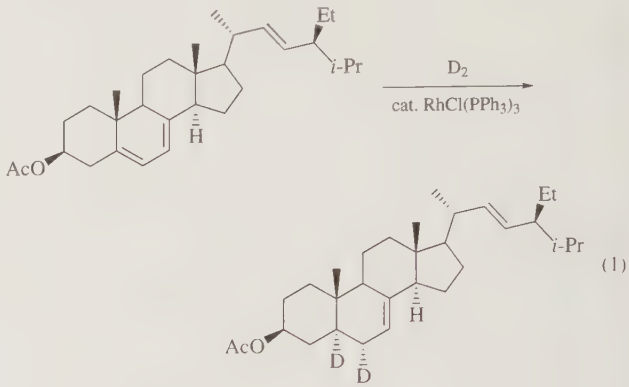


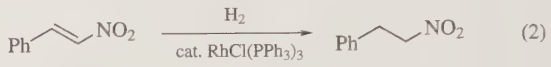
Scheme 1 Simplified mechanism for alkene hydorgenations mediated by $RhCl(PPh_3)_3$

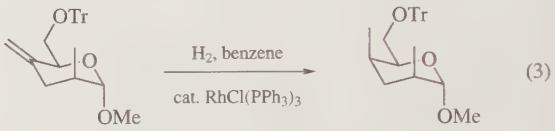
Two important conclusions emerge from these mechanistic considerations. First, $RhCl(PPh_3)_3$ is not a catalyst in the most rigorous sense, but a catalyst precursor. This distinction is critical to the experimentalist because it implies that there are other ways to generate catalytically active rhodium(I) phosphine complexes in solution. Wilkinson's 'catalyst' is a convenient source of homogeneous rhodium(I); it has been extensively investigated because it is easily obtained, and because it was discovered early in the development of homogeneous transition metal catalysts. However, for any transformation there always may be better catalyst precursors than $RhCl(PPh_3)_3$. Secondly, reactions involving a catalytic cycle such as the one shown in Scheme 1 are inherently more complicated than most in organic chemistry. Equilibria and rates for each of the steps involved can be influenced by solvent, temperature, additives, and functional groups on the substrate. Competing reactions are likely to be involved and, if they are, the performance of the catalytic systems therefore is likely to be sensitive to these parameters. Consequently, the purity of the Wilkinson's catalyst used is an important factor. Indeed, less pure catalyst occasionally gives superior results because removal of a fraction of the triphenylphosphine in solution by oxidation to triphenylphosphine oxide gives more of the dissociation product (**1**).

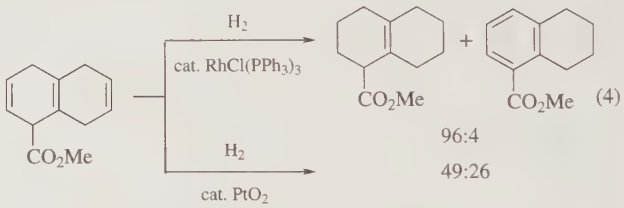
In summary, practitioners of organometallic catalysis should consider the possible mechanistic pathways for the desired transformation, then screen likely catalyst systems and conditions until satisfactory results are obtained. Wilkinson's catalyst is one of the many possible sources of homogeneous rhodium(I).

Hydrogenations. Wilkinson's catalyst is highly active for hydrogenations of unconjugated alkenes at ambient temperatures and pressures. Steric effects are important insofar as less hindered alkenes react relatively quickly, whereas highly encumbered ones are not reduced (eq 1).[5] Hydrogen in the presence of $RhCl(PPh_3)_3$ under mild conditions does not reduce aromatic compounds, ketones, carboxylic acids, amides, or esters, nitriles, or nitro (eq 2) functionalities. Moreover, hydrogenations mediated by Wilkinson's catalyst are stereospecifically *cis* (eq 1). These characteristics have been successfully exploited to effect chemo-, regio-, and stereoselective alkene reductions in many organic syntheses (eqs 1–3). For instance, steric effects force delivery of dihydrogen to the least hindered face of the alkene in (eq 3).[6] eq 4 illustrates that 1,4-cyclohexadienes can be reduced with little competing isomerization/aromatization,[7] unlike many other common hydrogenation catalysts.[5]





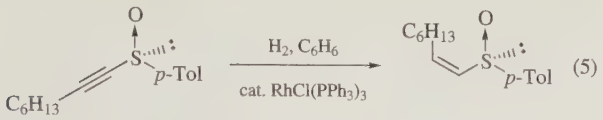




Strongly coordinating ligands can suppress or completely inhibit hydrogenations mediated by Wilkinson's catalyst; examples include 1,3-butadiene, many phosphorus(III) compounds, sulfides, pyridine, and acetonitrile. Similarly, strongly coordinating substrates are not hydrogenated in the presence of Wilkinson's catalyst, presumably because they bind too well. Compounds in this category include maleic anhydride, ethylene, some 1,3-dienes, and some alkynes. Conversely, transient coordination of functional groups on the substrate can be useful with respect to directing $RhCl(PPh_3)_3$ to particular regions of the molecule for stereoselective reactions. However, in directed hydrogenations Wilkinson's catalyst is generally inferior to more Lewis acidic cationic rhodium(I) and iridium(I) complexes.[8] The activity of Wilkinson's catalyst towards hydrogenation of alkenes has been reported to be enhanced by trace quantities of oxygen.[9]

Hydrogenations of alkynes mediated by Wilkinson's catalyst generally give alkanes. *Cis*-alkene intermediates formed in such reactions tend to be more reactive than the alkyne substrate, so this is usually not a viable route to alkenes. Some alkynes suppress the catalytic reactions of $RhCl(PPh_3)_3$ by coordination. Nevertheless, hydrogenation of alkynes mediated by $RhCl(PPh_3)_3$ can be useful in some cases, as in eq 5 in which the catalyst tolerates sulfoxide functionalities and gives significantly higher yields than the

corresponding reduction catalyzed by ***Palladium on Barium Sulfate***.[10]

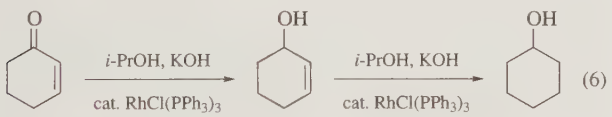


(5)

Wilkinson's catalyst can mediate the hydrogenation of allenes to isolated alkenes via reduction of the least hindered bond.[11] Di-*t*-butyl hydroperoxide is 'hydrogenated' to *t*-BuOH in the presence of $RhCl(PPh_3)_3$, though this transformation could occur via a radical process.[12]

Hydrogen Transfer Reactions. Wilkinson's catalyst should lower the energy barrier for dehydrogenations of alkanes to alkenes since it catalyzes the reverse process, but no useful transformation of this kind have been discovered. Presumably, the activation energy for this reaction is too great since alkanes have no coordinating groups. Alcohols and amines, however, do have ligating centers, and can dehydrogenate in the presence of Wilkinson's catalyst. These reactions have been used quite often, mostly from the perspective of hydrogen transfer from an alcohol or amine to an alkene substrate, although occasionally to dehydrogenate alcohols or amines.

2-Propanol solvent under basic conditions has been extensively used to transfer hydrogen to alkenes and other substrates. Elevated temperatures are usually required and under these conditions $RhCl(PPh_3)_3$ may be extensively modified prior to the catalysis. Ketones, alkenes (eq 6), aldimines (eq 7),[13] nitrobenzene, and some quinones are reduced in this way.



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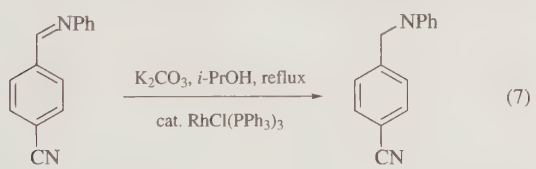
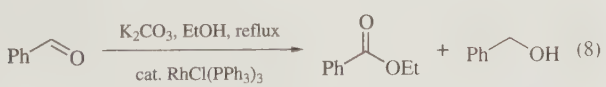


(7)

Wilkinson's catalyst mediates a Cannizzaro-like process with benzaldehyde in ethanol; the aldehyde serves as a dihydrogen source to reduce itself, and the benzoic acid formed is esterified by the solvent (eq 8).[14] Pyrrolidine is *N*-methylated by methanol in the presence of $RhCl(PPh_3)_3$, a reaction that presumably occurs via hydrogen transfer from methanol, condensation of the formaldehyde formed with pyrrolidine, then hydrogen transfer to the iminium intermediate (eq 9).[15]



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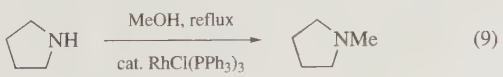
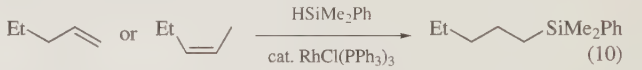


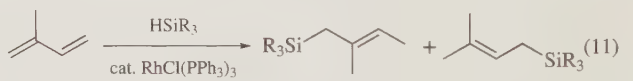
(9)

Hydrosilylations.[16] Wilkinson's catalyst is one of several complexes which promote hydrosilylation reactions, and it often seems to be among the best identified.[17] However, hydrosilylations with $RhCl(PPh_3)_3$ tend to be slower than those mediated by H_2PtCl_6. Good turnover numbers are observed, the catalyst eventually being inactivated by P–C bond cleavage reactions at the phosphine,[18] and other unidentified processes. Catalysts without phosphine ligands may be even more robust than $RhCl(PPh_3)_3$ because they are unable to decompose via P–C bond cleavage.[19] Wilkinson's catalyst is relatively efficient with respect to converting silanes to disilanes.[20] The latter reaction could be useful in its own right but in the context of hydrosilylation processes it means that the product yields based on the silane are less than quantitative.

For hydrosilylation of alkenes, the reaction rate increases with temperature and hence many of these reactions have been performed at 100 °C. Higher reaction rates are obtained for silanes with very electronegative substituents and low steric requirements (e.g. $HSi(OEt)_3 > HSi(i\text{-}Pr)_3$). Terminal alkenes usually are hydrosilylated in an anti-Markovnikov sense to give terminal silanes. Internal alkenes tend not to react (e.g. cyclohexene), or isomerize to the terminal alkene which is then hydrosilylated (eq 10). Conversely, terminal alkenes may be partially isomerized to unreactive internal alkenes before the addition of silane can occur. 1,4-Additions to dienes are frequently observed, and the product distributions are extremely sensitive to the silane used (eq 11).

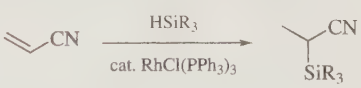


(10)

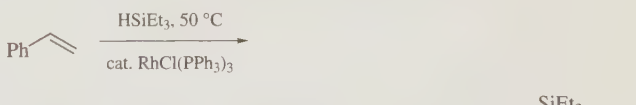


(11)

α,β-Unsaturated nitriles are hydrosilylated, even γ-substituted ones, to give 2-silyl nitriles with good regioselectivity (eq 12).[21] Secondary alkyl silanes are also formed in the hydrosilylation of phenylethylene. In fact, the latter reaction has been studied in some detail, and primary alkyl silanes, hydrogenation product (i.e. ethylbenzene), and *E*-2-silylphenylethylenes are also formed (eq 13).[22] Equimolar amounts of ethylbenzene (**2**) and *E*-2-silylphenylethylene (**4**) are produced, implying these products arise from the same reaction pathway. It has been suggested that this involves dimeric rhodium species because the relative amounts of these products increase with the rhodium:silane ratio; however, competing radical pathways cannot be ruled out. Certainly, product distributions are governed by the proportions of all the components in the reaction (i.e. catalyst, silane, and alkene), and the reaction temperature. Side products in the hydrosilylation of 1-octene include vinylsilanes and allylsilanes (eq 14).[23,24]



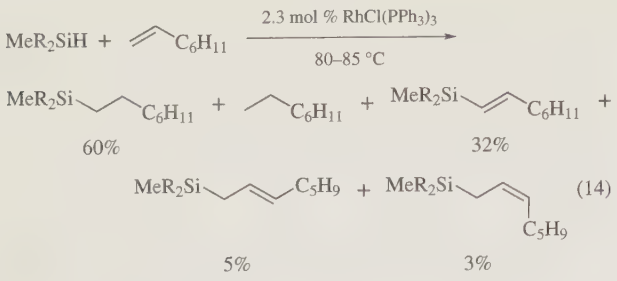
(12)



(13)

(2) (3) (4) (5)

mol % catalyst	(2):(3):(4):(5)
3.1	39: 34: 43: 3
0.12	3: 25: 2: 47

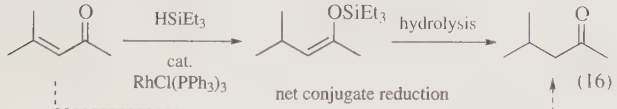


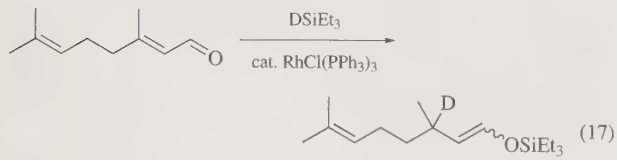
Hydrosilylation of alkynes gives both *trans* products (i.e. formally from *cis* addition), and *cis* products (from either isomerization or *trans* addition); H_2PtCl_6, however, gives almost completely *cis* addition to *trans* products.[25] Moreover, CC–H to CC–SiR_3 exchange processes can occur for terminal alkynes giving **6** (eq 15).[25–27] The product distribution in these reactions is temperature dependent, and other factors may be equally important. Nonstereospecific transition metal catalyzed hydrosilylations of alkynes are not confined to Wilkinson's catalyst, and the origin of the *trans* addition product has been investigated in detail for other homogeneous rhodium and iridium complexes.[19]

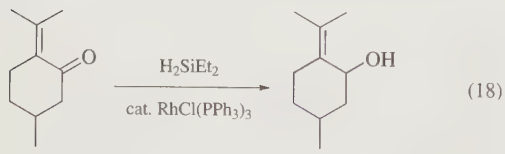
temperature	(6):(7):(8):(9)
65 °C	4: 31: 57: 8
80 °C	3: 55: 35: 7

Hydrosilylation of terminal alkenes has been used in a polymerization process to form new polymeric organic materials.[28]

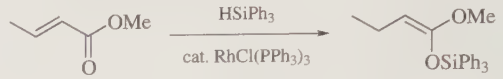
Hydrosilylation of α,β-unsaturated aldehydes and ketones gives silylenol ethers via 1,4-addition, even when the 4-position is relatively hindered.[29] Hydrolysis of the silyl enol ethers so formed gives saturated aldehydes. Combination of these reduction and hydrolysis steps gives overall reduction of alkenes conjugated to aldehydes, in selectivities which are generally superior to those obtained using hydridic reducing agents (eqs 16 and 17). Dihydrosilanes tend to reduce α,β-unsaturated carbonyl compounds to the corresponding alcohols, also with good regioselectivity (eq 18).



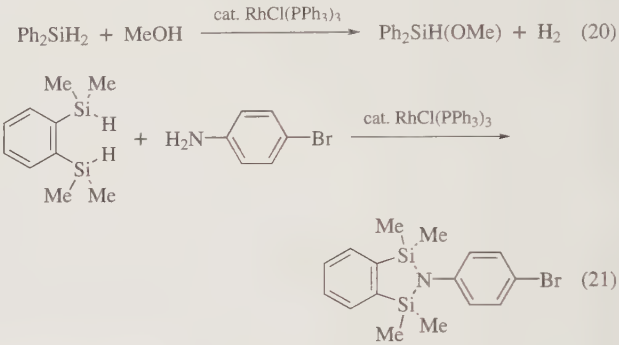




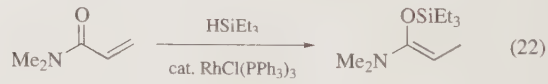
Similar hydrosilylations of α,β-unsaturated esters are useful for obtaining silyl ketene acetals with over 98:2 (*Z*) selectivity (eq 19);[30] this transformation is complementary to the reaction of α-bromo esters with zinc and chlorotrialkylsilanes, which favors the formation of the corresponding (*E*) products.[30] In cases where (*E*):(*Z*) stereoselectivity is not an issue, ***Rhodium(III) Chloride*** ($RhCl_3 \cdot 6H_2O$) may be superior to Wilkinson's catalyst.[31] Unconjugated aldehydes and ketones are reduced by silanes in the presence of $RhCl(PPh_3)_3$; trihydrosilanes react quicker than di- than monohydrosilanes.[32,33]



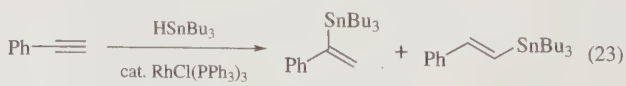
Alcohols (eq 20)[34] and amines (eq 21)[35] react with silanes in the presence of Wilkinson's catalyst to give the silylated compounds and, presumably, hydrogen. These reactions are useful in protecting group strategies.

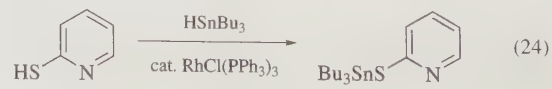


N,N-Dimethylacrylamide and triethylsilane combine in the presence of Wilkinson's catalyst (50 °C) to give a *O,N*-silylketene acetal as the pure (*Z*) isomer after distillation; this reaction can be conveniently performed on a gram scale (eq 22). The products have been used in new aldol methodology.[36]

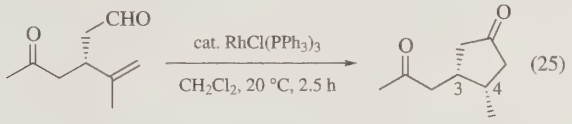


Hydrostannylations. Hydrostannanes add to alkynes in uncatalyzed reactions at 60 °C. Phenylacetylene, for instance gives a mixture of (*E*)- and (*Z*)-vinylstannanes, wherein the tin atom has added to the terminal carbons. In the presence of Wilkinson's catalyst, however, the hydrostannylation proceeds at 0 °C to give mostly the regioisomeric vinylstannanes (eq 23).[37] Terminal stannanes in the latter process seem to result from competing free radical additions. This may not be a complication with some other catalysts; the complexes $PdCl_2(PPh_3)_2$ and $Mo(\eta^3\text{-allyl})(CO)_2(NCMe)_2$ also mediate hydrostannylations of alkynes, and they are reported to be 100% *cis* selective.[38] Hydrostannanes and thiols react in a similar way to silanes and alcohols (eq 24).[39]





Hydroacylations. Alkenes with aldehyde functionality in the same molecule, but displaced by two carbon atoms, can cyclize via intramolecular hydroacylation reactions. Substituent effects can have a profound influence on these transformations. For instance, 3,4-disubstituted 4-pentenals cyclize to cyclopentanones without serious complications,[40] but 2,3-disubstituted 4-pentenals give a cyclopropane as a competing product (eqs 25 and 26).[41] Formation of the latter material illustrates two features which restrict the applicability of this type of reaction. First decarbonylation of the aldehyde can occur, in this case presumably giving a rhodium alkyl complex which then inserts the pendant alkene functionality. Secondly, decarbonylation reactions convert the catalyst into $RhCl(CO)(PPh_3)_2$, which tends to be inactive. Moreover, the reaction is only generally applicable to the formation of five-membered rings, and it is apparently necessary to use quite large amounts of Wilkinson's catalyst to ensure good yields (eq 27).[42] Rhodium(I) complexes other than $RhCl(PPh_3)_3$ can give better results in some cases.[43]



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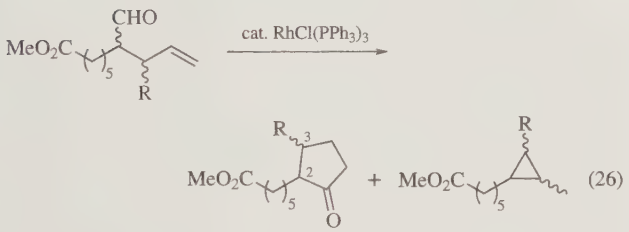
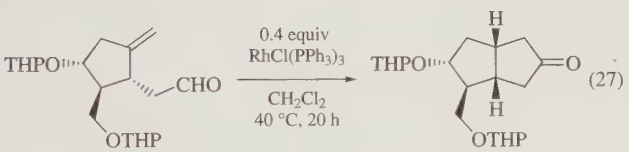
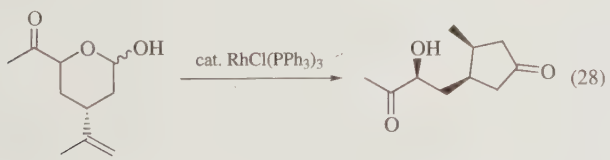


(26)



(27)

Lactols can be cyclized under the typical hydroacylation conditions (eq 28), presumably via equilibrium amounts of the corresponding aldehyde.[40] Finally, intermolecular hydroacylation has been formally achieved in the reaction of a pyridyl aldimine with ethylene under pressure at 160 °C; here the pyridine functionality anchors the aldimine to the rhodium, and decarbonylation is impossible (eq 29).



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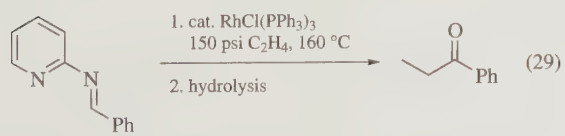
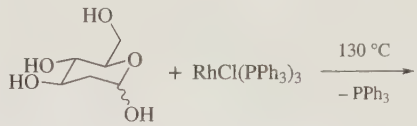
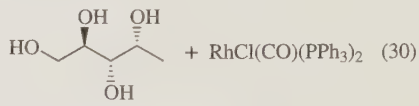


(29)

Decarbonylations. Wilkinson's catalyst has been known for some time to decarbonylate aldehydes, even heavily functionalized ones, to the corresponding hydrocarbons.[44] Some examples are shown in eqs 30–33, illustrating high stereochemical retention in the decarbonylation of chiral, cyclopropyl, and unsaturated aldehydes.[45,46] Acid chlorides are also decarbonylated by $RhCl(PPh_3)_3$.





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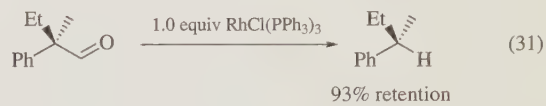
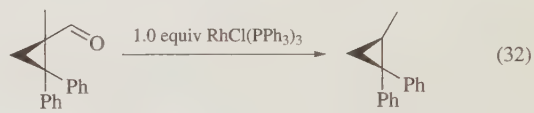


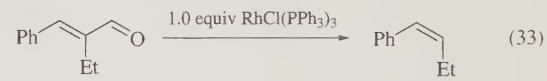
(31)

93% retention



(32)

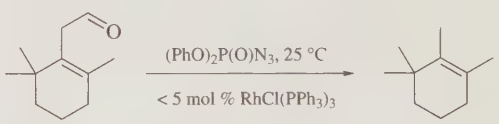
94% retention



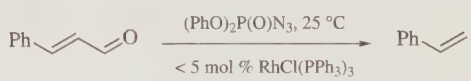
(33)

100% retention

The problem with all these reactions is that stoichiometric amounts of the catalyst are required, and the process is inordinately expensive. Consequently, it has only been used by those wishing to illustrate a decarbonylation occurs for some special reason, or in the closing stages of small scale syntheses of complex organic molecules. Very recently, however, it has been shown that the reaction can be made catalytic by adding ***Diphenyl Phosphorazidate***.[47] The role of the latter is to decarbonylate the catalytically inactive $RhCl(CO)(PPh_3)_2$, regenerating rhodium(I) without carbonyl ligands. Examples of this catalytic process are shown in eqs 34 and 35. The path is now clear for extensive use of $RhCl(PPh_3)_3$ for catalytic decarbonylation reactions in organic synthesis.



(34)

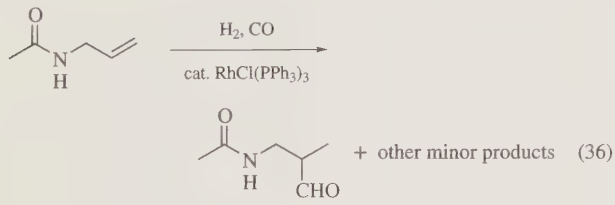


(35)

Catalytic decarbonylations of a few substrates other than aldehydes have been known for some time, e.g. conversion of benzoic anhydrides to fluorenones at high temperatures (ca. 225 °C).[48]

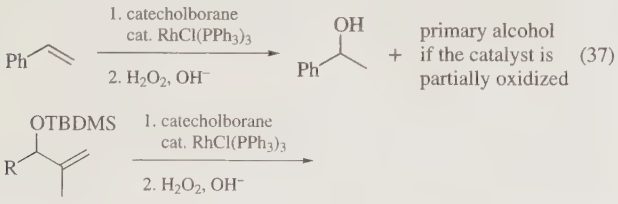
Hydroformylations.[49] Carbon monoxide reacts rapidly with $RhCl(PPh_3)_3$ to give $RhCl(CO)(PPh_3)_2$. With hydrogen, in the presence of triphenylphosphine, the latter carbonyl complex affords some ***Carbonylhydridotris(triphenylphosphine)rhodium(I)***, and this very actively mediates hydroformylations.[50] Reactions wherein $RhCl(PPh_3)_3$ is used as a hydroformylation catalyst probably proceed via this route. A more direct means of hydroformylation is to use $RhH(CO)(PPh_3)_3$. Nevertheless,

Wilkinson's catalyst (an unfortunate term here because Wilkinson also pioneered hydroformylations using RhH(CO)-$(PPh_3)_3$) has been used to effect hydroformylations of some substrates. Eq 36 is one example and illustrates that transient coordination of the acyl group with rhodium apparently leads to predominant formation of a 'branched chain' aldehyde, whereas straight chain aldehydes are usually formed in these reactions.[51] Other hydroformylation catalysts that have been studied include cobalt and iridium based systems.[49]



(36)

Hydroborations.[52] Addition of ***Catecholborane*** to alkenes is accelerated by Wilkinson's catalyst, and other sources of rhodium-(I) complexes.[53] Unfortunately, the reaction of Wilkinson's catalyst with catecholborane is complex; hence if the conditions for these reactions are not carefully controlled, competing processes result. In the hydroboration of styrene, for instance, the secondary alcohol is formed almost exclusively (after oxidation of the intermediate boronate ester, eq 37); however, the primary alcohol also is formed if the catalyst is partially oxidized and this can be the major product in extreme cases.[54,55] Conversely, hydroboration of the allylic ether (**12**) catalyzed by pure Wilkinson's catalyst gives the expected alcohol (**13**), hydrogenation product (**14**), and aldehyde (**15**), but alcohol (**13**) is the exclusive (>95%) product if the $RhCl(PPh_3)_3$ is briefly exposed to air before use.[54] The *syn*-alcohol is generally the favored diastereomer in these and related reactions (eq 38), and the catalyzed reaction is therefore stereocomplementary to uncatalyzed hydroborations of allylic ether derivatives.[56–58]



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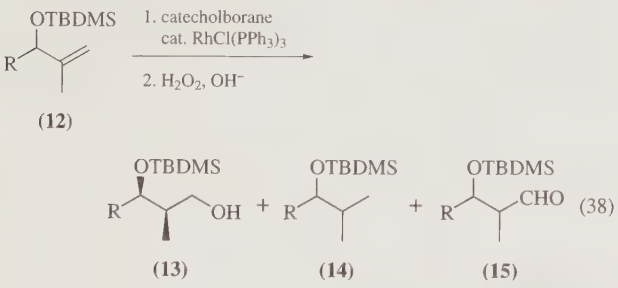
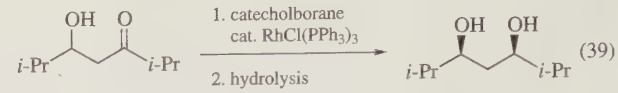


(38)

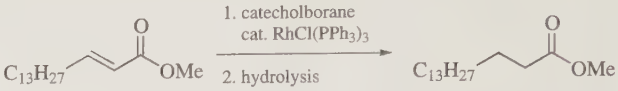
Other sources of rhodium(I) are equally viable catalysts for hydroborations, notably $Rh(\eta^3\text{-}CH_2CMeCH_2)(i\text{-}Pr_2PCH_2CH_2P\text{-}i\text{-}Pr_2)$ which gives a much cleaner reaction with catecholborane than Wilkinson's catalyst.[59] Other catalysts for hydroborations are also emerging.[60–62]

Catecholborane hydroborations of carbonyl and related functionalities are also accelerated by $RhCl(PPh_3)_3$ (eqs 39–41); however, several related reactions proceed with similar selectivities in the absence of rhodium.[63–65]



(39)

syn:*anti* = 12:1



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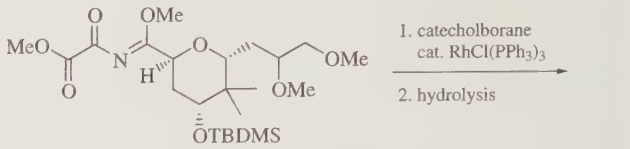
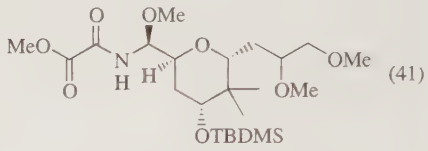
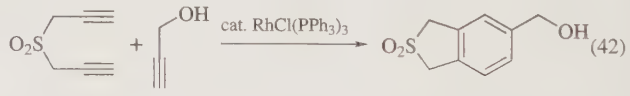




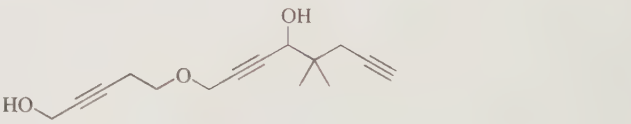
(41)

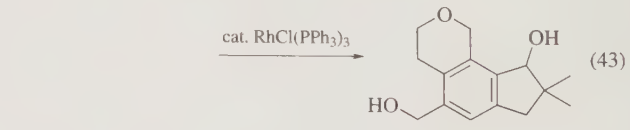
de 10:1

Cyclization, Isomerization, and Coupling Reactions. Inter- (eq 42)[66] and intramolecular (eq 43)[67] cyclotrimerizations of alkynes are mediated by Wilkinson's catalyst. This is an extremely efficient route to ring fused systems. Similarly, Diels–Alder-like [4 + 2] cyclization processes are promoted by $RhCl(PPh_3)_3$;[68] 'dienophile' components in these reactions need not be electron deficient, and they can be an alkene or alkyne (eqs 44 and 45). Allenes oligomerize in pathways determined by their substituents. For instance, four molecules of allene combine to give a spirocyclic system (eq 46), but tetraphenylallene isomerizes to give an indene (eq 47).[69]

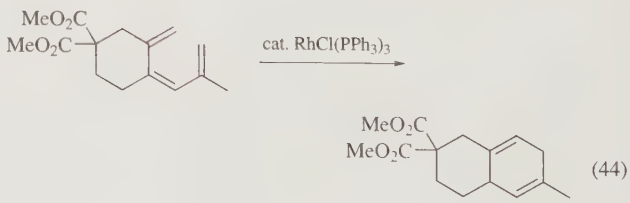


(42)

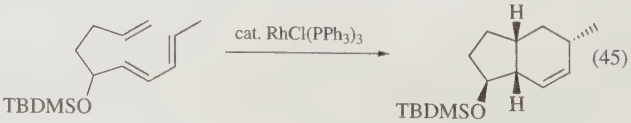




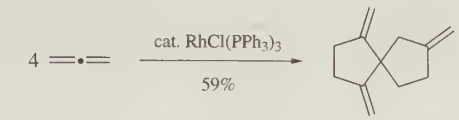
(43)



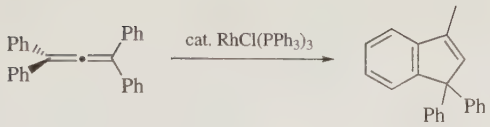
(44)



(45)

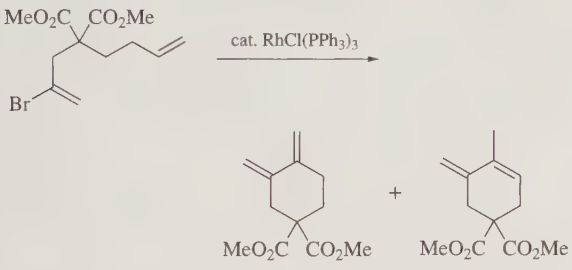


(46)

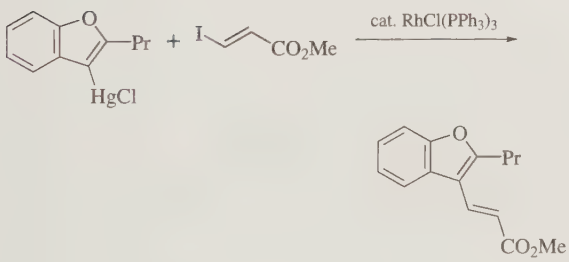


(47)

Wilkinson's catalyst is also capable of mediating the formation of C–C bonds in reactions which apparently proceed via oxidative addition of an unsaturated organohalide across the metal (eq 48),[70] or via transmetalation from an organometallic (eq 49).[71] These two transformation types are very similar to couplings developed by Heck so, predictably, some palladium complexes also mediate these reactions (see ***Tetrakis(triphenylphosphine)palladium(0)*** and ***Palladium(II) Acetate***).

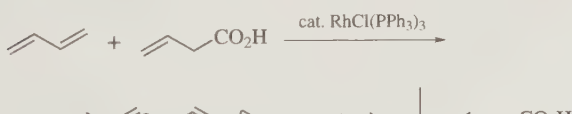


(48)

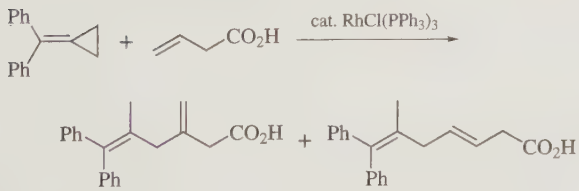


(49)

Intermolecular reactions of dienes, allenes, and methylenecyclopropanes with alkenes are mediated by $RhCl(PPh_3)_3$, although mixtures of products are usually formed (eqs 50–51).[72–75]

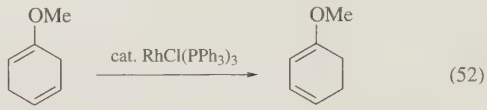


(50)



(51)

Wilkinson's catalyst mediates hydrogenation of 1,4-cyclohexadienes without double bond isomerization (see above), but at elevated temperatures in the absence of hydrogen it promotes isomerization to conjugated dienes (eq 52).[76] Isomerization of allylamines to imines followed by hydrolysis has also been performed using $RhCl(PPh_3)_3$ (eq 53),[77] although $RhH(PPh_3)_4$ and other catalysts are more frequently used for this reaction type.[78]



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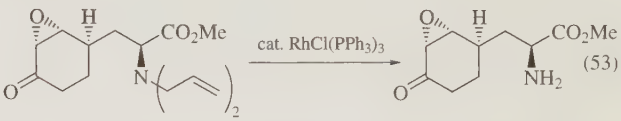
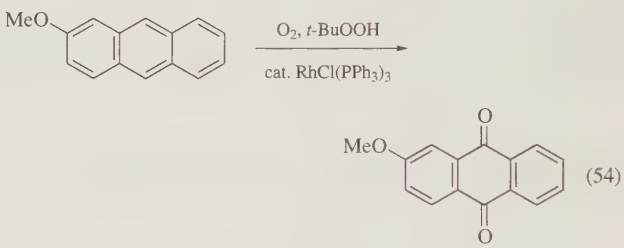


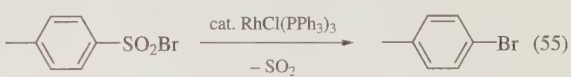
(53)

Oxidations. Cleavage of alkenes to aldehydes and ketones is promoted by Wilkinson's catalyst under pressures of air or oxygen,[79] but these reactions are inferior to ozonolysis because they tend to form a mixture of products. More useful are the oxidations of anthracene derivatives to anthraquinones in the presence of oxygen/***t-Butyl Hydroperoxide*** and catalytic $RhCl(PPh_3)_3$ (eq 54).[80,81] Wilkinson's catalyst reacts with oxygen to form an adduct so $RhCl(PPh_3)_3$ is clearly quite different from the true catalyst in all the reactions mentioned in this section.



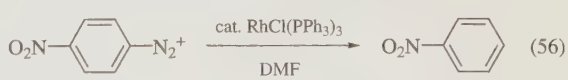
(54)

Other Transformations. At high temperatures (>200 °C) aromatic sulfonyl chlorides are desulfonated to the corresponding aryl halides in the presence of Wilkinson's catalyst (eq 55).[82] Benzamides and malonamide also decompose under similar conditions, giving benzonitrile and acetamide, respectively.[83]



(55)

Diazonium fluoroborates are reduced to the corresponding unsubstituted aryl compounds by Wilkinson's catalyst in DMF; the solvent is apparently the hydride source in this reaction (eq 56).[84]



(56)

Finally, aryl group interchange between triarylphosphines is mediated by Wilkinson's catalyst at 120 °C, but a near statistical mixture of the exchanged materials is formed along with some byproducts.[85]

First Update

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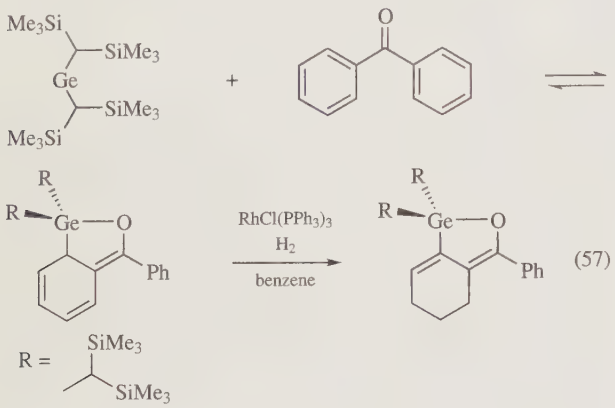
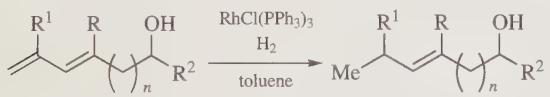
Hydrogenations. Wilkinson's catalyst does not promote hydrogenation of aromatic compounds under mild reaction conditions. However, in special cases, certain aromatic compounds such as benzophenone can be partially reduced by molecular hydrogen in the presence of Wilkinson catalyst via an indirect activation process involving a germylene (eq 57).[86] Further reduction of the two remaining double bonds is most likely inhibited by steric hindrance of the germylene.



(57)

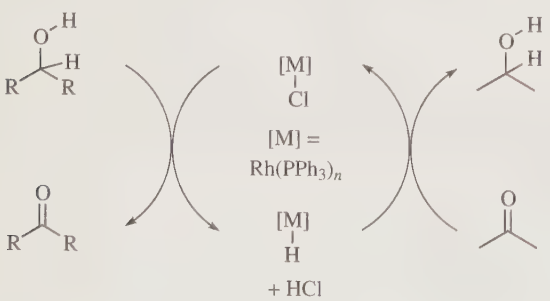
Examples of the regioselective hydrogenation of dienes by Wilkinson's catalyst to give allylic and homoallylic alcohols have been reported (eq 58).[87]



(58)

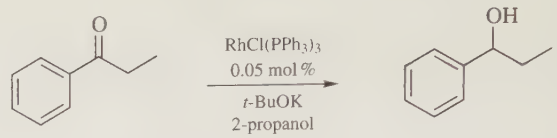
R = Ph, Cy, 1,2,3° alk
R^1 = H, Me
R^2 = 1,2° alk

Transfer Hydrogenations. Transition metal-catalyzed transfer hydrogenation is thought to occur via two different intermediates, monohydrides or dihydrides, depending on the transition metal species employed. For Wilkinson's catalyst the monohydridic pathway was shown to be operative with the aid of deuterium labeling experiments (eq 59).[88]



(59)

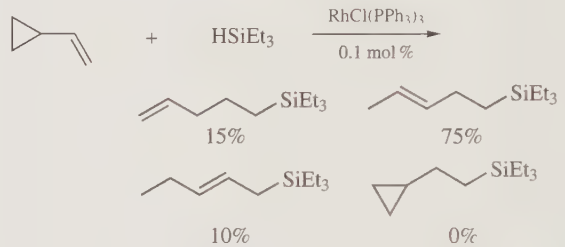
In certain cases, additives are observed to have an accelerating effect in the $RhCl(PPh_3)_3$-catalyzed hydrogen transfer reaction. By adding $Yb(OTf)_3$, propionophenone is reduced to the alcohol under milder reaction conditions than with the conventional $RhCl(PPh_3)_3$-catalyzed hydrogen transfer reaction (eq 60).[89]



(60)

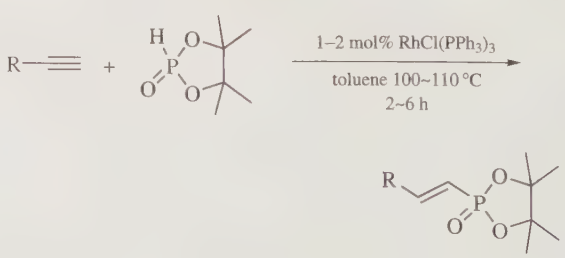
Yield (%)	
With $Yb(OTf)_3$	Without $Yb(OTf)_3$
85	65

Hydrosilylations. Hydrosilylation of vinylcyclopropane in the presence of Wilkinson catalyst is accompanied by ring cleavage of vinylcyclopropane leading to the formation of terminal silyl-substituted regioisomeric alkenes in 80% yield (eq 61).[90] In the hydrosilylation of vinylcyclopropane analogs, the ring opening of the cyclopropyl group dominates over the simple addition of the Si–H bond to the vinyl group. This process provides an alternative synthesis of silyl-substituted alkenes to the hydrosilylation of dienes.



(61)

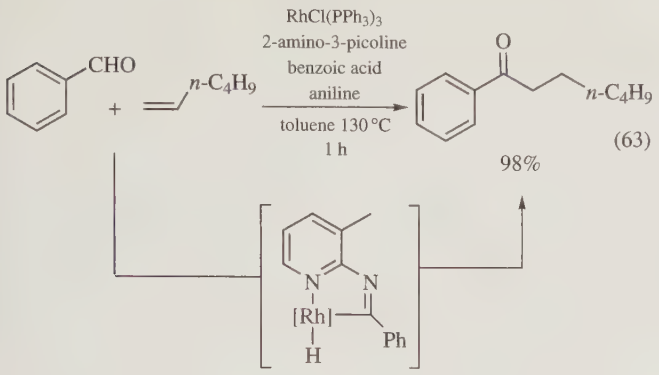
Hydrophosphorylations. Among the transition metal-catalyzed reactions for constructing carbon-hetero atom bonds, strategies for forming carbon-phosphorous bonds are relatively limited.[91] Most of the successful metal-catalyzed reactions of phosphorous(V) compounds have been conducted in the presence of a Pd catalyst at elevated temperatures.[91] However, with a highly reactive five-membered ring hydrogen phosphonate, Wilkinson's catalyst is capable of the hydrophosphorylation of alkynes to give the corresponding (*E*)-alkenylphosphonates with excellent regio- and stereoselectivities (eq 62).[92] Microwave-assisted $RhCl(PPh_3)_3$-catalyzed hydrophosphorylation of alkynes can also give the corresponding alkenyl phosphine oxide very efficiently under solvent-free conditions.[93]



(62)

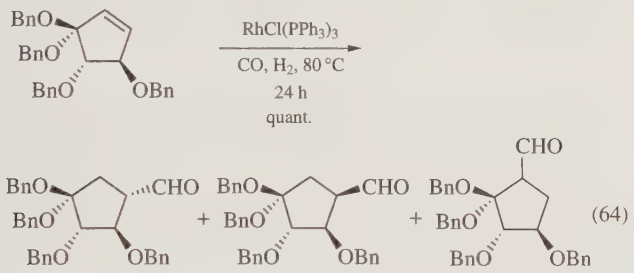
Hydroacylations. Wilkinson's catalyst is an extremely powerful catalyst for intermolecular hydroacylation when combined with several organococatalysts such as 2-amino-3-picoline, aniline, and benzoic acid (for details, see *2-amino-3-picoline*).[94]

Equation 63 illustrates how benzaldehyde undergoes intermolecular hydroacylation very efficiently with terminal olefins by the chelation-assistance of 2-amino-3-picoline by a process involving C–H bond activation.



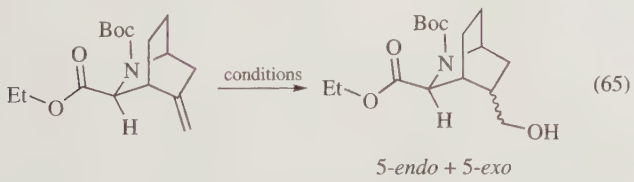
(63)

Hydroformylations. Wilkinson's catalyst can tolerate highly oxygenated functionality in hydroformylation reactions as illustrated by the cyclopentene of eq 64. This strategy has been applied to the synthesis of monosaccharide analogs such as a carba-D-fructofuranose.[95]



(64)

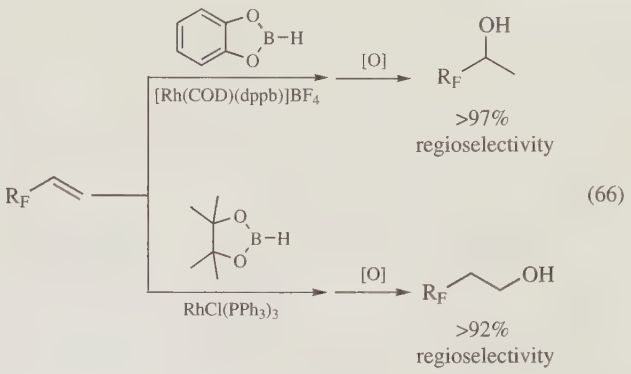
Hydroborations. Although the reaction of Wilkinson's catalyst with catecholborane is often complex, superior selectivity over the uncatalyzed reaction can be observed in $RhCl(PPh_3)_3$-catalyzed hydroborations (eq 65).[96]



(65)

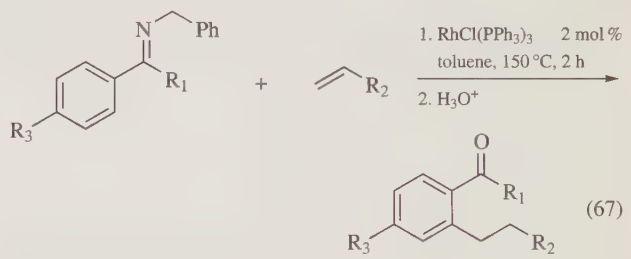
Conditions	*endo*/*exo*	Combined yield (%)
BH_3	89:11	50
$RhCl(PPh_3)_3$/CatBH	95:5	83

In the case of the hydroboration of perfluoroalkylolefins, the choice of Rh-complex and borane species can influence regioselectivity dramatically. For instance, while the reaction of perfluoroalkylolefins with catecholborane in the presence of a cationic Rh-catalyst produces the secondary alcohols predominantly after the oxidative work-up process, a Wilkinson's complex-catalyzed reaction with pinacolborane affords the primary alcohols (eq 66).[97]



(66)

C–H Functionalization by Ortho alkylation. Among the several complexes that promote orthoalkylation (originally discovered by Murai using a ruthenium catalyst in 1993),[98] Wilkinson's catalyst appears to be the most successful, in terms of its broad scope of substrates.[99] For instance, while allylic protons in most olefins, especially terminal ones, are not tolerated in Murai's ruthenium-catalyzed orthoalkylation, terminal olefins with or without allylic protons can be used successfully with Wilkinson's catalyst in the orthoalkylation of benzyl imines. Remarkably, even dienes and internal olefins are also substrates for this reaction (eq 67).



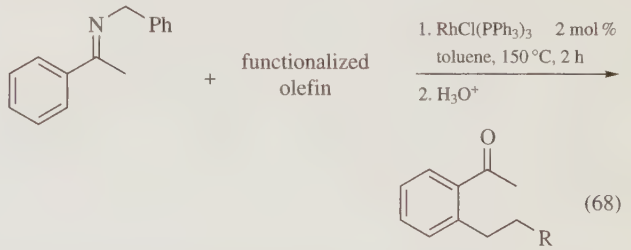
(67)

R_1 = Me, Et, *n*-Pent

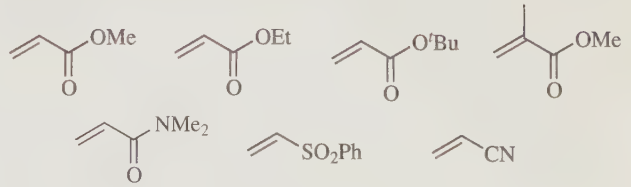
R_2 = *t*-C_4H_9, C_6F_5, Cy, *n*-C_4H_9, *n*-C_6H_{13}, *n*-$C_{10}H_{25}$, $(CH_3)_3Si$

R_3 = CF_3, H, CH_3O

The functional group tolerance of this reaction is illustrated by olefins containing ester, amide, sulfone, and nitrile groups which can be applied to $RhCl(PPh_3)_3$-catalyzed orthoalkylation with remarkable efficiency (eq 68).[100] These functionalized olefins are



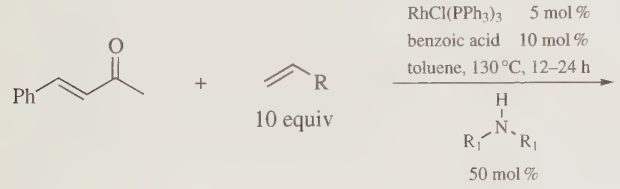
(68)

functionalized olefins


much more reactive than "nonfunctionalized" olefins. Nevertheless, when rhodium cationic species are employed as a catalyst, much higher yields of orthoalkylated products can be obtained under mild reaction conditions.

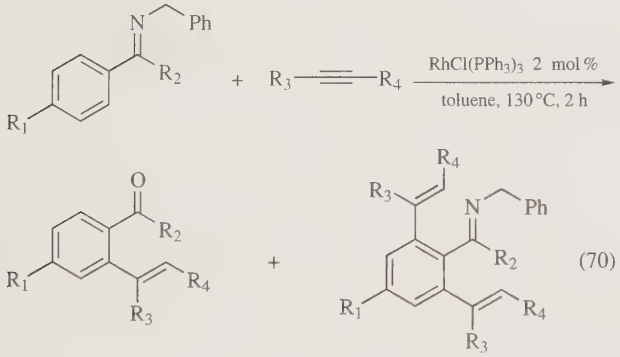
This chelation-assisted cyclometallation using Wilkinson's catalyst can be extended to β-alkylation through aliphatic sp^2 C–H bond activation (eq 69).[101] When an enone is allowed to react with excess olefin in the presence of $RhCl(PPh_3)_3$, benzoic acid, and secondary amine at 130 °C for 12 h, β-alkylated products can be obtained in good yields.

The Wilkinson's catalyst/benzyl imine system for orthoalkylation can be applied to $RhCl(PPh_3)_3$-catalyzed orthoalkenylation of aromatic benzyl imine with both terminal and internal alkynes.[102] Equation 70 illustrates reaction of the benzyl imine of acetophenone with several terminal alkynes giving mono- and doubly-alkenylated products, depending on the substituents in the alkyne and aromatic imine.



(69)

R = alkyl, $Si(CH_3)_3$



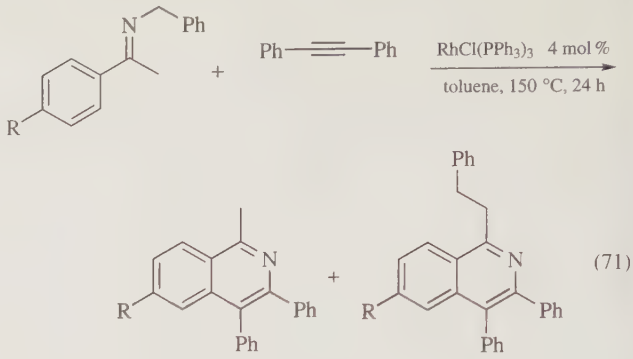
(70)

R_1 = H, CF_3, OMe R_3 = H, Ph

R_2 = Me, Et, ^{n}Pent R_4 = ^{n}Bu, ^{n}Hex, ^{t}Bu, Ph

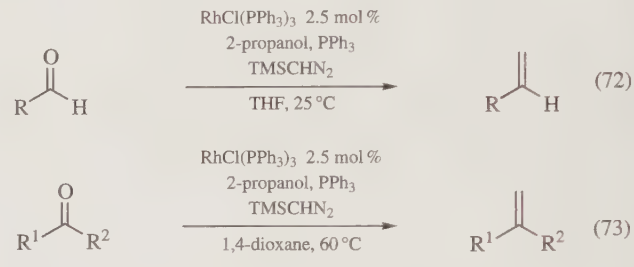
Under more vigorous reaction conditions, two isoquinoline derivatives are formed from the reaction of benzyl imine with diphenylacetylene (eq 71).

Carbonyl Methylenations. In an alternative to the classical Wittig reaction,[103] Wilkinson's catalyst mediates the olefination of carbonyl compounds in the presence of a diazo compound and triphenylphosphine.[104] This transformation is quite attractive because several drawbacks of the Wittig reaction, including the use of stoichiometric amounts of phosphonium salts, can be avoided. In the presence of 2-propanol, trimethylsilyldiazomethane, triphenylphosphine, and Wilkinson's catalyst can convert the ketone and aldehyde groups in various organic compounds into the corresponding methylene group (eqs 72 and 73).[104] Various other transition metals have been employed in the catalytic methylenation of carbonyl compounds in organic synthesis.[105–109]



(71)

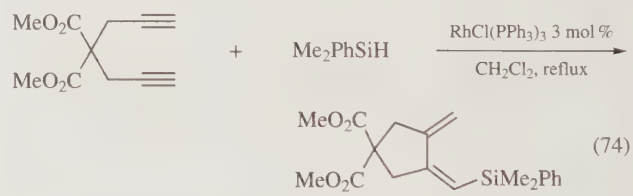
R = H, CF_3, OMe



(72)

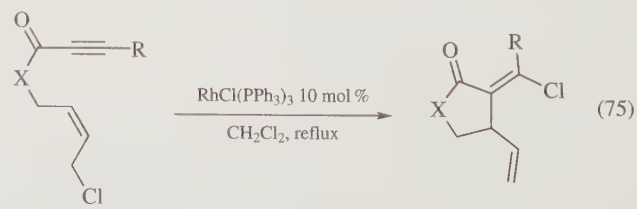
(73)

Cyclization, Isomerization, and Coupling Reactions. The cyclization of diynes is an efficient route to the formation of 1,2-dialkylidenecycloalkanes. When silanes are included in Wilkinson's complex-catalyzed reaction of 1,6-diynes, silylative cyclization occurs (eq 74).[110]



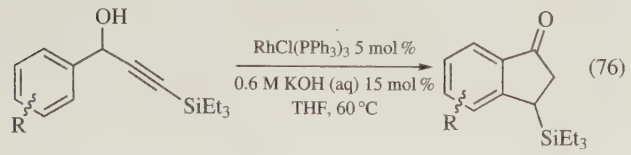
(74)

The cyclization of 1,6-enynes by $RhCl(PPh_3)_3$ can generate functionalized 1,3- or 1,4-diene cyclic compounds. For example, treatment of 1,6-enynes containing a haloalkenyl group with Wilkinson's catalyst in dichloromethane at reflux produces cyclization product which incorporates an intramolecular halogen shift: a wide spectrum of enynes can be applied in this transformation (eq 75).[111]



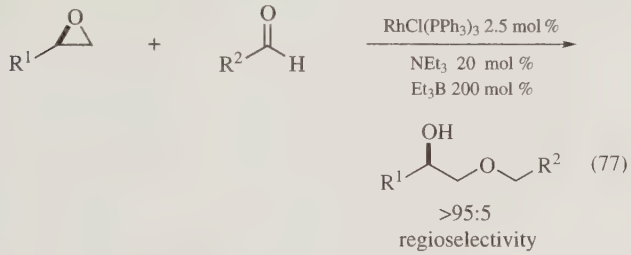
(75)

α-Arylpropargyl alcohols can be isomerized to indenones in the presence of Wilkinson's catalyst under mild conditions (eq 76).[112] This isomerization, which includes a 1,4-hydrogen shift, is regioselective for the less hindered position of the aromatic ring.



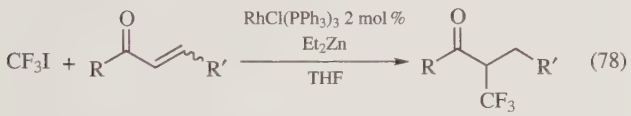
(76)

Wilkinson's catalyst can also catalyze the formation of C–O bonds via a reductive coupling reaction of epoxides with aldehydes in the presence of Et_3B as a reductant (eq 77).[113]



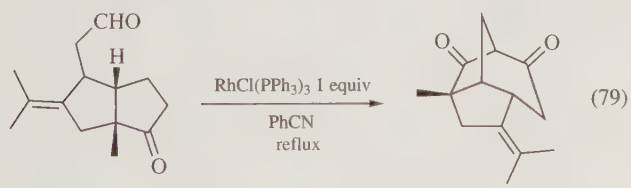
(77)

Treatment of α,β-unsaturated ketones with CF_3I in the presence of Et_2Zn and $RhCl(PPh_3)_3$ gives an α-trifluoromethylated product, thereby providing alternative to previous electrophilic reaction[114] using chalcogenium reagents or photochemical reactions[115] of enamine with CF_3I. Equation 78 illustrates α-trifluoromethylation of α,β-unsaturated ketones by Wilkinson's catalyst.[116]



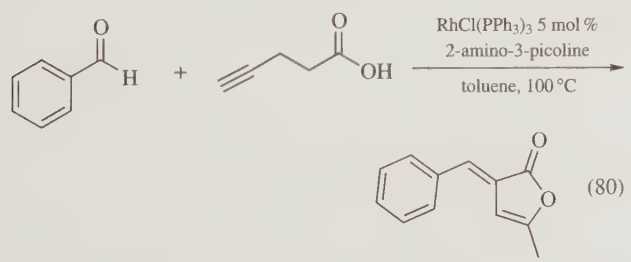
(78)

Wilkinson's catalyst mediates stoichiometric intramolecular C–C bond forming reactions with certain substrates containing acidic C–H bonds via an intramolecular hydride migration yielding a 1,3-diketone (eq 79).[117]



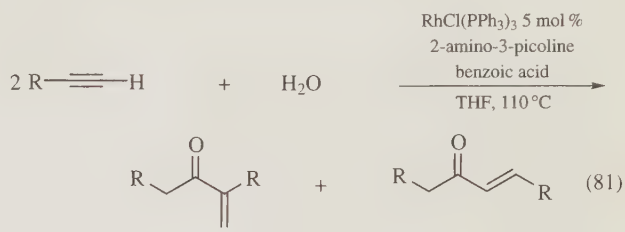
(79)

The reaction of benzaldehyde and 4-pentynoic acid in the presence of Wilkinson's catalyst and 2-amino-3-picoline exhibits the exclusive formation of (*E*)-3-benzylidene-3*H*-furan-2-one, instead of the usual enone hydroacylation product (eq 80).[118,119]



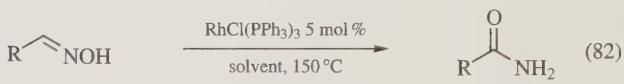
(80)

While enynes are common products in the reaction of 1-alkynes under Wilkinson's catalyst,[120] hydrative dimerization products of 1-alkyne with H_2O are obtained in the presence of an additional cocatalyst, 2-amino-3-picoline. For instance, when the reaction of terminal alkynes and H_2O is carried out using the catalytic system of $RhCl(PPh_3)_3$, 2-amino-3-picoline, and benzoic acid in THF, a mixture of branched α,β-enone and linear enone can be obtained in a 4:1 ratio (eq 81).[121]



(81)

Other Transformations. Aldoxime groups can be converted to amide groups in the presence of Wilkinson's catalyst with high selectivity and efficiency (eq 82),[122] with no requirement for additives.

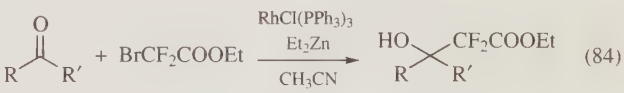


(82)

The synthesis of formaldehyde dithioacetals may be achieved through a reaction with thiols and dichloromethane in the presence of Wilkinson's catalyst and triethylamine (eq 83).[123] The reaction is simple and takes place under very mild reaction conditions.

(83)

Wilkinson's catalyst mediates the Reformatsky-type reaction of ethyl bromodifluoroacetate with various carbonyl compounds (eq 84).[124]



(84)

Related Reagents. Bis(bicyclo[2.2.1]hepta-2,5-diene)rhodium perchlorate; [1,4-bis(diphenylphosphino)-butane](norboradiene)rhodium tetrafluroborate catecholborane; (1,5-cyclooctadiene)[1,4-bis(diphenylphosphino)butane]iridium(I) tetrafluoroborate; (1,5-cyclooctadiene)(tricyclohexylphosphine)(pyridine) iridium(I) hexafluorophosphate octacarbonyldicobalt; palladium (II) chloride; tetrakis(triphenylphosphine)palladium(0); 2-amino-3-picoline; benzylamine.

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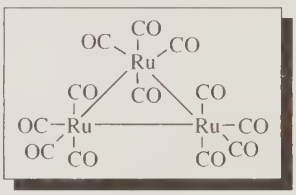
Ruthenium (0) Dodecacarbonyl, Triangulo

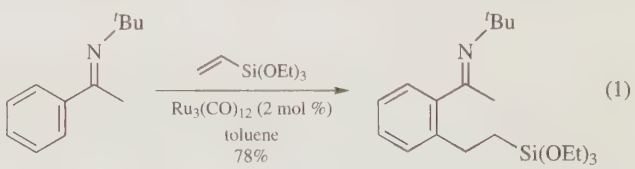


[15243-33-1] $C_{12}O_{12}Ru_3$ (MW 639.34)

(catalyst for C–H bond functionalizations; aromatic C–H bonds, vinylic C–H bonds, aldehydic C–H bonds, and sp^3 C–H bonds at an α-position in aliphatic amines).

Alternate Name: triruthenium dodecacarbonyl.
Physical Data: mp 150 °C (dec).
Solubility: soluble in most organic solvents.
Form Supplied in: orange-crystalline form; commercially available.
Analysis of Reagent Purity: IR (2060, 2030, 2010 cm^{-1}) and elemental analysis.
Handling, Storage, and Precautions: can be stored in air. May cause mild irritation to eyes and skin. Inhalation could lead to headache and dizziness.

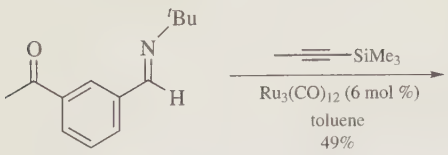
Catalytic Alkylation of Chelate-directed Aromatic C–H Bonds[2]. Triruthenium dodecacarbonyl catalyzes the metalation of *ortho* C–H bonds of aromatic imines followed by addition to olefins affording 1:1 coupling products in good to excellent yields (eq 1).[3] Coordination of the sp^2 nitrogen atoms in imino groups to the ruthenium brings the catalyst center in close proximity to the *ortho* C–H bonds, thus enabling the regioselective bond cleavage. Vinylsilanes and ethylene can be utilized to give products in high yields in this reaction. The use of acetylenes in place of olefins provides a route to the corresponding vinylation products (eq 2).[4]

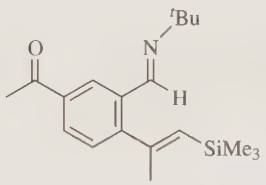


(1)

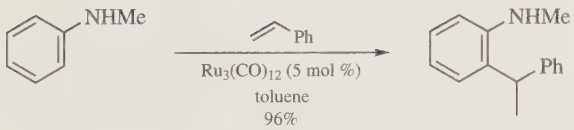
Nitrogen atoms that are sp^3 hybridized also function in the catalytic addition of aromatic C–H bonds to olefins. In contrast to the reactions in eqs 1 and 2, the $Ru_3(CO)_{12}$-catalyzed reaction of *N*-methylaniline with styrene gives the branched product (eq 3).[5]

Catalytic Carbonylation of Aromatic C–H Bonds. The direct carbonylation of pyridylbenzenes with olefins and carbon monoxide in the presence of $Ru_3(CO)_{12}$ catalyst affords



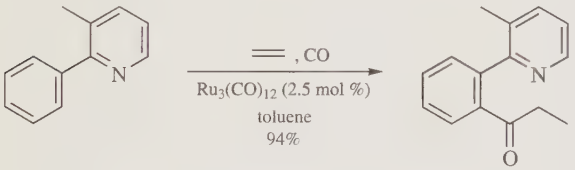


(2)

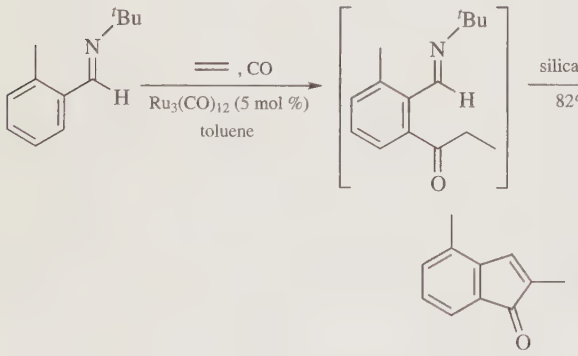


(3)

ortho-acylated derivatives (eq 4).[6] Other *N*-heterocycles such as pyrimidine,[6] oxazole,[7] pyrazole,[8,9] thiazole,[7] oxazoline,[7] and oxazine[7] in place of a pyridine ring can also act as directing groups for the regioselective carbonylation of C–H bonds in benzene rings. Although aromatic imines are applicable to a similar carbonylation, the primary carbonylation products are susceptible to intramolecular aldol condensation, and the reaction mixture must be treated with silica gel for 1 day, if indenones are to be obtained as the sole product (eq 5).[10]



(4)

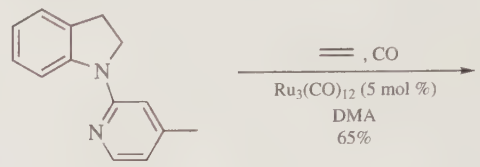


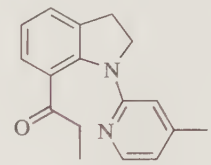
(5)

The carbonylation of indolines at the 7-position with ethylene and carbon monoxide has been achieved when a 2-pyridyl group is substituted at the indoline nitrogen atom (eq 6).[11] Fused imidazole rings in 1,2-disubstituted benzimdazoles also serve as the directing group to selectively undergo direct carbonylation at the 4-position (eq 7).[12]

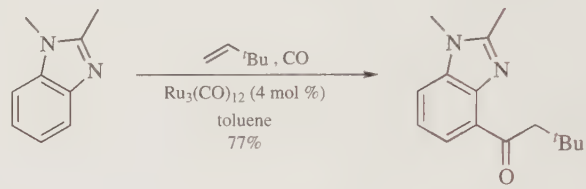
Pyridine itself can be reacted with olefins and carbon monoxide in the presence of a catalytic amount of $Ru_3(CO)_{12}$ to give α-acylated pyridines (eq 8).[13] A number of olefins react with the pyridine to afford the corresponding linear pyridyl ketones as the major products. The ruthenium-catalyzed carbonylation of 1,2-disubstituted imidazoles with olefins and carbon monoxide provides C–C bond formation at the 4-position (eq 9).[14,15]

Various functional groups, e.g., ether, acetal, ester, imide, and nitrile are tolerant to the reaction conditions. The reaction of 1-methylpyrazole under similar carbonylation conditions gives 3-pyrazolyl ketones (eq 10). This result is in contrast to the Friedel-Crafts acylation of a pyrazole ring, which yields 4-pyrazolyl ketones.[15]

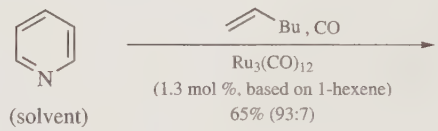


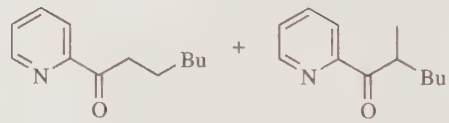


(6)

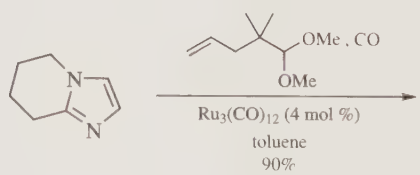


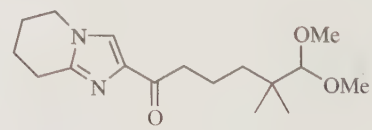
(7)



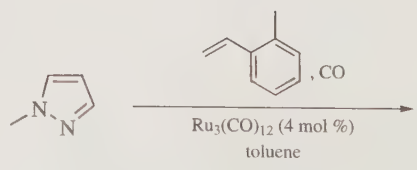


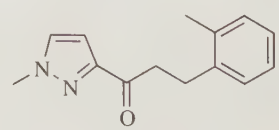
(8)





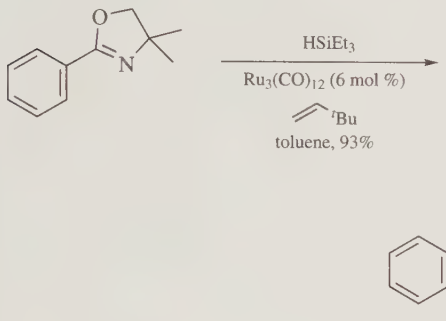
(9)





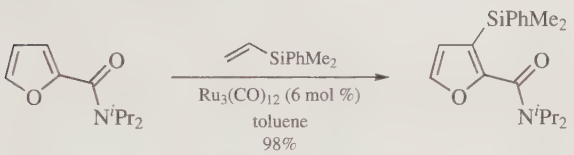
(10)

Catalytic Silylation of Aromatic C–H Bonds. Direct, catalytic functionalizations of *ortho* C–H bonds in aromatic oxazolines have been extended to silylation. Treatment of phenyloxazolines with triethylsilane using $Ru_3(CO)_{12}$ as a catalyst and *tert*-butylethylene as a hydrogen scavenger gives 2-(2-triethylsilyl) phenyloxazolines in good yields (eq 11).[16,17] Various functional groups containing sp^2 or sp^3 nitrogen atoms, other than oxazolines, are available for the catalytic silylation of aromatic C–H bonds as the directing group.[17,18]



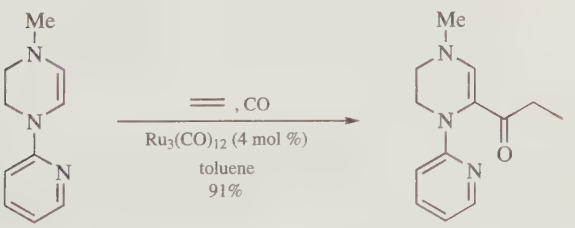
(11)

Heteroarylsilanes can be synthesized by the reaction of heteroaromatic ketones and amides with vinylsilanes with the aid of a $Ru_3(CO)_{12}$ catalyst (eq 12).[19] Ethylene is formed as a by-product and evaporates from the reaction system. This protocol is not applicable to aromatic compounds such as aromatic ketones and aromatic amides.



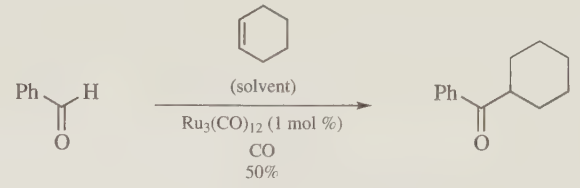
(12)

Catalytic Carbonylation of Vinylic C–H Bonds. $Ru_3(CO)_{12}$ catalyzes the reaction of *N*-(2-pyridyl)morpholines or *N*-(2-pyridyl) pyrazines with olefins and carbon monoxide affording the corresponding acylation products (eq 13).[20] The carbonylation takes place at the γ-position to the pyridine nitrogen.

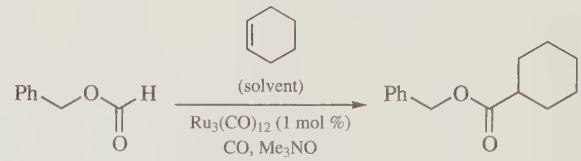


(13)

Catalytic Alkylation of Aldehyde, Formate, and Formamide C–H Bonds. The addition of C–H bonds in aromatic and heteroaromatic aldehydes to olefins in the presence of a $Ru_3(CO)_{12}$ catalyst under a CO atmosphere at 200 °C has been reported (eq 14).[21,22] An external CO pressure of 20 kg cm^{-2} is required to prevent both the decarbonylation of aroyl ruthenium intermediates and decomposition of the ruthenium catalyst. $Ru_3(CO)_{12}$ also catalyzes the addition of C–H bonds in formic acid esters[23] (eq 15) or amides[24] to olefins.

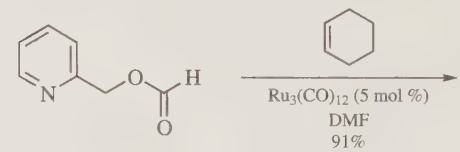


(14)

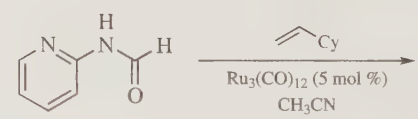


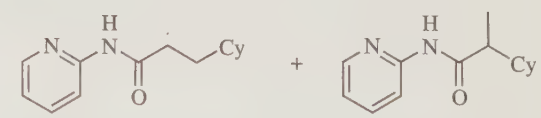
(15)

2-Pyridylmethyl formate undergoes the $Ru_3(CO)_{12}$-catalyzed addition of a formyl C–H bond to olefins in the absence of CO (eq 16).[25] The pyridyl moiety is coordinated to the ruthenium center and then forms a part of the chelating species after C–H bond cleavage, thus suppressing the decarbonylation of the ruthenium alkoxycarbonyl intermediate. The reaction of the formate with acetylenes under similar reaction conditions gives the corresponding α,β-unsaturated esters.[26] *N*-(2-pyridyl)formamide is alkylated with olefins yielding alkylamides in good yields (eq 17),[27] while *N*-(2-pyridylmethyl)formamide reacts very slowly and almost none of the desired product is obtained.



(16)



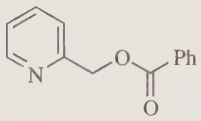


(17)

Catalytic Arylation of Formate and Formamide C–H Bonds. 2-Pyridylmethyl formate is coupled with aryl and vinyl halides using a bimetallic system, $Ru_3(CO)_{12}$ and $PdCl_2$ (eq 18).[28] C–H bond cleavage in the formate by the $Ru_3(CO)_{12}$ complex, followed by a Pd-catalyzed coupling reaction of organic electrophiles appears to occur during the catalytic cycle. *N*-(2-Pyridyl)formamide reacts with aryl iodides in a similar manner to give aromatic amides.[27]

Catalytic Alkylation of sp^3 C–H Bonds in Amines. $Ru_3(CO)_{12}$ catalyzes the addition of an sp^3 C–H bond adjacent

to a nitrogen atom of *N*-(2-pyridyl)alkylamines to olefins. Substitution of the pyridyl group at the amine nitrogen is crucial to this reaction. Examples are shown in eqs 19 and 20.[29,30]



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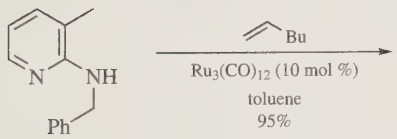

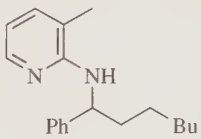

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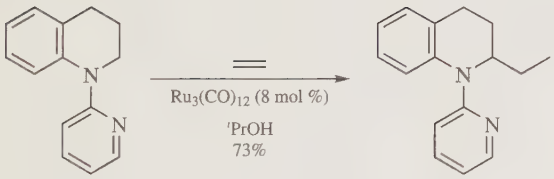

(20)

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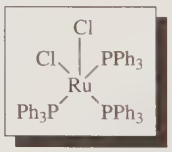
Yoshiya Fukumoto & Naoto Chatani
Osaka University, Osaka, Japan

Ruthenium(II) Dichlorotris(triphenylphosphine)



[15529-49-4] $C_{54}H_{45}Cl_2P_3Ru$ (MW 958.86)

(used in the hydrogenation of nitro groups,[10,12] imines,[15] and ketones,[14] and the selective oxidation of alcohols[21–23])

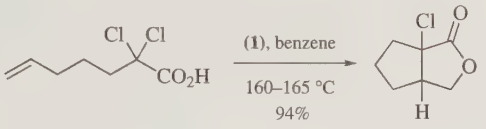
Physical Data: mp 132–134 °C.
Solubility: soluble in toluene, benzene, CH_2Cl_2.
Form Supplied in: red-brown or shiny black crystals.
Preparative Method: by refluxing hydrated ***Ruthenium(III) Chloride*** and ***Triphenylphosphine*** in ethanol according to the procedure of Wilkinson.[1b]

Original Commentary

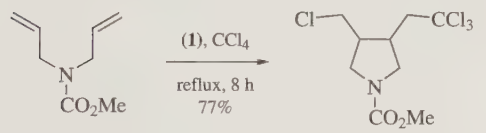
Janet S. Plummer
Parke-Davis Pharmaceutical Research, Ann Arbor, MI, USA

Carbocycles. The title reagent (**1**) is a versatile homogeneous catalyst. It is used in the reduction, oxidation, cyclization, and

isomerization of a variety of organic compounds. It is an effective catalyst for the Kharasch addition of a range of halogenated substances to alkenes.[3,4] α-Chloro-γ-lactones (eq 1)[5a] or carbocyclic α,γ-dichloroesters[5b] are formed by reaction of alkenic α,α-dichloro acids and esters in the presence of (**1**). The process occurs through a metal-complex radical and provides highly functionalized products. The reagent is also used in radical cyclizations of *N*-allylacetamides[6–8] and the stereoselective addition cyclization of 1,6-dienes (eq 2).[9] The synthesis of α,β-unsaturated ketones from primary alcohols and allyl acetates is catalyzed by (**1**).[10]

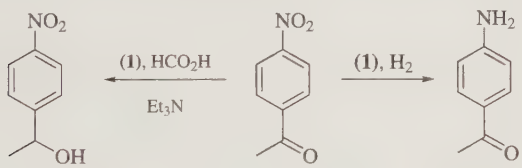


(1)



(2)

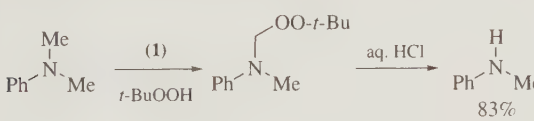
Reductions. The reagent (**1**) can promote hydrogen transfer from alcohols,[14,15] acids,[17] and amides, as well as other hydrogen donors, to activated double bonds,[14,15] carbonyl compounds, and nitro groups. It is an efficient homogeneous catalyst for the hydrogenation of nitroalkanes to amines,[11] nitroarenes to amino arenes,[12,13] and imines to amines (eq 3).[16]



(3)

The ruthenium-catalyzed reduction of diallyl-α-oxalyl carboxylates with ***Formic Acid*** provides α-hydroxycarboxylic acids in good yields.[17]

Oxidations. The reagent (**1**) can catalyze the oxidation of alkanes to tertiary alcohols,[18] amides to *t*-butyldioxyamides,[19] and tertiary amines to α-(*t*-butyldioxy)alkylamines[20] using ***t-Butyl Hydroperoxide***. *N*-Demethylation of tertiary methylamines is accomplished by hydrolysis of the α-(*t*-butyldioxy)alkylamine (eq 4). Alcohols have been oxidized to aldehydes and ketones in the presence of (**1**) and oxidants such as ***Bis(trimethylsilyl) Peroxide***,[21] molecular ***Oxygen***,[22] ***Acetone***,[23a] or ***N-Methylmorpholine N-Oxide***.[23b]

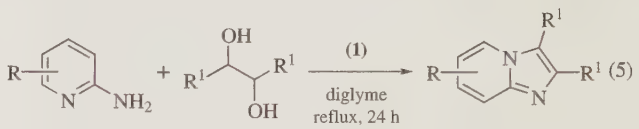


(4)

Isomerizations. The reagent (**1**) catalyzes the isomerization of α,β-ynones to (*E,E*)-α,β,γ,δ-dienones,[24] allylic alcohols to ketones,[25a] and 2-ynols to α,β-unsaturated aldehydes.[25b] The Claisen rearrangement of unsymmetrical diallyl ethers is catalyzed by (**1**) to yield α,δ-unsaturated aldehyes or ketones.[25c]

The reagent can be immobilized on a polystyrene support. The immobilized complex can be reused, thereby making this heterogeneous system more efficient than the homogeneous one. This heterogeneous catalyst has been used in the isomerization of allylarenes.[2,26]

Heterocycles. The reagent (**1**) is used in the *N*-alkylation of NH groups of azoles with alcohols under neutral conditions,[27] and in the synthesis of indoles[28] via an intramolecular *N*-alkylation. It is also used in the syntheses of important biologically active compounds such as imidazo[1,2-*a*]pyridines (eq 5).[29] Other important heterocycles such as 1,3-disubstituted 2,3-dihydroimidazol-2-ones are effectively prepared from *N,N*-disubstituted ureas and vicinal diols in presence of (**1**).[30] The reagent catalyzes the oxidation of the vicinal diol to the corresponding acyloin, and condensation of the urea with the acyloin followed by dehydration yields the desired product (eq 6).[31]



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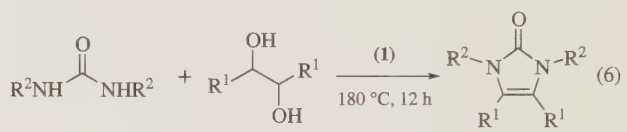
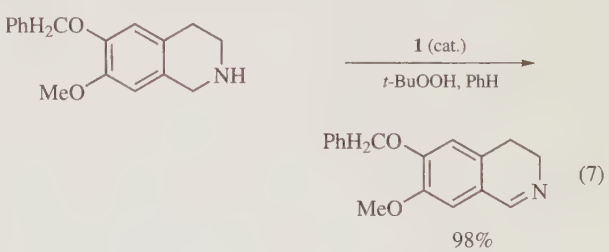


(6)

First Update

Shun-Ichi Murahashi & Changjia Zhao
Okayama University of Science, Okayama, Japan

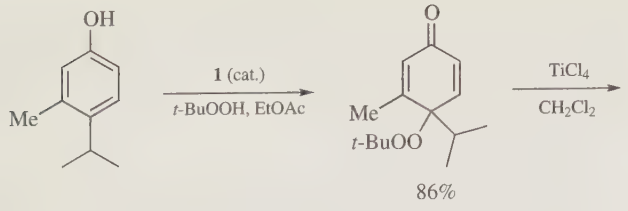
Oxidation. The complex **1** can catalyze the oxidation of secondary amines,[32] phenols,[33] and even hydrocarbons[34] with *t*-butyl hydroperoxide to give the corresponding oxidized products highly efficiently (eqs 7–9).



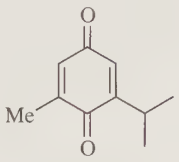
(7)

The title complex **1** can catalyze the oxidative cleavage of *vic*-diol to aldehyde with molecular oxygen on active carbon (eq 10).[35] In combination with TEMPO, $RuCl_2(PPh_3)_3$ catalyzes the aerobic oxidation of aliphatic primary and secondary alcohols highly efficiently to give aldehydes and ketones, respectively (eq 11).[36,37] In combination with hydroquinone, $RuCl_2(PPh_3)_3$ is used in the aerobic oxidation of primary alcohols to aldehydes (eq 12).[38]

Carbon-Carbon Bond Formation. The complex can promote α-alkylation of ketones with primary alcohols. For example, acetophenone can be alkylated with benzyl alcohol to afford 1,3-diphenylpropan-1-one in 82% yield (eq 13).[39]

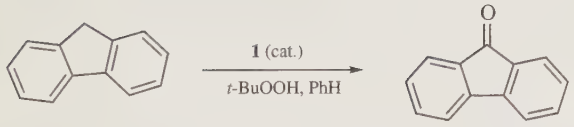


86%



(8)

93%



(9)

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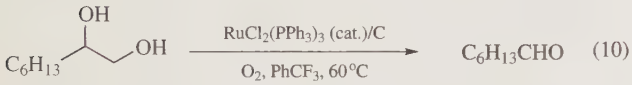

(10)

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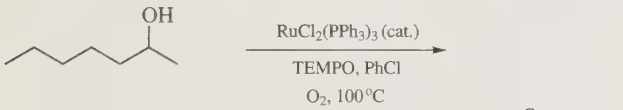
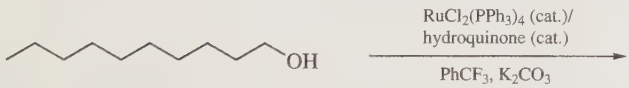


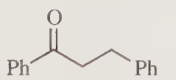
(11)

98%



(12)

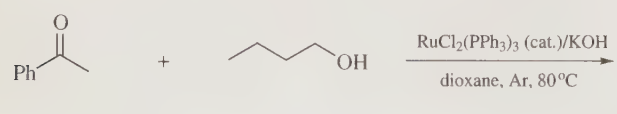
90%

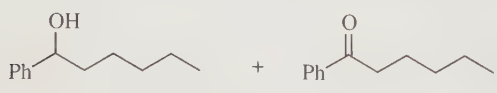


(13)

82%

Acetophenone undergoes reductive alkylation upon treatment with an alcohol and the catalyst **1** (eq 14).[40]

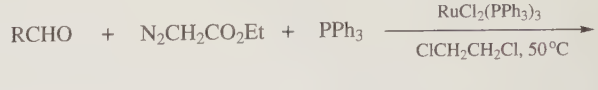




(14)

92%(**a**/**b**:97:3)

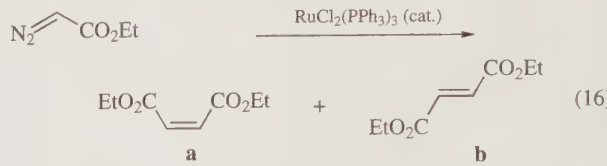
The complex **1** can catalyze the olefination of a variety of aldehydes with ethyl diazoacetate in the presence of triphenylphosphine (eq 15).[41]



(15)

90% (E/Z = 97:3)

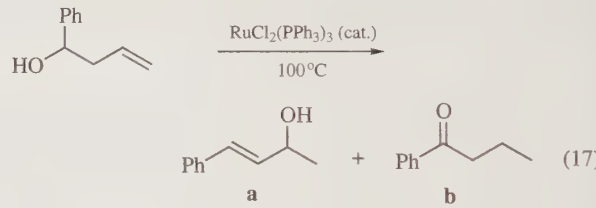
$RuCl_2(PPh_3)_3$ can promote the diazo coupling of ethyl diazoacetate to afford diethyl fumarate and diethyl maleate (eq 16).[42]



(16)

76% (**a**/**b**=0.18)

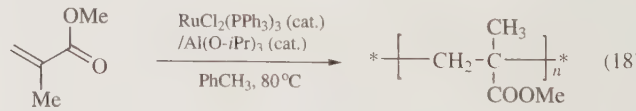
Isomerization. The functional groups of homoallylic alcohols catalyzed by $RuCl_2(PPh_3)_3$ catalyst can be repositioned (eq 17).[43]



(17)

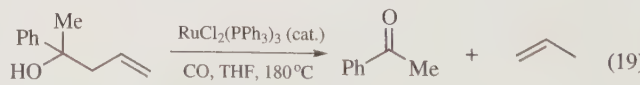
87% (**a**:**b**>20:1)

Polymerization. $RuCl_2(PPh_3)_3$ can be used in living radical polymerization of methyl methacrylate in combination with $Al(OiPr)_3$ to afford a star polymer in a controlled way (eq 18).[44]



(18)

Other Applications. The title compound can catalyze the β-allyl elimination of homoallyl alcohols to afford carbon-carbon cleavage products (eq 19).[45]

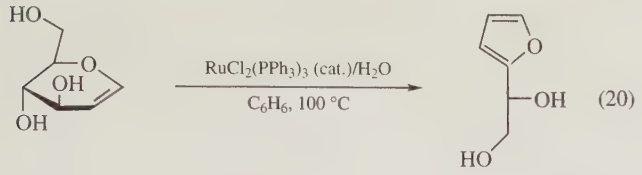


(19)

91%

The transformation of D-glucal to optically active furan diol can be carried out in the presence of the catalyst **1** (eq 20).[46]

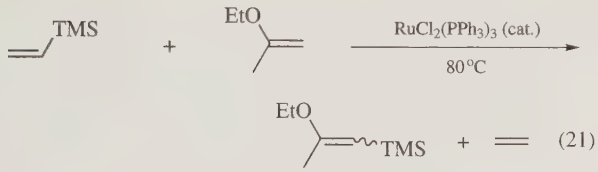
$RuCl_2(PPh_3)_3$ can promote the cross-disproportionation of vinyl-trisubstituted silanes with vinyl alkyl ethers (eq 21).[47]



(20)

2-(D-glycerol-1,2-dihydroxyethyl)furan

64%



(21)

Yield 56%
E/*Z* (4:1)

1. (a) *Aldrichim. Acta* **1982**, *15*, 13. (b) Wilkinson, G.; Osborn, J. A.; Jardine, F. H.; Young, J. F., *J. Chem. Soc. (A)* **1966**, 1711.
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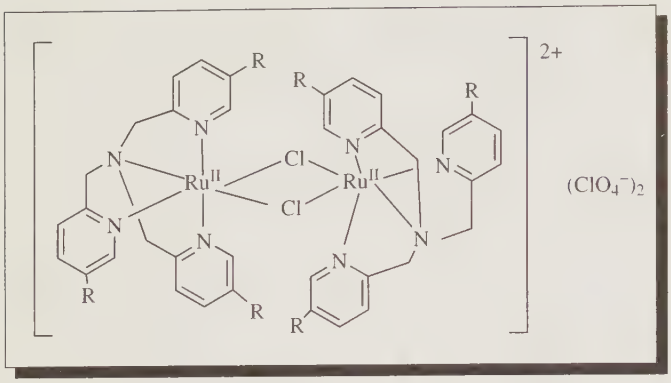
Ruthenium(II), bis[*N*,*N*-bis-[(2-pyridyl-κN)methyl]-2-pyridine-methanamine-*N*1,*N*2] di-μ-chloride



(R = H)

[212784-73-1] $C_{36}H_{36}N_8Cl_4O_8Ru_2$ (MW 1052.68)

(R = CH_3)

[212784-75-3] $C_{42}H_{48}N_8Cl_4O_8Ru_2$ (MW 1136.84)

(homogeneous catalysts for hydroxylation and ketonization of alkanes with alkyl hydroperoxides,[1] allylic oxidation, epoxidation of alkenes, sulfoxidation of sulfides, and co-oxygenation of alkanes with dioxygen[2])

Physical Data: redox potential (vs. Fc/Fc^+ as 0 V in CH_3CN/0.1 M TBAP at room temperature); 0.22 V ($Ru^{II}Ru^{II}/Ru^{II}Ru^{III}$) and 0.71 V ($Ru^{II}Ru^{III}/Ru^{III}Ru^{III}$) for R = H, 0.17 V ($Ru^{II}Ru^{II}/Ru^{II}Ru^{III}$) and 0.66 V ($Ru^{II}Ru^{III}/Ru^{III}Ru^{III}$) for R = CH_3.[3]

Solubility: soluble in CH_3CN, acetone, MeOH, CH_2Cl_2; insoluble in hydrocarbons and aromatics.

Form Supplied in: orange solids; not commercially available.

Preparative Methods: for R = H; to a degassed solution of TPA•3$HClO_4$ (0.68 g, 1.15 mmol) and NEt_3 (0.58 g, 5.73 mmol) in CH_3OH (20 mL), was added a solution of $RuCl_3$•$3H_2O$ (0.30 g, 1.15 mmol) in CH_3OH (20 mL) under N_2 via a cannula. The mixture was heated at reflux for 8 h and the brown precipitate was collected by filtration. The brown powder was washed with ether and dissolved into CH_3CN. Insoluble materials were removed by filtration through a Celite column (2 cm × 5 cm) to obtain a reddish orange solution. The solvent was removed via rotatory evaporator, and the resultant orange powder was washed well with ether then dried.

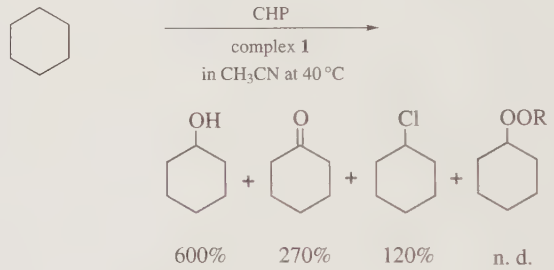
For R = CH_3; a mixture including 5-Me_3-TPA (0.665 g, 2 mmol), NEt_3 (1.012 g, 10 mmol), and $NaClO_4$ (1.22 g, 10 mmol) under N_2 was added via a cannula to a degassed solution of $RuCl_3$•$3H_2O$ (0.523 g, 2 mmol) in CH_3OH (20 mL). The mixture was heated at reflux for 12 h and then filtered to obtain a yellow-brown powder. The crude product was dissolved into CH_3CN and filtered through a Celite 535 column to afford a reddish orange solution. The orange powder, obtained by removing the CH_3CN, was washed with ether and dried.

Purification: if necessary, recrystallization from CH_3CN or CH_3OH gives single crystals of these compounds.

Handling, Storage, and Precautions: perchlorate salts of metal compounds with organic ligands are potentially explosive. Great care should be exercised. Air stable.

C–H Oxidation Reactions Using Alkyl Hydroperoxides. Catalytic oxygenation of alkanes to form alcohols and ketones has generated much interest, since this may provide effective, inexpensive pathways to these "value-added" compounds. To realize this goal, a number of transition-metal complexes have been prepared and their C–H reactivity using alkyl hydroperoxides as the terminal oxidants has been examined.[4] The two complexes, $[RuCl(TPA)]_2(ClO_4)_2$ (**1**) and $[RuCl(5\text{-}Me_3\text{-}TPA)]_2(ClO_4)_2$ (**2**) [TPA = tris(2-pyridylmethyl)amine and 5-Me_3-TPA=tris(5-methyl-2-pyridylmethyl)amine],[3] can utilize alkyl hydroperoxides as terminal oxidants toward catalytic hydrocarbon oxygenation. In order for the reactions to proceed well, the hydroperoxides must be *anhydrous*; therefore, *t*-butyl hydroperoxide (TBHP) and cumyl hydroperoxide (CHP) are purified as previously described[5] and used neat.

Catalytic oxygenation of cyclohexane was performed to generate cyclohexanol (CyOH), cyclohexanone (CyO), and chlorocyclohexane (CyCl) using **1** and **2** with 100 equiv of TBHP in acetonitrile at 40 °C under N_2. Catalytic turnover numbers were ~10 for CyOH and ~4 for CyO, with concomitant stoichiometric formation of CyCl, based on the catalyst. *t*-Butyl cyclohexylperoxide (*t*-BuOOCy) was detected and characterized by GC-MS measurement but not quantified. Reaction products are summarized in eq 1. These products are comparable to those obtained from the reaction by $[FeCl_2(TPA)]ClO_4$ with TBHP.[6]



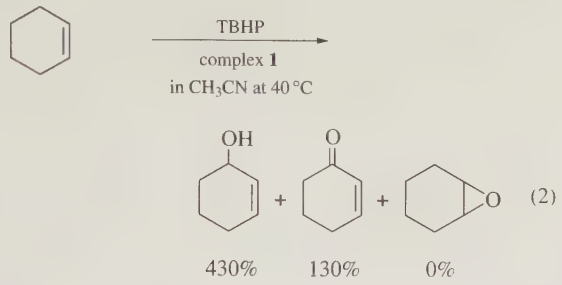
(1)

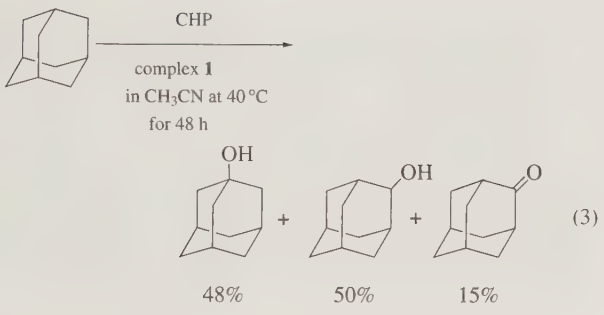
n. d. = not determined.

Monitoring the time-course for formation of cyclohexanol and cyclohexanone revealed a 5 h-induction period for the TBHP reaction and over 10 h for the CHP reaction. In addition to long induction periods, the presence of the radical scavenger 2,6-di-*t*-butyl-4-methylphenol (BHT) inhibited the reactions, suggesting a free radical mechanism. The presence of dioxygen also exerted significant effects on the reactions. Catalytic oxygenation of cyclohexane with TBHP and **1** under O_2 (~1 atm) gave higher rates in the formation of cyclohexanol and cyclohexanone compared with the reaction under air.

Catalytic oxygenation of cyclohexene was examined by TBHP with **1** in CH_3CN under N_2 at 40 °C for 168 h. In this reaction, allylic oxygenation was observed to give cyclohexen-1-ol (430%) as the main product and cyclohexen-1-one (130%) but no epoxidation as summarized in eq 2.

Catalytic oxygenation of adamantane under N_2 in CH_3CN at 40 °C for 48 h afforded 1-adamantanol, 2-adamantanol, and 2-adamantanone as shown in eq 3. The selectivity of the reaction represented by 3°/2° ratio (= 3 × [1-adamantanol]{[2-adamantanol]+[2-adamantanone]}) was determined for **1**-TBHP (2.7), **2**-TBHP (2.7), **1**-CHP (2.0), and **2**-CHP (3.1). These results suggest that each alkyl hydroperoxide gives a reactive species independent of the catalyst employed, but having similar reactivity.





Catalytic oxygenation of cyclohexene was also examined by TBHP with **1** under N_2 at 40 °C for 168 h. The formation of cyclohexen-1-ol (430% based on the catalyst) and cyclohexen-1-one (130%) was observed but there was no epoxidation. The yields were much lower than those using molecular oxygen with **1**.[2]

Complexes **1** and **2** showed difference in the reaction rates of cyclohexane oxygenation by TBHP: the rate is faster for **1** than that for **2**. As can be seen from their redox potentials shown above, those of **2** are lower than those of **1**. Thus, electron transfer reactions from Ru(II) centers to ROOH to form radical intermediates such as RO• should be retarded by redox potential in concert with steric hindrance around the metal center.

Reactions with Molecular Oxygen. Catalytic oxygenation of hydrocarbons by molecular oxygen under mild conditions is a long-held industrial goal since it offers the production of useful materials from abundant natural feed-stocks. Ruthenium complexes are attractive catalysts and the reactions likely involve high-valent Ru-oxo species as intermediates.[7]

Reactions were performed in CH_3CN under O_2 (1 atm) including 1.0×10^{-5} mol of **1**•1/2CH_3CN and 1000 equiv of substrate at room temperature. Product distributions are summarized in Table 1 with yields relative to the dimer. In the case of cyclohexene as a substrate, allylic oxygenation was found to be the main pathway and epoxidation as a minor reaction. In the absence of the complex, small amounts of the alcohol and ketone (six-times more than alcohol) were obtained, but no epoxide; 1/100 amount of cyclohexen-1-ol and 1/7 amount of cyclohexen-1-one were obtained relative to the reaction under catalytic conditions. These results suggest that the reactions are merely free radical autoxidations, but ruthenium species are involved as mentioned below.

To expand the availability of this catalytic oxygenation by **1** with dioxygen, other substrates were examined as shown in Table 1. Norbornene was epoxidized but the yield was very poor compared with that of cyclohexene, owing to the difficulty of nobornene allyl radical formation because of stereoelectronic effects. As for alkanes, cyclohexene was not oxidized as expected from observations mentioned so far, that is, allyl radical formation should be indispensable for the initiation of all the reactions. However, cyclohexene was oxygenated to give cyclohexanol and cyclohexanone in the presence of cyclohexene as co-substrate. When adamantane was employed as a substrate in the presence of cyclohexene, 3°/2° ratio of adamantane oxygenation was determined to be 4, which differed from the reaction using TBHP (2.7) or CHP (2.0).

Table 1 Catalytic oxygenation toward various substrates by **1** with dioxygen (1 atm) in CH_3CN at room temperature for 168 h

Substrate	Products (yield (%) based on catalyst)			
	OH (6100)	O (8500)	O (880)	
+ Me_2S	OH (7600)	O (3300)	O (0)	Me_2SO (2200)
	O (640)	b		
a	O (240)			
a	OH (10200)	O (14900)	O (1900)	
a	OH (700)	O (470)		

[a] Reaction time was 186 h.

[b] Other products were not quantified.

In order to gain more mechanistic insights into this catalytic oxygenation by the ruthenium dimer **1**, the addition of certain trapping reagents was explored. In the presence of BHT as a radical scavenger, all the reactions were terminated and no color change was observed for the reaction mixture. In the presence of 100 equiv of dimethyl sulfide (Me_2S), the epoxidation was quenched and dimethyl sulfoxide (DMSO) was obtained while cyclohexen-1-ol became dominant over cyclohexen-1-one. These results indicate that free radical formation is critical but 2-electron oxidation is involved in the epoxidation process and likely in the alcohol oxidation.

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Ruthenium(III) Chloride

[10049-08-8] Cl_3Ru (MW 207.42)
(hydrate)
[14898-67-0]

(Lewis acid;[1] catalyst for alkyne functionalization[8] and oxidation[4a])

Physical Data: mp >500 °C for anhydrous material.
Solubility: α-$RuCl_3$ (black lustrous crystals) insoluble in alcohol, water; β-$RuCl_3$ (dark-brown, fluffy crystals) soluble in alcohol.
Form Supplied in: available as anhydrous solid and hydrated solid.
Analysis of Reagent Purity: elemental analysis.

Original Commentary

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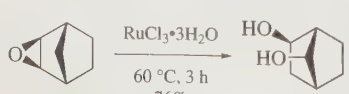
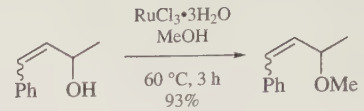
Zeneca Pharmaceuticals, Wilmington, DE, USA

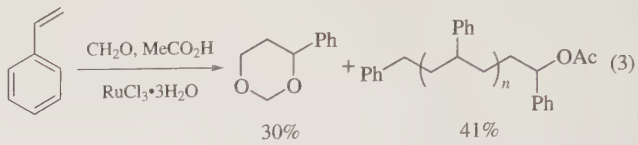
Lewis Acid. Ruthenium trichloride can serve as a mild Lewis acid. Treatment of norbornene oxide with this reagent results in a hydrocarbon skeletal rearrangement (eq 1).[1] Other ruthenium reagents such as ***Ruthenium(VIII) Oxide*** are ineffective at bringing about the desired transformation. Ruthenium trichloride, in the presence of alcohols, also catalyzes the formation of allylic ethers from allylic alcohols (eq 2).[2] It is likely that this process occurs via an allylic carbonium ion since racemization ensues when enantiomerically pure allylic alcohols are employed. The Prins reaction is catalyzed by ruthenium trichloride (eq 3).[3] While it is possible that this reaction is proceeding in a fashion analogous to the Wacker oxidation, simple Lewis acid activity can explain the observed products.



(1)

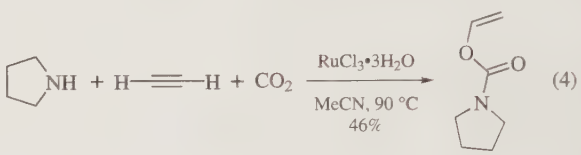


(2)

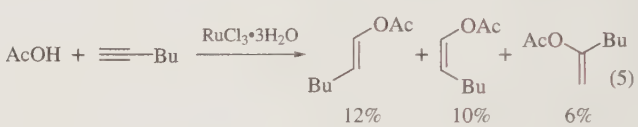


(3)

Alkyne Functionalization. Ruthenium trichloride catalyzes the reaction of ***Acetylene*** with ***Carbon Dioxide*** and secondary amines, providing vinyl carbamates in low to moderate yields (eq 4).[4] Primary amines do not participate in this reaction and ruthenium dodecacarbonyl fails to catalyze this process. In an analogous transformation, ruthenium trichloride catalyzes the addition of carboxylic acids to terminal alkynes (eq 5).[5] Higher selectivities and increased yields are obtained when ***Tri-n-butylphosphine*** is added to the reaction mixture.

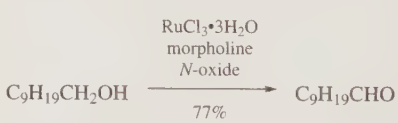


(4)



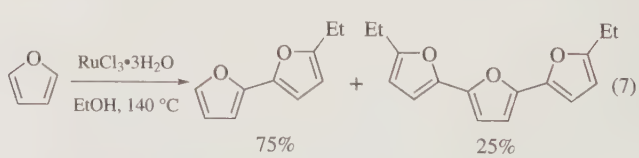
(5)

Oxidations. Ruthenium trichloride catalyzes the oxidation of alcohols in the presence of stoichiometric ***N-Methylmorpholine N-Oxide*** (eq 6).[6a] A slight preference is noted for primary over secondary alcohols. Also, tertiary amines are oxidized to amine oxides in the presence of ruthenium trichloride and molecular ***Oxygen***.[7a]



(6)

C–H Activation. Furan and thiophene undergo an alkylation–coupling process when exposed to ruthenium trichloride, an alcoholic solvent, and elevated temperatures (eq 7).[8]



(7)

First Update

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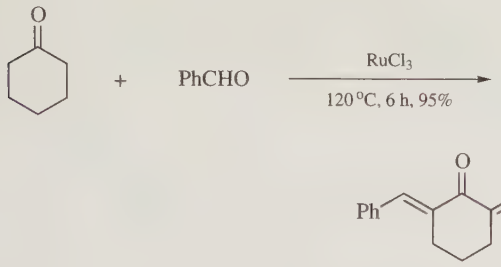
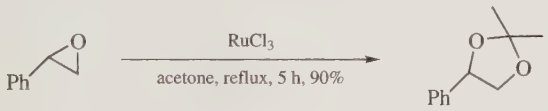
Lewis Acid. Anhydrous ruthenium(III) trichloride is effective to catalyze aldol condensation reaction of aldehydes and ketones

in a sealed tube at 120 °C without addition of solvent (eq 8).[9] With this ruthenium catalyst, cross-condensation of cyclic ketones with aromatic aldehydes as well as self-condensation of ketones and aldehydes can be achieved in high yields.



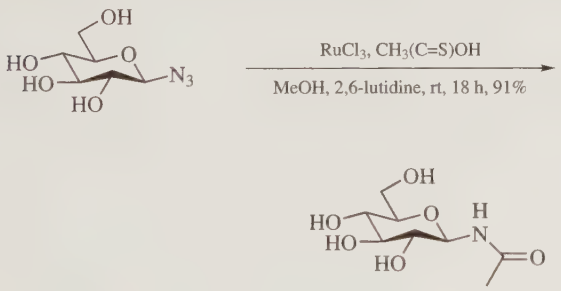
(8)

With catalytic amount of anhydrous ruthenium(III) trichloride, epoxides can be converted into 1,3-dioxolanes in refluxing acetone (eq 9).[10] High yield of 1,3-dioxolanes can be obtained from epoxides bearing both electron-releasing and electron-withdrawing substituents.



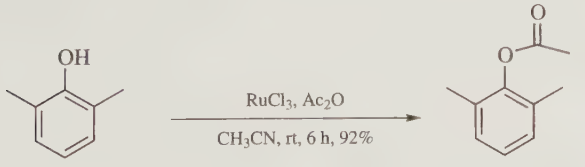
(9)

Ruthenium(III) trichloride can catalyze amide synthesis from azides and thioacids at room temperature (eq 10).[11] It is believed that the amide synthesis proceeds via reaction of an activated Ru(III)-thiocabonyl complex with azides. This method allows the efficient synthesis of acetamide of glucoses without tedious manipulation of protecting groups.



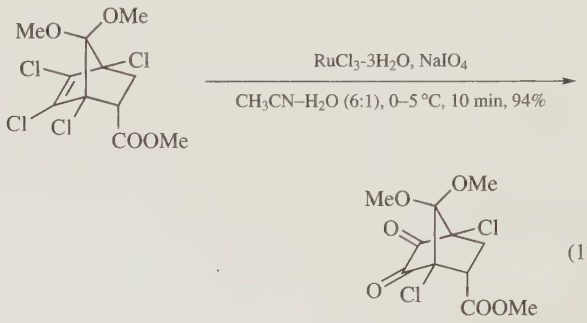
(10)

Acylation of a variety of phenols, alcohols, thiols, and amines can be achieved by using ruthenium(III) trichloride as catalyst at room temperature under mild reaction conditions (eq 11).[12] This ruthenium catalyzed acylation gives high yields for sterically hindered substrates as well as substrates bearing acid-sensitive functional groups (such as allyloxy, *t*-butyl, and silyl ethers).



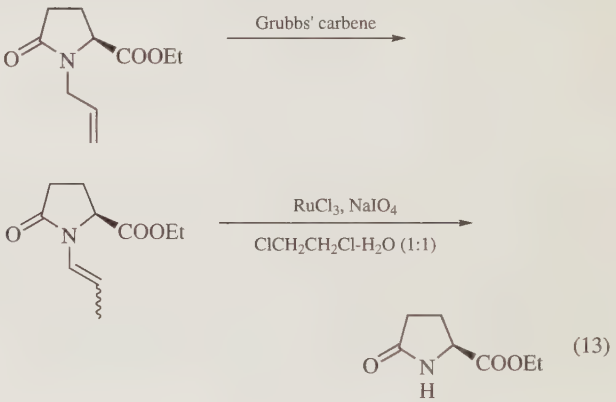
(11)

Oxidations. With sodium periodate as oxidant, ruthenium(III) trichloride can catalyze oxidation of conformationally rigid vicinal dihaloalkenes to α-diketones in acetonitrile-water (6:1) at 0–5 °C (eq 12).[13] In general, reaction of tetrachloro derivatives proceeds faster than the analogous tetrabromo derivatives.



(12)

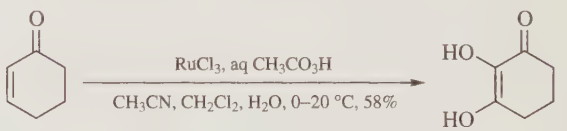
Ruthenium(III) trichloride with sodium periodate can effect catalytic oxidative cleavage of the allyl protecting group in lactams (eq 13).[14] Allylic amide is first converted into the corresponding enamide by treatment with Grubbs' carbene. The C=C double bond of the isolated enamide can be oxidatively cleaved by $RuCl_3$-$NaIO_4$ in 1,2-dichloroethane-H_2O (1:1). Interestingly, this oxidation method is compatible with a diversity of functional groups including oxidation-sensitive furans and electron rich arene rings.



(13)

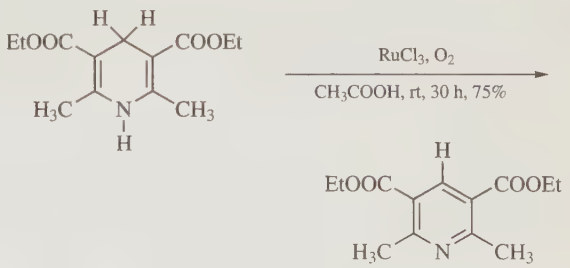
55% yield over two steps

Using peracetic acid as oxidant, ruthenium(III) trichloride can catalyze oxidation of cyclic α,β-unsaturated carbonyl compounds to the corresponding α-*oxo*-ene-diols (eq 14).[15]



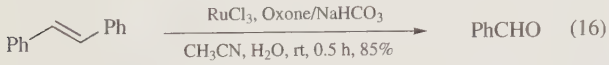
(14)

Under aerobic condition, ruthenium(III) trichloride effects catalytic oxidation of Hantzsch 1,4-dihydropyridines in acetic acid at room temperature (eq 15).[16]

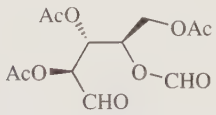


(15)

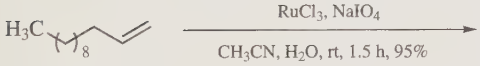
With either Oxone or $NaIO_4$ as oxidant, ruthenium(III) trichloride can function as an efficient catalyst for oxidative cleavage of alkenes into carbonyl compounds.[17] Three optimized reaction protocols are designed for the oxidative cleavage of aryl alkenes (eq 16), aliphatic alkenes (eq 17), and terminal aliphatic alkenes (eq 18) to their corresponding aldehydes in high yields.

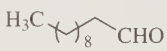


(16)



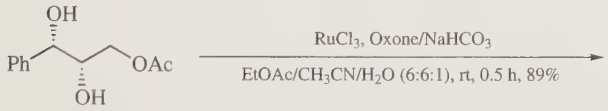
(17)



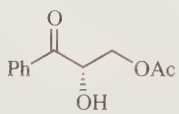


(18)

With Oxone as oxidant, ruthenium(III) trichloride can effect catalytic monooxidation of *vic*-diols in a highly regioselective manner (eq 19).[18] It is believed that this reaction proceeded through a nucleophilic attack of SO_5^{2-} on a cyclic intermediate of RuO_4 and *vic*-diol. It is interesting to note that oxidation occurs selectively at the more electron-rich hydroxy group.



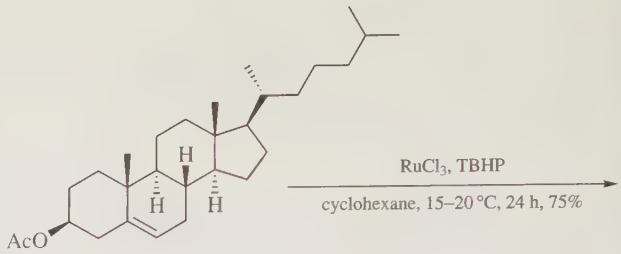
98% ee

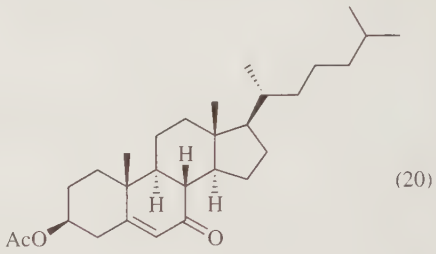


(19)
98% ee

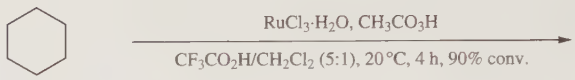
C–H Activation. Using *tert*-butyl hydroperoxide (TBHP) as oxidant, ruthenium(III) trichloride effects catalytic allylic oxidation of steroidal alkenes to the corresponding enones (eq 20).[19] It is found that higher yield can be obtained by using solvent with low polarity, and the C=C double bond remains intact in the oxidation reaction.

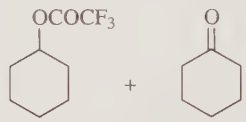
Using peracetic acid as oxidant, ruthenium(III) trichloride can catalyze C–H bond oxidation of cyclohexane to afford cyclohexyl trifluoroacetate and cyclohexanone in CF_3COOH/CH_2Cl_2 at room temperature (90% conversion, selectivity=85:15) (eq 21).[20]





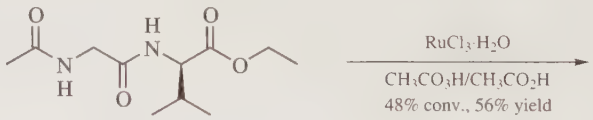
(20)

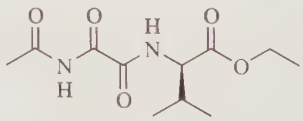




(21)
85:15

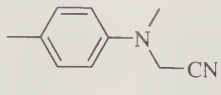
With peracetic acid as oxidant, ruthenium(III) trichloride selectively oxidizes the C^{α} position of glycine residues in short peptides to give α-ketoamides (eq 22).[21] Unsatisfactory results are obtained with other ruthenium catalysts such as $RuCl_2(PPh_3)_3$, $[RuCl_2(CO)_3]_2$, $RuCl_2(bpy)_2$, and $Ru(acac)_3$, etc.





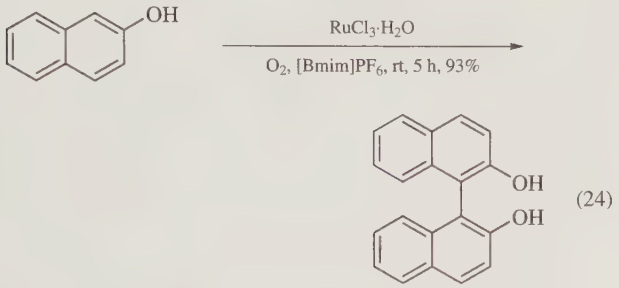
(22)

Under molecular oxygen atmosphere, ruthenium(III) trichloride can catalyze oxidative cyanation of tertiary amines with sodium cyanide (eq 23).[22] Using methanol and acetic acid as solvents, cyclic amines and *N*,*N*-dimethylaniline with either electron-donating or electron-withdrawing substituents on the aromatic rings can be converted to the corresponding α-aminonitriles in high yields. Interestingly, this reaction chemoselectively oxidizes the *N*-methyl group in the presence of other alkyl groups.



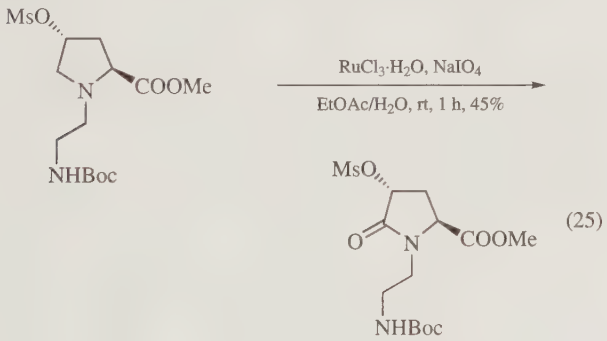
(23)

Under aerobic conditions, ruthenium(III) trichloride can catalyze oxidative coupling of β-naphthols to afford binaphthols using ionic liquid ([Bmim]PF_6) as solvent (eq 24).[23] The ruthenium(III) trichloride-([Bmim]PF_6) reaction system can be reused in three to four subsequent experiments with a gradual decrease in activity. For example, the yields of oxidative coupling of 2-naphthol with 10% Ru(III) trichloride in ([Bmim]PF_6) are found to be 93%, 89%, 85%, and 79% in four consecutive reaction cycles.



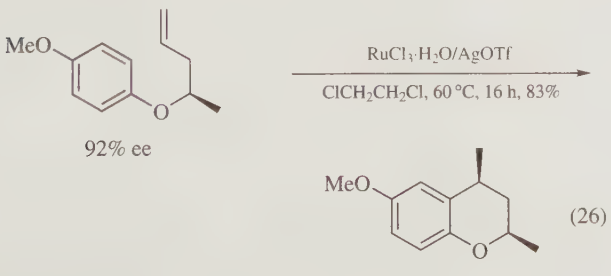
(24)

With $NaIO_4$ as oxidant, regioselective oxidation of *N*-alkylpyrrolidines to pyrrolidin-5-ones can be achieved by using catalytic amount of ruthenium (III) trichloride in EtOAc/H_2O (eq 25).[24] The N^{α}-*endo*-methylene group of a series of substituted pyrrolidines was selectively oxidized under this biphasic reaction system. Similar yields can be obtained when the reactions are performed in $CH_3CN/CCl_4/H_2O$ solvent system.



(25)

Combination of ruthenium(III) trichloride with silver triflate is an efficient catalytic system for intramolecular electrophilic hydroarylation under mild reaction conditions with good functional group compatibility (eq 26).[25] Good to excellent yields of cyclized products including chromanes, tetralins, terpenoids, and dihydrocoumarins can be obtained. Interestingly, neither $RuCl_3$ or AgOTf alone can catalyze the hydroarylation reaction.



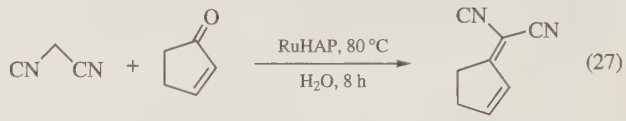
92% ee
(*cis*:*trans* = 4:1)

(26)

Second Update

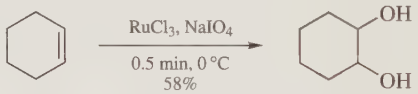
Ernest S. Gore
Johnson Matthey, West Deptford, NJ, USA

Lewis Acid. Kaneda and co-workers[26] have shown that more efficient use of $RuCl_3$ can be achieved when it is supported on hydroxyapatite (RuHAP). The supported reagent could be recycled at least three times and was used to promote Diels-Alder reactions with yields of 82–92% and *exo*/*endo* ratios from 90/10 to 100/0. Another use of the supported reagent was aldol reactions of nitriles with carbonyls in water (eq 27).

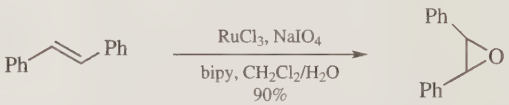


(27)

Oxidations. Two reviews [27,28] include references on the use of $RuCl_3$ as an oxidation catalyst. $RuCl_3$ can be used as a catalyst to oxidize olefinic bonds. The usual result is cleavage of the bond to carboxylic acids or ketones if the olefin is tetrasubstituted.[29] However, under certain conditions diols[30] or epoxides[31] can be obtained (eqs 28 and 29).

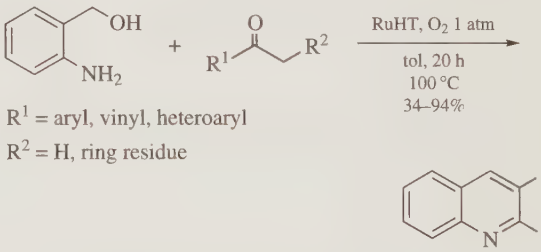


(28)



(29)

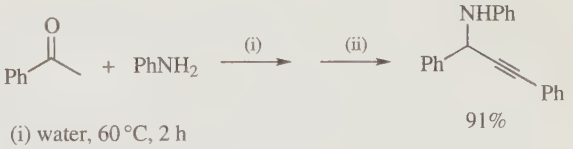
Recently, advances have been made in the oxidation of organic substrates with O_2 using supported $RuCl_3$ as the catalyst. Quinolines could be prepared from 2-aminobenzyl-alcohol and carbonyl compounds[32] with $RuCl_3$ supported on hydrotalcite (HT) (eq 30).



(30)

Alcohols, diols, and amines were oxidized with O_2 using $RuCl_3$ supported on alumina,[33] and organosilanes were oxidized to silanols using $RuCl_3$ supported on hydroxyapatite.[34]

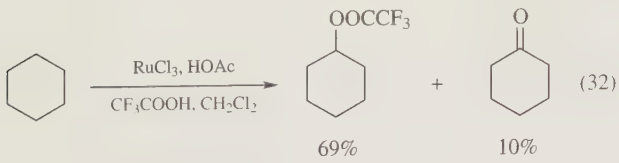
C–H Activation. Imines, formed as intermediates from aldehydes and aniline, serve as substrates for alkyne addition when using $RuCl_3$ and CuBr as cocatalysts.[35]



(31)

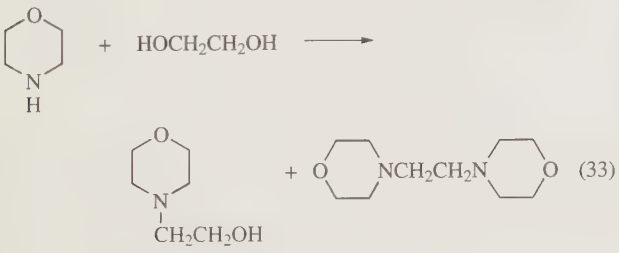
(i) water, 60 °C, 2 h
(ii) PhCCH, $RuCl_3$/CuBr, 40 °C, 18 h

Trifluoroacetate (CF_3COO^-) can be added to cyclohexane in the presence of $RuCl_3$ (eq 32).[36]



(32)

N-Alkylation. Amines have been *N*-alkylated with alcohols using $RuCl_3$ as catalyst.[37,38] The products of the reaction are critically dependent on the ratio of $PR_3/RuCl_3$ (eq 33).



(33)

I **II**

Ratio of $PPh_3/RuCl_3$	**I** (%)	**II** (%)
0	17	80
11	94	<0.01

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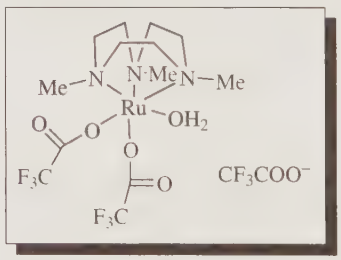
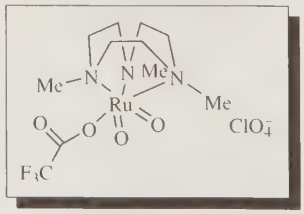
Ruthenium(III) *N,N′,N″*,-Trimethyl-1,4,7-triazacyclononane + Ruthenium(II) *cis*-diaquabis(6,6′-dichloro-2,2′-bipyridine)bistriflate



$[Ru(Me_3tacn)(CF_3CO_2)_2OH_2]CF_3CO_2$

[478980-00-6] $RuC_{15}H_{23}F_9N_3O_7$ (MW 629.22)



cis-$[Ru^{VI}(Me_3tacn)(CF_3CO_2)O_2]ClO_4$

(catalyst for alkene epoxidation[1,2] and alcohol oxidation[2,3])

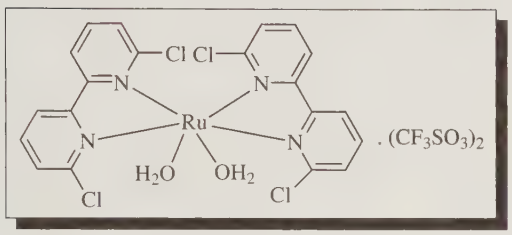
Physical Data: a pale yellow microcrystalline solid.

Solubility: insoluble in *n*-hexane, diethyl ether, dichloromethane, chloroform, and acetonitrile but slowly dissolves in methanol or ethanol to give a pale yellow solution.

Analysis of Reagent Purity: elemental analysis and FAB-MS.

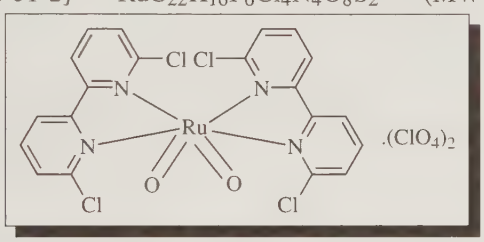
Preparative Methods: prepared by refluxing $[Ru(Me_3tacn)Cl_3]$[4] with CF_3CO_2Ag in aq CF_3CO_2H (eq 1).[1] The resulting red solution was hot-filtered to remove the insoluble AgCl. Slow evaporation of the solvent afforded a pale-yellow microcrystalline solid that was collected on a frit, washed with ice-cold water, and dried in vacuo.

$$[Ru(Me_3tacn)Cl_3] \xrightarrow[CF_3CO_2H/H_2O,\ \text{reflux}]{CF_3CO_2Ag} [Ru(Me_3tacn)(CF_3CO_2)_2OH_2]CF_3CO_2 \quad (1)$$



cis-$[Ru^{II}(6,6'\text{-}Cl_2bpy)_2(OH_2)_2](CF_3SO_3)_2$

[120596-51-2] $RuC_{22}H_{16}F_6Cl_4N_4O_8S_2$ (MW 885.23)



cis-$[Ru^{VI}(6,6'\text{-}Cl_2bpy)_2O_2](ClO_4)_2$

(catalyst for oxidation of alcohols[5] and alkanes;[5,6] hydrogenation[7,8])

Physical Data: a red crystalline solid.

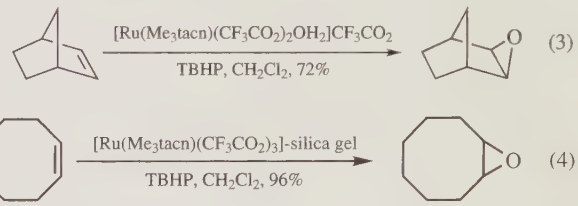
Solubility: soluble in acetonitrile and water.

Analysis of Reagent Purity: ^1H NMR spectra can be recorded using CD_3CN as solvent. Elemental analysis, FAB-MS, and UV-visible spectroscopy (in H_2O), and cyclic voltammetry can be used for characterization and purity analysis.

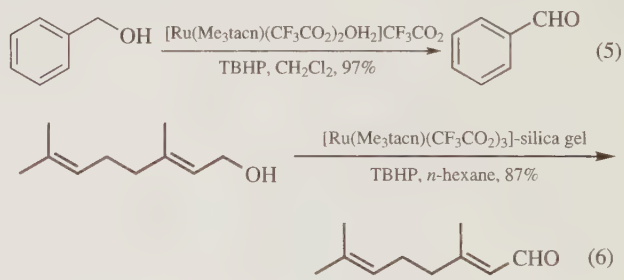
Preparative Methods: prepared by heating a mixture of *cis*-$[Ru^{II}(6,6'\text{-}Cl_2bpy)_2Cl_2]\cdot 2H_2O$ and CF_3SO_3Ag in water at 70 °C for 30 min (eq 2).[5] The resulting red solution was filtered to remove the insoluble AgCl. Slow evaporation of the solvent provided a red crystalline solid.

$$cis\text{-}[Ru^{II}(6,6'\text{-}Cl_2bpy)_2Cl_2]\ 2H_2O \xrightarrow[H_2O,\ 70\ °C]{CF_3SO_3Ag} cis\text{-}[Ru^{II}(6,6'\text{-}Cl_2bpy)_2(OH_2)_2]\ (CF_3SO_3)_2 \quad (2)$$

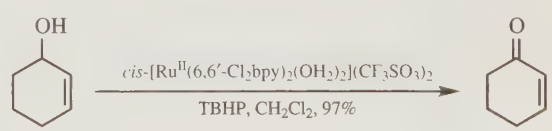
Epoxidation of Alkenes. $[Ru(Me_3tacn)(CF_3CO_2)_2OH_2]CF_3CO_2$ can function as an effective catalyst for epoxidation of a variety of alkenes using *tert*-butylhydroperoxide (TBHP) as terminal oxidant under mild reaction conditions. Using $[Ru(Me_3tacn)(CF_3CO_2)_2OH_2]CF_3CO_2$ as catalyst, norbornene can be epoxidized to *exo*-2,3-epoxynorborane exclusively in 72% yield at 25 °C in 8 h (eq 3).[1] Notably, no rearranged product such as cyclohexene, carboxyaldehyde, or norcamphor is detected in this reaction. $[Ru(Me_3\ tacn)(CF_3CO_2)_2OH_2]CF_3CO_2$ can be immobilized in silica gel by simple impregnation.[2] This silica gel supported ruthenium catalyst can also effect epoxidation of alkenes using *tert*-butylhydroperoxide. Cyclooctene can be effectively epoxidized in 96% yield at 25 °C in 14 h (eq 4). This supported ruthenium catalyst can be recycled and reused for consecutive alkene epoxidation reactions without significant loss of catalytic activity.



Oxidation of Alcohols. $[Ru(Me_3tacn)(CF_3CO_2)_2OH_2]CF_3CO_2$ can effect oxidation of alcohols to their corresponding aldehydes and/or ketones using *tert*-butylhydroperoxide in dichloromethane, and more than 6000 turnovers can be achieved.[3] Under the ruthenium-catalyzed reaction conditions, benzyl alcohol (200 mmol) can be oxidized to benzaldehyde in 97% isolated yield with 700 catalyst turnovers (eq 5). Likewise, the highly reactive and robust silica gel supported-$[Ru(Me_3tacn)(CF_3CO_2)_3]$ catalyst can also effect heterogeneous oxidation of alcohols in high yields with up to 9000 turnovers.[2] Geraniol can be selectively oxidized to give the corresponding geranial with 87% yield at 45 °C in 16 h (eq 6). Both the allylic and the trisubstituted C=C double bonds of geraniol remain intact under the oxidation conditions. The Ru-silica gel catalyst has been subjected to eight successive oxidations of 1-phenyl-1-propanol with no loss of ruthenium content.



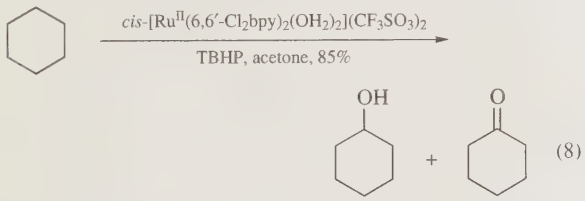
cis-$[Ru^{II}(6,6'\text{-}Cl_2bpy)_2(OH_2)_2](CF_3SO_3)_2$ is a robust catalyst for oxidation of alcohols including aliphatic, cyclic, and allylic alcohols using *tert*-butylhydroperoxide. With 0.1 mol % of the ruthenium catalyst, 2-cyclohexen-1-ol can be oxidized to 2-cyclohexen-1-one exclusively in 97% yield in acetone at room temperature within 48 h (eq 7).[5]



In addition, *cis*-$[Ru^{II}(6,6'\text{-}Cl_2bpy)_2(OH_2)_2](CF_3SO_3)_2$ can be oxidized to *cis*-$[Ru^{VI}(6,6'\text{-}Cl_2bpy)_2O_2](ClO_4)_2$ in 60% yield

using aqueous solution of $(NH_4)_2[Ce^{IV}(NO_3)_6]$ containing $NaClO_4$.[5,9] This isolated ruthenium-dioxo complex is a powerful stoichiometric oxidant for alcohol oxidation.

Oxidation of Alkanes. *cis*-$[Ru^{II}(6,6'\text{-}Cl_2bpy)_2(OH_2)_2](CF_3SO_3)_2$ can catalyze oxidation of alkanes to alcohols and ketones with *tert*-butylhydroperoxide as oxidant. High catalyst turnover number (up to 4000) can be achieved.[6] With 0.07 mol % of *cis*-$[Ru^{II}(6,6'\text{-}Cl_2bpy)_2(OH_2)_2](CF_3SO_3)_2$, cyclohexane can be oxidized to cyclohexanol and cyclohexanone with a ratio of 1:1.6 in 85% combined yield in 24 h using acetone as solvent (eq 8).[5] However, the oxidation reactions are inhibited by addition of π-acid ligands such as CH_3CN.



(8)

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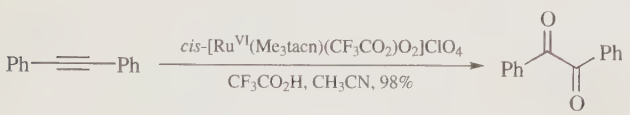
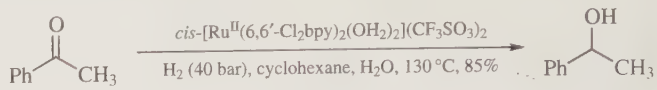
cis-$[Ru^{II}(6,6'\text{-}Cl_2bpy)_2(OH_2)_2](CF_3SO_3)_2$ can be immobilized into MCM-41 (a mesoporous molecular sieve) with loading up to 8.4 weight % for catalytic C–H oxidation of alkanes.[10] This Ru/MCM-41 catalyst exhibits high product turnover number (up to 24 960) in oxidation of cyclohexane by *tert*-butylhydroperoxide and shows good catalytic activity with 0.02 to 2.4 weight % of loading of the Ru complex. As a robust and recyclable catalyst, a 0.1 weight % Ru/MCM-41 catalyst exhibits similar catalytic activity in three consecutive cyclohexane oxidations with turnover number being 3500, 3495, and 3492 in the first, second, and third experiment, respectively.

Oxidation of Alkynes. $[Ru(Me_3tacn)(CF_3CO_2)_2OH_2]CF_3CO_2$ can be oxidized to *cis*-$[Ru^{VI}(Me_3tacn)(CF_3CO_2)O_2]ClO_4$ upon treatment with a saturated solution of $(NH_4)_2[Ce^{IV}(NO_3)_6]$ followed by $NaClO_4$-induced precipitation in 55% isolated yield.[11] This *cis*-dioxo ruthenium complex reacts with alkynes by transferring two oxygen atoms to a C≡C bond via a [3 + 2] cycloaddition pathway. In a stoichiometric oxidation by this *cis*-dioxo ruthenium complex, diphenylacetylene is converted into benzil in 98% yield in a degassed CF_3CO_2H/CH_3CN solution at room temperature within 15 min (eq 9). No side-products including benzoic acid and diphenylacetic acid are detected.

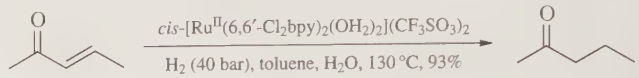


(9)

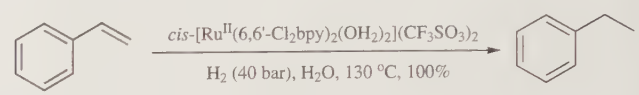
Hydrogenation. *cis*-$[Ru^{II}(6,6'\text{-}Cl_2bpy)_2(OH_2)_2](CF_3SO_3)_2$ can be employed as an efficient catalyst for the hydrogenation of carbonyl compounds and alkenes in a biphasic reaction system.[7,8] The catalytic hydrogenation experiment can be conducted by heating the water soluble Ru-Cl_2bpy catalyst (0.1 mol %) and substrate in an organic/aqueous solvent system at 130 °C under hydrogen atmosphere (40 bar) in an autoclave. Acetophenone can be hydrogenated into 1-phenylethanol in 85% within 4 h (eq 10). For mesityl oxide, hydrogenation occurs preferentially at its C=C double bond to afford 4-methylpentan-2-one in 93% yield in 4 h with the carbonyl group remaining intact (eq 11). Furthermore, hydrogenation of styrene proceeds smoothly to provide ethylbenzene in 100% yield within 1 h (eq 12).



(10)



(11)



(12)

cis-$[Ru^{II}(6,6'\text{-}Cl_2bpy)_2(OH_2)_2](CF_3SO_3)_2$ is also effective for catalytic hydrogenation of carbon dioxide to formic acid with triethylamine in ethanol.[12] The hydrogenation can be performed with an equimolar ratio of H_2 and CO_2 at 100 °C or 150 °C in an autoclave, and turnover numbers up to 5000 can be achieved. However, the reaction is sluggish without addition of triethylamine.

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Ruthenium(VIII) Oxide[1]

RuO_4

[20427-56-9] O_4Ru (MW 165.07)

(strong oxidant for many functional groups; can cleave double bonds, aromatic rings, and diols[1])

Alternate Name: ruthenium tetroxide.

Physical Data: yellow form: mp 25.5 °C; bp 40 °C; *d* 3.29 g cm^{-3}. Brownish orange form: mp 27 °C; bp 108 °C (dec).

Solubility: slightly sol water; highly sol $CHCl_3$, CCl_4.

Form Supplied in: although the reagent is commercially available either in solid form or stabilized aqueous solution, it is usually prepared in situ from black solid RuO_2 (mw 133.07) *[120236-10-1;*·xH_2O, *32740-79-7]* or dark brown (or black) $RuCl_3$ (mw 207.42) *[10049-08-8;*·xH_2O, *14898-67-0]*, in stoichiometric or catalytic amounts, and an oxidation agent; both of the above Ru salts are widely available.

Handling, Storage, and Precautions: handle in a fume hood only. Inhalation should be avoided; vapors irritating to eyes and respiratory tracts, since it readily oxidizes tissue, leaving a deposit of ruthenium dioxide.[2] It attacks rubber and reacts explosively with paper filter and alcohol, and violently with ether, benzene, and pyridine.[3] However, *the use of the catalytic system greatly minimizes the risk in its manipulation*, and its usage is strongly recommended.

Original Commentary

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University of La Laguna, Tenerife, Spain

Introduction. When RuO_4 was introduced into organic synthesis it was generally used in stoichiometric amounts, usually prepared by oxidation of ***Ruthenium(III) Chloride*** or RuO_2 with aqueous periodate or hypochlorite and then extracted into carbon tetrachloride. This yellow solution could be roughly analyzed by treating an aliquot with ethanol to reduce the tetroxide to the black dioxide, which was collected and weighed.[4]

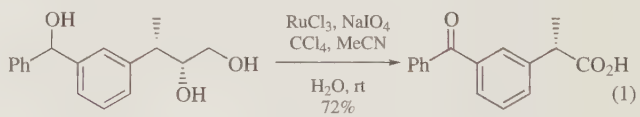
However, since ruthenium compounds are expensive and occasionally it is difficult to separate the products from precipitated ruthenium dioxide, it is more convenient to use a system formed by a catalytic amount of the ruthenium compound (RuO_2 or $RuCl_3$) along with an appropriate co-oxidant, usually in a biphasic solvent system. These reagents actually act as catalysts, because they are reoxidized after the reaction with organic compounds by one of the oxidants previously mentioned. Ruthenium tetroxide is usually prepared in situ from ruthenium dioxide or ruthenium trichloride by oxidation with ***Sodium Hypochlorite***,[5] ***Sodium Bromate***,[6] ***Peracetic Acid***,[6] periodic acid,[7] ***Sodium Periodate***,[8] ***Oxygen***,[9] cerium sulfate,[10] ***Potassium Permanganate***,[10] electrochemically generated ***Chlorine***,[11] or ***Potassium Monoperoxysulfate*** (Oxone®).[12]

It appears that contact between RuO_4 and the material to be oxidized takes place in the organic phase, where they are both most soluble. The ruthenium dioxide produced when oxidation occurs is insoluble in all solvents and migrates to the interface where it contacts the co-oxidant (in the aqueous layer) and is reoxidized. Thus best results are obtained when the mixture is shaken or stirred vigorously throughout the course of the reaction to achieve good contact between all components.

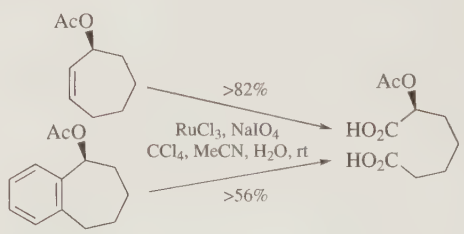
It has been pointed out that $RuCl_3 \cdot H_2O$ is not a good Ru source under acidic conditions (pH < 5), because it initially gives an orange Ru^{IV} chloro aquo complex, which is slowly oxidized to RuO_4. In such cases, RuO_2 is the alternative recommended.[10] In the reactions carried out at pH > 9, any RuO_4 produced in the aqueous phase is unstable, being reduced to green perruthenate (RuO_4^-), and subsequently to orange ruthenate (RuO_4^{2-}). Both species are insoluble in CCl_4. Although in most of the cited mixtures RuO_4 is considered the oxidant, it cannot be ruled out that the real oxidant is another lower valent ruthenium species. The only way to ensure that RuO_4 is really the oxidizing agent is if it is isolated after its preparation, as cited in the early literature.[2,4] UV analysis of the RuO_4 solutions can provide some information about this, because RuO_4 gives absorption bands at λ_{max} 310 nm (strong) and 380 nm. These bands are replaced by others at λ_{max} 310 nm (strong), 385 nm (strong), and 460 nm when base is added to the solution, corresponding to the formation of the perruthenate ion (RuO_4^-) and subsequently to absorption bands at λ_{max} 385 nm and 460 nm (strong), produced by RuO_4^{2-}.[1,13]

RuO_4 is a strong oxidant. However, conditions for ruthenium-catalyzed reactions are very mild; usually a few hours (or less) at room temperature (or below) is sufficient. A thorough study of oxidations with RuO_4 generated in situ from $RuO_2 \cdot xH_2O$ and $RuCl_3 \cdot xH_2O$ shows the importance of the presence of water in the reaction.[10,14] Thus many ruthenium-catalyzed reactions have been performed in the CCl_4–H_2O solvent system. The addition of ***Acetonitrile*** to the system greatly improves yields and reaction times,[8] especially when carboxylic groups are present or generated in the reaction. MeCN probably disrupts the insoluble carboxylate complexes and returns the ruthenium to the catalytic cycle, acting as a good ligand for the lower valent (III/II) ruthenium present.[15]

An important feature of RuO_4-catalyzed oxidations is that the stereochemistry of the stereocenters close to the reaction site (eqs 1 and 2)[16,17] remains unaffected.



(1)

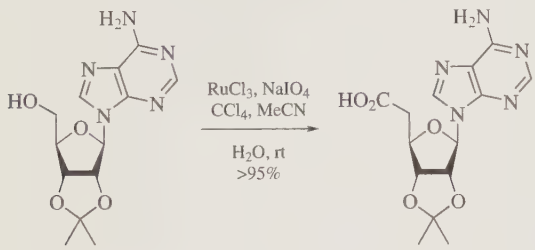


(2)

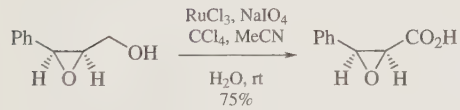
In a typical procedure,[8] to a stirred mixture of 2 mL of CCl_4–2 mL of MeCN–3 mL of H_2O/mmol of organic compound are added 4.1 mmol of ***Sodium Periodate***/mmol of organic compound and 2.2 mmol% of $RuCl_3 \cdot xH_2O$ ($RuO_2 \cdot xH_2O$ is equally effective) sequentially. The mixture is stirred vigorously at 0–25 °C until the end of the reaction (TLC or GC monitoring). Then 20 mL of diethyl ether are added and the vigorous stirring is continued for 10 min to precipitate black RuO_2. The reaction mixture is then dried ($MgSO_4$) and filtered through qualitative Whatman filter paper 2.

The solid residue is then washed with diethyl ether (3 × 5 mL). The combined organic phases are concentrated to yield the crude oxidation product.

Functional Group Oxidations without Bond Cleavage. One of the most common synthetic uses of ruthenium-catalyzed oxidations is the reaction with alcohols. A mixture of RuO_2 or $RuCl_3$ with strong co-oxidants converts primary alcohols to carboxylic acids[18] (eq 3),[19] including epoxy alcohols (eq 4),[8] but under milder (***Iodosylbenzene***,[20] molecular oxygen,[21] ***Calcium Hypochlorite*** (eq 5),[22] or amine *N*-oxides[23]) or controlled conditions,[19] aldehydes are obtained (eq 6).[24]



(3)



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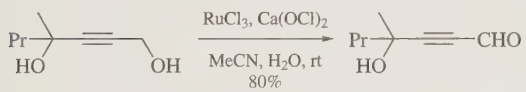

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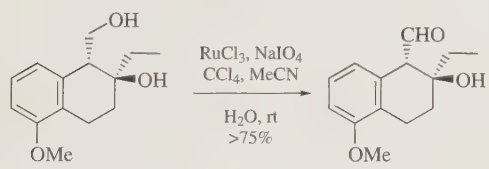
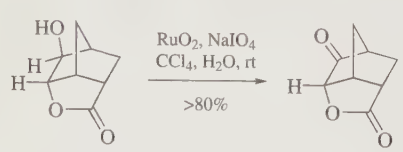


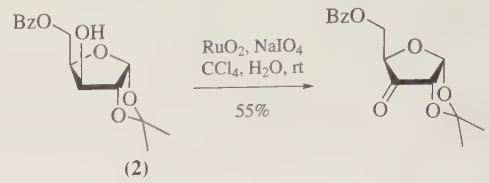
(6)

Secondary alcohols are transformed into ketones.[1,3,25] The yields obtained from the oxidation of secondary alcohols are usually excellent. Since the reactions are carried out under very mild conditions, there is little danger of the product undergoing secondary reactions. Ketones can also be prepared using a great variety of other oxidants[26] (see, for example ***Chromium(VI) Oxide*** and ***Dimethyl Sulfoxide*** based oxidant reagents), which in some cases are more readily available and less expensive. However, RuO_4 is recommended for reactions which require a vigorous oxidant under mild conditions. Thus it can be used to oxidize alcohols which are resistant to other oxidants: (**1**) is successfully oxidized with RuO_4, while attempts made with 15 other standard oxidizing procedures failed (eq 7);[27] oxidation of (**2**) is successful in good yield using RuO_4 (eq 8), being fruitless with CrO_3 in either ***Pyridine***, ***Acetone***, ***Acetic Acid***, or Al(O-*i*-Pr)$_3$, $KMnO_4$, ***Lead(IV) Acetate*** in acetone, with CrO_3 in *i*-BuOH giving the ketone in very low yield.[28] Numerous examples of the advantages of RuO_4 over ***Dipyridine Chromium(VI) Oxide*** for the oxidation of carbohydrates have been cited.[29]



(7)

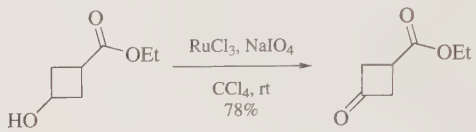
(**1**)



(8)

(**2**)

RuO_4 is also reported to provide higher yields when other oxidizing procedures give poor yields. As examples can be cited the conversions of cyclobutanols to cyclobutanones (eq 9)[30] and the transformation of lactones into the corresponding ketocarboxylates under basic conditions (60–97%) (eq 10). Significantly higher yields are obtained compared with $KMnO_4$ under alkaline conditions.[31]



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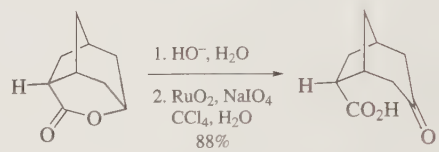
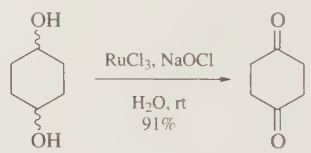


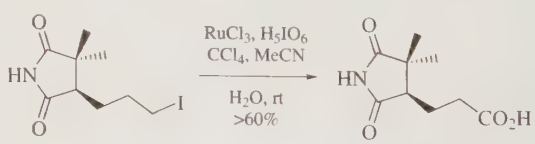
(10)

Vicinal diols can be oxidized to diketones but only in low yields, the principal reaction being the oxidative cleavage of the C–C bond.[1] If the hydroxyl groups are not adjacent, then diketones can be prepared (eq 11).[32]



(11)

The catalytic procedure is also applicable to the oxidation of aldehydes to carboxylic acids,[1,2,23,33] primary alkyl iodides to carboxylic acids (eq 12),[34] aromatic hydrocarbons to quinones,[25] and sulfides to sulfones,[25] including an improved and simple method to obtain water-soluble sulfones using periodic acid as the co-oxidant in high concentration conditions (eq 13).[35]



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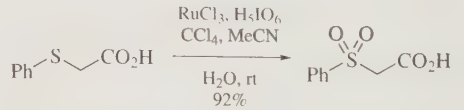
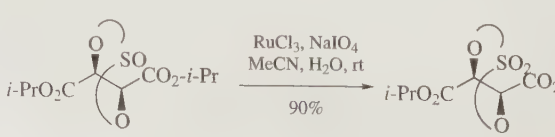


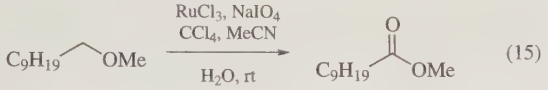
(13)

Oxidation of 1,2-cyclic sulfites to 1,2-cyclic sulfates with RuO_4 has been reported as a part of a method to activate diols for further nucleophilic attack (eq 14).[36]

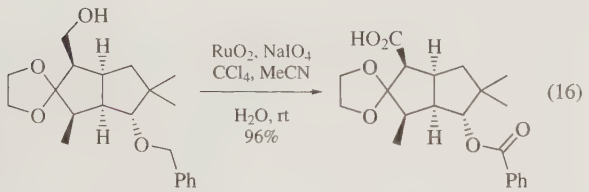


(14)

Along with these types of oxidations, RuO_4 is used to carry out transformations that involve oxidation of methylene groups α to heteroatoms such as oxygen and nitrogen. Thus it is possible to convert acyclic ethers into esters, such as methyl ethers into methyl esters (eq 15),[8] ethyl ethers into acetates,[37] and benzyl ethers into benzoates (eq 16).[38] It is possible to avoid the benzyl–benzoyl group transformation by carrying out the reaction at 0 °C and/or in the presence of base (eq 17).[39]



(15)



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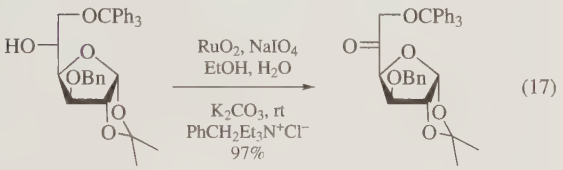
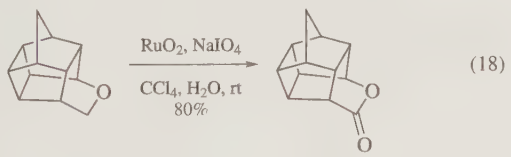
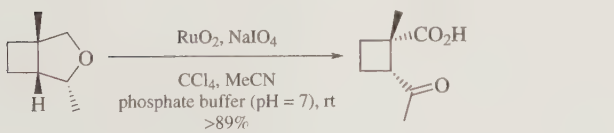


(17)

Cyclic ethers are also oxidized, yielding lactones (eq 18).[40] Although secondary positions are usually more reactive towards oxidation than tertiary positions, the regioselectivity of RuO_4 can be strongly dependent on steric factors (eq 19).[41] In those cases in which lactones are unstable under aqueous conditions (notably δ- and ε-lactones), the corresponding diacids are the final products, presumably via the intermediacy of lactols (eq 20).[42]



(18)



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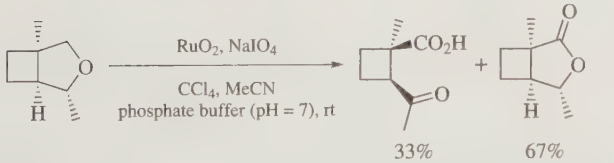
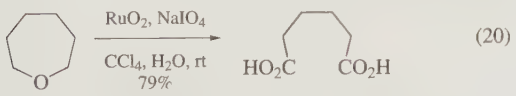
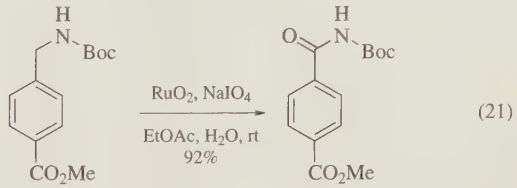




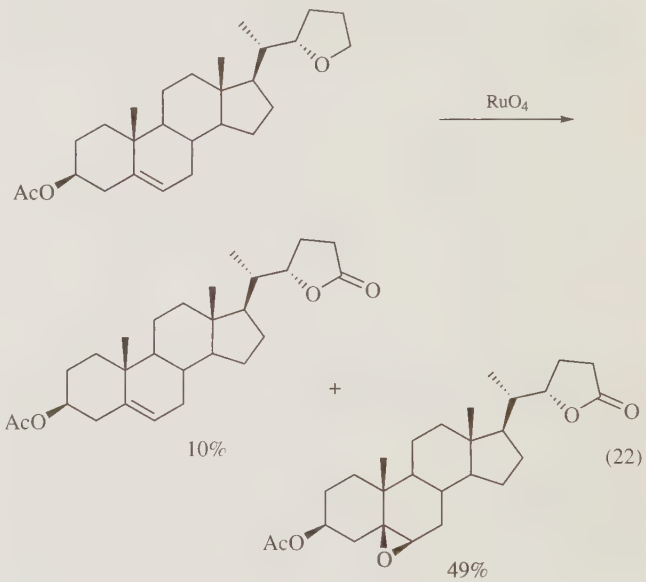
(20)

RuO_4 also oxidizes alkyl amines to mixtures of nitriles and amides,[43] cyclic amines to lactams,[44] and amides (cyclic or acyclic) to imides (eq 21),[45] including an improved procedure that uses ethyl acetate as the organic solvent in the biphasic solvent system, enhancing both the solubility of the substrates and the rate of reaction.[46]



(21)

RuO_4 usually reacts with unsaturated systems, giving cleavage of the C–C bonds. Although epoxide formation has been detected in small amounts (ca. 1%),[47] it can be the principal reaction when the double bond is located in a very hindered position (eq 22).[48] With 1,5-dienes, unexpected oxidation results are obtained. Thus oxidation of geranyl acetate leads to a tetrahydrofuran mixture, instead of the cleavage products (eq 23).[8] Nonterminal alkynes are also oxidized without cleavage, yielding vicinal diketones (eq 24).[49]



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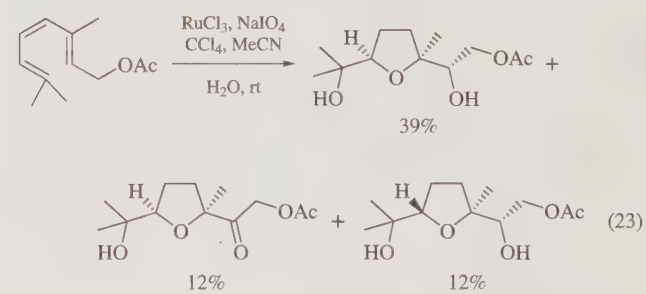

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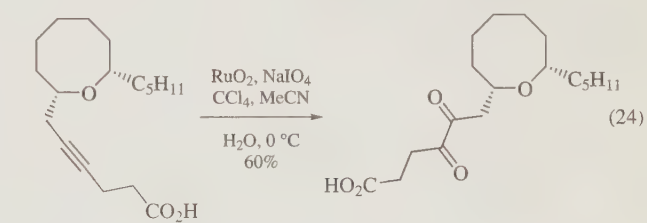
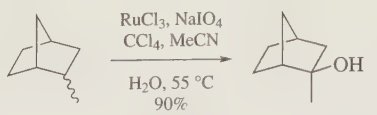


(24)

RuO_4 is also capable of oxidizing C–H bonds in bridged bicyclic and tricyclic alkanes to alcohols by insertion of oxygen (eq 25).[50] Although epoxides survive RuO_4 oxidations, when such functionality is located in this kind of bridged system a tandem ruthenium-catalyzed rearrangement/oxidation occurs (eq 26).[51]



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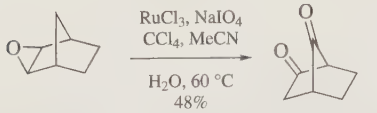
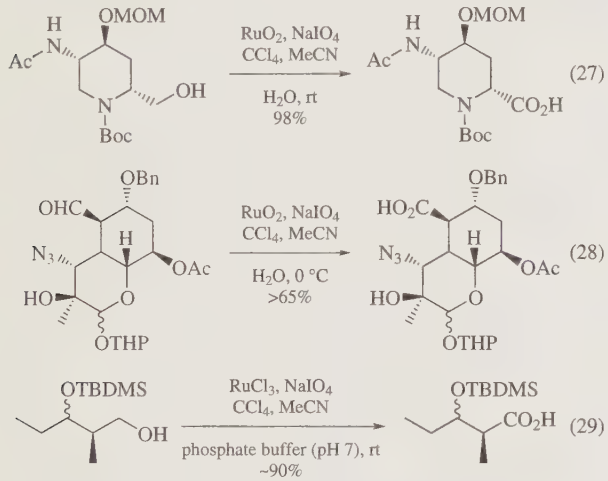


(26)

Most of the common protecting groups used in organic synthesis are stable under RuO_4 oxidation conditions (eq 27).[52] Generally it is only necessary to carry out the reaction at 0 °C or perform it under buffered conditions when acid-sensitive groups are present, such as tetrahydropyranyl (eq 28)[33] or silyl ethers (eq 29).[53]

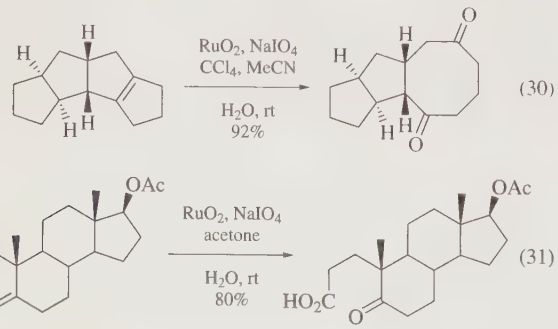


(27)

(28)

(29)

Functional Group Oxidations with Bond Cleavage. Carbon–carbon double bonds are readily cleaved by RuO_4 to give ketones and aldehydes or carboxylic acids. In this respect the greater vigor of RuO_4 as an oxidant stands in marked contrast to that of ***Osmium Tetroxide*** (eq 30),[54] which also reacts with C–C double bonds but does not cleave them. While carboxylic acids are usually the final products, sometimes under neutral conditions aldehydes can be obtained from double bonds that are not fully substituted.[55] The cleavage of such double bonds proceeds by the route: alkene → dialdehyde → diacid.[5a] RuO_4 is also indicated to carry out oxidations of substrates with double bonds resistant to other oxidizing agents, such as OsO_4, ***Potassium Permanganate***, and ***Ozone*** (eq 31).[56] Degradative oxidations of unsaturated C–C bonds with loss of carbon atoms occur with terminal alkynes (eq 32),[5b] cyclic allylic alcohols (eq 33),[57] and α,β-unsaturated ketones.[57]



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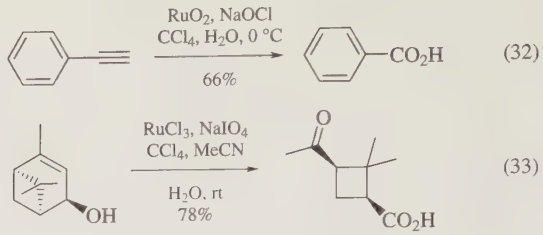
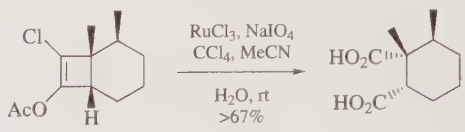


(32)

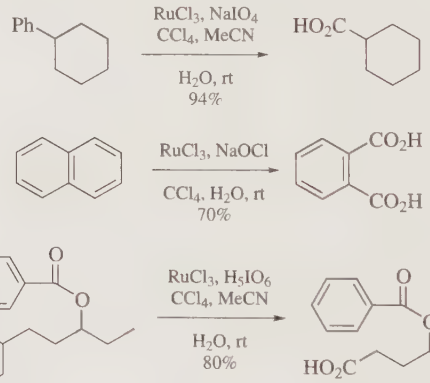
(33)

RuO_4 also cleaves α-chloroenol derivatives obtained from α,α′-dichlorocyclobutanones to give dicarboxylic acids through successive treatment with ***n-Butyllithium***, ***Acetic Anhydride***, and ***Sodium Periodate***–RuO_2 (eq 34).[58,59]



(34)

RuO_4-catalyzed oxidation of arenes can proceed in two ways: (a) the phenyl ring can be cleaved from R–Ph to R–CO_2H (eq 35);[8] (b) the phenyl ring can be degraded to form a dicarboxylic acid in polycyclic aromatic hydrocarbons (eq 36).[60] An electron-donating substituent favors cleavage of the substituted ring, while an electron-withdrawing substituent favors cleavage of the unsubstituted ring. Thus selective oxidation of the more activated ring can be performed with high selectivity. When acid-sensitive groups are not present, an improved procedure that utilizes periodic acid instead of sodium periodate can be used, preventing the problems associated with the precipitated sodium iodate, allowing the reaction to go to completion, and permitting oxidation reactions to be run on larger scales (eq 37).[61]

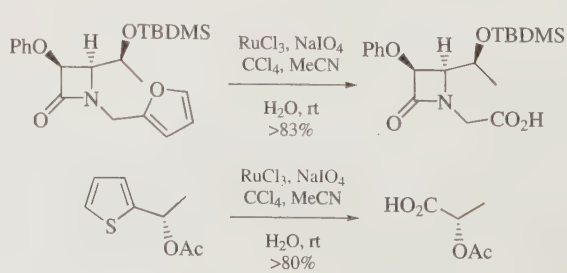


(35)

(36)

(37)

Furan[62] (eq 38),[63] thiophene (eq 39),[64] and benzopyridine rings (eq 40)[65] are also cleaved by catalytic RuO_4 to carboxylic acids. When pyridine derivatives are not oxidized, they can be transformed into their *N*-oxides prior to the oxidation to decrease the ability of the nitrogen to complex with ruthenium, albeit with low yields (eq 41).[64]



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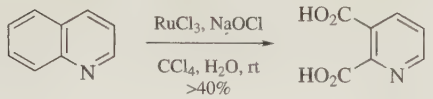

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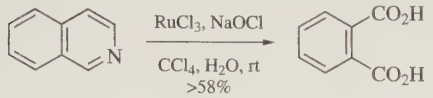
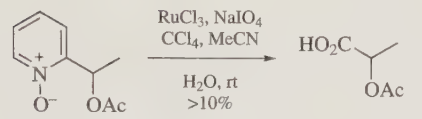
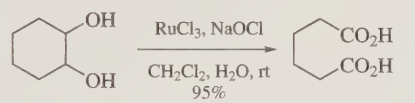


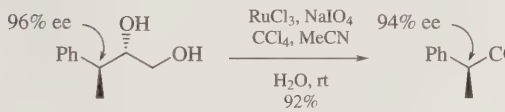


(41)

Vicinal diols are cleaved to give carboxylic acids (eq 42) following the route: glycol → α-ketol → diacid. A diketone is apparently not an intermediate in this oxidation.[5a] The mildness of the reaction conditions is underscored by the lack of epimerization shown in (eq 43).[8] This feature has been proved to be general when RuO_2–$NaIO_4$ is used to oxidize chiral diol benzoates, this being a useful method to synthesize chiral α-benzoylcarboxylic acids (eq 44).[66]



(42)



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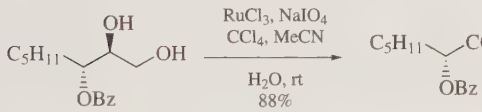
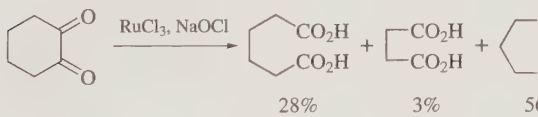


(44)

Other vicinal dioxygenated functionalities present (eq 45)[5a] or generated in situ undergo oxidation with C–C bond cleavage by RuO_4 to give carboxylic acids, with (eq 46)[67] or without (eq 47)[68] loss of carbon atoms.



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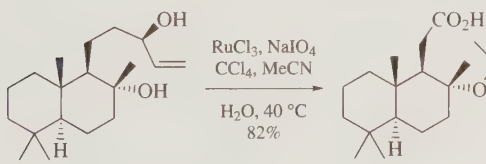

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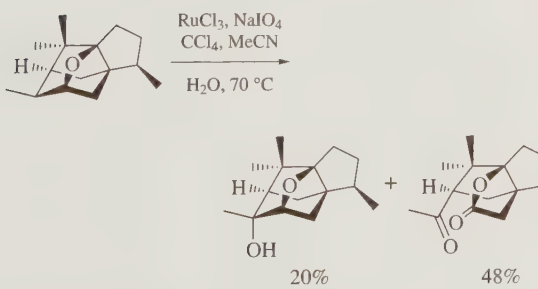
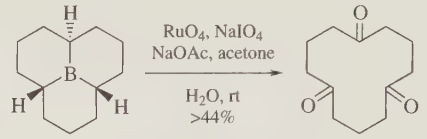


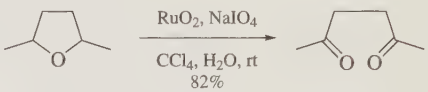
(47)

RuO_4 is also used to cleave oxidatively carbon–boron bonds in cyclic alkylboranes, presenting advantages over the usage of Cr^{VI} for the same purpose or even the oxidation of the corresponding alcohols (eq 48).[69]



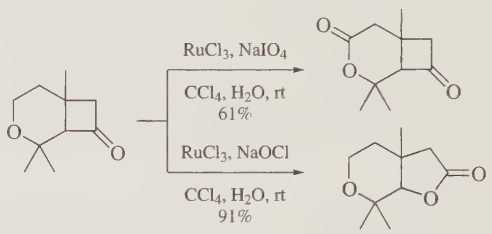
(48)

Another formal carbon–heteroatom bond cleavage occurs in the oxidation of cyclic ethers that give cyclic products unstable to the oxidation conditions (eq 49).[42]



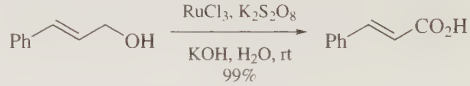
(49)

As pointed out, ketones are stable under RuO_4 oxidation conditions, although cyclic ketones can undergo Baeyer–Villiger reaction when ***Sodium Hypochlorite*** is used as co-oxidant (eq 50).[70]



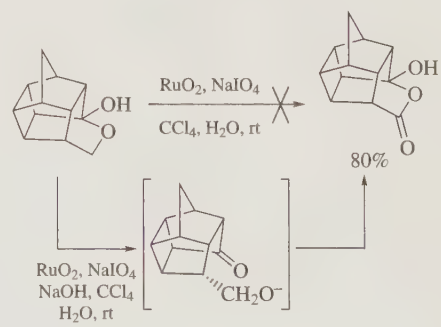
(50)

Other Ruthenium-Based Oxidation Reagents. Less reactive oxidants are obtained by lowering the oxidation state of ruthenium. One example is the ruthenate ion (RuO_4^{2-}) which, as mentioned above, is formed when RuO_4 is treated with alkaline solutions. The most important synthetic applications of such ions is in the oxidation of alcohols in basic media to give carboxylic acids or ketones.[71] In general, RuO_4^{2-} does not appear to oxidize isolated C–C double bonds at room temperature (eq 51).[72]



(51)

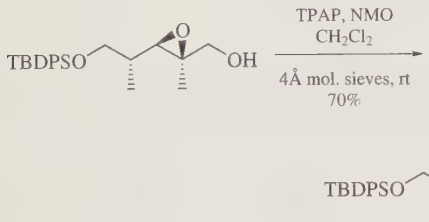
When there is no reductive pathway for the elimination of ruthenate esters, RuO_4^{2-} has been used as an alternative to RuO_4 (eq 52).[40]



(52)

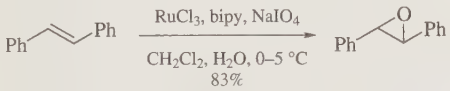
The perruthenate ion RuO_4^- is also useful for the oxidation of primary alcohols, nitroalkanes, primary halides, and aldehydes to acids.[73] When tetraalkylammonium salts are added to the RuO_4^- solutions, stable tetraalkylammonium perruthenates

are obtained. Tetra-*n*-butylammonium perruthenate (TBAP) and tetra-*n*-propylammonium perruthenate (TPAP) are used to oxidize successfully alcohols to carbonyl compounds (eq 53),[23] and sulfides to sulfones[74] under very mild conditions, employing as co-oxidant ***N-Methylmorpholine N-Oxide*** (NMO) (see ***Tetra-n-propylammonium Perruthenate***).



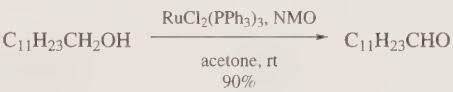
(53)

The behavior of inorganic transition metal oxidizing agents can be modified by the introduction of ligands. Electron-rich ligands, which increase the basicity of the metal and moderate its oxidizing power, have been used to improve the selectivity of these oxidation reactions. Thus porphyryl–[75] and bipyridyl–Ru complexes epoxidize alkenes, instead of cleaving the double bond (eq 54).[47]

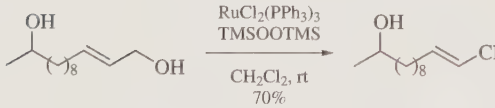


(54)

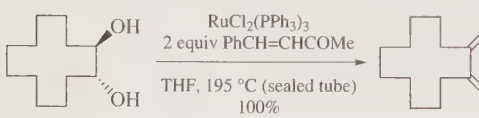
Several other Ru complexes, along with co-oxidants or hydrogen acceptors, are used as catalysts in oxidation reactions, $RuCl_2(PPh_3)_3$ and $RuH_2(PPh_3)_4$ being the most commonly utilized. The conversion of alkanes and alcohols to aldehydes or ketones is achieved with $RuCl_2(PPh_3)_3$[76] and molecular oxygen,[77] ***Bis(trimethylsilyl) Peroxide***,[78] ***Iodosylbenzene***,[20] ***N-Methylmorpholine N-Oxide*** (eq 55),[79] ***t-Butyl Hydroperoxide***,[80] and hydrogen acceptors.[81] Selective oxidations of primary vs. secondary alcohols are possible (eq 56),[78] and it is also possible to stop the oxidation of primary alcohols at the aldehyde stage by simply controlling the co-oxidant equivalents and reaction times.[20] α-Diketones can be obtained from vicinal diols (eq 57)[82] and non-terminal alkynes (eq 58).[83]



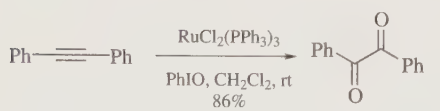
(55)



(56)

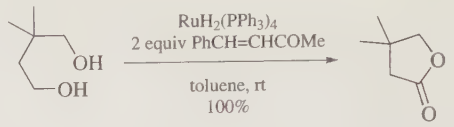


(57)



(58)

The combination of $RuH_2(PPh_3)_4$ plus a hydrogen acceptor, like benzalacetone or ***Acetone***, converts unsymmetrically substituted 1,4- and 1,5-diols into β-substituted γ-lactones and γ-substituted δ-lactones, respectively (eqs 59 and 60),[84] also allowing the oxidative condensation of alcohols, or aldehydes and alcohols, to give esters (eq 61).[85]



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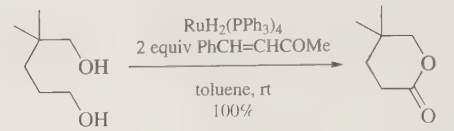
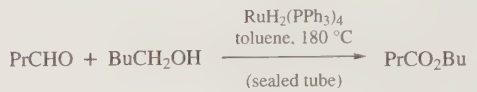
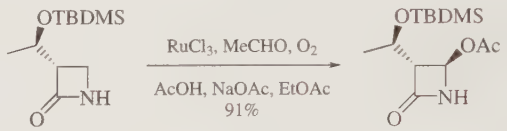


(60)



(61)

Oxoruthenium species are also useful in organic oxidations. Thus oxoruthenium(V) complexes obtained from lower valent ruthenium species effect α-oxygenation of tertiary amines[86] and β-lactams (eq 62).[87] $[PPh_4][RuO_2(OAc)Cl_2]\cdot 2AcOH$ generated from RuO_4 is used to oxidize alcohols and benzyl halides to carbonyl compounds.[88]



(62)

First Update

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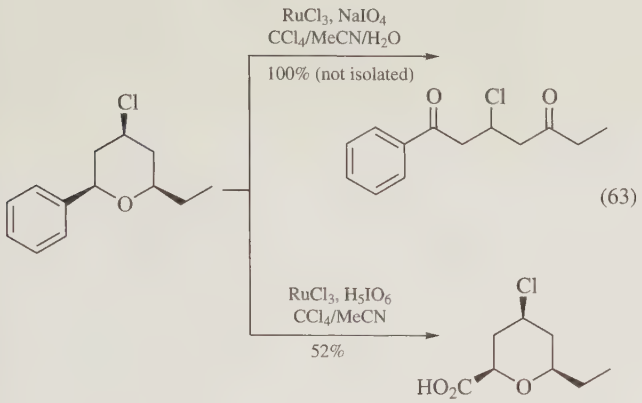
Eli Lilly Research Laboratories, Indianapolis, IN, USA

Introduction.[89] RuO_4 has found widespread use within organic synthesis as a powerful and versatile oxidant for a wide variety of synthetic transformations. Several recent examples of previously known transformations have been described such as oxidation of quinolines to pyridine-2,3-dicarboxylic acids,[90] furans to carboxylic acids,[91] alkynes to α-diones,[92] and alkynes to carboxylic acids.[93] The generation of RuO_4 in a mixture of dimethyl carbonate and water, a more environmentally friendly solvent system than the traditional CCl_4/acetonitrile/water mixture, has been shown to facilitate many of these transformations as well as conversion of primary alcohols to carboxylic acids.[94]

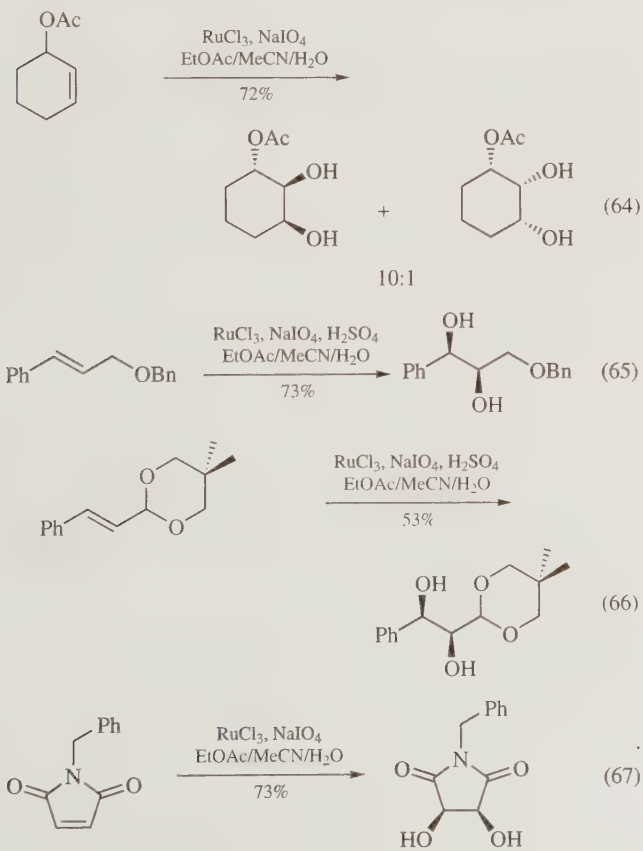
More recent efforts to understand and control the reaction parameters that effect chemoselectivity have increased the usefulness of this reagent. Solvent effects, pH, temperature, and reaction time have all been found as critical parameters that determine the course the reaction takes when employing RuO_4 as the reagent. The choice of stoichiometric oxidant and presence of water or lack thereof can change the pathway of the reaction (eq 63).[95] Some evidence suggests RuO_4-mediated oxidation of sulfides occurs via a concerted mechanism.[96]

Dihydroxlyation of Olefins And Related Transformations. Generally, RuO_4 reacts with olefins effecting C–C bond cleavage to provide ketones or carboxylic acids. In contrast osmium



(63)

tetraoxide (OsO_4) converts olefins to 1,2-diols without C–C bond fissure, a difference that has been analyzed by quantum chemical calculations.[97] However, it has been found that catalytic RuO_4 can act much in the same way as more expensive and toxic OsO_4 in converting olefins to 1,2-diols with high stereoselectivity (eq 64).[98] Two factors that limit the formation of more highly oxidized products are the use of short reaction times (30 s to a few minutes) while maintaining the reaction temperature at 0 °C. The addition of catalytic protic acid, most favorably 10–20 mol % sulfuric acid, allows for reduction of the ruthenium catalyst loading from 7% to 0.5%.[99] The reaction is chemoselective with respect to most moieties susceptible to oxidation by RuO_4. Thus, both phenyl rings and α-methylenes of ethers are stable to the conditions (eq 65) as are some acid sensitive groups such as acetals (eq 66). Increasing the amount of acid resulted in more fission products as did higher temperature (rt vs 0 °C). The usefulness of this reaction has been demonstrated on multi-kilogram scale (eq 67),[100] and it has been used to prepare simple fullerene diols.[101]



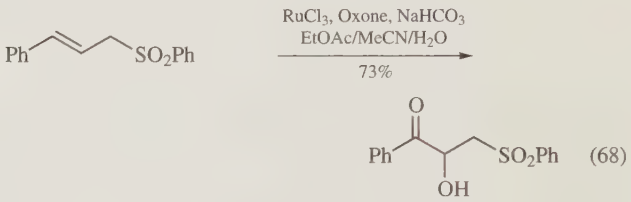
(64)

(65)

(66)

(67)

Ketohydroxylation of olefins can be accomplished with the combination of ruthenium(III) chloride with peracetic acid,[102] but also can be facilitated with RuO_4 by slight adjustment of the reaction conditions that effect dihydroxylation (eq 68).[103] The use of potassium monoperoxysulfate (Oxone®) as the stoichiometric oxidant in place of sodium periodate along with addition of sodium bicarbonate while minimizing water are all keys to success of the reaction. The reaction is highly regioselective as well. Oxidation of a chloroalkene with RuO_4, an alternative to the more generally used OsO_4 or potassium permanganate, also provided an α-hydroxy ketone (eq 69).[104]



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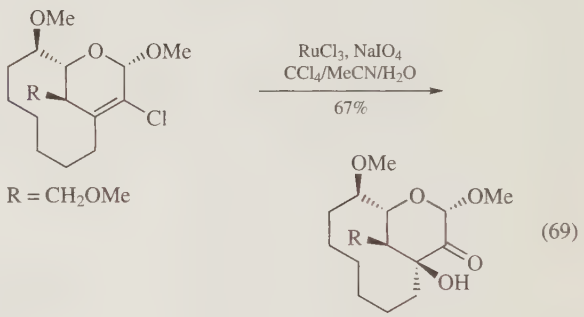
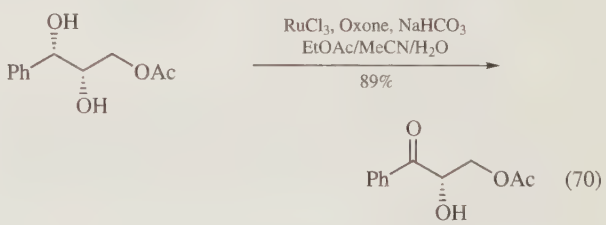


(69)

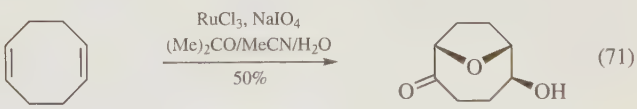
In an asymmetric variant, enantiomerically enriched α-hydroxy ketones have been prepared from nonracemic diols, generated via Sharpless dihydroxylation conditions, that are then treated with RuO_4 under the aforementioned protocol to provide nonracemic α-hydroxy ketones with no loss of enantiomeric excess (eq 70).[105] Again, regioselectivity of the reaction is well controlled.



(70)

(98% ee)

Intramolecular variants of dihydroxylations with dienes that afford oxygen heterocycles have also been demonstrated both with cyclic dienes (eq 71)[106] and acyclic dienes (eqs 72 and 73).[107,108] Choice of solvent is generally crucial. Otherwise lower yields and/or higher amounts of other reaction by-products are obtained.



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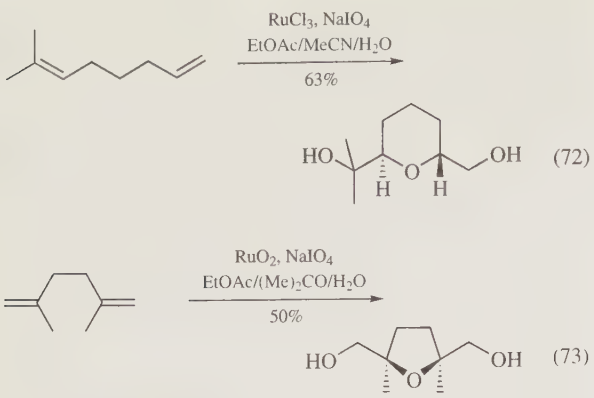
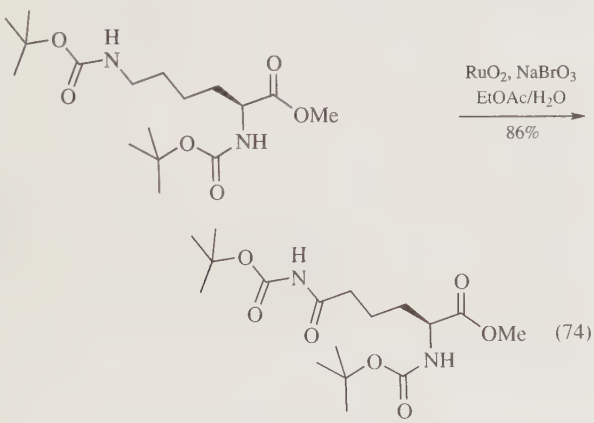


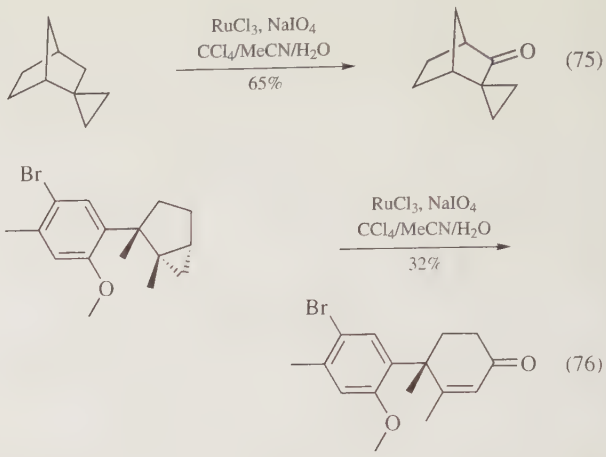
Oxidations Involving C–H Functionalization α to Nitrogen or Oxygen. Oxidation with RuO_4 of C–H bonds α to oxygen[8,37–41] or nitrogen atoms[43–46] is a fairly general transformation. The nitrogen is usually part of an amide or carbamate moiety thereby providing the corresponding imide while the oxygen is an ether affording either an acetal/ketal or an ester functionality after oxidation. Thus, the usefulness of this reaction has been exploited in making numerous unnatural amino acid derivatives such as shown in (eq 74.)[109] The steric bulk of the Boc-protecting group inhibits further oxidation at the α-position of an ester and conversion to an α-keto ester.



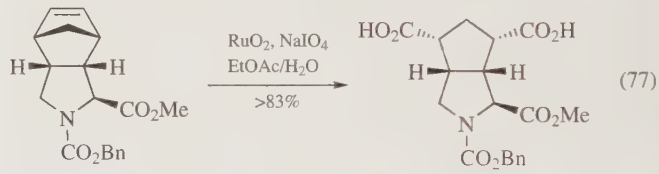
The pH of the reaction mixture can have a profound effect upon oxidation of amino acids with side chains containing either an amine or an aromatic group. Thus, tyrosine is converted to aspartic acid in 50% yield at pH 3 while it is converted to malonic acid in 42% yield at pH 9.[110]

The mechanism[111] and the effects of solvent and substituents [112] of ether oxidations have been examined in some detail leading to a conclusion that mechanisms containing carbocation intermediates are unsupported.

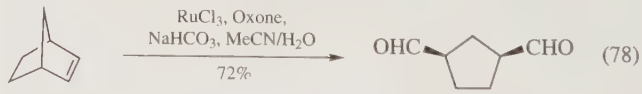
Oxidations Involving C–H Functionalization of Unactivated Alkanes. The mechanism[111] and the effects of solvent and substituents[112,113] of oxidation of unactivated C–H bonds has also been examined. Although most reactions of hydrocarbons generate an alcohol product; the oxidation of C–H bonds α to a cyclopropyl ring usually affords the corresponding cyclopropyl ketone (eq 75).[114] In some cases concomitant rearrangement can occur during oxidation (eq 76).[115]



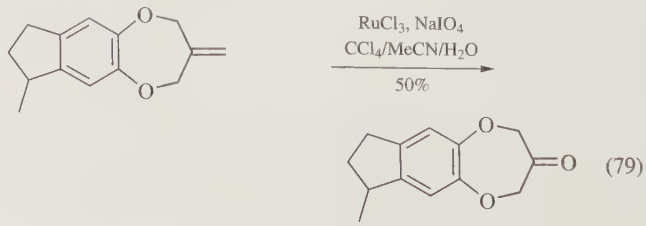
Functional Group Oxidations with C–C Bond Cleavage. The use of RuO_4 as an agent for C–C bond cleavage is a widely useful transformation. In general, oxidation of 1,2-disubstituted olefins affords carboxylic acids as the primary products and can be used to provide regioselectively diacids if the olefin is part of ring system (eq 77).[116] The use of cyclohexane with RuO_4 generated from $RuCl_3/IO(OH)_5$ has been shown to be superior organic cosolvent to ethyl acetate, acetone, and the more commonly used CCl_4 for olefin and alkyne cleavage to carboxylic acids.[117]



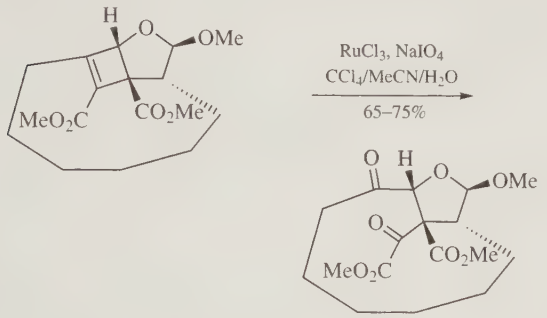
Aldehydes can be obtained as the major product of olefin oxidative cleavage in contrast to the more common production of carboxylic acids. The key variables to maximize the yield of aldehyde are the substitution pattern of the olefin oxidized, the choice of solvent, equivalents and choice of stoichiometric oxidant, and reaction time (eq 78).[118] Alcohols can be obtained from RuO_4-catalyzed olefin cleavage by working up the reaction with sodium borohydride, then with sodium periodate followed by another treatment of sodium borohydride.[119] Presumably, the reaction sequence goes through an intermediate α-hydroxy ketone.



1,1-Disubstituted olefins can be efficiently cleaved in a single step with RuO_4 to unmask a ketone moiety (eq 79)[120] in contrast to a two-step procedure of dihydroxylation of the olefin followed by oxidative cleavage of the diol.



Oxidative C–C bond cleavage by RuO_4 can be used as a strategy to create macrocycles from smaller bicyclic systems containing olefins that are oxidatively cleaved (eq 80).[121] Bicyclic ethers containing alcohols at the ring fusion carbon can be converted via oxidative cleavage to medium-ring keto-lactones when treated with RuO_4 as well (eq 81).[122]



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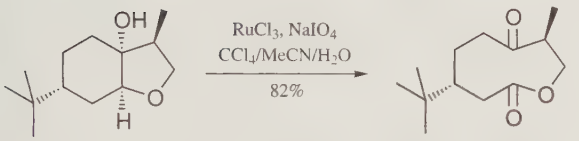

(81)

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Selenium(IV) Oxide

SeO_2

[7446-08-4] O_2Se (MW 110.96)

(oxidant of activated, saturated positions)

Alternate Name: selenium dioxide.
Physical Data: mp 315 °C (subl); *d* 3.95 g cm^{-3}.
Solubility: sol water, methanol, ethanol, acetone, acetic acid.
Form Supplied in: off-white powder;[1] widely available.
Purification: by sublimation, or by treatment with HNO_3.[28]
Handling, Storage, and Precautions: toxic; corrosive; causes intense local irritation of skin and eyes; use in a fume hood.

Allylic Hydroxylation. Selenium(IV) oxide is known primarily for hydroxylation of activated carbon-bearing positions, particularly at allylic (or propargylic) sites. Studies by Guillemonat and others have led to the following hydroxylation selectivity rules:[2,3]

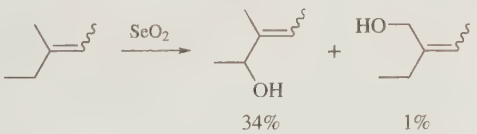
1) Hydroxylation occurs α to the more substituted end of the double bond.

2) The order of facility of oxidation is $CH_2 > CH_3 > CH$.

3) When the double bond is in a ring, oxidation occurs within the ring when possible, and α to the more substituted end of the double bond.

4) Oxidation of a terminal double bond affords a primary alcohol with allylic migration of the double bond.

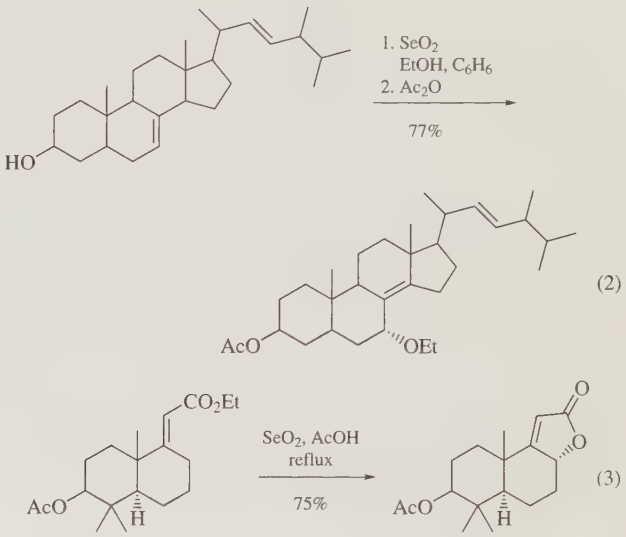
An example of rules (1) and (2) is shown in the oxidation of 3-methyl-3-butene, where the allylic methylene position is oxidized in preference to the methyl or methine positions (eq 1).[2]



(1)

Alkene-selective oxidation of 5,6-dihydroergosterol in ethanol, an example of rule (3), occurs at C-14 and is followed by allylic rearrangement to give a 7α-ethoxy product (eq 2).[4] The mechanism of the allylic oxidation reaction is proposed to be initiated by ene addition, followed by dehydration and [2,3]-sigmatropic rearrangement of the resultant allylseleninic acid.[5,6] In a key step of the synthesis of α-onocerin, α-oxidation in acetic acid leads to an unsaturated γ-lactone product in good yield (eq 3).[7]

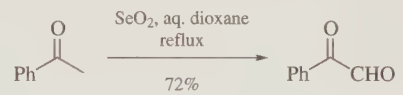
The milbemycins have been hydroxylated in the 13β-position by selenium dioxide.[8] Because selenium dioxide forms selenious acid (H_2SeO_3) in the presence of water, hydroxylations of alkenes containing acid-labile groups (e.g. acetals) have been run in pyridine.[9]



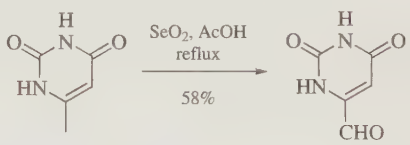
(2)

(3)

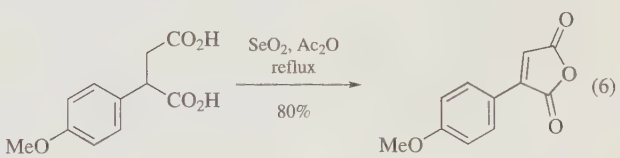
Higher-Order Oxidations. Selenium dioxide can introduce carbonyl functionality at activated positions, and can also effect dehydrogenation[10–13] at highly activated saturated sites. For instance, phenylglyoxal is isolated in high yield from α-oxidation of acetophenone (eq 4).[14] On a large scale, dissolution of the selenium dioxide in aqueous dioxane at 55 °C is required prior to acetophenone addition. Similarly, 6-methyluracil is readily converted to orotaldehyde in acetic acid (eq 5).[15] Oxidation of aryl-substituted succinic acids to maleic anhydride analogs occurs readily in acetic anhydride (eq 6).[16] This is a preferred method, since oxidations of this type with ***N-Bromosuccinimide*** give bromoarene byproducts. Additionally, selenium dioxide in the presence of ***Trimethylsilyl Polyphosphate*** has been used to aromatize cyclohexenes and cyclohexadienes.[17] Using only a slight excess (1.2 molar equiv) of selenium dioxide in pyridine, methyl 2-methyl-4-pyrimidinecarboxylate has been prepared regioselectively from 2,4-dimethylpyrimidine after methanolysis of the carboxylic acid product (eq 7).[18] Interestingly, ***Sulfuric Acid***-catalyzed oxidation of 1-octene in acetic acid affords a 1,2- diacetate product (eq 8).[19] Only a trace amount of 1-acetoxy-3-octene is observed.



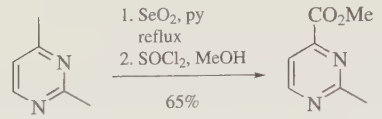
(4)



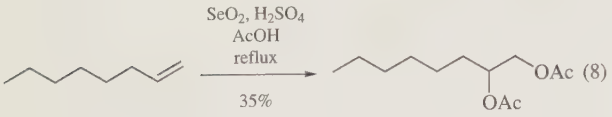
(5)



(6)

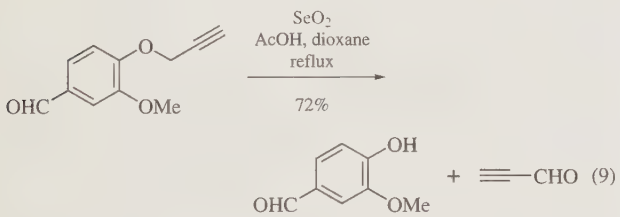


(7)

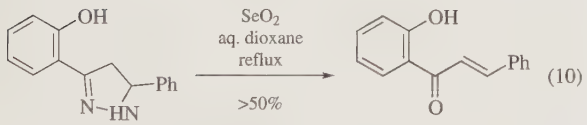


(8)

Oxidative Cleavage. Attack of selenium dioxide at activated positions can lead to oxidative bond cleavage when appropriate leaving groups are present. Aryl propargyl ethers undergo oxidation at the α-alkynyl position to afford a phenolic species and propargyl aldehyde (eq 9).[20] The analogous aryl allyl ether fragmentations occur in somewhat lower yields. (Hydroxyaryl) pyrazolines have been oxidized, with nitrogen extrusion, to afford 2′-hydroxychalcone products (eq 10).[21] Oxidations of pyrazolines with ***Bromine***, ***Potassium Permanganate***, ***Chromium(VI) Oxide***, and other reagents result in pyrazole formation.

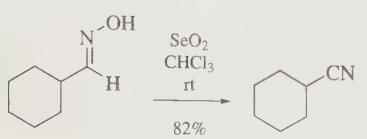


(9)

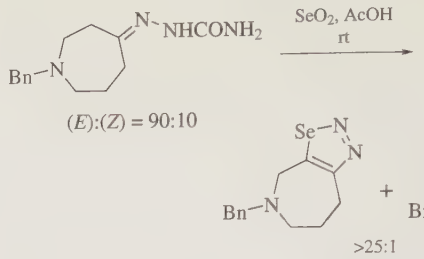


(10)

Miscellaneous Transformations. Alkyl and aryl nitriles can be prepared from the corresponding aldehydes via conversion to the aldoxime, followed by catalytic selenium dioxide-mediated elimination (eq 11).[22,23] Aliphatic nitriles are formed at rt, while aryl nitrile formation requires heating. 1,2,3-Selenadiazoles have been synthesized by treatment of an *N*-benzylazepine 4-semicarbazone with selenium dioxide (or selenoyl dichloride) (eq 12).[24,25] The *N*-benzyl proximal product is formed with high regioselectivity vis-à-vis the distal product in polar solvents. Nonpolar solvents give ca. 3:1 mixtures (proximal/distal). The oxygen-catalyzed reaction of trialkylboranes with 1 equiv of selenium dioxide affords a dialkyl selenide as the major product.[26] Similarly, dialkyl selenides have been prepared by reaction of alkyllithiums or Grignard reagents with selenium dioxide.[27]



(11)



(12)

Related Reagents. Selenium(IV) Oxide–*t*-Butyl Hydroperoxide.

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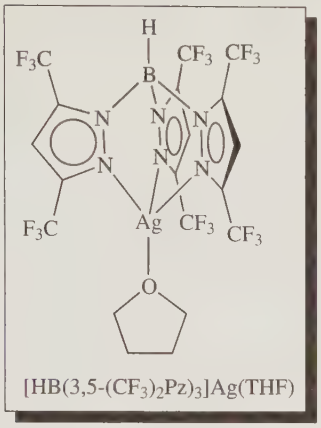
Silver(I) [tris[3,5-bis(trifluoromethyl)-1*H*-pyrazolato-*N*1]hydroborato(1-)-*N*2, *N*2′, *N*2‴]-tetrahydrofuran



[171203-65-9]
THF complex
[171900-57-5] $C_{19}H_{12}AgBF_{18}N_6O$ (MW 800.99)

Physical Data: for [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF): mp dec. > 60 °C, ^{1}H NMR (C_6D_6, TMS) δ 1.40 (m, 4 H, THF), 3.56 (m, 4 H, THF), 6.26 (s, 3 H, Pz); ^{19}F NMR (C_6D_6, ext. ref. $CFCl_3$) δ −58.9, −60.1.

Solubility: [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF) is soluble in common organic solvents such as THF, Et_2O, toluene, benzene, hexanes, CH_2Cl_2, $CHCl_3$.

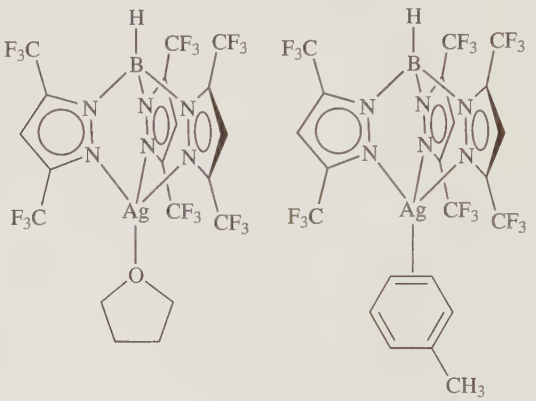
Form Supplied in: [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag can be conveniently obtained as its THF adduct [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF), which is a white crystalline solid.

Preparative Method: [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF) was prepared by a metathesis reaction between [HB(3,5-$(CF_3)_2$Pz)$_3$]Na(THF) and AgOTf. [HB(3,5-$(CF_3)_2$Pz)$_3$]Na(H_2O) can also be used instead of the THF adduct [HB(3,5-$(CF_3)_2$Pz)$_3$]Na(THF) in the above reaction.

Purification: [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF) can be purified by recrystallization at −15 °C from hexane containing a few drops of THF.

Handling: [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF) could be handled in air for short periods without any significant decomposition. However, prolonged storage at room temperature under visible light leads to slow discoloration and/or decomposition. Therefore, [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF) is best stored under nitrogen, protected from light, in a low temperature freezer. This silver adduct is also soluble in chlorinated solvents but, due to slow decomposition over a period of several hours, those solvents should be avoided as a medium for storage.

Preparation and C–H Activation Chemistry of [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF). There are a few catalytic processes presently available for the functionalization of unactivated carbon-hydrogen bonds.[1–6] One of the most promising routes among these has been the insertion of carbene units to C–H bonds.[3,6–8] Diazo compounds like ethyl diazoacetate (EDA) are excellent carbene precursors while certain copper- and rhodium-based compounds such as rhodium(II) carboxylates, rhodium(II) carboxamidates, rhodium(II) phosphates, and copper(I) adducts of tris(pyrazolyl)borates serve as effective catalysts for this process.[3,6,9–12] We have demonstrated recently that [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF) (where [HB(3,5-$(CF_3)_2$Pz)$_3$]$^-$ = hydrotris (3,5-bis(trifluoromethyl)pyrazolyl)borate) also catalyzes the carbene insertions into unfunctionalized C–H bonds under remarkably mild conditions.[7] In general, any [HB(3,5-$(CF_3)_2$Pz)$_3$]AgL that generates the "[HB(3,5-$(CF_3)_2$Pz)$_3$]Ag" moiety by releasing L serves as a catalyst. Compounds like [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF) (**1**) and [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(toluene)[13] (**2**) (CAS 199943-65-2) containing labile ligands "L" are good choices. These silver reagents also catalyze the Büchner reaction[14] and carbene insertion reactions to C–X (X = Cl, Br, I) bonds.[15] Recently, the C–H activation chemistry of the closely related silver(I) complex [HB(3,4,5-Br_3Pz)$_3$]Ag(THF) was also reported.[8]

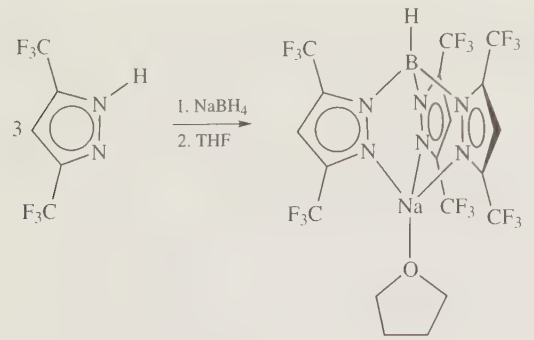


1 **2**

[HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF)[13,16] and [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(toluene)[13] are also excellent starting materials for the preparation of a variety of rare inorganic and organometallic complexes containing silver(I). These include [HB(3,5-$(CF_3)_2$Pz)$_3$]AgL′ where L′ = ethylene,[13] acetylene,[13] carbon monoxide,[17] azidoadamantane,[18] ethylene oxide,[19] propylene sulfide,[19] dimethyl diazomalonate,[20] and various aminotroponiminato complexes of tin(II) and germanium(II) donors.[21,22] [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF) and [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(toluene) also function as good [HB(3,5-$(CF_3)_2$Pz)$_3$]$^-$ transfer agents. For example, [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF) reacts with InCl producing [HB(3,5-$(CF_3)_2$Pz)$_3$]In.[16,23] [HB(3,5-$(CF_3)_2$Pz)$_3$]ZnEt could be obtained by treating [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF) and $ZnEt_2$.[24]

Preparation of [HB(3,5-$(CF_3)_2$Pz)$_3$]Na(THF). [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF) can be synthesized by a two-step process.[16] The first step involved the synthesis of the sodium derivative [HB(3,5-$(CF_3)_2$Pz)$_3$]Na(THF) starting with 3,5-bis(trifluoromethyl)-1*H*-pyrazole (3,5-$(CF_3)_2$PzH) and $NaBH_4$ (eq 1).[25] Some details of the synthesis of the sodium adduct [HB(3,5-$(CF_3)_2$Pz)$_3$]Na(THF) are given below.

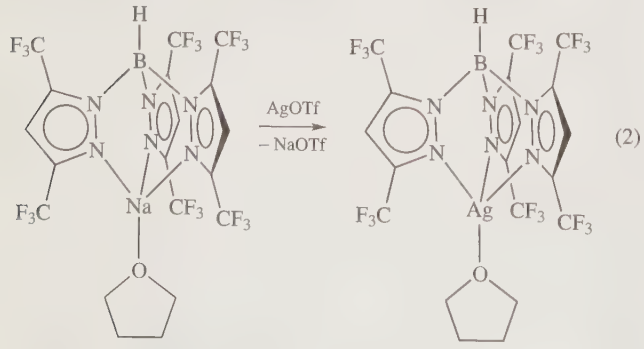
Under nitrogen, $NaBH_4$ (0.265 g, 7.0 mmol) and freshly sublimed 3,5-$(CF_3)_2$PzH (5.0 g, 24.5 mmol) were placed in a 100 mL round bottom flask equipped with a reflux condenser and a stirbar. Dry kerosene (0.5 mL, dried by running through a short alumina column) was added to the mixture, and the mixture was gradually heated in an oil bath under nitrogen to about 200 °C.



[HB(3,5-$(CF_3)_2$Pz)$_3$]Na(THF)

When the temperature reaches about 90 °C, 1 mL of dry toluene was added from the top of the condenser. This is mainly to break the solid cake and to wash down the subliming 3,5-$(CF_3)_2$PzH. The temperature was maintained at 195–205 °C for 6 h (without overheating). The mixture was allowed to cool to room temperature. After removing toluene under vacuum, petroleum ether (10 mL) was added to the resulting solid, stirred for a few minutes, and the solution was filtered to obtain a white solid. This solid was extracted into diethyl ether (use several aliquots), and the combined ether extracts were placed in a sublimator. Volatile materials, including any unreacted 3,5-$(CF_3)_2$PzH was removed under vacuum at 70 °C. Resulting solid [HB(3,5-$(CF_3)_2$Pz)$_3$]Na was dissolved in THF (20 mL) and stirred overnight. The solvent was removed under vacuum to obtain [HB(3,5-$(CF_3)_2$Pz)$_3$]Na (THF) as a white solid (78%). Good quality crystals were obtained by recrystallization from toluene/THF. mp 117–118 °C; ^{1}H NMR (C_6D_6, TMS) δ 1.37 (m, 4 H, THF), 3.52 (m, 4 H, THF), 6.27 (s, 3 H, Pz); ^{19}F NMR (C_6D_6, ext. ref. $CFCl_3$) δ −58.33 (d, J = 3.6 Hz), −62.15 (s); ^{1}H NMR ($CDCl_3$, $C(H)DCl_3$) δ 1.90 (m, 4 H, THF), 3.85 (m, 4 H, THF), 6.81 (s, 3 H, Pz); ^{19}F NMR ($CDCl_3$, ext. ref. $CFCl_3$) δ −58.80 (d, J = 3.6 Hz), −62.37 (s).

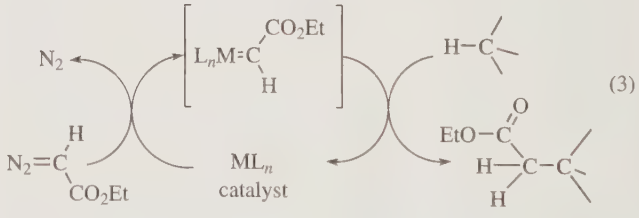
Preparation of [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF). The sodium adduct [HB(3,5-$(CF_3)_2$Pz)$_3$]Na(THF) undergoes metathesis with AgOTf producing the related silver(I) tris(pyrazolyl)borate complex in high yield. [HB(3,5-$(CF_3)_2$Pz)$_3$]Na(H_2O)[25] can also be used instead of [HB(3,5-$(CF_3)_2$Pz)$_3$]Na(THF) in this preparation (eq 2). The details are given below.



[HB(3,5-$(CF_3)_2$Pz)$_3$]Na(THF) [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF)

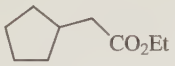
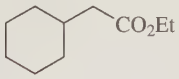
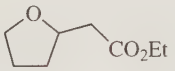
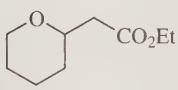
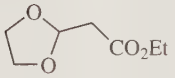
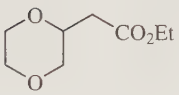
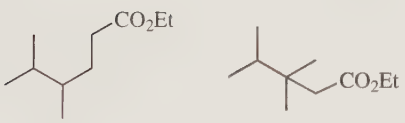
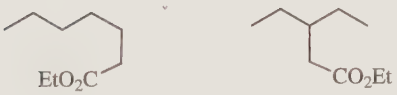
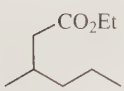
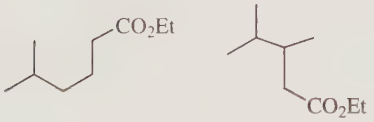
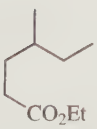
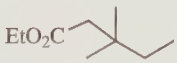
Silver(I) trifluoromethanesulfonate (0.463 g, 1.8 mmol) was treated with [HB(3,5-$(CF_3)_2$Pz)$_3$]Na(THF) (1.7 mmol) in THF at room temperature under nitrogen. The mixture was stirred overnight and the solvent was removed under reduced pressure. The residue was extracted into hexane, filtered through a bed of Celite, and the hexane was removed from the filtrate to obtain [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF) as a white solid. 92% yield, mp dec. >60 °C, ^{1}H NMR (C_6D_6, TMS) δ 1.40 (m, 4 H, THF), 3.56 (m, 4 H, THF), 6.26 (s, 3 H, Pz); ^{19}F NMR (C_6D_6, ext. ref. $CFCl_3$) δ −58.9, −60.1. The related copper(I) complex [HB(3,5-$(CF_3)_2$Pz)$_3$]Cu(THF) could also be obtained following a similar procedure. [HB(3,5-$(CF_3)_2$Pz)$_3$]Na(THF) (0.475 g, 0.664 mmol) and Cu(OTf)$_2$·benzene complex (0.167 g, 0.332 mmol) were mixed in dry degassed THF and stirred overnight under N_2. The solvent was removed under reduced pressure and the resulting solid material was extracted into hexane. The mixture was filtered through a bed of Celite, and the filtrate was collected and dried under reduced pressure to obtain [HB(3,5-$(CF_3)_2$Pz)$_3$]Cu(THF) in 63.3% yield. ^{1}H NMR (C_6D_6, TMS): δ 1.45 (m, 4 H, THF), 3.88 (m, 4 H, THF), 6.22 (s, 3 H, Pz).

C–H Activation Chemistry of [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF). [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF) catalyzes activation of unfunctionalized C–H bonds by means of the insertion of carbene group:$CHCO_2Et$ from ethyl diazoacetate.[7] The reactions proceed at room temperature and the yields are high (eq 3). For example, it is possible to synthesize ethyl 2-cyclohexyl acetate in 88% yield using a mixture of cyclohexane, ethyl diazoacetate (EDA), and 5 mol % of the catalyst [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF). As shown in Table 1, a variety of other cyclic, linear, and branched hydrocarbons can be used as substrates. Data also suggest that the tertiary ≈ secondary > primary order of regioselectivity for insertion into C–H bonds. Interestingly, for the C–H bond activation of ether substrates like THF, [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF) is a poor choice compared to the closely related copper catalyst [HB(3,5-$(CF_3)_2$Pz)$_3$]Cu(THF).[26]



General Procedure for C–H Insertion Reactions. Reactions were carried out under nitrogen in the absence of light. Ethyl diazoacetate (114 mg, 1.00 mmol) in the hydrocarbon or ether (5 mL) was added by automatic syringe over 1 h to a stirred solution of the [HB(3,5-$(CF_3)_2$Pz)$_3$]Ag(THF) (0.05 mmol) in the hydrocarbon or ether (1.5 mL). Decomposition of the ethyl diazoacetate was evident from the rapid evolution of nitrogen. The resulting mixture was stirred overnight at ambient temperature. The solution was concentrated and the residue was purified by flash chromatography (SiO_2, 9:1 hexanes/Et_2O) to obtain the products.

Table 1 [HB(3,5-$(CF_3)_2Pz)_3$]Ag(THF)-catalyzed carbene insertion into C–H bonds (adapted with permission from *Organometallics* **2004**, *23*, 1200–1202. Copyright 2004 American Chemical Society)[7]

Entry	Substrate	Products	Yield (%)[a]
1			88[b]
2			88[b]
3			24[c] α only
4			41[d] α only
5			0
6			0
7		 80 20	85[b]
8		 41 12  47	81[b]
9		 tr. 27   59 14	87[b]

[a]These *isolated* yields are based on the average of at least two experiments and on the amount of ethyl diazoacetate (EDA) used. Product distribution observed by ^{1}H NMR spectroscopy.

[b]The material balance for is accounted for by carbene dimerization products diethyl fumarate and maleate.

[c]Nearly equal amounts of dimers and unreacted EDA were found in the product mixture.

[d]Product mixture contains 40% dimers and 6% EDA. Unreacted EDA was obtained from Entries 5,6.

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Triethylborane

[97-94-9] $C_6H_{15}B$ (MW 98.02)

(precursor of triethylborohydride reducing agents;[1] enoxytriethylborates and -diethylboranes for aldol[19,22] and alkylation[17] reactions; regio- and stereoselective reactions of allyltriethylborates;[26,27] alkylating reagents;[1b] stereocontrol of carbanion reactions;[39,41] radical initiator[44])

Physical Data: mp −93 °C; bp 95 °C; *d* 0.677 g cm^{-3}.

Solubility: soluble in ethanol, acetone, THF, ether, hexane, benzene, $CHCl_3$.

Form Supplied in: colorless liquid; widely available. Since it is highly flammable, triethylborane diluted with hexane or THF (1.0 M solution) is also available.

Handling, Storage, and Precautions: neat triethylborane ignites instantaneously upon contact with air. The reagent should be handled with a syringe under Ar or N_2 atmosphere. It is stable toward moisture and water, and reputed to be toxic. Use in a fume hood.

Original Commentary

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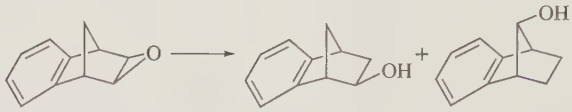
Tohoku University, Aoba, Sendai, Japan

Reducing Reagents. ***Lithium Triethylborohydride***, known as 'Super-Hydride', is prepared in THF by the reaction of lithium hydride with triethylborane (eq 1).[1] Alkali metal trialkylborohydrides are exceptionally powerful nucleophilic reducing agents capable of cleaving cyclic ethers,[2] reducing hindered halides,[3] *p*-toluenesulfonate esters of hindered and cyclic alcohols,[4] epoxides,[5] and activated alkenes[6] rapidly and quantitatively to the desired products. The advantage of $LiEt_3BH$ is especially evident in the reduction of labile bicyclic epoxides (eq 2). Thus benzonorbornadiene oxide, which invariably gives rearranged products with conventional reducing agents, undergoes facile reduction with $LiEt_3BH$ yielding 93% of *exo*-benzonorborneol in >99.9% isomeric purity. The reactivity of the trialkylborohydrides and the stereochemical course of their reactions are strongly influenced by the steric bulk of the alkyl group on boron.[7] The lithium hydride route (eq 1) provides a convenient entry only to the relatively unhindered lithium trialkylborohydrides. However, ***Potassium Hydride*** reacts rapidly and quantitatively with the hindered trialkylboranes, such as tri-*s*-butylborane, yielding the corresponding sterically hindered trialkylborohydride ***Potassium Tri-s-butylborohydride***.[8] A general synthesis of lithium trialkylborohydrides has been developed using lithium trimethoxyaluminohydride (eq 3).[9]

$$LiH + BEt_3 \xrightarrow[25\ ^\circ C]{THF} LiEt_3BH \quad \text{Super-Hydride} \qquad (1)$$



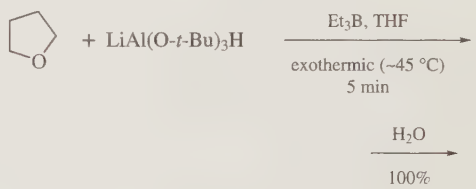
(2)

$LiEt_3BH$, THF, 65 °C, 24 h	93%	<0.1%
$LiAlH_4$, Et_2O, reflux, 24 h	15%	85%
BH_3, THF, reflux, 4 h	54%	23%
Li, ethylenediamine, 50 °C, 24 h	31%	15%

$$R_3B + LiAl(OMe)_3H \xrightarrow[0.25\ h,\ 100\%]{THF,\ 25\ ^\circ C} LiR_3BH + Al(OMe)_3\downarrow \qquad (3)$$

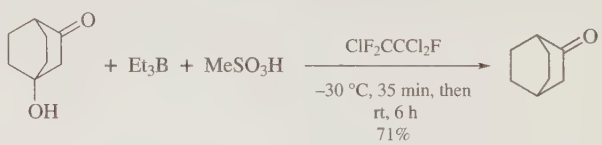
R = Et, Bu, *s*-Bu, *i*-Bu

The combination of ***Lithium Tri-t-butoxyaluminum Hydride*** and triethylborane induces a rapid, essentially quantitative, reductive ring opening of THF to produce 1-butanol upon hydrolysis (eq 4).[10] Cyclohexene oxide and 1-methylcyclohexene oxide are instantaneously and quantitatively cleaved to their corresponding carbinols. Oxetane is readily cleaved to give 1-propanol in 98% yield. The reductive cleavage of both tetrahydropyran and oxepan is very sluggish and incomplete.



(4)

Triethyl- or triisopropylborane/***Trifluoromethanesulfonic Acid*** (triflic acid) is a convenient reagent for the selective reduction of hydroxy substituted carboxylic acids, ketones, and aldehydes to yield the corresponding carbonyl compounds (eq 5).[11] Not only tertiary hydroxy but also primary, secondary, and benzylic hydroxy groups are reduced in good to high yields. In general, the triisopropylborane/triflic acid system gives better results than triethylborane/triflic acid.

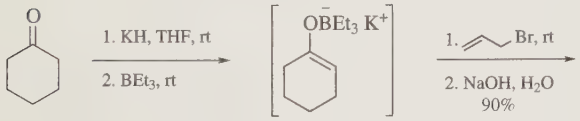


(5)

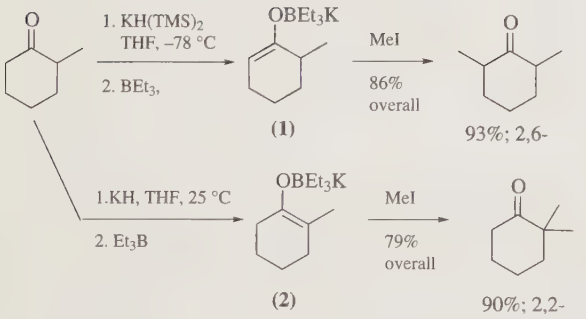
Preparation of R_2BOR' is generally carried out by treating alcohols R′OH with trialkylboranes R_3B in the presence of activating reagents like pivalic acid[12] or air.[13] However, Et_2BOMe can be prepared simply by mixing Et_3B with MeOH in THF at room temperature.[14] Using the Et_2BOMe thus generated as a chelating agent, *syn*-1,3-diols are prepared in >98% stereochemical purity by reducing β-hydroxy ketones with ***Sodium Borohydride***.[14]

Enoxytriethylborates and Enoxydiethylboranes. Potassium enolates of ketones react with an unhindered trialkylborane such as triethylborane to form a potassium enoxytriethylborate,

which undergoes selective α-monoalkylation with alkyl halides in high yields (eq 6).[15] In the absence of Et_3B, the potassium enolate itself gives a mixture of 43% mono- and 31% diallylated cyclohexanone along with 28% of recovered cyclohexanone. Monomethylation, -benzylation, and -propargylation of acetophenone also proceed in high yield in the presence of Et_3B. Lithium enolates, such as those obtained from acetophenone and cyclohexanone, do not form the corresponding enoxytriethylborates. Use of ***Potassium Hexamethyldisilazide*** as a base at −78 °C generates the less stable enolate **1** with high regioselectivity, while use of potassium hydride at 25 °C generates the most stable enolate **2** with >90% regioselectivity (eq 7).[16] The alkylations of these enolates proceed without complication in the presence of Et_3B (eq 7). Comparable regioselectivities are observed in the alkylations of 2-heptanone.

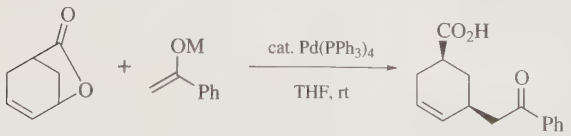


(6)



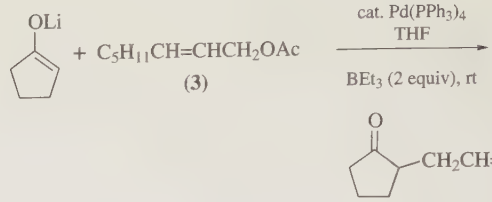
(7)

Allylation of potassium enoxyborates can be catalyzed by ***Tetrakis(triphenylphosphine)palladium(0)***.[17] Zinc enolates, readily obtained by treating lithium enolates with dry ***Zinc Chloride***, also undergo the Pd-catalyzed allylation with high regio- and stereoselectivities. Overall retention is observed with respect to the allylic cation center (eq 8).[17] In the presence of $Pd(PPh_3)_4$ catalyst and 2 equiv of BEt_3, lithium enolates of cyclopentanone and cyclohexanone derivatives react with (*E*)- or (*Z*)-allylic acetate **3** to provide (*E*)- or (*Z*)-allylation products with high stereospecificity (eq 9).[18] Both the Pd catalyst and BEt_3 are essential for the stereospecific allylation.



M = BEt_3K or ZnCl

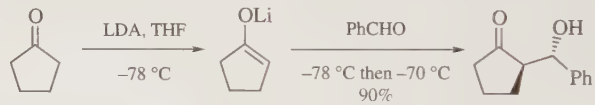
(8)



(9)

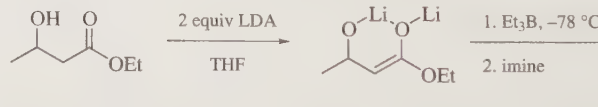
(*E*)-(**3**) 77% (*E*):(*Z*) = 98:2
(*Z*)-(**3**) 73% (*Z*):(*E*) = >97:3

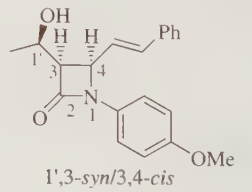
The aldol reaction of preformed lithium enolates with aldehydes in the presence of trialkylboranes, such as BEt_3 and $B(n\text{-}Bu)_3$, leads to product mixtures rich in the more stable *anti*-aldol (eq 10).[19] Use of 3 equiv of BEt_3 gives high *anti* selectivity, while the stereoselectivity is low when 1 equiv of BEt_3 is used (eq 10). When lithium enolates are generated from silyl enol ethers and ***n-Butyllithium*** in THF, use of 1 equiv of BEt_3 is enough to produce high *anti* selectivity. The condensation of the lithio dianion of ethyl 3-hydroxybutyrate with *N*-anisyl cinnamylideneimine in the presence of Et_3B produces excellent 1′,3-*syn*/3,4-*cis* stereoselectivity (eq 11), whereas 1′,3-*syn*/3,4-*trans* selectivity is obtained in the presence of *t*-BuMgCl.[20] Aldol condensation of acetaldehyde and benzaldehyde with the lithium enolate of ethyl *N,N*-dimethylglycine in the presence of 1 equiv of Et_3B results in the formation of the corresponding *syn* 3-hydroxy-2-amino acid esters with excellent stereocontrol (>95% de).[21] The stereochemical outcome of these reactions is rationalized via the selective formation of the (*Z*)-enolate of ethyl *N,N*-dimethylglycine in the presence of triethylborane.



(10)

1 equiv BEt_3, *anti*:*syn* = 1:1
3 equiv BEt_3, *anti*:*syn* = 97:3



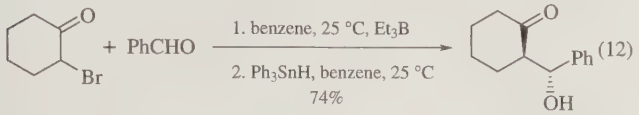


(11)

1′,3-*syn*/3,4-*cis*

There are several methods for generation of enoxyboranes (boron enolates).[22] Ketenes react with dialkylthioalkylboranes, $R_2BS(t\text{-}Bu)$, to yield alkenyloxyboranes formally derived from thioesters.[22a] A variety of ketones and carboxylic acid derivatives are converted to boron enolates upon treatment with dialkylboryl triflates in the presence of a tertiary amine, and the subsequent aldol condensation of these boron enolates has been studied[22b,c] Trialkylboranes readily react with diazoacetaldehyde to give alkenyloxyboranes.[22d] Trialkylboranes spontaneously transfer an alkyl group to the β-position of β-unsubstituted α,β-unsaturated aldehydes and ketones to give alkenyloxyboranes, which are produced regio- but not stereospecifically.[22e] In the presence of 1–10 mol % of diethylboryl pivalate, Et_3B and ketones

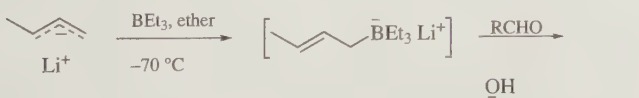
$RCOCH_2R'$ react at 85–110 °C to give diethyl(vinyloxy)boranes, $Et_2BOCR{=}CHR'$, in 70–90% yield.[22f] Reaction of α-bromo ketones with ***Triphenylsilane*** in the presence of Et_3B provides boron enolates which react with carbonyl compounds to give β-hydroxy ketones in good yields (eq 12).[23] The Et_3B-induced Reformatsky type reaction of α-iodo ketones with aldehydes or ketones proceeds without Ph_3SnH.[23,24] α-Bromocyclopentanone and -cyclohexanone provide *anti*-adducts with high diastereoselectivity (78–100%), whereas the reaction of 7-bromo-6-dodecanone with benzaldehyde gives a 65:35 mixture of the *syn*- and *anti*-adduct. It is proposed that vinyloxy(diethyl)boranes are involved as intermediates.



(12)

anti:syn = 78:22

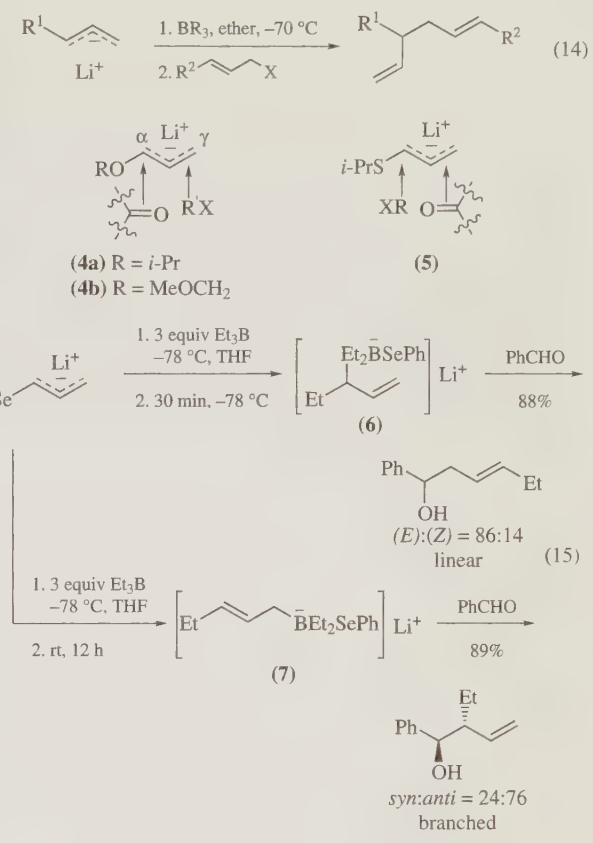
Allylborates. 2-Butenyllithium reacts with aldehydes to afford the *anti*- and *syn*-β-methylhomoallyl alcohols in nearly equal amounts. However, if trialkylboranes such as Et_3B are present, the *anti*-product predominates (eq 13).[25] The corresponding allylic borate complexes are presumably involved as intermediates. Lithium allylic boronates, prepared by the addition of trialkylboranes (Et_3B, ***Tri-n-butylborane***, or *n*-Bu-9-BBN) to an ether solution of allylic lithium compounds, regioselectively react with allylic halides to produce head-to-tail 1,5-dienes (eq 14).[26] Regio- and stereocontrol via boron ate complexes is applicable to not only simple allylic but also heteroatom substituted allylic anions.[27] The allyloxy carbanions **4** generally react with alkyl halides at the α-position, but react with carbonyl compounds at the γ-position. The Et_3B (or ***Triethylaluminum***) ate complexes of **4** react with aldehydes, ketones, and reactive halides at the α-position. The (alkylthio)allyl carbanion **5** reacts with alkyl halides at the γ-position, but with carbonyl compounds at the α-position. The Et_3B (or Et_3Al) ate complexes of **5** react with aldehydes, ketones, and allylic halides at the α-position. In general, the aluminum ate complex gives higher regioselectivity than the boron ate complex. The regioselectivity of Me_3Si- or pyrrolidine (*N*-atom)-substituted allylic anions is also controlled by the addition of Et_3B (or Et_3Al).[27] Either branched or linear homoallyl alcohols may be prepared by the reaction of (phenylselenyl)allyl carbanion with aldehydes and triethylborane under appropriate reaction conditions (eq 15).[28] The ethyl group of Et_3B in the initially formed ate complex $PhSeCH(BEt^-{}_3)CH{=}CH_2$ Li^+ undergoes a facile migration from boron to the α-carbon to give **6**, which reacts with benzaldehyde to give the linear adduct. The prolonged reaction period at higher temperatures induces the allylic rearrangement of **6** to **7**, resulting in the formation of the branched adduct.



(13)

anti:*syn*

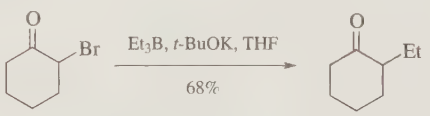
R = Ph, 90% 82:18
R = Me, 78% 85:15



(14)

(15)

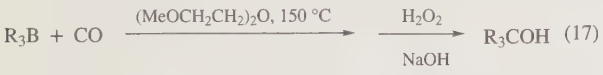
Alkylating Reagents. Monoalkylation of ketones is accomplished by reaction of trialkylboranes with α-bromo ketones under the influence of ***Potassium t-Butoxide*** in THF.[29] For example, α-bromocyclohexanone reacts with Et_3B to give α-ethylcyclohexanone (eq 16).[29] The reaction involves formation of the anion of the α-bromo ketone, formation of the boron ate complex, and rearrangement of Et from boron to the α-carbon. The use of potassium 2,6-di-*t*-butylphenoxide as a base, instead of *t*-BuOK, provides better results.[30] α-Bromoacetone, chloroacetonitrile, ethyl bromoacetate, and ethyl dibromoacetate are alkylated using this hindered base and R_3B.[30] The reaction of Et_3B with ethyl 4-bromocrotonate in the presence of one equiv of the new base affords ethyl 3-hexenoate (79% *trans*).[31] Monoalkylation of dichloroacetonitrile with Et_3B is achieved in 89% yield, and the dialkylation is carried out by using 2 equiv of base and 2 equiv of Et_3B (97% yield).[32]

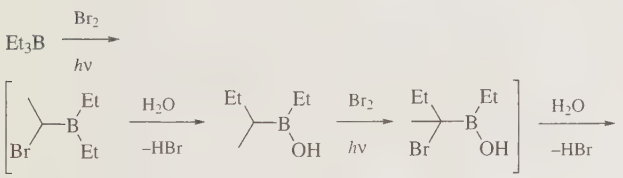


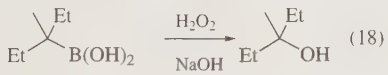
(16)

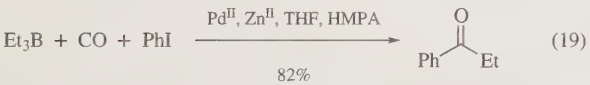
Trialkylcarbinols are prepared by the reaction of trialkylboranes with carbon monoxide in diglyme followed by oxidation with ***Hydrogen Peroxide*** (eq 17).[1b] Alternatively, trialkylcarbinols are obtained by the reaction of trialkylboranes with ***Chlorodifluoromethane*** (or ***Dichloromethyl Methyl Ether***) under the influence of lithium triethylmethoxide,[1b,33] or by the cyanidation reaction of trialkylboranes with ***Sodium Cyanide–Trifluoroacetic Anhydride*** followed by oxidation.[1b,34] Bromination of triethylborane under irradiation in the presence of water followed by oxidation gives 3-methyl-3-pentanol in 88% yield (eq 18).[35] In order to

effect successful α-bromination–migration, slow addition of bromine is important to avoid polybromination. The use of ***N-Bromosuccinimide*** in the presence of water increases the yield in eq 18 to 97%.[36] The bromination–migration reaction is applicable to simple trialkylboranes and dialkylborinic acids. The cross-coupling reaction of *B*-alkyl-9-borabicyclo[3.3.1]nonanes (*B*-R-9-BBN) with 1-halo-1-alkenes or haloarenes (R′X) in the presence of a catalytic amount of ***Dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II)*** and bases, such as NaOH and K_2CO_3, gives the corresponding alkenes or arenes (R–R′).[37] The use of catalytic amounts of $Cl_2Pd[PPh_3]_2$ in combination with ***Bis(acetylacetonato)zinc(II)*** effects carbonylative coupling of trialkylboranes with aryl iodides to give unsymmetrical ketones in 60–80% yields (eq 19).[38]

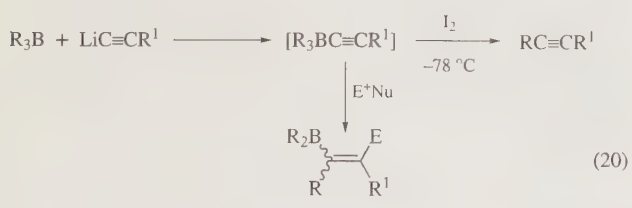






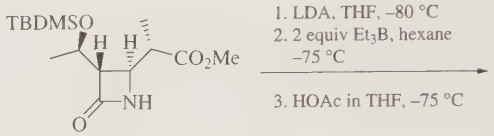


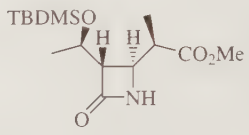
Alkynes are easily synthesized by the reaction of iodine with alkyne 'ate' complexes, readily formed in situ from R_3B and lithium acetylides (eq 20).[1b] Treatment of the alkyne 'ate' complexes with mild electrophiles E^+ results in β-attack on the triple bond and a migration of the organic group R from boron to carbon (eq 20).[1b] The protonation reaction with HX yields a mixture of *cis*- and *trans* alkenes, and mixtures of alkene isomers are also obtained in reactions involving MeI, MeOTs, allyl bromide, and oxirane. However, a single stereoisomer results from the reactions with other electrophiles.



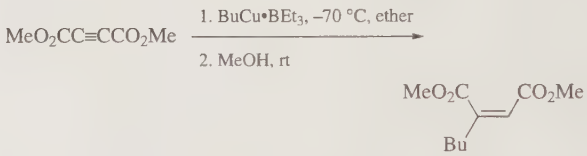
ENu = HX, MeI, MeOTs,  , oxirane, Bu_3SnCl, R_2BCl, Ph_2PCl, CO_2, $BrCH_2COR$, $BrCH_2CO_2Et$, $BrCH_2C{\equiv}CH$, ICH_2CN

Stereochemical Control Element. Triethylborane acts as a stereo- and regiocontrol element in certain carbanionic reactions; several examples have been demonstrated in eqs 10, 11 and 13–15. Triethylborane-mediated epimerization of a 1α-methylcarbapenem intermediate proceeds with high stereoselectivity to give the 1β-methyl diastereomer (eq 21).[39] The 1β-methyl derivative is also obtained via alkylation of an 2-azetidinon-4-ylacetic acid derivative by using LDA–Et_3Al–MeI.[39] The deuteration of α-lithiobenzyl methyl sulfoxide in the presence of Et_3Al occurs with inversion, while the reaction in the absence of the additive occurs with retention; the use of Et_3B gives a mixture of the retention and inversion product.[40] The reagent $RCu{\cdot}BEt_3$, prepared in situ from RCu and BEt_3 in ether at −70 °C, adds to α,β-alkynic carbonyl compounds with high stereospecificity, which cannot be achieved with conventional reagents such as R_2CuLi (eq 22).[41]



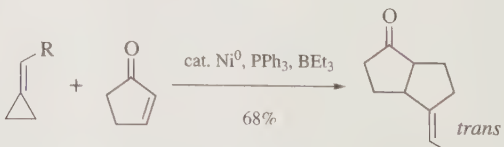


β:α = 93:7



$BuCu{\cdot}BEt_3$	85%	(*Z*):(*E*) = >99:1
BuCu	95%	= 85:15
Bu_2CuLi	98%	= 60:40

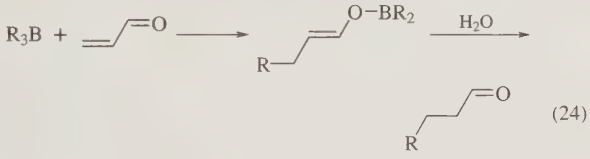
Lewis Acids and Radical Reactions. Methylenecyclopropanes react with 2-cyclopentenone in the presence of a Ni^0 catalyst (such as ***Bis(1,5-cyclooctadiene)nickel(0)***), ***Triphenylphosphine***, and triethylborane to afford 6-methylenebicyclo[3.3.0]octan-2-ones (eq 23).[42] Treatment of tantalum–alkyne complexes with dimethylhydrazones and ***Trimethylaluminum*** in a DME, benzene, and THF solvent system at 45 °C gives (*E*)-allylic hydrazines stereoselectively, although the use of Et_3B results in formation of the product in very low yield.[43]



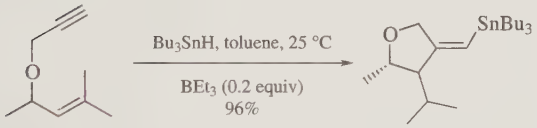
R = C_5H_{11} *trans*:*cis* = 85:15

Trialkylboranes do not undergo facile addition reactions to carbonyl groups. However, rapid conjugate addition reactions occur with α,β-unsaturated carbonyl compounds, such as ***Acrolein*** and ***Methyl Vinyl Ketone*** (eq 24).[1b] The reaction proceeds through a radical mechanism. Trialkylboranes also participate in facile radical chain reactions with disulfides (e.g. ***Diphenyl Disulfide***), producing the corresponding thioethers (RSPh).[1b] Triphenylgermane adds easily to alkynes (RC≡CH) in the presence of Et_3B to give (*E*)- or (*Z*)-alkenyltriphenylgermanes ($RCH{=}CHGePh_3$) in

good yields.[44] The (*Z*)-isomers predominate at −78 °C, whereas the hydrogermylation at 60 °C favors the (*E*)-isomer. Similarly, Et_3B is as efficient as ***Azobisisobutyronitrile*** for initiation of the hydrostannylation of alkynes, resulting in vinyltins.[45] The reaction is sluggish in the absence of oxygen. Triethylborane can also initiate radical cyclization of unsaturated alkynes to vinylstannanes (eq 25).[45] The 1,4-reduction of α,β-unsaturated ketones and aldehydes with ***Triphenylstannane*** or ***Tri-n-butylstannane*** proceeds in the presence of Et_3B to give the corresponding saturated ketones and aldehydes in good yields, whereas the same reaction of α,β-unsaturated esters with Ph_3SnH affords the tin hydride conjugate adduct.[46] Thiols[47a] and perfluoroalkyl iodides[47b] undergo similar addition reactions to alkynes in the presence of catalytic amounts of Et_3B. Treatment of 1-allyloxy-1-phenyl-2-bromo-1-silacyclopentanes with Bu_3SnH in the presence of catalytic amounts of Et_3B provides the cyclization products, which can be converted to 1,4,6-triol derivatives (eq 26).[48] Alkoxymethyl radicals (2-oxahex-5-enyl or 2-oxahept-6-enyl radicals), generated conveniently from phenylseleno precursors upon treatment with AIBN or Et_3B, cyclize to afford substituted tetrahydrofurans and tetrahydropyrans.[49]



(24)



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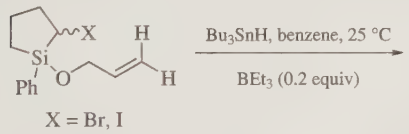
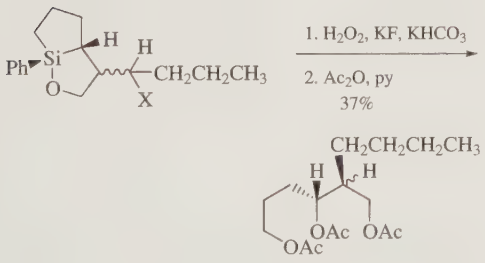
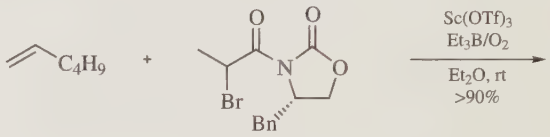
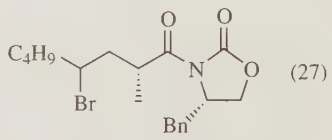




(26)

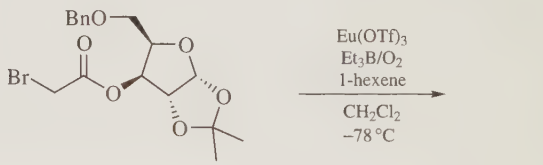
Atom Transfer Radical Reaction and Related Processes. Et_3B/O_2 is particularly suitable for the atom transfer radical reactions of halogenated compounds. γ-Haloesters are readily prepared by reacting α-haloesters with alkenes in the presence of Et_3B/O_2.[51] The mild conditions offered by Et_3B/O_2 allow for the stereoselective addition of 3-(2-bromopropanoyl)-4-benzyloxazolidin-2-one to alkenes in the presence of Lewis acids (eq 27).[52] Interestingly, a high degree of long-range diastereoselectivity is realized in the reaction of a sugar-derived α-bromo ester with 1-hexene (eq 28).[53] This type of reaction has also been intensively studied with particular interest in the stereoselective construction of asymmetric centers via allylation[54,55] and cyclization (eq 29).[56] The successful stereocontrol achieved in these reactions reflects one advantageous property of Et_3B/O_2, namely, low-temperature initiation.

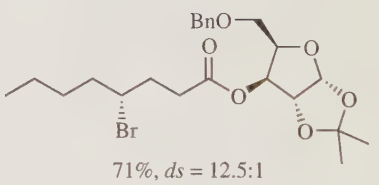




(27)

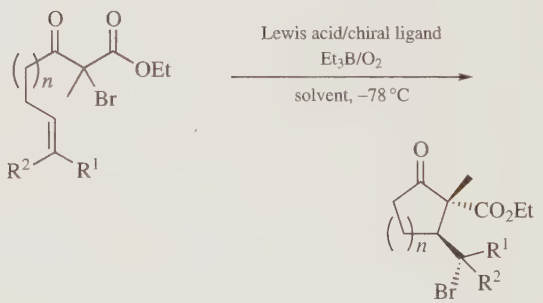
R:*S* = 96:4





(28)

71%, *ds* = 12.5:1



(29)

n = 1,2
60–80%
up to 95% ee

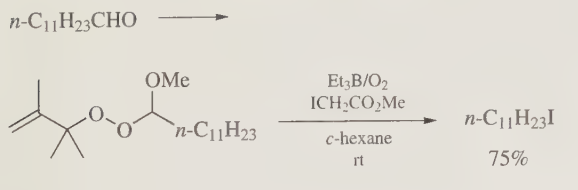
First Update

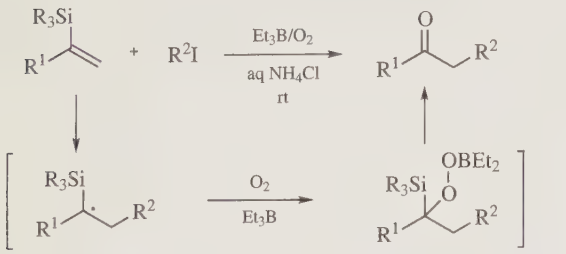
Takehiko Yoshimitsu
Meiji Pharmaceutical University, Tokyo, Japan

Triethylborane (Et_3B) rapidly undergoes autoxidation with molecular oxygen (O_2) to produce an ethyl radical that serves as a versatile free radical source. Et_3B/O_2 possesses several attractive features: efficient ethyl radical generation at low temperature (*e.g.*, −78 °C); Lewis acidity and oxophilicity of Et_3B; and compatibility with aqueous media. Accordingly, Et_3B and O_2 (often supplied as air) used in combination have a wide range of applications as an initiator and a chain carrier in radical reactions.[50]

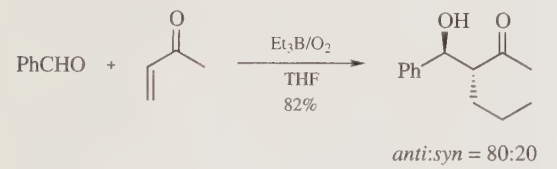
The Et_3B/O_2-induced atom transfer radical oligomerization of allyl iodoacetate and *N*-allyl- and *N*-(3-butenyl)iodoacetamides followed by deoligomerization provides a new route to functionalized lactones and lactams.[57] The decarbonylative transformation of aldehydes via the homolytic decomposition of unsaturated peroxyacetals is initiated with alkyl radical transfer from methyl

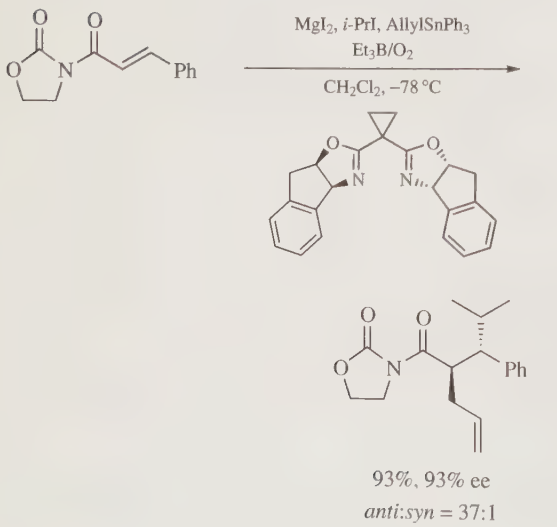
2-iodoacetate in the presence of Et_3B/O_2 (eq 30).[58] Alkynes such as trimethylsilylacetylene, ethyl propiolate, and phenylacetylene serve as suitable acceptors for alkyl radicals generated from alkyl iodides with Et_3B/O_2.[59] Under similar aerobic conditions, 2-silyl-1-alkenes react with alkyl iodide to provide ketones (eq 31).[60]



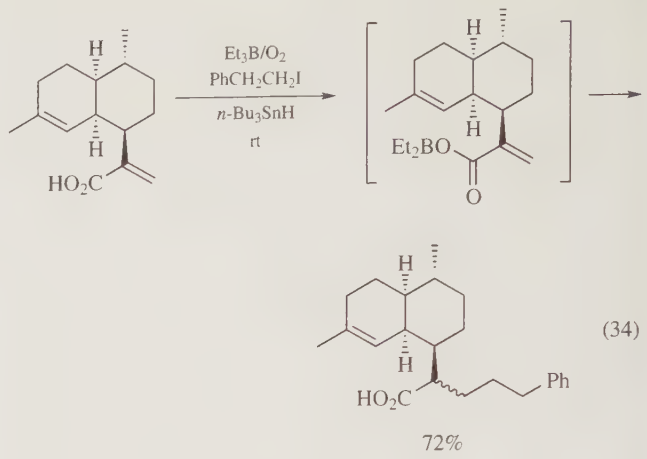


Conjugate Addition. Although the alkyl radical transfer from trialkylborane/O_2 to enones followed by aldolization is known,[61] the one-pot conjugate addition-aldol reaction is also possible (eq 32).[62] The success of the reaction is attributed to a chemoselective ethyl radical transfer to enones rather than aldehydes. The Lewis acid-promoted enantioselective conjugate addition of alkyl radicals generated from alkyl iodides to α,β-unsaturated amides proceeds under the Et_3B/O_2/*n*-Bu_3SnH condition.[63] The related methods are applied to the diastereoselective reaction,[64] the tandem C–C bond formation at the β and α centers (eq 33)[65] and the construction of contiguous γ/β[66] and γ/β/α centers.[67]

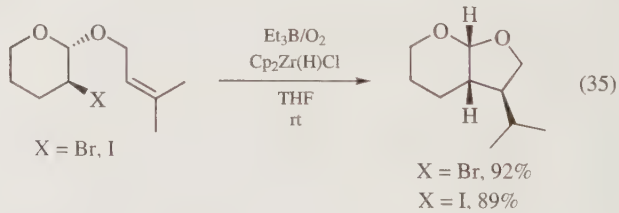


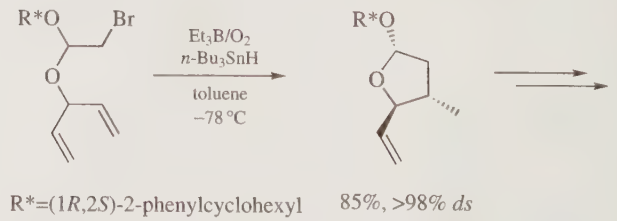


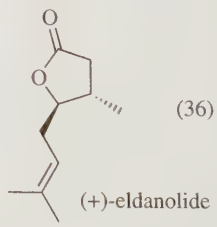
Various electron-deficient alkenes, such as α-sulfinylcycloalkenones,[68] 1-aryl-2,2-dicyanoethene,[69] and α,β-unsaturated carboxylic acids,[70] are compatible with the conjugate addition. In the last case, Et_3B enhances the reactivity of the radical acceptor owing to the formation of an acyloxydiethylborane intermediate (eq 34).



Stereoselective Radical Cyclizations, Cascade and Related Processes. Various reductive radical cyclizations are initiated with Et_3B/O_2/*n*-Bu_3SnH as well as tin-free combinations involving $Et_3B/O_2/Cp_2Zr(H)Cl$ (eq 35),[71] $Et_3B/O_2/HGaCl_2$,[72] $Et_3B/O_2/HInCl_2$,[72] Et_3B/O_2/tri-2-furanylgermane,[73] Et_3B/O_2/*N*-ethylpiperidinium hypophosphite (EPHP),[74] $Et_3B/O_2/Ph_4Si_2H_2$,[75] and Et_3B/O_2/phosphinic acid.[76] Excellent diastereoselectivity is obtained at −78 °C for the Et_3B/O_2/*n*-Bu_3SnH-induced radical cyclization of bromo acetal, whereas the selectivity decreases under thermal initiation conditions (*n*-Bu_3SnH/AIBN/80 °C) (eq 36).[77] Analogous cyclizations have led to the stereoselective construction of prostaglandin,[78] indolizidine,[79] pamamycin-607,[80a] and acetogenin[80b] frameworks.

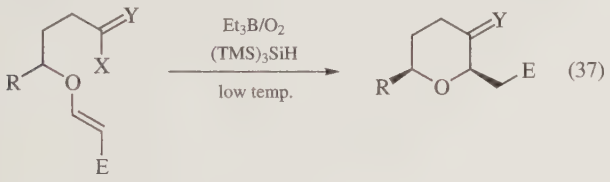






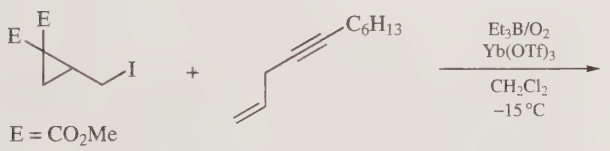
The intramolecular addition of an acyl radical to vinylogous carbonates and sulfonates under the $Et_3B/O_2/(TMS)_3SiH$ condition stereoselectively produces five-, six-, seven-membered cyclic

ethers (eq 37).[81a,b] The reagent system that enables low-temperature initiation has been proven to be crucial to suppressing the decarbonylation of acyl radical intermediates. The stereoselectivity in the radical cascade approach to benzo[*a*]quinolizidines is also significantly improved under low-temperature conditions using Et_3B/O_2/*n*-Bu_3SnH.[82] The cascade reaction of functionalized 1,5-enynes effectively affords polycyclic heteroannular systems possessing quaternary centers.[83] The atom transfer radical cascade reaction of 1,4-dienes and 1,4-enynes with 2-(iodomethyl)cyclopropane-1,1-dicarboxylate, a homoallyl radical precursor, is promoted by Et_3B/O_2 (eq 38).[84] Indole derivatives possessing labile functional groups can be synthesized under mild conditions by the cyclization of 2-alkenylthioanilides using Et_3B/O_2/*n*-Bu_3SnH (eq 39).[85] The Et_3B/O_2 combination successfully initiates the tin- or silane-mediated cyclization of such thermally unstable substrates as propargyl bromide flanked by the (alkynyl)-$Co_2(CO)_6$ unit (eq 40).[86]

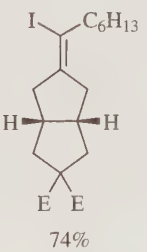


(37)

X = Br, SePh
Y = O, H_2, CH_2
E = SO_2Ph, CO_2Me

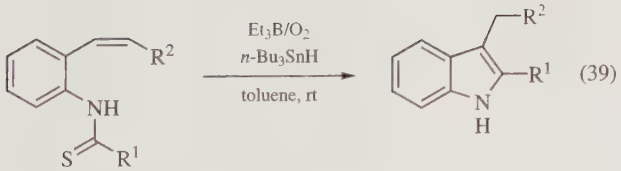


E = CO_2Me



(38)

74%



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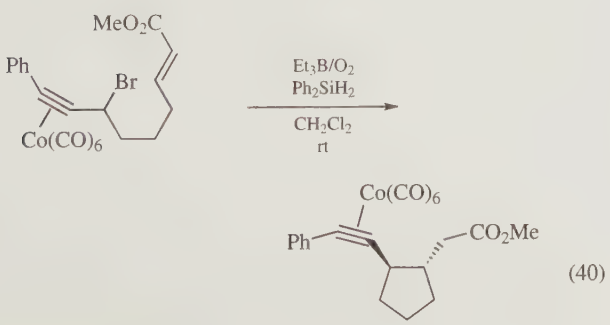
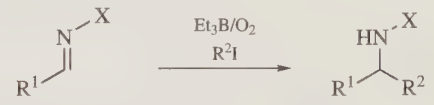
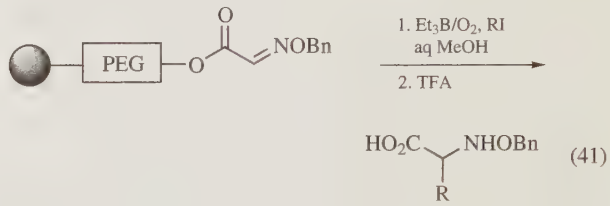


(40)

Radical Addition to Imines. The addition of carbon radicals to imine derivatives has been intensively studied and the effectiveness of Et_3B/O_2 as a radical promoter has been demonstrated. The chemistry involves the intermolecular radical addition of alkyl iodides to oxime ethers, hydrazones, aldimines, and glyoxylic nitrones (eq 41).[87–91] The stannyl radical addition-cyclization of alkenyl oxime ethers can be conducted by using Et_3B/O_2/*n*-Bu_3SnH to provide functionalized pyrrolidines.[92] It has been shown that Et_3B/O_2 is applicable to solid-phase organic synthesis.[93]

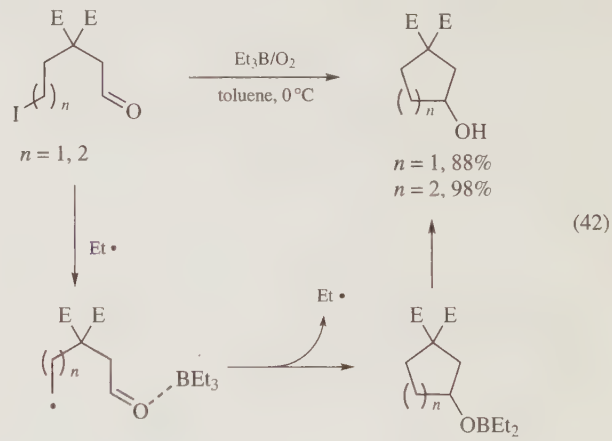


X=OR, NR_2, alkyl, etc.



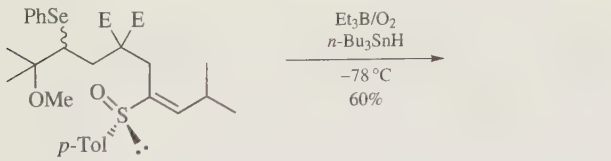
(41)

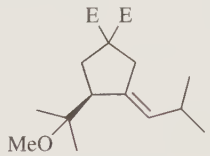
Radical Addition to Carbonyl Groups. Because of the Lewis acidity and the oxophilicity of Et_3B, oxyradical intermediates are efficiently captured by Et_3B to promote the intramolecular addition of alkyl radicals to aldehydes.[94–96] This method has been extended to tin-free chemistry: the cyclization of δ- and ω-iodoaldehydes in the absence of *n*-Bu_3SnH efficiently affords cycloalkanols (eq 42).[96]



(42)

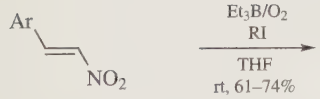
Radical Substitution. At low temperature, Et_3B/O_2 in combination with *n*-Bu_3SnH makes possible the sequential radical cyclization/elimination of chiral sulfoxides to selectively provide cyclopentane derivatives (eq 43).[97] *trans*-β-Alkylstyrenes are synthesized via the radical substitution of β-nitrostyrenes with alkyl radicals generated from alkyl iodides with Et_3B/O_2 (eq 44).[98] Electron-rich aromatic compounds, such as pyrrole, furan, and thiophene, undergo homolytic aromatic substitution with α-halo esters under the Et_3B/O_2 condition (eq 45).[99] In the latter two heteroaromatics, $Fe_2(SO_4)_3 \cdot H_2O$ is necessary for efficient aromatization.





(43)

54% ee



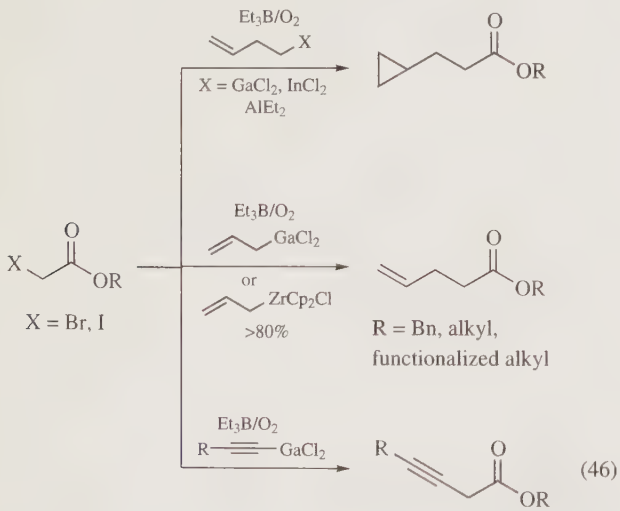
(44)

R = 2, 3° alkyl

(45)

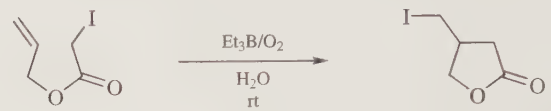
X=NH, 47%
X=O, 60%
X=S, 56%
} [with Fe(III)]

Et_3B/O_2-Induced Reaction with Organometallic Reagents. α-Halo carbonyl compounds are efficiently allylated with allylzirconium[100] and allylgallium reagents[101] and cyclopropanated with homoallylic gallium, indium, and aluminum reagents[102] in the presence of Et_3B/O_2 (eq 46). Alkynyl gallium species also react with α-halo carbonyl compounds under the same conditions to afford α-alkynylated carbonyl compounds.[103] The initiation with Et_3B/O_2 is crucial for the successful alkynylation.



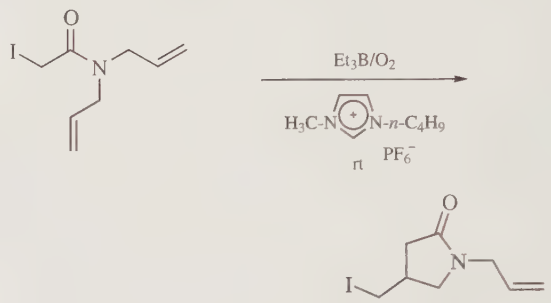
(46)

Radical Reactions in Aqueous and Ionic Liquid Media. Et_3B/O_2 is of considerable interest to scientists in the field of environmentally benign chemistry. As Et_3B/O_2 is a good source of ethyl radicals even in such protic solvents as water and alcohols, the system has found significant applications in aqueous reactions.[104] The Et_3B/O_2-induced radical addition of α-iodo-γ-butyrolactone[105] and ethyl bromoacetate[106] to alkenes and alkynes can be conducted in water. Interestingly, Et_3B/O_2 initiates the atom transfer radical cyclization of allyl iodoacetate even in trifluoroacetic acid.[107] The Et_3B/O_2-induced radical allylation of α-halo carbonyl compounds in aqueous media using allylgallium reagents[101] as well as the atom transfer lactonization (eq 47)[108] and lactamization[109] takes place efficiently. The Et_3B/O_2 system has proven to be compatible with ionic liquids for initiating the atom transfer cyclization (eq 48)[110] and hydrostannylation of alkynes.



(47)

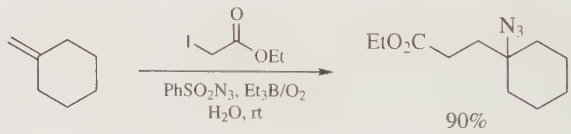
67% (no reaction in PhH)



(48)

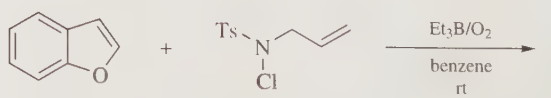
85%

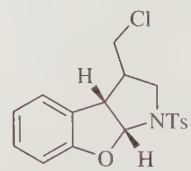
Radical C–N Bond Formation. The radical carboazidation of alkenes and the azidation of alkyl iodides in water are initiated with Et_3B/O_2 (eq 49).[111] These methods are environmentally friendly and highly efficient. Nitrogen-centered radicals generated from *N*-allyl-*N*-chlorotosylamide (eq 50)[112] and *N,N*-dichlorobenzenesulfonamide (dichloramine-B)[113] with Et_3B/O_2 undergo addition reactions with alkenes and 1,3-dienes. Treatment of *N*-tosyliodoaziridine derivatives with Et_3B/O_2 produces azahomoallyl radicals that undergo iodo transfer [3+2] cycloaddition reactions with electron-rich alkenes such as enol ethers to provide pyrrolidine derivatives (eq 51).[114]



(49)

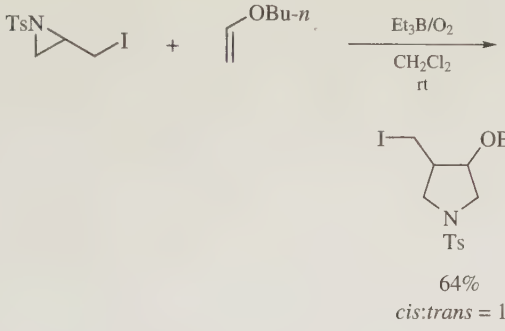
90%





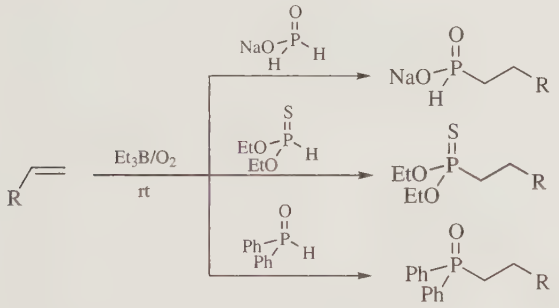
(50)

82%
endo:*exo* = 83:17



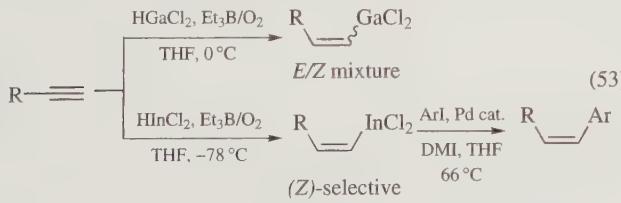
(51)

C–P Bond Formation. Phosphorus-centered radicals are generated from hypophosphite,[115] diethyl thiophosphite,[116,117] and diphenylphosphine oxide[118] with Et_3B/O_2 (eq 52). These radicals undergo facile addition reactions with alkenes to provide monosubstituted phosphinic acids, phosphonothioates, and functionalized diphenylphosphine oxides, all of which are highly versatile compounds.



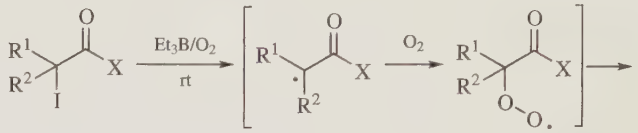
(52)

C–Si, C–Ga, and C–In Bond Formation. The hydrosilylation of alkynes with various organosilanes, which is similar to hydrostannylation,[45] hydrogermylation,[44] and thiolation[47a] under the Et_3B/O_2 condition, provides synthetically useful organosilanes.[119] In addition to Ph_3GeH,[44] tri-2-furanylgermane in the presence of Et_3B/O_2 undergoes radical addition reactions with internal and terminal alkenes at room temperature.[120] The Et_3B/O_2-induced hydrogallation and hydroindation of C–C multiple bonds enable novel access to organogalliums and organoindiums (eq 53).[121] In these reactions, several functionalities are found intact and the resulting organogallium and organoindium species are compatible with various transformations involving addition to electrophiles and Pd-mediated cross-coupling reactions. The hydrogallation, however, shows lower *(Z)*-selectivity than the hydroindation, due to isomerization.

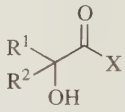


(53)

C–O Bond Formation. The treatment of α-iodocarboxylic acid derivatives with Et_3B/O_2 provides the corresponding α-hydroxy acid derivatives (eq 54).[122] This process involves iodine atom abstraction with an ethyl radical from Et_3B/O_2 and subsequent oxygenation with molecular oxygen. Et_3B serves as an initiator, a chain carrier, and a reducing agent in this reaction. 9-(Iodomethyl)anthracene is also oxygenated in a similar way.[123]



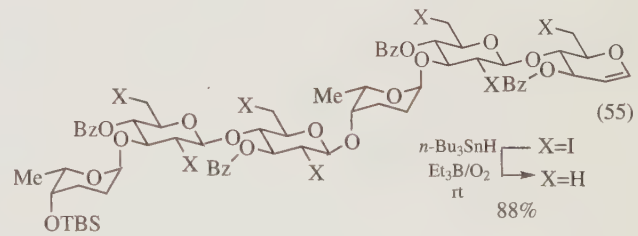
X = OR, NR_2, SR



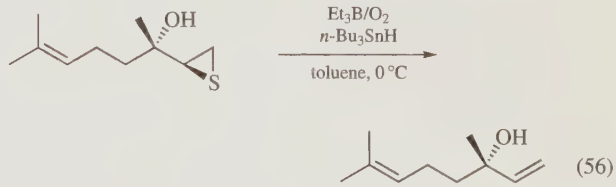
(54)

69–98%

Reduction. A large number of alkyl iodides and bromides are easily reduced at ambient or low temperature with *n*-$Bu_3SnH/Et_3B/O_2$, and this method is widely used. For instance, the polyhalogenated compound is reduced to furnish the hexasaccharide motif of landomycin A (eq 55).[124] As the alternatives to tin reagents, $(TMS)_3SiH$,[125] $HGaCl_2$,[72] $HInCl_2$[72] $Ph_4Si_2H_2$,[126] and tri-2-furanylgermane[73] in combination with Et_3B/O_2 are also effective in reducing organic halides. The catalytic use of tri-2-furanylgermane in the presence of $NaBH_4$ is possible. Using *n*-$Bu_3SnD/Et_3B/O_2$, deuterium-labeled compounds are readily obtained via radical reduction.[127] Thiirane is efficiently converted into an alkene at 0 °C under the Et_3B/O_2/*n*-Bu_3SnH condition (eq 56).[128] The dual role of Et_3B as a radical initiator and an in situ derivatization agent that directs the diastereochemical course of the reduction has been presented (eq 57).[129] A similar approach to the divergent synthesis of *syn*- and *anti*-propionate motifs is also known.[130] The compatibility of Et_3B with an aqueous environment makes possible the use of hydrophilic organosilanes as reducing agents. Alkyl iodides, bromides, and aryl iodides are thus reduced by this system (eq 58).[131]



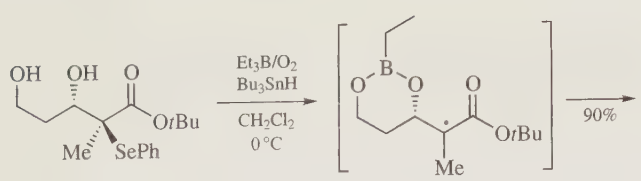
(55)

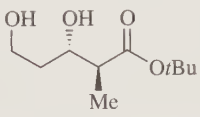


(56)

(+)-linalool

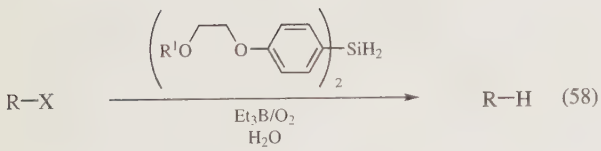
84%





(57)

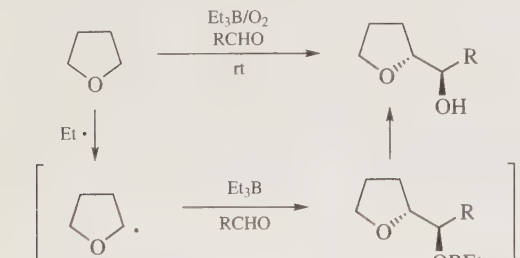
anti:syn = 20:1



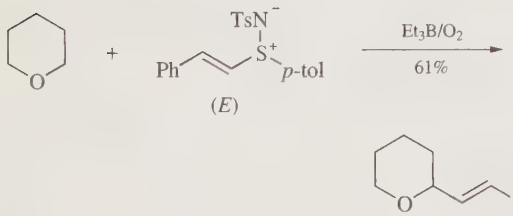
(58)

R^1 = H, Me, CH_2CH_2OMe

C–H Functionalization. Et_3B/O_2 serves as a direct or an indirect mediator of the C–H bond functionalization of organic molecules. For instance, Et_3B/O_2 promotes the diastereoselective α-C–H hydroxyalkylation of THF with aldehydes (eq 59).[132a] The continuous admission of air to the reaction mixture is crucial for the successful transformation, although the same reaction can be carried out using Et_3B/*tert*-butyl hydroperoxide.[132b] Et_3B/O_2 is also used for the alkenylation of a tetrahydropyran with unsaturated sulfimides (eq 60).[133] The analogous addition of THF[134a] and cyclohexane[134b] to aldimines under the Et_3B/O_2 condition provides aminoalkylated compounds.

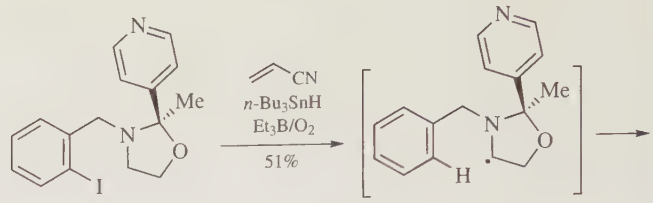


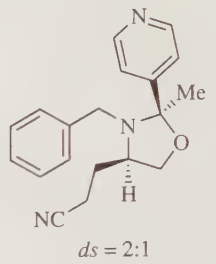
(59)



(60)

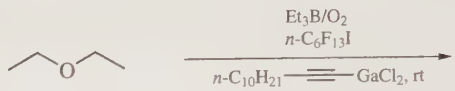
The indirect C–H functionalization α to the nitrogen of an *N,O*-acetal via radical translocation provides α-alkylated ethanolamine derivatives (eq 61).[135] The Et_3B/O_2 initiation gives rise to a clean reaction without having to conduct a tediously slow addition of the tin reagent. The treatment of perfluoroalkyl iodide with alkynyl gallium reagent in the presence of Et_3B/O_2 affords an α-alkynylated ether derivative (eq 62).[103] In this reaction, a highly electrophilic perfluoroalkyl radical produced in situ undergoes hydrogen abstraction α to the ethereal oxygen.

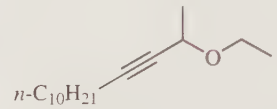




(61)

ds = 2:1





(62)

Second Update

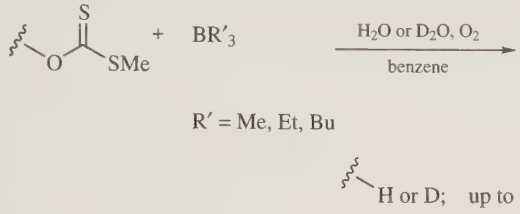
John L. Wood & Laura Nicole Schacherer
Yale University, New Haven, CT, USA

Radical Deoxygenation via Complexation with Water. It has been recently reported that triethylborane (see also trimethylborane and tributylborane) reacts with water, and produces Lewis acid–base complexes. These adducts were demonstrated to have significantly altered bond dissociation energies of the O–H bond in H_2O, such that the complexes act as good hydrogen-atom donors in the presence of radicals.[136] This was demonstrated experimentally by the Barton–McCombie type deoxygenation of primary, secondary and tertiary bridgehead xanthates using only trialkylboranes, water (or D_2O), and O_2 to access protio- or deuteroalkanes in excellent yield and deuterium incorporation. The mechanism of this reaction invokes the chemistry of trialkylboranes in two ways: first as a radical initiator via homolytic reaction with molecular oxygen, and secondly via the trialkylborane complex with water that ultimately acts as a hydrogen-atom donor with the xanthate-derived radicals (eq 63). The combination of triethylborane, water, and air can thus function as an alternative to toxic tin hydrides (see also Bu_3SnH).

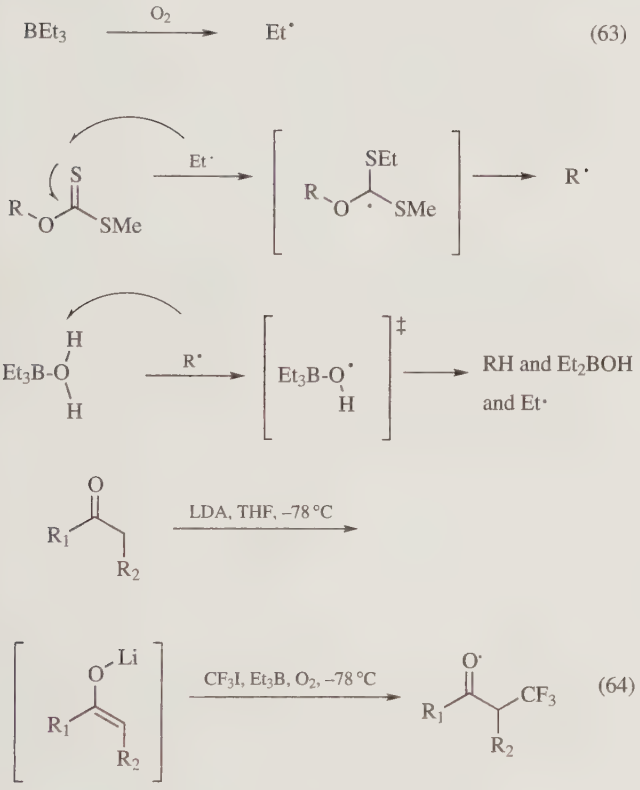
Radical Trifluoromethylation of Lithium Enolates. Triethylborane can be used as a radical initiator with trifluoromethyl iodide to produce trifluoromethyl radicals via halogen-atom transfer.[137] These electrophilic trifluoromethyl radicals react nearly instantaneously with lithium enolates (produced from reaction of ketones with LDA) to provide the α-trifluoromethylated ketones in good yield (eq 64).[138]

Substituted Sulfonium Ylides. While triethylborane reacts with sulfur ylides to provide polymers, it has been shown that

reaction with substituted sulfonium ylides and LiHMDS yields substituted organoboranes (eq 65). The reaction with chiral sulfonium ylides provides a new method to access chiral organoboranes. These can be further elaborated to give chiral alcohols or amines with excellent enantioselectivity.[139]

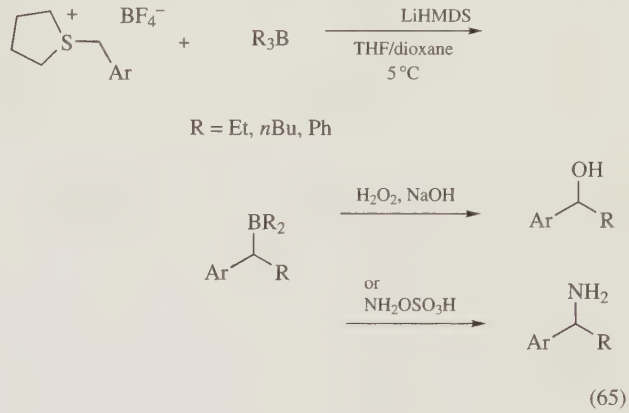


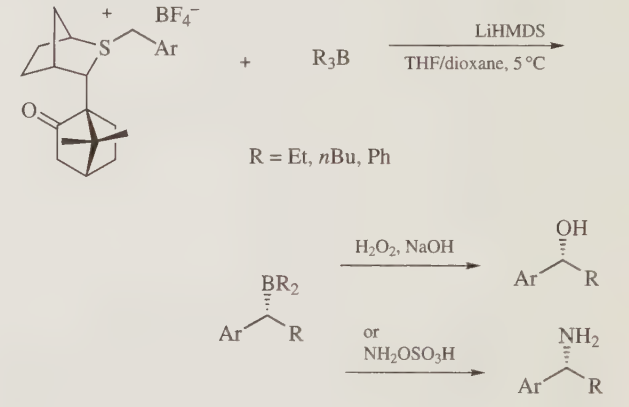
Mechanism:



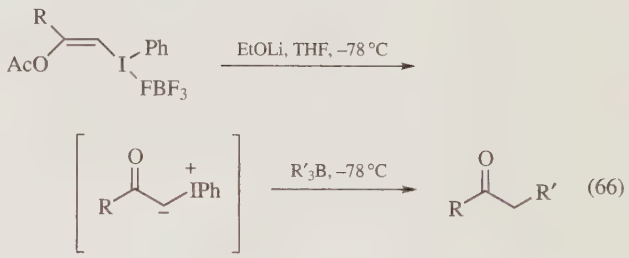
Unstabilized Iodonium Ylides. Unstabilized iodonium ylides (generated from EtOLi, eq 66) react with triethylborane (as well as other trisubstituted boranes) to initially produce a boron ate complex. Subsequent 1,2-alkyl migration from boron and hydrolysis of the α-boryl ketone gives the mono-alkylated ketone in good yield.[140] While the α-boryl ketones cannot be isolated, they can be utilized in situ for aldol reactions at low temperature.

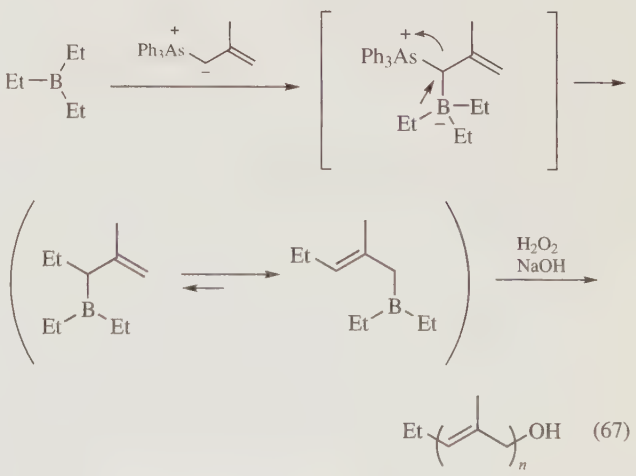
Polymerization with Ylides. Triethylborane also reacts with methallyltriphenylarsonium ylides to produce an ate complex, and as 1,2-ethyl migration from boron occurs, triphenylarsine is lost.[141] However, a [1,3] sigmatropic rearrangement then occurs to produce the more substituted olefin and less-hindered organoborane (eq 67). Polymerization continues until all arsonium ylide is consumed, producing three-carbon extended polymers. It has also been reported that triethylborane is one of many triorganoboranes that can be polymerized with dimethylsulfoxonium methylide.[142] This highly efficient polymerization also proceeds via an ate complex and 1,2-alkyl migration (eq 68).

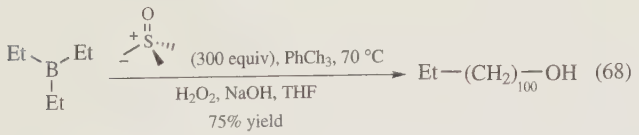




product yield: > 68%
product ee: > 95%

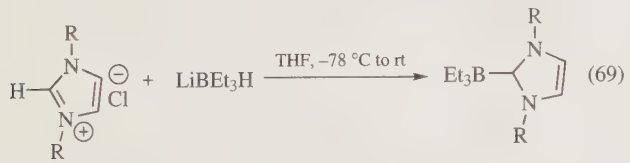






(68)

Lithium Triethylborohydride with *N*-Heterocyclic Carbene. *N*-Heterocyclic carbenes can be accessed from the imidazolium salts with the use of base. However the treatment of these salts with lithium triethylborohydride results in the formation of an *N*-heterocyclic carbene adduct that can be isolated and characterized (eq 69).[143] The mechanism involves first deprotonation of the imidazolium salt, followed by complexation of the resulting carbene with triethylborane. These adducts have been shown to be efficient at transferring *N*-heterocyclic carbene ligands to metal centers.[144]

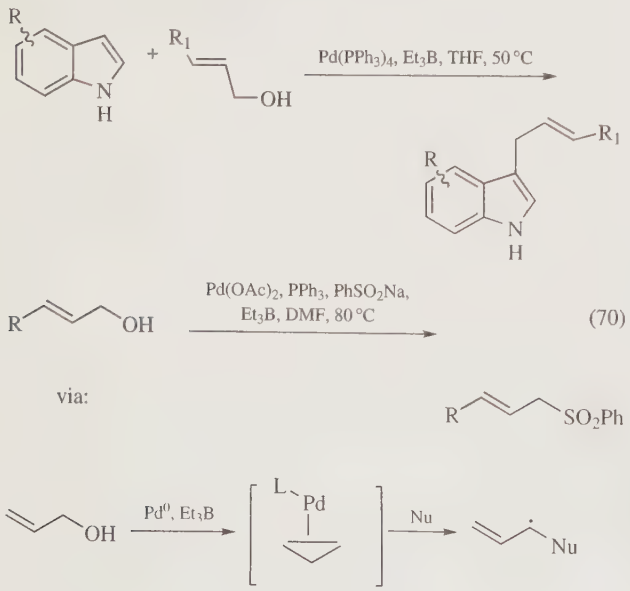


(69)

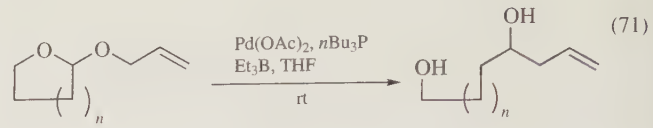
R = *i*Pr
R = Mes

Yield: 80%, 46%

Pd-catalyzed Activation of Allyl Alcohols with Triethylborane. A number of reports focus on the palladium-catalyzed activation of allylic alcohols with triethylborane. These reports involve the allylation of either heteroaromatics or other nucleophiles (eq 70), possibly via a π-allylpalladium species.[145] As shown in eq 71, however, the putative π-allylpalladium species can also be intercepted in an intramolecular sense to access allylated aldehydes from tetrahydrofuranyl or tetrahydropyranyl allyl ethers.[146] The mechanistic role of the triethylborane in these reactions is not proven, but is necessary and may include Lewis-acid activation of the allyl alcohol. Similarly, in an example of amphiphilic activation of a bis-allyl alcohol, Pd-catalysis and triethylborane activation is used in a two-step process to first electrophilically and then nucleophilically allylate an aldehyde to provide ultimately secondary alcohols (eq 72).[147]

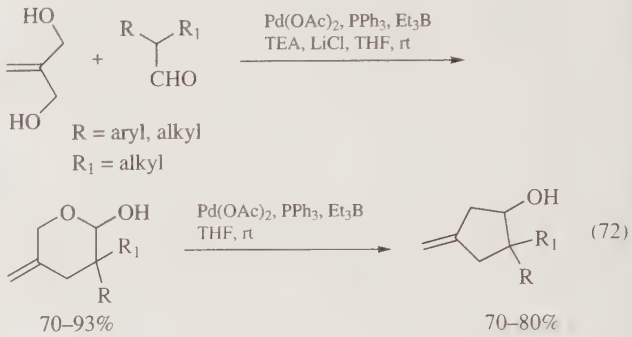


(70)



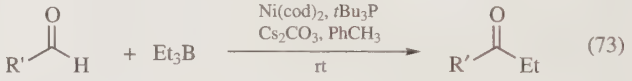
(71)

$n = 2$; yield = 86%
$n = 1$; yield = 56%



(72)

Nickel-catalyzed Processes with Triethylborane. The alkylation of aldehydes was reported using triethylborane and nickel catalysis (eq 73).[148] While triethylborane has been used in conjunction with nickel-mediated processes previously, this is the first example of a metal-catalyzed 1,2-addition of trialkylboranes to aldehydes. The mechanism of this reaction may involve an η^2-coordinated nickel complex.



(73)

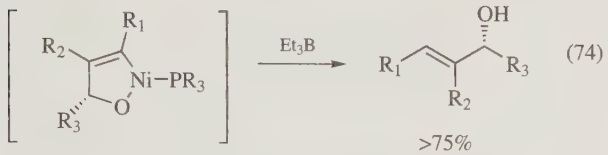
R′ = alkyl, aryl

It was demonstrated in 1998 that catalytic nickel, in conjunction with triethylborane, results in the homoallylation of benzaldehyde.[149] The triethylborane appeared to be acting as a reducing agent, as the borane was necessary for the reductive coupling to occur. Since that time, a number of nickel-catalyzed reductive couplings utilizing triethylborane have been reported including: asymmetric coupling of alkynes and aldehydes,[150] alkynes and α-oxy-aldehydes,[151] alkynes and epoxides,[152] asymmetric coupling of enynes and ketones,[153] as well as epoxides and aldehydes with either nickel or rhodium catalysis.[154] In the case of the reductive coupling between alkynes and aldehydes or ketones, the mechanism is believed to invoke an oxametallocyclopentene intermediate (eq 74), which is reduced by the triethylborane. Couplings between alkynes and epoxides follow a different course in that epoxide ring opening occurs first via oxidative addition, accessing a oxametallacyclobutane, which then cyclizes onto the alkynes. The oxametallocyclohexene (eq 75) that results is then reduced with triethylborane as shown, and β-hydride elimination provides the product alcohols.

Exploring the chemistry of the nickel-catalyzed oxidative addition into epoxides led to the exploration of the coupling of epoxides with electrophiles such as aldehydes. It was found that both catalytic nickel or Wilkinson's catalyst and triethylamine could be used with triethylborane to effect this reductive

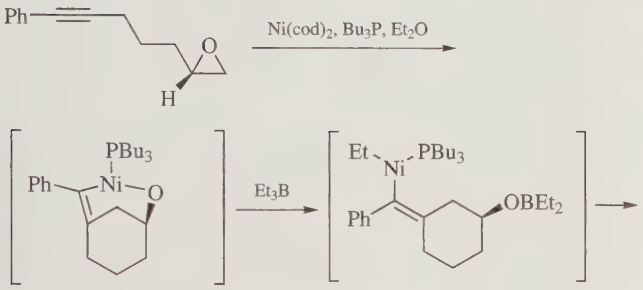
coupling. In this case, however, it is believed that the triethylborane simply serves to produce Et_2BCl in situ (eq 76).

R_1 = aryl R_2 = alkyl, substituted alkyl
R_3 = alkyl, aryl



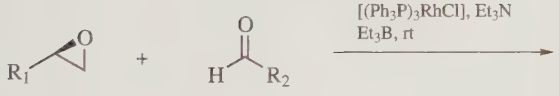
(74)

>75%
>80% ee



(75)

45%



R_1 = alkyl (1°, 2°, 3°), aryl
R_2 = aryl, heteroaryl

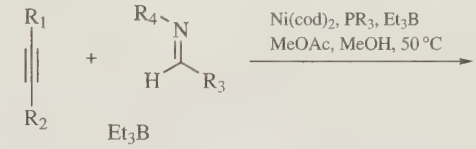
(76)

12–96%

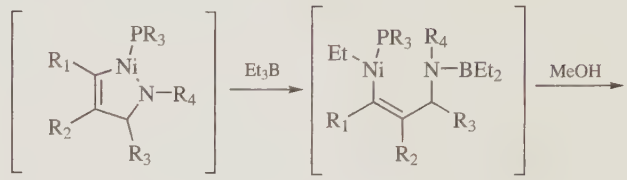
Nickel-catalyzed three component couplings of alkynes, imines and triethylborane have also been reported. The reaction affords allylic amines via a putative azametallocyclopentene intermediate (eq 77).[155] Similar to the reductive coupling of alkynes and aldehydes (eq 74), this intermediate is also reduced with triethylborane.

This use of triethylborane differs from the reductive couplings of alkynes and aldehydes (eq 74) only in that coordinating solvents prevent β-hydride elimination. Therefore reductive elimination from nickel is instead observed, resulting in ethyl incorporation into the allylic amine products. An asymmetric version of this reaction has also been reported.[155]

Related Reagents. B-allyl-9-borabicyclo 3.3.1 nonane; crotyldimethoxyborane; di-*n*-butylboryl trifluoromethanesulfonate; lithium triethylborohydride; potassium tri-*s*-butylborohydride.



R_1 = aryl, alkyl
R_2 = alkyl
R_3 = aryl, alkyl
R_4 = alkyl



(77)

30–96%

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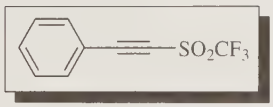
Trifluoromethyl Sulfonyl Ethynyl Benzene[1]



[52843-77-3] $C_9H_5F_3O_2S$ (MW 234.19)

(reactive dienophile, Michael acceptor, precursor to substituted vinyl sulfones, alkynylating agent)

Alternate Name: phenyl(trifluoromethanesulfonyl)acetylene; phenylethynyl trifluoromethyl sulfone.

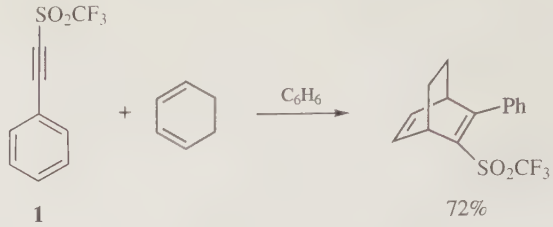
Physical Data: mp 29.0–31.5 °C; bp 57–62 °C (0.1 mm Hg).

Preparative Methods: originally prepared by treatment of the lithium salt of phenylacetylene with trifluoromethanesulfonic (triflic) anhydride.[2] The corresponding sodium acetylide provides the title compound in higher yield.[3] Addition of the lithium salt to triflic anhydride (inverse addition) limits the production of unwanted by products.[4] Typical isolated yields are ~75%.

Purification: vacuum distillation; column chromatography (SiO_2).

Handling, Storage, and Precautions: moisture sensitive; thermally labile.

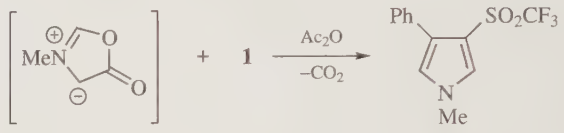
Cycloaddition Reactions. The trifluoromethylsulfonyl group is a powerful electron withdrawing substituent. Consequently, acetylenic trifluoromethyl sulfones (triflones) are activated toward reactions typical of electron deficient alkynes. Treatment of phenylethynyl trifluoromethyl sulfone (**1**) with conjugated dienes results in facile Diels–Alder cycloaddition.[2] Cyclopentadiene, 1,3-cyclohexadiene (eq 1), and 1,3-diphenylisobenzofuran, all give the reaction in good yield.



(1)

1 72%

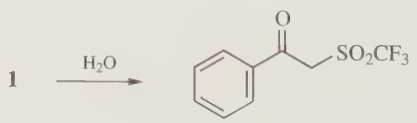
Kinetic experiments indicate that triflone **1** is a more reactive dienophile than dimethylacetylene dicarboxylate. The mesoionic intermediate **2** generated from *N*-formyl glycine and acetic anhydride reacts with **1** in a [3 + 2] fashion. The substituted pyrrole is obtained after loss of CO_2 (eq 2).[5]



(2)

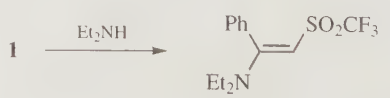
2 81%

Conjugate Addition Reactions. The electron withdrawing ability of the trifluoromethyl sulfonyl group renders triflone **1** particularly susceptible to the reaction with nucleophiles via conjugate addition. This property is also responsible for the moisture sensitivity of **1** as the reaction with H_2O affords the α-sulfonyl ketone **3** (eq 3).[3,6] Other nucleophiles, such as amines and alcohols, react with **1** to afford the corresponding enamines and enol ethers. The *E*-configured vinyl triflone isomers are the major or exclusive products (eq 4).[3,6] Reaction of **1** with other nucleophiles (benzoic acid, potassium phthalimide) gives *Z*-vinyl triflone products. Organocuprates and organocopper reagents also give the reaction.[7] Fuchs and co-workers have used acetylenic triflone **1** as a precursor of substituted vinyl halides.[4,6] Such vinyl halides proved to be suitable participants in palladium-catalyzed Stille-type cross-coupling reactions. Addition of HX (X = halide) across the alkynyl triple bond initially affords the *Z*-triflone **4** stereoselectively and in high yield. Isomerization of the alkene can then be effected under photochemical conditions to give *E*-triflone **5** (eq 5). Both **4** and **5** can be converted to more highly substituted vinyl triflones via application of standard cross-coupling reaction protocols.



(3)

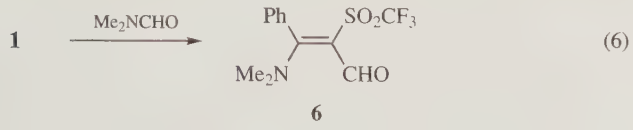
3



(4)

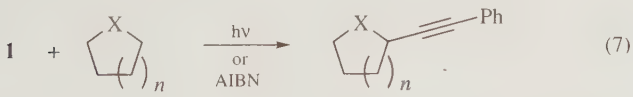
The initial product of conjugate addition to **1** is a sulfonyl-stabilized vinyl anion. This species can participate in subsequent reactions, particularly if an electrophilic center is present on the

original nucleophilic moiety. An example of this reaction manifold is illustrated in eq 6.[8] Dimethylformamide is believed to serve first as a nucleophile in the conjugate addition to triflone **1**. The formamide then acts as an internal formylating agent leading to the production of **6**. The amphiphilic reactivity of **1** has also been exploited in the preparation of various heterocyclic ring systems.[9,10]



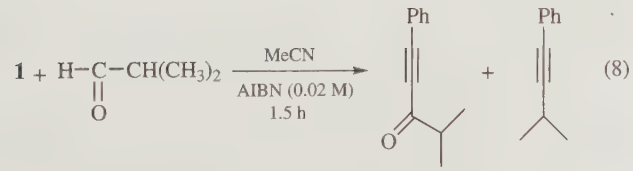
6 (6)

Alkynylation of C-H Bonds. Perhaps the most intriguing reaction of acetylenic triflones (including **1**) involves the alkynylation of C-H bonds via a radical chain mechanism.[11] The reaction is initiated by light or traditional radical initiators (e.g., AIBN). The mechanism is believed to entail abstraction of a hydrogen atom from an unactivated C-H bond by the extremely electrophilic trifluoromethyl radical. The resulting alkyl radical then adds to triflone **1**, formally at the α-carbon, to generate a vinyl radical that collapses to an alkyne with concomitant loss of SO_2 and the chain propagating trifluoromethyl radical. Mechanistic studies have ruled out the intermediacy of vinylidene carbenes.[12] The reaction is of broad scope and a number of cyclic and acyclic hydrocarbons, ethers, and sulfides are regioselectively alkynylated in high yield (eq 7).[11] The reaction has proven suitable for the functionalization of crown ethers.[13] For transformations that require the use of a solvent, 1,2-dichloroethane and acetonitrile have given satisfactory results. It is noteworthy that heteroatom substituted vinyl triflones (readily prepared from **1** via conjugate addition—vide supra) are also effective alkenylating agents toward unactivated substrates (e.g., THF, cyclohexane).[6] Aldehydic C-H bonds are susceptible to alkynylation by **1** as well. Again, a radical chain mechanism has been proposed to account for this transformation. Mixtures of ethynyl ketone (major) and the corresponding decarbonylated (minor) products are usually obtained (eq 8).[14] The aldehydic C-H bond present in formate esters is unreactive under these conditions.



(7)

X = O, n = 1 (88%)
X = O, n = 2 (88%)
X = CH_2, n = 1 (63%)
X = CH_2, n = 2 (83%)



(8)

2.3:1.0
88%

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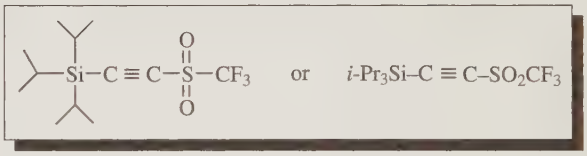
Triisopropylsilylethynyl Triflone



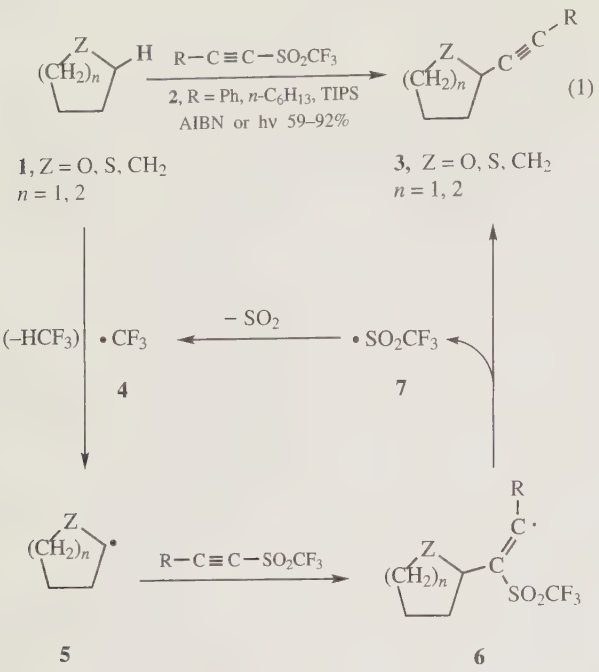
[196789-82-9] $C_{12}H_{21}F_3O_2SSi$ (MW 314.44)

(reagent for radical alkynylation of C–H or C–I bonds)

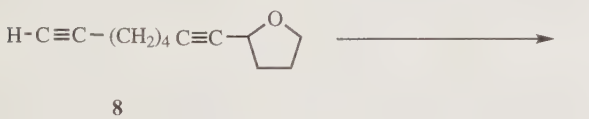
Alternate Name: TIPS-acetylene triflone or TIPS-ethynyl triflone.
Solubility: most aprotic organic solvents.
Form Supplied in: colorless liquid not commercially available.
Analysis of Reagent Purity: reagent must be made fresh.
Handling, Storage, and Precautions: sensitive to free radical sources.

Only two recent papers[1,2] have described this reagent, which is used for free radical initiated alkynylation. In the first paper, the direct alkynylation of C–H bonds proceeds as summarized in eq 1 by the facile C–H bond abstraction by the very electrophilic trifluoromethyl radical **4** generated by cleavage of the CF_3SO_2 radical (**7**) and loss of SO_2. The alkyl radical **5** so generated reacts with the triflone reagent **2** to form the vinyl radical (**6**) which in turn eliminates the SO_2CF_3 radical (**7**) to propagate the chain and afford the attached alkynyl group in **3**.

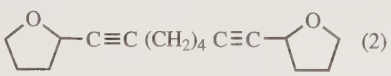
The TIPS variant in eq 1 is used not only neat on the cyclic C–H substrates THF, tetrahydrothiophene, and cyclohexane, but also in acetonitrile with adamantane, which substituted exclusively at the tertiary C–H (50% yield). Alkynylation was also successful with distal functionality, i.e. R = $(CH_2)_2OSiR_3$ and $(CH_2)_3Cl$, but the triflone could not be formed with ether functionality closer to the acetylene.



Previously, the alkynylation had been reported[3,4] with other attached hydrocarbon groups (R = Ph and *n*-hexyl in eq 1). The presence of a second acetylene group in the hydrocarbon group R was successful only with four methylenes, but not fewer, separating the two acetylenes. However, with enough separation the outer acetylene succeeded with only H-substitution to yield **8** in eq 2 and the product could be carried through triflation and a second alkynylation to form **9**.



8

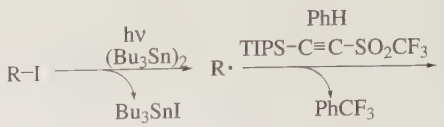


9

The necessary silyl triflone reagents proved difficult or impossible to make with less hindered silanes (TMS or TBDMS) by the reaction of the silyl-acetylene anion (*n*-BuLi/Et_2O/−78 °C) with Tf_2O. It was this triflation which failed with the proximal ethers and substituted acetylenes above.

In the second paper,[2] the reaction was extended to alkynylate C–I bonds photolytically by the added intermediacy of hexabutyldistannane to generate the radical from the iodide. Bromides were inert in this alkynylation, suggesting that this differential reactivity of the two halogens should prove advantageous in synthetic applications.

The reaction outlined in eq 3, was conducted photolytically in benzene solution, with the benzene presumably scavenging the trifluoromethyl radical, as it is scavenged in eq 2. A dozen examples of iodides were successful in yields generally over 60% and with retention of configuration. These room-temperature examples show the reaction to be compatible with such diverse functionality as free hydroxyl, ester, amide, thiazole, and potential β-elimination substrates, and succeeded with primary, secondary, and tertiary iodides.



The special value of the TIPS group lies in its easy removal (TBAF/25 °C/2 h) to make the acetylene available for further substitution. Furthermore, the present availability of the TIPS-protected acetylene triflone should make possible a further exploration of the addition and cycloaddition reactions of the acetylene activated by the strong electron-withdrawing power of the triflone group.

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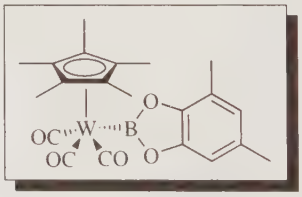
Tungsten(II) Tricarbonyl(4,6-dimethyl-1,3,2-benzodioxaborol-2-yl)[(1,2,3,4,5,-η)-1,2,3,4,5-pentamethyl-2,4-cyclopentadien-1-yl)



[193952-55-5] $C_{21}H_{23}BO_5W$ (MW 550.11)

(transition metal boron reagent[1–3] for stoichiometric borylation of alkanes and arenes under photochemical conditions)

Alternate Name: tricarbonyl(3,5-dimethylcatecholatoboryl)(η^5-pentamethyl-2,4-cyclopentadien-1-yl)tungsten.

Solubility: soluble in hydrocarbon solvents.

Form Supplied in: amber crystalline solid.

Analysis of Reagent Purity: ^{1}H NMR (C_6D_6) δ 6.83 (s, 1H), 6.49 (s, 1H), 2.30 (s, 3H), 2.13 (s, 3H), 1.82 (s, 15H); ^{11}B NMR (pentane, BF_3·OEt_2) δ 53.

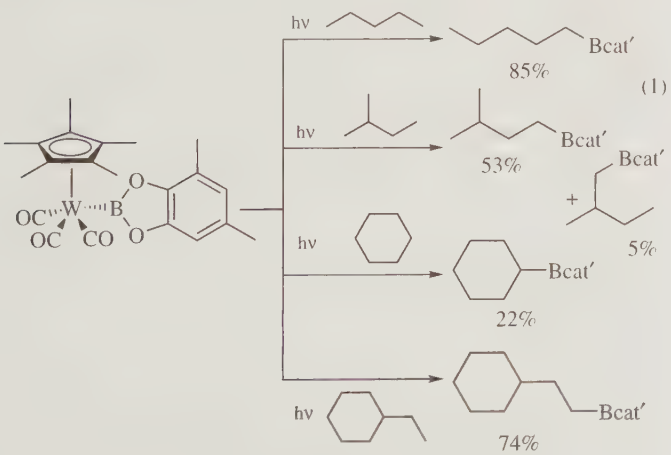
Preparative Methods: addition of ClBcat(Me_2) in pentane to a pentane suspension of NaCp*W(CO)$_3$ at ambient temperature followed by filtration, concentration, and crystallization at −30 °C from pentane solution.[4]

Purification: recrystallization at −30 °C from pentane solution.

Handling, Storage, and Precautions: air and moisture sensitive, not compatible with donor solvents like alcohol and THF, should be stored and handled under an inert atmosphere or by using standard Schlenk techniques.

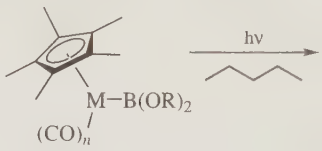
General Aspects. $Cp^*W(CO)_3[Bcat(Me)_2]$ is one of the first transition metal boryl complexes reported for the conversion of alkanes to borylated products with exquisite selectivity.[5] Alkylboronic or arylboronic esters are obtained, which are easily hydrolyzed to the corresponding alkyl- or arylboronic acids or converted to aldehydes, ketones, carboxylic acids, and alcohols.[6] $Cp^*W(CO)_3[Bcat(Me)_2]$ can be readily prepared by the salt elimination reaction of $NaCp^*W(CO)_3$ and $ClBcat(Me_2)$. Its reactions with alkanes or arenes are conducted under photochemical conditions and produce 1-alkylboronic or arylboronic esters in yields as high as 85%.[4] Because of the unusual terminal regioselectivity of such systems, $Cp^*W(CO)_3[Bcat(Me)_2]$ has been used as a model complex in various experimental and computational studies for elucidating reaction mechanism.[7,8] The high reactivity of $Cp^*W(CO)_3[Bcat(Me)_2]$ for C–H bond activation is due to the favorable kinetics provided by Lewis acidity of the boryl ligand and favorable thermodynamics for the formation of the strong B–C bond. Sterically blocking and eliminating active $C(sp^2)$–H bonds by the methyl groups in the aryl moiety and the Cp ligand of the complex is essential to enable alkane functionalization. $Cp^*W(CO)_3[Bcat(Me)_2]$ also reacts with phosphines to produce $Cp^*W(PX_3)(CO)_2[Bcat(Me)_2]$ under both photochemical and thermal conditions.

Photochemical, Stoichiometric Borylation of Alkanes via Direct C–H Activation. Many reactions involving C–H bonds in alkanes typically show either low selectivity or a selectivity that is tertiary > secondary > primary.[9] In contrast, the photochemical reaction of $Cp^*W(CO)_3[Bcat(Me)_2]$ with alkanes produces 1-alkylboronic esters. The results in eq 1 show exquisite selectivity for alkane functionalization at primary position. The primary vs. secondary reactivity is highlighted by the reaction of $Cp^*W(CO)_3[Bcat(Me)_2]$ with cyclohexane, which occurred in only 22%. The good selectivity for the two terminal positions of isopentane provides strong evidence that steric effects dominate the reaction selectivity.



(1)

Yields of 1-pentylboronic ester from photochemical reaction of several transition metal $Cp^*M(CO)_n[Bcat(Me)_2]$ complexes with pentane are shown in eq 2 and Table 1.[4] Those results emphasize the importance of steric effects. The third-row tungsten complex gives higher yield of functionalized pentane than the first and second-row metal complexes.



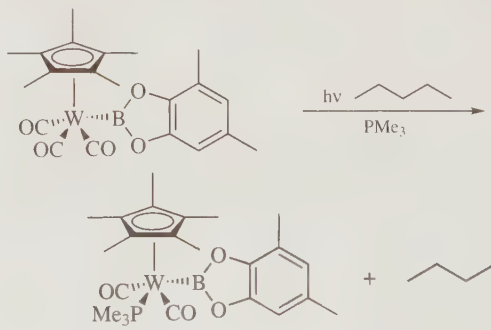
(2)

Table 1 Yields of 1-pentylboronate ester from photochemical reaction of transition metal boryl complexes with pentane

Compound	Yield (%)
$CpFe(CO)_2Bcat$	<1
$Cp^*Fe(CO)_2Bcat$	<1
$CpFe(CO)_2[Bcat(^tBu)_2]$	<1
$Cp^*Fe(CO)_2[Bcat(^tBu)_2]$	15
$Cp^*Fe(CO)_2[Bcat(Me)_2]$	20
$Cp^*Ru(CO)_2[Bcat(Me)_2]$	40
$Cp^*W(CO)_3Bcat$	20
$Cp^*Mo(CO)_3[Bcat(Me)_2]$	7
$Cp^*W(CO)_3[Bcat(Me)_2]$	85

Photochemical, Stoichiometric Borylation of Arenes via Direct C–H Activation. $Cp^*W(CO)_3[Bcat(Me)_2]$ shows comparable reactivities towards benzene and pentane. The photochemical reaction of $Cp^*W(CO)_3[Bcat(Me)_2]$ with benzene produces phenylboronic ester in 86% yield. However, $Cp^*W(CO)_3[Bcat(Me)_2]$ does not react with benzene under thermal conditions.

Ligand Substitution at the Tungsten Center. Photolysis of $Cp^*W(CO)_3[Bcat(Me)_2]$ in pentane in the presence of PMe_3 results in the formation of phosphine complex $Cp^*W(PMe_3)(CO)_2$-$[Bcat(Me)_2]$ and 1-pentyl$[Bcat(Me)_2]$, which indicates that ligand substitution and alkane functionalization are competing under photochemical conditions (eq 3). The ratio of two products is determined by the concentration of the phosphine. At elevated temperature (70–120 °C), $Cp^*W(CO)_3[Bcat(Me)_2]$ reacts with PMe_3 to generate some monophosphine substituted complex $Cp^*W(PMe_3)(CO)_2[Bcat(Me)_2]$ along with a small amount of $Cp^*W(PMe_3)(CO)_2H$, but no phenylboronic esters are found in the product mixture.



(3)

PMe_3	ratios measured at 50% conversion
2 equiv	0.3 : 1
4 equiv	0.6 : 1

Related Reagents. Iron, 1,3,2-benzodioxaborol-2-yldicarbonyl(η^5-2,4-cyclopentadien-1-yl); iron, dicarbonyl(4,6-dimethyl-1,3,2-benzodioxaborol-2-yl)[(1,2,3,4,5,-η)-1,2,3,4,5-pentameth-yl-2,4-cyclopentadien-1-yl); ruthenium, dicarbonyl(4,6-dimethyl-1,3,2-benzodioxaborol-2-yl)[(1,2,3,4,5,-η)-1,2,3,4,5-pentameth-yl-2,4-cyclopentadien-1-yl).

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Tungstoboric Acid, Tetrakis(tetrabutylammonium) Salt

$[N(C_4H_9)_4]_4H[BW_{12}O_{40}]\cdot nH_2O$

[83844-83-1] $C_{64}H_{145}BN_4O_{40}W_{12}$ (MW 3827.87)

Tungstoboricferric acid, tetrakis(tetrabutylammonium) salt

$[N(C_4H_9)_4]_4H_2[BW_{11}Fe(H_2O)O_{39}]\cdot nH_2O$

[214259-61-7] $C_{64}H_{148}BFeN_4O_{40}W_{11}$ (MW 3702.89)

Tungstoboricmanganic acid, tetrakis(tetrabutylammonium) salt

$[N(C_4H_9)_4]_4H_2[BW_{11}Mn(H_2O)O_{39}]\cdot nH_2O$

[546084-10-0] $C_{64}H_{148}BMnN_4O_{40}W_{11}$ (MW 3701.98)

(catalysts for oxidation of cycloalkanes with hydrogen peroxide and for epoxidation with hydrogen peroxide)

Alternate Names: $[N(C_4H_9)_4]_4H[BW_{12}O_{40}]\cdot nH_2O$

tungstate(5-), tetracosa-μ-dodecaoxo[μ_{12}-[tetrahydroxyborato (5-)-κO:κO:κO:κO′:κO′:κO′:κO″:κO″:κO″:κO‴:κO‴:κO‴]]dodeca-, tetrakis(*N*,*N*,*N*-tributyl-1-butanaminium) hydrogen;
1-butanaminium, *N*,*N*,*N*-tributyl-, hydrogen tetracosa-μ-dodecaoxo[μ_{12}-[tetrahydroxyborato(5-)-κO:κO:κO:κO′:κO′:κO′:κO″:κO″:κO″:κO‴:κO‴:κO‴]]dodecatungstate (4:1:1);
tetrakis(tetrabutylammonium) hydrogen dodecatungstoborate(5-);
tetrakis(tetrabutylammonium) hydrogen 12-tungstoborate(5-).

$[N(C_4H_9)_4]_4H_2[BW_{11}Fe(H_2O)O_{39}]\cdot nH_2O$

tungstate(6-), (aquaferrate)tetracosa-μ-oxoundecaoxo[μ_{12}-[tetrahydroxyborato(5-)κO:κO:κO:κO′:κO′:κO′:κO″:κO″:κO″:κO‴:κO‴:κO‴]]undeca-, tetrakis(*N*,*N*,*N*-tributyl-1-butanaminium) dihydrogen;
1-butanaminium, *N*,*N*,*N*-tributyl-, hydrogen (aquaferrate)tetracosa-μ-oxoundecaoxo[μ_{12}-[tetrahydroxyborato(5-)-κO:κO:κO:κO′:κO′:κO′:κO″:κO″:κO″:κO‴:κO‴:κO‴]]undecatungstate (6-) (4:2:1);
tetrakis(tetrabutylammonium) dihydrogen undecatungstoborateferrate(6-).

$[N(C_4H_9)_4]_4H_2[BW_{11}Mn(H_2O)O_{39}]\cdot nH_2O$

tungstate(6-), (aquamangnate)tetracosa-μ-oxoundecaoxo[μ_{12}-[tetrahydroxyborato(5-)κO:κO:κO:κO′:κO′:κO′:κO″:κO″:κO″:κO‴:κO‴:κO‴]]undeca-, tetrakis(*N*,*N*,*N*-tributyl-1-butanaminium) dihydrogen;
1-butanaminium, *N*,*N*,*N*-tributyl-, hydrogen (aquamanganate) tetracosa-μ-oxoundecaoxo[μ_{12}-[tetrahydroxyborato(5-)-κO:κO:κO:κO′:κO′:κO′:κO″:κO″:κO″:κO‴:κO‴:κO‴]]
undecatungstate(6-) (4:2:1);
tetrakis (tetrabutylammonium) dihydrogen undecatungstoboratemanganate (6-).

Physical Data: white solid, loss of hydration water up to 100 °C, starts decomposing at 160 °C, totally decomposed to a mixture of oxides at 550 °C. λ_{max} (CH_3CN) = 267 nm; ^{11}B NMR: −7.6 ppm (solid state MAS, relative to $Na_2B_4O_{10}\cdot H_2O$), −18.0 ppm (CH_3CN, relative to H_3BO_3); cyclic voltammetry in acetonitrile: *Ep* = −1.04 V, −1.53 V vs. Ag/AgCl.[1]

Iron(III)-substituted anion: yellow solid, loss of hydration water up to near 200 °C, starts decomposing at 200 °C, totally decomposed to a mixture of oxides at 650 °C. λ_{max} (CH_3CN) = 258 nm.

Manganese(III)-substituted anion: orange solid, loss of hydration water up to near 200 °C, starts decomposing at 200 °C, totally decomposed to a mixture of oxides at 650 °C. λ_{max} (CH_3CN) = 260, 473, 511(shoulder) nm.

All compounds have a typical infrared spectra, with three very strong bands around 950, 900, and 820 cm^{-1} attributed to W=O and W-O-W stretching vibrations.[2–4]

Solubility: all compounds are soluble in acetonitrile, dichloromethane, 1,2-dichloroethane, dimethylsulfoxide, and *N*,*N*-dimethylformamide.

Form Supplied: not commercially available.

Purification: one narrow signal in ^{11}B solid state NMR spectra allows distinction of $[BW_{12}O_{40}]^{5-}$ from other boron-containing anions.[8,9] Other suggested techniques: cyclic voltammetry[1] and X-ray powder diffraction, as the compounds are isomorphous, crystallizing with the cubic structure found for related tungstophosphates.[10]

Preparation: precipitation from aqueous solution by addition of $[N(C_4H_9)_4]Br$ to aq $[BW_{12}O_{40}]^{5-}$, prepared in situ,[2,5] or $K_5[BW_{12}O_{40}]\cdot nH_2O$,[2] followed by purification and recrystallization.[2]

Iron(III)-substituted anion: preparation of the anion $[BW_{11}Fe(H_2O)O_{39}]^{6-}$ in aqueous solution from Na_2WO_4, H_3BO_3, and $Fe(NO_3)_3$[3,4,6] followed by phase transfer to 1,2-$C_2H_4Cl_2$ with $[N(C_4H_9)_4]Br$, and workup of the organic solution.[3]

Manganese(III)-substituted anion: preparation of the anion

$[BW_{11}Mn(H_2O)O_{39}]^{6-}$ in aqueous solution from $KMnO_4$, $Mn(CH_3CO_2)_2$, Na_2WO_4, and H_3BO_3[7] followed by phase transfer to 1,2-$C_2H_4Cl_2$ with $[N(C_4H_9)_4]Br$, and workup of the organic solution.[4]

Handling, Storage, and Precautions: storage in desiccator, light-protected. No particular safety precautions.

Introduction. The heteropolyanions $[BW_{12}O_{40}]^{5-}$ and $[BW_{11}M(H_2O)O_{39}]^{6-}$, M = Fe^{III}, Mn^{III}, have the same molecular structure (the Keggin structure, Figure 1). The latter are related to the former by substitution of a W=O group by a M–OH_2 fragment. Thus they present a 1st row transition metal centre surrounded by a stable inorganic environment. Both tungsten and the metal M may be catalytically active. Catalysis (homogeneous and heterogeneous) with Keggin-type and other polyoxometalates has been reviewed.[11–14] The tetrabutylammonium salts are convenient for oxidative catalysis of organic substrates due to their solubility in nonaqueous solvents.

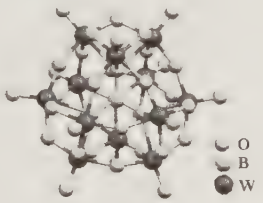
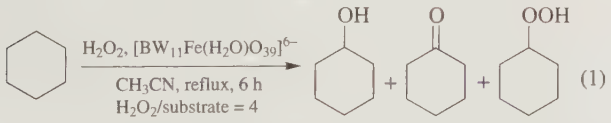


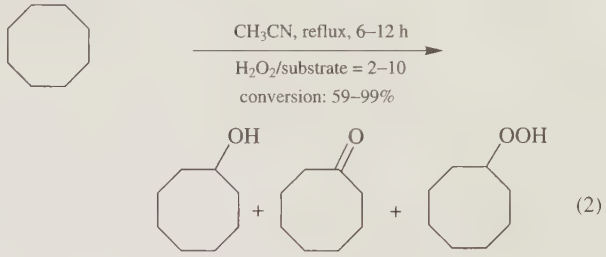
Figure 1 Keggin structure of $[BW_{12}O_{40}]^{5-}$

Oxidation of Cycloalkanes. Oxidation of cycloalkanes in refluxing acetonitrile solution, with aq hydrogen peroxide, in the presence of $[BW_{12}O_{40}]^{5-}$ or $[BW_{11}M(H_2O)O_{39}]^{6-}$, M = Fe^{III}, Mn^{III}, yielded mainly the corresponding cycloalkyl-alcohol, -ketone, and -hydroperoxide (eq 1). No cocatalysts were necessary. Oxidation of cyclohexane,[3] cyclooctane,[3] and cyclododecane[9,15] has been described. Hydroperoxides were identified by GC-MS, with methane negative chemical ionization and tandem mass spectrometry.[16] Conversion and selectivities vary with the heteropolyanion used and reaction conditions, namely the concentration of reagents. The reactions were inhibited by radical scavengers, which suggest a radical mechanism. Oxidation of cyclohexane was obtained with high conversion and turnover numbers as high as 1300, with good oxidation efficiency (higher than 60%).

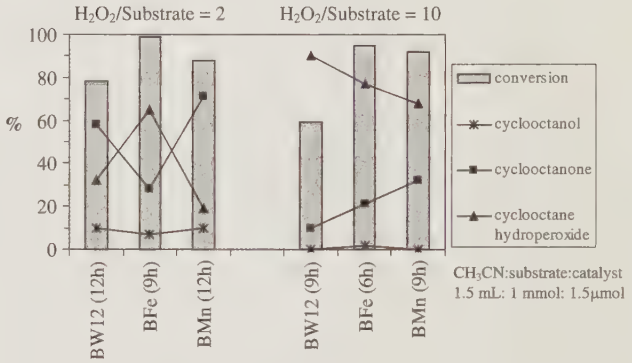


conversion: 99%
selectivity: 15% 32% 53%

In the case of cyclooctane, the reactions performed with H_2O_2/substrate molar ratio near the stoichiometric value gave cyclooctanone as the main product, whereas the use of an excess of hydrogen peroxide afforded mainly cyclooctanone and cyclooctane hydroperoxide, with the latter as the major product (eq 2). Conversion and selectivity values are shown in Figure 2 for the catalysts $[BW_{12}O_{40}]^{5-}$ (BW_{12}), $[BW_{11}Fe(H_2O)O_{39}]^{6-}$ (BFe), and $[BW_{11}Mn(H_2O)O_{39}]^{6-}$ (BMn).

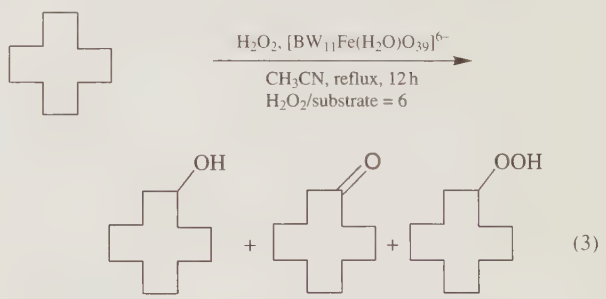


Oxidation of cyclooctane (conversion and selectivity)



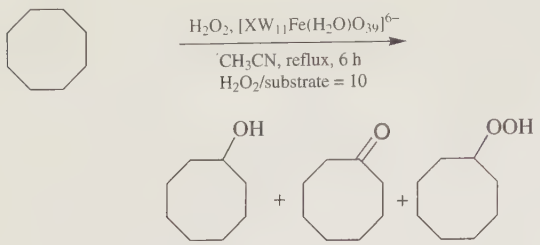
Fgiure 2 Oxidation of cyclooctane

Oxidation of cyclododecane catalyzed by $[BW_{11}Fe(H_2O)O_{39}]^{6-}$ yielded two or three main products. Cyclododecanol and cyclododecanone were found to be the principal products, with yields in the range 15–20% and 35–40%, respectively. For reactions with excess of H_2O_2, a significant amount of cyclododecane hydroperoxide was also found (eq 3).



selectivity: 20–22% 50–52% 17–20%
conversion: 30–70%

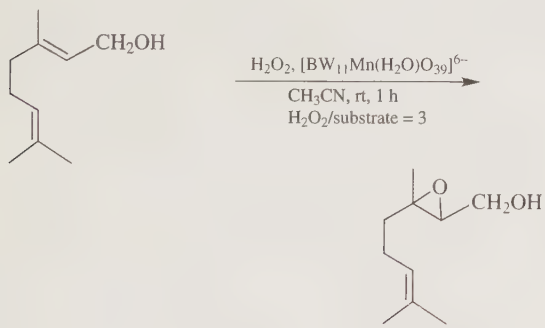
Other studies on the oxidation of cycloalkanes with hydrogen peroxide in acetonitrile solution, catalyzed by Keggin-type polyoxotungstates (tungstophosphates and tungstosilicates), have been reported.[15,17,18] The performance of $[BW_{11}Fe(H_2O)O_{39}]^{6-}$ in the catalysis of cyclooctane oxidation (eq 4) is quite similar to that of the related anion $[PW_{11}Fe(H_2O)O_{39}]^{4-}$.[18] Not many systems using polyoxometalates are known that afford hydroperoxides in oxidations with H_2O_2,[19] but their formation catalyzed by metal complexes is known.[20,21] Catalytic oxidations with hydrogen peroxide have been described in two monographs.[22,23] The catalytic oxidation of cyclohexane has been reviewed.[24]



(4)

X = P selectivity: conversion: 89%	0%	26%	74%
X = Si selectivity: conversion: 62%	8%	30%	62%
X = B selectivity: conversion: 95%	2%	21%	77%

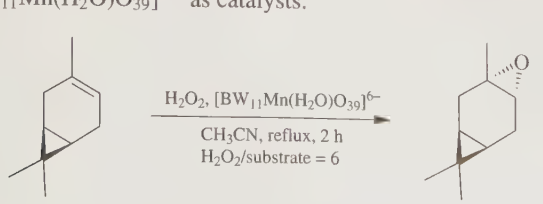
Epoxidation of Monoterpenes. Epoxidation of geraniol (eq 5) in acetonitrile with H_2O_2, catalyzed by $[BW_{12}O_{40}]^{5-}$ and $[BW_{11}Mn(H_2O)O_{39}]^{6-}$ afforded the 2,3-epoxygeraniol with high conversion (80% and 96%, respectively) and selectivity (near 87%) after 1–3 h at room temperature while protected from light.[4] Similar results were obtained in the oxidation of nerol.[4] Reaction courses were not affected by the addition of radical scavengers. Preferential epoxidation at the C_2-C_3 double bond of geraniol has been observed in the presence of some metal catalysts[25,26] and polyoxometalates,[27,28] but in many other reported cases the regioisomeric product distribution seems to be dominated by the relative electron density of the two double bonds, which favors epoxidation at the C_6-C_7 position.[27]



(5)

conversion: 96%
selectivity: 86%

Selective epoxidation of (+)-3-carene to α-3,4-epoxycarane (eq 6) was obtained in the presence of $[BW_{11}Mn^{III}(H_2O)O_{39}]^{6-}$ with moderate conversion. Higher conversions could be obtained with lower selectivity either with $[BW_{12}O_{40}]^{5-}$ or $[BW_{11}Mn(H_2O)O_{39}]^{6-}$ as catalysts.[4]



(6)

conversion: 37%
selectivity: 100%

Other Studies with $[BW_{12}O_{40}]^{5-}$. Other catalytic studies involving different compounds with the anion $[BW_{12}O_{40}]^{5-}$ can be found in the literature. In all cases $[BW_{12}O_{40}]^{5-}$ had a comparatively poor performance. For this reason they are not discussed here. The following studies were found:

Photooxidation of CH_3OH to formaldehyde, in aqueous acidic media, catalyzed by $K_5[BW_{12}O_{40}]\cdot nH_2O$ [11078-54-9], with simultaneous production of H_2.[29]

Acid-catalyzed decomposition of isobutyl propanoate,[30] esterification of propanoic acid with 2-methyl-1-propanol,[30] and alkylation of *p*-xylene with 2-methylpropene,[31] in the presence of $H_5[BW_{12}O_{40}]\cdot nH_2O$ [12297-12-0].

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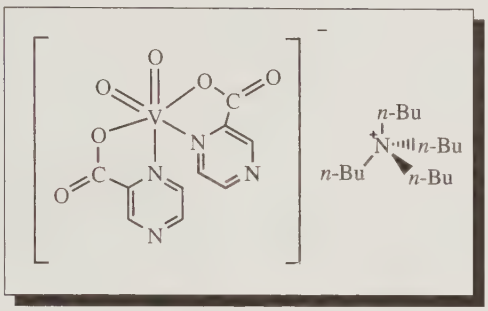
V

Vanadium(VI) Dioxobis(pyrazine-2-carboxylate) Tetrabutylammonium



[251317-59-6] $C_{26}H_{42}N_5O_6$ (MW 571.59)

(reagent used for the oxidation of organic compounds)

Physical Data: light yellow crystals.

Solubility: soluble in water, acetonitrile, dichloromethane.

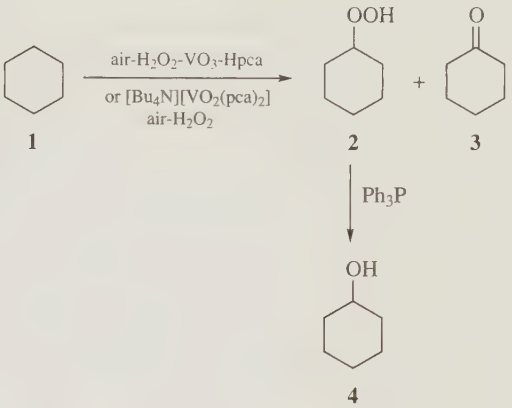
Analysis of Reagent Purity: IR (cm^{-1}): 862s, 873s, and 1668vs. ^1H NMR (acetone-d_6): δ 0.94 ppm (12 H, t, $J = 7.5$, CH_3), 1.43 ppm (8 H, m, $J = 7.3$, CH_2), 1.83 ppm (8 H, m, $J = 7.5$, CH_2), 3.50 ppm (8H, m, $J = 8.1$, CH_2), for NBu_4^+; 8.52 ppm (2 H, dd, J(H5–H3) = 1.46 and J(H5–H6) = 2.64, H5), 8.86 ppm (2 H, d, J(H6–H5) = 2.68, H6) and 9.18 ppm (2 H, d, J(H3–H5) = 1.48 Hz, H3) for pca ligand. ^{51}V NMR (acetone-d6): $\delta -525$ ppm. MS (electrospray, negative): *m/z* 329.

Preparative Method: the reagent is easily synthesized and isolated by dissolving the compound NBu_4VO_3 (681 mg, 2 mmol) in 20 mL of CH_3CN or water. After complete dissolution, pyrazine-2-carboxylic acid (Hpca) (492 mg, 4 mmol) is added, and the solution is stirred under reflux for 5 h. After filtration of the green solution and evaporation of the solvent, a yellow-green powder is obtained which can be purified to obtain light yellow crystals in 61% yield.

Purification: the powder is dissolved in the minimum quantity of CH_2Cl_2 and diluted with an equal quantity of cyclooctane, leading to the formation of light yellow crystals after a few days.

Handling, Storage, and Precautions: air stable complex. Potentially explosive when exposed to oxygen and hydrogen peroxide in the presence of organic compounds at elevated temperatures.

Oxidation of Cyclohexane. The well-known homogeneous vanadium oxidative system air–H_2O_2–VO_3–Hpca was extensively studied for the oxidation of a large number of organic compounds (alkanes, alkenes, alcohols, aromatic hydrocarbons).[1] This system requires the presence of the ligand (Hpca), the catalyst (VO_3^-), the promoter (hydrogen peroxide), and the oxidant (O_2). Cyclohexane oxidation under an $^{18}O_2$ atmosphere showed incorporation of ^{18}O in the products, which means that the $^{18}O_2$ is the real oxidant.[2,3] This system delivers the best performance with a ratio [V]/[Hpca] of 1/4.[2–12]



(1)

The complex $[NBu_4][VO_2(pca)_2]$ is proposed to be formed in situ by the reaction between Hpca and VO_3^- in the oxidation. In order to confirm this hypothesis, the proposed complex was used as a catalyst for the oxidative functionalization of cyclohexane (**1**) using Hpca or $HClO_4$ as cocatalyst, H_2O_2 as promoter, and O_2 as oxidant (eq 1). The results were compared with those obtained for the system air-H_2O_2–VO_3–Hpca.[2,3] Both reactions were carried out at 40 °C for 24 h using acetonitrile as solvent and 30% aq hydrogen peroxide.[2] The main product of both reactions is cyclohexyl hydroperoxide (**2**) that is reduced with triphenylphosphine to give cyclohexanol (**4**) in quantitative yield. Cyclohexanone (**3**) is also formed by direct oxidation. The results are compared in Table 1.

Table 1 Comparison of the products yields with $[NBu_4][VO_2(pca)_2]$ and with the system $[NBu_4][VO_3]$/Hpca in the oxidative functionalization of cyclohexane at 40 °C for 24 h (after reduction with Ph_3P)[2,3]

		Products (%)		
Catalyst	Cocatalyst	**3**	**4**	TON[c]
$[NBu_4][VO_3]$[a]	Hpca	1.18	22.50	1100
	-	0.32	4.31	215
$[NBu_4][VO_2(pca)_2]$[b]	Hpca	1.81	18.10	924
(prepared)	$HClO_4$	1.12	18.10	892

[a] Catalyst/Cocatalyst ratio = 1/4.

[b] Catalyst/Cocatalyst ratio = 1/2 (the prepared catalyst already has 2 pca^-).

[c] TON = mol of detected products per mol of vanadium.

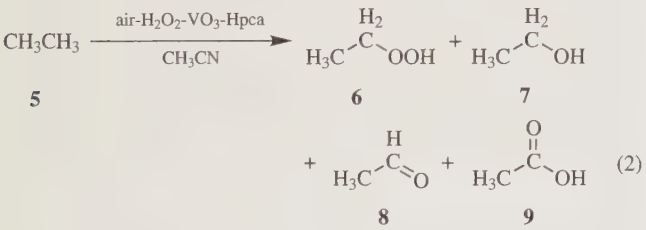
The results in Table 1 show that the catalyst tetrabutylammonium dioxobis(pyrazine-2-carboxylate)vanadium generates **3** and **4** with similar selectivity and activity to the system air–H_2O_2–VO_3–Hpca. This confirms the hypothesis that $[NBu_4][VO_2(pca)_2]$ is the intermediate in this system. Assays using $[NBu_4][VO_2(pca)_2]$ as catalyst and varying the cocatalyst show that the additional cocatalyst is necessary for the reaction. Its function is to donate protons, as shown by the substitution of $HClO_4$ for Hpca which gives similar yields.

Oxidation of Methane. Methane can be oxidized by $[Bu_4N]VO_3$/Hpca (ratio 1/4), using 35% aq hydrogen peroxide as promoter, air as oxidant and acetonitrile as solvent to produce methyl hydroperoxide, formaldehyde, formic acid, CO_2, and CO. No methanol peak is detected in these experiments prior to

reduction with PPh_3. The amount and ratio of the products are dependent on the temperature; as the temperature increase, the relative and absolute amounts of formaldehyde, formic acid, and CO_2 increase, while methyl hydroperoxide decreases. Furthermore, it is observed that carrying out a controlled reaction in the absence of methane, still leads to formation of formaldehyde, formic acid, and CO_2, which indicates that some portion of these products is from oxidation of acetonitrile.[13,14] The maximum amount of methyl hydroperoxide (5% yield after 4 h, 97 cycles) is obtained at 298 K.[13]

Water can be used as a solvent in order to eliminate oxidation of acetonitrile. In this case, methyl hydroperoxide is formed as the only product below 343 K, whereas above 343 K formaldehyde and formic acid are also formed in low amounts. A maximum amount of the methyl hydroperoxide (5% yield after 4 h and 24% yield after 24 h) is obtained at 323 K.[14]

Oxidation of Lower Alkanes. Ethane (**5**) is oxidized to a mixture of ethyl hydroperoxide (**6**), ethanol (**7**), acetaldehyde (**8**), and acetic acid (**9**) using $[Bu_4N]VO_3$/Hpca (ratio 1/4) and air in 35% aq hydrogen peroxide-acetonitrile (eq 2).[15] The product yields are shown in Table 2.



(2)

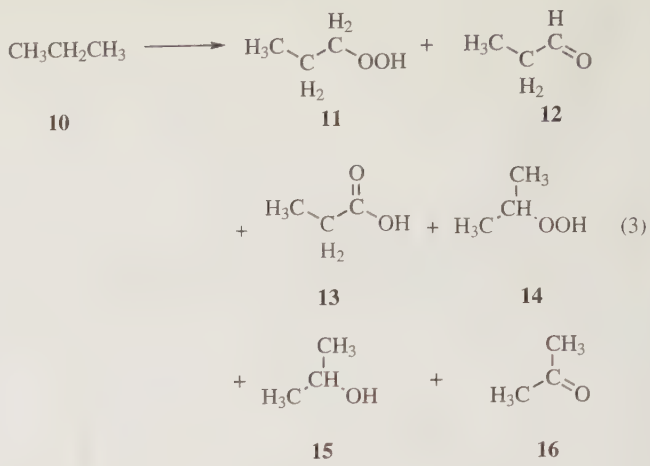
Table 2 Products of the oxidation of ethane using the system air–H_2O_2–VO_3–Hpca (25 bar of ethane, 10 bar of air, 1×10^{-6} mol L^{-1} of $[NBu_4]VO_3$, 4×10^{-6} mol L^{-1} of Hpca, 2×10^{-3} mol L^{-1} of 35% aq hydrogen peroxide)[16]

		Products/10^{-4} mol L^{-1}				
Temperature (K)	Time (h)	**6**	**7**	**8**	**9**	TON[a]
313	1	1	0.8	1.2	0	300
	2	1.8	1.3	2.1	0	520
	4	3.0	2.0	4.1	1.0	1010
	8	5.1	2.7	5.5	4.0	1730
348	1	1.0	1.3	2.5	0	480
	2	2.0	2.6	4.8	2.8	1700
	4	4.0	4.7	7.3	5.3	2130

[a]TON = mol of detected products per mol of vanadium.

Using the same conditions, propane is oxidized giving the products (eq 3) shown in Table 3. This reaction is strongly dependent on temperature and reaction time; at higher temperatures more fully oxidized products are detected in the reaction solution. This can be attributed to the oxidation of some primary products to generate secondary products.[15]

The reaction of 2-methylpropane, using the same conditions, leads mainly to oxidation of the tertiary carbon, forming *tert*-butanol (**22**) as the principal product (eq 4). The yields for the products of this reaction are shown in Table 4.[15]

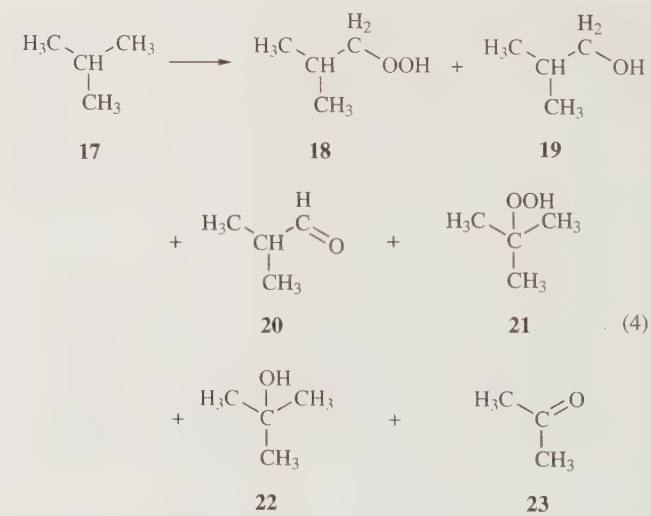


(3)

Table 3 Products of the oxidation of propane using the system air–H_2O_2–VO_3–Hpca (7 bar of propane, 5 bar of air, 1×10^{-6} mol L^{-1} of $[NBu_4]VO_3$, 4×10^{-6} mol L^{-1} of Hpca, 2×10^{-3} mol L^{-1} of 35% aq hydrogen peroxide)[15]

		Products/10^{-4} mol L^{-1}						
Temperature (K)	Time (h)	**11**	**12**	**13**	**14**	**15**	**16**	TON[a]
296	6	0.2	0.15	0	0.5	0.6	0.2	180
	17	0.7	0.4	0	0.7	1.2	0.6	390
313	2	0.4	0.1	0	0.8	0.1	0.2	160
	4	0.8	0.2	0	1.2	0.3	0.4	290
	6	1.1	0.3	0	1.6	0.7	0.7	440
	9	1.1	0.2	0.1	1.6	1.1	0.8	490
348	1	0.3	0.3	3.0	0.6	0.3	0.5	500
	2	0.1	0.3	6.0	0.3	0.2	0.8	770
	3	0	0.2	9.8	0	0.1	1.0	1110

[a]TON = mol of detected products per mol of vanadium.



(4)

Under the same conditions, the reaction with *n*-butane gives after 1 h at 40 °C, butyl-1-hydroperoxide (0.2×10^{-4} mol L^{-1}), butan-1-ol (0.1×10^{-4} mol L^{-1}), butanaldehyde (0.4×10^{-4} mol L^{-1}), butyl-2-hydroperoxide (0.1×10^{-4} mol L^{-1}), butan-2-ol (1.8×10^{-4} mol L^{-1}), and butanone (0.2×10^{-4} mol L^{-1}) with a total turnover of 280.[15]

The oxidation of *n*-pentane under the same conditions generates exclusively pentan-2-one and pentan-3-one. After 1 h at 350 K

a total conversion of 6.6% (TON = 580) is obtained, of which 4.1% is pentan-2-one and 2.5% pentan-3-one. After 5 h the total conversion is 8% (TON = 700) with 5% penta-2-one and 3% penta-3-one. No pentyl hydroperoxide was observed.[16]

Table 4 Products of the oxidation of 2-methylpropane using the system air–H_2O_2–VO_3–Hpca (Reaction conditions: 2.5 bar of 2-methylpropane, 25 bar of air, 1×10^{-6} mol L^{-1} of $[NBu_4]VO_3$, 4×10^{-6} mol L^{-1} of Hpca, 2×10^{-3} mol L^{-1} of H_2O_2 (35% aq solution)[15]

	Products/10^{-4} mol L^{-1}						
Temperature (K)	**18**	**19**	**20**	**21**	**22**	**23**	TON[a]
296	0.7	0.2	1.5	0.4	2.4	0.1	530
313	0.2	0.4	0.5	0.3	0.9	0.1	240
348	0.5	0.5	1.1	1.6	3.1	0.3	710

[a]TON = mol of detected products per mol of vanadium.

Oxidation of Other Higher Alkanes. *n*-Heptane (**24**) is oxidized by the system air–H_2O_2–VO_3–Hpca at 296 K in acetonitrile with 30% aq hydrogen peroxide for 24 h affords the hydroperoxides (**24–27**), the alcohols (**28–31**), and the carbonyls (**32–35**) (eq 5) with 86%, 4% and 10% selectivity, respectively. The total turnover number is 282 but the conversion of *n*-heptane is only 6%. When anhydrous hydrogen peroxide is used, the conversion increases to 13.5%, however the selectivity for hydroperoxides is reduced to 71% (TON 623). The site selectivity C(1):C(2):C(3):C(4) of both systems (taking into account the number of hydrogen atoms at carbon atoms 1, 2, 3, and 4) is 1:3:3:3 for both reactions after 1 h and 1:4:4:4 for aq and 1:5:5:5 for anhydrous hydrogen peroxide after 24 h, showing an increase in the preference for the oxidation of secondary carbons with time. The results of these reactions are shown in Table 5.[17]

(5)

24

25 W=H,OOH; **29** W=H,OH; **33** W=O;
26 X=H,OOH; **30** X=H,OH; **34** X=O;
27 Y=H,OOH; **31** Y=H,OH; **35** Y=O;
28 Z=H,OOH; **32** Z=H,OH; **36** Z=O;

* when not otherwise specified, X,Y,Z, and W represent H_n

In the oxidation of 2-methylhexane (**37**) and 3-methylhexane (**55**) with 30% aq hydrogen peroxide, more than 90% of the products formed are hydroperoxides, while using anhydrous hydrogen peroxide only generates 67% of the hydroperoxides (eqs 6 and 7). The turnover numbers are higher for the reactions with anhydrous hydrogen peroxide, but they are in the same range as observed for *n*-heptane (**24**). Tables 5 and 6 show the selectivities for primary, secondary, and tertiary carbons, normalized for the number of hydrogen atoms.[17] The selectivity for the tertiary carbon atoms is higher for the reaction with 30% aq than for anhydrous hydrogen peroxide. In the oxidation of **37** the selectivity for secondary and tertiary carbon atoms increases during the reaction course while a nonuniform behavior is observed for **55**.

(6)

37

38 U=H,OOH; **44** U=H,OH; **50** U=O;
39 Z=H,OOH; **45** Z=H,OH; **51** Z=O;
40 Y=H,OOH; **46** Y=H,OH; **52** Y=O;
41 X=H,OOH; **47** X=H,OH; **53** X=O;
42 W=H,OOH; **48** W=H,OH; **54** W=O;
43 V=OOH; **49** V=OH;

* when not otherwise specified, X, Y, Z, W, U, and V represent H_n

(7)

55

56 T=H,OOH; **63** T=H,OH; **70** T=O;
57 U=H,OOH; **64** U=H,OH; **71** U=O;
58 Z=H,OOH; **65** Z=H,OH; **72** Z=O;
59 Y=H,OOH; **66** Y=H,OH; **73** Y=O;
60 X=H,OOH; **67** X=H,OH; **74** X=O;
61 V=H,OOH; **68** V=H,OH; **75** V=O;
62 W=OOH; **69** W=OH;

* when not otherwise specified, X, Y, Z, W, U, T, and V represent H_n

Table 5 Oxidation of *n*-heptane by the system air–H_2O_2–VO_3–Hpca in acetonitrile at 296 K (0.1 mmol of n-Bu_4NVO_3, 0.4 mmol of Hpca, 4.6 mmol of the hydrocarbon and 2 mmol of either 30% aq hydrogen peroxide or anhydrous H_2O_2. The reaction volume was adjusted with acetonitrileto 9.8 mL)[17]

		Products (%)				
		Hydroperoxides	Alcohols	Carbonyls		Selectivity[b]
H_2O_2	Time (h)	**25–28**	**29–32**	**33–36**	TON[a]	C(1):C(2):C(3):C(4)
Aqueous	3	0.90	0.02	0.12	50	1.0:3.3:3.1:3.0
30%	24	5.19	0.22	0.60	282	1.0:4.2:4.0:4.0
Anhydrous	3	3.41	0.24	0.80	209	1.0:3.6:3.5:3.2
	24	9.44	0.87	2.96	623	1.0:5.3:5.2:5.2

[a]TON = mol of detected products per mol of vanadium.

[b]Normalized for number of hydrogen atoms at carbons atoms 1, 2, 3, and 4.

Table 6 Oxidation of 2-methylhexane by the system air–H_2O_2–VO_3–Hpca in acetonitrile at 296 K (0.1 mmol of n-Bu_4NVO_3, 0.4 mmol of Hpca, 4.6 mmol of the hydrocarbon, and 2 mmol of either 30% aq hydrogen peroxide or anhydrous H_2O_2. The reaction volume was adjusted with acetonitrile to 9.8 mL)[17]

		Products (%)				
		Hydroperoxides	Alcohols	Carbonyls		Selectivity[b]
H_2O_2	Time (h)	**38–43**	**44–49**	**50–54**	TON[a]	1°:2°:3°
Aqueous	3	2.06	0.05	0.05	108	1.0:4.2:12.9
	24	8.16	0.12	0.12	396	1.0:5.2:15.6
Anhydr.	3	4.07	0.31	0.31	259	1.0:3.2:10.0
	24	7.14	0.93	0.93	496	1.0:4.0:12.8

[a]TON = mol of detected products per mol of vanadium.

[b]Normalized for number of hydrogen atoms at primary, secondary, and tertiary (1°, 2°, and 3°) carbons.

Table 7 Oxidation of 3-methylhexane by the system air–H_2O_2–VO_3–Hpca in acetonitrile at 296 K (0.1 mmol of n-Bu_4NVO_3, 0.4 mmol of Hpca, 4.6 mmol of the hydrocarbon, and 2 mmol of either 30% aq hydrogen peroxide or anhydrous H_2O_2. The reaction volume was adjusted with acetonitrile to 9.8 mL)[17]

		Products (%)				
		Hydroperoxides	Alcohols	Carbonyls		Selectivity[b]
H_2O_2	Time (h)	**56–62**	**63–69**	**70–75**	TON[a]	1°:2°:3°
Aqueous	3	1.11	0.08	0.15	64	1.0:5.4:1.1
	24	4.97	0.21	0.32	259	1.0:6.0:7.0
Anhydr.	3	3.48	0.2	0.65	191	1.0:4.4:5.7
	24	8.09	0.83	2.26	524	1.0:4.7:6.0

[a]TON = mol of detected products per mol of vanadium.

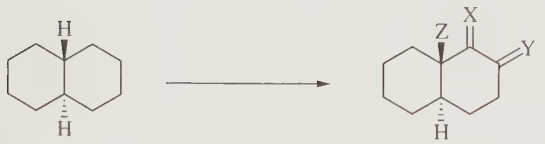
[b]Normalized for number of hydrogen atoms at primary, secondary, and tertiary (1°, 2°, and 3°) carbons.

The oxidations of *cis*-decalin (**76**) and *trans*-decalin (**82**) are important to understanding the stereoselectivity of this catalytic system (eqs 8 and 9).[17]

(8)

76

77 Z=OH;
78 X=H,OH;
79 Y=H,OH;
80 X=O;
81 Y=O;



(9)

82

83 Z=OH;
84 X=H,OH;
85 Y=H,OH;
86 X=O;
87 Y=O;

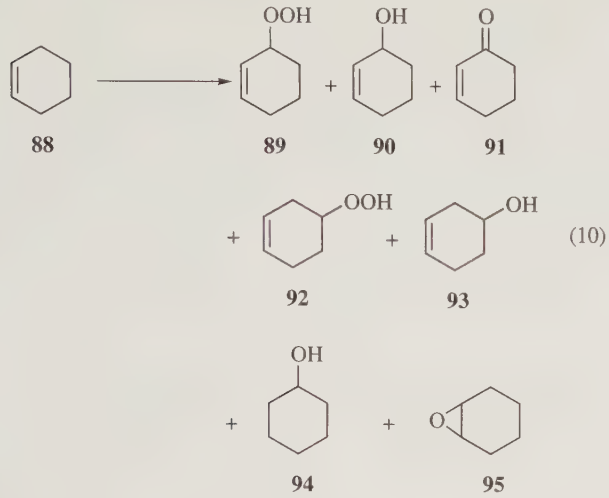
After reduction of the products with PPh_3, the oxidation of **76** gives mainly *trans*-decalin-9-ol (**83**) and *cis*-decalin-2-ol (**79**) with yields of 28.4% and 32.0%, respectively. *cis*-Decalin-1-ol (**78**), *cis*-1-decalone, and *cis*-2-decalone are obtained in moderate conversions (13.0%, 11.0%, and 10.0%). *cis*-Decalin-9-ol (**77**) is obtained in only 6.0% yield. In the oxidation of **82**, the principal products are *trans*-decalin-9-ol (**83**), *trans*-decalin-1-ol (**84**), and *trans*-decalin-2-ol (**85**) with yields of 17.0%, 21.5%, and 33.0%. *trans*-1-decalone (**86**) and *trans*-2-decalone (**87**) were obtained with 14.0% and 11.0% yields. *cis*-Decalin-9-ol (**77**) is also obtained with a 3.5% yield. In the oxidation of both decalins, the ratio **83/77** is the similar, suggesting that both reactions have the same intermediate.

Oxidation of Cyclohexene. Cyclohexene (**88**) can be oxidized by $[Bu_4N]VO_3$/Hpca (ratio 1/4), using 30% hydrogen peroxide in water and air in acetonitrile to yield the seven products (**89–95**) (eq 10). The cleavage of the allylic C–H bond results in cyclohexen-2-enyl hydroperoxide (**89**) as the principal product (9.4% yield after 30 h). The hydroperoxide (**92**) is formed in smaller amounts, 0.6% after 30 h. The alcohols **90** and **94** are obtained at 1.6% and 1.4% after 30 h. The cyclohex-2-enone (**91**), cyclohexen-3-ol (**93**), and cyclohexene oxide (**95**) are obtained in very small amounts. The total turnover number is 675.[18]

Oxidation of Aromatic Hydrocarbons. Oxidation of toluene using $[Bu_4N]VO_3$/Hpca (ratio 1/4), 30% aq hydrogen peroxide and air in acetonitrile gives a mixture of isomeric cresols in the ratio *meta:ortho:para* = 54:12:34. Naphthalene is oxidized over 12 h at 323 K, mainly to 1,4-naphthoquinone (38% with respect to naphthalene). The isomeric 1,2-naphthoquinone is also formed but in markedly lower amounts. Anthracene can also be oxidized to obtain 9,10-anthraquinone with good yields (79%).[19] Oxidation of benzene gives phenol in 2.8% yield after 3 h at 323 K.[20] Phenol is able to coordinate to the metal ion, thus deactivating the catalyst.[21]

Oxidation of Alcohols. Oxidation of propan-1-ol and propan-2-ol can be carried out using $[Bu_4N]VO_3$/Hpca (ratio 1/4),

20% aq hydrogen peroxide, and air in acetonitrile at 323 K, with urea added to the reaction system. Propan-1-ol gives propanal with 4.4% yield after 2 h and propan-2-ol gives acetone with 4.2% yield after 8 h.[20] Benzyl alcohol is oxidized to benzaldehyde and cyclohexanol to cyclohexanone after 5 h at 323 K, with yields of 3% and 0.26%, respectively.[19]



(10)

Related Reagents. Tetrabutylammonium vanadate; pyrazine-2-carboxylic acid.

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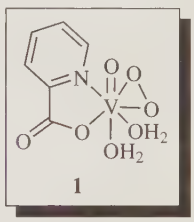
Vanadium(V) Diaquaoxoperoxy(2-pyridinecarboxylate-$\kappa N1,\kappa O2$)



1

[85082-23-1] $C_6H_8NO_7V$ (MW 207.09)

(reagent used for the oxidation of hydrocarbons)

Solubility: soluble in water, acetonitrile, methanol, dimethylformamide, hexamethylphosphorous triamide.

Form Supplied in: red crystals.

Analysis of Reagent Purity: the infrared spectrum exhibits absorptions at 975 cm^{-1} (oxo stretching vibration, ν(V–O)), 935, 580, and 550 cm^{-1} (C_{2v} peroxo vibrations). The other infrared absorptions are assigned to coordinated water (broad absorption at 3300 cm^{-1}) and to the bidentate 2-pyridinecarboxylate group ($\nu(C–O)_{as}$ at 1670 cm^{-1}, $\nu(C–O)_s$ at 1380 cm^{-1}). The ^1H NMR in D_2O reveals δ 7.5–8.5 (m, 3H), 9.5 (d, 1 H). The ^{51}V NMR spectrum in water shows an intense line at δ −590 ppm (325 Hz), in MeOH at δ −553 ppm (350 Hz), and in CH_3CN at δ −522 ppm (375 Hz).

Preparative Methods: V_2O_5 (4.52 g, 25 mmol) and 2-pyridinecarboxylic acid (PicH, 6.15 g, 50 mmol) are dissolved at 0 °C in 20 mL of aq 30% H_2O_2 with continuous stirring for 4 h. (*Caution*: The reaction should be carried out in an open vessel and under rigorous temperature control in order to prevent H_2O_2 decomposition). The impure orange precipitate is filtered, rapidly washed with a minimum amount of ice-cold water and then with diethyl ether, and dried in vacuum. The yield is 90%.

Purification: the powder is dissolved in a minimum amount of acetonitrile. The same amount of cyclooctane is added and the formation of red crystals is observed after several days.

Handling, Storage, and Precautions: the complex is stable in a refrigerator in the solid state for several weeks. It is not explosive even when heated. No toxicity data are available.

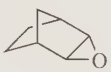
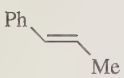
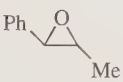
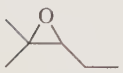
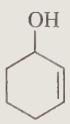
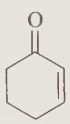
Epoxidation of Olefins. Epoxidation of olefins with vanadium diaquaoxoperoxy(2-pyridinecarboxylate) ($VO(O_2)$(Pic)-

$(H_2O)_2$ (**1**) is not stereoselective and cleavage products are observed.[1] When 2-methyl-2-pentene (eq 1) is used, an epoxide is formed at the beginning of the reaction, but it is subsequently consumed to produce oxidative cleavage products. A control experiment showed that the epoxide was mostly oxidized to acetone and propionaldehyde under the reaction conditions.[2] The red solution turns yellow at the end of the reaction due to the formation of a new unreactive dinuclear complex.[2]


(1)

The stoichiometric oxidation of olefins by **1** at room temperature under a nitrogen atmosphere produces epoxides and oxidative cleavage products as shown in Table 1.[2]

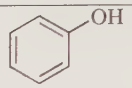
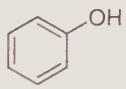
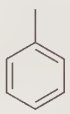
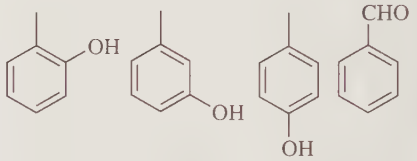
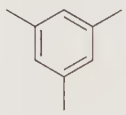
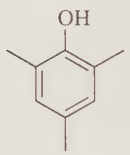
Table 5 Stoichiometric oxidation of olefins at 20 °C using 0.04 mol L^{-1} of **1**, 2 mol L^{-1} of olefin and acetonitrile[a] or CH_2Cl_2[b] as solvent[2]

Olefin	Time (min)	Yield of Products (%)		
	15[a]	 19	 8	CH_3CHO 20
	120[a]	 2	 12	CH_3CHO 3
	9[a]	 22		
	90[a]	 6	PhCHO 45	CH_3CHO 40
	90[a]			C_2H_5CHO
	90[b]	 30	 7	 7

The selectivity for epoxides and the conversion to oxidative cleavage products depends on the nature of the substrate. Due to the different solubility of the reagents, an accurate comparison between the different reactions is rather difficult. The reactivity of the olefins increases with their nucleophilic character, following the order: disubstituted > monosubstituted. Olefins containing phenyl substituents give more oxidative cleavage products than those bearing aliphatic substituents. Cyclohexene gives a non-negligible amount of allylic alcohol and ketone together with cyclohexene oxide.[3] *cis*-2-Butene is much more reactive than *trans*-2-butene. The epoxidation reaction is essentially nonstereospecific, although *cis*-2-butene gives an approximate 2:1 mixture of *cis* and *trans* epoxide, compared to 6:1 for *trans*-2-butene.[2]

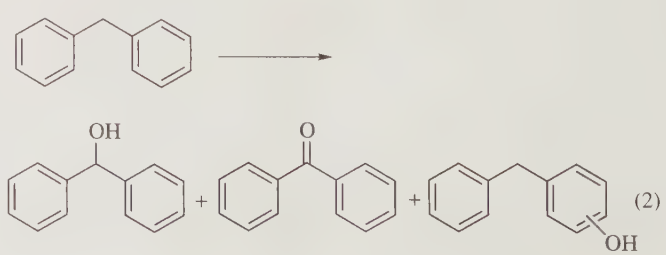
Oxidation of Aromatic Hydrocarbons. **1** has been reported to be particularly effective in benzene hydroxylation.[4,5] Phenolic compounds are the main products detected, without formation of any coupled materials. Table 2 lists oxidation of benzene, toluene, and mesitylene with **1**.[2]

Table 6 Stoichiometric hydroxylation of aromatic hydrocarbons at 20 °C using 0.04 mol L^{-1} of **1**, 2 mol L^{-1} of olefin and acetonitrile[a] or methanol[b] as solvent[2]

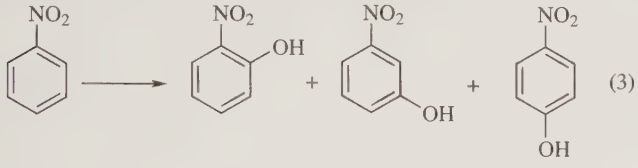
Substrate	Time (min)	Yield of Products (%)
	120[a]	 56
	360[b]	 3
	45[a]	 24 10 16 2
	15[a]	 31

1 oxidizes benzene in CH_3CN at 20 °C into phenol with 56% yield. In methanol, **1** is almost inactive because the oxidation is best carried out in a nonprotic solvent. Hydroxylation of toluene mostly occurs at the ring positions, yielding *o*-, *m*-, and *p*-cresols in a 48:20:32 ratio. Only traces of benzylic alcohol were detected, indicating a strong preference for attack on the aromatic rather than on the aliphatic positions. Mesitylene gives the corresponding phenol in 31% yield after only 15 min.[2]

Oxidation of diphenylmethane with **1** at 37 °C gives diphenylmethanol, benzophenone, and a mixture of benzylphenols (eq 2)[6,7] with a total yield of 54% after 360 h using a 1:1 mixture of CH_3CN and H_2O (0.11 mol L^{-1} of $HClO_4$). When using an 8:5 CH_3CN/H_2O ratio, a yield of 24% is obtained after 168 h.[3]

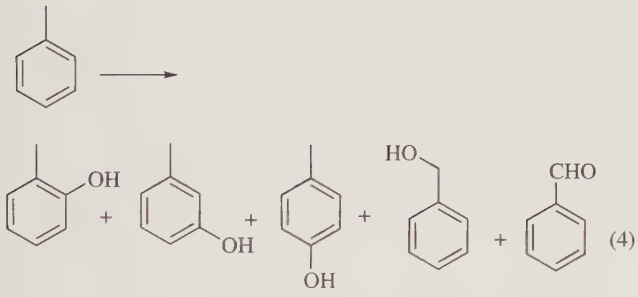

(2)

Nitrobenzene is oxidized at room temperature using 30% aq H_2O_2 as oxidant and **1** as catalyst (eq 3). The *o*-, *m*-, and *p*-nitrophenols are obtained with 17%, 53%, and 30% selectivity, respectively. In the oxidation of toluene (eq 4) under similar conditions, *o*-cresol, *m*-cresol, *p*-cresol, benzyl alcohol, and benzaldehyde are obtained with 32%, 27%, 9%, 4%, and 28% selectivity, respectively.[8] The stoichiometric oxidation of toluene is more selective for *p*-cresol giving an *o*-/*m*-/*p*-cresol ratio of 2.4/1/1.6, while in the catalytic reaction an *o*-/*m*-/*p*-cresol ratio of 2.4/2/0.6 is obtained. Importantly, the stoichiometric oxidation generates fewer side-chain oxidation products.



(3)

17 53 30



(4)

32 27 9 4 28

Oxidation of Alkanes. **1** oxidizes alkanes stoichiometrically with good selectivity.[2] *n*-Hexane is oxidized at room temperature in acetonitrile, giving a 1:40:20 selectivity for the carbons 1, 2, and 3, respectively. In the oxidation of 3-methylhexane under similar conditions, the selectivity is not as pronounced, giving a 1:7:9 ratio for the oxidation of carbons 1, 2, and 3.[9]

Stoichiometric oxidation of cyclohexane with **1** in a 1:1 CH_3CN/CCl_4 mixture gives cyclohexanol, cyclohexanone, and cyclohexyl chloride with 13%, 10%, and 2% yields, respectively (Table 3).[2] Cyclohexyl chloride is formed in a radical reaction with CCl_4.[10] The hydroxylation of alkanes preferentially occurs at the tertiary positions, as shown in the case of *iso*-butane and decalin. Oxidation of *n*-octane gives an almost statistical mixture of 2-, 3-, and 4-octanols and octanones, without noticeable amounts of terminal oxygenated products.[2] Significant epimerization at the C_9 position was observed in the hydroxylation of *cis*-decalin by **1** (*cis*-:*trans*-9-decalol = 7:1), indicating intermediacy of the *cis*-9-decalyl radical.[11]

The stoichiometric oxidation of disubstituted cyclohexanes with **1** in acetonitrile at room temperature (such as decalins and dimethylcyclohexanes (DMCH)) occurs with partial retention of the configuration (*cis*-disubstituted cyclohexanes give rise to the predominant formation of the respective *cis*-*tert*-alcohol). The *cis*/*trans* ratios in the oxidation of *cis*-decalin, *trans*-decalin, *cis*-1,2-DMCH, *trans*-1,2-DMCH, *cis*-1,4-DMCH, and *trans*-1,4-DMCH are 4.15, 0.17, 3.85, 0.13, 1.00, and 0.29, respectively.[9]

Biological Applications. **1** has also been tested in vitro and in vivo (intraperitoneal and/or subcutaneous injection) as a controlling agent for plasma glucose.[12,13] It achieved a 20% decrease in plasma glucose in BB rats at a lowest effective dose (LED) of 0.4 μmol kg^{-1}, while the lowest dose producing mortality was more than 15 times higher. By contrast, the similar monohydrated compound showed an LED of 24 μmol kg^{-1}, which was only half the lowest dose producing mortality.[13,14]

Table 7 Stoichiometric hydroxylation of alkanes at 20 °C using 0.04 mol L^{-1} of **1**, 2 mol L^{-1} of olefin, and 9:1 CH_3CN/CCl_4 mixture as solvent

Substrate	Time (min)	Yield of Products (%)
	180	   13 10 2
*iso*butane	300	*t*-BuOH 20
cis-decalin	180	*cis*-9-decalol, 6.9; *trans*-9-decalol, 1.0; 1-decalol, 2.4; 2-decalol, 0.4; 1-decalone, 3.7; 2-decalone, 2.2
n-octane	300	2-octanol, 1.5; 3-octanol, 0.5; 4-octanol, 0.5; 2-octanone, 2.4, 3-octanone, 2.9; 4-octanone, 2.8

Related Reagents. Vanadium oxide; 2-pyridinecarboxylic acid.

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- Carbon Tetraiodide 43

Ulf Schuchardt — *Universidade Estadual de Campinas, Campinas, SP, Brazil*
- Rhenium(VII) Aquamethyloxodiperoxy 276
- Rhenium(VII) Methyloxodiperoxy 283
- Vanadium(VI) Dioxobis(pyrazine-2-carboxylate) Tetrabutylammonium 371
- Vanadium(V) Diaquaoxoperoxy(2-pyridinecarboxylato-$\kappa N1,\kappa O2$) 375

Masakatsu Shibasaki — *University of Tokyo, Tokyo, Japan*
- Gallium Trichloride 181

Nigel S. Simpkins — *University of Nottingham, Nottingham, UK*
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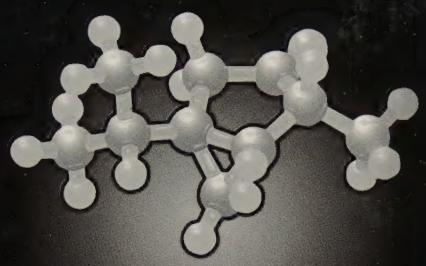
Handbook of Reagents for Organic Synthesis

Reagents for Direct Functionalization of C–H Bonds



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Syntheses requiring high material throughput are made even more challenging when targeting pure enantiomers. Asymmetric reactions employing chiral catalysts and prochiral substrates are highly attractive because one molecule of catalyst generates a multitude of chiral progeny. Modern synthesis is rapidly evolving by creating new transformations that employ C–H bonds as the locus for specific functionalization. This Handbook presents short, informative articles on some 80 reagents that summarize the current state-of-the-art using chiral strategies efficiently to increase molecular complexity. These transformations include arene and heteroarene functionalizations, the introduction of heteroatoms, the formation of chiral centers, rings and multiple bonds, and enantiogenesis.

All the information compiled in this volume is also available in electronic format on Wiley InterScience. The electronic Encyclopedia of Reagents for Organic Synthesis (e-EROS) includes all the reagents described here plus many more reagents of other types and for other uses. e-EROS offers text and structure search and is updated twice a year. For more information visit:

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