

2.01

Azetidines, Azetines and Azetes: Monocyclic

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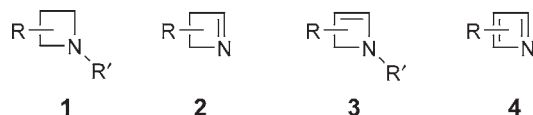
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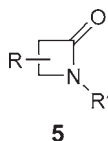
2.01.1 Introduction

This chapter deals with the recent aspects on four-membered rings containing one nitrogen atom. This class of compounds has been thoroughly studied in the decade since 1995. Since this subject has been covered previously in CHEC(1984) <1984CHEC(7)237> and in CHEC-II(1996) <1996CHEC-II(1B)507>, the present chapter intends to update previous concentration on major new preparations, reactions, and concepts. At the beginning of each main section, a sentence or short paragraph explaining the major advances since the publication of the earlier chapters in CHEC-II(1996) <1996CHEC-II(1B)507> is provided.

There is not much change in scenario with regard to the pace of development on azetidines **1**, 1-azetines **2**, 2-azetines **3**, and azetes **4**. While the latter three subclasses are still underdeveloped, the chemistry of azetidines is growing steadily. These compounds are treated in similar pattern as in CHEC-II(1996) <1996CHEC-II(1B)507>.



As usual the chemistry of azetidin-2-ones **5**, derivatives of azetidines, has seen an enormous focus because of the biological significance of these substances and their derivatives. Azetidin-2-ones have been again dealt with separately rather than as derivatives of azetidines because of the increasing interest in these β -lactam compounds.



Obviously a complete coverage of the material dealing with monocyclic azetidines in this limited page allocation is impossible and selectivity toward usefulness has been employed.

2.01.2 Azetidines

2.01.2.1 Introduction

A large number of applications in agrochemistry and in the pharmaceutical field continue to stimulate interest in the chemistry of this class of strained azaheterocycles <2002CRV29, 2004CRV2353, 2004CRV6177>. The discovery of the trinitroazetidines as potentially useful energetic materials and application of many azetidines in asymmetric synthesis has given impetus to studies on this class of compounds <2004RMC133>. Several novel routes to this class of compounds and certain interesting applications have been reported since the publication of CHEC(1984) and CHEC-II(1996) <1984CHEC(7)237, 1996CHEC-II(1B)507>. These reviews have to be considered as standard reference works for the period up to 1994.

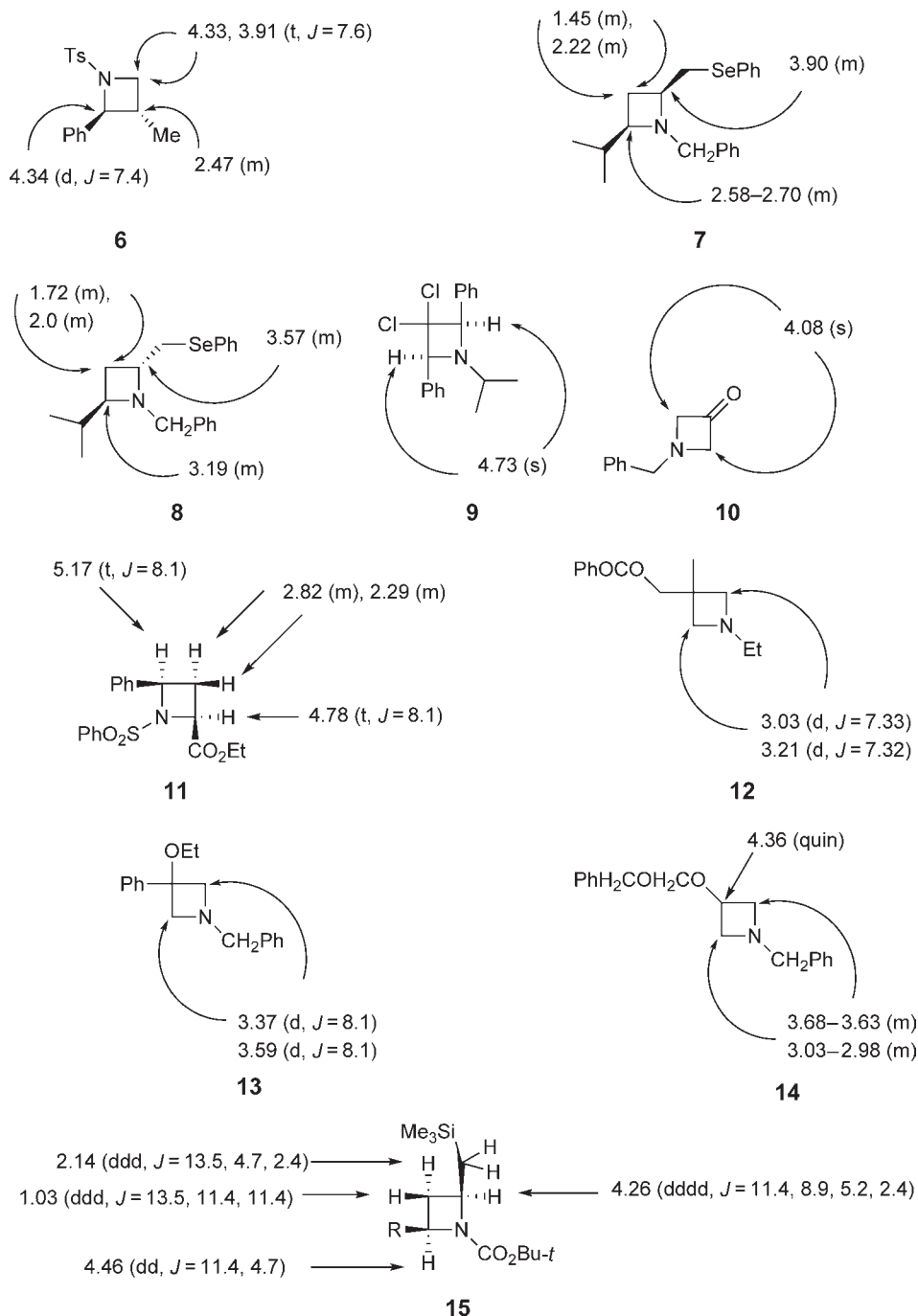
2.01.2.2 Theoretical Methods

The strain in azetidines influences the tendency for ring formation enormously <1996CHEC-II(1B)507>. Within the homologous series of azaheterocycles, the tendency for cyclization is smallest for the nitrogen-containing four-membered ring ($5 > 3 > 6 > 7 \approx 4$). For some other studies on gas phase proton affinity and *ab initio* calculations on the azetidin-yl radical, CHEC-II(1996) <1996CHEC-II(1B)507> should be consulted.

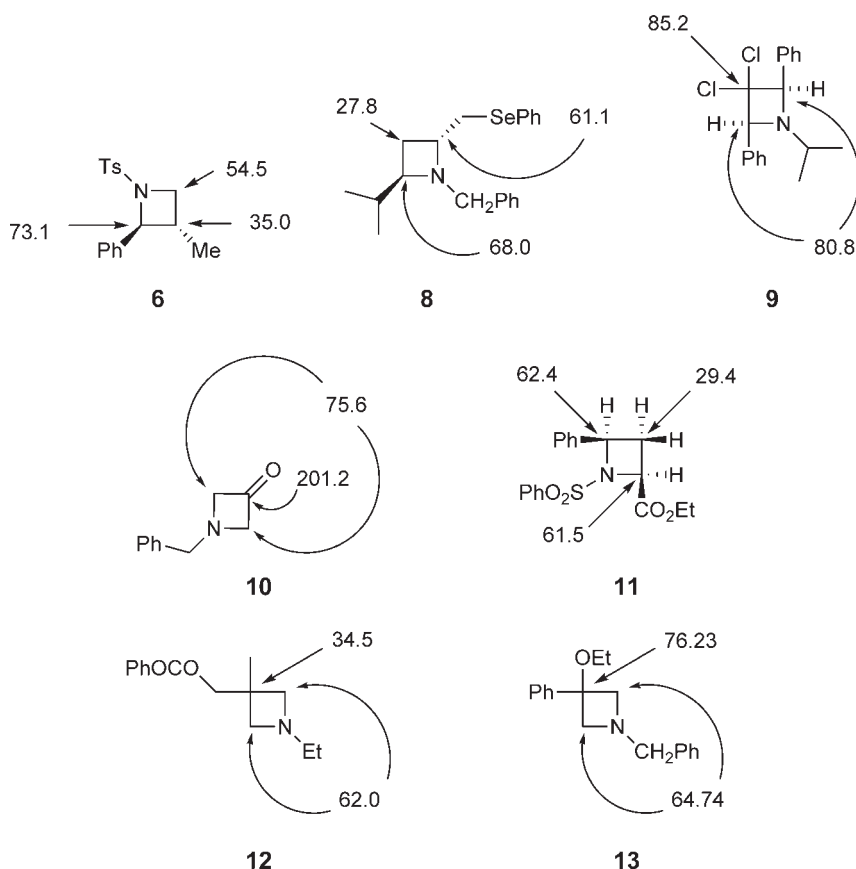
2.01.2.3 Experimental Structural Methods

Several ^1H and ^{13}C NMR data of azetidines and azetidin-3-ones have been reported. A significant variation is observed in geminal coupling constants of the methylene group attached to nitrogen of different classes of azetidines. The substituents at the nitrogen atom and the conformations of the compounds appear to affect the J values.

The ^1H NMR data (δ values in ppm; J values in Hz, CDCl_3) of selected azetidines **6-15** are shown in [Scheme 1](#) <2000JOC2253, 2005S3508, 2001TL2373, 2002EJO995, 1998JOC6, 1995J(P1)2605, 1995T5465>. The ^{13}C NMR data (δ values in ppm, CDCl_3) of selected azetidines are shown in [Scheme 2](#) <2000JOC2253, 2005S3508, 2002EJO995, 1998JOC6, 1995J(P1)2605, 1995T5465>.

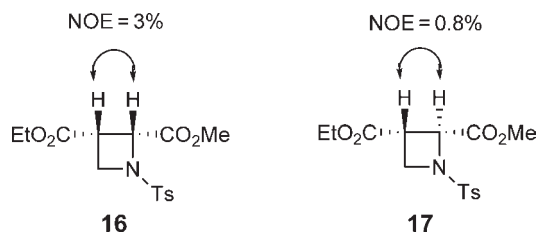


Scheme 1



Scheme 2

Nuclear Overhauser effect (NOE) experiments have been used to determine the stereochemical relationship between the groups on adjacent carbon atoms of the ring [<1997JOC5953, 2002OL1299, 2005SL1559>](#). For example, *cis*-azetidine **16** and *trans*-azetidine **17** have been characterized using NOE experiments ([Scheme 3](#)) [<2005SL1559>](#).



Scheme 3

The crystal structure determination of (*S*)-1-nitrosoazetidine-2-carboxylic acid revealed that the azetidine ring nitrogen atom was slightly pyramidalized [<2004AXE181>](#). The configuration of azetidine-based vicinal diamines has been determined by X-ray analysis [<2004EJO3893>](#). Single crystal X-ray analyses have been performed on 1-tosyl-3-benzyl-oxyazetidine [<2005JOC1408>](#), ((*R*)-1-((*S*)-1-phenylethyl)azetidine-2-yl)(piperidin-1-yl)methanone [<1996JCX639>](#) and 2,3-bis(imino)azetidine [<2002IC6493>](#).

2.01.2.4 Thermodynamic Aspects

Most azetidines are stable compounds and can be chromatographed, either by gas chromatography or by flash chromatography. It is known that 3-azetidinones are labile compounds and usually decompose at room temperature.

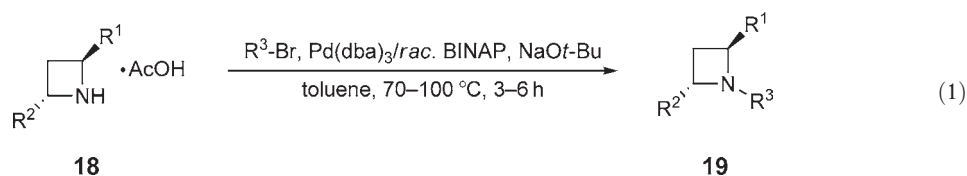
Inversion of the pyramidal nitrogen of azetidines is a major feature of these azaheterocycles. The $\Delta G^\ddagger$ for the inversion is at best only a few kcal (around 10 kcal mol^{-1}) <1996CHEC-II(1B)507>.

The rotational barriers of 1-nitroso-, 1-formyl-, and 1-(*N,N*-dimethylcarbamoyl)azetidines, compared with those of analogous cyclic amides, suggested that amide conjugation was weaker when the nitrogen was part of an azetidine ring.

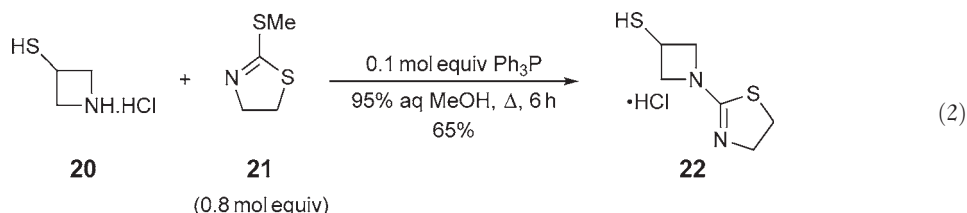
2.01.2.5 Reactivity of the Azetidine Ring

2.01.2.5.1 Electrophilic attack at nitrogen

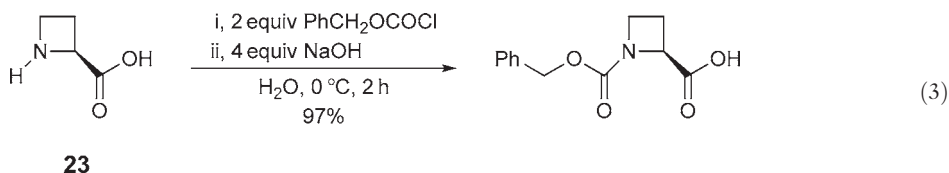
The azetidinium acetates **18** are suitable substrates for the synthesis of 1-arylazetidines **19** <2000EJO1815>. The palladium-catalyzed coupling reaction of azetidines **18** with aryl bromides has led to the synthesis of 1-arylazetidines **19** (Equation 1). This reaction required the presence of a strong base such as *t*-butoxide.

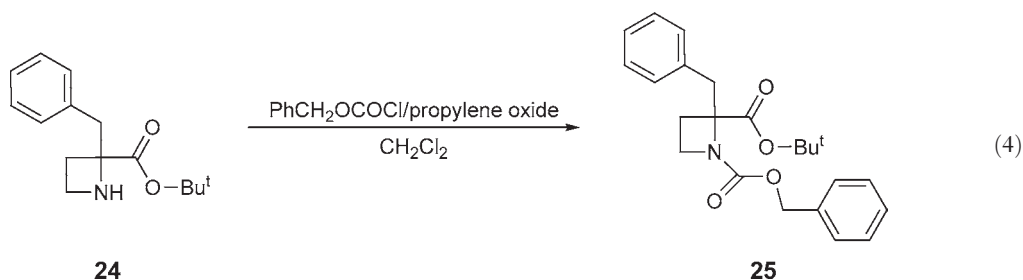


The reaction of azetidine-3-thiol hydrochloride **20** with 2-methylthio-1,3-thiazoline **21** in the presence of a catalytic amount of triphenylphosphine afforded 2-(3-mercaptoazetidin-1-yl)-1,3-thiazoline hydrochloride **22** (Equation 2), which is useful for the pendant moiety of new oral 1β -methylcarbapenem antibiotic L-084 <2002H(56)433>.

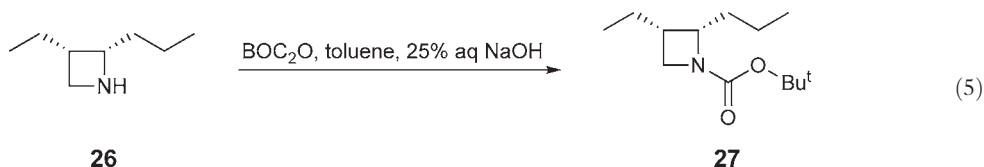


The protection of the nitrogen atom in azetidines is often required during transformations of other functionalities on the ring carbon(s). The benzyloxycarbonyl group is a suitable protecting group because it can be easily removed. The *N*-benzyloxycarbonylation of azetidine-2-carboxylic acid **23** was achieved by employing benzyl chloroformate and sodium hydroxide in water (Equation 3) <2004TL3607>. This method was found more efficient compared to those using an organic base like triethylamine or pyridine, or 4-dimethylaminopyridine (DMAP) in a mixture of dioxane and water. The *N*-benzyloxycarbonylation of *t*-butyl 2-benzylazetidine-2-carboxylate **24** to the corresponding *N*-benzyloxycarbonyl derivative **25** was realized by benzyl chloroformate in propylene oxide and dichloromethane (Equation 4) <2004BML2253>. In many cases, *N*-unsubstituted azetidines are transformed into *t*-butylcarbamates for easier isolation and purification as shown in the transformation of azetidine **26** to *N*-BOC-protected azetidine **27** (Equation 5) <2004EJO4471, 2004EJO3893, 2002TL4633, 2004SL2751>.





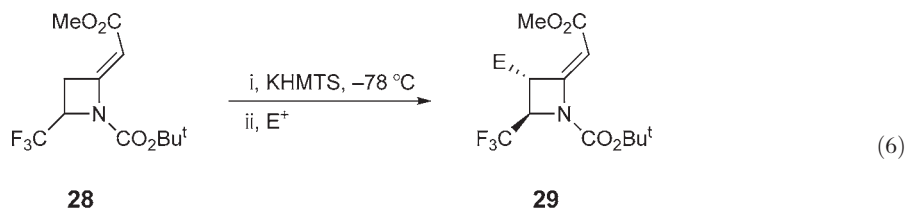
(4)



(5)

2.01.2.5.2 Electrophilic attack at carbon

Treatment of 1-(*t*-butoxycarbonyl)-2-(methoxycarbonylmethylene)-4-(trifluoromethyl)azetidine **28** with potassium bis(trimethylsilyl)amide at -78°C followed by reaction with an alkyl halide or an aldehyde afforded 3-alkyl-substituted azetidines **29** (Equation 6) <2003OL4101>. This procedure is of particular importance to the synthesis of azetidines with an alkyl substituent at the C-3 position.

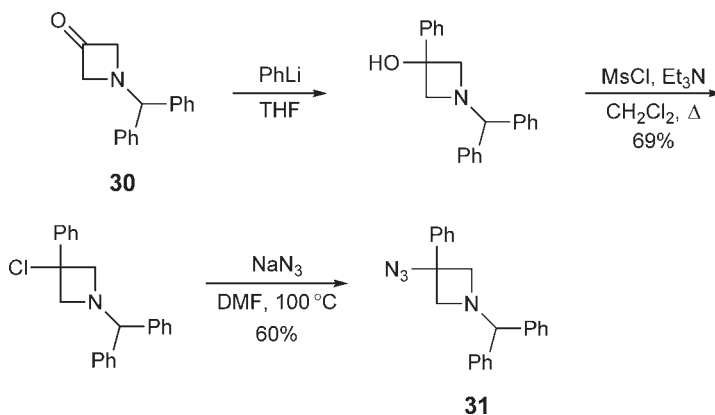


(6)

E = Me (75%), 3,5-F₂C₆H₃CH₂ (68%), PhCH(OH) (71%)

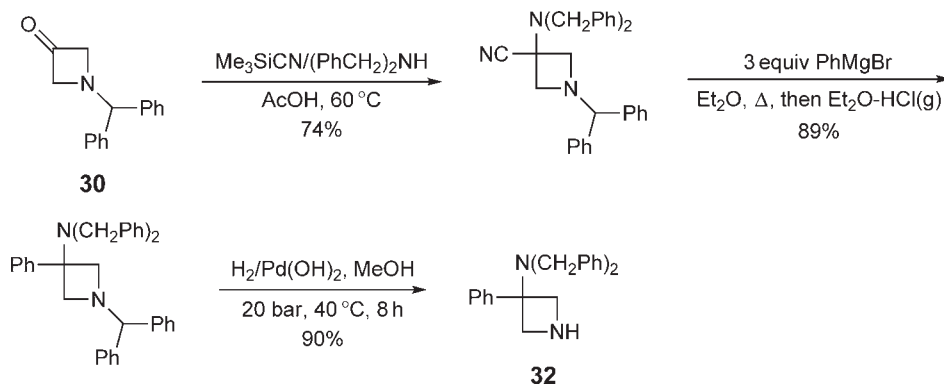
2.01.2.5.3 Nucleophilic attack at carbon

A series of nucleophilic reactions has been utilized in the transformation of 1-benzhydrylazetidin-3-one **30** to 1-benzhydryl-3-azido-3-phenylazetidine **31** (Scheme 4) <1995SC803>. 1-Benzhydrylazetidin-3-one **30** has been



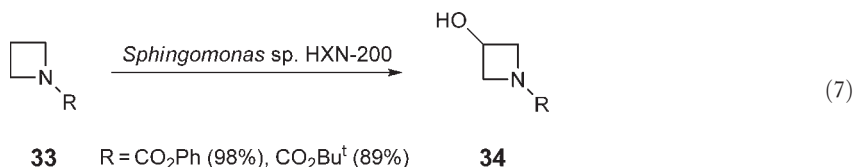
Scheme 4

used in the synthesis of 3-amino-3-phenylazetidine **32** as well (Scheme 5) <1995SC803>. Addition of methylmagnesium bromide to *N*-benzhydrylazetidin-3-one, followed by a Ritter-type reaction on the resulting azetidin-3-ol, has been described <1996TL1297>.

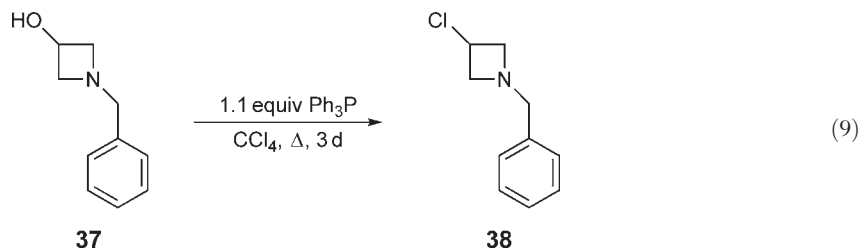
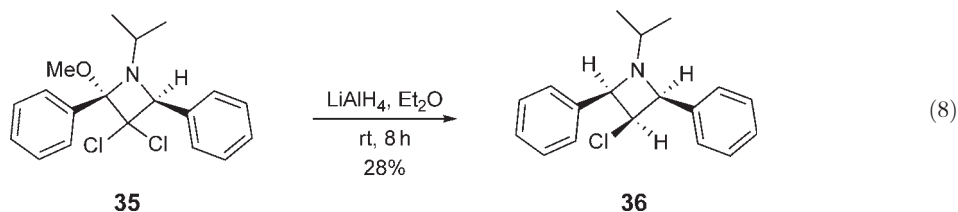


Scheme 5

Hydroxylation of azetidine-1-carboxylates **33** with a biocatalyst, *Sphingomonas* sp. HXN-200, gave the corresponding 3-hydroxyazetidines **34** (Equation 7) <2002OL1859>.



The reaction of 3,3-dichloro-2-methoxyazetidine **35** with lithium aluminium hydride in ether afforded 3-chloroazetidine **36** (Equation 8). The substitution of the methoxy group by hydride via an azetinium intermediate and subsequent conversion of the geminal dichloro derivative to the monochloroazetidine via a single electron transfer reaction yielded this compound <1998JOC6>. Treatment of 1-benzyl-3-hydroxyazetidine **37** with triphenylphosphine in carbon tetrachloride yielded 1-benzyl-3-chloroazetidine **38** (Equation 9) <2004JOC2703>.

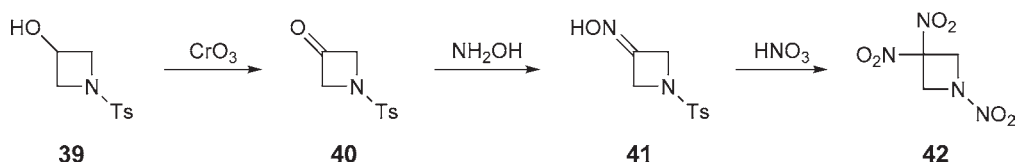


2.01.2.5.4 Nucleophilic attack at hydrogen (Deprotonation)

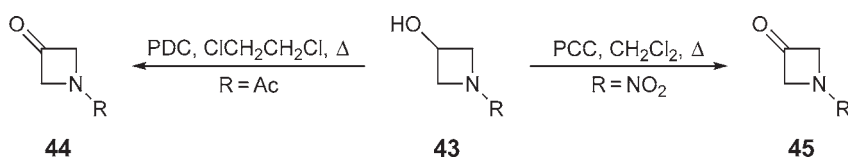
Deprotonation at the ring carbon(s) and following reactions are treated in Section 2.01.2.5.2.

2.01.2.5.5 Oxidation reactions

The oxidation reaction of 1-tosyl-3-hydroxyazetidine **39** has been utilized in the synthesis of the highly energetic 1,3,3-trinitroazetidine **42**. The oxidation product 3-azetidinone **40** was transformed into its oxime **41**, which after oxidative nitrolysis yielded 1,3,3-trinitroazetidine **42** (Scheme 6) <1995JOC1959>. Other reagents that have been used for the transformation of azetidin-3-ols **43** into azetidin-3-ones **44** and **45** include pyridinium dichromate in refluxing dichloroethane, pyridinium chlorochromate (PCC) in refluxing dichloromethane (Scheme 7) <1996JOC5453>, and phosphoric acid-dicyclohexylcarbodiimide <1995CPB797>.

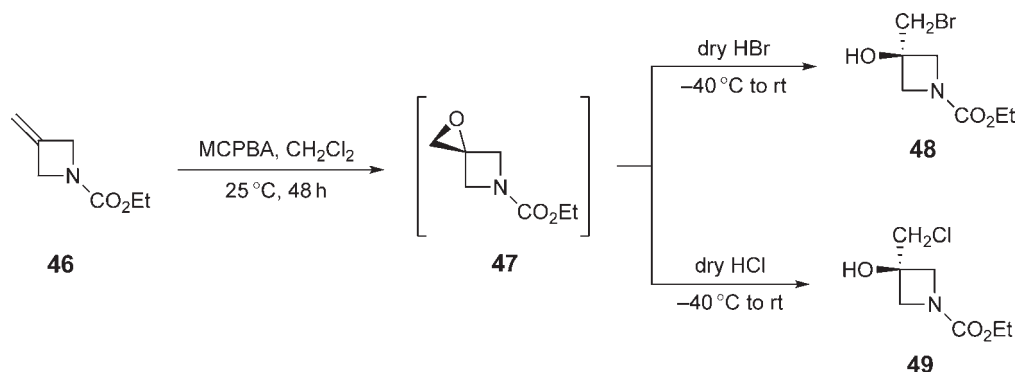


Scheme 6



Scheme 7

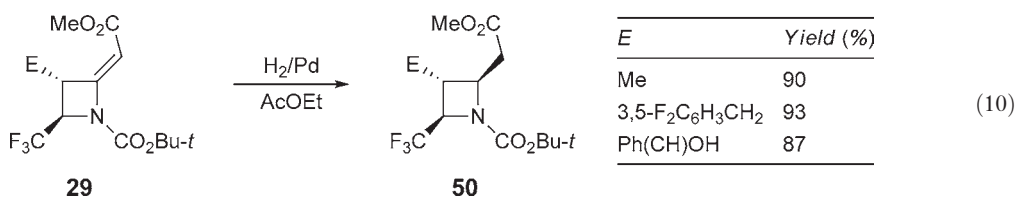
The epoxidation of the carbon–carbon double bond in ethyl 3-methyleneazetidine-1-carboxylate **46** using *m*-chloroperbenzoic acid and the regioselective ring opening of the resulting epoxide **47** with HBr and HCl led to the synthesis of ethyl 3-bromomethyl-3-hydroxyazetidine-1-carboxylate **48** and ethyl 3-chloromethyl-3-hydroxyazetidine-1-carboxylate **49**, respectively (Scheme 8) <1997JOC4434>.



Scheme 8

2.01.2.5.6 Reduction reactions

Catalytic hydrogenation of the carbon–carbon double bond at C-3 of azetidines **29** over Pd/C in ethyl acetate gave azetidines **50** with the 2-alkyl group *cis* to the trifluoromethyl group (Equation 10) <2003OL4101>.

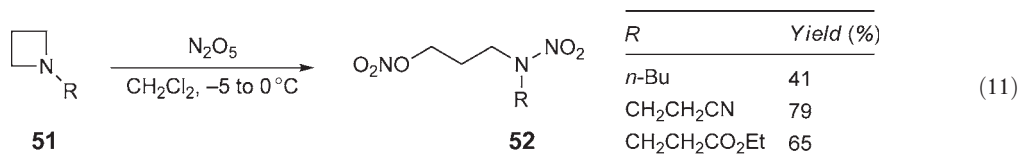


2.01.2.5.7 Ring opening reactions

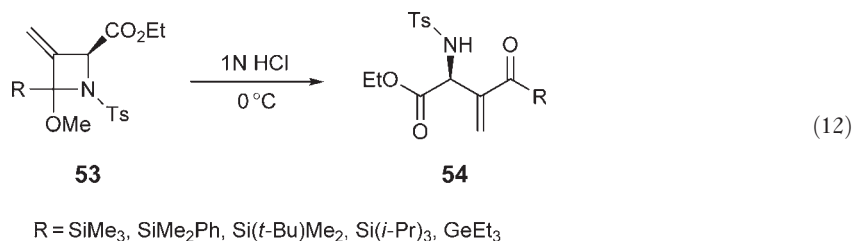
The ring opening reactions of azetidine derivatives have been employed for the synthesis of various acyclic and heterocyclic compounds of biological interest. It would therefore be appropriate to discuss the reactions leading to acyclic and cyclic products separately.

2.01.2.5.7(i) Ring opening reactions leading to acyclic products

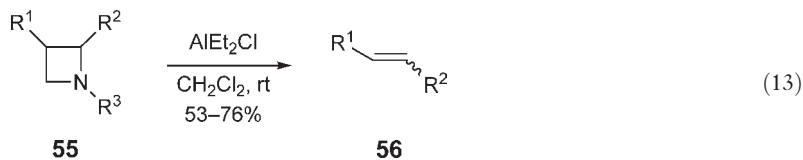
Treatment of the *N*-alkyl-substituted azetidines **51** with dinitrogen pentoxide in dichloromethane at subambient temperature led to azetidine ring opening forming the corresponding 1,3-nitramine nitrates **52** (Equation 11) <1995T5073>. The ring opening was observed to depend on the type of substituent at nitrogen. For example, the *N*-picrylazetidine ring was inert to this reaction, whereas 2,4,6-tris-(1-azetidyl)-1,3,5-triazine gave the corresponding nitramine nitrate in 60% yield. The reaction of aziridine carbamate paralleled the reactivity of the *N*-alkylazetidines but the azetidyl ureas and amides afforded the *N*-nitroazetidine instead of the ring-opened products.



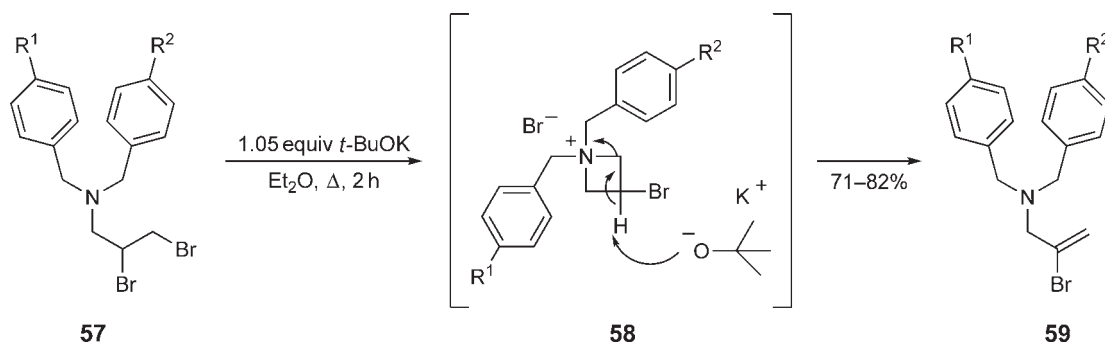
The ring opening of 4,4-disubstituted 1-tosyl-3-methyleneazetidine-2-carboxylates **53** proceeded smoothly under acidic condition to yield the chiral acyl silane **54** (Equation 12) in quantitative yields and with an enantiomeric excess up to 97% <2003OL3691>.



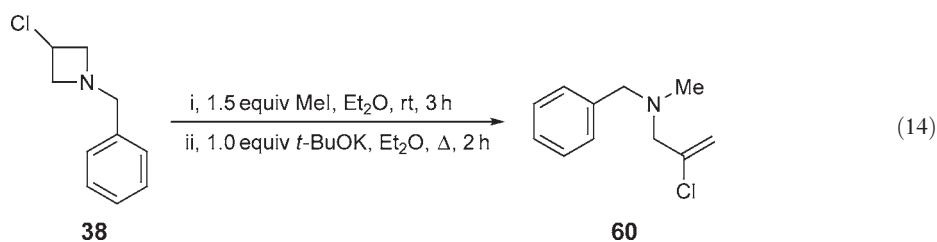
The reactivity of azetidines **55** toward diethylaluminium chloride has been investigated <1999JOC9596>. Azetidines having 4-methoxyphenyl, styryl, or 2-furyl groups at C-2 and a benzyl or allyl substituent at nitrogen efficiently reacted with diethylaluminium chloride to give alkenes **56**, including vinyl ethers and conjugated dienes stereoselectively through a fragmentation process (Equation 13). The azetidines bearing a phenyl or a 4-nitrophenyl group at C-2 and a 4-methoxyphenyl substituent at nitrogen were unreactive. These results thus indicated that an electron-donating group is able to stabilize the positive charge at the C-2 position, and the basic azetidine nitrogen is necessary for the fragmentation to occur.



The reaction of *N,N*-di(arylmethyl)-*N*-(2,3-dibromopropyl)amines **57** with potassium *t*-butoxide in diethyl ether under reflux for 2 h furnished *N,N*-di(arylmethyl)-*N*-(2-bromo-2-propenyl)amines <2004JOC2703>. A neighboring group participation of the *N,N*-dibenzyl function forming the 3-bromoazetidinium salt **58**, which underwent deprotonation by potassium *t*-butoxide, explained the formation of products **59** (Scheme 9). This mechanism is supported by the fact that the quaternization of 1-benzyl-3-chloroazetidine **38** with iodomethane followed by treatment with potassium *t*-butoxide yielded the anticipated vinyl chloride **60** (Equation 14).



Scheme 9

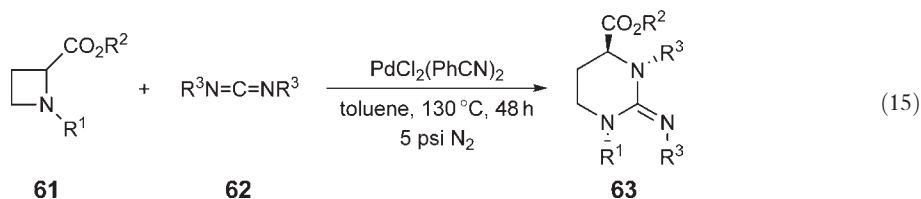


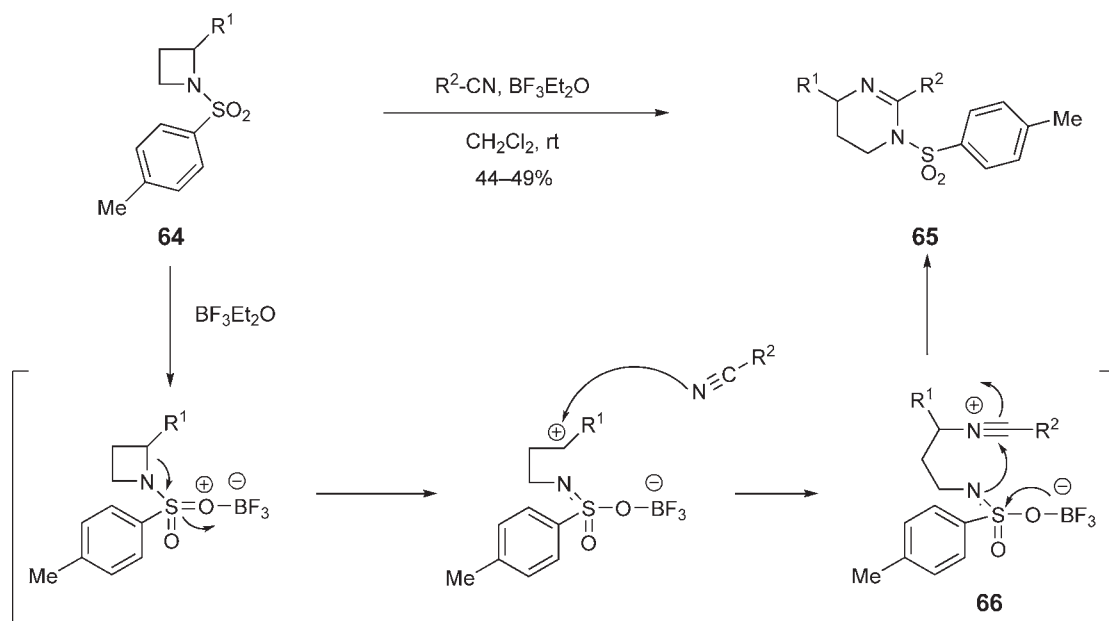
2.01.2.5.7(ii) Ring opening reactions leading to cyclic products

1-Alkylazetidine-2-carboxylates **61** react with carbodiimides **62** in the presence of bis(benzonitrile)palladium dichloride to form tetrahydropyrimidin-2-imines **63** in excellent yields (Table 1) (Equation 15) <1995JOC253>. The reaction has been observed to be both regio- and stereospecific, the cycloaddition occurring with retention of configuration of the carbon centers bearing the substituent groups. *N*-Tosyl-2-aryl azetidines **64** react as formal 1,4-dipoles with various activated or nonactivated alkenes <2001CC958> and with nitrile <2004OL4829> in the presence of $\text{BF}_3\text{-Et}_2\text{O}$ forming piperidines and tetrahydropyrimidine derivatives **65**, respectively. The mechanism of this [4+2] cycloaddition reaction (Scheme 10) is similar to the [3+2] cycloaddition of aziridines <2004TL1137>. The Lewis acid can attack the sulfonyl oxygen of azetidines **64**, while the nitrile group attacks the benzylic center in a typical Ritter fashion leading to the formation of nitrilium salt **66**, which can cyclize to form the tetrahydropyrimidines **65**.

Table 1 Reaction of 1-alkylazetidine-2-carboxylates **61** with carbodiimides **62** (Equation 15)

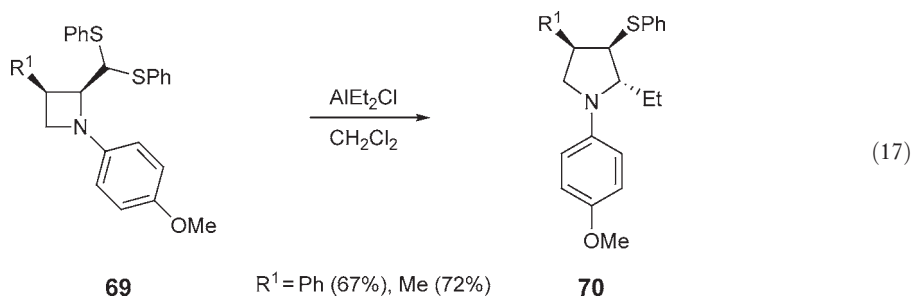
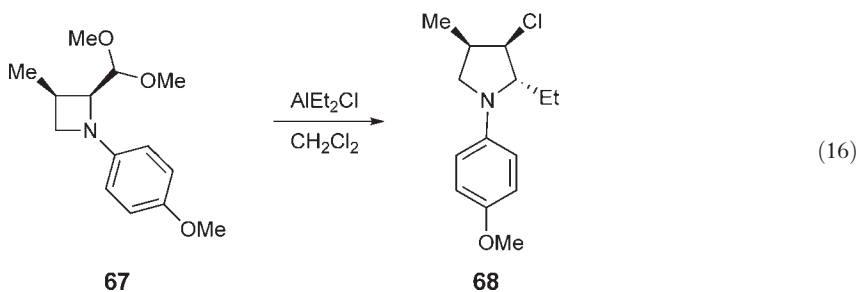
R^1	R^2	R^3	Yield (%)
Bu^t	Me	Ph	92
Bu^t	PhCH_2	Ph	94
Bu^t	PhCH_2	4-MeC ₆ H ₄	64
Bu^t	PhCH_2	4-ClC ₆ H ₄	97
Bu^t	Me	4-ClC ₆ H ₄	95
C ₆ H ₁₁	Me	4-ClC ₆ H ₄	88

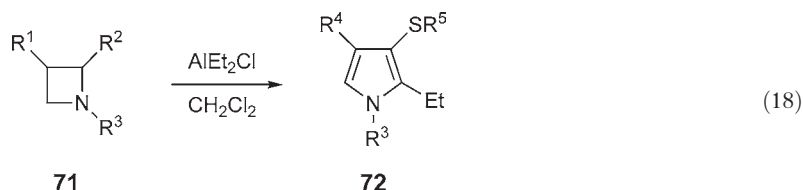




Scheme 10

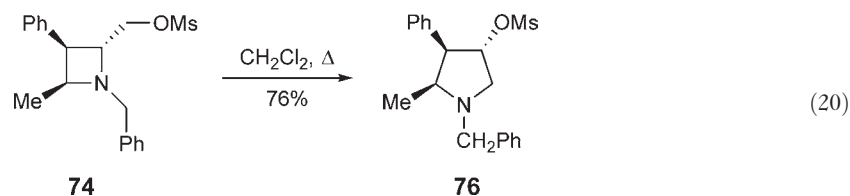
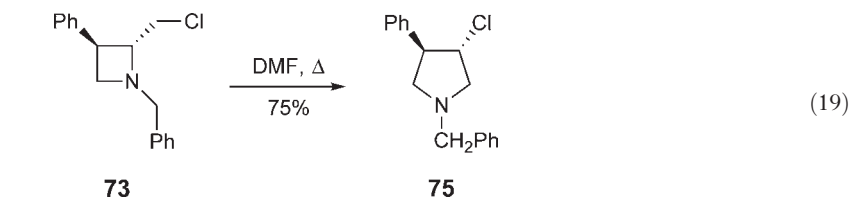
Contrary to azetidines **55** having 4-methoxyphenyl, styryl, or 2-furyl groups at C-2 and a benzyl or allyl substituent at nitrogen, which reacted with diethylaluminium chloride to give alkenes **56** (Equation 13), the *N*-4-methoxyphenyl-substituted azetidine-2-acetals **67** reacted with diethylaluminium chloride in a stereocontrolled manner to yield pyrrolidine derivatives **68** (Equation 16). A similar reaction of azetidine **69** yielded the pyrrolidine derivatives **70** bearing a phenylthio group at C-3 (Equation 17), indicating the involvement of a different mechanism than in the case of azetidine-2-acetals <1999JOC9596>. The reaction of azetidine-2-thioacetal **71** bearing a phenoxy or exocyclic double bond substituent at C-3 of the azetidine ring, which can promote aromatization, with diethylaluminium chloride gave pyrroles **72** (Equation 18) in moderate to good yields (Table 2).



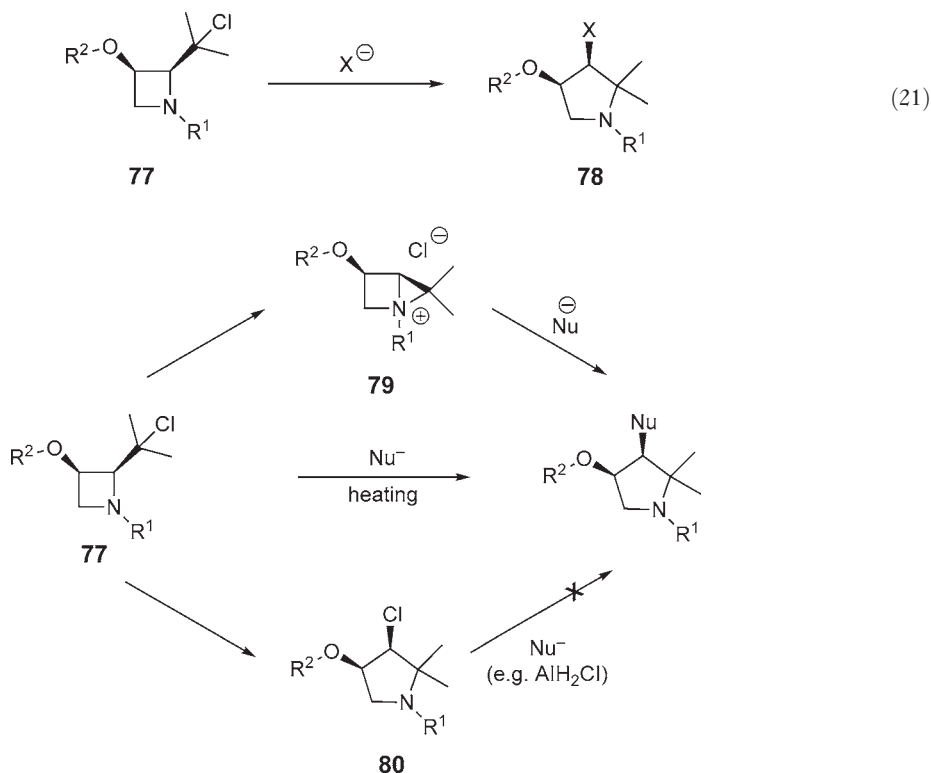
**Table 2** Reaction of azetidine-2-thioacetals **71** with diethylaluminium chloride (Equation 18)

R^1	R^2	R^3	R^4	R^5	Yield (%)
PhO	1,3-Dithiolan-2-yl	4-MeOC ₆ H ₄	H		67
Isopropylidene	1,3-Dithiolan-2-yl	4-MeOC ₆ H ₄	<i>i</i> -Pr		38
PhO	CH(SPh) ₂	4-MeOC ₆ H ₄	H	Ph	55
PhO	CH(SPh) ₂	CH ₂ Ph	H	Ph	72

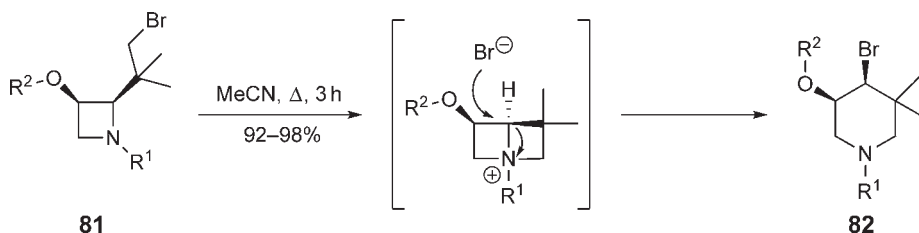
Heating of 2-(chloromethyl)azetidine **73** or 2-(mesyloxymethyl)azetidine **74** in chloroform or dimethylformamide induced a stereospecific ring enlargement to give 3-chloropyrrolidine **75** (Equation 19) or 3-methanesulfonyloxypyrrolidine **76** (Equation 20) <2003TL5209>. A concerted mechanism was proposed for these transformations, which was based on the very high energy of the possible bicyclic azetidinium ion, involved in a stepwise mechanism, and supported by AM1 calculations, as well as the failure to detect such an azetidinium ion by nuclear magnetic resonance (NMR) spectroscopy. However, this has been refuted by the reaction of 2-(1-chloroalkyl)azetidines **77** with various nucleophiles under different conditions (Table 3) leading to pyrrolidine derivatives **78** (Equation 21), which has been explained through the intermediacy of bicyclic azetidinium intermediates **79** <2006OL1105>. It was argued that a concerted mechanism for such reactions would involve the formation of a 3-chloropyrrolidine intermediate **80**, which should be convertible to pyrrolidines. However, when such an intermediate was synthesized and reacted with monochloroalane, it failed to give the anticipated pyrrolidines (Scheme 11). The reactions of 2-(2-bromoalkyl)azetidines **81** with nucleophiles afforded the piperidine derivatives **82** in a similar manner (Scheme 12).

**Table 3** Reaction of 2-(1-chloroalkyl)azetidines with nucleophiles (Equation 21)

R^1	R^2	Reaction conditions	X	Yield (%)
Allyl	Bn	Δ , MeCN, 18 h	Cl	46
Allyl	Me	Δ , MeCN, 18 h	Cl	44
Bu ^t	Bn	10 equiv NaOH, 100 °C, 18 h, DMSO	OH	46
Allyl	Bn	10 equiv KCN, 100 °C, 18 h, DMSO	CN	44
Allyl	Bn	10 equiv NaN ₃ , 100 °C, 18 h, DMSO	N ₃	52

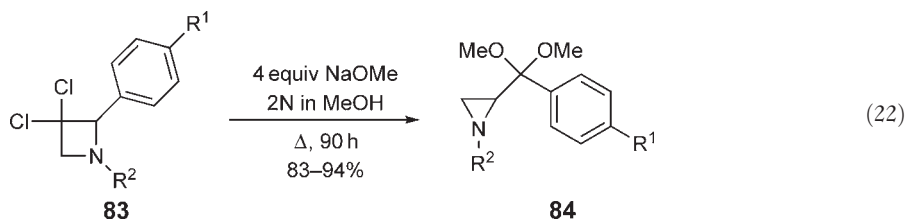


Scheme 11



Scheme 12

3,3-Dichloroazetidines **83** are easily converted into aziridine derivatives **84** in excellent yields by sodium methoxide in methanol (Equation 22). Conversion to the aziridine ring system has been explained by the intermediacy of a 2-azetine ring system <2002JOC2075>.



2.01.2.6 Reactivity of Substituents Attached to the Ring Carbon Atoms

The azetidine ring is stable during a variety of transformations of the functional groups present on the ring carbon(s). The reaction of 1-ethoxycarbonyl-3-(bromomethyl)-3-chloroazetidines **85** with 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU),

1,5-diazabicyclo[4.3.0]non-5-ene (DBN), and potassium *t*-butoxide has been observed to result into dehydrohalogenation giving the azetidines **86** and **87** (Equation 23) depending upon the reaction conditions (Table 4) <1997JOC4434>. The results could be explained without invoking the intermediacy of bridged halonium ions. Treatment of the *N*-substituted 3-(bromomethyl)-3-chloroazetidines with activated zinc resulted into an eliminative dehalogenation to yield 3-methylenazetidines **46** and **89** (Scheme 13) <1996JHC837, 1999SC885>. Ozonolysis of the carbon–carbon double bond in compounds **46** and **89** gave the corresponding azetidin-3-ones **44** and **90**. Simple functional group transformations of the ester group on azetidine **91** led to the synthesis of 4-trifluoromethylazetidin-2-yl alkene **92** and carboxylic acid **93** (Scheme 14) <2003OL4101>.

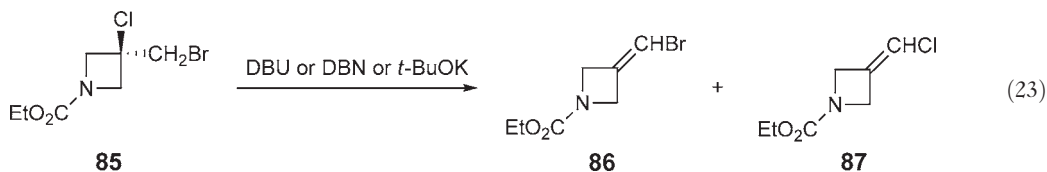
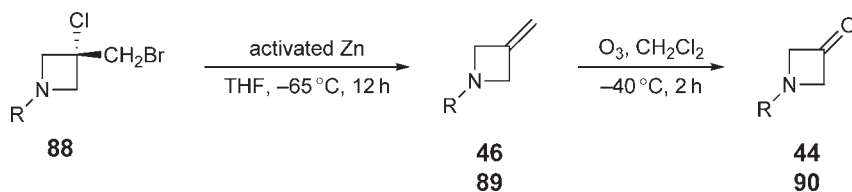


Table 4 Reaction of 1-ethoxycarbonyl-3-(bromomethyl)-3-chloroazetidines **85** with DBU, DBN, and potassium *t*-butoxide (Equation 23)

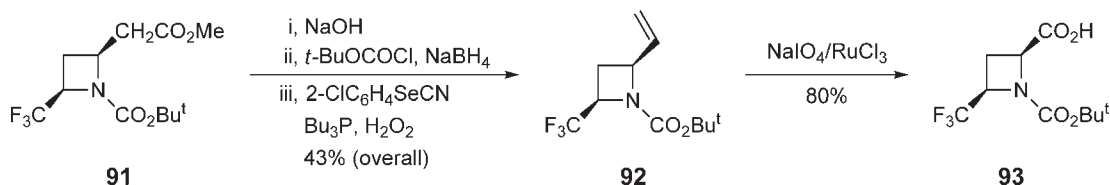
Reagents	Conditions	Ratio of (86):(87)
DBU (2.5 equiv)	80–100 °C, 0.5 h	45:55
DBU (2.5 equiv)	25 °C, 8 h	70:30
DBN (2.0 equiv)	80–100 °C, 15 min	50:50
Bu ^t OK	25 °C, 8 h	100:0



88: R = CO₂Et, COMe, COPh; **46**: R = CO₂Et; **89**: R = COMe, R = COPh

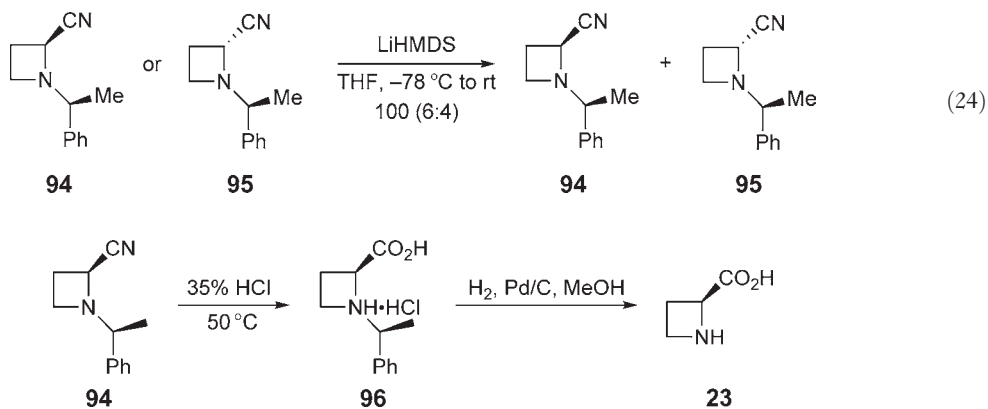
44: R = COMe; **90**: R = COPh

Scheme 13

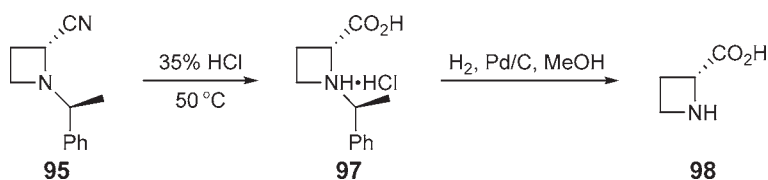


Scheme 14

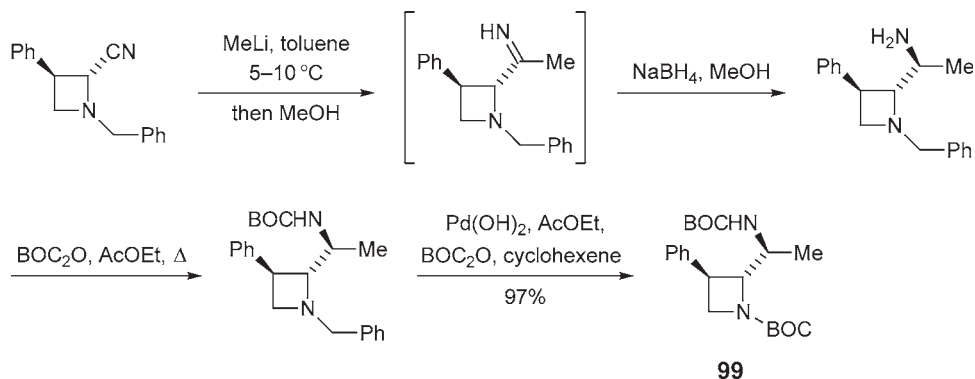
The diastereomers **94** and **95** of 2-cyanoazetidine could be equilibrated by reacting either **94** or **95** with LiHMDS, leading to a thermodynamic mixture of diastereomers in a 3:2 ratio (Equation 24) <2005JOC9028>. The cyano group in these azetidines can be easily hydrolyzed with hydrochloric acid followed by *N*-deprotection of the resulting azetidine-2-carboxylic acid hydrochlorides **96** and **97** to afford the corresponding azetidine-2-carboxylic acids **23** and **98**, respectively (Schemes 15 and 16), which are precursors for many biologically important compounds. The reduction of carboxylic acid to alcohol in azetidine-2-carboxylic acid was achieved by LiAlH₄ <1998SL1164>. A number of other useful azetidine derivatives **99** (Scheme 17) <2004EJO3893>, **100** and **101** (separated by flash chromatography) (Scheme 18) <2003TA2407>, **102** (Scheme 19) <2003TL5209>, and **103** (Scheme 20) <2004TL7525> have been synthesized by transformations starting from the cyano group on the azetidines.



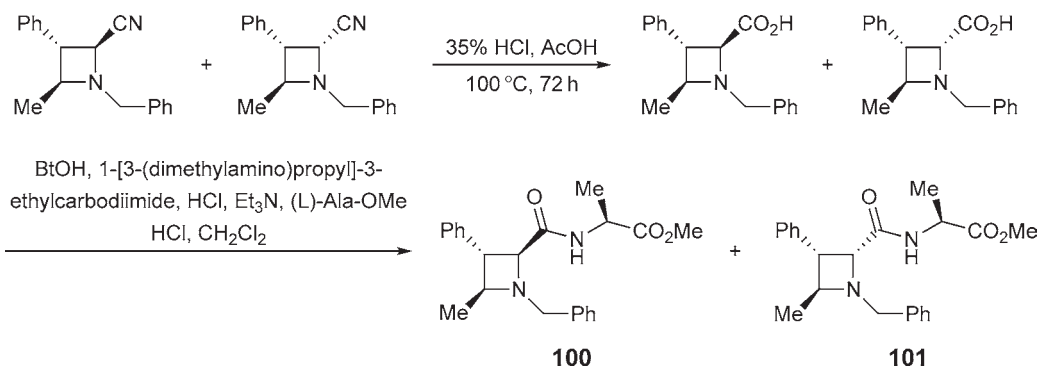
Scheme 15



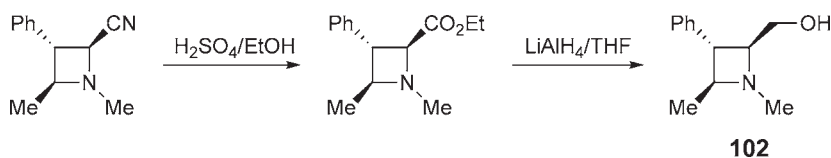
Scheme 16



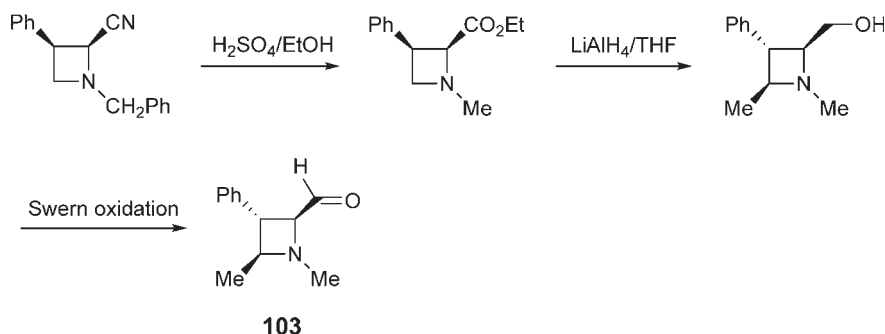
Scheme 17



Scheme 18

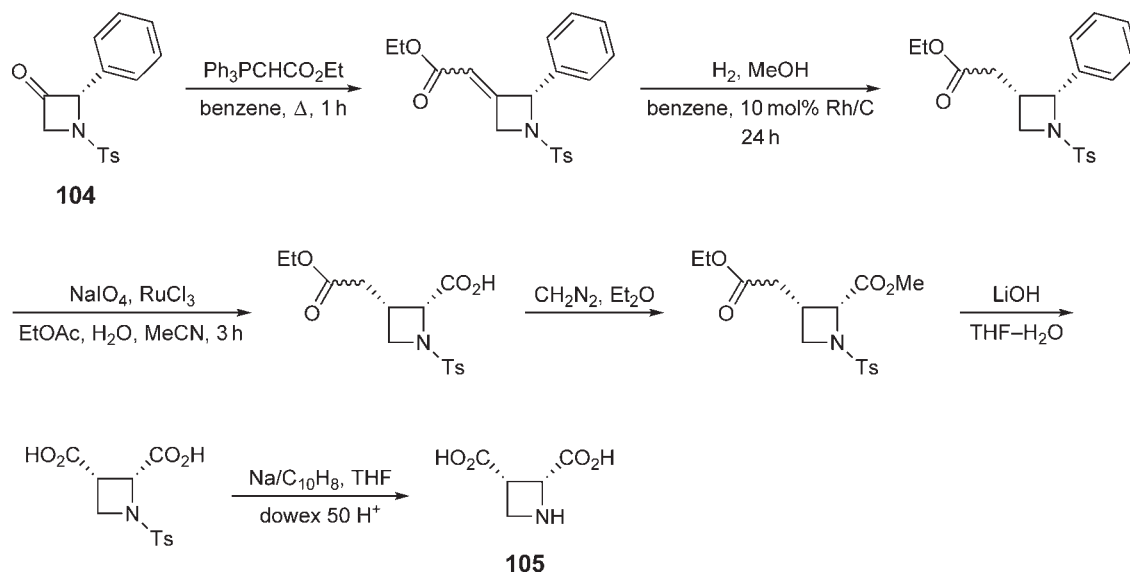


Scheme 19

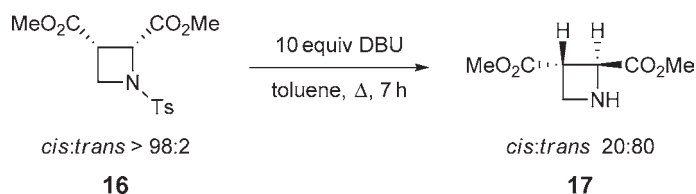


Scheme 20

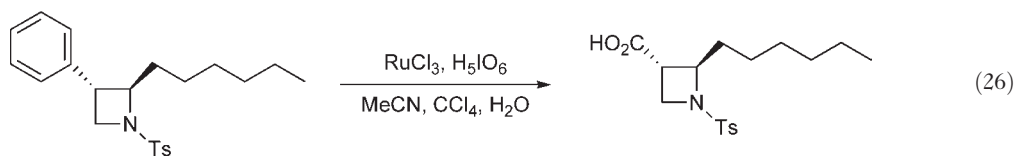
1-Tosyl-2-phenylazetidin-3-one **104** serves as a precursor of azetidine-2,3-dicarboxylic acid **105**, which is a potent inhibitor of sodium-dependent glutamate uptake [<2005SL1559>](#). The key steps in the synthesis involve a very efficient Wittig alkenylation of azetidin-3-one **104**, followed by a highly stereoselective rhodium-catalyzed hydrogenation (Scheme 21). Epimerization of *cis*-1-tosyl-azetidine-2,3-dicarboxylate **16** to *trans*-1-tosyl-azetidine-2,3-dicarboxylate **17** was performed using DBU as a base (Equation 25). An example of the oxidation of a phenyl group to a carboxylic group utilized periodic acid as the stoichiometric oxidant instead of sodium periodate (Equation 26) [<2005S3508>](#).



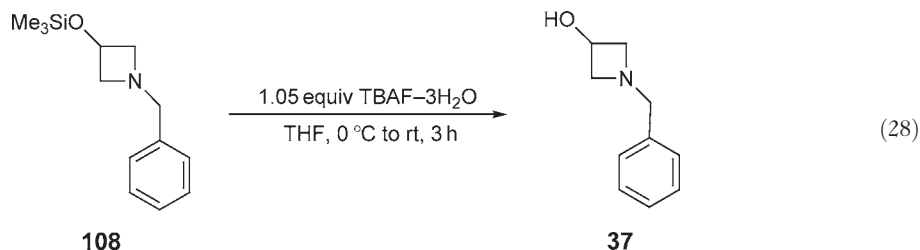
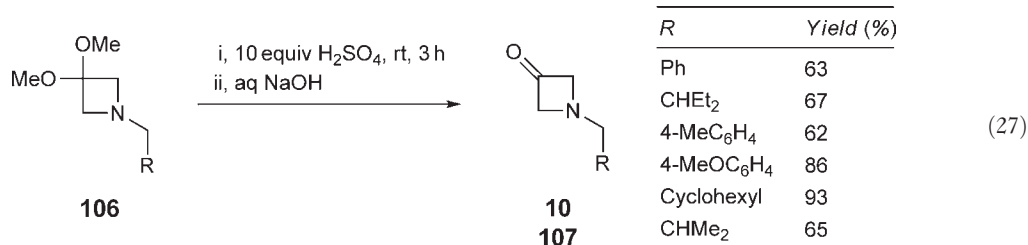
Scheme 21



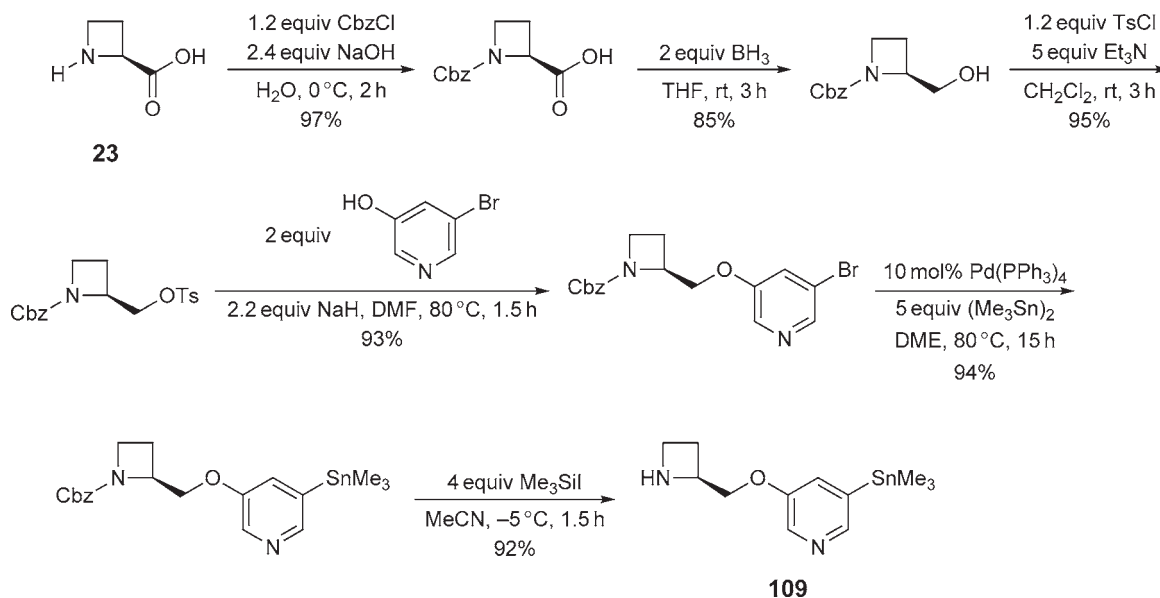
(25)



The hydrolysis of the acetal moiety in *N*-substituted 3,3-dimethoxyazetidines **106** with concentrated sulfuric acid is a straightforward methodology for the preparation of 1-benzylazetidin-3-one **10** and some other *N*-alkyl-substituted azetidin-3-ones **107** (Equation 27) <2001TL2373>. The hydroxyl group, protected as an ether in acyclic precursors prior to cyclization, is deprotected after cyclization by hydrolysis using suitable reagents to yield the corresponding hydroxyazetidines <2004JOC2703>. For example, 1-benzyl-3-trimethylsilyloxyazetidine **108** yielded 1-benzyl-3-hydroxyazetidine **37** on treatment with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) (Equation 28) <2004JOC2703>.

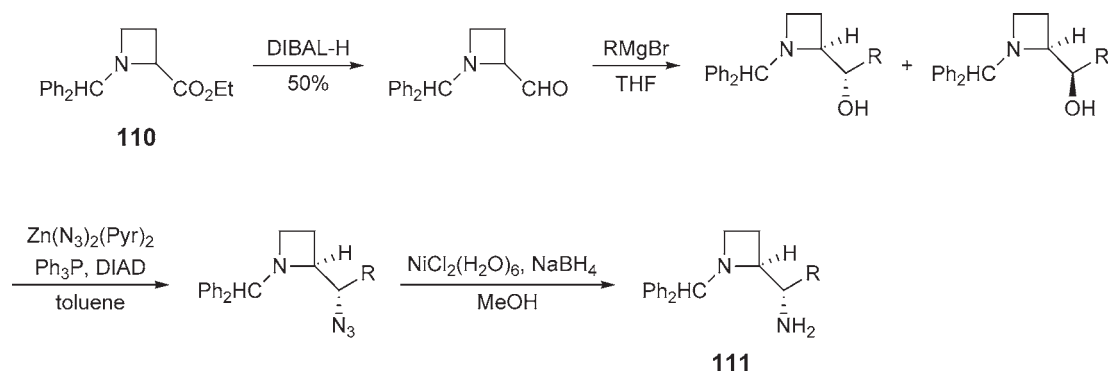


The synthesis of a new precursor of 5-IA-85380, a specific radiotracer for $\alpha_4\beta_2$ nicotinic acetylcholine receptors, that is, (*S*)-5-trimethylstannyl-3-(2-azetidylmethoxy)pyridine **109**, has been accomplished in six steps and 62% overall yield by functional group transformations of the carboxyl group in (*S*)-azetidine-2-carboxylic acid **23** (Scheme 22) <2004TL3607>.



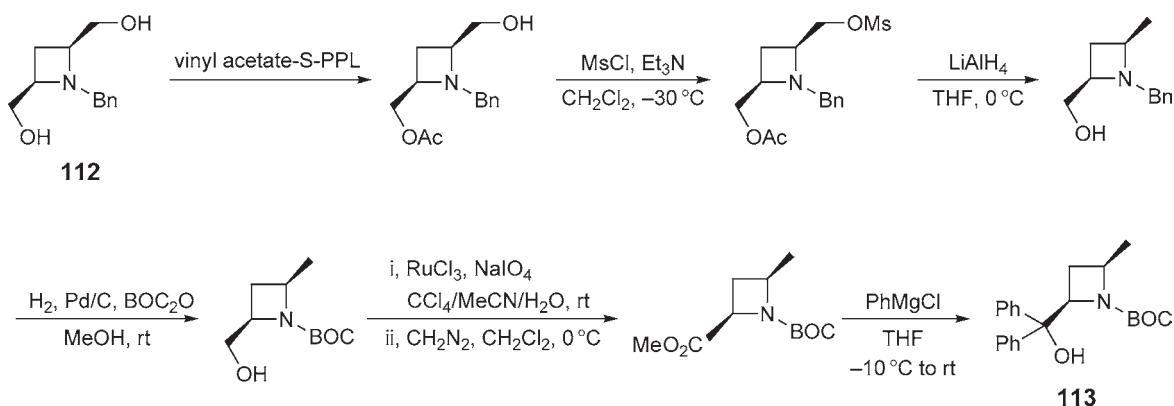
Scheme 22

A series of transformations in 1-benzhydrylazetidine-2-carboxylate **110** has led to the synthesis of 1-benzhydryl-2-aminoalkylazetidines **111**, known to have ORL-1 receptor binding properties (Scheme 23) <2002BML3157>.

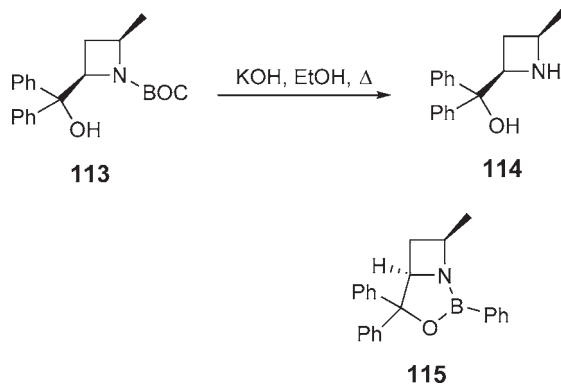


Scheme 23

Chiral azetidines have been synthesized by lipase-catalyzed selective acylation of the hydroxyl group in 2,4-bis(hydroxymethyl)azetidine **112** (Scheme 24) <2001TA605>. The resulting alcohol **113** was then transformed into an amino alcohol **114** (Equation 29), which represents an interesting precursor for the chiral catalyst **115**.

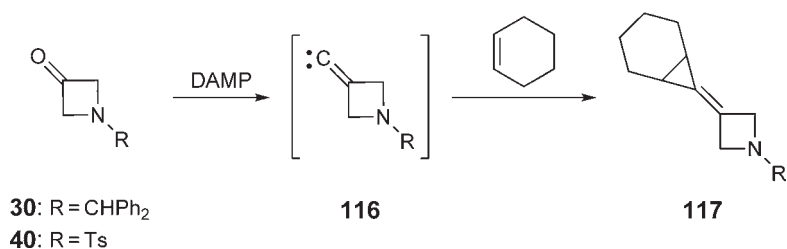


Scheme 24



(29)

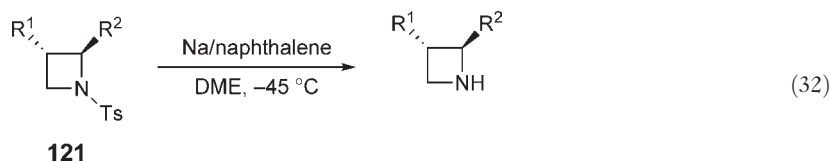
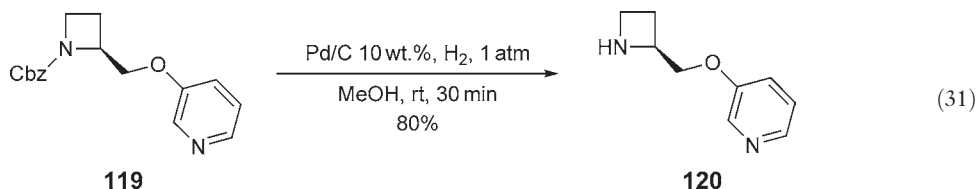
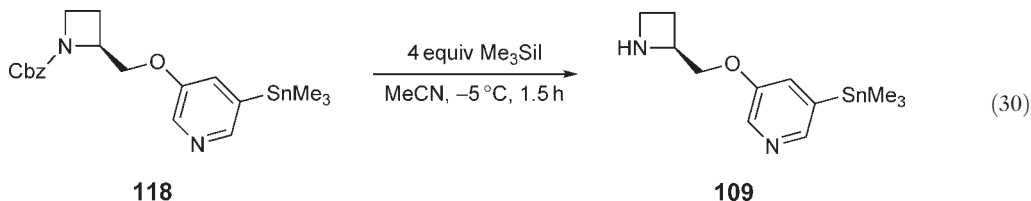
Azetidin-3-ones have been used as precursors of N-substituted 3-azetidinyliidenecarbenes **116** (Scheme 25). The 1-benzhydryl- and 1-tosylazetidin-3-ylcarbenes **116**, generated *in situ* by base-promoted reactions of 1-benzhydryl-azetidin-3-one **30** and of 1-tosylazetidin-3-one **40** with diethyldiazomethylphosphinate (DAMP), were trapped by cyclohexene to afford the corresponding methyleneecyclopropanes **117** <1996TL8101>.



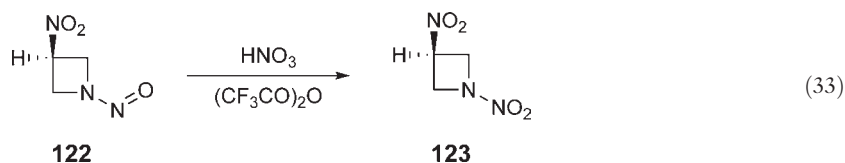
Scheme 25

2.01.2.7 Reactivity of Substituents Attached to the Ring Nitrogen Atom

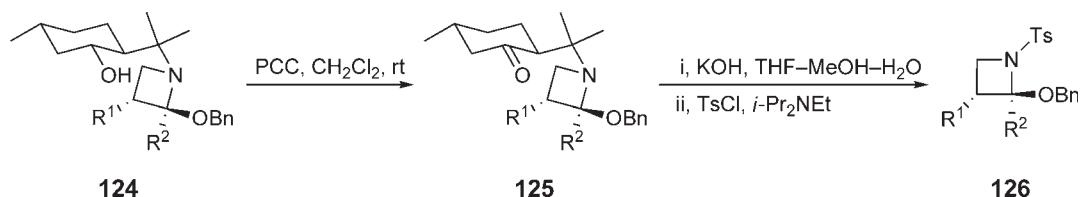
The removal of substituents at nitrogen has been applied routinely with azetidine derivatives. The benzyloxycarbonyl (Cbz) group in azetidine **118** was removed by trimethylsilyl iodide (Equation 30) <2004TL3607>. The *t*-butoxycarbonyl (BOC) group has been removed by HCl in diethyl ether <2004TL3607> or ethyl acetate <2003CPB96>. The catalytic hydrogenolysis has been used for facile deprotection of the Cbz group in azetidine **119** leading to azetidine **120** (Equation 31) <2004TL3607>, and for the removal of the α -phenylethyl group <2005JOC9028>. *N*-Debenzylation has been accomplished by employing palladium hydroxide and cyclohexene (hydrogen source) <2004EJO3893, 2002TL4633> or hydrogen gas in the presence of palladium hydroxide <2000EJO1815>. The latter methodology has also been used for the deprotection of a benzhydryl group <1995SC803>. An oxidative removal of an *N*-tosyl group can be accomplished using periodic acid in the presence of ruthenium tetroxide as a catalyst <2005S3508>, whereas an oxidative cleavage of a *N*-(4-methoxyphenyl) group is routinely achieved by cerium ammonium nitrate <2004SL2751>. The reductive *N*-detosylation in azetidines **121** has been achieved nicely utilizing Na/naphthalene in dimethoxyoxane at -45°C (Equation 32) <2004EJO4471> or Na/naphthalene in THF over Dowex 50 H^+ resin <2005SL1559>.



An oxidation of the nitroso group in 1-nitroso-3-nitroazetidine **122** by nitric acid in trifluoroacetic anhydride led to the synthesis of 1,3-dinitroazetidine **123** (Equation 33) <1998SC3949>, which serves as a substrate for the synthesis of the highly energetic 1,3,3-trinitroazetidine.



The removal of the menthyl appendage in azetidines **124** has been effected by oxidation with PCC to 8-aminomenthone derivatives **125**, which were treated with potassium hydroxide to enantiopure azetidine derivatives [<2005JOC1408>](#). The latter compounds were isolated as *N*-tosyl derivatives **126** by treatment with tosyl chloride in diisopropylethylamine ([Scheme 26](#)).



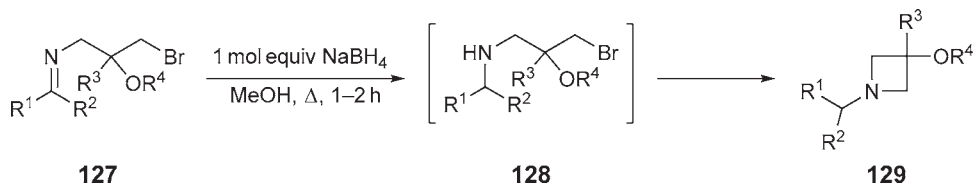
Scheme 26

A fluoride ion-induced desilylation of the trimethylsilyl group at *N*-[bis(trimethylsilyl)methyl]azetidin-3-ols served as a useful method for the preparation of 1-methylazetidin-3-ols [<1998SL510>](#).

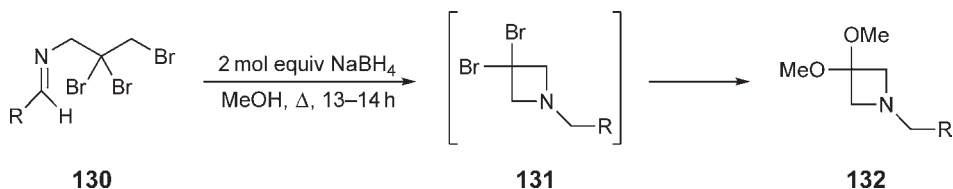
2.01.2.8 Ring Synthesis

2.01.2.8.1 Ring closure of γ -haloamines

Intramolecular cyclization of amines carrying a leaving group at the γ -position constitutes a very powerful method for the synthesis of azetidines. *N*-(Alkylidene)- γ -bromoamines **127** have proved to be excellent starting materials for such a transformation. The reduction of these imines with sodium borohydride in methanol to the corresponding γ -bromoamines **128** followed by cyclization afforded 3-alkoxy-1,3-disubstituted azetidines **129** ([Scheme 27](#)) [<1995T5465>](#). A similar reaction of tribromoimines **130** led to the formation of 3,3-dibromoazetidines **131** ([Scheme 28](#)) [<2001TL2373>](#). A nucleophilic displacement of the bromo atoms in the latter compounds yielded aminoacetals **132**.

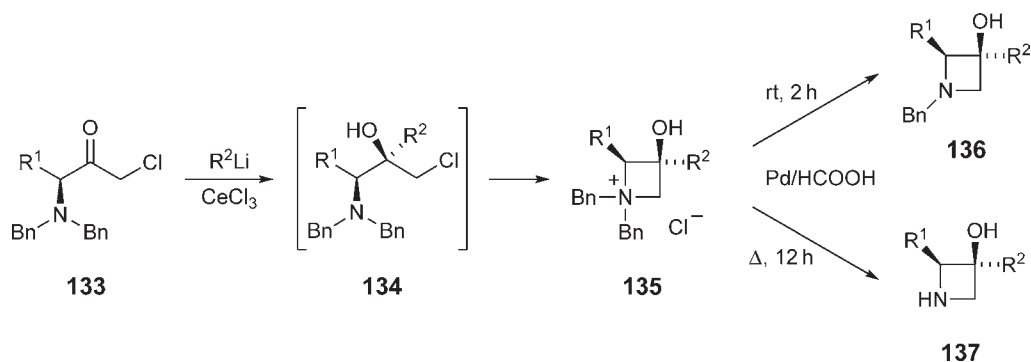


Scheme 27

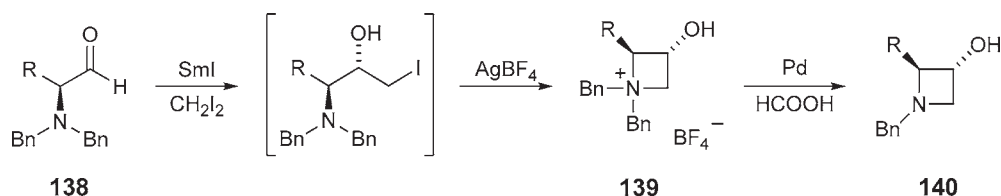


Scheme 28

Reduction of *N,N*-dibenzylaminoalkyl chloromethyl ketones **133**, followed by spontaneous intramolecular ring closure of the resulting γ -chloroamines **134**, afforded azetidinium salts **135**, which were subsequently deprotected toward chiral 3-hydroxyazetidines **136** and **137** (Scheme 29) <1997JOC1815>. In a similar approach, α -amino aldehydes **138** were converted into 3-hydroxyazetidinium salts **139** upon treatment with diiodomethane and samarium iodide, followed by stabilization using AgBF_4 . *N*-Dealkylation with Pd afforded enantiopure azetidines **140** (Scheme 30) <2000TL1231>.

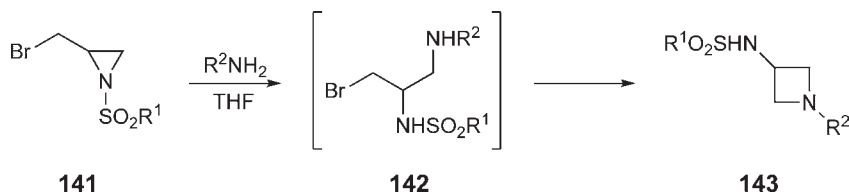


Scheme 29

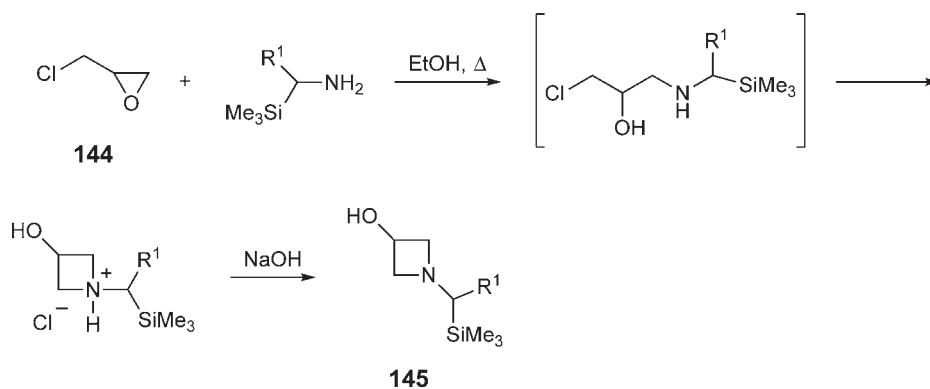


Scheme 30

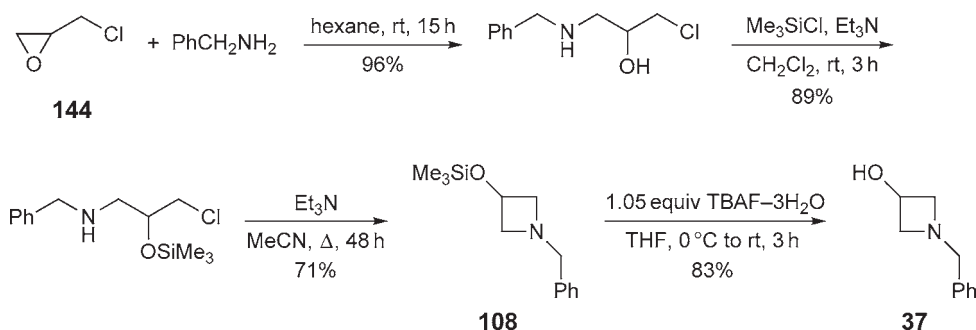
Ring opening of 2-(bromomethyl)-1-sulfonylaziridines **141** with amines in tetrahydrofuran formed γ -bromosulfonamides **142**, which led to the formation of 3-aminoazetidines **143** by intramolecular nucleophilic substitution (Scheme 31) <2000TL10295>. A similar reaction of 2-(chloromethyl)oxirane **144** with amines has been employed for the synthesis of 3-hydroxyazetidines **145** and **37** (Schemes 32 and 33) <1998SL510, 2004JOC2703>. The epoxide bearing an aminomethyl group could be cleaved regioselectively with ethylmagnesium bromide to form the corresponding γ -bromoamine derivatives, which cyclized to yield 3-hydroxyazetidines <1997TL6059>. The reaction of ester enolates **146** with chiral 1-aminoalkyl chloromethylketones **133** in tetrahydrofuran at low temperature yielded γ -chloroamines **147** (Scheme 34) <2002OL1299>. Evaporation of the solvent at room temperature, however, afforded 3-hydroxyazetidinium salts **148**, which were transformed into 3-hydroxyazetidines **149** by hydrogenolysis.



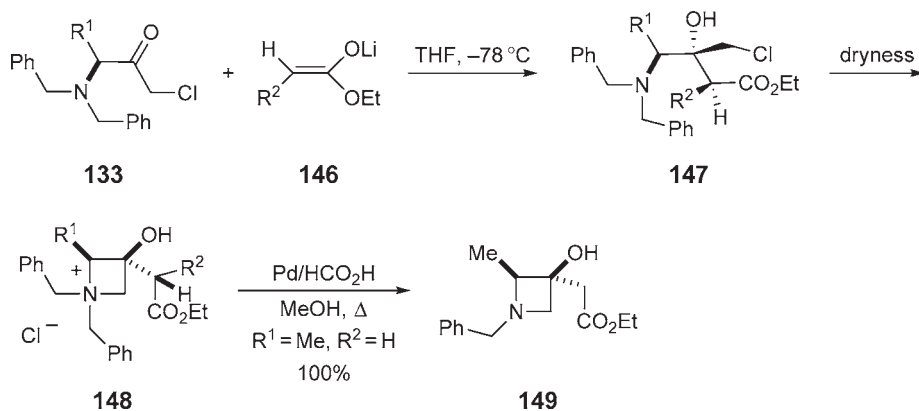
Scheme 31



Scheme 32

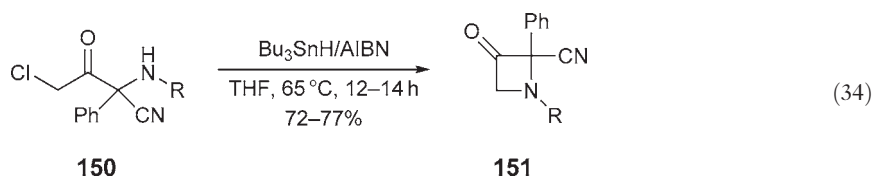


Scheme 33



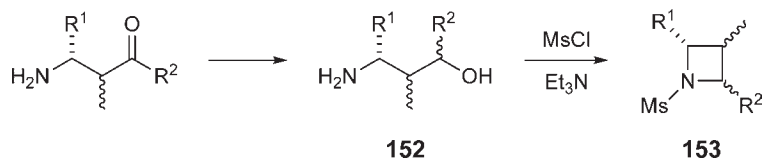
Scheme 34

The radical intramolecular cyclization of α -anilino- α -(chloromethylcarbonyl)phenylacetonitriles **150** is induced by tri-*n*-butyltinhydride/azoisobutyronitrile to afford 1-aryl-2-cyano-2-phenylazetidines **151** (Equation 34) <1997JCM254>.



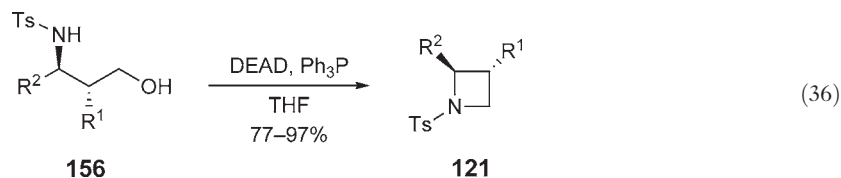
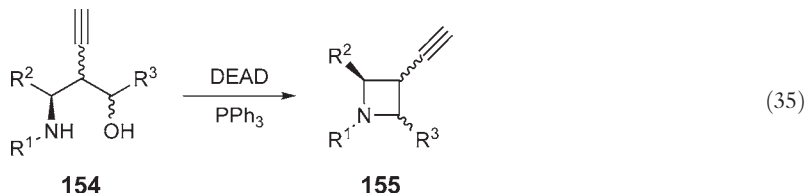
2.01.2.8.2 Ring closure of γ -aminoalcohols

Intramolecular nucleophilic displacement of an activated alcohol by amines using γ -aminoalcohols constitutes a very powerful method for the synthesis of azetidines. This approach has been applied for the preparation of penaresidins <1997TL3813, 1997J(P1)97, 2003TL977>, conformationally constrained analogues of phenylalanine derived from the natural amino acid azetidine-2-carboxylic acid <1999BML1437> and other azetidine-2-carboxylic acids <2000JOC6780>, and some analogues of biologically active compounds such as taxol <2003BML1075>, nucleosides <2003TL5267, 1997CAR123, 1997CAR253>, and azetidine-2-phosphonic acids <2001CCC507>. The scope of this intramolecular alkylation has been studied starting from aminoalcohols **152** (Scheme 35) <1996JOC5659, 1999JOC4362>. Treatment of the latter compounds with methanesulfonyl chloride in the presence of triethylamine yielded azetidines **153**. This study highlighted the fact that this cyclization does not always proceed through an S_N2 pathway, and that in some cases an S_N1 process can compete.

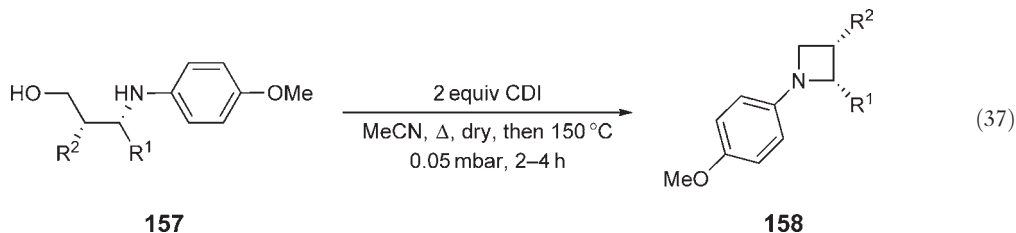


Scheme 35

Mitsunobu reactions have also been used for the cyclization of γ -aminoalcohols toward azetidines. γ -Aminoalcohols **154**, prepared from enantiopure ethynylaziridines, have been transformed into azetidines **155** upon treatment with dimethyl acetylenedicarboxylate and triphenylphosphine (Equation 35) <2001JOC1867>. *N*-Tosyl-substituted γ -aminoalcohols **156** yielded the corresponding 1-tosylazetidines **121** (Equation 36) with excellent diastereomeric (de = 99%) and enantiomeric excess (ee up to 99%) <2004EJO4471, 2005S3508>.

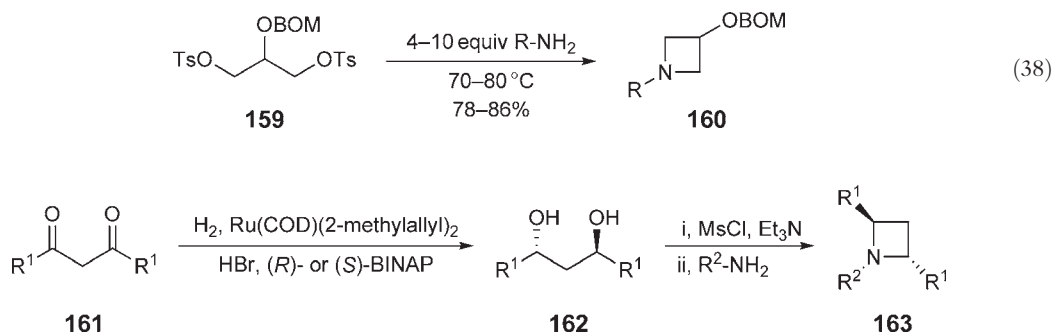


Dehydrative cyclization of *N*-(4-methoxyphenyl) protected γ -aminoalcohols **157** by the Staab reagent (1,1'-carbonyldiimidazole, CDI) led to the formation of *N*-(4-methoxyphenyl)azetidines **158** (Equation 37) <2004SL2751>. The reactions were carried out in a Kugelrohr apparatus. The imidazole formed in the reaction was separated by filtration through silica gel.



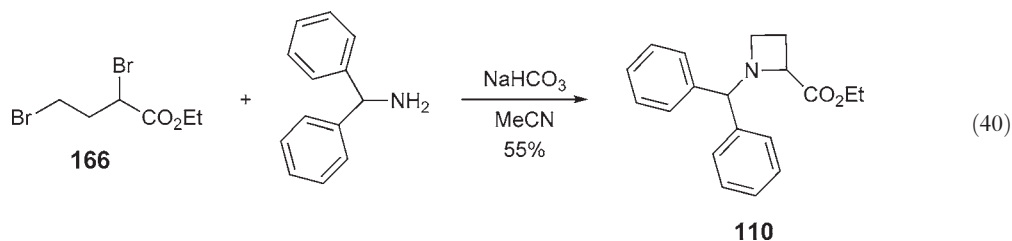
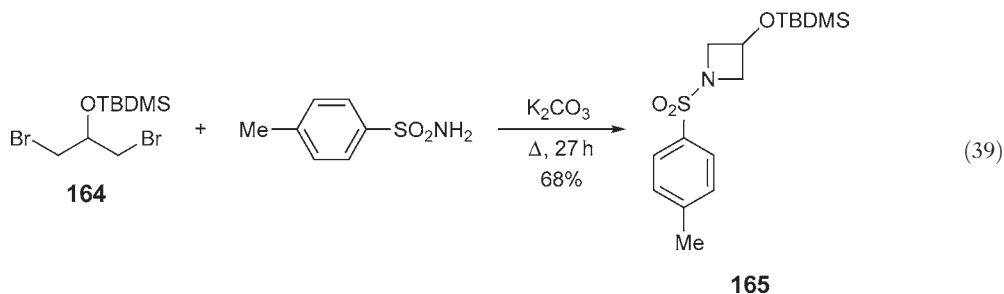
2.01.2.8.3 Reactions of 1,3-dielectrophiles with primary amines

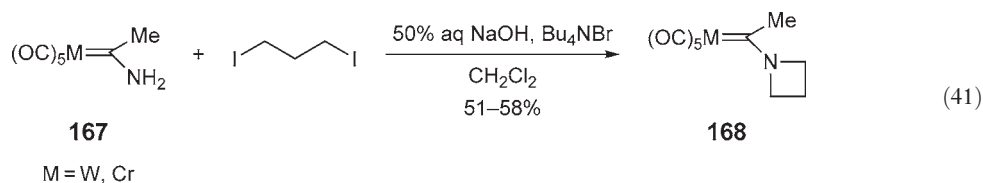
Primary amines can be bis-alkylated using 1,3-dielectrophiles to furnish azetidine derivatives. The dielectrophiles used for this purpose are usually 1,3-dibromo compounds, 1,3-diols, and mesylates or tosylates of 1,3-diols. The reaction of 2-benzyloxymethoxy-1,3-bis(4-methylbenzenesulfonyloxy)propane **159** with an excess of amines led to the synthesis of *N*-alkyl-3-(benzyloxymethoxy)azetidines **160** in very good yields (Equation 38) <1995SC603>. The ready availability of 1,3-diols in enantiopure form makes them appealing substrates for asymmetric synthesis of azetidines. The preparation of *C*₂-symmetric azetidines is described from *anti*-1,3-diols <2000EJO1815>. An enantioselective reduction of diketones **161** using [Ru/(*R*) or (*S*)-BINAP] catalytic systems led to the synthesis of *anti*-1,3-diols **162**, which, after mesylation followed by cyclization with amines, yielded azetidines **163** with ee's higher than 95% (Scheme 36). The use of bis-ethylenediamine for the cyclization step yielded a bis-azetidine. However, sterically hindered diols (*R*¹ = Prⁱ) could not be bis-alkylated.



Scheme 36

The reaction of *t*-butyldimethylsilyl ether **164** of 1,3-dibromo-2-propanol with *p*-toluenesulfonamide in the presence of potassium carbonate gave the corresponding *N*-*p*-tosyl-3-azetidinol **165** (Equation 39) <1995JOC1959>. 2,4-Dibromobutanoate **166** reacted with benzhydryl amine in the presence of sodium bicarbonate to yield ethyl 1-benzhydrylazetidine-2-carboxylate **110** (Equation 40) <2002BML3157>. The reactions of (2*S*,4*R*)-diethyl 2,4-dibromopentadienoate and of (2*S*,4*S*)-diethyl 2,4-dibromopentadienoate with benzylamine took place in refluxing benzene for 24 h to afford the *meso* and *racemic* 1-benzylazetidine-2,4-dicarboxylates, respectively <2001TA605>. These azetidines have been used to synthesize optically pure azetidines in few steps using chemoenzymatic methods, which are described in the reactivity section. The reaction of aminocarbene complexes of tungsten or chromium carbonyl with 1,3-diiodopropane yielded the corresponding *N*-metal-carbene complex-substituted azetidines **168** (Equation 41) <1996CL827>.

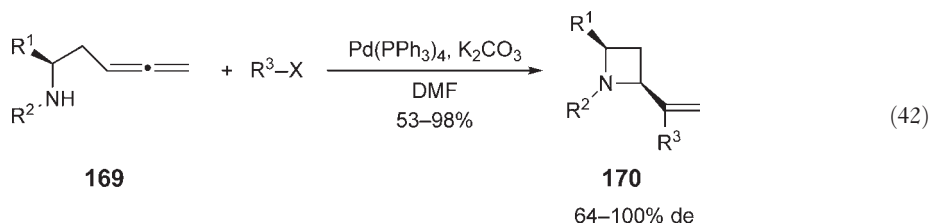




At present, the most convenient way for the preparation of 1,3-disubstituted azetidines involves the alkylation of a primary amine with the bis-triflate of a 2-substituted 1,3-propanediol species in the presence of diisopropylethylamine <2006JOC7885>.

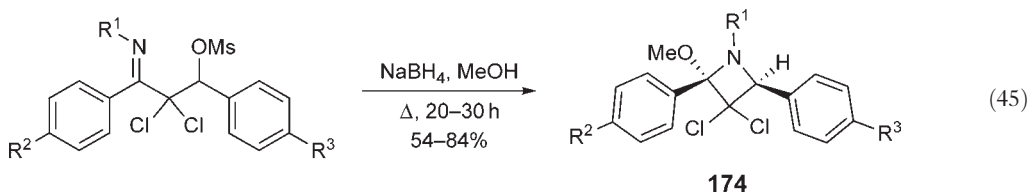
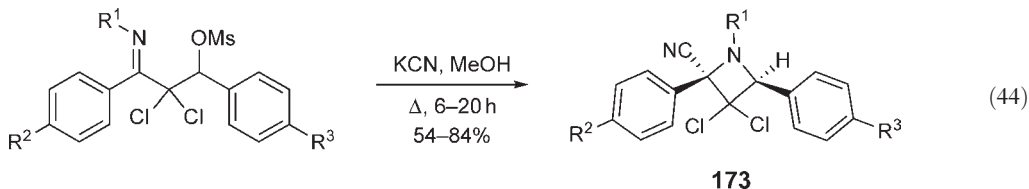
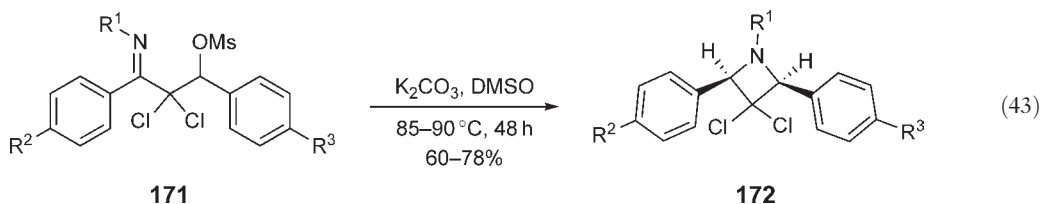
2.01.2.8.4 Ring closure of β -aminoallenes

The cyclization of β -aminoallenes is an emerging elegant synthetic methodology for the preparation of functionalized azetidines. The reaction of enantiopure β -aminoallenes **169** with alkenyl or aryl halides in the presence of a palladium(0) catalyst and potassium carbonate yielded 2,4-*cis*-azetidines **170** (Equation 42) <1999OL717, 1999TL7393>. The high *cis*-diastereoselectivity was explained on the basis of steric interactions in the intermediate π -allylpalladium complexes <2001JOC4904>.



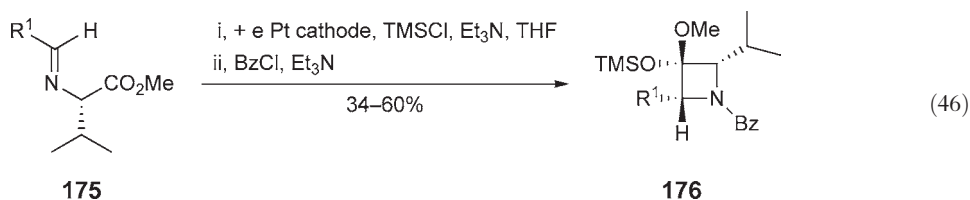
2.01.2.8.5 Reactions of α,α -dichloro- β -mesyloxyimines

Cyclization of α,α -dichloro- β -mesyloxyimines **171** by means of potassium carbonate in DMSO constitutes a novel approach to a relatively unexplored class of azaheterocycles, that is, 3,3-dichloroazetidines **172** (Equation 43) <1998JOC6>. The use of nucleophilic reagents like potassium cyanide or sodium borohydride in methanol afforded 2-cyano-3,3-dichloroazetidines **173** (Equation 44) and 2-methoxy-3,3-dichloroazetidines **174** (Equation 45), respectively.



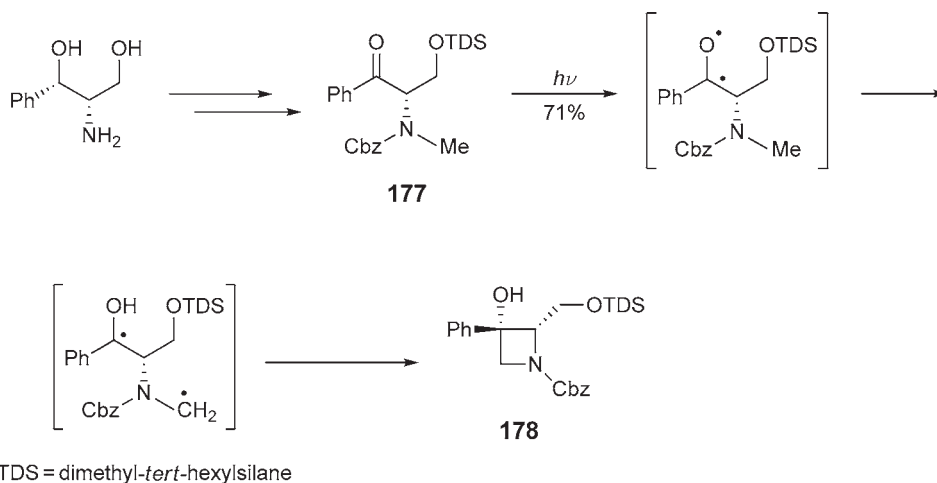
2.01.2.8.6 Electrochemical synthesis

The electroreductive cyclization of chiral aromatic α -iminoesters **175**, prepared from (*S*)- α -amino acids such as (*S*)-valine, (*S*)-leucine, and (*S*)-phenylalanine, in the presence of chlorotrimethylsilane and triethylamine afforded mixed ketals of *cis*-2,4-disubstituted azetidin-3-ones **176** stereospecifically (>99% de and 85–99% ee) (Equation 46) <2003JA11591>. The best result was obtained using tetrabutylammonium chlorate as a supporting electrolyte and a platinum cathode.

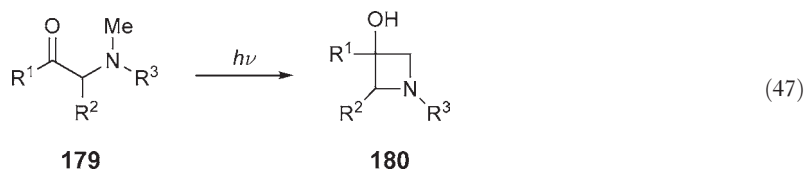


2.01.2.8.7 Photochemical synthesis

The aminoketone **177**, obtained in a few steps from the commercially available diol, cyclizes on irradiation with ultraviolet (UV) light affording (*2S,3S*)-benzyl 2-((2,3-dimethylbutan-2-yl)dimethylsilyloxy)methyl)-3-hydroxy-3-phenylazetidine-1-carboxylate **178** <1998HCA1803>. The reaction took place through a 1,2-diradical, which rearranged to a 1,4-diradical (Scheme 37, TDS = dimethyl-*tert*-hexylsilane). This diradical recombined to give azetidine **178**. The [2+2] photocycloaddition of some difluoroboron complexes with *trans*-stilbene gave azetidines together with cyclobutane derivatives <2004HCA292>. The photocyclization of α -aminoketones **179** yielded the 3-hydroxyazetidines **180** (Equation 47) <2000MI245>.

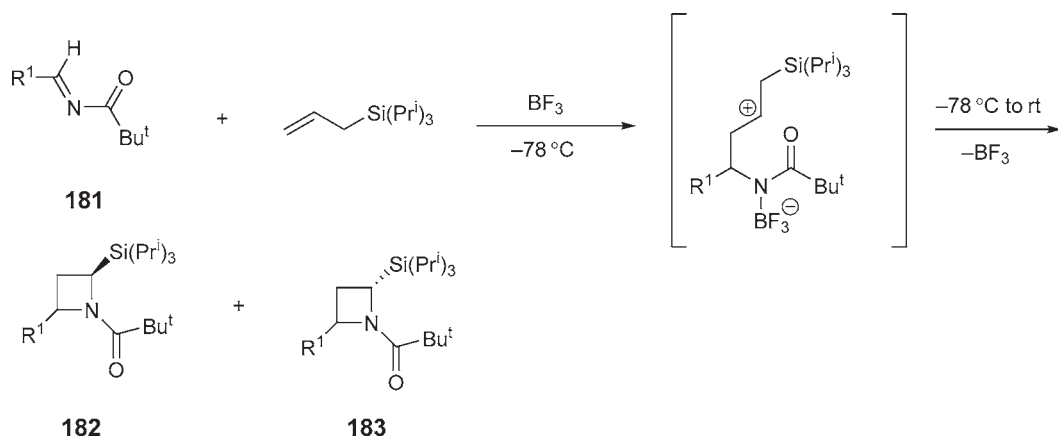


Scheme 37



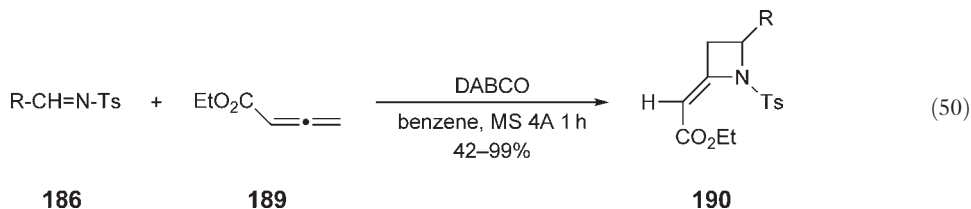
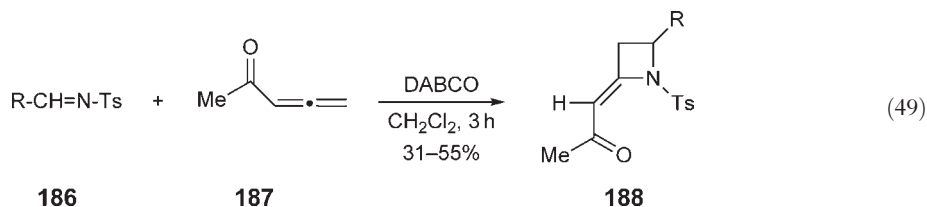
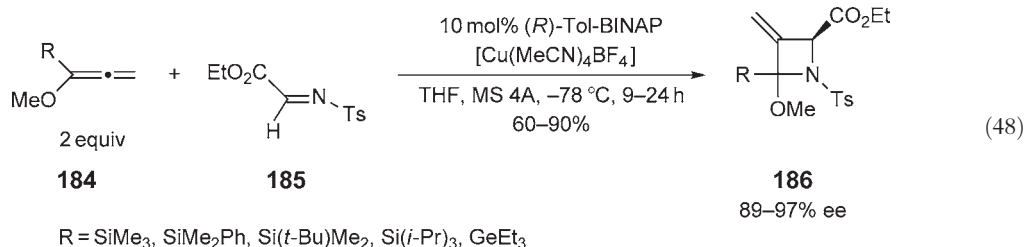
2.01.2.8.8 Cycloaddition reactions

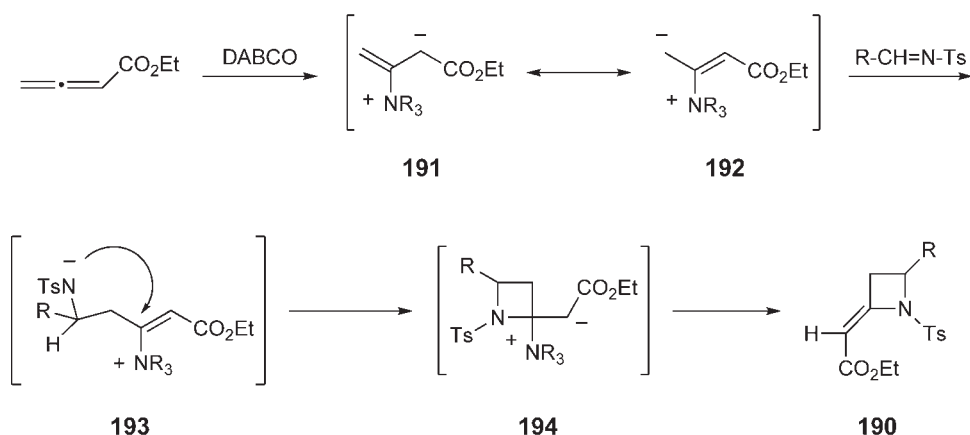
Lewis acid-catalyzed [2+2] cycloaddition reactions of *N*-pivaloylaldimines **181** gave azetidines **182** and **183** (Scheme 38) <1995CL789>. Boron trifluoride etherate proved to be a better catalyst than zinc chloride, affording azetidines **182** and **183** in better yields. This transformation has been explained through the intermediacy of a β -silyl cation.



Scheme 38

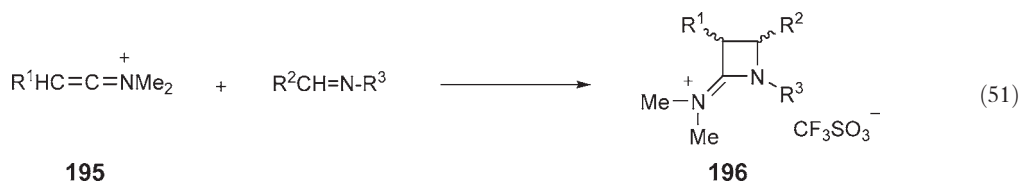
A [2+2] cycloaddition reaction of 1-methoxyallenylsilanes **184** with α -iminoesters **185** has been carried out in the presence of $\text{Cu}(\text{MeCN})_4\text{BF}_4/(\text{R})\text{-Tol-BINAP}$ to afford 3-methylene-azetidine-2-carboxylates **53** in good yields with excellent enantiomeric excesses (Equation 48) <2003OL3691>. The reactions of *N*-tosyl-substituted aromatic aldimines **186** with penta-3,4-dien-2-one **187** in the presence of 1,4-diazabicyclooctane (DABCO) yielded azetidines **188** (Equation 49) <2003OL4737>. A similar reaction of aldimines **186** with ethyl 2,3-butadienoate **189** furnished azetidines **190** (Equation 50). The suggested mechanism of formation involved reaction of the Lewis base DABCO with ethyl 2,3-butadienoate forming the zwitterionic intermediate **191**, which can be resonance-stabilized as the allylic anion **192** (Scheme 39). The latter intermediate added onto the imine giving rise to intermediate **193**, which underwent a Michael-type intramolecular nucleophilic attack to give the zwitterionic intermediate **194**. The elimination of NR_3 from the latter intermediate afforded the azetidines with regeneration of base.





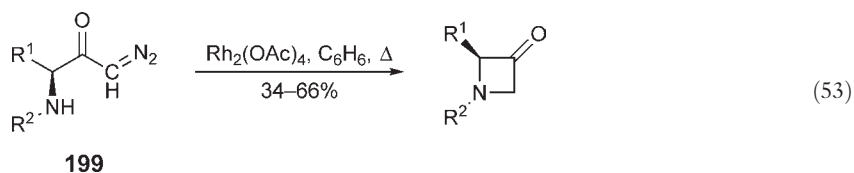
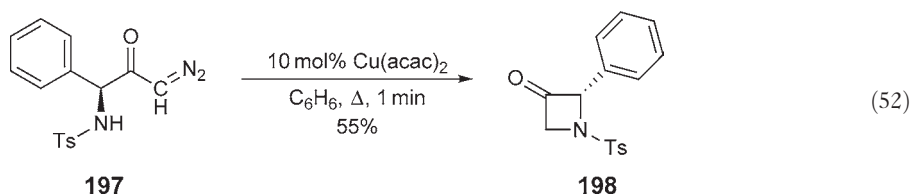
Scheme 39

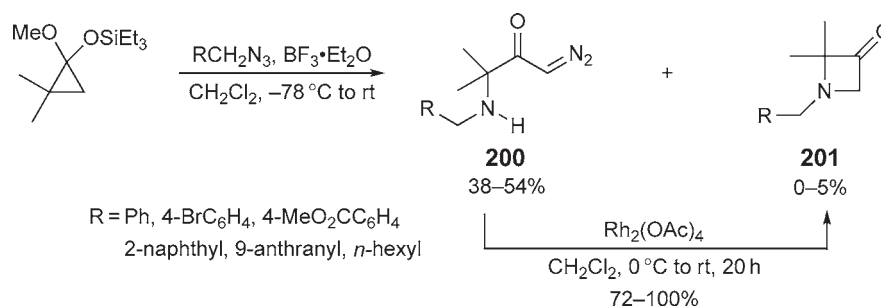
The cycloaddition of keteniminium triflates **195**, formed from tertiary amides by the action of triflic anhydride, with imines formed the azetidine iminium salts **196** (Equation 51) <1996JOC8480>.



2.01.2.8.9 Metal-catalyzed insertion reactions of α -diazocarbonyl compounds

Thermal decomposition of α -amino acid-derived α -diazoketones **197** in the presence of bis(acetylacetonato)copper(II) led to the formation of N-substituted azetidin-3-ones **198** (Equation 52) <1999J(P1)2277, 2004TL3355, 2005SL1559>. A similar reaction of α -diazoketones **199** has been carried out in the presence of dirhodium tetraacetate (Equation 53) <1998SC403>. The metal carbenoids generated in these reactions undergo an intramolecular N-H insertion. α -Diazoketones **200**, obtained from the reaction of alkyl azide with triethyl(1-methoxy-2,2-dimethylcyclopropoxy)silane, are cyclized in the presence of dirhodium tetraacetate to give azetidin-3-ones **201** (Scheme 40) <2000OL1657>.





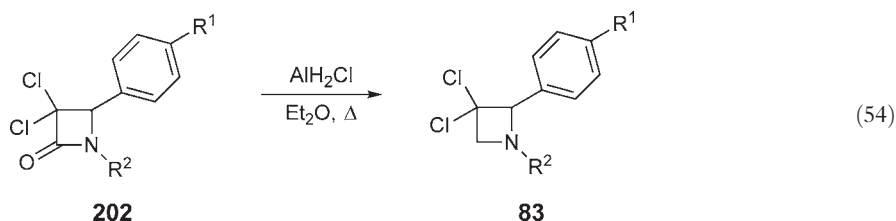
Scheme 40

2.01.2.8.10 Reduction of azetidin-2-ones (β -lactams)

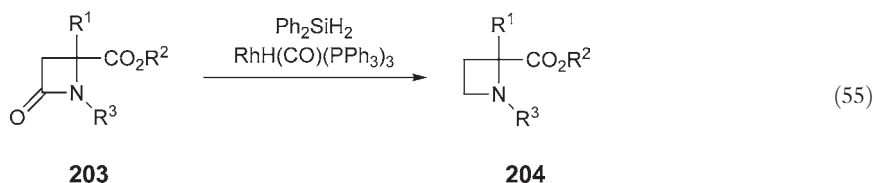
Reduction of azetidin-2-ones is a powerful method to synthesize azetidines. The reduction has been performed with a wide variety of reagents like lithium aluminium hydride, diisobutyl aluminium hydride, monochloro and dichloroalanes, and diphenylsilane. Chloroalanes have proved to be the most useful reagents among them. The synthesis of a scarce class of azaheterocycles, that is, 1-aryl-3,3-dichloroazetidines **83**, is accomplished in excellent yields (Table 5) by reduction of 3,3-dichloroazetidin-2-ones **202** using monochloroalane (Equation 54) <2002JOC2075>. Accordingly, the reduction of monochlorinated 3-chloroazetidin-2-ones resulted in the corresponding 3-chloroazetidines, which proved to be excellent substrates for further elaboration via nucleophilic displacement of the chloride through intermediate bicyclic aziridinium salts <2006T6882>. Many other 1,2,3-trisubstituted azetidines have been synthesized using this methodology <1999JOC9596>.

Table 5 Synthesis of 3,3-dichloroazetidines (Equation 54)

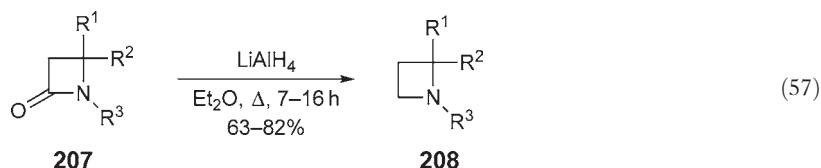
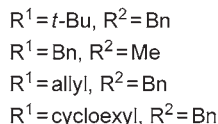
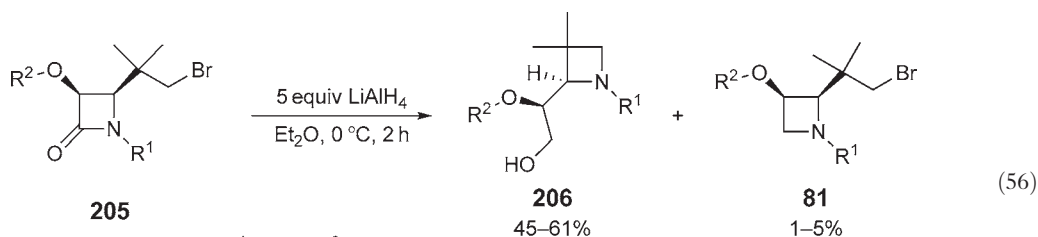
R^1	R^2	Yield (%)
H	Pr^i	97
H	<i>c</i> -hex	98
Me	Pr^i	82
F	Pr^i	95
MeO	Pr^i	90



Diphenylsilane is compatible with the ester group at C-4 in azetidin-2-ones **203** and reduces only the amide carbonyl group affording azetidin-2-carboxylates **204** (Equation 55) <2004TL2193>. Removal of the *p*-methoxybenzyl group from azetidin-2-carboxylates **204** allowed the preparation of conformationally strained amino ester hydrochlorides.

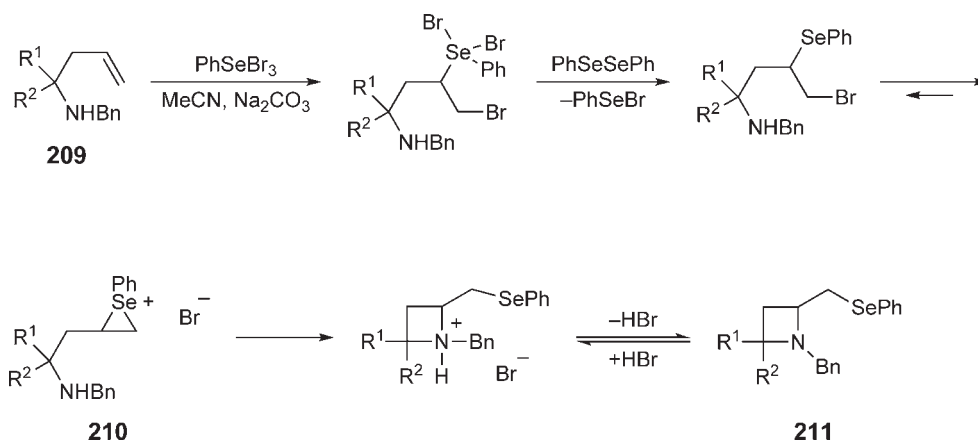


Treatment of 4-(2-bromoalkyl)azetidin-2-ones **205** with LiAlH_4 in diethyl ether yielded 2-(1-alkoxy-2-hydroxyethyl)-azetidines **206** and small amounts (1–5%) of *cis*-4-(2-bromoalkyl)azetidines **81** (Equation 56) <2006OL1101>. A 1,2-fission of the starting material followed by a nucleophilic substitution of bromide led toward the formation of these compounds. 1,4,4-Trisubstituted azetidin-2-ones **207** could be reduced to the corresponding azetidines **208** using lithium aluminium hydride in diethyl ether under reflux for 7–16 h (Equation 57) <1996JOC6500>.



2.01.2.8.11 Miscellaneous syntheses

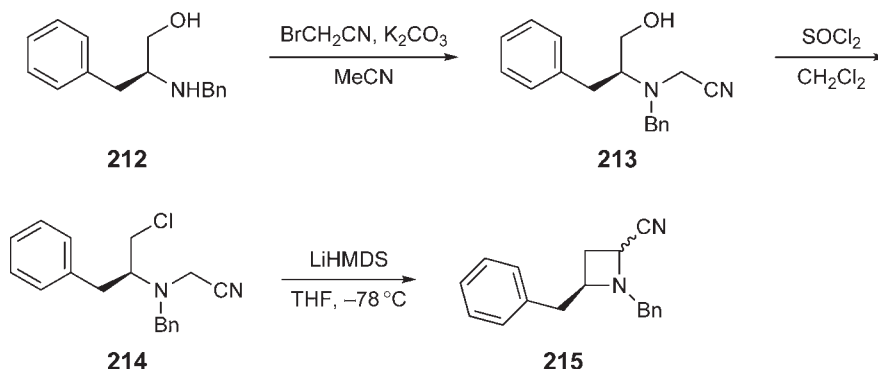
Treatment of α -alkyl and α,α -dialkyl homoallylic amines **209** with phenyl selenium halides ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) in acetonitrile containing sodium carbonate produced mixtures of azetidines and pyrrolidines <1997TL1393, 2002EJO995>. The ratio of azetidine to pyrrolidine increased according to the steric hinderance around the α -carbon and with the nature of the counterion X^- ($\text{PhSeCl} < \text{PhSeBr} < \text{PhSeI}$). The mechanistic investigations led to the conclusion that seleniranium halide intermediates **210** were involved in ring closure to azetidines **211** (Scheme 41).



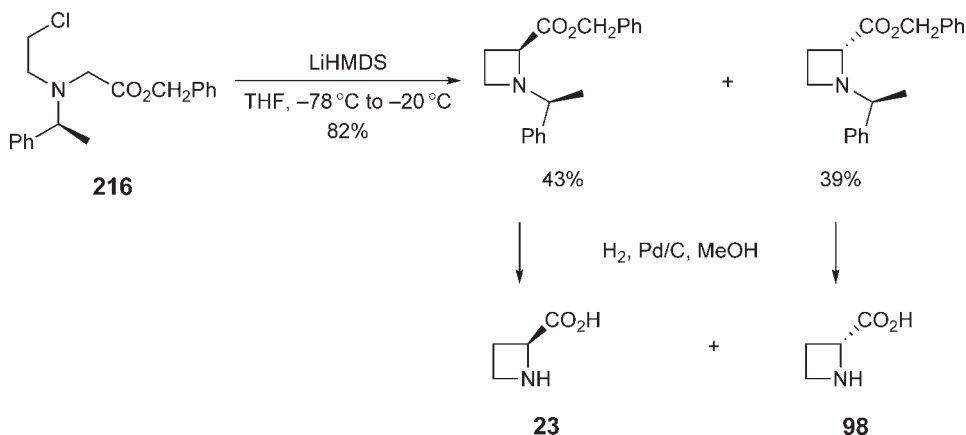
Scheme 41

A three-step reaction sequence starting from β -amino alcohol **212** has been utilized in the synthesis of 2-cyanoazetidine (Scheme 42) <2002TA297, 2006SL78>. The *N*-benzyl-substituted β -amino alcohol was first *N*-cyanomethylated to give the corresponding *N*-benzyl-*N*-cyanomethyl β -amino alcohol **213**. The latter compound was stereoselectively transformed into chlorinated amine **214** using thionyl chloride. An intramolecular alkylation of

214 with LiHMDS afforded 2-cyanoazetidine **215**. A similar methodology using β -chloro amine **216** bearing a benzyl ester group instead of a cyanomethyl group at nitrogen atom has been employed for the synthesis of (*S*)-azetidine-2-carboxylic acid **23** and (*R*)-azetidine-2-carboxylic acid **98** (Scheme 43) <2005JOC9028>.



Scheme 42

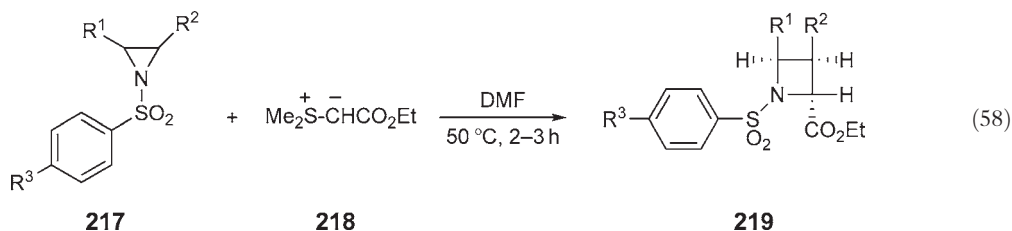


Scheme 43

2.01.2.9 Ring Synthesis by Transformation of Another Ring

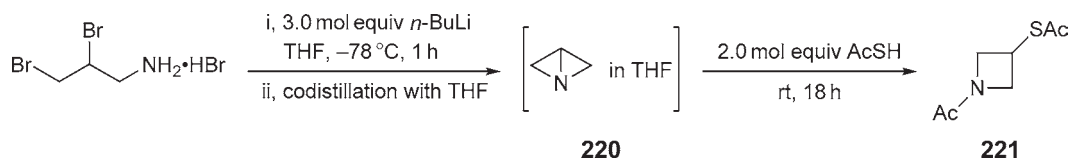
2.01.2.9.1 Transformation of three-membered rings

The reaction of 1-arylsulfonylaziridines **217** with dimethylsulfoniumethoxycarbonyl methylide **218** is a fairly general approach for stereoselective synthesis of 1-arylsulfonylazetidines **219** bearing an ethoxycarbonyl functionality (Equation 58) <1995J(P1)2605>. However, the products are obtained in moderate yields. The reaction involves a regioselective transfer of an ethoxycarbonyl-substituted methylene group from the ylide to 1-arylsulfonylaziridines.

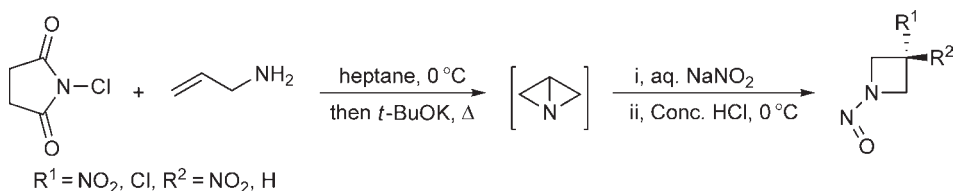


1-Azabicyclo[1.1.0]butanes serve as a precursor for various N-substituted azetidines. A THF solution of 1-azabicyclo[1.1.0]butane, obtained from 2,3-dibromopropanamine hydrobromide, yielded azetidine derivatives on treatment with various reagents such as HCl-EtOH , $\text{HBr-ClCO}_2\text{Et}$, Ts_2O , HCO_2H (2.7N) HCl-MeOH , or $\text{Ac}_2\text{O-HCl}$.

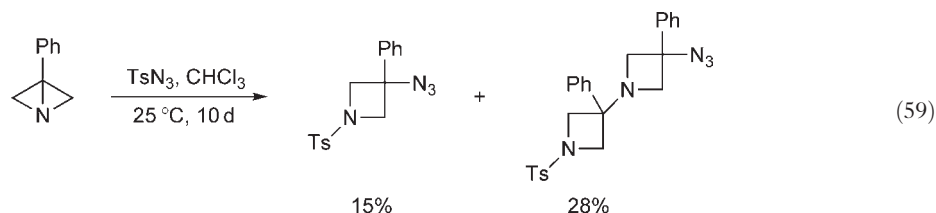
(3N) <2002H(56)433>. A similar treatment of azacyclobutane **220** with AcSH afforded 1-acetyl-3-acetylthioazetidine **221** (Scheme 44). The reactions presumably proceeded in a concerted manner, in which an electrophilic group attacks the N-1 position of the strained molecule **220** followed by cleavage of the N(1)–C(3) σ -bond, followed by reaction of a nucleophilic group with the cationic C-3 position. Some other reagents used to synthesize N-substituted azetidine derivatives from 1-azabicyclo[1.1.0]butane include ethyl chloroformate <1997JOC4434, 1999SC885>, acetyl chloride, benzoyl chloride <1999SC885>, NaNO₂–HCl (Scheme 45) <1998SC3949>, and tosyl azide in chloroform (Equation 59) <1999H(50)131>.



Scheme 44

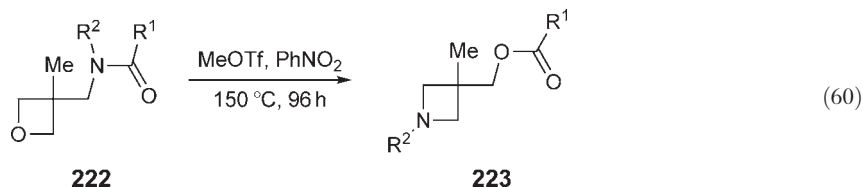


Scheme 45

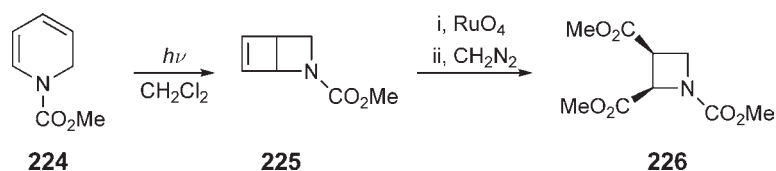


2.01.2.9.2 Transformation of four-membered rings

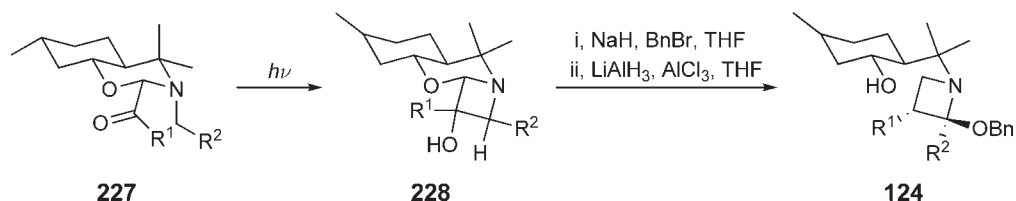
The oxetane *t*-amides **222** undergo a ring expansion–contraction sequence in the presence of a Lewis acid to azetidine derivatives **223** (Equation 60) <2000JOC2253>. The overall reaction sequence has been described as ‘double isomerization’. The four-membered oxetane ring first enlarged to a [2.2.2]-dioxazabicyclic, which in turn rearranged to the final azetidine derivatives.



A valuable strategy for the synthesis of monocyclic azetidine derivatives involves the cleavage of another ring in fused-azetidine ring systems. Irradiation of ethyl pyridine-1(2*H*)-carboxylate **224** with UV light using a high-pressure mercury lamp through a pyrex filter yielded a cyclobutene-fused azetidine-1-carboxylate **225** (Scheme 46) <2003CPB96>. An oxidative cleavage of the cyclobutene ring in this compound gave the monocyclic azetidine tricarboxylic acid, which was isolated as trimethyl ester **226** after treatment with diazomethane. The photocyclization of the chiral 2-acyl-3-allyl- or 2-acyl-3-benzyl-substituted perhydro-1,3-benzoxazines **227** afforded the fused tricyclic azetidine derivatives **228** (Scheme 47) <2005JOC1408>. The reductive ring opening of the *N,O*-ketal moiety in the latter compounds yielded the monocyclic azetidine derivatives **124**.

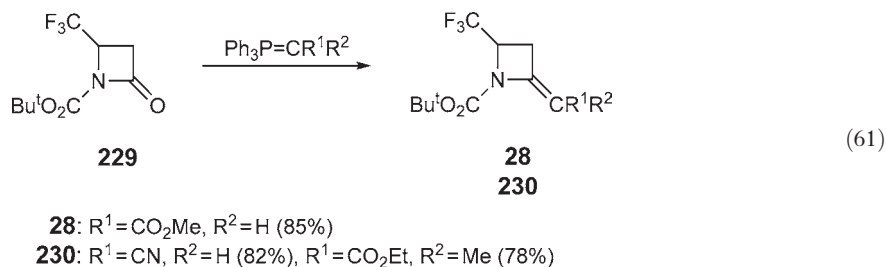


Scheme 46



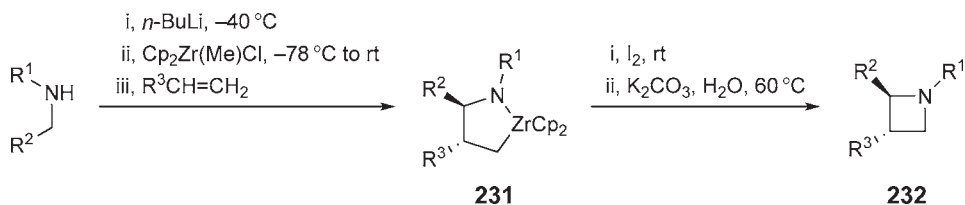
Scheme 47

The β -lactam carbonyl group transformations have been utilized successfully in the synthesis of azetidine derivatives. The reduction of the carbonyl group in azetidin-2-ones yielding azetidine derivatives is described in Section 2.01.2.8.10. Treatment of *N*-BOC-protected 4-(trifluoromethyl)azetidin-2-one **229** with a stabilized Wittig reagent yielded the azetidines **28** and **230** (Equation 61) <2003OL4101>.



2.01.2.9.3 Transformation of five-membered rings

The azazirconacyclopentane derivatives **231**, obtained from the reactions of amines with zirconocene methyl chloride followed by addition of the corresponding terminal alkenes, have led to the formation of azetidine derivatives **232** on treatment with iodine (Scheme 48) <1997JOC5953>.

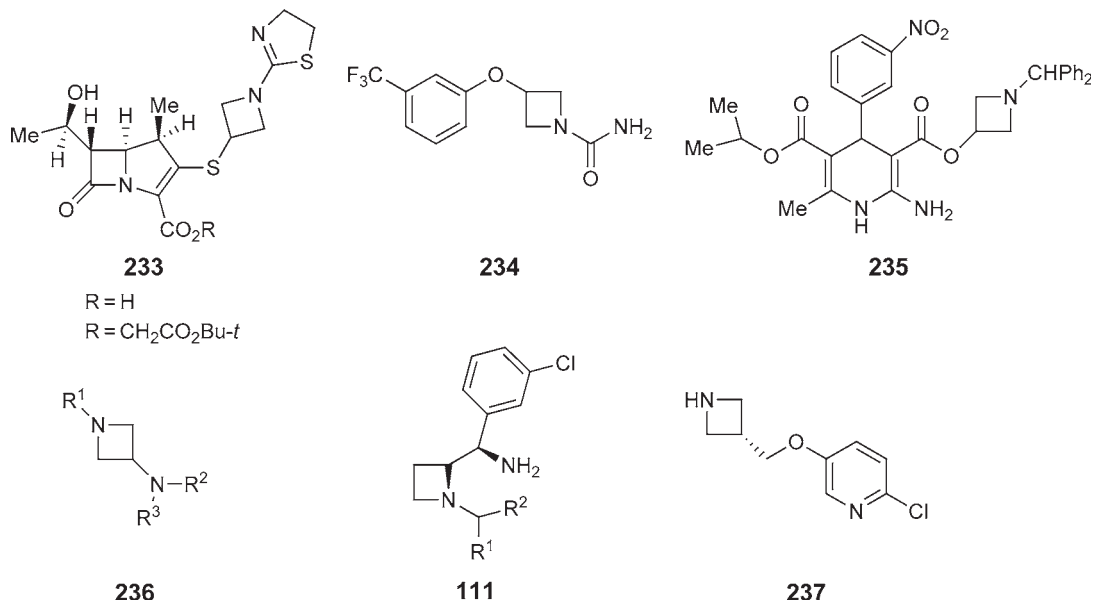


Scheme 48

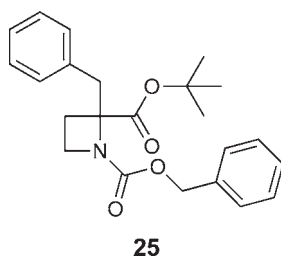
2.01.2.10 Important Compounds and Applications

The hydrate of azetidin-3-one, 3,3-dihydroxyazetidine was isolated from the supernatant of a culture of *Bacillus mesentericus* <2000MI105>. This azetidine is a new growth-promoting factor, stimulating the growth of several strains of *Bifidobacterium* <2000MI105>. 3-Hydroxyazetidine is used as a precursor of oral carbapenem antibiotics L-036 **233**

and L-084 **234**, antiepileptic dezinamide **235**, and antihypertensive azelnidipine [<1995EPP632039>](#). 3-Aminoazetidines **236** have received attention in recent years because of their antibacterial activity [<1995SC803>](#), while (2-aminomethyl)azetidines **111** have been described as G-protein receptor ligands [<2002BML3157>](#) and antimicrobial agents [<1999JP11147883>](#). The azetidine **237** is a nonopioid analgesic agent [<1996JME817>](#).

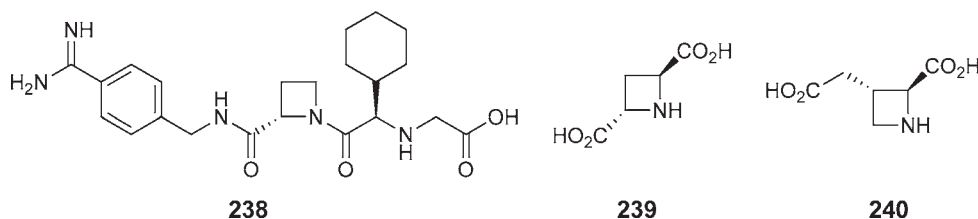


Azetidine **25** has shown promising anti-human cytomegalovirus (HCMV) activity. Human cytomegalovirus is a ubiquitous member of the herpes virus family. The EC₅₀ value obtained for this compound has been found to be similar to that of the standard reference compound ganciclovir and slightly better than that of cidofovir [<2004BML2253>](#).



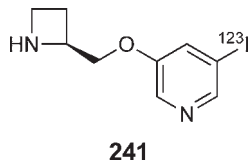
Azetidin-2-phosphonates are considered as mimics of the corresponding α -amino acids. This resemblance is responsible for the wide range of biological activities displayed by such compounds and the applications they have found in medicine and agriculture [<1996T10685, 1996TA21, 2001TL2185, 2001EJO3031, 1995JA10879>](#).

The derivatives of the plant growth inhibitor (*S*)-azetidine-2-carboxylic acid are of significant importance as active pharmaceutical ingredients [<2006OPP427>](#). For example, azetidine **238** is a thrombin inhibitor [<2001MI171>](#). Glutamate **239** has been observed to act as an activator of the metabotropic receptors, whereas analogue **240** appears to be a potent kainite receptor agonist, as well as a potent inhibitor of sodium-dependent glutamate uptake [<1996BML2559>](#).



1,3,3-Trinitroazetidine is an energetic material that is sensitive to detonation on impact <1995JOC1959>.

The iodinated analogue of A-85380 <1998JME3690>, (S)-5-[¹²³I]iodo-3-(2-azetidinylmethoxy)pyridine **241**, is a ligand used for single photon emission computerized tomography (SPECT) imaging of human and nonhuman nicotinic acetyl choline receptors *in vivo*.



Several 2-ketoazetidines have shown dipeptidyl peptidase IV (DPP IV) inhibition property <2004BML5579>. 2-Thiazole, 2-benzothiazole and 2-pyridyl ketones were optimal S1' binding groups for potency against DPP IV. Both 2-(*R*)- and 2-(*S*)-isomers are equipotent. Certain stabilized azetidin-2-ones maintained their *in vitro* potency and inhibited DPP IV in the plasma for up to 6 h.

2.01.3 Azetidin-2-ones and Related Azetidine Derivatives

2.01.3.1 Introduction

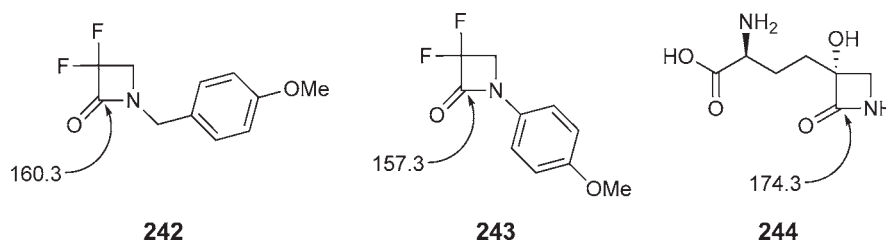
The chemistry of the important class of azetidin-2-ones (β -lactams) has seen an explosive growth in the decade since 1995. The reports on enzyme inhibition, cholesterol absorption inhibition, and cancer inhibition by compounds bearing an azetidin-2-one skeleton have stimulated much interest in the chemistry of such compounds. Monocyclic β -lactams serve as precursors for the synthesis of many biologically important compounds including bicyclic β -lactam antibiotics. Pertinent references on various aspects of the chemistry of β -lactams will be provided. More detailed information on specific extended topics is covered in appropriate reviews <2003T7631, 2004RMC69, 2004RMC92, 2004CME1889, 2004CME1921, 1997CSR377, 1996CHEC-II(1B)1003, B-1997MI(4)1002, 2006RMC109>. The sections on the chemical reactivity and the synthesis of azetidin-2-ones are extended. However, less emphasis is given to the reactivity of substituents attached to ring carbon and nitrogen atoms. Azetidin-2-thiones and highly functionalized azetidin-2-ones, for example, azetidine-2,3-dione, azetidine-2,3-dimines, 3-iminoazetidin-2-ones, etc., will be covered in a separate section.

2.01.3.2 Theoretical Methods

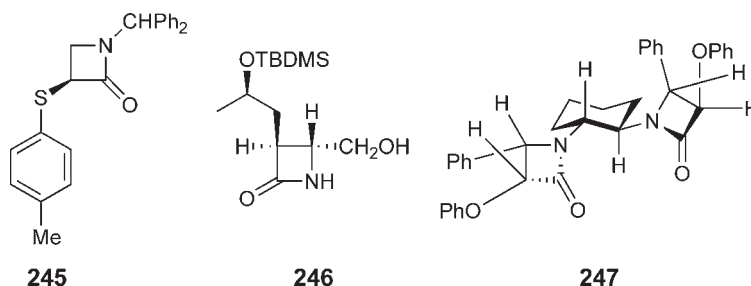
The optimized geometries of the *cis*- and *trans*-azetidin-2-ones have been determined by MOPAC-AM1 calculations. The angle between the planes of the carbonyl linkage and the C-2, C-4 axis turned out to be 4.6° in (3*R*,4*S*)- and 4.7° in (3*R*,4*R*)-azetidin-2-ones <1995TL4217>. An *ab initio* study has been performed to investigate intramolecular hydrogen bonding in many monocyclic azetidin-2-ones such as oxamazins, thiamazines, *N*-oxomethoxy- and 1-(thiomethoxy)azetidin-2-ones <2004JST(684)181>.

2.01.3.3 Experimental Structural Methods

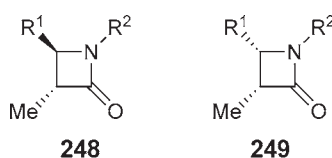
The infrared (IR) spectra of azetidin-2-ones show a strong absorption around 1745 cm⁻¹. However, the carbonyl group in *N*-benzyl- or benzhydryl-substituted azetidin-2-ones absorb at around 1770–1780 cm⁻¹ <2003S2483>. The most powerful tool for the determination of relative stereochemistry of azetidin-2-ones is ¹H NMR spectroscopy. The coupling constant for vicinal protons at C-3 and C-4 is 4.5–6.0 Hz for *cis*-derivatives and 2.0–2.5 Hz for *trans*-derivatives. The ¹³C NMR spectra of azetidin-2-ones show the typical carbonyl resonance at δ 166–170. However, values outside this range are possible if strong electron-withdrawing or electron-donating groups are present on the adjacent carbon atoms. For example, the ¹³C NMR spectra (CDCl₃) of *N*-substituted 3,3-difluoroazetidin-2-ones **242** and **243** showed a carbonyl carbon signal in the range of δ 157–160 <2003S2483>, whereas the carbonyl group in 3-hydroxyazetidin-2-one **244** resonated at δ 174.3 ppm (D₂O) <2004TL8191>.



Studies using X-ray crystallography of azetidin-2-ones indicate that the ring is planar. Several 3,3-dichloro-1,4-diarylazetidin-2-ones [<2001ANS909, 1999AXC2115, 1999AXC2117, 1999AXC1511, 1997AXC1945, 1996AXC1779, 1996ZK735>](#), 1,2-diaryl-3,3-diphenyl-2-azetidinones [<2000AXC207>](#), and the 3-unsubstituted azetidin-2-one **245** [<1995TL115>](#) have been investigated by X-ray analysis. The two phenyl rings in the 3,3-diphenylazetidin-2-one were positioned perpendicular to each other [<2000AXC207>](#). The absolute configurations of the *trans*-3,4-disubstituted azetidin-2-ones **246** [<2001T10155, 2005CJC28>](#) and *cis*-bis-azetidin-2-ones **247** [<2005T2441>](#) have been assigned by single crystal X-ray diffraction analysis.



The absolute configurations of azetidin-2-ones **248** and **249** have been determined by CD spectra [<1995TL115, 1995TL4217>](#). The CD spectra of the *cis*-isomers revealed a positive Cotton effect, whereas the *trans*-isomers displayed a negative one. The application of the octant rule demonstrated that the methyl group at C-3 and aryl group at C-4 in *trans*-azetidin-2-ones were located in the negative octant, resulting in a relatively large negative Cotton effect. On the other hand, the same substituents in *cis*-isomers were located in octants of different sign. Although both the substituents were antagonistic to the circular dichroism, the positive octant made a larger contribution resulting in a positive Cotton effect.



- a:** R¹=Ph, R²=Ph
b: R¹=Ph, R²=4-MeOC₆H₄
c: R¹=2-Furyl, R²=MeOC₆H₄

2.01.3.4 Thermodynamic Aspects

Compounds containing an azetidin-2-one ring are quite stable at room temperature. The presence of certain substituents on the ring atom(s), however, has been observed to affect the thermal stability of the ring. For example, the azetidin-2-ones bearing alkenyl groups on C-3 and C-4 positions of the ring undergo ring cleavage by [3,3]-sigmatropic rearrangement on refluxing in toluene (see [Section 2.01.3.8, Equation 137](#)) [<2001TL3081>](#). Attempts to add bromine onto the carbon-carbon double bond of the isopropenyl group, present at C-4 of the azetidin-2-one rings, also led to cleavage of the ring at 0°C (see [Section 2.01.3.8, Equation 138](#)) [<2005JOC8717>](#).

Among the *cis*- and *trans*-azetidin-2-ones (Figure 1), the *trans*-isomers are thermodynamically more stable than their *cis*-counterparts. Heating of the *cis*-isomers in toluene at 230 °C led to isomerization affording the corresponding *trans*-isomers <2000JOC4453>.

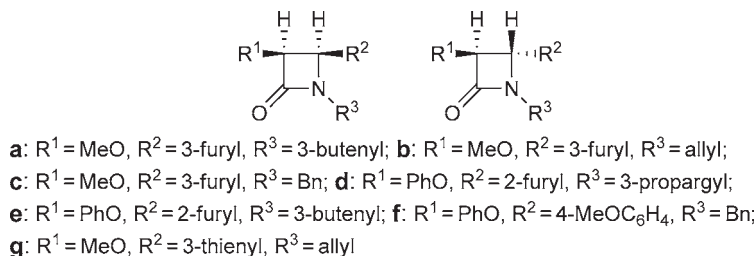


Figure 1

The azetidin-2-one derivatives bearing a hydrogen bond-forming group have been observed to melt at higher temperatures than those having no such group. For example, the azetidin-2-one bearing a 2-aminophenyl group at C-4 has a melting point of 195–199 °C, whereas the mp of the azetidin-2-one with a 2-nitrophenyl group amounts to 142 °C (Figure 2) <2005ARK53>.

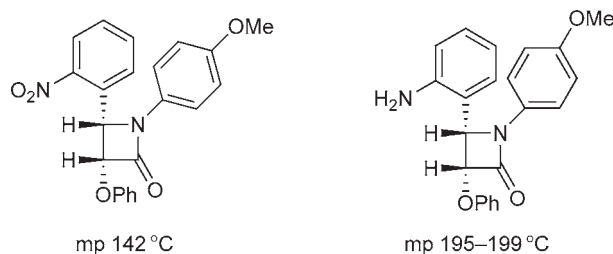
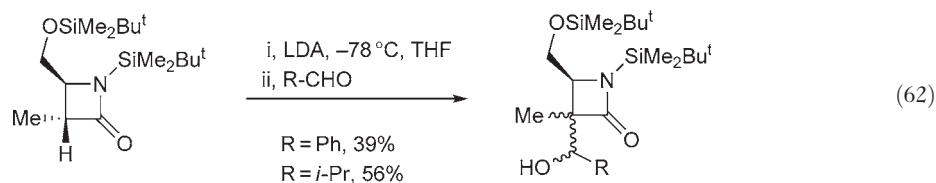


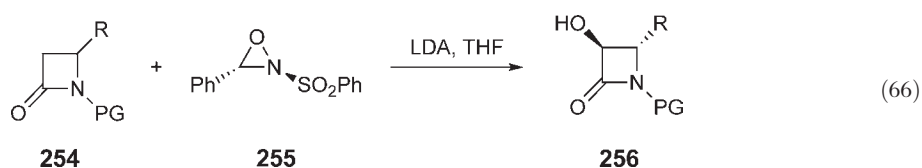
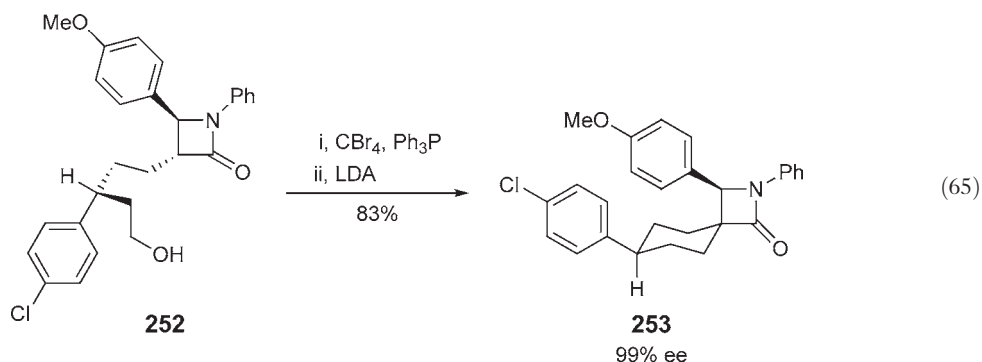
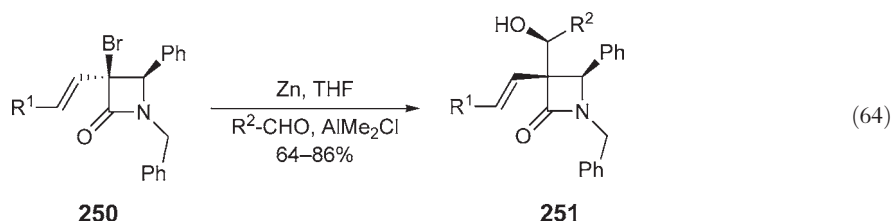
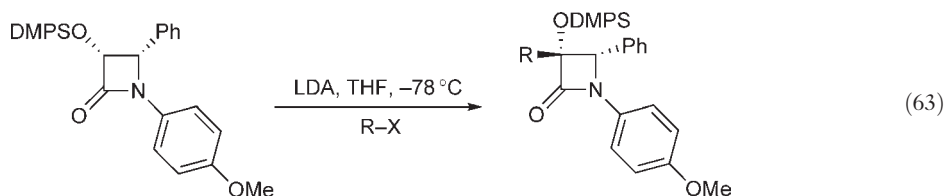
Figure 2

2.01.3.5 Reactivity of the β -Lactam Ring

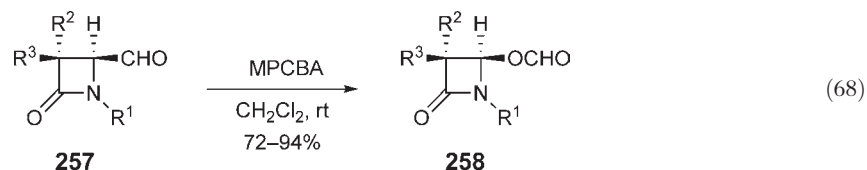
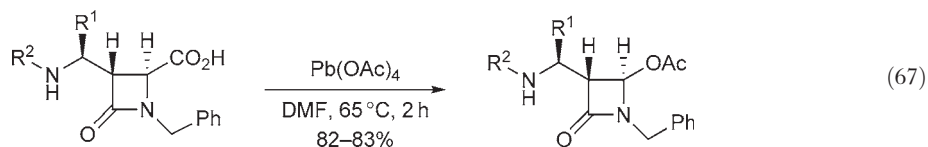
2.01.3.5.1 Electrophilic attack at carbon

Various substitutions of hydrogen at the C-3 and C-4 positions in β -lactams have been performed by electrophilic reagents. The 3-position is activated by the carbonyl function, which makes it possible to generate a reactive amide enolate. The reaction of electrophiles at C-3 on the less hindered face of the enolate derived from 4-substituted azetidin-2-ones resulted into formation of product with retention of stereochemistry (Equation 62) <1995J(P1)351>. Similar *C*-alkylation is reported in some other azetidin-2-ones (Equation 63) <1996TL6495, 1995T8941>. A zinc metal-promoted nucleophilic addition of 3-alkenyl-3-bromoazetidin-2-ones **250** to aromatic and aliphatic aldehydes and nitriles led to the formation of the corresponding alcohols **251** (Equation 64) and ketones, respectively <2005S61>. Methylation at the C-3 position of the *cis*-3-alkenyl-1,4-diarylazetidin-2-ones was achieved by electrophilic attack of methyl iodide in $\text{Bu}^n\text{Li}/\text{THF}$ <2006T1564>, whereas the arylation is reported by halogen–lithium exchange in 3,3-dichloroazetidin-2-ones <2005S193>. An intramolecular C-alkylation in azetidin-2-one **252** yielded the cholesterol absorption inhibitor spiroazetidin-2-one **253** (Equation 65) <1996JOC8341>. The reaction of azetidin-2-ones **254** with oxaziridine **255** in the presence of lithium diisopropylamide (LDA) formed 3-hydroxyazetidin-2-ones **256** (Equation 66) <1998TL5895>.





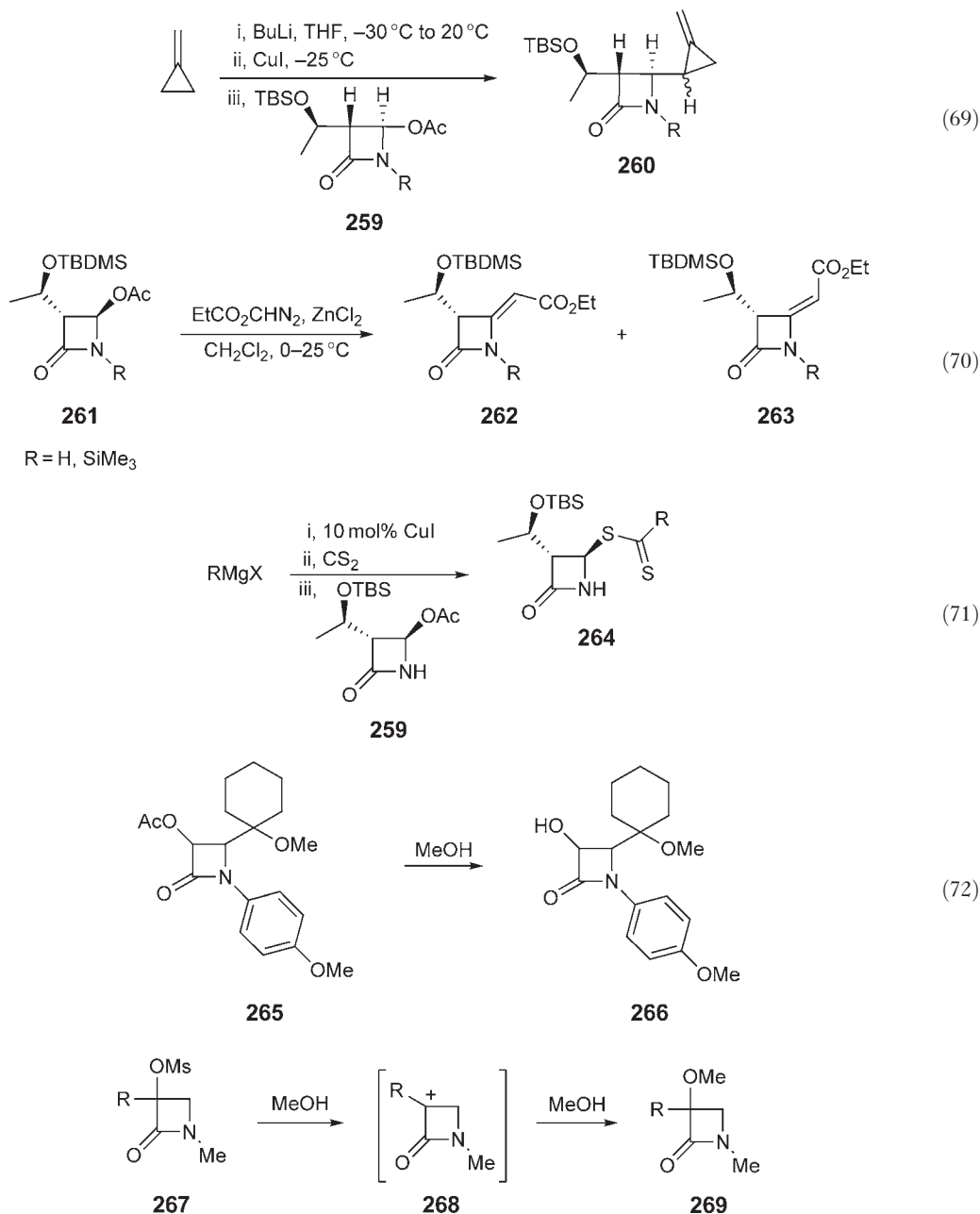
The carboxylic group at C-4 is transformed into an acetoxy group by a Kolbe type-II oxidative decarboxylation reaction using lead(IV) acetate (Equation 67) <2001J(P1)2566>. The formyl group at C-4 in azetidin-2-ones **257** is known to undergo a Baeyer–Villiger rearrangement to give 4-formyloxyazetidin-2-ones **258** stereoselectively (Equation 68) <1995TL3401>. A fluoride ion induces desilylative α -hydroxylation with aldehydes at C-4 of the 3-alkylidene-4-trimethylsilylazetidin-2-ones <1996CPB466>.



2.01.3.5.2 Nucleophilic attack at carbon

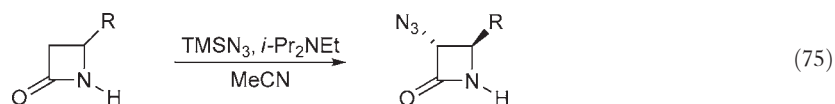
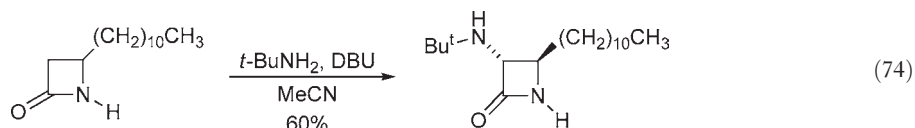
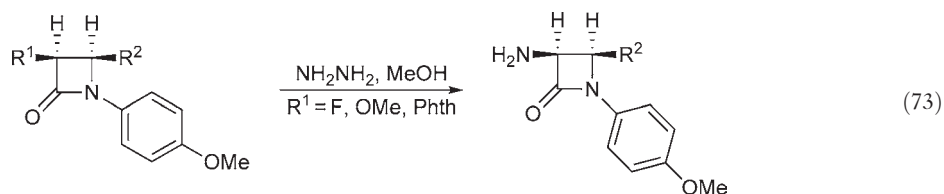
Various nucleophilic reagents have been employed to introduce the desired functionality at C-3 and C-4 positions of the azetidin-2-ones. The functionalization of an acetoxy group at C-4 has been exploited several times with a variety of reagents. For example, coupling of the organocuprate lithium bis(methylenecyclopropyl)cuprate at C-4 of

4-acetoxiazetidin-2-one **259** resulted in substitution of the acetoxy group with a methylenecyclopropyl group, affording 4-methylenecyclopropylazetidin-2-one **260** (Equation 69) <2000TL10347>. The reaction of 4-acetoxiazetidin-2-ones **261** with ethyl diazoacetate in the presence of zinc chloride yielded 4-(1-ethoxycarbonylmethylidene)azetidin-2-ones **262** and **263** (Equation 70) <2002TL233>. The nucleophile, generated from a copper(I)-catalyzed reaction of Grignard reagents with carbon disulfide, displaced the acetoxy group from the azetidin-2-one **259** offering a general and efficient synthesis of azetidinone dithiocarboxylic esters **264** in 31–75% yields (Equation 71) <1995TL771>. A titanium chloride-assisted reaction of azetidin-2-ones with an alkylketone replaced the 4-acetoxy group by a ketoalkyl group <2004T867>. Treatment of the 3-acetoxiazetidin-2-ones **265** with methanol yielded 3-hydroxyazetidin-2-ones **266** (Equation 72) <2005ARK43>. Solvolysis of the mesylate derivatives of 3-aryl-3-hydroxyazetidin-2-ones **267** presumably proceeds through a 3-carbocationic intermediate **268**, which is captured by solvent to yield azetidin-2-ones **269** (Scheme 49) <1996JA12331>. No competing proton loss was observed in this reaction. However, the azide ion in DMSO or dimethylformamide (DMF) reacted via a bimolecular substitution mechanism.

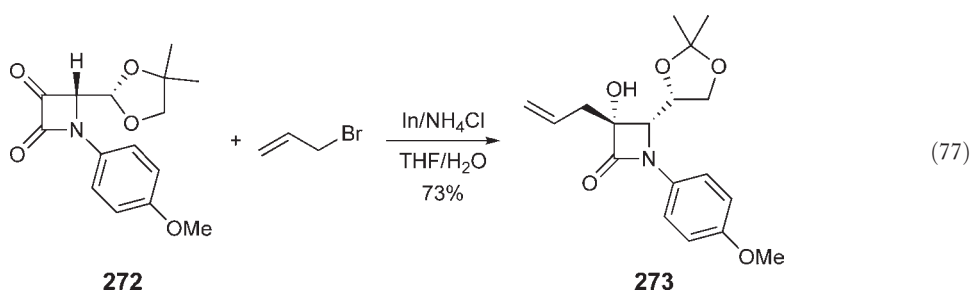
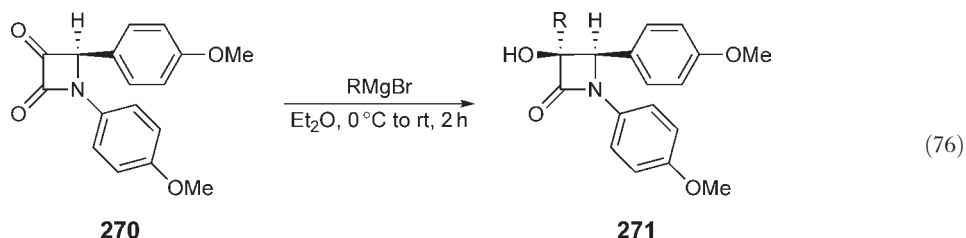


Scheme 49

The phthalimido group at the C-3 position of 1,4-disubstituted azetidin-2-ones is substituted conveniently by an amino group on treatment with hydrazine hydrate in methanol to yield 1,4-disubstituted 3-aminoazetidin-2-ones (Equation 73) <2003TA3949>. The introduction of an amino group and an azido group at C-3 of the C-3-unsubstituted azetidin-2-ones has been accomplished by using *t*-butyl amine in the presence of a stronger base DBU (Equation 74), and trimethylsilyl azide (Equation 75), respectively <2003JOC27>.



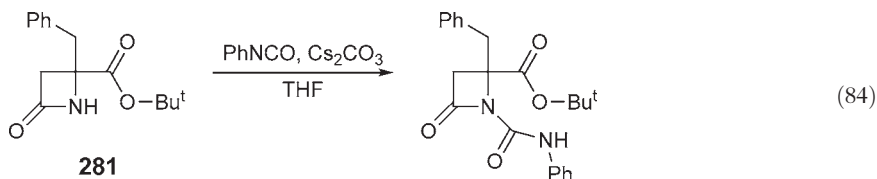
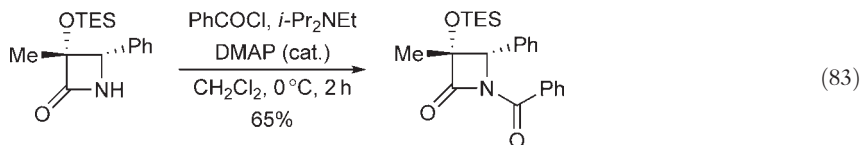
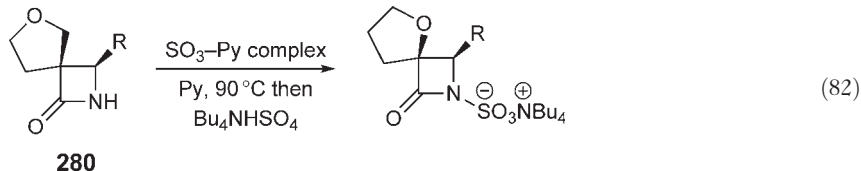
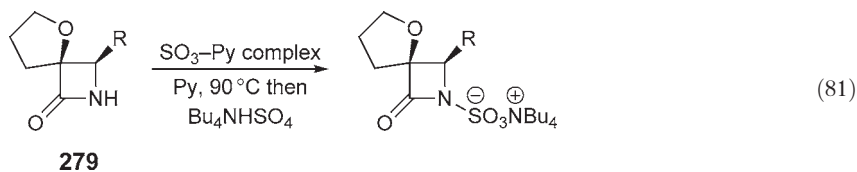
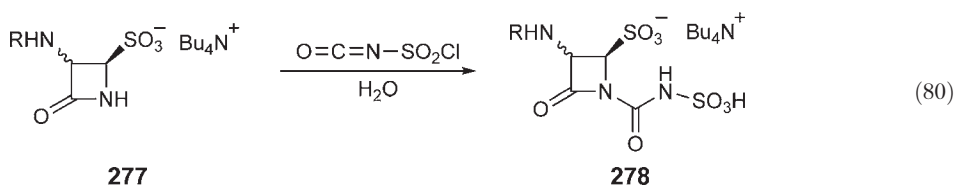
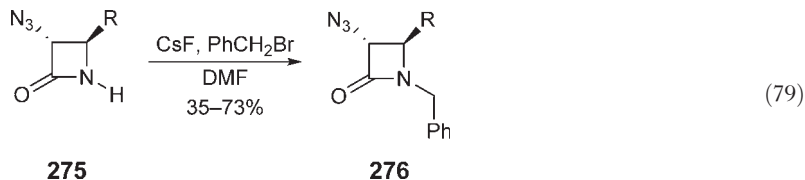
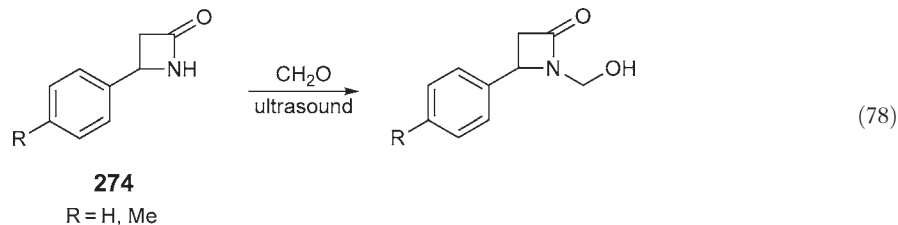
The nucleophilic reaction of Grignard reagents with azetidin-2,3-dione **270** yielded mainly *cis*-3-hydroxyazetidin-2-ones **271** (Equation 76) <2006S115>. A regio- and stereoselective reaction of azetidine-2,3-dione **272** with an organoindium compound led to the formation of azetidin-2-one-tethered homoallylic alcohol **273** (Equation 77), which has been used as precursor of spirocyclic azetidin-2-ones <2004TL6429>.



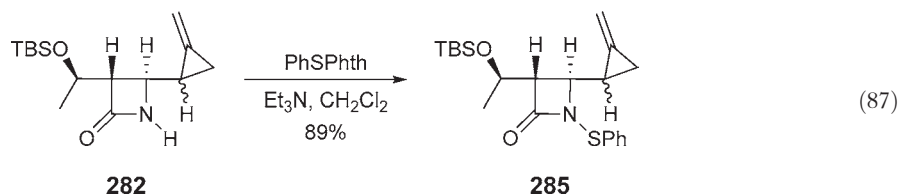
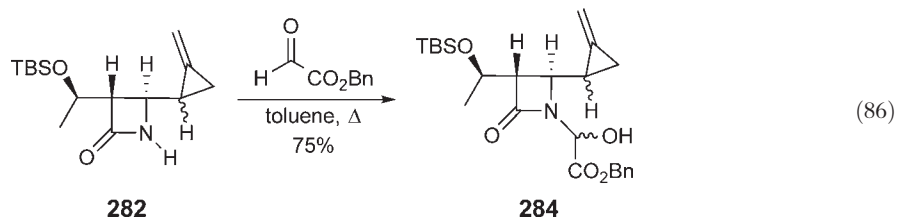
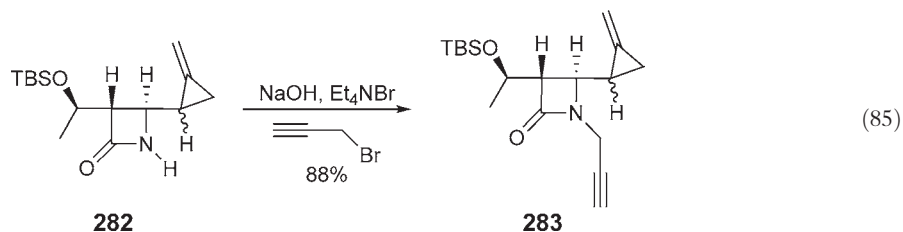
2.01.3.5.3 Electrophilic attack at nitrogen

N-Hydroxymethylation of 4-arylazetidin-2-ones **274** has been achieved by employing formaldehyde under sonification (Equation 78) <2000TA2351>. A mild fluoride-mediated N-benylation of the 3-azidoazetidin-2-ones **275** yielded the corresponding 1-benzyl-3-azidoazetidin-2-ones **276** (Equation 79) <2003JOC27>. The azetidin-2-one **277** reacted with chlorosulfonylisocyanate to form the corresponding 2-oxoazetidin-1-carbonyl sulfamic acid **278** (Equation 80) <2000T3985>. N-Sulfonylation of azetidin-2-ones **279** and **280** has been achieved using sulfur trioxide-pyridine complex (Equations 81 and 82) <2002J(P1)571> and sulfonyl chlorides in the presence of an organic base <2006MOL49>. N-Benzoylation (Equation 83) and N-acetoxylation of azetidin-2-ones have been described <1996TL6495, 2004BML2253>. Many other N-substitutions have been achieved by using the

corresponding halides in the presence of butyllithium/THF <2003JOC27>. Various electron-withdrawing groups can be introduced at nitrogen atom in the presence of NaHMDS <1999TL1827>. N-Carbamylation of 4-benzyl-4-(*t*-butyloxy)azetidin-2-one **281** has been carried out by phenyl isocyanate (Equation 84) <2004BML2253>.



The reaction of 4-(methylenecyclopropyl)azetidin-2-one **282** with propargyl bromide in the presence of tetraethylammonium bromide with benzyl glyoxalate and with *N*-(phenylthio)phthalimide yielded the azetidin-2-ones **283–285** bearing a propargyl group, an (α -hydroxy)methylbenzyloxycarbonyl group, and a phenylthio group at the nitrogen atom, respectively (Equations 85–87) <2000TL10347>.

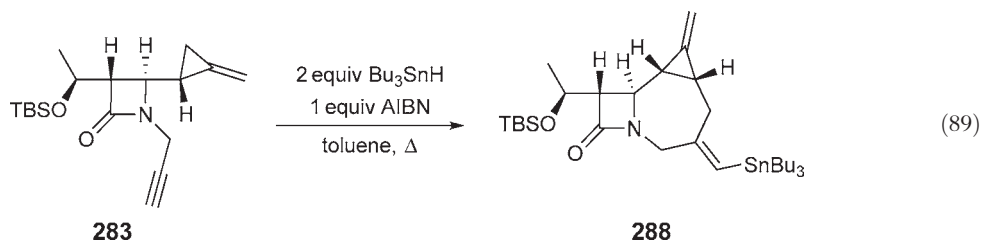
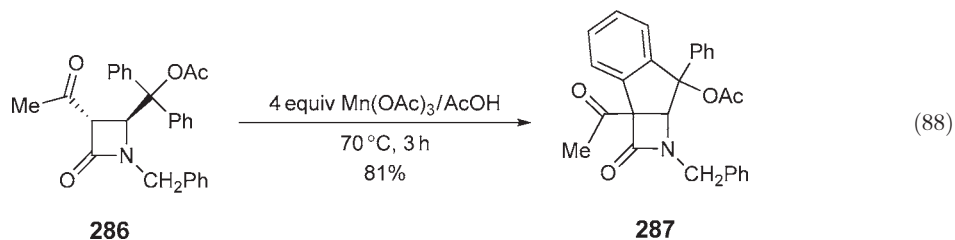


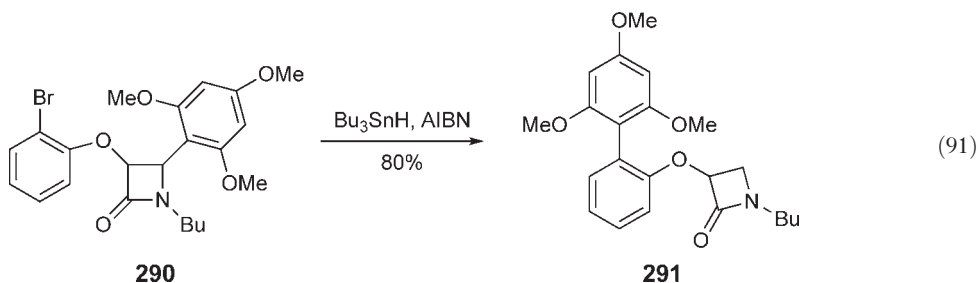
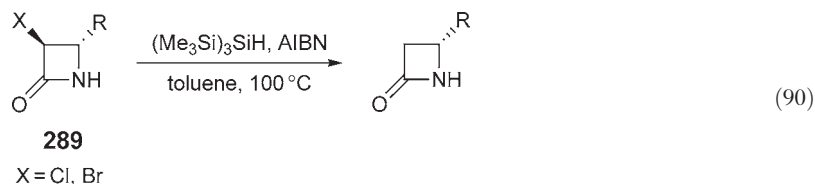
2.01.3.5.4 Nucleophilic attack at hydrogen (deprotonation)

Deprotonation of azetidin-2-ones at C-3 or C-4 and following reaction with electrophiles are treated in [Section 2.01.3.5.1](#).

2.01.3.5.5 Radical and photochemical conversions

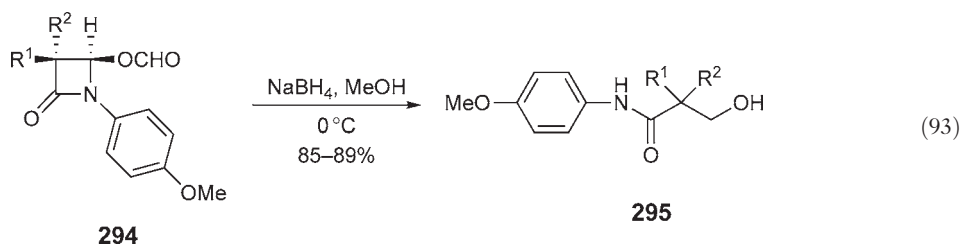
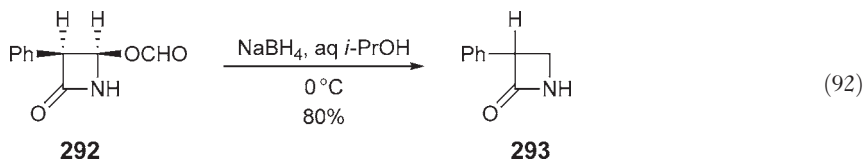
A manganese(III)-catalyzed radical cyclization of substituents at C-3 and C-4 of 1-benzyl-3-acetyl-4-(acetoxyphe-nyl)methylazetidin-2-one **286** afforded the fused tricyclic azetidin-2-one **287** (Equation 88) <2000TL3261>. Intramolecular radical cyclization of 4-(methylenecyclopropyl)-1-propynylazetidin-2-one **283** afforded the fused tricyclic azetidin-2-one **288** (Equation 89) <2000TL10347>. Reductive dehalogenation at C-3 of the azetidin-2-ones **289** is accomplished using tris(trimethylsilyl)silane in the presence of 2,2'-azobisisobutyronitrile (AIBN) (Equation 90) <2000OL1077>. Treatment of 3-(2-bromophenyl)-4-azetidin-2-ones **290** with tributyltin hydride led to intramolecular aryl-aryl coupling and 4-dearylation forming azetidin-2-one **291** (Equation 91) <1998TL6589>.



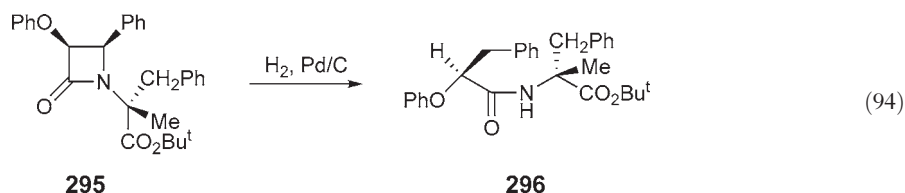


2.01.3.5.6 Reduction reactions

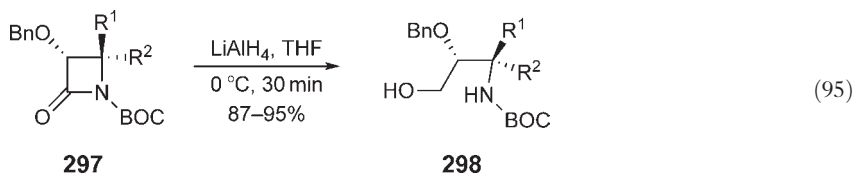
The reduction reactions of azetidin-2-ones with a wide variety of reagents such as lithium aluminium hydride, diisobutyl aluminium hydride, monochloroalane and dichloroalane, and diphenylsilane leading to the formation of azetidines have been described in [Section 2.01.2.8.10](#). The reduction of *cis*-4-formyloxy-3-phenylazetidin-2-one **292** with sodium borohydride yielded 3-phenylazetidin-2-one **293** (Equation 92) [<1995TL3401>](#). The reduction of a C(=O)Ph group at C-4 of azetidin-2-ones to CH(OH)Ph group has also been accomplished using sodium borohydride [<2003T5259>](#). On the other hand, reduction of different *N*-(4-methoxyphenyl)-4-formyloxyazetidin-2-ones **294** (Equation 93) [<1995TL3401, 2005TA971>](#), 3-methyl-2-oxoazetidin-1,4-dicarboxylates [<1995T11581>](#), and 3-phenoxy/acetoxo-4-aryl-1-(4-methoxyphenyl)azetidin-2-ones [<2006TL2209>](#) with sodium borohydride gave the corresponding α -substituted β -hydroxyamides **295** as the ring-opened products in high yields.



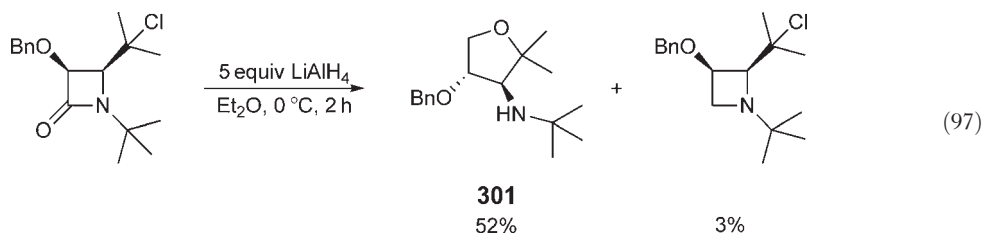
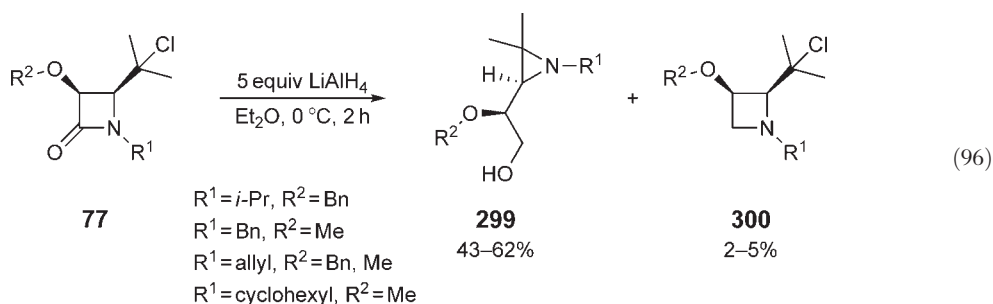
The catalytic reduction of *N*-substituted 3-phenoxy-3-phenylazetidin-2-one **295** yielded the ring-opened *N*-substituted 2-phenoxy-3-phenylpropanamide **296** (Equation 94) [<1995ACR383>](#).



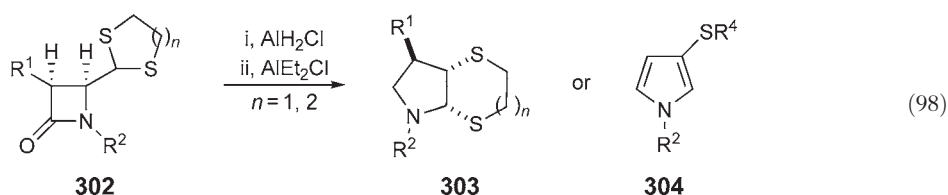
The reduction of azetidin-2-ones **297** with LiAlH_4 furnished γ -amino alcohols **298** in quantitative yields (Equation 95), which is a key intermediate for the synthesis of pyridones [<2002TL3843, 2003T6445, 2003JOC2471>](#).



The reduction of 4-(1-chloroalkyl)azetidin-2-ones **77** with 5 molar equivalents of LiAlH_4 in diethyl ether yielded 2-(1-alkoxy-2-hydroxyethyl)aziridines **299** in good yields together with small amounts of 2-(1-haloalkyl)-azetidines **300** (Equation 96) <2006OL1101>. The formation of the former compound has been explained through an azetidinium salt while the latter product was formed through an azetinium ion. It was observed that when the azetidin-2-one had a *t*-butyl group at nitrogen, it gave rise to an oxolane derivative instead of an aziridine (Equation 97).



The reduction of azetidin-2-one **302** containing a thioacetal moiety at C-4 to the corresponding acetal azetidine, followed by diethylaluminium chloride promoted C(2)–N(1) bond cleavage, afforded bicyclic pyrrolidines **303** and pyrroles **304** (Equation 98) <1999JOC9596, 1998TL467>.

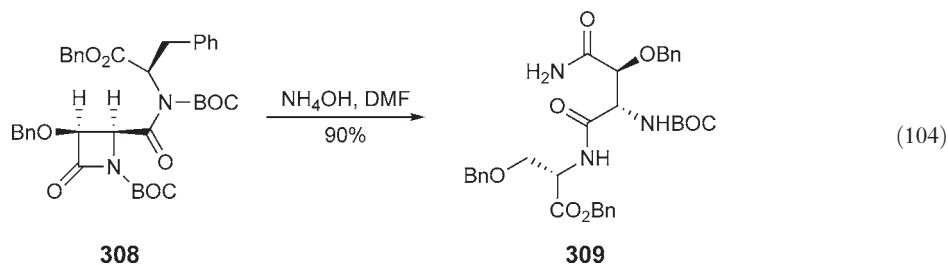
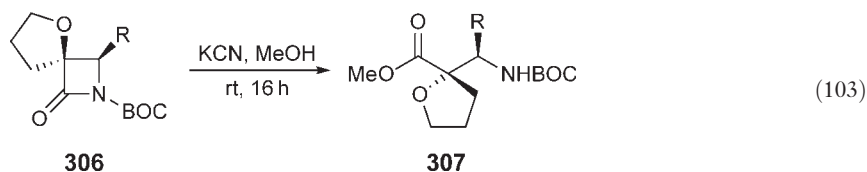
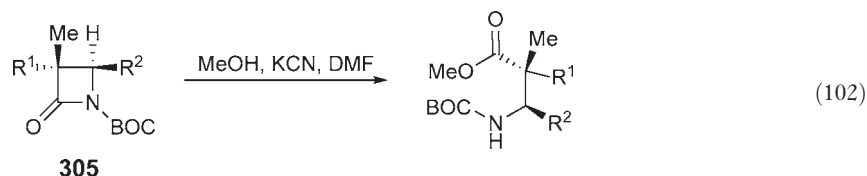
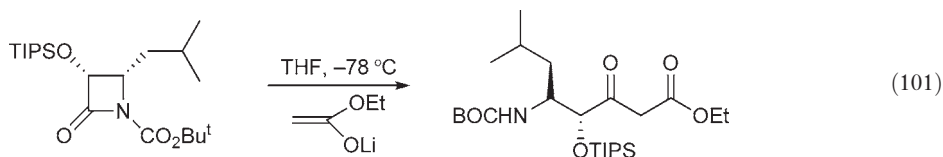
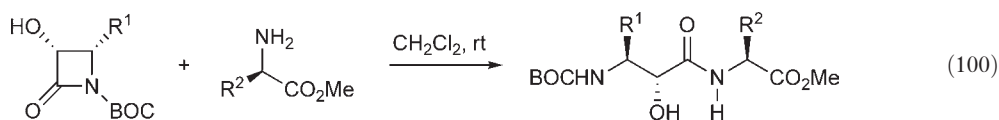
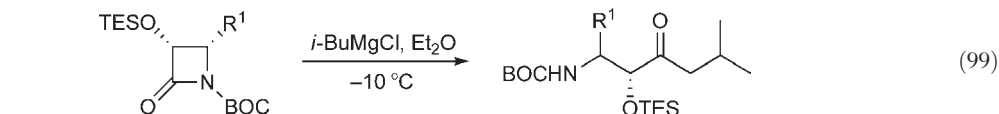


2.01.3.5.7 Ring opening reactions

The ring opening reactions of azetidin-2-ones are performed with different types of oxidizing, reducing (discussed in the preceding section), and nucleophilic reagents. The most common β -lactam ring opening reaction is the N(1)–C(2) bond cleavage, which occurs by nucleophilic attack across the carbonyl carbon <1997CSR377, 1999TL1827>. This reaction makes azetidin-2-ones a very good synthon for β -amino acids and their derivatives of biological importance. However, many suitably designed azetidin-2-ones undergo intramolecular reactions to furnish the ring expansion product after initial β -lactam ring opening. The reactions leading to acyclic products and cyclic products are therefore described separately.

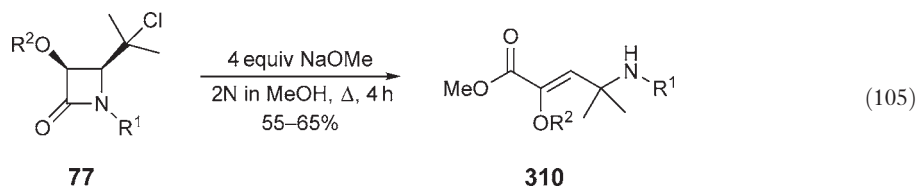
2.01.3.5.7(i) Ring opening leading to acyclic products

Various nucleophiles such as alkoxides, amines, Grignard reagents (Equation 99), amino acids (Equation 100), and metal enolates (Equation 101) have been used for this purpose <1997CSR377>. Methanolysis of 1-benzyl-3-hydroxy-4-phenylazetidin-2-one furnished the phenylisoserine methyl ester <1998BML1619>. A similar cleavage has been achieved by treating azetidin-2-one **305** with potassium cyanide in methanol and dimethylformamide (Equation 102) <1998JA12237, 2001TL1251>. The cleavage of azetidin-2-ones **306**, spirofused with a tetrahydrofuran ring, by potassium cyanide in methanol at room temperature, yielded β -aminoester **307** (Equation 103) <2002SL69>. Ring cleavage of azetidin-2-one **308** afforded the dipeptide **309** required for the synthesis of an α -hydroxy aspartic acid-derived tripeptide found in the macrocyclic antibiotic lysobactin (Equation 104) <1996CC161>. A number of orthogonally protected α -alkyl aspartic acids and α -alkyl asparagines were synthesized by alcoholysis of 4-benzyl-4-carboxyazetidin-2-ones <2003TL6145>. Treatment of these azetidin-2-ones with H-Ala-OMe yielded β -aspartic dipeptides.

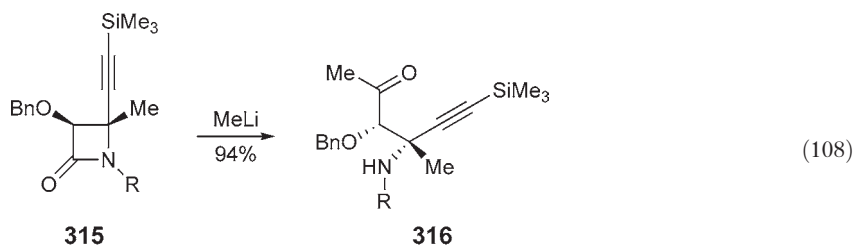
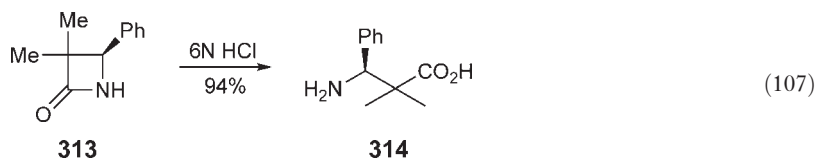
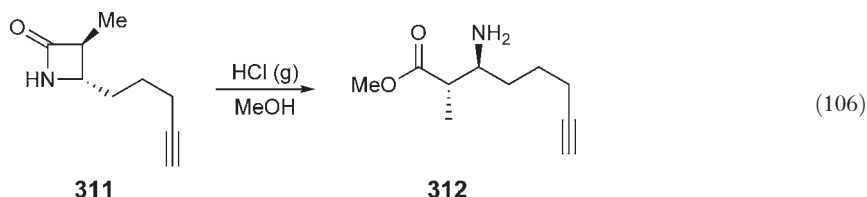


Theoretical studies using the results of molecular dynamics simulation of *N*-methylazetidin-2-one in aqueous solution predicted a stepwise mechanism for the hydrolysis <1998JA2146>. In the alkaline hydrolysis, the first reaction step involved the formation of a tetrahedral intermediate, which required a desolvation of the hydroxyl anion, which is difficult to simulate by calculations. Afterwards, the reaction proceeded through either a concerted or stepwise mechanism for ring opening and proton transfer.

Treatment of the *cis*-4-(1-chloro-1-methylethyl)azetidin-2-ones **77** with an excess of 2N sodium methoxide in methanol yielded the ring-opened products **310** (Equation 105) <2005PAC2061>. The formation of the products was explained by nucleophilic ring opening of the azetidin-2-ones followed by an intramolecular cyclization by attack of the amino group on the halogenated carbon atom. The base-induced cleavage of the new heterocycle led to the formation of the ring-opened products.

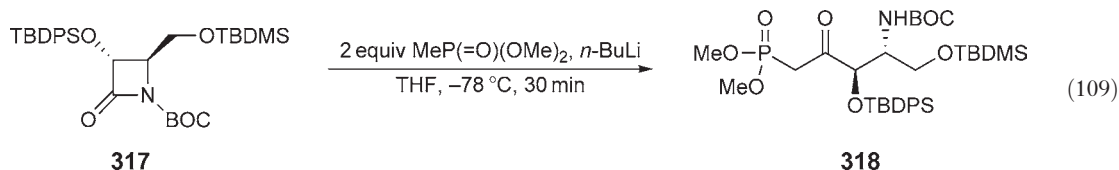


An acidic hydrolysis of (3*S*,4*S*)-3-methyl-4-(pent-4-ynyl)azetidin-2-one **311** yielded (2*S*,3*S*)-methyl-3-amino-2-methyl-7-octynoate **312** (Equation 106), which is part of the structure of onchidin, a dimeric cyclic depsipeptide <1997TA1847>. The hydrolysis of 3,3-dimethyl-4-phenylazetidin-2-one **313** with hydrochloric acid to the known β -amino acid **314** (Equation 107) was used for the determination of the absolute configuration of the starting azetidin-2-one <1995TL729>. Treatment of the 4-alkynylazetidin-2-ones **315** with methylithium yielded ketone **316** (Equation 108), used in the synthesis of dihydropyran <2002OL749>.

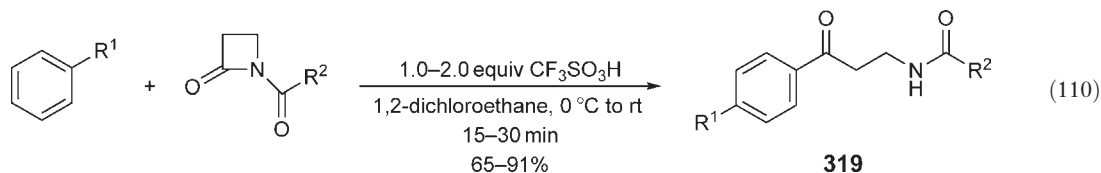


R = PMP, CBz

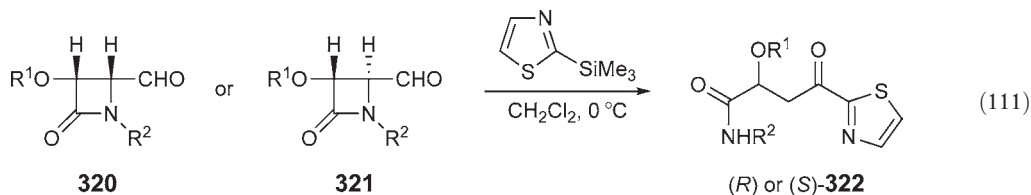
The ring opening of activated azetidin-2-one **317** by a phosphonate-stabilized carbanion yielded the β -ketophosphonate **318** (Equation 109) <2002TL9641>. The Horner–Wadsworth–Emmons alkenylation and subsequent reduction of the latter compound affords a β -aminoketone, which is used in the synthesis of sphingosine and phytosphingosine.



The nucleophilic attack by many benzenoid and nonbenzenoid aromatic rings (with the exception of nitrobenzene) on the β -lactam ring carbonyl in the presence of trimethanesulfonic acid yielded the ring-opened β -aminoaromatic ketones **319**, demonstrating the application of azetidin-2-ones as Friedel–Crafts acylating agents (Equation 110) <2002T8475>.

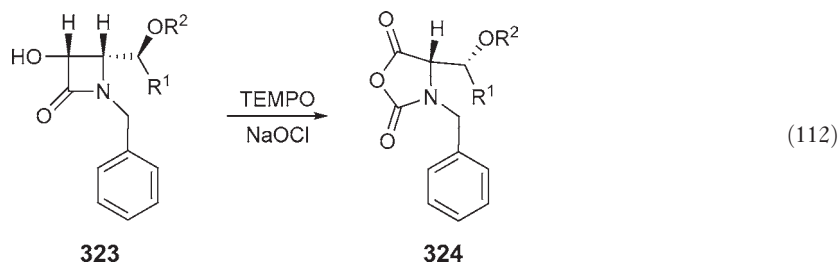


A novel N(1)–C(4) cleavage of azetidin-2-one **320** or **321** forming α -alkoxy- γ -keto amides **322** has been observed by addition of 2-(trimethylsilyl)thiazole to *cis*- or *trans*-4-formylazetidin-2-ones (Equation 111) <2004OL1765>.

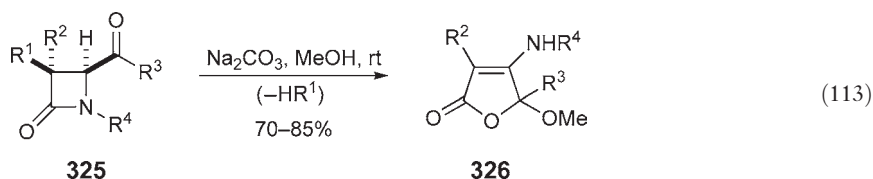


2.01.3.5.8 Ring opening leading to ring expansion products

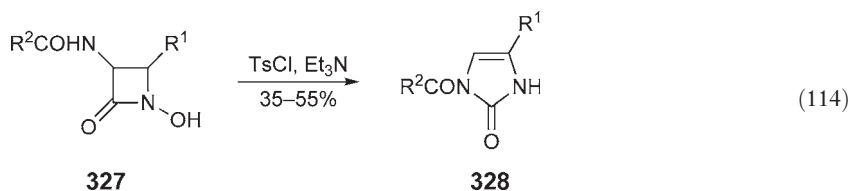
The ring opening of *cis*-azetidin-2-ones **323** with 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) and sodium hypochlorite furnished the ring expansion product isoxazolidine-2,5-dione **324**, which is used in the synthesis of the macrocyclic antibiotic lysobactin (Equation 112) <2000PAC1763>.



Treatment of the azetidin-2-ones **325** with sodium carbonate in methanol at room temperature afforded the unsaturated γ -lactones **326** (Equation 113) <2000JOC3453>. Formation of the enaminone is rationalized through a tandem E1cb-elimination rearrangement of the enolate generated initially, followed by ring opening of the resulting highly strained 2-azetinone.

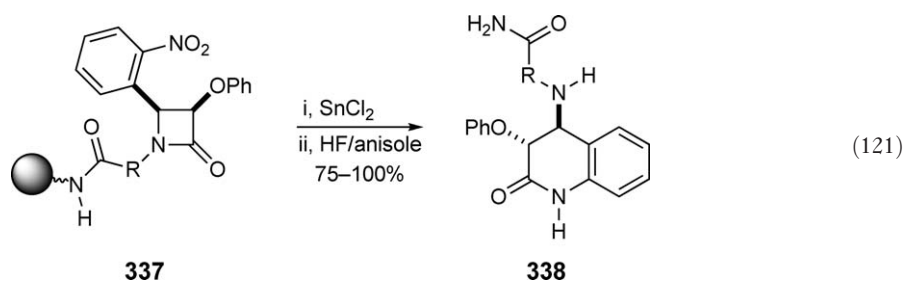
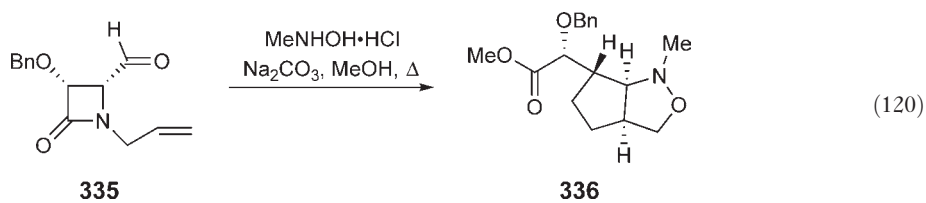
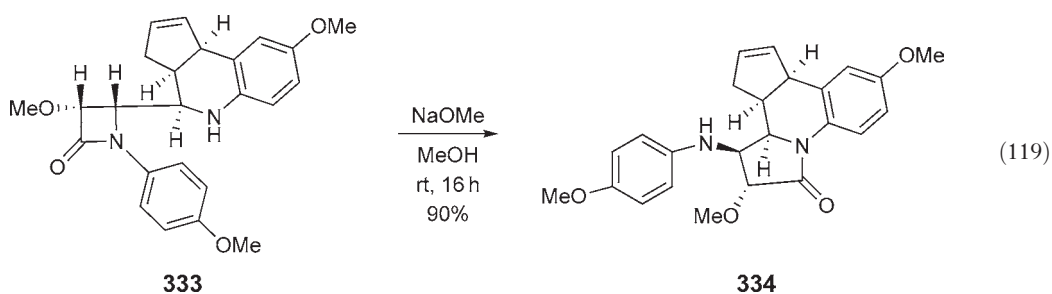
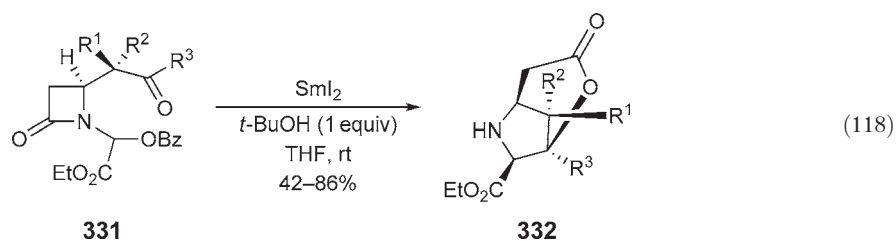
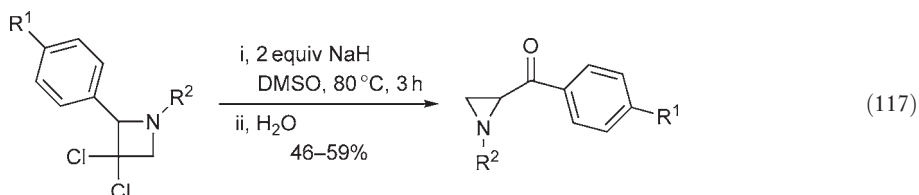
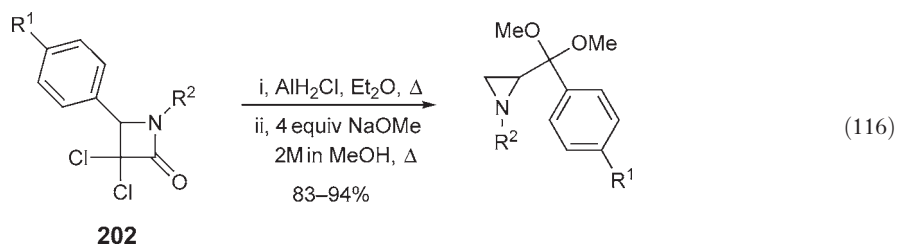


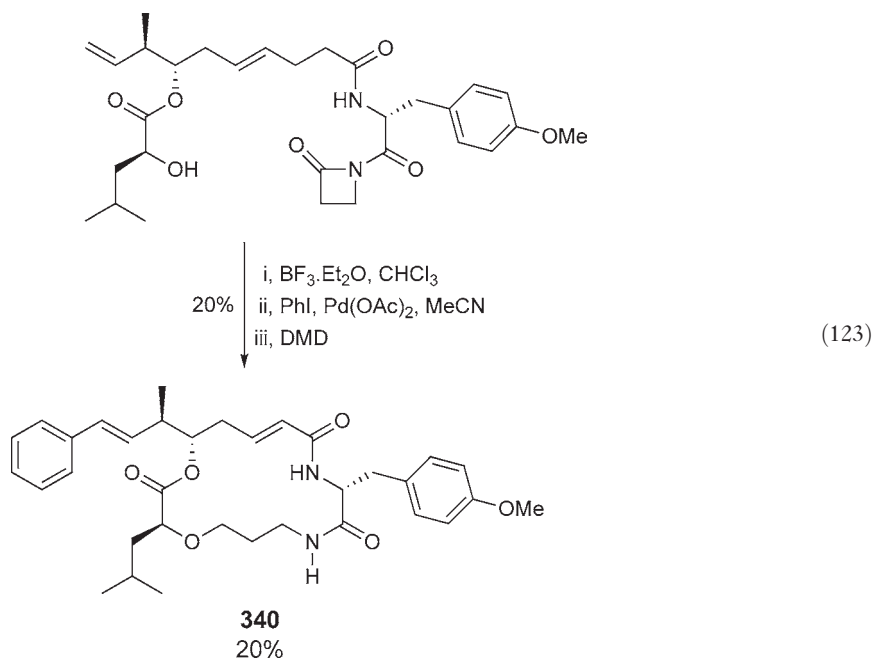
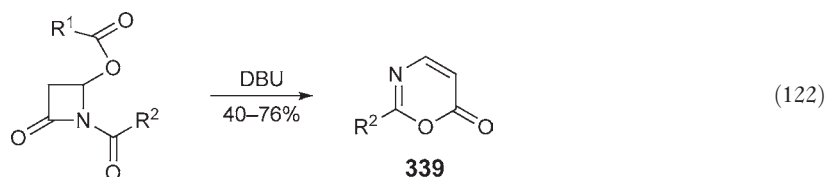
The reactions of 3-amido-1-hydroxyazetidin-2-ones **327** with *p*-toluenesulfonyl chloride in the presence of triethylamine provided the ring-expanded 4-imidazolin-2-ones **328** (Equation 114) <1995TL1617>. The key step in the mechanism of this reaction involved the ring opening by cleavage of the C(2)–C(3) bond, which is followed by double bond migration and an intramolecular nucleophilic addition of the amide nitrogen to an intermediate isocyanate.



(115)

Ring sizes from three to complex macrocycles can be synthesized using azetidin-2-ones. The reductive and nucleophilic ring opening reactions applied to the synthesis of various heterocyclic compounds have been discussed in Sections 2.01.3.5.6 and 2.01.3.5.7, respectively. The chemistry of functional groups present on the ring has been thoroughly explored in the synthesis of a wide variety of fused heterocyclic compounds [<2004CME1921>](#). Only selected examples are described here. An easy synthesis of aziridines from 2-aryl-3,3-dichloroazetidin-2-ones [202](#) (Equation 116) has been recently reported via reduction of the latter compounds to 3,3-dichloroazetidines [<2002JOC2075>](#). 2-Aryl-3,3-dichloroazetidin-2-ones are also transformed into aziridines through 2-azetines by sodium hydride in DMSO (Equation 117) [<2002JOC2075>](#). An intramolecular reductive cyclization of azetidin-2-ones [331](#) followed by an N- to O-acyl migration involving cleavage of the β -lactam ring has resulted into the formation of highly functionalized proline derivatives [332](#) as single diastereomers (Equation 118) [<2002JOC2411>](#). 2-Azetidinones [333](#), synthesized by an aza-Diels–Alder reaction of a 2-azetidinone-tethered imine, have been transformed into a fused tetracyclic indolizidinone system using sodium methoxide (Equation 119) [<2001SL1531>](#). Treatment of 4-oxoazetidin-2-carbaldehyde [335](#) with *N*-methylhydroxyl amine hydrochloride led to the formation of a fused bicyclic pyrrolidinyl acetate [336](#) (Equation 120) [<2002SL85>](#). Reduction of the nitro group, present at the C-4 phenyl group of azetidin-2-ones [337](#), into an amino group, followed by intramolecular nucleophilic ring opening by attack of the amino group across the lactam carbonyl group furnished the ring-expanded 4-amino-3,4-dihydro-2(1*H*)-quinolinones [338](#) (Equation 121) [<2005ARK53, 1997TL3349>](#). A cyclization of the monocyclic azetidin-2-one to the corresponding bicyclic β -lactam followed by ring expansion opens up an asymmetric route for piperazine-derived peptides [<1997TL4643>](#). The synthesis of 2-substituted 1,3-oxazin-6-ones [339](#) is reported by the action of DBU on *N*-acyl-4-acyloxyazetidin-2-ones (Equation 122) [<2000OL965>](#). A base-promoted β -elimination across the C(3)–C(4) bond of the β -lactam ring giving rise to a highly strained azetin-2-one, followed by an electrocyclic ring opening to the corresponding *N*-acylimidoalkene, explained the formation of heterocycle [339](#). The β -lactam framework has also been employed in the synthesis of complex macrocyclic heterocycles. For example, the antimetabolic agent cryptophycin [340](#) has been synthesized from a monocyclic azetidin-2-one (Equation 123) [<2001OL1813>](#).

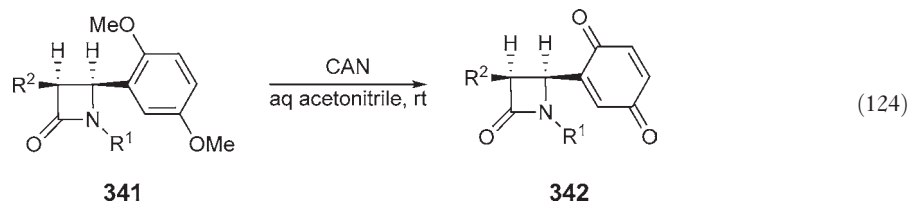


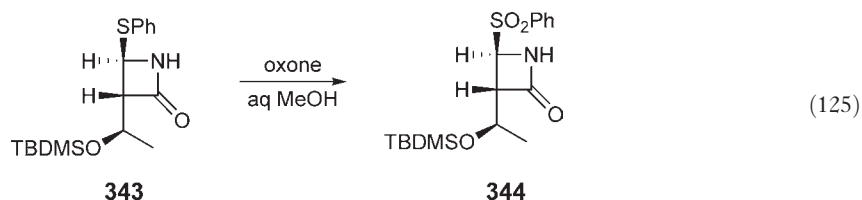


2.01.3.8 Reactivity of Substituents Attached to the Ring Carbon Atoms

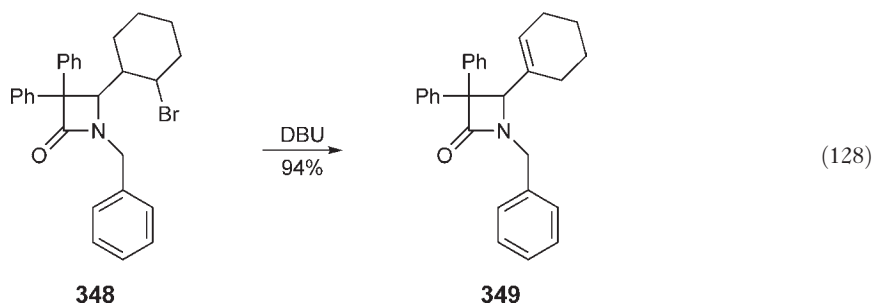
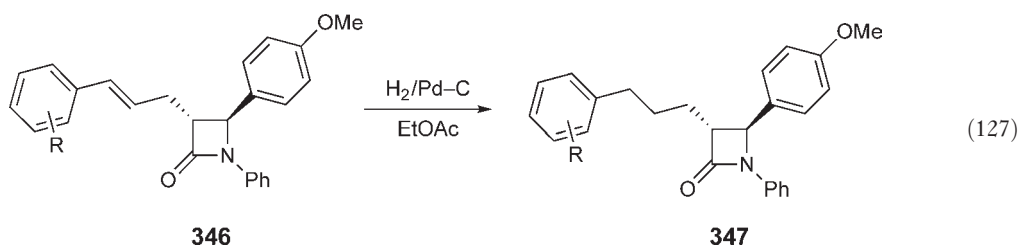
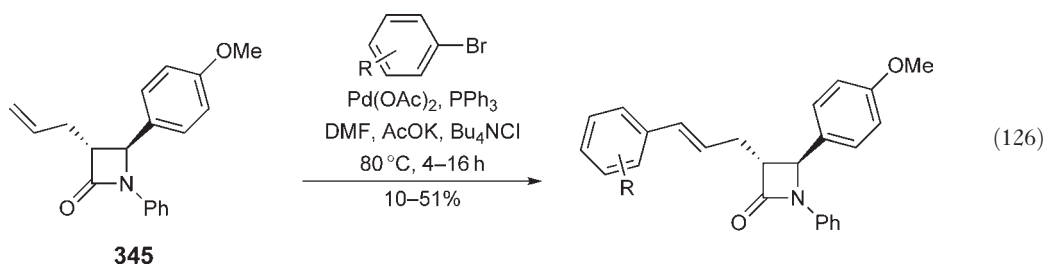
A brief selection of reactions in which substituents attached to ring carbon atoms are involved in transformations is discussed. A large number of such reactions have been covered already in the different sections of this chapter. The transformations involving the formyl group at C-4 of the azetidin-2-ones have been reviewed recently [<2004CME1921>](#).

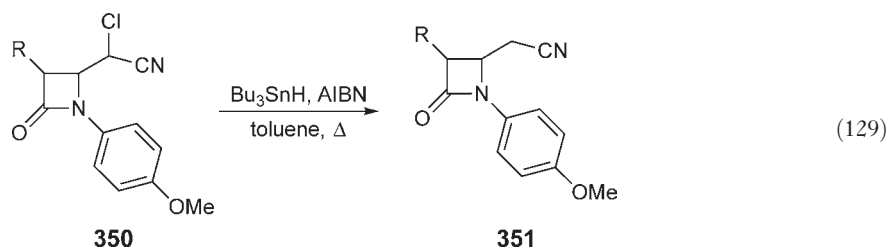
The 2,5-dimethoxyphenyl group at C-4 of the azetidin-2-ones **341** is oxidized by cerium ammonium nitrate in aqueous acetonitrile to afford the azetidin-2-ones **342** (Equation 124) bearing a quinone moiety at C-4 with retention of stereochemistry [<2001TL1503>](#). Some other aromatic groups at C-4, such as 4-methoxyphenyl, 2-furyl and 2-thienyl, are oxidized to a carboxylic group by ruthenium tetroxide, generated *in situ* from H_5IO_6 or NaIO_4 and ruthenium chloride [<2001J\(P1\)2566>](#). An oxidation of the sulfide at C-4 of the 4-(phenylthio)azetidin-2-one **343** afforded 4-phenylsulfonylazetidin-2-ones **344** (Equation 125) [<2000MI935>](#).



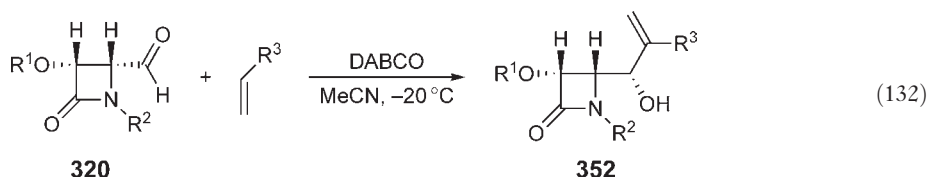
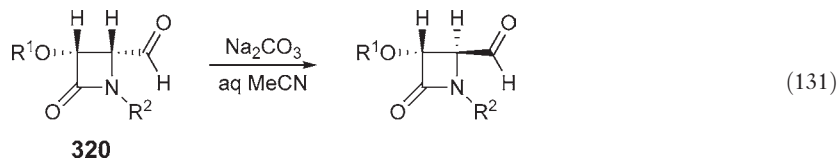
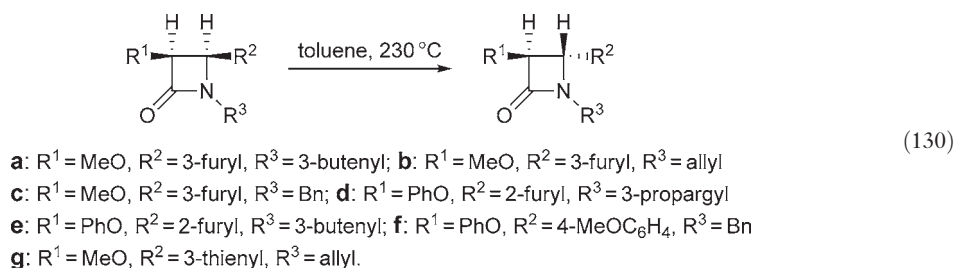


Arylation of an olefinic group at C-3 of azetidin-2-one **345** has been reported in the presence of a palladium catalyst (Equation 126) <2000T5735>. The olefinic group in azetidin-2-one **346** undergoes palladium-catalyzed hydrogenation to afford 3-(3-aryl)propylazetidin-2-ones **347** (Equation 127). A DBU-mediated dehydrohalogenation of the 1-bromocyclohexyl ring at C-4 of azetidin-2-one **348** formed 4-cyclohexenylazetidin-2-one **349** (Equation 128) <2001TL4409>. The reductive dehalogenation of the C-4 substituent of azetidin-2-ones **350** was studied using various reagents such as $\text{H}_2/\text{Pd-C}$, Zn-AcOH , and tributyltin hydride in order to synthesize (4-oxo-azetidin-2-yl)acetonitrile **351** <2004JCM558>. Only the application of tributyltin hydride yielded the desired product either exclusively or predominantly (Equation 129), the other two reagents yielded a ring-opened product besides the desired one. However, the exact yields of the products could not be determined due to difficulties in purification. An olefinic group at C-3 in azetidin-2-ones has been transformed into a formyl group by ozonolysis, and into a dimethoxymethyl group by ozonolysis and subsequent treatment with trimethoxymethane <2001J(P1)2566>.

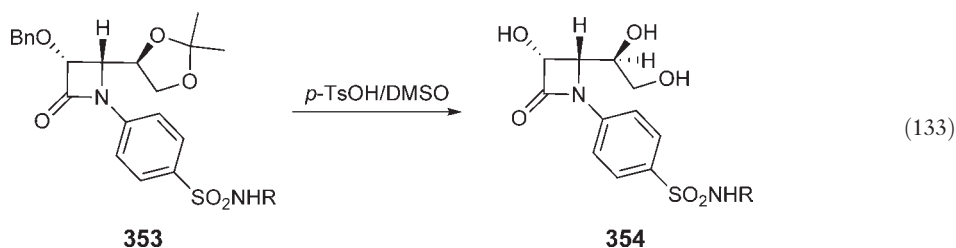




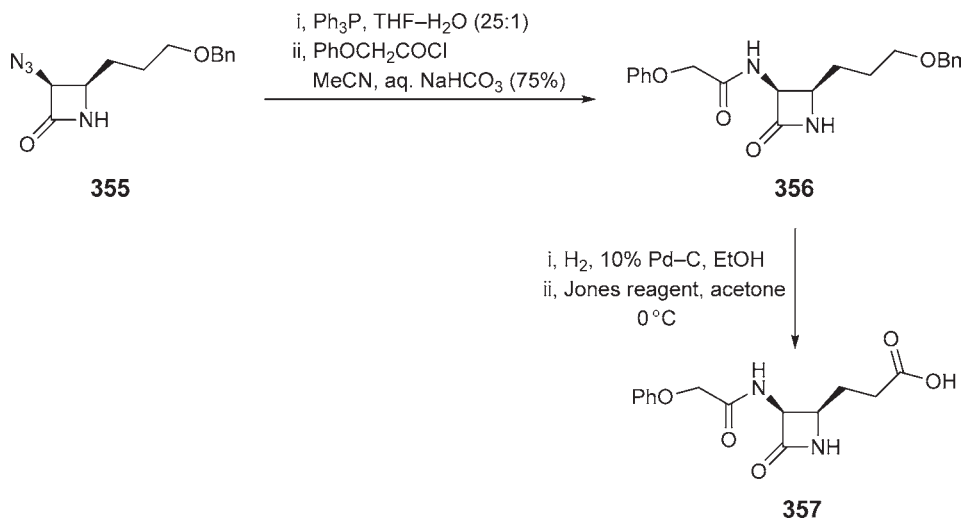
Isomerization of *cis*-azetidin-2-ones to *trans*-azetidin-2-ones has been observed either thermally (Equation 130) <2000JOC4453> or in the presence of a base as a catalyst (Equation 131) <2000JOC3459>. A formyl group in azetidin-2-ones undergoes Wittig-olefination <2000JOC3459>. A DABCO-promoted reaction of a formyl group at C-4 with various activated vinyl systems gives Baylis–Hillman adducts **352** (Equation 132) <2001JOC1612>. The imino groups, derived from the formyl group at C-4, undergo aza Diels–Alder reactions <2001SL1531>.



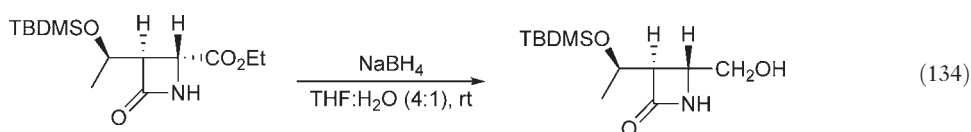
A carboxylic group at C-4 has been methylated using diazomethane <2001JOC3538>. The hydrolysis of an acetoxy group at C-3 to a hydroxyl group and of an acetal at C-4 in azetidin-2-one **353** to the corresponding diol **354** is achieved using *p*-toluenesulfonic acid in dimethyl sulfoxide (Equation 133) <2000SC246>. Although the γ -lactam ring suffers cleavage upon treatment with base, the *N*-diphenylacylindolin-2-one ring spirofused at C-3 of the azetidin-2-ones survived at the cost of the *N*-diphenylacyl moiety on refluxing in ethanolic sodium hydroxide <2000JHC1355>.



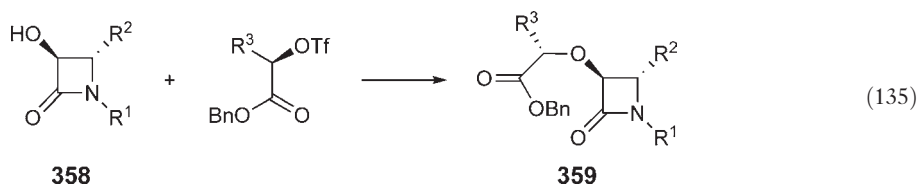
Reduction of an azide functionality at C-3 of azetidin-2-one **355** followed by acylation afforded 3-amidoazetidin-2-one **356** (Scheme 50). O-Debenzylation, followed by treatment with the Jones reagent, afforded a *cis*-3,4-disubstituted azetidin-2-one **357**, which is a precursor of the antibiotic loracarbef <2001TL4519>. The reduction of an ethoxycarbonyl group and an acetoxy group at C-3 to a hydroxyl group has been accomplished by sodium borohydride (Equation 134) <2001T10155>.

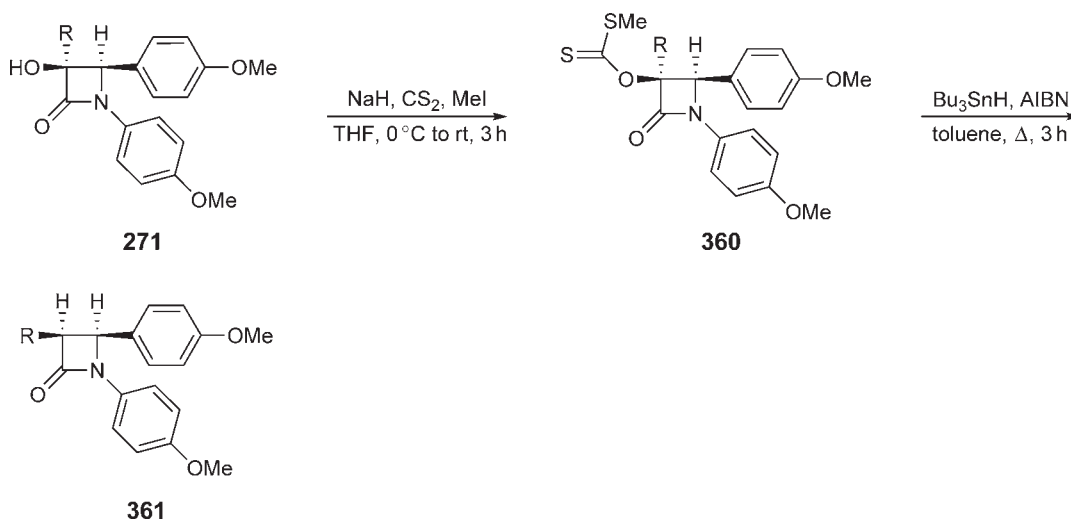


Scheme 50

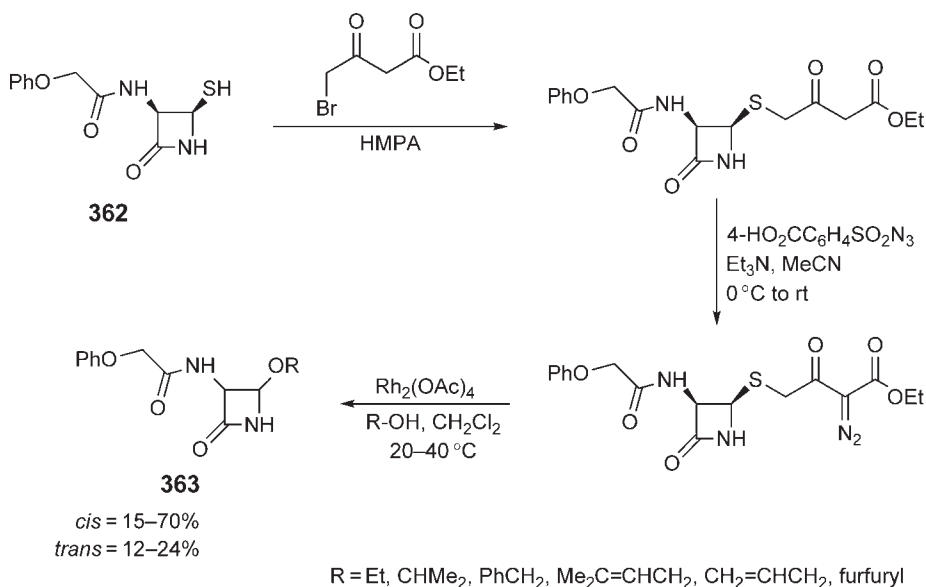


The hydroxyl group at C-3 of 1,4-disubstituted 3-hydroxyazetidin-2-ones **358** reacted with an ester bearing an active methine proton to give azetidin-2-one **359** (Equation 135) <1998TL5895>. The reaction of *trans*-3-hydroxyazetidin-2-one **271** with carbon disulfide followed by methylation changed the hydroxyl group into a xanthate ester, forming azetidin-2-one **360** (Scheme 51) <2006S115>. The reductive removal of the xanthate ester led to the formation of *cis*-azetidin-2-ones **361**. The transformation of 4-mercaptoazetidin-2-one **362** to 4-alkoxyazetidin-2-one **363** has been accomplished via introduction of an SCH₂CO₂Et group at C-4 of the azetidin-2-one (Scheme 52) <2001CJC1259>. A diazo transfer reaction and subsequent Rh(II)-catalyzed electrocyclic ring opening afforded 4-alkoxyazetidin-2-ones **363**.



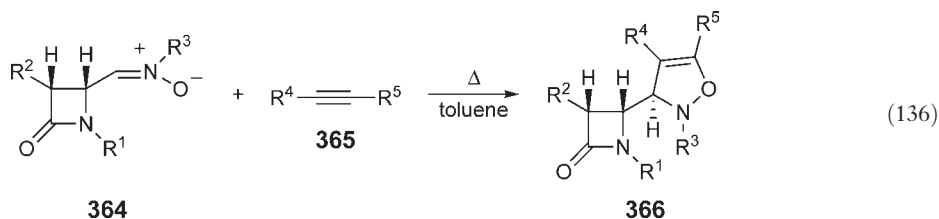


Scheme 51

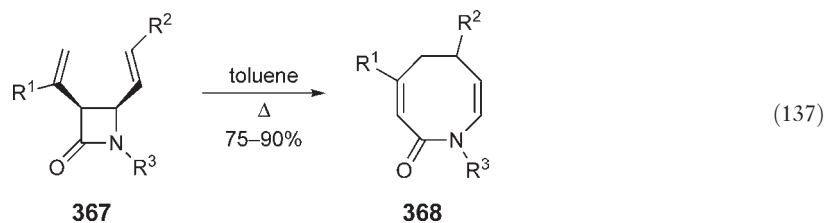


Scheme 52

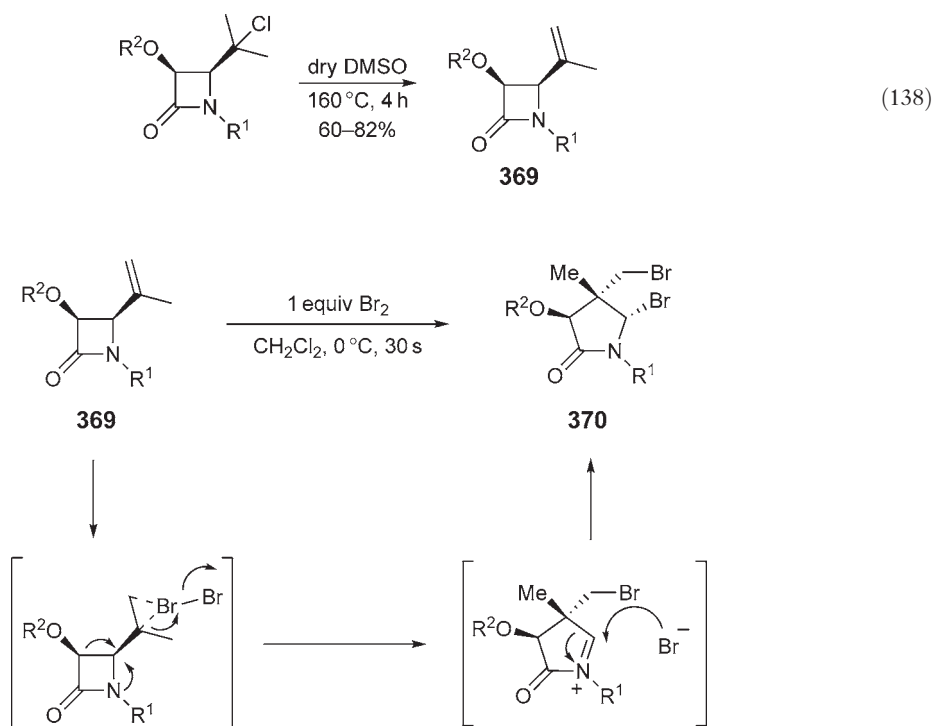
The 1,3-dipolar cycloaddition reactions of racemic as well as enantiopure azetidin-2-one-tethered nitrones **364** with alkenes and alkynes **365** (Equation 136) yielded isoxazolidinyl- or isoxazolinylazetidin-2-ones **366**, exhibiting good regio- and facial stereoselectivity (Equation 136) <2002JOC7004>.



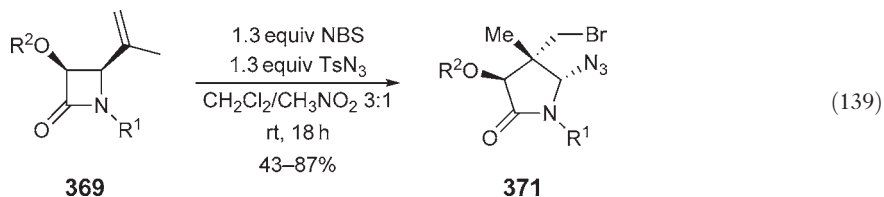
The presence of alkenyl groups attached to adjacent ring carbons C-3 and C-4 of the azetidin-2-ones **367** offers an opportunity to use a thermal [3,3] sigmatropic rearrangement for the synthesis of eight-membered lactams, through C(3)–C(4) bond cleavage [<2001TL3081>](#). A stereoselective synthesis of tetrahydroazocinones **368** was developed starting from azetidin-2-one-tethered 1,5-dienes ([Equation 137](#)).



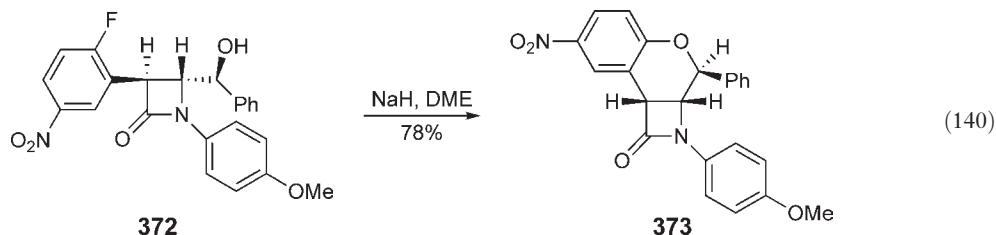
The dehydrochlorination of 4-(1-chloroalkyl)azetidin-2-ones with dimethyl sulfoxide offers a new route to 3,4-*cis*-4-isopropenylazetidin-2-ones **369** ([Equation 138](#)) [<2005JOC8717>](#). The reaction of the latter compounds with bromine ([Scheme 53](#)) or with a mixture of *N*-bromosuccinimide and trimethylsilylazide ([Equation 139](#)) led to an electrophile-induced ring expansion toward pyrrolidin-2-ones **370** and **371**.



Scheme 53



The carbonyl group at C-4 of the 3-aryl-4-benzoylazetidin-2-one is reduced with sodium borohydride to the corresponding hydroxyl group [<2003T5259>](#). Treatment of azetidin-2-one **372** with sodium hydride gave a fused tricyclic azetidin-2-one **373** (Equation 140) as a result of an intramolecular nucleophilic substitution reaction of the alkoxide with an aromatic group at the C-3 position.

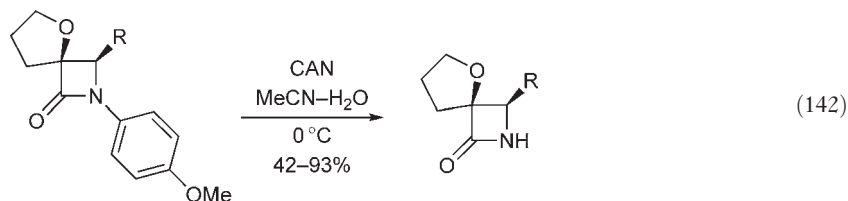
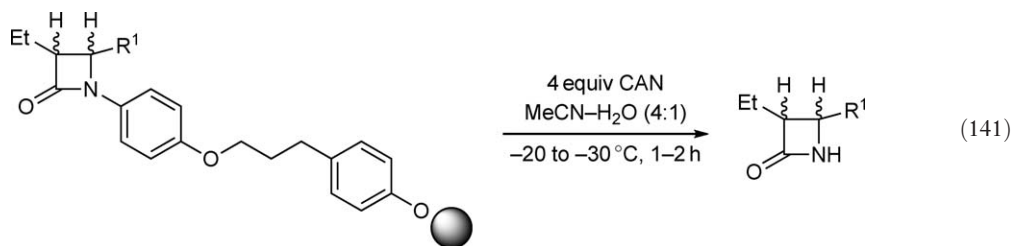


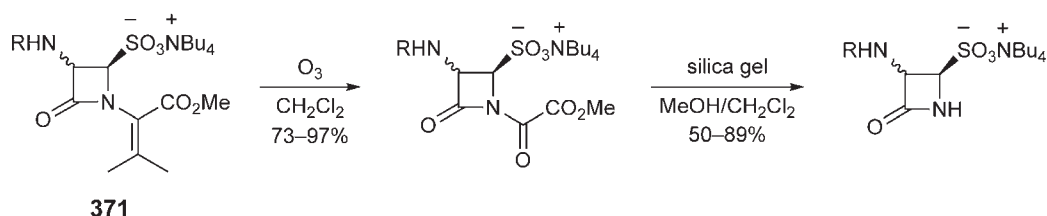
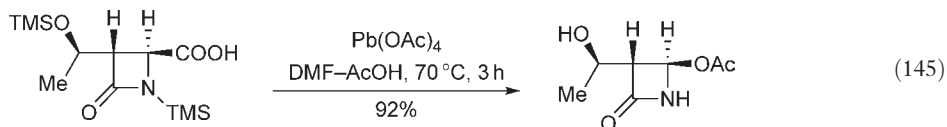
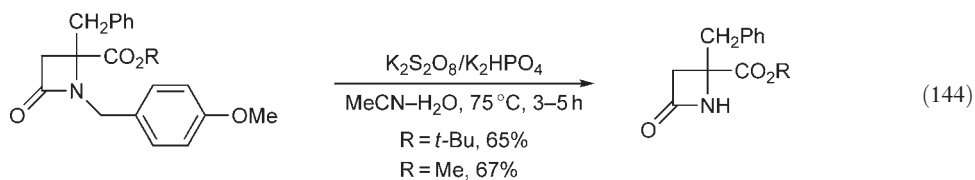
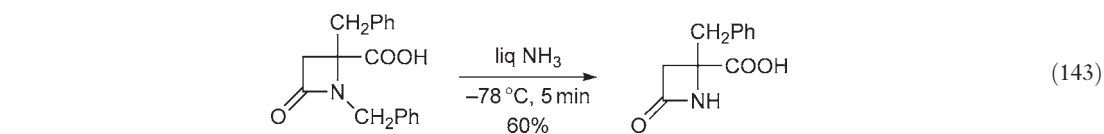
The ester group of 3-substituted 4-acetoxiazetidin-2-ones is replaceable in reactions with β -(1-cyclohexenyl)dialkylboranes to form 3-cyclohexenylazetidin-2-ones in a varying *cis-trans* ratio [<1995JA9604>](#). Transformations of the 4-acetoxy group to a CH(Me)COOH group [<1996TL4967>](#) are also known.

2.01.3.9 Reactivity of Substituents Attached to the Ring Nitrogen Atom

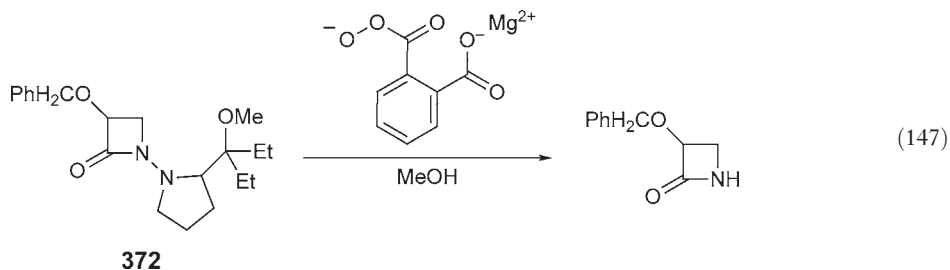
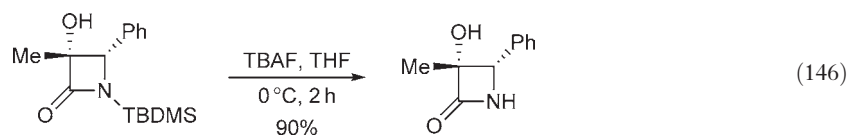
The protection and deprotection of the nitrogen atom of azetidin-2-ones hold a prime position in synthetic methodologies leading to functionalized and N-unsubstituted azetidin-2-ones. Some leading references on frequently used protective groups, and their removal from nitrogen, are given below, including some selected examples. In some cases, the N-substituent is not necessarily considered as the protective group, for example, 1-hydroxyazetidin-2-one, but removal of this substituent has been investigated.

The oxidative removal of a polymeric group [<2000CEJ133>](#) and a 4-methoxyphenyl group [<1995TL729, 2002J\(P1\)571, 2006MOL49, 1997TA1847>](#) from azetidin-2-ones is readily accomplished using cerium ammonium nitrate (CAN) (Equations 141 and 142). Reductive removal of a benzyl group has been achieved by Li in NH₃ (Equation 143), whereas a 4-methoxybenzyl group has been removed by employing K₂S₂O₈ (Equation 144) [<1997JOC5873, 2001JOC3538>](#) or by catalytic hydrogenation in the presence of Pd(OH)₂ [<2004TL2193>](#). N-Desilylation occurred with lead(IV) acetate in DMF–AcOH, but the carboxylic group in the substrate was transformed into an acetoxy group (Equation 145) [<2000JAN1231>](#). The ozonolysis of an α,β -unsaturated ester group at nitrogen atom in 3,4-disubstituted azetidin-2-ones **371** furnished a ketoester group, which could be removed over silica gel (Scheme 54) [<2000T3985>](#). Removal of *t*-butyldimethylsilyl (TBDMS) is reported on treatment with TBAF (Equation 146) [<1996TL6495>](#). Magnesium monoperoxyphthalate in methanol successfully cleaved the N–N bond of *N*-(1-pyrrolidinyl)azetidin-2-one **372** (Equation 147) [<2000AGE2893>](#) and of *N*-(*N'*-methyl-*N'*-*p*-tolyl)aminoazetidin-2-ones [<2003T10195>](#) to give the corresponding 1-unsubstituted azetidin-2-ones.

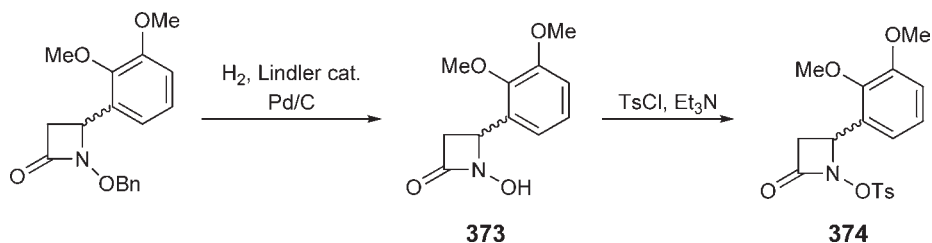




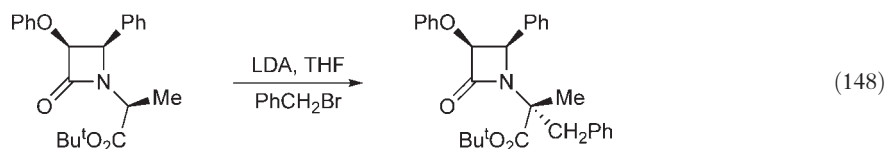
Scheme 54



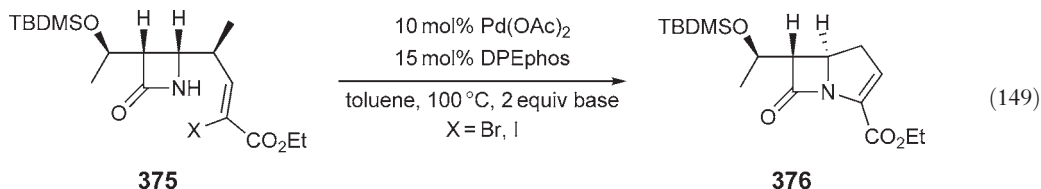
Reductive O-debenzylation yielded *N*-hydroxyazetidin-2-one **373** (Scheme 55) <2000T5719>. The latter compound afforded *N*-tosyloxyazetidin-2-one **374** on treatment with TsCl in triethylamine. A substituent with an active methine proton on the ring nitrogen underwent benzylation via a lithium enolate (Equation 148) <1995ACR383>.



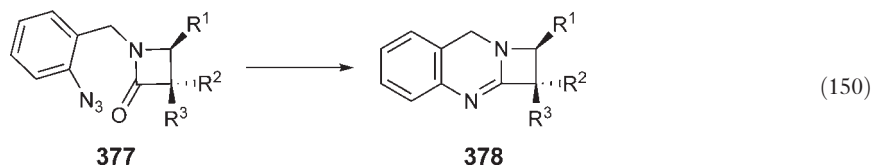
Scheme 55



A palladium-catalyzed C–N bond-forming reaction of the azetidin-2-ones **375** formed the carbapenem derivative **376** (Equation 149) <2002TL111>.



An intramolecular aza-Wittig reaction of the β -lactam carbonyl group with azide present at the α -position of the *N*-benzyl substituent in azetidin-2-ones **377** gives the fused tricyclic heterocyclic compound **378** (Equation 150) <1998SL1288>.



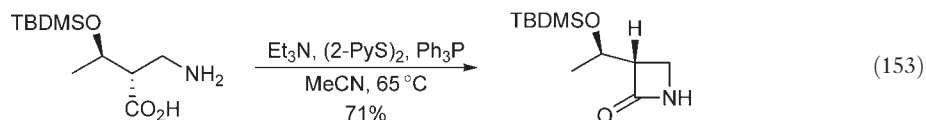
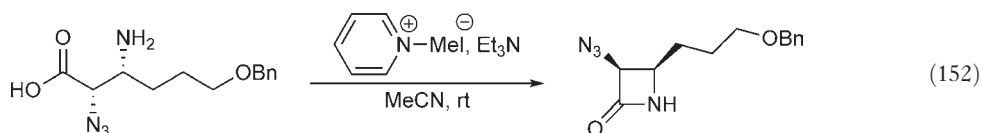
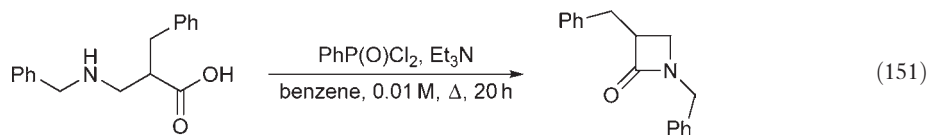
Very recently, the combination of a reactive group at C-4 (an aldehyde or an imine) and a ω -haloalkyl group at nitrogen in different azetidin-2-ones enabled the synthesis of pharmaceutically relevant piperazine, morpholine, and 1,4-diazepane annulated β -lactams upon reductive ring closure <2006JOC7083>.

2.01.3.10 β -Lactam Ring Synthesis from Acyclic Precursors

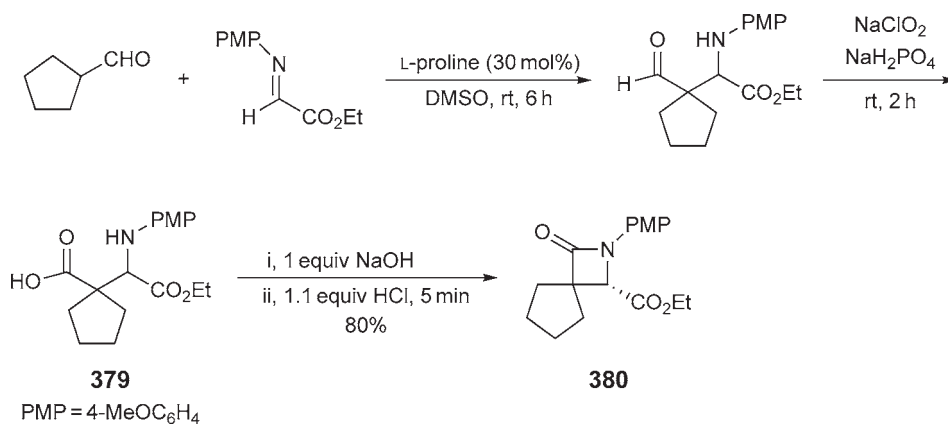
A large number of syntheses of azetidin-2-ones have been developed. All categories of bond formation, such as N–C(2), N–C(4), C(2)–C(3), and C(3)–C(4), and several types of cycloaddition reactions have witnessed an explosive appearance. A number of theoretical studies on the synthesis of azetidin-2-ones have been carried out <1998MI245>. Some other synthetic methods such as ketene–imine cycloaddition <1998CHE1222>, asymmetric ketene–imine cycloaddition <2004CME1837>, ester–enolate addition <1996MI119>, radical cyclizations <1998RHA169>, and electrophilic cyclization of unsaturated amides <1998T13681> have been reviewed. Reviews on eco-friendly routes <1997JIC943> and combinatorial and solid-phase syntheses <1998AJC875, 1998MI51, 2003AGE2340> are also available. The various types of azetidin-2-one syntheses will be discussed, but major synthetic routes, for example, the ester enolate–imine cycloaddition and ketene–imine cycloaddition, cannot be covered completely. Eco-friendly approaches and methods of asymmetric synthesis are emphasized.

2.01.3.10.1 Cyclization of β -amino acids

The cyclization of an appropriate amino acid is the most obvious approach to the synthesis of azetidin-2-ones. The intramolecular condensation of β -amino acids is accomplished by a large variety of activating agents including phenyl phosphorodichloridate and triethylamine in benzene (Equation 151) <2001T1883>, 1-methylpyridinium iodide and triethylamine in acetonitrile (Equation 152) <2001TL4519>, *N,N*-(diethoxyphosphinyl)benzo-1,2,5-thiadiazolidine-1,1-dioxide <1996BKC290>, phosphorodimorpholidic halides <1996BKC656>, camphor-derived oxazoline *N*-oxide <2000OL1053, 2000EJO1595, 1999CC2365>, phenylphosphonic dichloride <2001T1883>, and a mixture of 2,2'-dipyridyl sulfide, triethylamine and triphenylphosphine (Mukaiyama's reagent) (Equation 153) <1996TL5565, 2000JOC8372>.



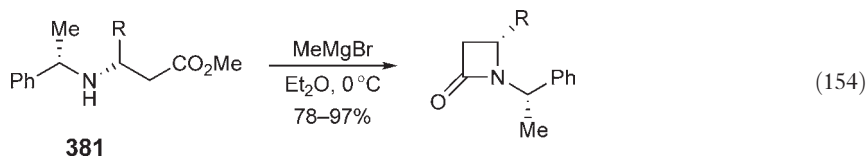
The intramolecular cyclization of β -carboethoxy- β -amino acid **379**, synthesized from L-proline-catalyzed Mannich reaction of aldehydes with an iminoester and subsequent oxidation, with sodium hydroxide yielded the cyclopentane-spiro-fused azetidin-2-one **380** (Scheme 56) <2004OL2507>.

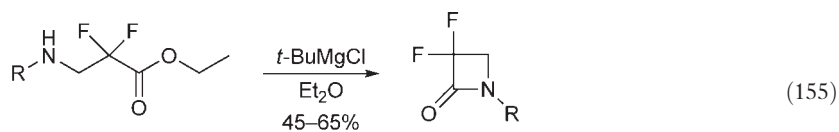


Scheme 56

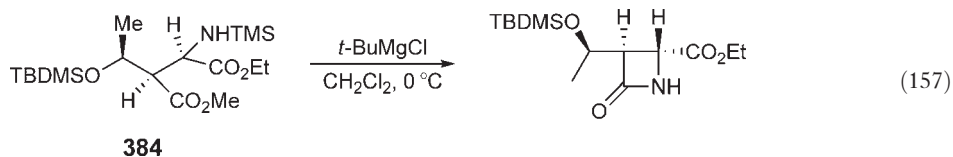
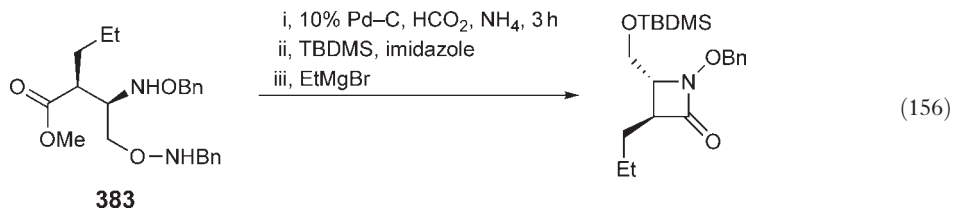
2.01.3.10.2 Cyclization of β -amino esters

The cyclocondensation of β -amino esters **381** has been performed in a classical way with Grignard reagents (Breckpot reaction) (Equation 154) <1995CC1109, 1996TL4095>. Recently, 3,3-difluoroazetidin-2-ones **242**, **243**, and **382** have been synthesized in moderate to good yields using this methodology (Equation 155) <2003S2483>. As an alternative, *N*-benzyloxy- or *N*-trimethylsilylaminoesters **383** or **384** have been treated with Grignard reagents for stereocontrolled synthesis of azetidin-2-ones (Equations 156 and 157) <2000JAN1231, 2001T10155, 2004OBC1274>.

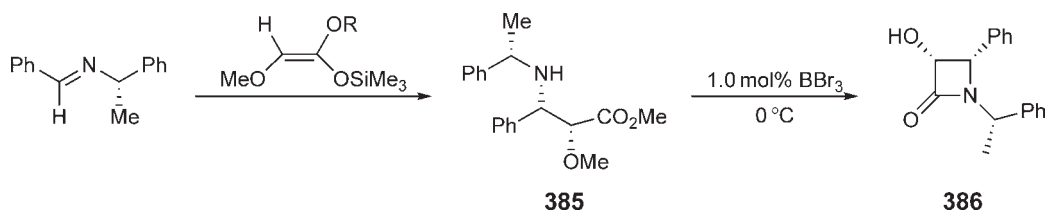




R = **242**: 4-MeOC₆H₄CH₂, **243**: 4-MeOC₆H₄, **382**: Ph₂CH

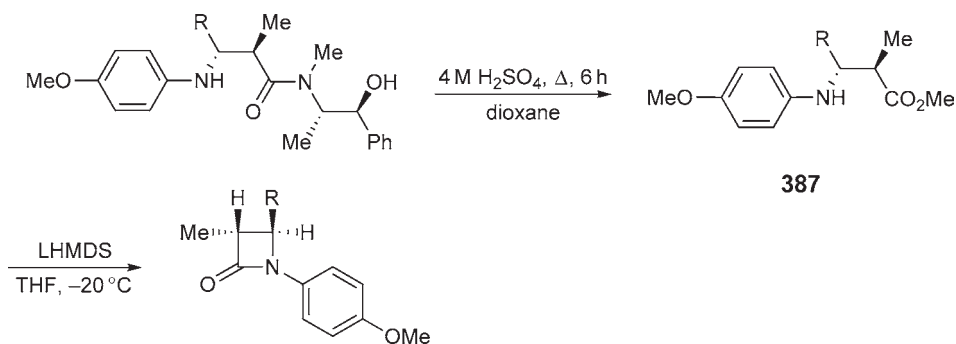


The β -aminoester **385**, synthesized by coupling of a chiral imine with a ketene acetal, cyclized toward *cis*-3-hydroxy-4-phenylazetidin-2-one **386** in the presence of boron tribromide (Scheme 57) <1998BML1619>.



Scheme 57

The β -amino esters **387**, obtained by hydrolysis of the corresponding β -amino amides, have been cyclized in the presence of lithium hexamethyldisilazide (LHMDS)/THF to furnish the *trans*-3,4-disubstituted azetidin-2-ones (Scheme 58) <2001JOC9030>.

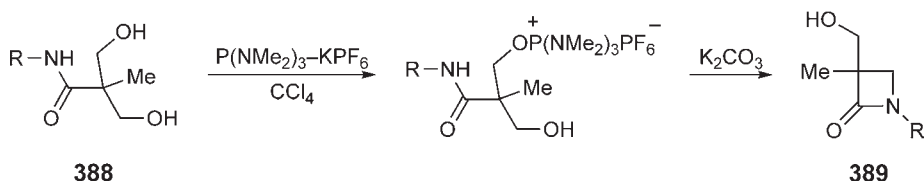


Scheme 58

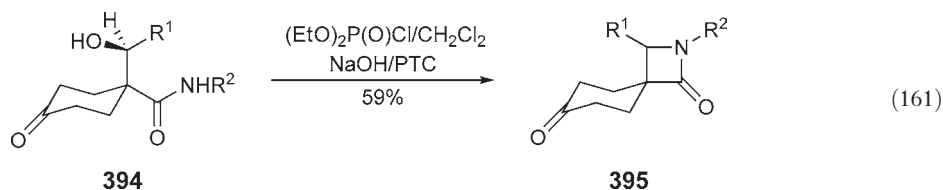
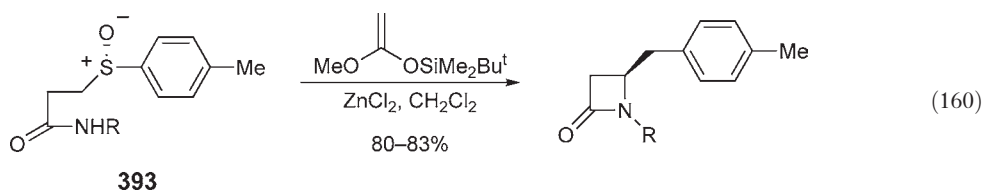
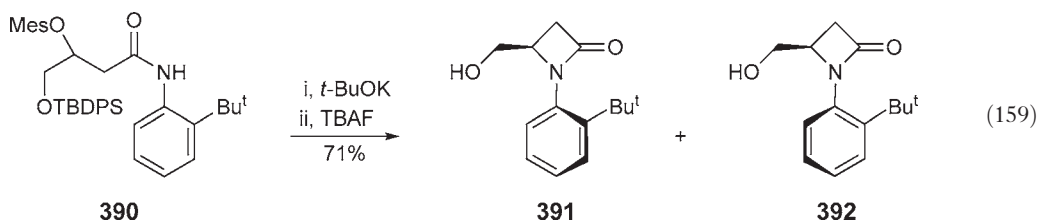
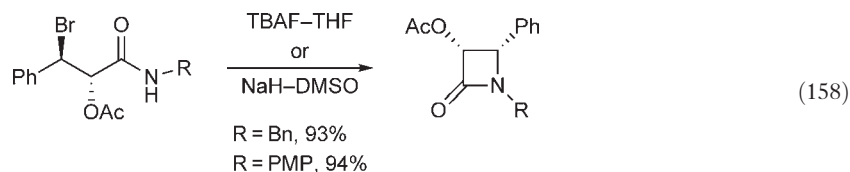
2.01.3.10.3 Cyclization of β -functionalized amides

Carboxylic amides or related substrates, substituted with leaving groups at the β -position, are suitable substrates for the synthesis of azetidin-2-ones. Relatively stable or labile, *in situ* generated, leaving groups can be applied. Selective activation of 3-hydroxy-2-hydroxymethyl-2-methylpropanamide **388** with P(NMe₂)₃-KPF₆ and subsequent

intramolecular cyclization with potassium carbonate yielded N-substituted 3-hydroxymethyl-3-methylazetidin-2-ones **389** (Scheme 59) <1995CC1279>. A cyclocondensation has also been performed using Mitsunobu reaction conditions <1996TL965, 2001TL1247>, β -chlorocarboxamides using sodium carbonate in dimethylformamide <1996JHC427>, β -bromocarboxamides using TBAF in tetrahydrofuran or sodium hydride in dimethylformamide (Equation 158) <1998TA983>, and β -hydroxy- or β -mesyloxycarboxamide using potassium *t*-butoxide in tetrahydrofuran <1997TA1847>. The activation of β -mesyloxycarboxamide **390** with potassium *t*-butoxide followed by treatment with TBAF yielded azetidin-2-ones **391** and **392** in a ratio of 1:50 (Equation 159) <2000TL8539>. The synthesis of enantiomerically enriched (80–85% ee) azetidin-2-ones is reported by the Pummerer-type cyclization of chiral, nonracemic β -amid sulfoxides **393** (Equation 160) <1995TL115>. Activation of the hydroxyl group of 3-hydroxy-3-arylpropanamides **394** by transformation to a phosphonate followed by cyclization yielded spiroazetidin-2-ones **395** (Equation 161) <1997JOC6412>.



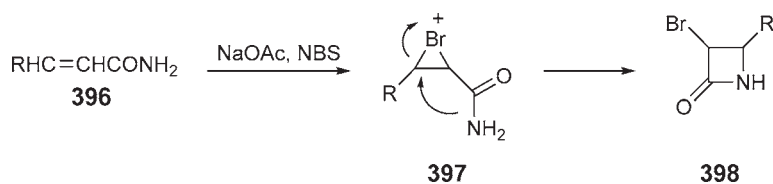
Scheme 59



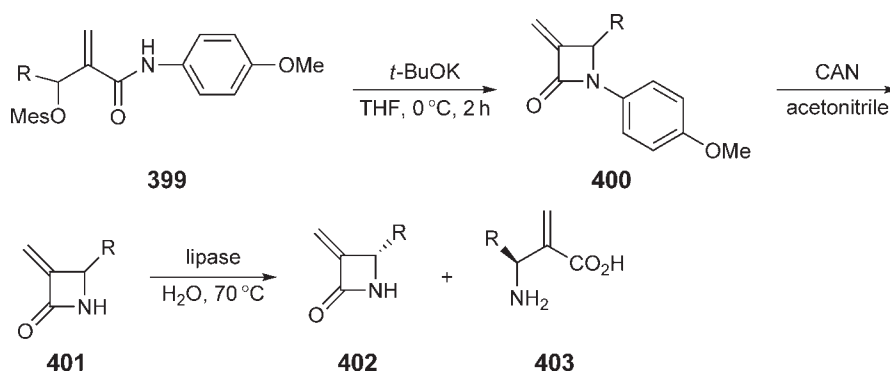
The amides derived from β -hydroxy- α -amino acids, obtained from the reaction of the latter with resin-bound hydroxylamine, have been cyclized under the Mitsunobu conditions to afford 3-aminoazetidin-2-ones. The free azetidin-2-ones were cleaved from the resin by reduction with samarium iodide <2001OL337>.

The α,β -unsaturated amides **396** (where R = aryl or heteroaryl) cyclized in the presence of sodium acetate and *N*-bromosuccinimide, presumably through the bromonium ion intermediate **397**, to furnish N-unsubstituted

4-aryl-3-bromoazetidin-2-ones **398** (Scheme 60) <1999J(P1)2435>. Cyclization of the β -mesyloxy amide **399** gave the racemic mixture of 1,4-disubstituted 3-methylideneazetidin-2-one **399** (Scheme 61). N-Deprotection of the latter compound to azetidin-2-one **401**, followed by resolution employing lipase, yielded the azetidin-2-one **402** and the amino acid **403** <1997TA833, 2000JOC4919>.



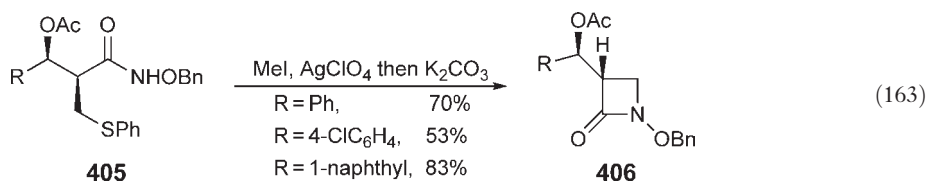
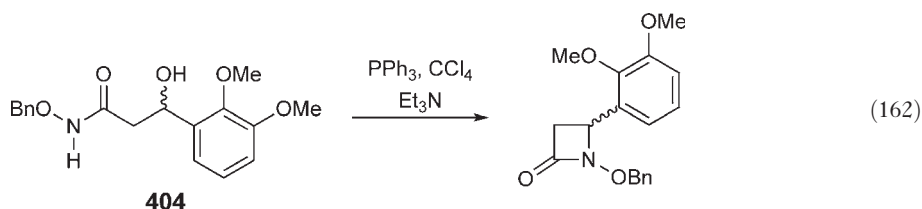
Scheme 60

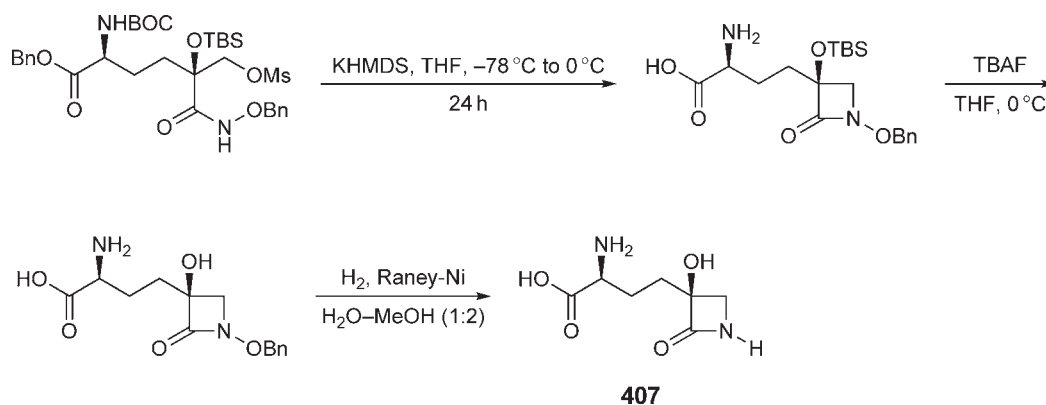


Scheme 61

2.01.3.10.4 Cyclization of hydroxamates

Hydroxamates **404** undergo intramolecular cyclization by the action of carbon tetrachloride–triphenylphosphine in the presence of a base (Equation 162) <1999JA5353, 2000T5719, 2003JOC27>. Treatment of the hydroxamates **405** with methyl iodide in the presence of AgClO_4 converted the phenylthio group into a sulfonium group, which was then removed by the amide nitrogen under basic conditions to give azetidin-2-ones **406** (Equation 163) <2003T9931, 1998J(P1)2167>. A concise and high-yielding synthesis of (–)-tabtoxinine- β -lactam **407**, the cause of tobacco wildfire disease, has been achieved by cyclization of the hydroxamate as the key step (Scheme 62) <2004TL8191>.

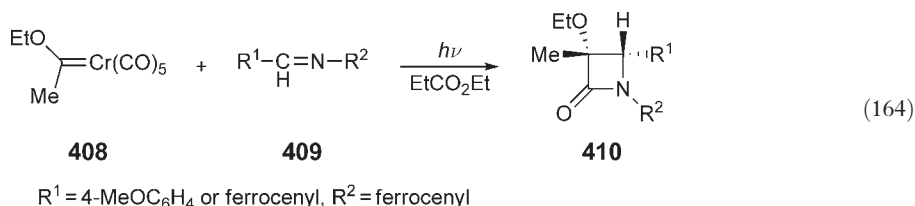




Scheme 62

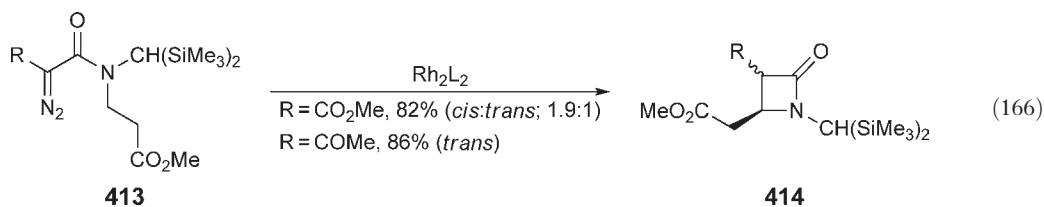
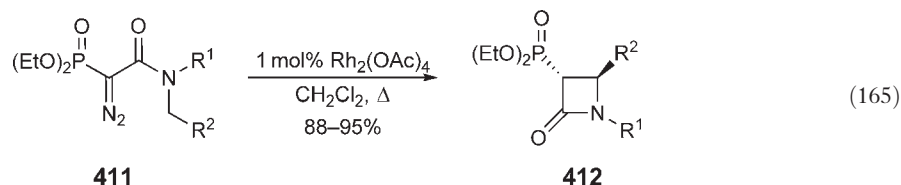
2.01.3.10.5 Cycloaddition of chromium–carbene complexes with imines

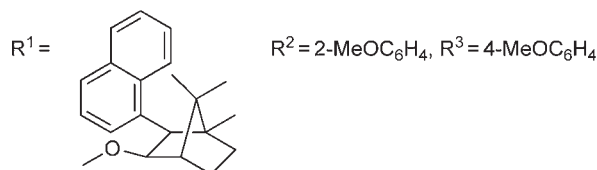
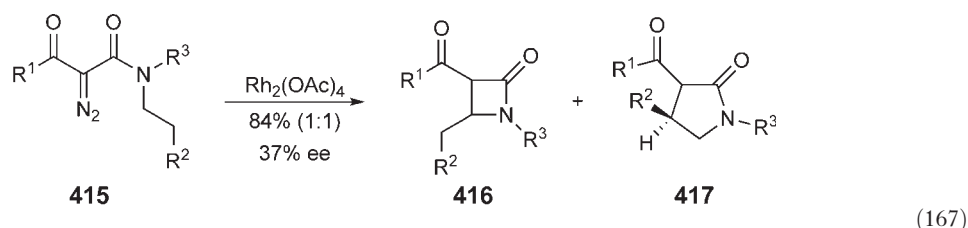
The photochemical reaction of chromium–carbene complexes **408** with ferrocene-containing imines **409** is reported to yield novel azetidin-2-ones containing one or two ferrocene moieties (Equation 164) <2001JOC8920>. The yield decreased when an aminoferrocene moiety was attached to the carbene carbon. The complex with ferrocene directly bonded to the carbene carbon was totally inert in this reaction.



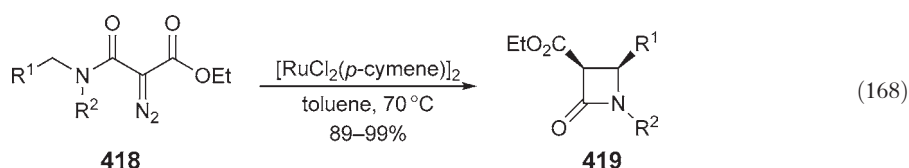
2.01.3.10.6 Intramolecular insertions of metal carbenoids from diazo compounds

The dirhodium tetraacetate-catalyzed intramolecular C–H insertion in α -diazo- α -(diethoxyphosphoryl)acetamides **411** led to the formation of *trans*-azetidin-2-ones **412** in excellent yields (Equation 165) <2003TL6571, 2003EJO3798>. The presence of a bulky *t*-butyl group at nitrogen led to predominant formation of the *cis*-isomer in this reaction, which epimerized to the *trans*-isomer during purification by flash chromatography. The Rh(II)-catalyzed reaction of *N*-[bis(trimethylsilyl)]methyl-*N*-methylpropanoate- α -diazoamides **413** yielded mainly *trans*-azetidin-2-ones **414** (Equation 166) <2002TL6173>. A mixture of a β -lactam and a γ -lactam was obtained in the reaction of α -diazoamide bearing a benzyl group as a protecting group <2003OL2259>. In the Rh(II)-catalyzed reaction of chiral α -diazocarbonyls, the formation of γ -lactams was preferred <1996TL145>. However, the amide **415** yielded a 1:1 mixture of β -lactam **416** and γ -lactam **417** in a total yield of 84% (Equation 167).



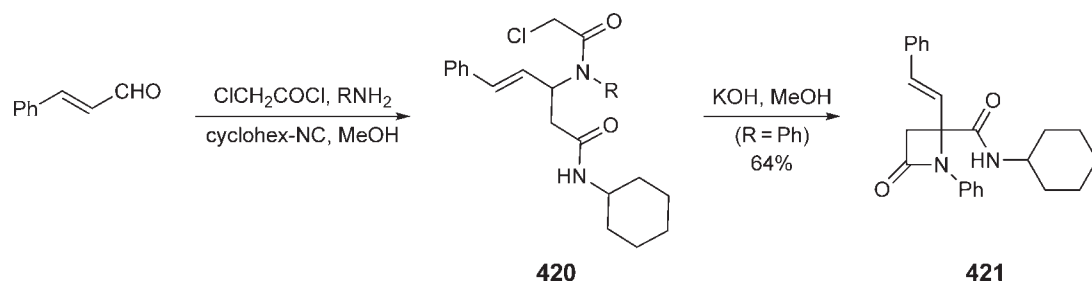


Ruthenium porphyrins are effective catalysts for the cyclization of *N*-tosylhydrazones via intramolecular carbenoid C–H insertion to afford azetidin-2-ones [<2003OL2535, 2003TL1445>](#). A non-porphyrin-based ruthenium catalyst, $[\text{RuCl}_2(p\text{-cymene})]_2$, has been developed recently for catalytic carbenoid transformation [<2005OL1081>](#). A $[\text{RuCl}_2(p\text{-cymene})]_2$ -catalyzed stereoselective cyclization of α -diazoacetamides **418** by intramolecular C–H insertion produced azetidin-2-ones **419** in excellent yields and excellent (>99%) *cis*-stereoselectivity (Equation 168).

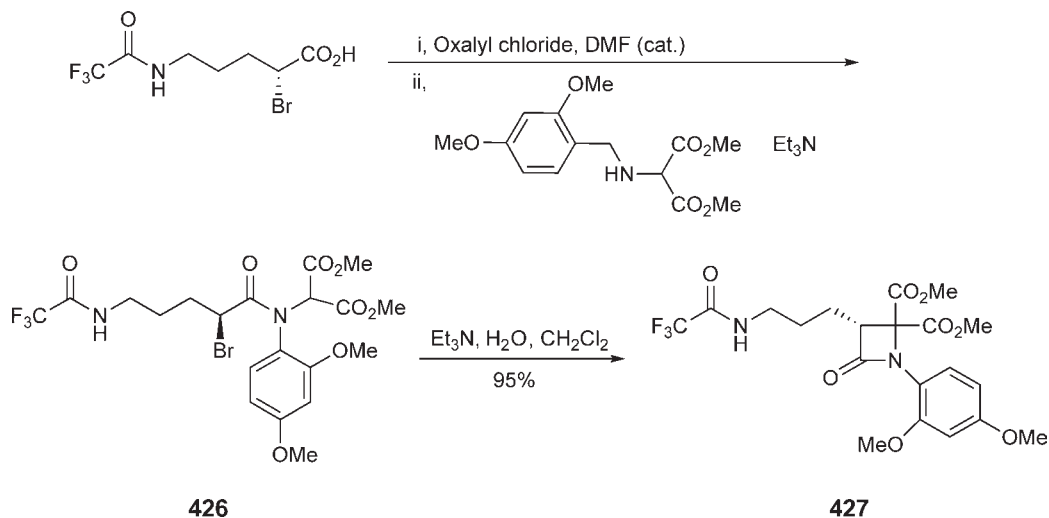
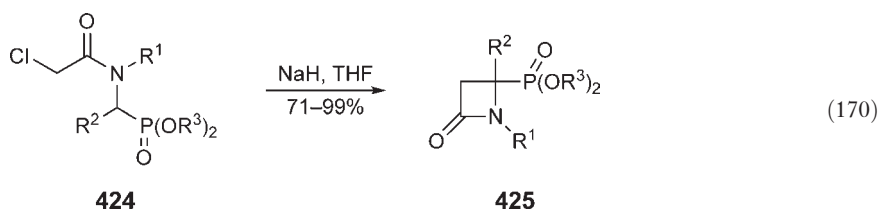
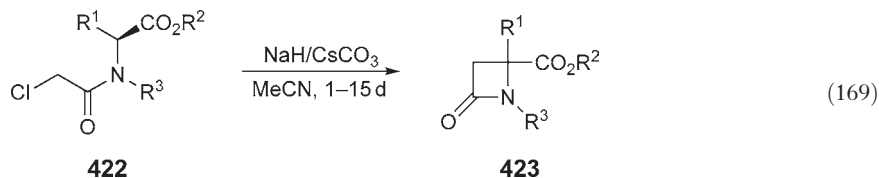


2.01.3.10.7 Formation of the C(3)–C(4) bond of azetidin-2-ones

The three-component Passerini-type reaction has been applied to the synthesis of azetidin-2-ones [<1997TL2519>](#). Treatment of (*E*)-cinnamaldehyde with chloroacetic acid, cyclohexyl isocyanide, and an amine furnished α -chloroacetamides **420**, which cyclized in the presence of a base to afford the azetidin-2-ones **421** (Scheme 63). Formation of the C(3)–C(4) bond of the azetidin-2-ones from threonine derivatives is based on the acidity of the methine group [<2001TA89>](#). Similarly, *N,N*-disubstituted 2-chloroacetamides **422**, containing an active methine group, are also cyclized by either sodium hydride or cesium carbonate to give 3-unsubstituted 4-alkyl-4-carboxyazetidin-2-ones **423** (Equation 169) [<2001JOC3538, 2000SL1249>](#). The asymmetric induction observed during cyclization of the *N,N*-disubstituted 2-chloroacetamides, ascribed to ‘chirality memory’, is dependent on the substrate [<2003TA2161>](#), and can be controlled by the appropriate choice of the solvent and base [<2003SL1007>](#). The asymmetric synthesis of 4-alkyl-4-carboxyazetidin-2-ones (yields 55–77%, ee up to 82%) has also been achieved through base (Cs_2CO_3) mediated cyclization of *N*- α -chloroacyl derivatives bearing (+)- or (–)-10-(*N,N*-dicyclohexylsulfamoyl)isborneol as a chiral auxiliary [<2002JOC3953>](#). The ring closure of α -chloroamidophosphonates **424** with sodium hydride yielded 1-substituted 4-aryl-4-oxoazetidin-2-ylphosphonates **425** (Equation 170) [<2003TL1619, 2005S3603>](#). When treated with a base, *N*-chloroacetyl-1-aminoalkenyl phosphonates derived from cinnamaldehyde exclusively lead to phosphono- β -lactams without any trace of the corresponding six-membered lactam. These findings were rationalized on the basis of some high-level *ab initio* calculations (GAUSSIAN 03) [<2006JA8468>](#). The cyclization of α -bromo amide **426**, obtained from the reaction of α -bromo acid chloride with protected malonate, in the presence of triethylamine occurred with inversion of configuration to give azetidin-2-one **427** (Scheme 64), which is a precursor of the tryptase inhibitor BMS-262084 [<2002JOC3595>](#).

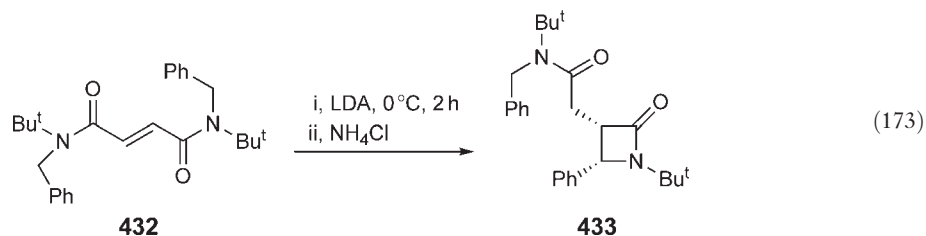
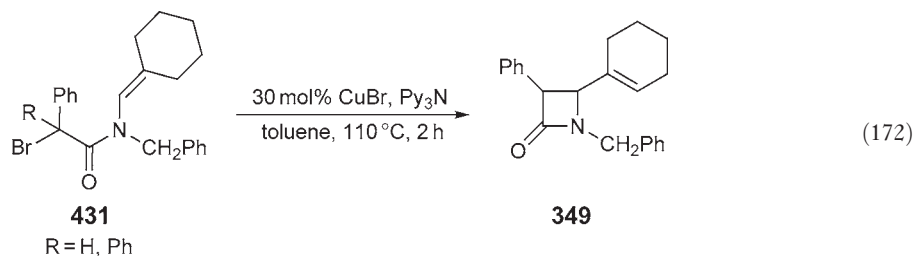
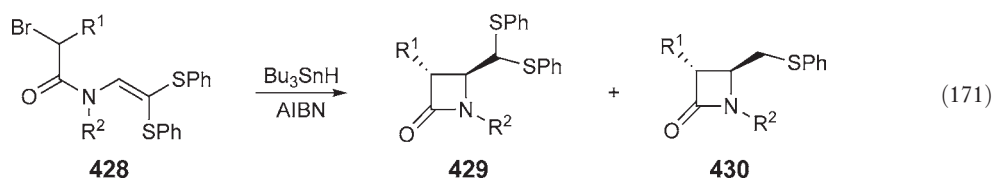


Scheme 63

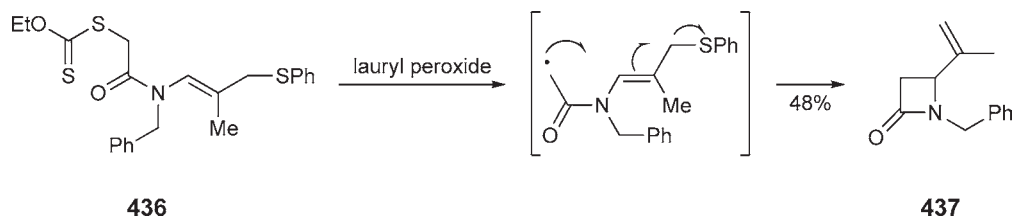
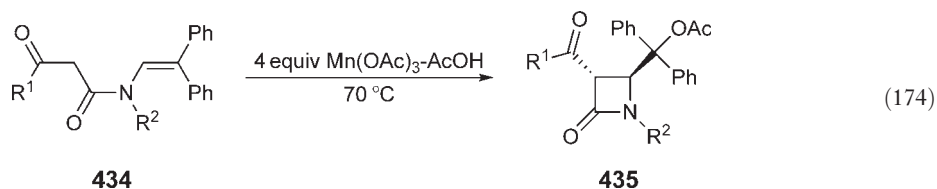


Scheme 64

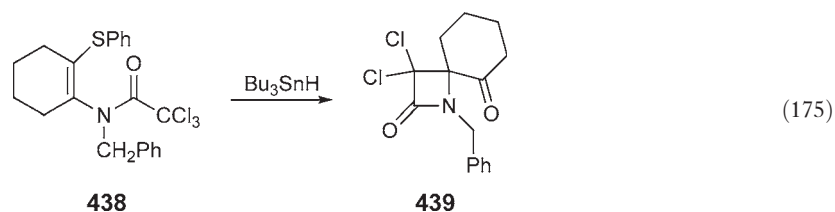
The intramolecular radical cyclizations of *N*-vinylacetamides [$R^1CH_2CON(R^2)CH=CHR^3$] to *trans*-3,4-disubstituted azetidin-2-ones have drawn increasing attention [<1995SL912, 1996TL1397>](#). *N*-Ethenyl- α -bromoamides **428** undergo sulfur-directed radical cyclization on treatment with tributyltin hydride, forming azetidin-2-ones **429** and **430** (Equation 171) [<1995JOC1276>](#). The debrominated amide was isolated as a side product (7–14%) in this reaction. A C(3)–C(4) bond-forming copper-mediated atom transfer radical cyclization of *N,N*-disubstituted bromodiphenylacetamide or *N,N*-disubstituted α -bromophenylacetamide **431** furnished azetidin-2-one **349** (Equation 172) [<2001TL4409, 2001TL2901>](#). The acrylamide **432** bearing a β -electron-withdrawing group underwent a 4-*exo-trig* cyclization to form azetidin-2-one **433** after lithiation at the benzylic position by LDA (Equation 173) [<2003CC2582>](#).



There are many studies on manganese(III)-promoted radical cyclizations [<1995TL9039, 1998T12029>](#). The influence of chiral auxiliaries on the stereocontrol of radical cyclizations has been investigated [<1995SL915, 1996T489>](#). Treatment of 2-acyl-*N*-(2,2-diphenyl-1-ethenyl)-*N*-alkylacetamides **434** with manganese(III) acetate yielded the *trans*-azetidin-2-ones **435** (Equation 174) [<2000TL3261>](#). Similar *trans*-3,4-disubstituted azetidin-2-ones were obtained from the radical cyclization of *N*-vinyl-2-bromobutanamide derivatives [<1996T13867, 1997T9611>](#), and *N*-vinyl-2-(methoxycarbonyl)ethanamide promoted by manganese(III) acetate [<1997T13129>](#) or cerium ammonium nitrate [<1997TL1829>](#). Xanthate derivatives of *N*-ethenylacetamides **436** undergo radical cyclization in the presence of lauryl peroxide to yield azetidin-2-one **437** (Scheme 65) [<1998T2087>](#). *N,N*-Disubstituted trichloroacetamide **438** cyclized under certain conditions upon treatment with tributyltin hydride to yield an azetidin-2-one **439** (Equation 175) [<1998TL75>](#).



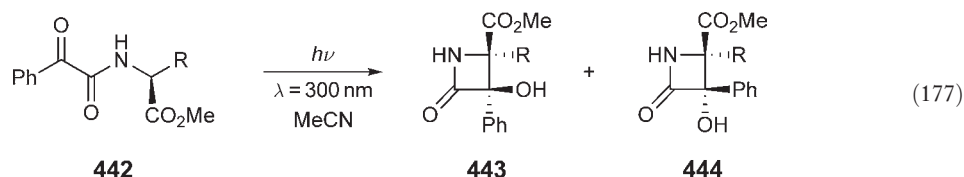
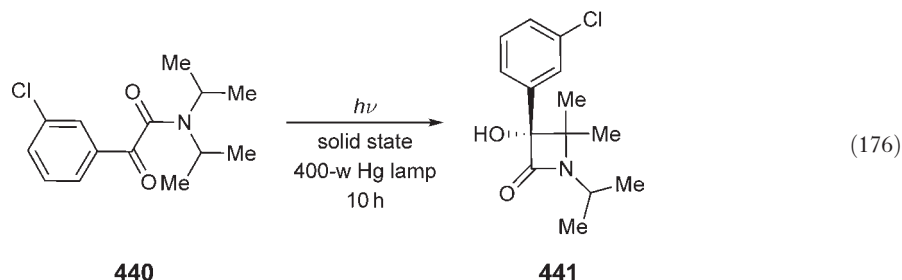
Scheme 65



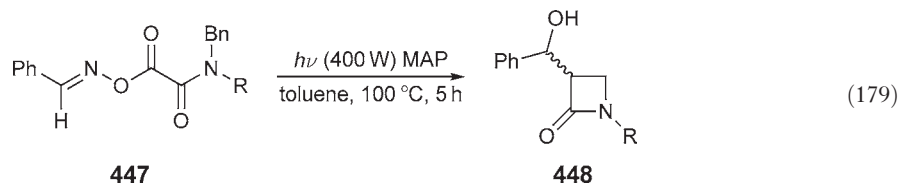
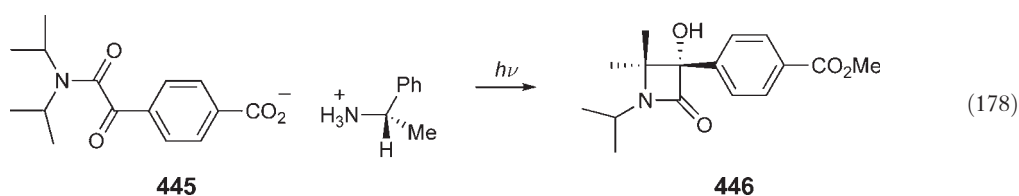
2.01.3.10.8 Photochemical synthesis of azetidin-2-ones

The photochemical generation of metal-bound ketenes from carbene–chromium complexes and the subsequent coupling with imines to give azetidin-2-ones is treated separately (Section 2.01.3.10.5).

An asymmetric photocyclization of α -oxoamide **440** in solid state afforded azetidine-2-one **441** (Equation 176) <1996J(P2)61>. The substrate with a chloro group on either *ortho*- or *para*-position of the phenyl ring, however, afforded a racemate. Photocyclization of the phenylglyoxamides **442** of enantiomerically pure α -amino acid methyl esters produced azetidin-2-ones **443** and **444** in moderate to high diastereoselectivity, with the *cis*-isomer as the major component (Equation 177) <2002SL131>.



A solid-state photochemical reaction of *N,N*-dialkylaryl glyoxamide carrying an ionic chiral auxiliary yielded 1-isopropyl-3-hydroxyazetidin-2-one with high enantioselectivity <2001S1253>. Irradiation of inclusion crystals of 2-(*N*-acyl-*N*-alkylamino)cyclohex-2-enones with a chiral host molecule derived from tartaric acid resulted into enantioselective photocyclization forming spirofused azetidin-2-ones <2000JOC2728>. Novel photochemical routes to 3-hydroxyazetidin-2-ones **446** <2002OL1443> (Equation 178) and 3-(hydroxyl(phenyl)methyl)azetidin-2-ones **448** (Equation 179) <2002CC2086, 2004OBC716> are described from α -oxoamide **445** and *N*-alkyl-2-enyloxime oxalate amides **447**, respectively. The preparation of azetidin-2-ones has been accomplished by photocyclization of the *N*-carbamoyl radicals generated from *N*-substituted *N*-benzyl-(1-methyl)cyclohexa-2,5-diene-1-carboxamide <2000CC2327, 2004OBC421>.

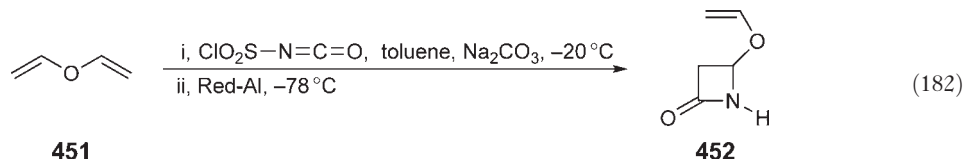
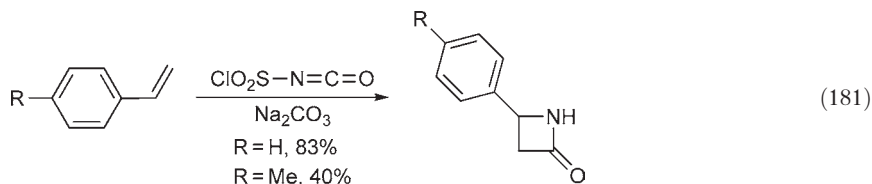
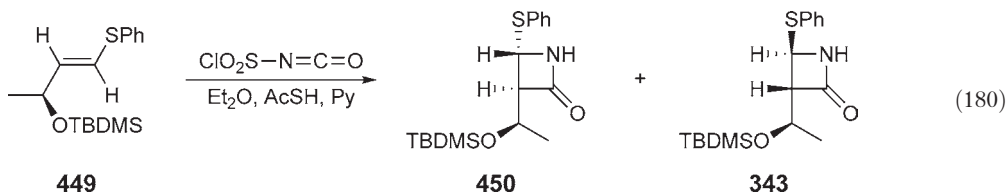


The photoreactions of *N*-(trimethylsilyl)methyl- or *N*-(tributylstannyl)methyl-substituted α -ketoamides resulted into the formation of complex mixtures including azetidin-2-ones and oxazolidinones with or without the trimethylsilyl or tributylstannyl moiety <2004JOC1215>. It was observed that the reaction of *N*-(trimethylsilyl)methyl-substituted α -ketoamides proceeded by competitive hydrogen abstraction and sequential single electron transfer (SET)-desilylation pathways, whereas the reaction of *N*-(tributylstannyl)methyl-substituted α -ketoamides preferred the sequential SET-destannylation pathway.

2.01.3.10.9 Cycloaddition of isocyanates with alkenes

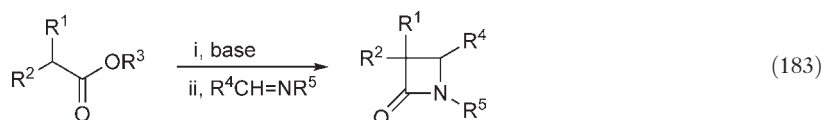
The reaction of isocyanates with alkenes toward azetidin-2-ones requires activation of the former by electro-withdrawing groups or activation of the alkenes by electron-donating groups <2004COR463>.

The classical reaction with chlorosulfonyl isocyanate has been extended to *E*-vinyl sulfide **449** to give a 2.5:1 diastereomeric mixture of 4-(phenylthio)azetidin-2-ones **343** and **450** (Equation 180) <2000MI935>. The facial selectivity in the cycloaddition has been explained by the conformational preference of the allylic groups in the transition structure. A similar reaction with styrene resulted into synthesis of the racemic 4-aryl-azetidin-2-one (Equation 181) <2000TA2351>. The divinyl ether **451** reacted with acid-free chlorosulfonylisocyanate to form 4-vinyloxyazetidin-2-one **452** (Equation 182) <1996SL895, 1997TA2553, 1998TL8349>. Most of the results in the reactions of isocyanate with vinyl ethers could be rationalized by a *s-trans*-conformational preference of the ether in the transition state <1997JOC3135, 1999J(P2)217>. The [2+2] cycloaddition reaction of chlorosulfonylisocyanate with sugar alkoxyallene showed that *gem*-terminal dimethylallenes reacted more readily than their methyl-free congeners. In contrast to the reactions of the corresponding vinyl ethers, the allene cycloadditions proceeded with lower asymmetric induction <2000TA3131>. The highest stereoselectivity was 39% and the main diastereomer had the (*R*)-configuration at C-4.

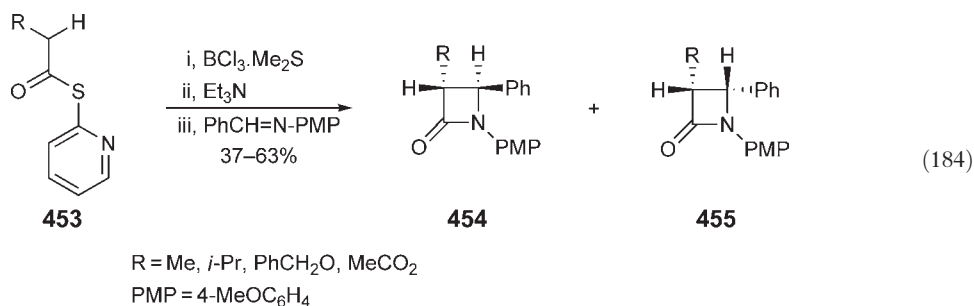


2.01.3.10.10 Ester-enolate-imine condensation

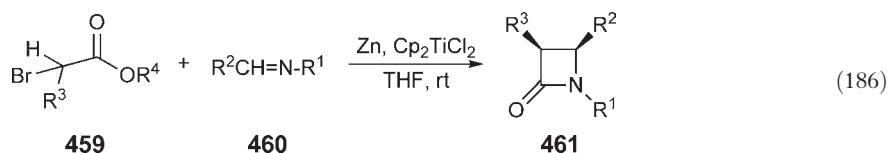
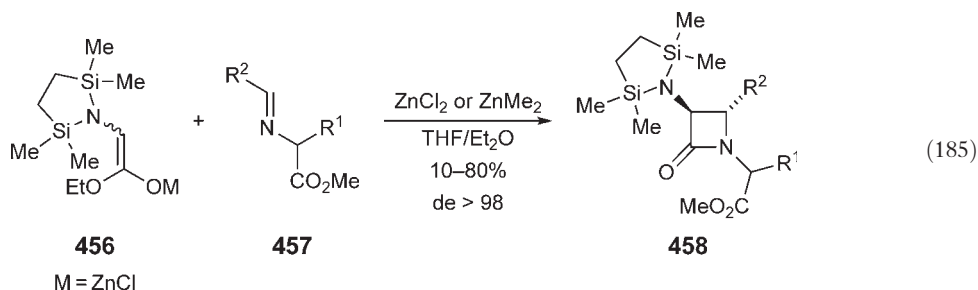
The one-pot condensation of an ester enolate with an imine is a very powerful synthetic procedure toward azetidin-2-ones (Equation 183). Various types of esters and imines can be utilized. Although in the vast majority the reactions have been mediated by lithium, various other metals mediate the reaction as well. Some examples include zinc, aluminium, tin, boron, indium, and titanium <1996MI119>. Theoretical studies on these reactions have been reviewed <1998JCC1826>.



Different metal enolates of chiral esters possessing amino alcohols derived from (+)-camphor as an auxiliary condensed with an imine to afford 4-(*R*)- or 4-(*S*)-azetidin-2-ones <1995TL729>. Enolates, derived from 2-pyridylthioesters **453** by treatment with a BCl₃-Me₂S complex, reacted with *N*-benzylidene-4-methoxyaniline to give a diastereomeric mixture of azetidin-2-ones **454** and **455** containing the *trans*-isomer **454** as the major product (Equation 184) <1995T8941>. The amino alcohols can be applied both as a metal ligand and as a base to generate the enolate. A chair conformation involving (*E*)-configured imines was proposed for the transition state to explain the stereoselection of the boron trichloride-promoted reaction.

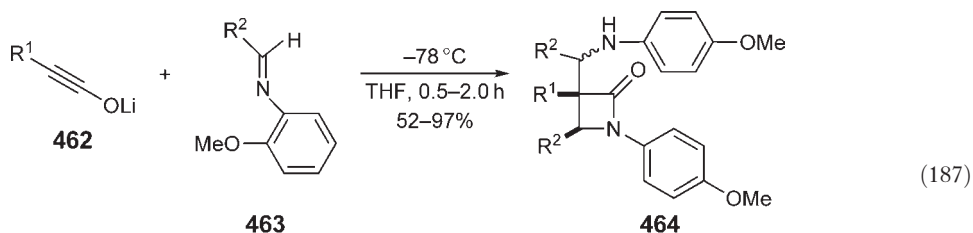


The Reformatsky reaction of an imine, an α -bromoester, zinc dust, and a catalytic amount of iodine in dioxane under high-intensity ultrasound irradiation has been evaluated for the synthesis of azetidin-2-ones [<2004T2035>](#). Zinc-mediated condensation of the ester enolate [456](#) with imino esters [457](#) derived from α -amino acids led to an asymmetric synthesis of azetidin-2-ones [458](#) [<1995JOC4331>](#) (Equation 185). The configuration of the stereogenic center of the chiral auxiliary controls the absolute stereochemistry of the two newly formed stereogenic centers. α -Bromoalkanoates [459](#) reacted with imines [460](#) in the presence of $\text{Zn}/\text{Cp}_2\text{TiCl}_2$ to form *cis*-azetidin-2-ones [461](#) (Equation 186) [<2003TL2611>](#). The cycloaddition of the zinc enolate derived from ethyl bromodifluoroacetate onto *N,N',N''*-trisubstituted hexahydro-1,3,5-triazines (Schiff base trimer) afforded 3,3-difluoroazetidin-2-ones [<2003S2483>](#). However, this method is inferior to the one which used cyclization of β -amino esters for the preparation of such compounds [<2003S2483>](#), because in most of the cases the azetidin-2-one was a minor product besides three other compounds.

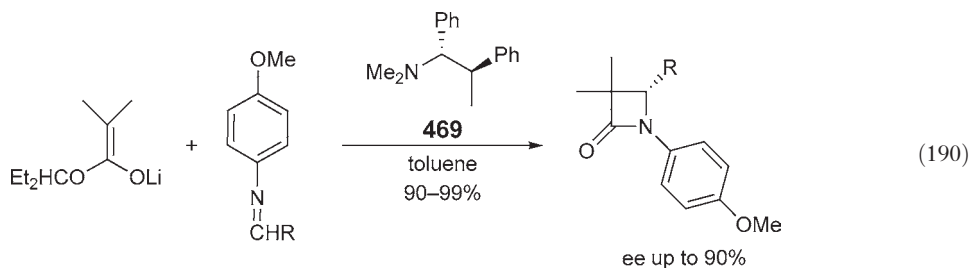
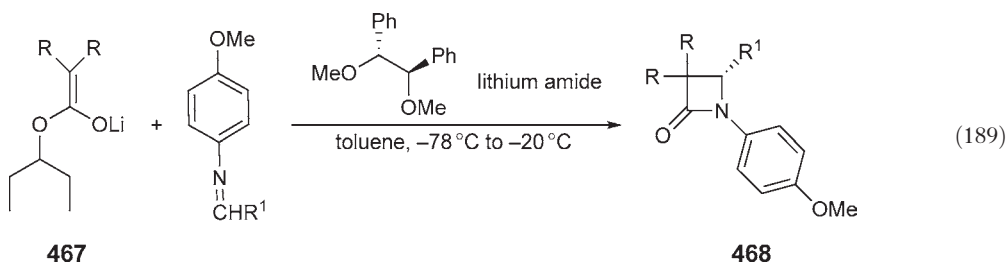
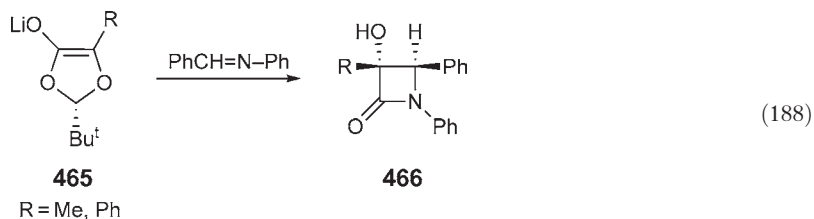


Lithium ynoates [462](#) add onto *N*-sulfonylimines [<1998H\(49\)113>](#) and *N*-2-methoxyphenylimines [463](#), activated by the presence of an *o*-methoxy group on the *N*-phenyl ring, to yield the azetidin-2-ones [464](#) as a single isomer in a 2:1 molar reaction of the imines with ynoates (Equation 187) [<2000TL5943>](#). The coordination of the methoxy group with lithium activates the imine [<2000OL1891>](#). Lithium ester enolate addition across imines has been used for the construction of optically active azetidin-2-ones [<2000H\(52\)1001>](#). Cycloaddition of lithium enolates of 5-substituted (2*S*,5*S*)-2-(*t*-butyl)-1,3-dioxolan-4-ones [465](#) with *N*-benzylideneaniline toward (3*R*)-3-hydroxyazetidin-2-ones [466](#) is a rather direct approach to chiral β -lactams with complete control of stereochemistry at C-3 (Equation 188) [<1997TA2527>](#). The Seebach synthetic principle of self-regeneration of stereocenters was used in the synthesis of 3-alkyl-3-hydroxyazetidin-2-ones from imines and (2*S*)-chiral enolates of 1,3-dioxolan-4-ones [<1999JOC4643>](#). Cycloaddition of aldimines having a *N*-(*t*-butyldimethylsilyl) substituent with an ester enolate gives *trans*-3,4-disubstituted azetidin-2-ones, which is complementary to the *cis*-compound obtained when the *N*-substituent is trimethylsilyl [<1997S886>](#). A ternary complex composed of an aldimine, a chiral ether ligand, and an achiral lithium amide gives high stereoselectivity at C-4 of azetidin-2-ones [468](#) (Equation 189) formed on reaction with an ester enolate [<1997JA2060>](#). Tridentate chiral amines (Equation 190) [<1999CC715, 1999T11219>](#), a chiral aminoether [<2000CPB1577, 2000MI125>](#), and chiral bisoxazolines [<1999CPB1>](#) have been used to increase the enantioselectivity of lithium ester enolate–imine cycloaddition reactions. The reactions of menthyl isobutyrate with imines were influenced by a catalytic amount of a chiral tridentate aminodiether ligand to give the corresponding

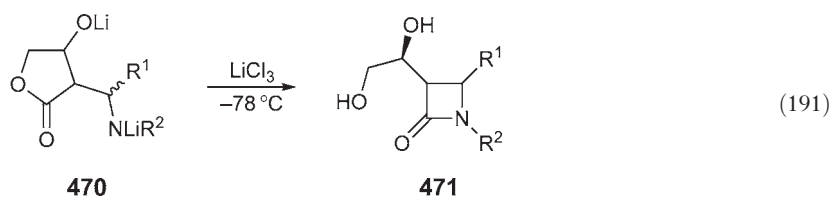
azetidin-2-ones with high enantioselectivity <2004SI1471>. Lithium enolates have been found to be superior to other metal derivatives for both yields and diastereoselectivity in some cases <2000H(53)1479>. Immobilized lithium ester enolates have also been utilized recently <2000OL907>. A silylimine–lithium enolate addition protocol has been used in the synthesis of 3,3-diethoxyazetidin-2-ones <1999TL1827>. Fluorine-containing azetidin-2-ones have been synthesized using ester–enolate imine cycloaddition <1996T209, 1996T255>. The lithium enolate from 4-hydroxy- γ -lactone reacted with imines to form amine **470**, which cyclized in the presence of lithium chloride at low temperature to form azetidin-2-ones **471** (Equation 191) with a cholesterol absorption inhibition property <1998BMC1429, 1999JOC3714>.



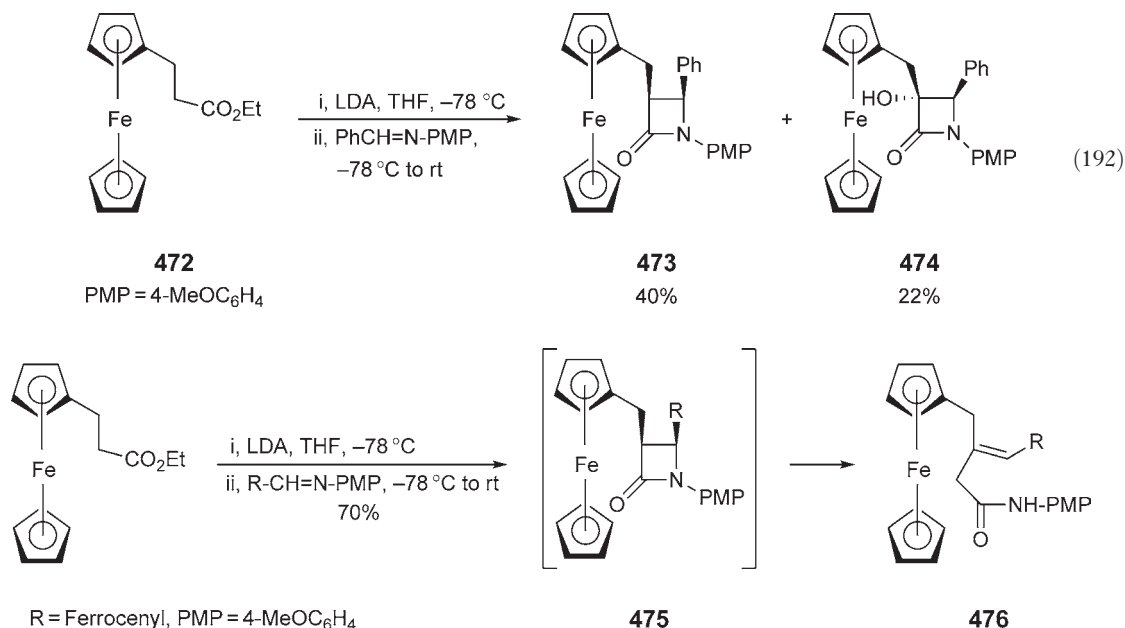
a: $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Ph}$; **b:** $\text{R}^1 = \text{Me}$, $\text{R}^2 = 1\text{-naphthyl}$; **c:** $\text{R}^1 = \text{Me}$, $\text{R}^2 = 2\text{-naphthyl}$
d: $\text{R}^1 = \text{Me}$, $\text{R}^2 = 4(\text{MeO}_2\text{C})\text{Ph}$; **e:** $\text{R}^1 = \text{Bu}$, $\text{R}^2 = \text{Ph}$; **f:** $\text{R}^1 = \text{Bu}$, $\text{R}^2 = 1\text{-naphthyl}$
g: $\text{R}^1 = \text{Bu}$, $\text{R}^2 = 2\text{-naphthyl}$



R = Ph, 4-MeOPh, 1- and 2-naphthyl, $\text{CH}_2\text{CH}_2\text{Ph}$, MeC=CHPh



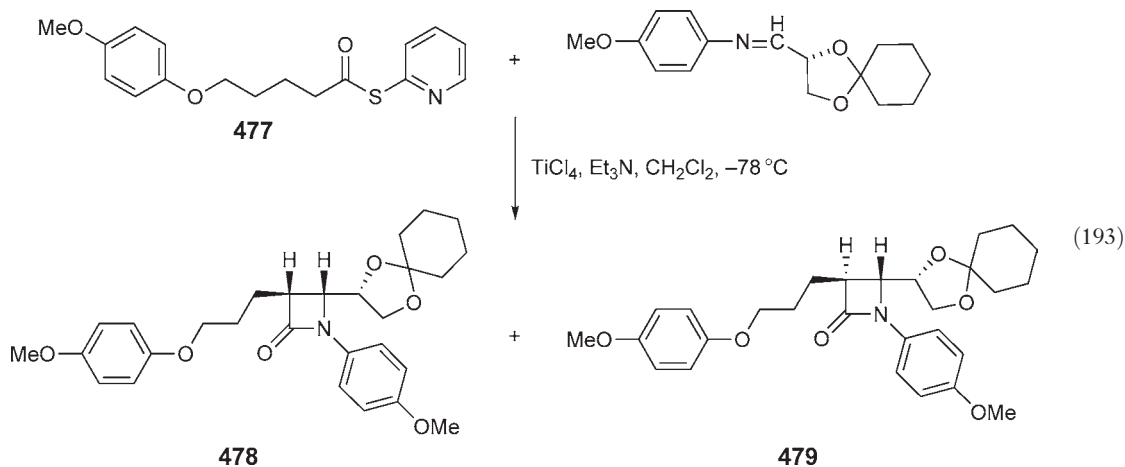
The reaction of *N*-benzylidene-4-methoxyaniline with the lithium enolate derived from ethyl 3-ferrocenylpropanoate **472** provided an easy access to azetidin-2-ones **473** and **474** with ferrocene tethered to the C-3 position through a methylene group (Equation 192) <2001JOC8920>. However, the azetidin-2-one **475**, formed in the reaction of an enolate with the imine of ferrocene carbaldehyde, furnished an amide **476** by N(1)–C(4) cleavage (Scheme 66).

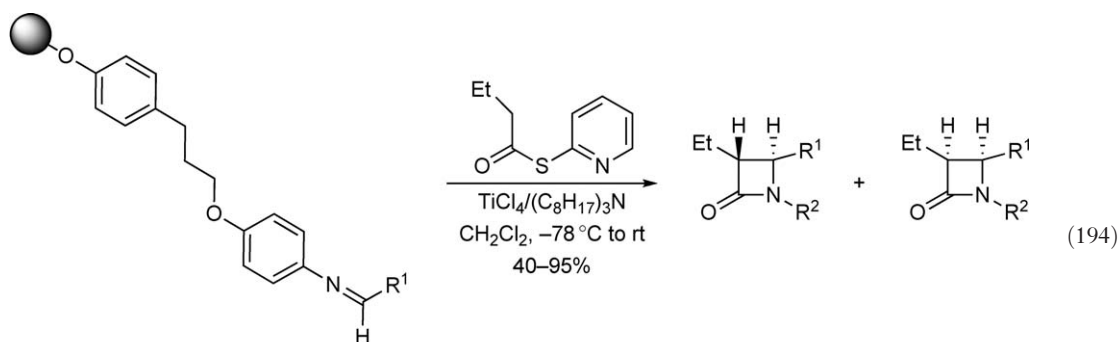


Scheme 66

The titanium enolate of (*S*)-2-pyridylthio-5-(4-methoxyphenyl)pentanoate **477** reacted with imines to give *cis*- and *trans*-azetidin-2-ones **478** and **479** (Equation 193), which were separated by flash-chromatography after deprotection with aqueous trifluoroacetic acid <2003JOC2952>. The titanium enolate of (*S*)-2-pyridylthiobutanoate has been condensed with imines over a soluble polymer support, monomethylether poly(ethylene)glycol (MeOPEG) with an average molecular weight of 5000 affording the diastereomeric mixture of azetidin-2-ones in fair to high yields (Equation 194) <2000CEJ133>. A 4-(3-propyl)phenyl residue was used as the spacer and a 4-oxophenylamino group as the moiety bearing the reactive functionality. The cholesterol absorption inhibitors azetidin-2-ones **480** have been synthesized using a titanium enolate and imines (Scheme 67) <1996JOC8341, 1999TA4841>.

The reaction of imines with 2-pyridyl thioesters in the presence of aluminium tribromide or ethylaluminium dichloride afforded *trans*-3,4-disubstituted azetidin-2-ones <1996T2583>. Similar stereoselective addition of silylketene thioacetals to imines is known in the presence of Lewis acids <1996T2573>. An indium-mediated reaction of ethyl bromoacetate with imines yielded 3-unsubstituted azetidin-2-ones in reasonable yields (Equation 195) <2000J(P1)2179>.

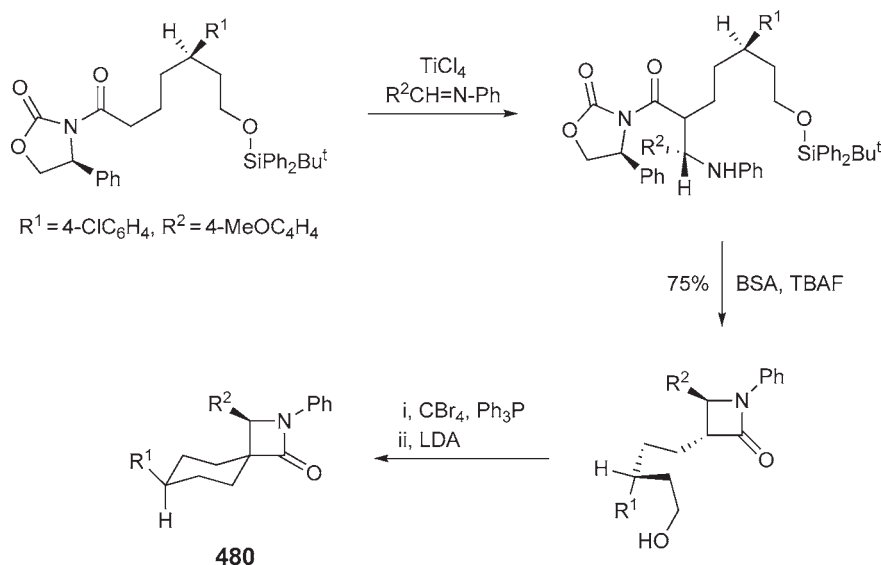




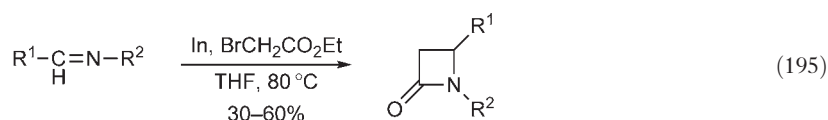
● = MeO-(CH₂CH₂O)_n-CH₂CH₂- average M_w 5000 daltons

R¹ = Ph, 2-thienyl, (E)-PhCH=CH, Et, Ph, CO₂Et

R² = C₆H₄O(CH₂)₃C₆H₄O



Scheme 67

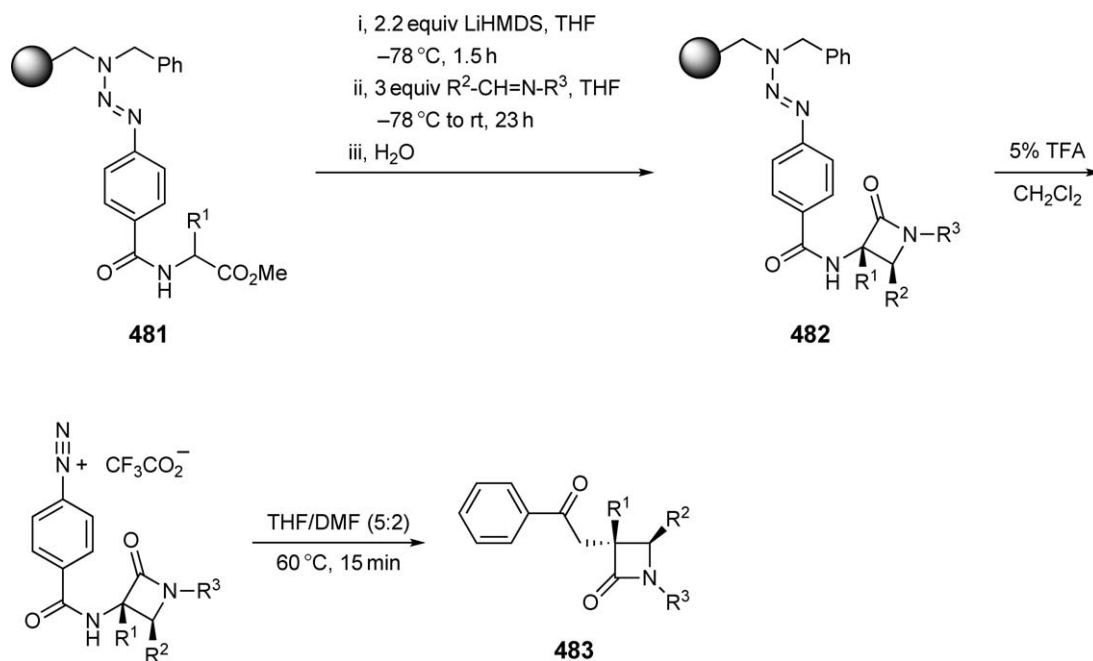


Various imines and imine precursors reacted with immobilized ester-enolate-derived triazene esters **481** to give polymer-bound azetidin-2-ones **482** (Scheme 68). The esters were bound to a benzylamine resin by a triazene linker employing diazonium salts. Traceless cleavage from the triazene linker yielded the desired azetidin-2-ones **483** <2002JOC8034>.

Very recently, the reaction of the dianion-enolate of a Cbz-protected α -amino ester with a cyanomethylamine as an imine precursor toward several β -lactam derivatives has been described <2007BML358>.

2.01.3.10.11 Cyclocondensation of ketenes and imines

One of the most common methods for the synthesis of azetidin-2-ones is the reaction of imines with ketenes, which is known as the Staudinger ketene–imine cycloaddition. Although commonly described as a [2+2] cycloaddition, it is generally accepted that reaction is in fact stepwise <1999EJO3223>. The first step of the reaction involves a nucleophilic attack of an imino nitrogen on the sp-hybridized carbon of a ketene to form a ‘zwitter-ionic’ intermediate, which cyclizes to form the azetidin-2-one ring. The ketene is mostly generated either from acid chlorides and related derivatives in the presence of tertiary amines thermally, or from 2-diazoketones either thermally or photochemically <2005CSY377>. Searching for greener technologies, the use of microwave technology to generate ketenes has been reported <1995TL213,

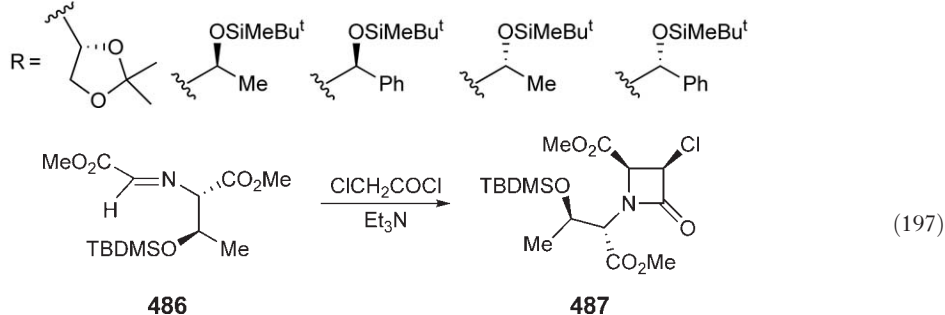
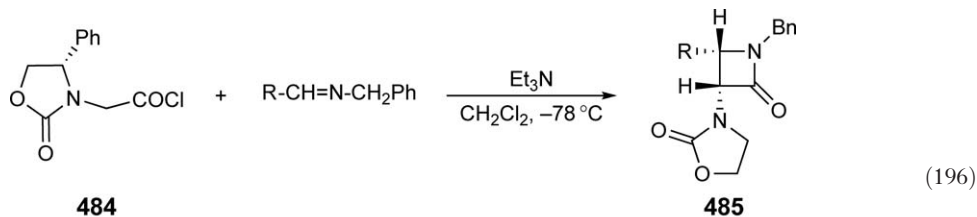


Scheme 68

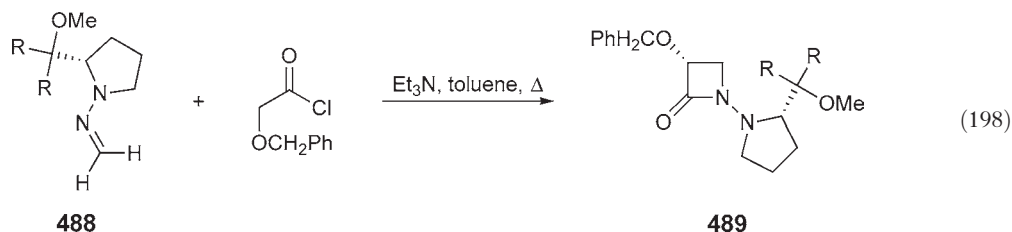
[1996TL6989](#)>, as well as polymer-supported synthesis [<2006RMC109>](#). The stereochemistry of the azetidin-2-one can be *cis*, *trans*, or a mixture of both isomers depending on the substrates and the reaction conditions. Recently, the relative stereoselectivity of β -lactam formation in the Staudinger reaction has been reviewed [<2006JA6060, 2006JOC6983>](#). Calculations using density functional theory indicate that when the ketene is available prior to the cyclization stage the preferred product is exclusively or very largely the *cis*-stereoisomer. However, if the imine reacts directly with the acyl chloride, exclusive or preferential formation of the *trans*-isomer takes place [<1998JOC5869, 1998PCB7877>](#).

Cycloaddition of diverse types of ketenes and imines leading to the formation of azetidin-2-ones is reported. A major thrust in the area is to evolve diastereoselective and enantioselective reactions. The reactions of chiral ketenes with achiral imines, chiral imines with achiral ketenes, chiral imines with chiral ketenes, and catalytic asymmetrical Staudinger reactions have been investigated. In general, a higher level of asymmetric induction is achieved by using either chiral ketenes or chiral imines derived from chiral aldehydes in comparison to the use of a chiral imine derived from an achiral aldehyde with an achiral ketene. Both carboxylic acid chlorides and carboxylic acids themselves have been used as ketene precursors. Some phosphonium salts have also been used as precursors of ketenes [<1999IJB1121>](#). Triphosgene [<2002T2215, 2003TA453>](#), PhOP(O)Cl_2 [<1996T5585>](#), benzenesulfonyl chloride [<2001JCM321>](#), 2,2'-dibenzothiazolyl disulfide [<2004SL2824>](#), 2-chloro-1-methylpyridinium iodide [<1998S1161>](#), trichloroacetonitrile-triphenylphosphine [<2000SC4177>](#), $(\text{COCl})_2$ [<2000T5735>](#), and *N,N'*-carbonyldiimidazole [<2006JOC5804>](#) have been used in the reactions using carboxylic acid as a ketene precursor. Nonactivated alkyl acid chlorides reacted with imines in the presence of tributylamine in toluene to form 3-alkylazetidin-2-ones [<1995TL2555>](#). Chiral imines derived from (1*S*)-(+)-camphor 10-sulfonic acid ([1996TA2733](#)), (+)-(1*S*,2*S*)-2-amino-1-phenylpropan-1,3-diol ([1996T8989](#)), L-malic acid [<1995SL1067>](#), phenylethylamines ([1995TL8821](#)), and bicyclic terpenes [<1996T3741>](#) have been exploited as a chiral auxiliary, as have chiral oxazolidinoneacetyl chlorides ([1996AGE1239](#)), and Oppolzer sultam-substituted acetyl chlorides [<1996T5579, 1997CC233>](#). The Evans-Sjögren ketene, generated from (*S*)-2-(2-oxo-4-phenyloxazolidine-3-yl)acetyl chloride **484**, reacts with chiral imines [<1996JOC9186>](#) to form *cis*-azetidin-2-ones **485** (Equation 196). The stereochemistry of the reaction is controlled by the ketene, independently of the stereochemistry of the imines. A monoterpene-based chiral acid has been reacted with achiral imines in the presence of PhOP(O)Cl_2 to afford *cis*-3-hydroxyazetidin-2-ones [<1996T5585>](#). However, the chiral auxiliary is lost in this method due to its oxidative removal. The use of a 2-bromoacyl chloride instead of the acid afforded both enantiomers of the azetidin-2-one in pure form [<2000TA1477>](#). The chiral auxiliary is successfully removed using zinc in acetic acid. Triphosgene has been used efficiently as an activator of the acid in the Staudinger reaction using acids as precursors of ketenes [<2002T2215>](#). In the reaction of a (–)-ephedrin-based acid with imines using triphosgene as an activator to afford azetidin-2-ones, the chiral auxiliary was removed by refluxing the compounds

with aqueous tetrahydrofuran in the presence of PTSA <2003TA453>. An asymmetric synthesis of azetidin-2-ones using D-(+)-glucose derived imines is reported <2003T2309>. Threonine-derived imines **486** reacted with chloroacetyl chloride in the presence of triethylamine to give *cis*-azetidin-2-ones **487** (Equation 197). The diastereoselectivity of the reaction increased as the size of the protecting group on the hydroxyl group increased <2000SC3685>.



The reactions of *N,N*-dialkylhydrazones with benzoyloxyketene <2002AGE831> and aminoketene <2004OL2749> precursors appear to be a new general approach to the enantioselective synthesis of 4-substituted 3-alkoxyazetidin-2-ones and 3-aminoazetidin-2-ones. Such hydrazones **488**, derived from formaldehyde, afforded 4-unsubstituted azetidin-2-ones **489** (Equation 198) in 80–96% yields and dr's up to 99:1 <2004CEJ6111>.



The role of some chiral bifunctional amines and optically active cinchona alkaloid derivatives (Figure 3) as catalysts has been explored in catalytic asymmetric Staudinger reactions. Bicarbonate salts have been used as viable alternatives to

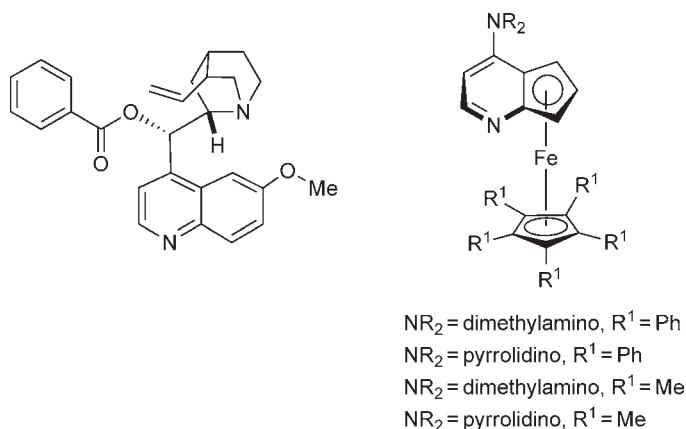
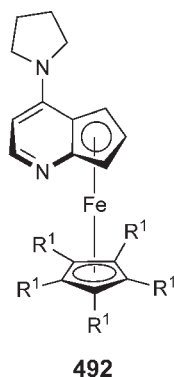
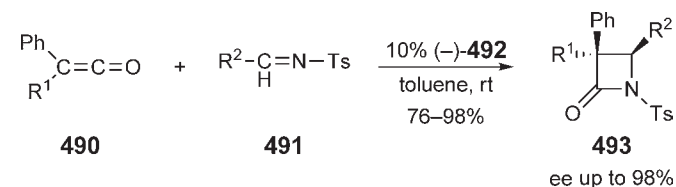
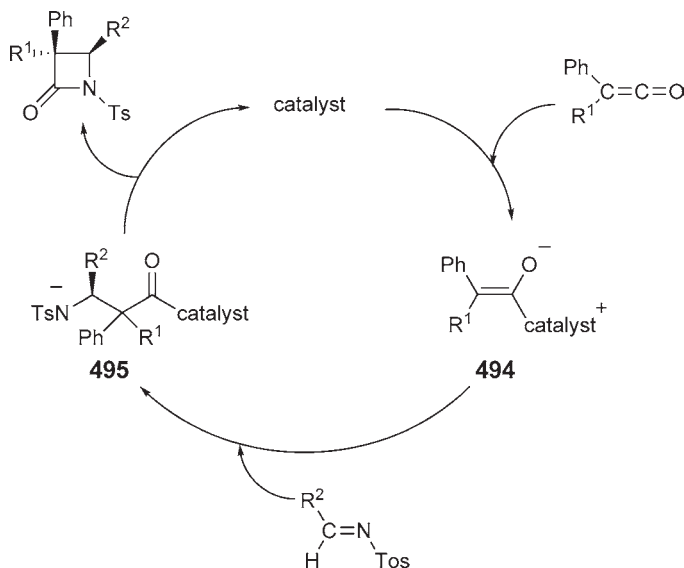


Figure 3

more expansive bases used for the *in situ* generation of ketenes and their synthetic equivalents in the catalytic asymmetric synthesis of azetidin-2-ones <2003SL1937>. The presence of a bifunctional catalytic system consisting of a chiral base benzoylquinine and an achiral Lewis acid in the Staudinger reaction medium gave *cis*-1,3,4-trisubstituted azetidin-2-ones in good yields and ee's up to 99% <2000JA7831, 2002OL1603, 2002JA6626>. The reactions of many symmetrical and unsymmetrical ketenes **490** with *N*-tosylimines **491** of aromatic, aliphatic, and α,β -unsaturated aldehydes in the presence of a planar-chiral azaferrocene derivative **492** as a catalyst are known to form azetidin-2-ones **493** in excellent yields and enantiomeric excess (Equation 199) <2002JA1578>. The mechanism involved addition of the catalyst across ketenes to form a zwitter-ionic intermediate **494**, which reacted with imines to form another zwitter-ionic intermediate **495**. The latter intermediate cyclized with regeneration of the catalyst to form azetidin-2-ones (Scheme 69).



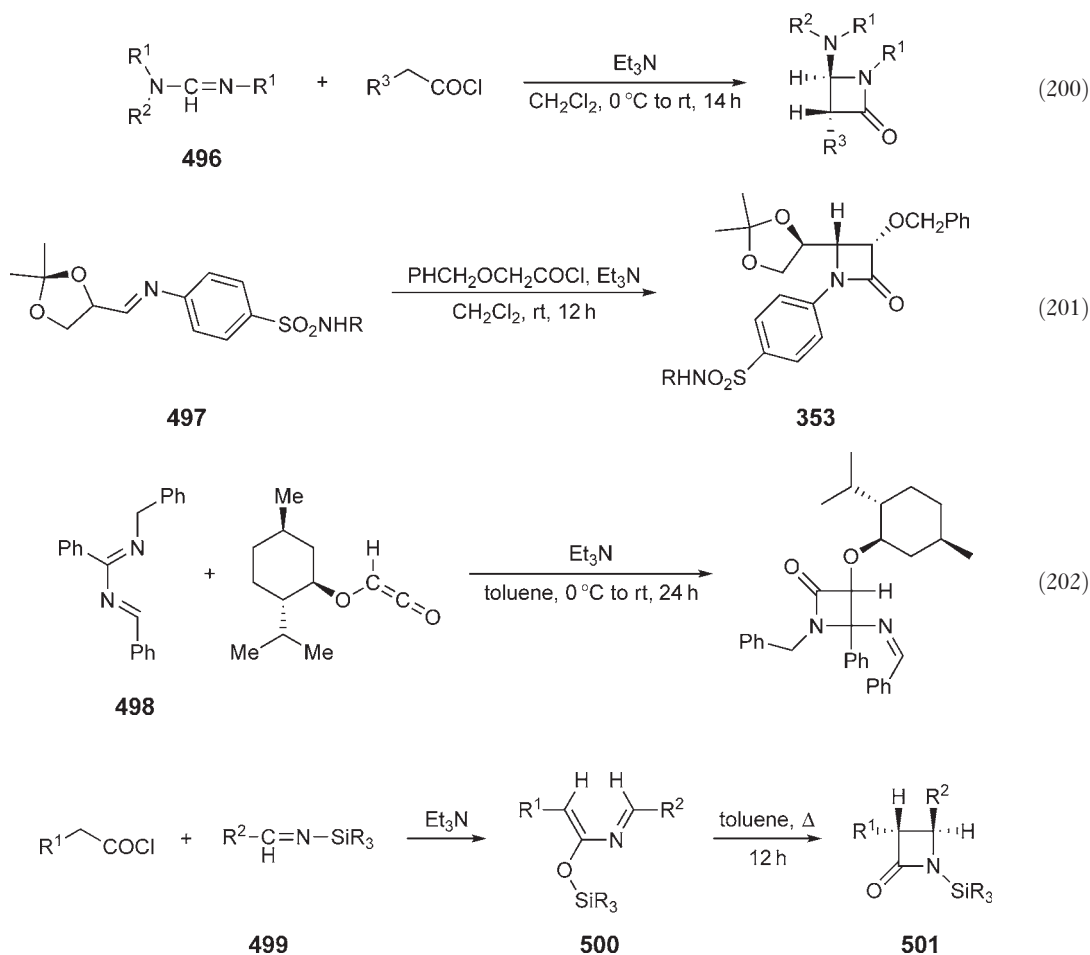
(199)



Scheme 69

Imines with bulky groups at nitrogen give rise to the formation of *trans*-azetidin-2-ones <2000TL6551>. Stereocontrolled syntheses have been carried out using chloral imines <2004TL6563>, tricarbonyl(η^6 arene)chromium(0)complexed imines

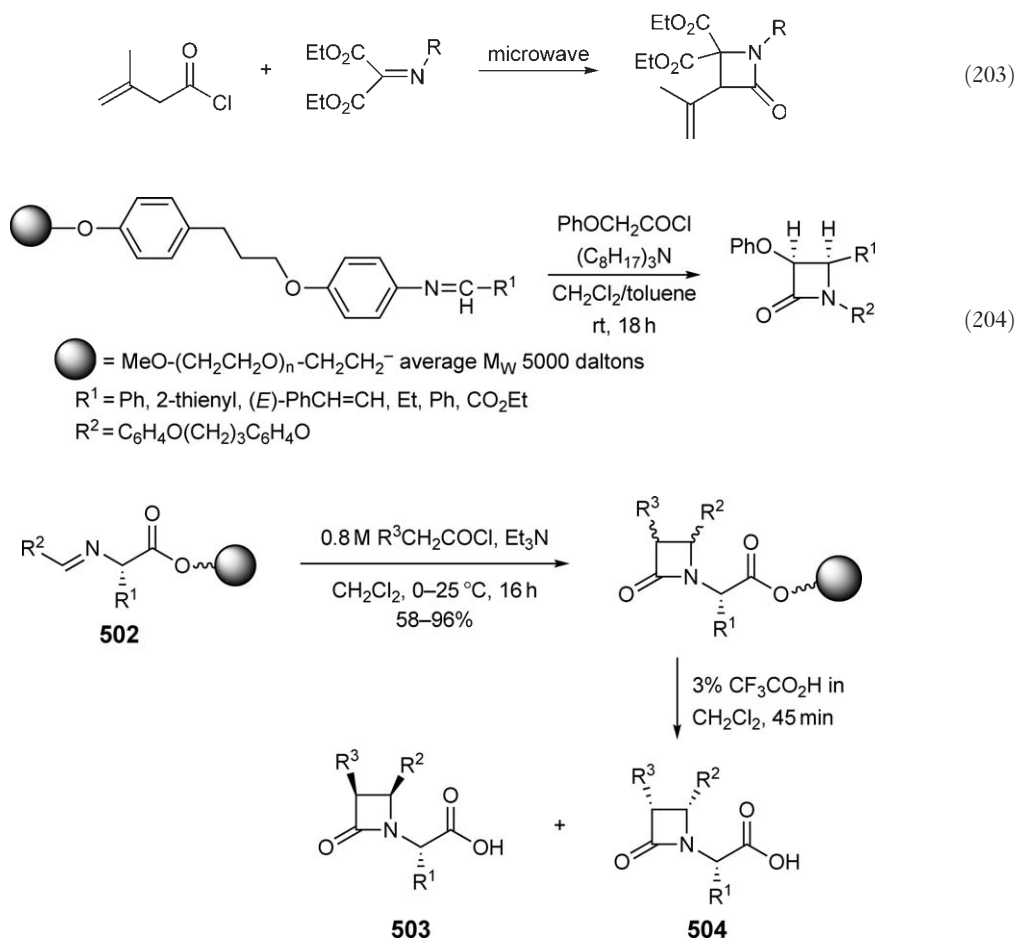
<2003TA3949>, *N*-silylimines <1999TL8495>, amidines **496** (Equation 200) <2000T7811>, α -oxohydrazones <2003T10195>, chiral imines of (*R*)-glyceraldehyde acetonide having a *N*-sulfonamide side chain **497** (Equation 201) <2000SC246>, 1,3-diazabuta-1,3-diene **498** and chiral ketenes (Equation 202) <2001T7205>, and chiral imines of (*S*)-glyceraldehyde acetonide <2001ACT279>. The reaction of *N*-silylimines **499** with ketenes, now referred as a two-step Staudinger reaction, is a real proof for the stepwise nature of this reaction. 3-Aza-1,3-diene intermediates **500** have been isolated in this case, and afforded *N*-trialkylsilyl-substituted azetidin-2-ones **501** on refluxing in toluene (Scheme 70) <1996TL4409, 1996SL1017, 1999TL8495, 2000OL1077, 2003T9577>. The enol ether group is crucial for the stabilization of the dienes and also plays an important role in promoting the conrotatory ring-closure process <2000EJO2379>. Computational methods showed that the energy of activation of isomerization of the *N*-silylimines was lower than that of formation of the C–N bond, which was responsible for the observed stereochemistry <2000JOC8458>. Density functional theory calculations for the reactions of *N*-rhenamine, [Re(N=CH₂)(CO)₃(N₂C₂H₄)], with ketenes also rendered energy profiles which supported a two-step mechanism <2003JA3706>. The reaction of different 1,3-azadienes with ketenes afforded either azetidin-2-ones or [4+2] cycloaddition products, pyrimidinones <2002ARK106, 2000OL2725>. These results could be explained by conformational studies on 1,3-azadienes. *Ab initio* and density functional calculations on the conformational preferences of 1,3-azadienes revealed that the *s-cisoid* was the preferred conformation on the PE surface of the (*E*)-isomer, which led to the formation of pyrimidinones. However, the preference for (*E*)-*cisoid* geometry diminished under solvent conditions due to relatively less pronounced electron delocalization in the presence of a solvent. The formation of azetidin-2-one thus occurred through the 1(*Z*)-*s-trans* conformation of the 1,3-azadienes.



Scheme 70

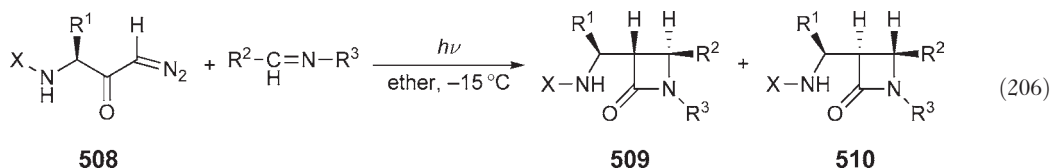
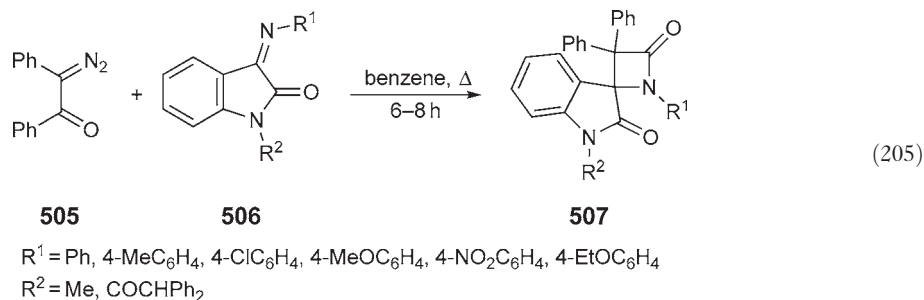
The past decade has witnessed considerable interest in solvent-free ketene–imine cycloaddition reactions employing microwave irradiation (Equation 203) <1995TL213, 1996TL6989, 1997H(44)405, 2005JOC334, 2005IJB2093>.

and also soluble polymer support has been used <1998TL1257, 2000CEJ133, 2005S530>. The monomethylether of polyethyleneglycol (MeOPEG) has been used as a solid support for the Staudinger reaction of phenoxyketene with imines (Equation 204) <2000CEJ133>. [2+2] Cycloaddition of tentagel resin-bound imines **502**, derived from amino acids, with ketenes forms a diastereomeric mixture of azetidin-2-ones (Scheme 71) <1996JA253>. A solid-phase synthesis of *trans*-3-alkyl-4-arylazetidin-2-ones **503** and **504** from nonactivated acid chloride has been accomplished <2004TL4085>. The resin-bound aldimines and a solution-generated ketene has been used to afford *cis*-azetidin-2-ones <2004JOC5439>. A new polymer-supported reagent has been used for the synthesis of azetidin-2-ones under sonification <2004JOC9316>. An efficient asymmetric synthesis of azetidin-2-ones was accomplished using chiral acid chlorides or chiral aldehydes in the polymer-supported Staudinger reaction <2002TA905>. The solid-phase synthesis of azetidin-2-ones by the Staudinger reaction has been monitored by ^{19}F NMR spectroscopy <2003T3719>. A new solid-support strategy ('sequential column asymmetric catalysis') has been developed for the synthesis of enantiopure azetidin-2-ones <2002CEJ4115>. In this strategy, reagents and catalyst are attached to a solid-phase support and loaded onto sequentially linked columns. The substrates are present in the liquid phase that flows through the column. As a substrate encounters each successive column, it grows in complexity.

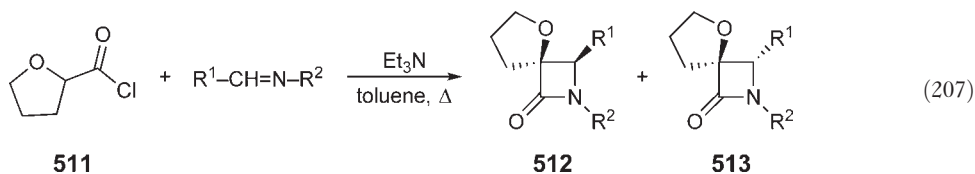


Scheme 71

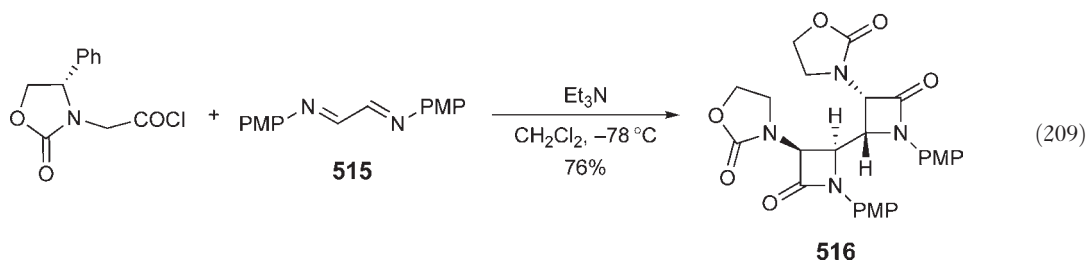
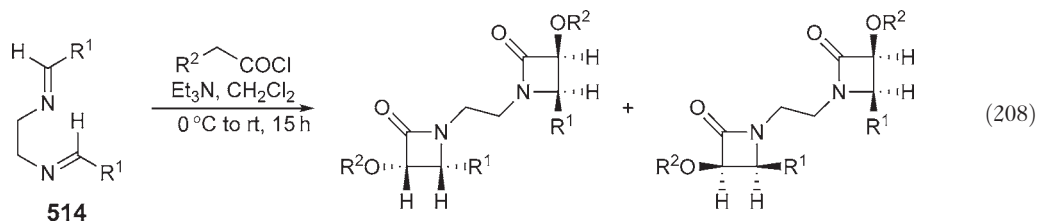
α -Diazoketones rearrange after extrusion of nitrogen to generate ketenes. Thermal decomposition of the 2-diazo-1,2-diphenylethanone **505** in the presence of indolinone imines **506** afforded the spiroazetidin-2-ones **507** (Equation 205) <1997IJB951, 2006JHC1665>. The photochemical reactions of 2-diazoketones **508**, obtained from protected amino acids, with imines afforded mainly *trans*-azetidin-2-ones **509** and **510** (Equation 206) <1997JOC5873, 1999S650, 2001J(P1)2566>.



Spiroazetidin-2-one frameworks have been prepared by the Staudinger reaction employing either cyclic ketenes or cyclic imines. The reaction of cyclic ketenes derived from *N*-acyl-thiazolidine-2-carboxylic acids <2004T93, 2005HCA1580>, tetrahydrofuran-2-carbonyl chloride **511** (Equation 207), and tetrahydrofuran-3-carbonyl chloride <2002J(P1)571> with a range of imines including *N*-phenylsulfonyl imines furnished spiroazetidin-2-ones **512** and **513**. The reaction of acyclic ketenes with cyclic imines derived from 7-oxanorbornene <2002TL6405> and from indolinone imines <2000IJB304, 2004CL440, 2004SL2025> gave spiroazetidin-2-ones.

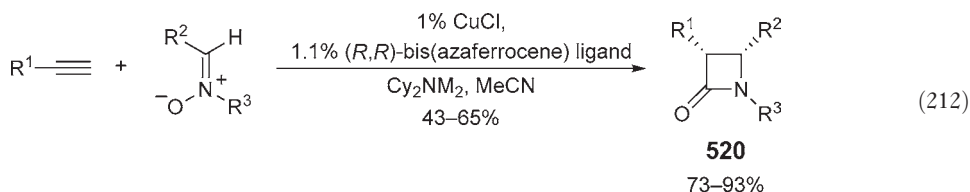
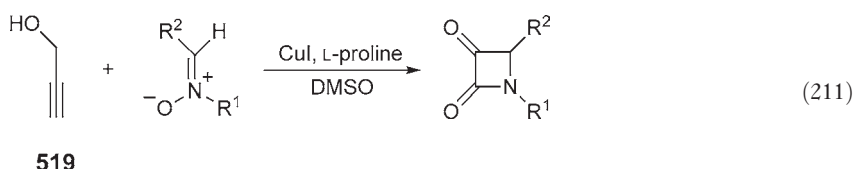
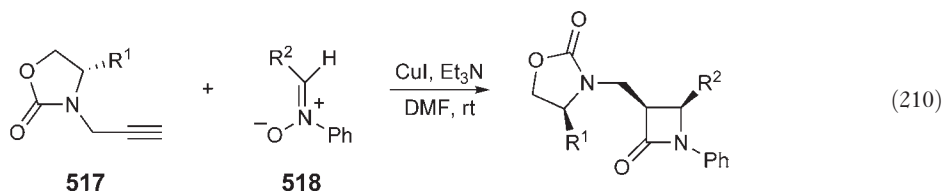


The application of ethylenediamine-derived bis-imines **514** (Equation 208) <2000T8555>, diaminoarylmethanes <2001BKC493>, *trans*-1,2-diaminocyclohexane, and 2,3-diaminobutane <2005T2441>, in the Staudinger reaction afforded *cis*-bis-azetidin-2-ones. The reaction of an Evans–Sjögren ketene with *p*-anisylidimines **515** <1996JOC9156> gives a single enantiomer of the *cis,cis*-C4,C4'-bis-azetidin-2-ones **516** (Equation 209).

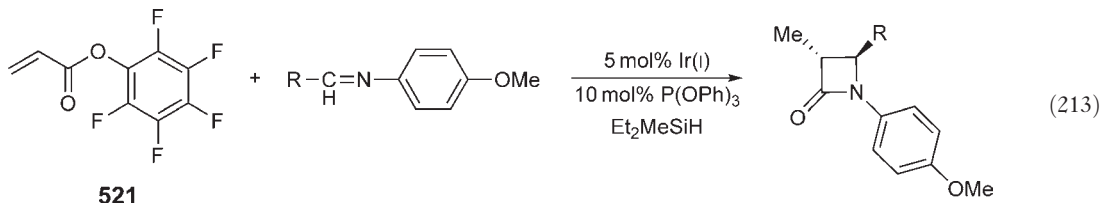


2.01.3.10.12 Cyclocondensation of alkynes and nitrones

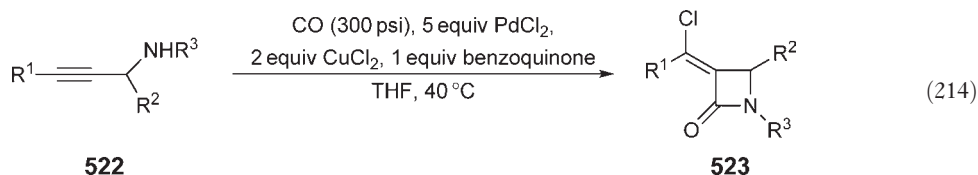
The cycloaddition of terminal alkynes with nitron, known as the Kinugasa reaction, has been used for an asymmetric synthesis of *cis*-azetidin-2-ones with reasonable enantioselectivity using chiral oxazolidinyl propynes **517** and nitrones **518**, in the presence of copper(I) (Equation 210) <2002TL5499> and copper(II) <2003CC2554> salts. A similar cycloaddition of propargyl alcohol **519** is mediated by Cu(I) in the presence of L-proline (Equation 211) <2004SL1637>. A 1,3-cycloaddition of methylenecyclopropane with acyclic nitrones followed by acidic thermal rearrangement of the resulting spiro[cyclopropane-1,5'-isooxazolidines] provided azetidin-2-ones <2004EJO2205>. A C_2 -symmetrical planar chiral bis(azaferrocene)ligand was used to achieve a catalytic enantioselective Kinugasa reaction to yield azetidin-2-ones **520** with good enantiomeric excess and *cis*-diastereoselectivity (Equation 212) <2002JA4572>. The use of a sterically demanding trialkyl amine was necessary in this reaction to obtain good *cis*-diastereoselectivity.

2.01.3.10.13 Miscellaneous β -lactam syntheses

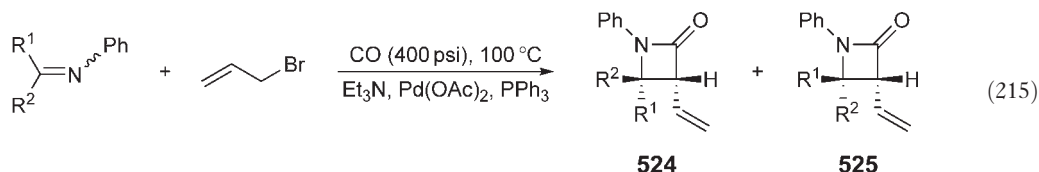
Reductive coupling of acrylates **521** and imines in the presence of iridium provides azetidin-2-ones bearing aromatic, alkenyl, and alkynyl side chains, with high diastereoselection (Equation 213) <2002OL2537>. The reaction has been proposed to occur through a reductive Mannich addition–cyclization mechanism.



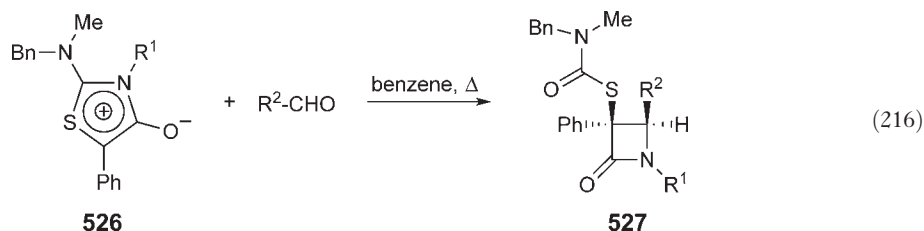
The palladium chloride-catalyzed cyclocarbonylation reaction of propargylic amines **522** afforded (*E*)- α -chloroalkylideneazetidin-2-ones **523** in moderate to good yields (Equation 214) <2005JOC2588>. The reaction of the optically active propargylic amines yielded the corresponding (*E*)- α -chloroalkylideneazetidin-2-ones with ee's ranging from 93% to 98%. The reaction required the presence of copper(II) chloride and benzoquinone in order to obtain high yields. Copper(II) chloride may serve as an oxidant and as a chloride source, whereas the benzoquinone plays a key role in reductive elimination besides oxidation.



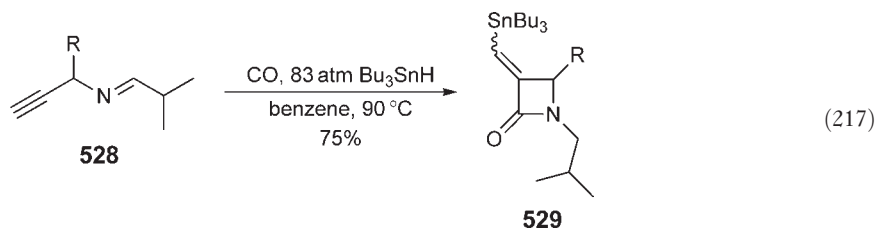
Allyl halides of different structures, under CO pressure, undergo a carbonylative [2+2] cycloaddition in the presence of palladium acetate, triphenylphosphine, and triethylamine to afford azetidin-2-ones [2004EJO1357](#), [2004T6895](#). A reaction of allyl bromides with imines led to the formation of azetidin-2-ones **524** and **525** with a high degree of stereoselectivity and **524** being the major product ([Equation 215](#)) [2006T1564](#).



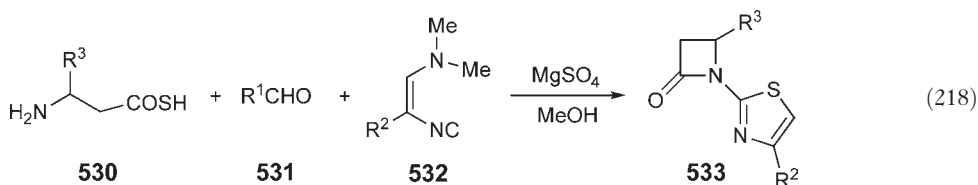
Treatment of 1,3-thiazolium-4-olates **526** with aliphatic aldehydes yielded a series of highly functionalized azetidin-2-ones **527** ([Equation 216](#)) [2003JOC6338](#). The formation of this compound has been explained by ring fragmentation of an initial [3+2] cycloadduct.

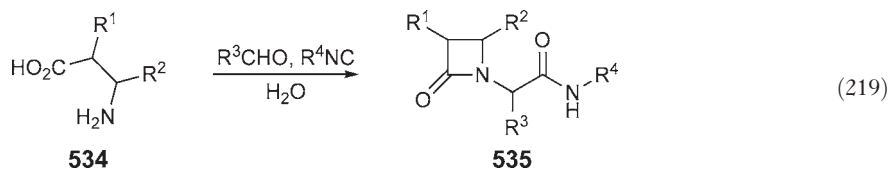


A radical-mediated stannylcarbonylation of aza-enynes **528** by means of a 4-*exo*-annulation approach enabled the formation of α -stannylmethylenazetidin-2-ones **529** ([Equation 217](#)) [2003JA5632](#).



Recently, some three-component reactions have been used to construct the azetidin-2-one framework. A three-component reaction of β -aminothiocarboxylic acid **530**, aldehydes **531**, and 3-(dimethylamino)-2-isocyanoacrylates **532** has been used for the preparation of azetidin-2-ones **533** ([Equation 218](#)) [2002TL6897](#). The reaction of amino acids **534** with an aldehyde and isocyanides proceeded well in water to yield azetidin-2-ones **535** in excellent yields ([Equation 219](#)) [2004JA444](#).

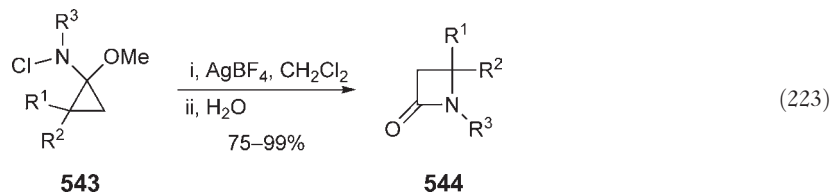
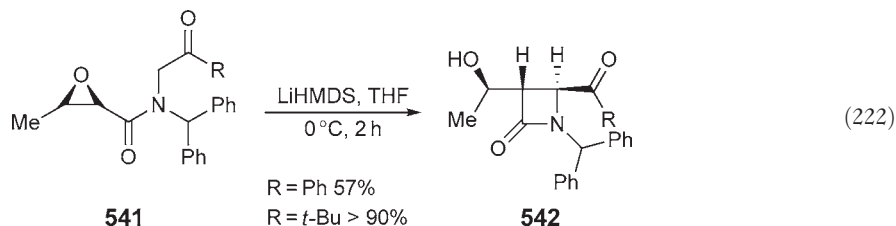
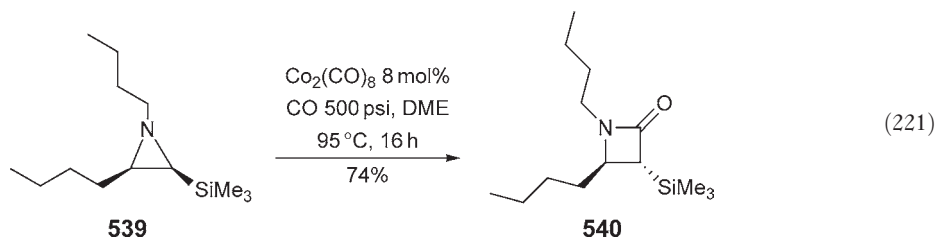
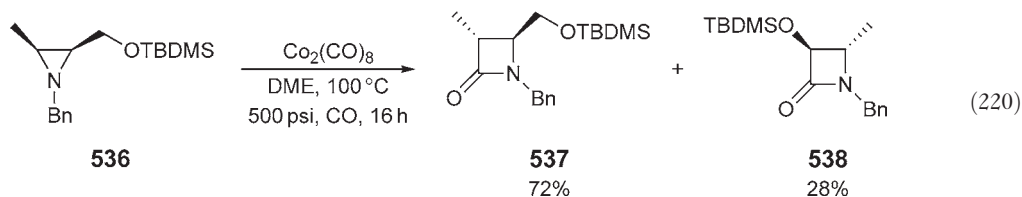




2.01.3.11 β -Lactam Ring Synthesis by Transformation of Another Ring

2.01.3.11.1 Transformation of three-membered rings

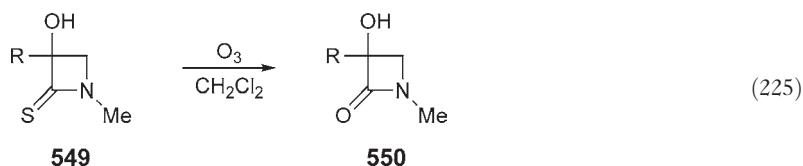
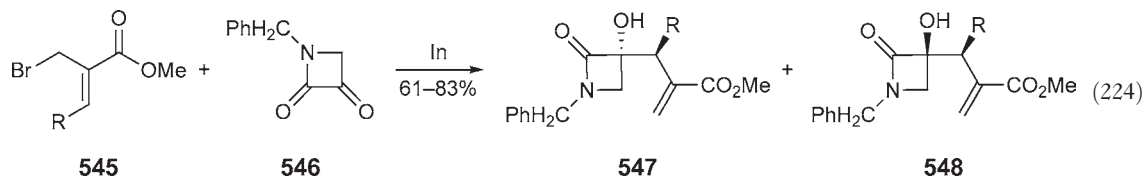
Carbonylative ring expansion of O-protected hydroxymethylaziridines **536** yielded *trans*-azetidin-2-ones **537** and **538** (Equation 220) <1999JOC518>, whereas *C*-(trimethylsilyl)aziridine **539** <2002JOC2335> afforded *trans*-azetidin-2-one **540** (Equation 221) as a single diastereomer and regioisomer in good yield. Ring opening of the aziridine resulted into inversion of configuration leading to the *trans*-azetidin-2-one. The ring-opened regioselectively at the carbon atom bearing the trimethylsilyl group in aziridine **539**. The rhodium-complexed dendrimers on a resin showed high activity for the carbonylative ring expansion of the aziridines to azetidin-2-ones <2004JOC3558>. A C-alkylation in epoxide **541**, formed in a few steps from L-threonine, formed (3*S*,4*S*)-1-benzhydryl-3-[(5*R*)-1'-hydroxyethyl]-4-acylazetidin-2-ones **542** (Equation 222) <2000T3209>. 1-Alkoxypropylamines **543** undergo silver-induced ring expansion to form 4-alkoxycarbonyl-4-alkylazetidin-2-ones **544** (Equation 223) <2003JOC6685, 1996JOC6500>.



Very recently, the ring opening of α -substituted- α -methoxycarbonyl-*N*-nosylaziridines has been reported as a practical access to enantiopure α , α' -disubstituted β -lactam scaffolds, which are novel types of ditopic reverse turn surrogates <2007OL101>.

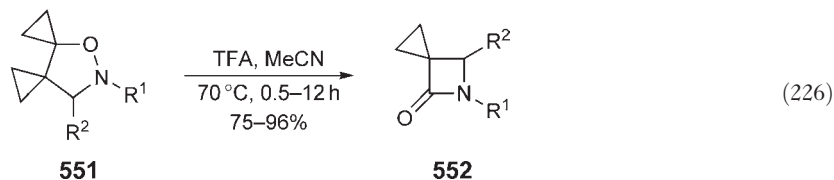
2.01.3.11.2 Functional group transformations on four-membered rings

The functional group transformations on azetidine-2,3-dione rings using organometallics leading to the formation of 3-hydroxyazetidin-2-ones have been described in [Section 2.01.3.5.2](#). Indium-mediated allylation reactions of azetidin-2,3-diones afforded 3-hydroxyazetidin-2-ones [<1998H\(49\)97>](#). The additions of 2-alkylidene-3-bromopropanoates **545** to 1-benzylazetidin-2,3-dione **546** in the presence of an indium catalyst occurred regioselectively at the C-3 carbonyl affording 3-hydroxyazetidin-2-one **547** and **548** (Equation 224) [<1998H\(47\)107, 1998JOC5643>](#). Ozonolysis of 3-hydroxyazetidin-2-thiones **549** yielded 3-hydroxyazetidin-2-ones **550** (Equation 225) [<1995JA5859>](#).



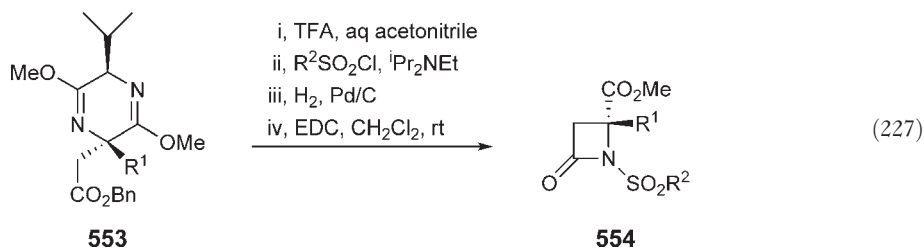
2.01.3.11.3 Transformation of five-membered rings

Treatment of bis-spirocyclopropanated isoxazolidines **551** with trifluoroacetic acid in acetonitrile furnishes 3-spirocyclopropanated azetidin-2-ones **552** in excellent yields (Equation 226) [<2004EJO4158>](#).



2.01.3.11.4 Transformation of six-membered rings

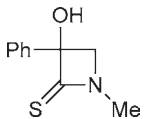
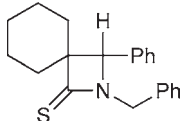
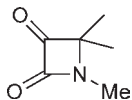
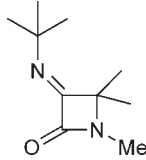
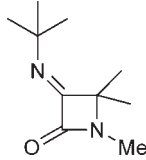
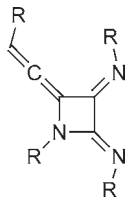
Transformation of piperazine derivatives **553** in a few steps led to the synthesis of *N*-arylsulfonylazetidin-2-ones **554** (Equation 227) [<2003SL2398>](#).



2.01.3.12 Specific Classes of Azetidin-2-one Derivatives

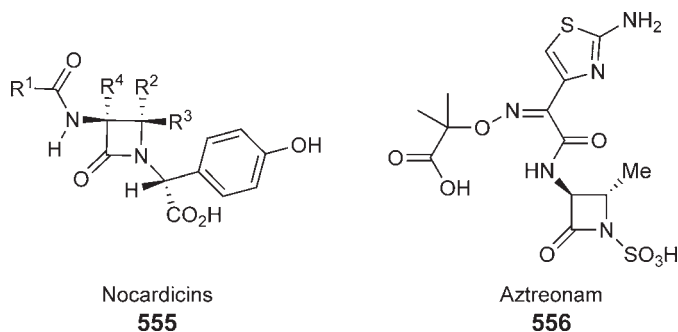
This section gives leading references on specific classes of azetidin-2-one derivatives and focuses on the preparation of these compounds ([Table 6](#)).

Table 6 Related azetidin-2-one derivatives

Compound	Preparation	References
	<i>N,N</i> -Dimethylacetylthioamide + LDA <i>N,N</i> -Dimethylmethanethioamide + methyl benzoates + LDA	1995JA5859
	<i>N,N</i> -Dibenzylcyclohex-1-enecarbothioamide	1996JA10644
	3-Hydroxyazetidin-2-one + P ₂ O ₅ /DMSO <i>N</i> -Lithiated imines + CO + MeI	2000JPR585, 2006S115, 2005ARK43
	3-(<i>N</i> - <i>t</i> -Butyl- <i>N</i> -chloro)aminoazetidin-2-ones + DBU then sat. oxalic acid	1998SC1989 2003JOC27
	3-(<i>N</i> - <i>t</i> -Butyl- <i>N</i> -chloro)aminoazetidin-2-ones + DBU/MeCN	2003JOC27
	<i>N</i> -(1-12-Dicarba-closo-dodecaboran-1-yl)formamide + triphosgene in CH ₂ Cl ₂ and Et ₃ N	2002IC6493

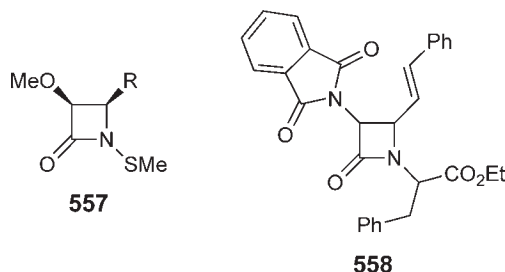
2.01.3.13 Important Compounds and Applications

Azetidin-2-ones have been investigated until the early 1990s mainly for their antibacterial activity. As the first monocyclic azetidin-2-one discovered from a natural source, nocardicins **555** are more active against Gram(–) bacteria than Gram(+) bacteria. The first monocyclic azetidin-2-one that found a clinical application is aztreonam **556**, which belongs to the class of monobactams – azetidin-2-ones bearing an *N*-sulfonate group. The literature review for the current decade since 1995, however, reveals diverse types of biological activities associated with monocyclic azetidin-2-ones <2003RMC305, 2004RMC69>.

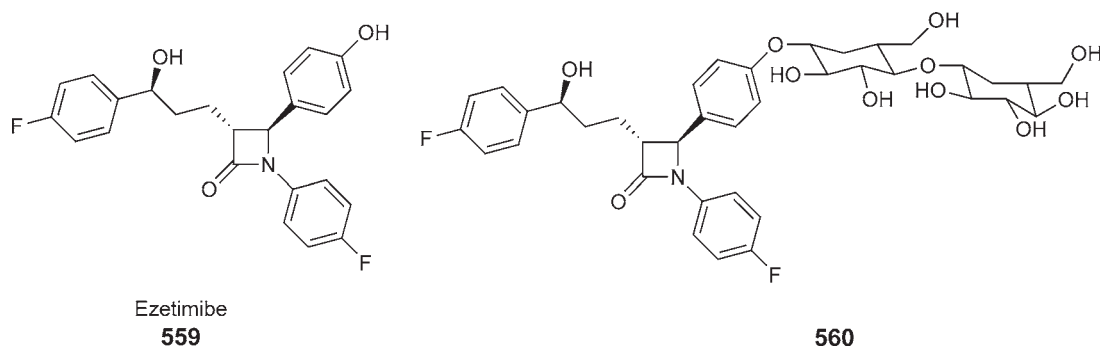


3-Chloro- and 3,3-dichloroazetidin-2-ones showed moderate to good antibacterial activity against some Gram(–) and Gram(+) bacteria <2000FA147, 2000IJB716>. 1-*n*-Butyl-3-halo-4-(2-arylindol-3-yl)azetidin-2-ones have been shown to have significant antibacterial and antifungal activity <2004HAC494>. Many *cis*-3-methoxy-4-alkyl/aryl-1-

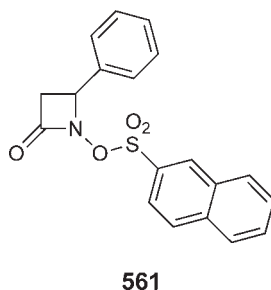
(methylthio)azetidin-2-ones **557** exhibit significant activity against MRSA strains <2000T5571, 2002BML3229>. 3-Phthalimidoazetidin-2-one **558** showed good activity against *Bacillus subtilis* and moderate activity against *Staphylococcus citreus* <2004MOL939>.



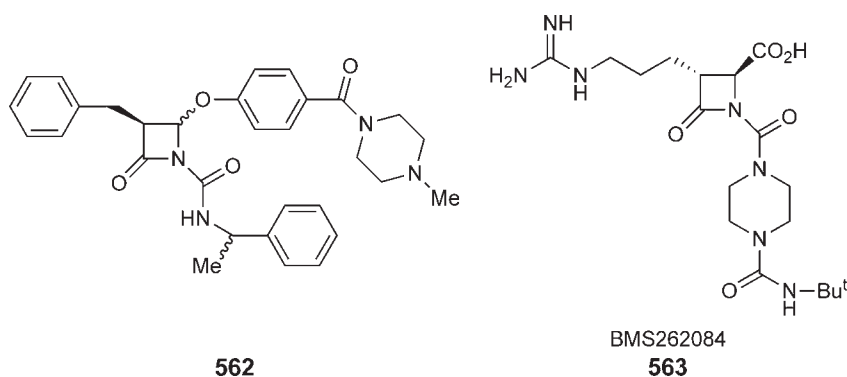
The most notable discovery in the area of monocyclic azetidin-2-ones is its development as cholesterol absorption inhibitors. The monocyclic azetidin-2-one **559**, earlier known as SCH58235, was discovered to have potential cholesterol absorption inhibition property in the late 1990s <1998JME973>. This compound is now in clinical application with the name ezetimibe to treat hypercholesterolemia <2004JME1>. It has been observed recently that the new nonhydrolyzable glycoside **560**, prepared using the scaffold of ezetimibe, is also a potent inhibitor of cholesterol absorption <2004AGE4653>.



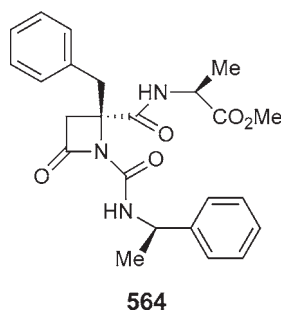
The resistance posed by newly developing strains of bacteria is a major cause of concern for researchers involved in developing antibiotics worldwide. The enzymes responsible for inactivating the β -lactam antibiotics are known as β -lactamases. However, many azetidin-2-ones have shown promising inhibitory activity on these β -lactamases. 2-Oxo-4-phenylazetidin-1-yl naphthalene-2-sulfonate **561** has been shown to inactivate the class A TEM-1 β -lactamase <2000T5719, 1995JA5938>.



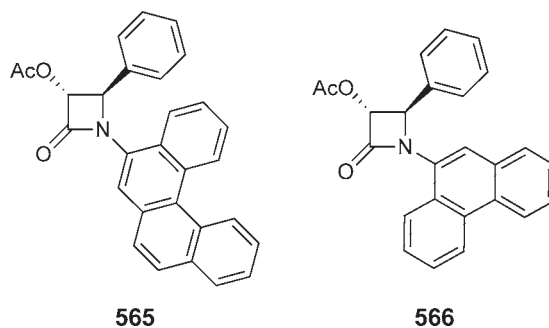
Azetidin-2-ones have also shown good inhibitory activity on human chymase—a chymotrypsin-like serine protease, which is thought to play an important role in cardiovascular diseases and chronic inflammation following fibrosis, such as cardiac, renal, and pulmonary fibrosis. Aspartic acid-derived 1-amido-3-benzylazetidin-2-one **562** has shown significant activity against chymase <2001BMC3065>. Some monocyclic azetidin-2-ones, for example, BMS262084 **563**, have been identified as potent and selective tryptase inhibitors <2002BML2229, 2002JOC3595>. The utilization of tryptase inhibitors has recently drawn attention for the treatment of asthma <1999MI463>.



Some phenylalanine-derived monocyclic azetidin-2-ones, for example, **564**, have been reported as modest inhibitors of human cytomegalovirus (HCMV) serine protease <2004BML2253>. HCMV is a ubiquitous member of the herpes virus family. Severe manifestations of HCMV can be seen in individuals with a weakened immune system due to late-stage cancer and AIDS, or by immunosuppressive therapy following organ transplantation.



Monocyclic azetidin-2-ones have been explored for their anticancer activity. The (3*S*,4*S*)-1-(4-methoxyphenyl)-3-methyl-4-(2-acetoxybenzoyloxymethyl)-4-(2,2-dicyanovinyl)azetidin-2-ones have shown anticancer activity *in vitro* with respect to a wide range of monolayer cultures of cancer cells <2003CHE587>. *Trans*-1-*N*-chrysenyl-3-acetoxy-4-phenylazetidin-2-one **565** and 1-*N*-phenanthrenyl-3-acetoxy-4-phenylazetidin-2-one **566** have shown selective anticancer activity against two leukemia and carcinoma cell lines <2004BMC2523>.

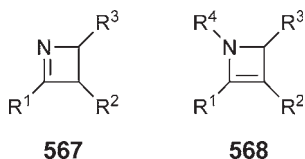


A series of azetidin-2-ones has been evaluated for anti-hyperglycemic activity <2004MI80>. The derivatives with a phthalimido group at C-3, cyclohexyl or isopropyl group at nitrogen, and styryl or 4-methoxyphenyl group at C-4 showed potential anti-hyperglycemic activity, which might be due to increased utilization of glucose either through increased insulin activity or through the induction of the glycogen synthetase enzyme.

2.01.4 Azetines

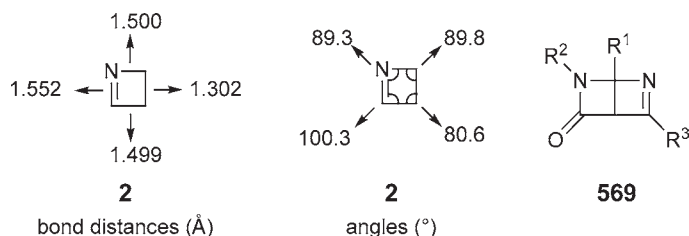
2.01.4.1 Introduction

Azetines comprise a rare class of constrained azaheterocycles with high synthetic potential due to their usually unstable nature. This class can be divided into 1-azetines **567** on the one hand and 2-azetines **568** on the other hand, depending on the position of the double bond. As described in CHEC-II(1996) <1996CHEC-II(1B)507>, isolated 2-azetines are mostly stabilized by an electron-withdrawing group at nitrogen, and 1-azetines by a conjugating electron-donating substituent at the 2-position and/or an electron-withdrawing substituent at the 3-position. The chemistry of azetines is still not much developed, despite the fact that since the early 1980s basic and fundamental information was available for the further unraveling of this class of compounds <1984CHEC(7)237>.

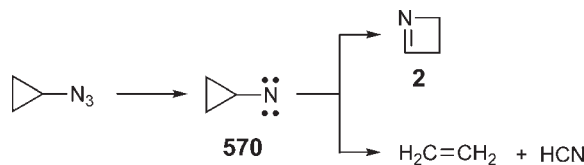


2.01.4.2 Theoretical Methods

Ab initio calculations on 1-azetine **2** have been carried out at the HF and MP2/6-31G(d,p) levels of theory to compare with the structures, orbital hybridization, bond orders, and charge distributions of the Dewar pyrimidinones **569**, supporting the abnormally elongated C–N bond distance in pyrimidinones observed by X-ray analysis. The bond distances and angles in azetine **2** have been obtained by theoretical calculations <1997JOC2711>.

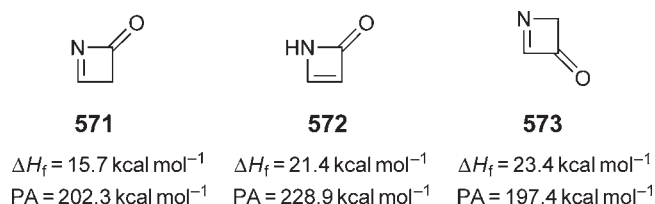


A computational study at the HF/6-31G* level revealed that the activation energy of the ring expansion reaction of cyclopropylazide **570** toward azetine **2** was 2.84 kcal mol⁻¹, whereas the activation energy of the fragmentation toward ethylene and HCN was 0.64 kcal mol⁻¹ (Scheme 72) <2002TL745>.



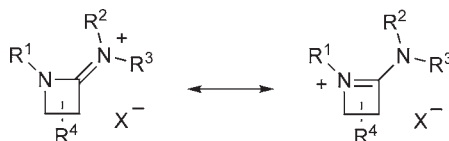
Scheme 72

The electrocyclic ring opening of 2-azetine has been investigated theoretically by means of HF, MP2, and B3LYP calculations, demonstrating a large preference for inward rotation of the nitrogen lone pair and outward rotation of the NH group <2001JOC6669>. A computational investigation of the enthalpies of formation (ΔH_f) and proton affinities (PAs) of azetinones **571–573** has been reported <2003IJM91>.



Theoretical calculations (HF/6-31G** and B3LYP/6-31++G**) were used to study the mechanisms of ring opening reactions of simple azetidinone **572** <1999JMT(468)119>.

A computational study of thermal [2+2] cycloaddition reactions between imines and keteniminium salts toward azetidine derivatives has been reported (Scheme 73) <1999JOC1831>.

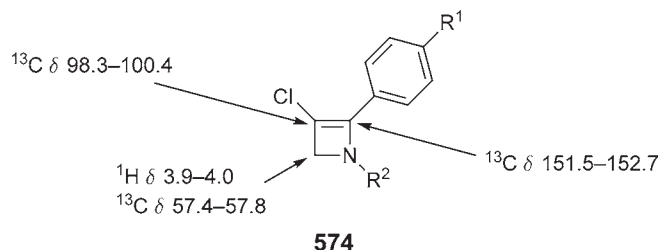


Scheme 73

2.01.4.3 Experimental Structural Methods

Azetines are considered as planar structures (see CHEC-II(1996)). Data from X-ray crystallography on amidinium-type four-membered rings supported this fact. A single crystal X-ray analysis has been performed on a 1-azetine derivative (compound **608**, R=Ph) <2003JA3690>.

The reactions of 3,3-dichloroazetidines to afford aziridines were performed in an NMR tube to prove the intermediacy of 2-azetines **574** <2002JOC2075>. The ¹H and ¹³C NMR data of 2-azetines are reported. The ¹H and ¹³C NMR data of 1-azetines are described in CHEC-II(1996) <1996CHEC-II(1B)507>.



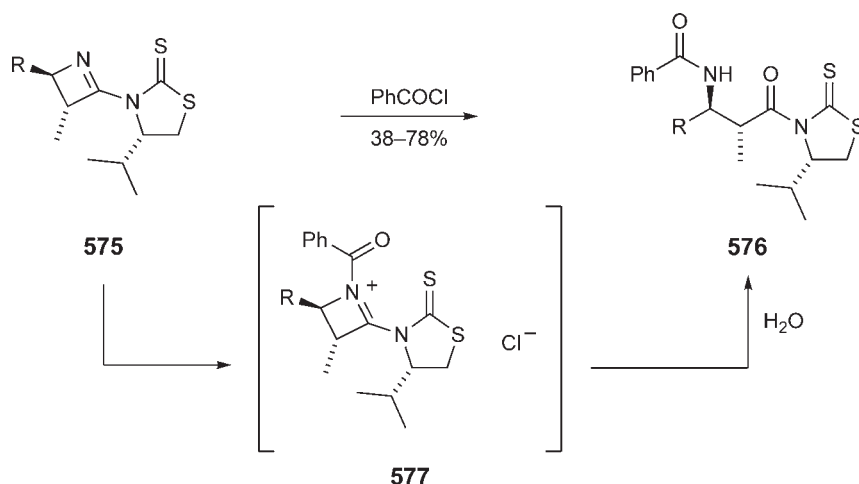
An azetinone is observable by means of a peak at 1814 cm⁻¹ in the matrix IR spectrum (for 3,4-diphenylazetin-2(1H)-one), but only at the mildest flash vacuum thermolysis temperatures, 325–400 °C <2004JOC1909>.

2.01.4.4 Reactivity of Azetines

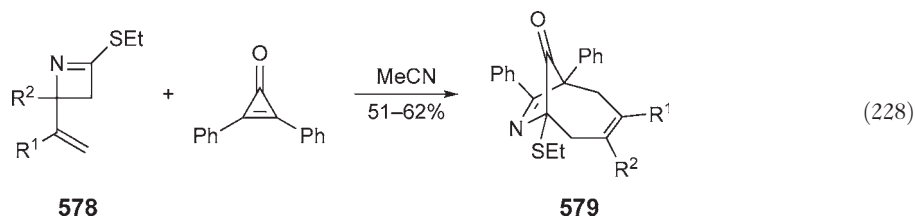
2.01.4.4.1 1-Azetines

Azetines **575**, synthesized by the reaction of *N*-acyl thiazolidinethione enolates with enolizable aldoxime ethers, have been successfully converted into the corresponding *N*-acyl-substituted β -aminocarbonyl compounds **576** by simple exposure to benzoyl chloride <2003JA3690>. The reactions presumably involved an acyliminium salt **577**, which hydrolyzed to yield **576** (Scheme 74).

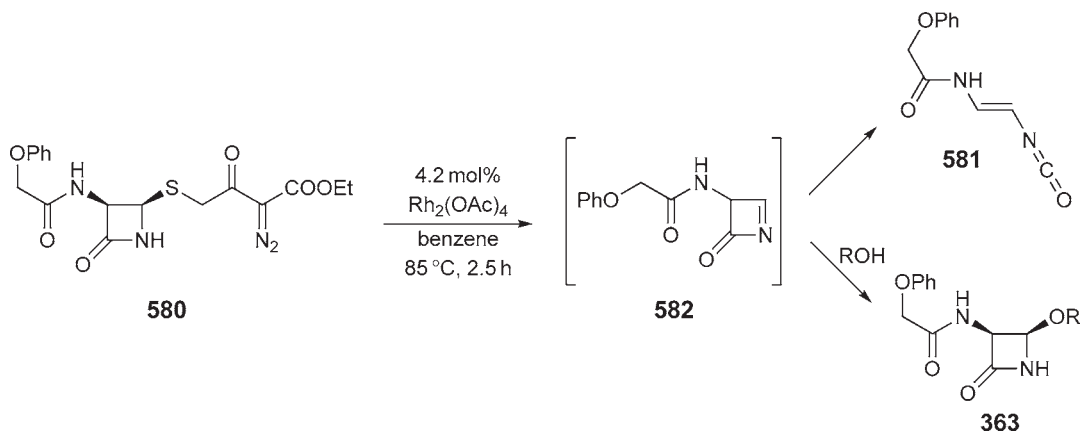
Treatment of 2-(ethylthio)azetines **578**, synthesized from 2-thioxoazetidines using a solution of Meerwein's reagent (Et₃O⁺BF₄⁻), with diphenylcyclopropanone resulted in the unexpected 7-azabicyclo[4.2.1]nonanes **579** (Equation 228) <2006TL425>.



Scheme 74



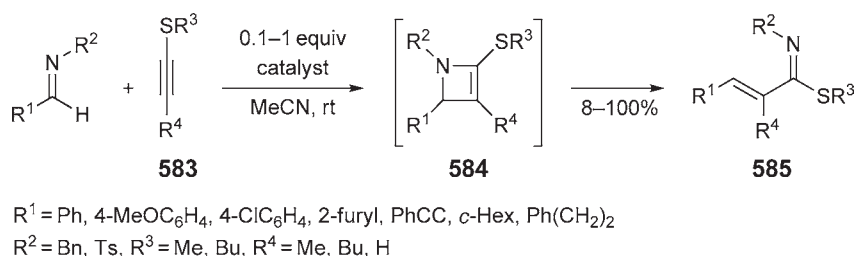
Treatment of β -lactam **580** with rhodium acetate resulted in the formation of vinyl isocyanate **581** via electrocyclic ring opening of the intermediate *N*-acylaminoazetinone **582** (Scheme 75). The latter azetinone **582** has been trapped with several alcohols, resulting in *cis*-disubstituted β -lactams **363** <2001CJC1259>.



Scheme 75

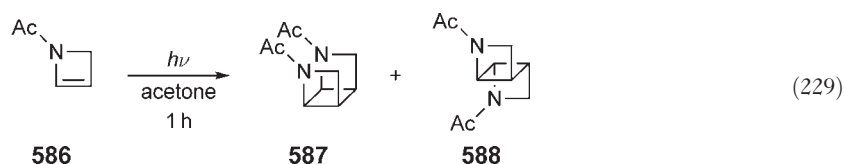
2.01.4.4.2 2-Azetines

α,β -Unsaturated thioimidates have been prepared by means of a new reaction of imines with alkynyl sulfides **583** (Scheme 76). This reaction is assumed to proceed through a [2+2] cycloaddition in the presence of a Lewis acid ($\text{Sc}(\text{OTf})_3$, $\text{Yb}(\text{OTf})_3$, BF_3OEt_2) to form 2-azetine intermediates **584**, which are unstable and immediately fragment to the thioimidates **585**. Attempts to isolate and detect azetines **584** failed <1996JOC1902>. The analogous reaction using alkynyl selenides instead of alkynyl sulfides has been described, affording α,β -unsaturated selenylimidates via intermediate azetine derivatives <2000TL945>.

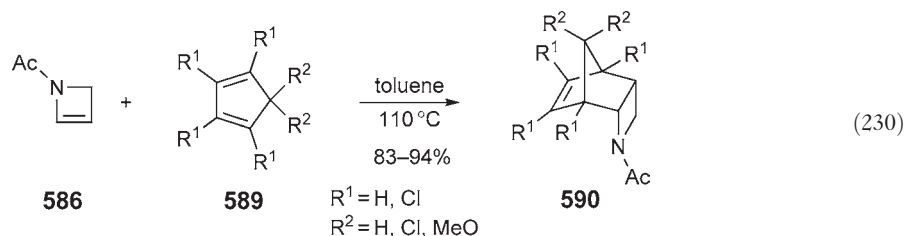


Scheme 76

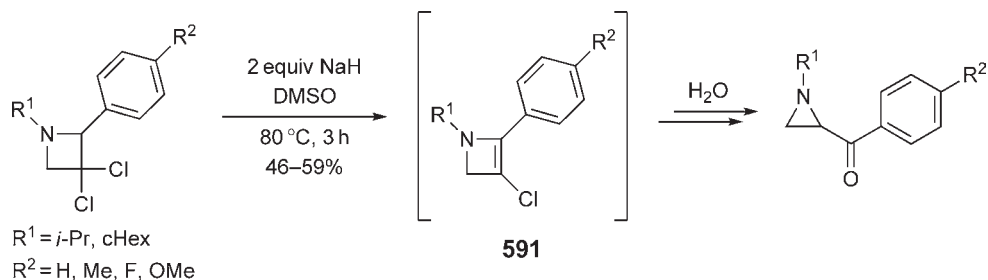
Exposure of 1-acetyl-2-azetine **586** to a point light source resulted in a 1:1 mixture of two adducts in 52% yield, and no other adducts were observed (Equation 229). The conformation of these adducts was confirmed by X-ray analysis of their corresponding *N*-nitro analogues after treatment of adducts **587** and **588** with trifluoroacetyl nitrate <1998TL5481>.



The Diels–Alder reaction of 1-acetyl-2-azetine **586** with various dienes **589** has been reported to give the corresponding adducts **590** in excellent yields (Equation 230) <1999TL443>.

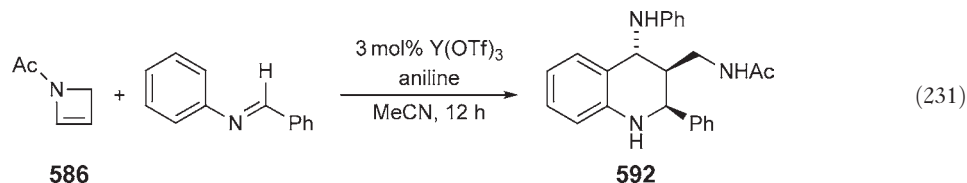


1-Alkyl-2-aryl-3,3-dichloroazetidines have been converted into 1-alkyl-2-arylaziridines via intermediate 2-azetines **591** upon treatment with sodium hydride in DMSO, followed by aqueous workup (Scheme 77). The intermediate 2-aryl-3-chloro-2-azetines **591** were characterized by ^1H and ^{13}C NMR by performing the reaction in an NMR tube <2002JOC2075>.

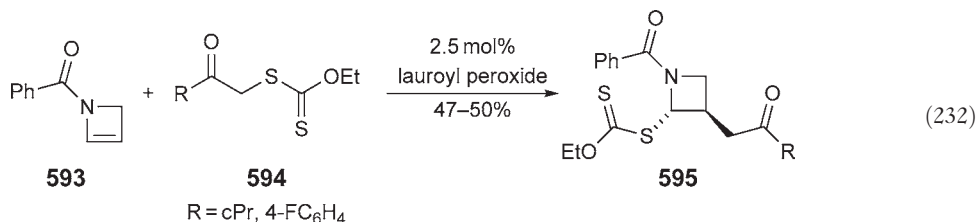


Scheme 77

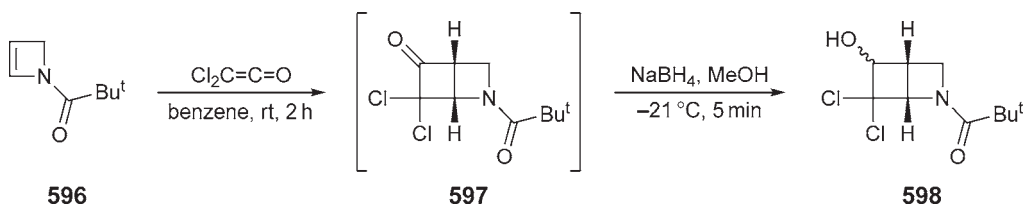
1-Acetyl-2-azetine **586** underwent a one-pot formal [4+2] cycloaddition reaction with *N*-benzylideneaniline in the presence of aniline to give 2,3,4-trisubstituted quinolines **592** (Equation 231) <2002CC444, 2002TL5469>.



Intermolecular radical additions of azetine **593** to xanthates **594** afforded the azetidine adducts **595**, mainly as the *trans*-isomers (Equation 232) <2000TL9815>.

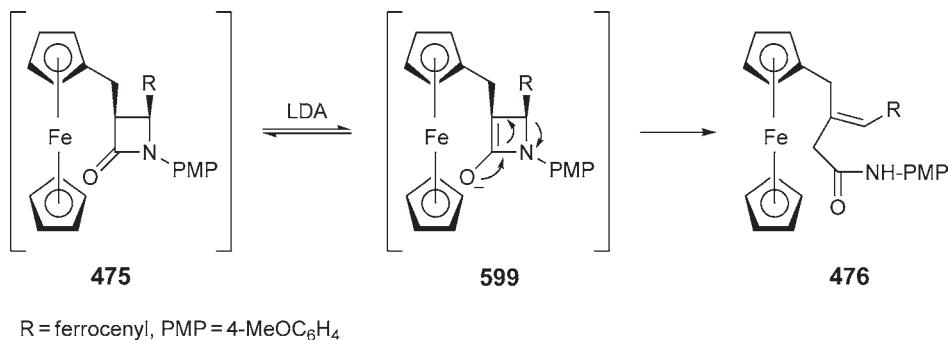


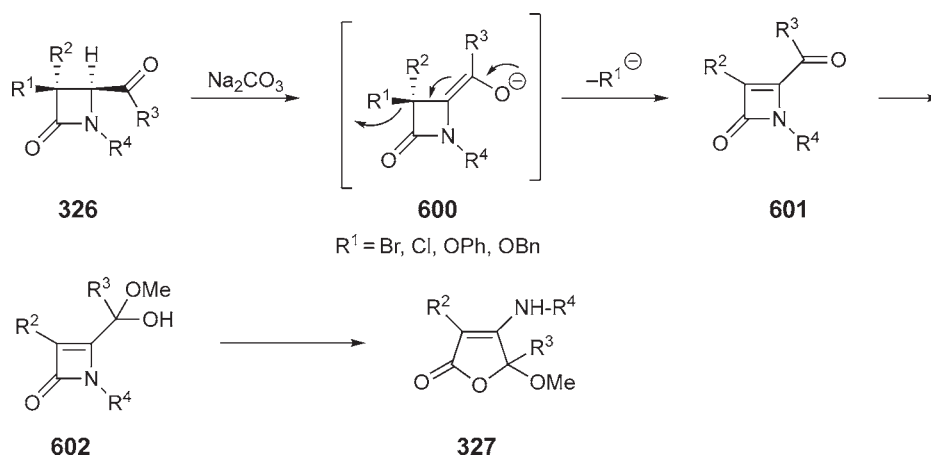
A [2+2] cycloaddition reaction of 1-[azet-1(2*H*)-yl]-2,3-dimethylpropan-1-one **596** to dichloroketene leading to cycloadduct **597** has been described <2006TL6377>. An immediate reduction of the ketone group in the unstable cycloadduct afforded cyclobutanol-fused azetidine **598** (Scheme 78).



Scheme 78

The azetidin-2-one **475** bearing a ferrocene moiety at C-4 undergoes deprotonation to form 2-azetine **599**, which undergoes ring cleavage to afford the amide **476** (Scheme 79) <2001JOC8920>.



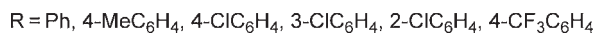
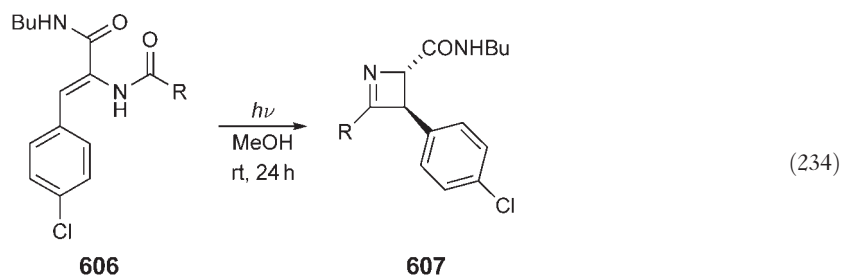
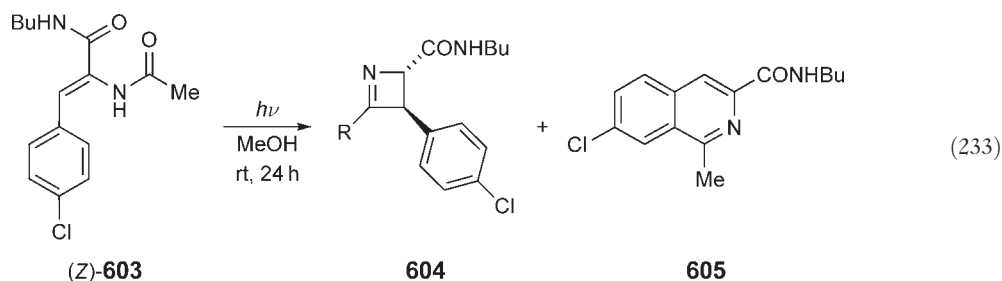


Scheme 80

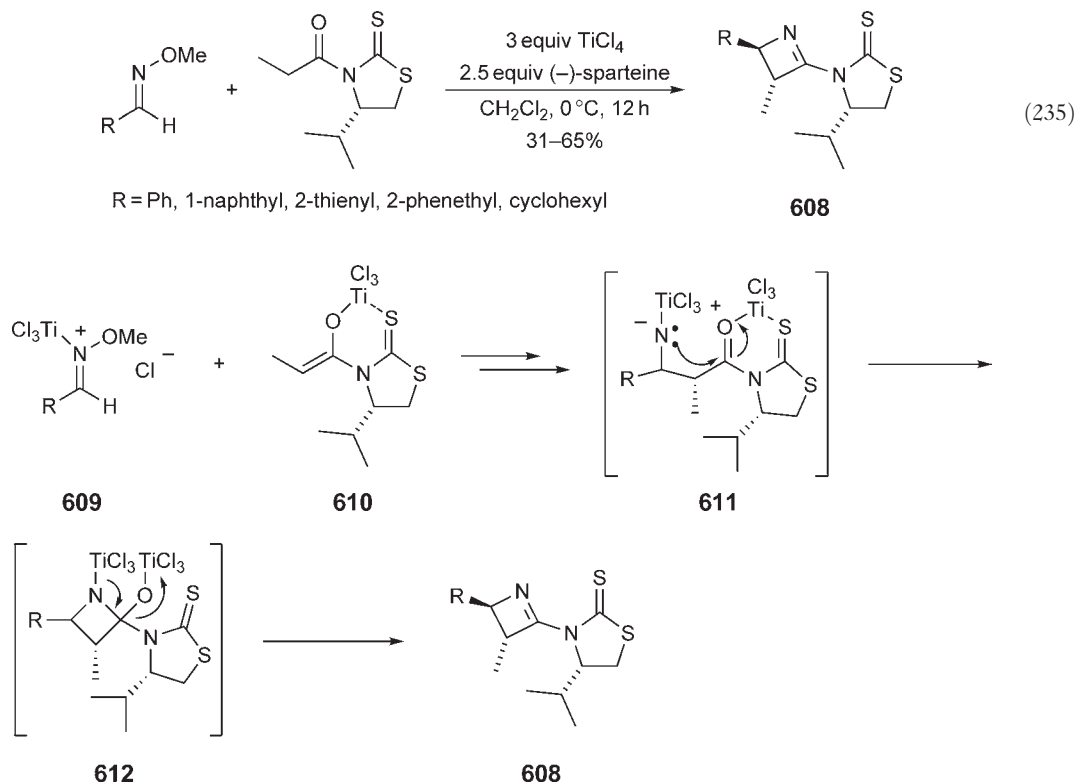
2.01.4.5 Synthesis of Azetines

2.01.4.5.1 1-Azetines

Irradiation of a nitrogen-purged methanol solution of (*Z*)-*N*-butyl-2-acetylamino-3-(4-chlorophenyl)acrylamide **603** ($\text{R} = \text{Me}$) with Pyrex-filtered light ($>280 \text{ nm}$) resulted in a mixture of *trans*-azetine **604** (21%) and isoquinoline **605** (29%) (Equation 233) <1996TL5917, 2000H(53)2261>. This method has been evaluated starting from a variety of acrylamide derivatives, for example, toward the synthesis of 1,2-dihydrobenzo[*f*]quinolinones <1998TL4083>. In both cases, minor quantities of the corresponding *cis*-azetines were detected in the crude mixtures. Besides dihydrobenzoquinolinones, benzoisoquinolines have been isolated <2000H(53)271>. The irradiation of *N*-benzoyl derivatives **606** ($\text{R} = \text{Ph, 4-MeC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 3\text{-ClC}_6\text{H}_4, 2\text{-ClC}_6\text{H}_4, 4\text{-CF}_3\text{C}_6\text{H}_4$), however, afforded only 1-azetine derivatives **607** without formation of isoquinolines (Equation 234) <1998H(48)25, 2000T2941, 2002H(57)269>. The mechanism of this cyclization has been evaluated based on substituent and solvent effects <2001T5515>. Furthermore, the same protocol has been used for the synthesis of papaverine analogues starting from (*Z*)-*N*-phenylacetyl- α -dehydro-(3,4-dimethoxyphenyl)alaninamide derivatives <2003H(60)1779>, the effect of a *meta*-substituent has been studied <2003H(60)637>, and an asymmetric version using chiral auxiliary-substituted *N*-acetyl- α -dehydroamino acids toward 1,2-dihydrobenzoquinolinone derivatives has been reported <2002H(57)1591>.

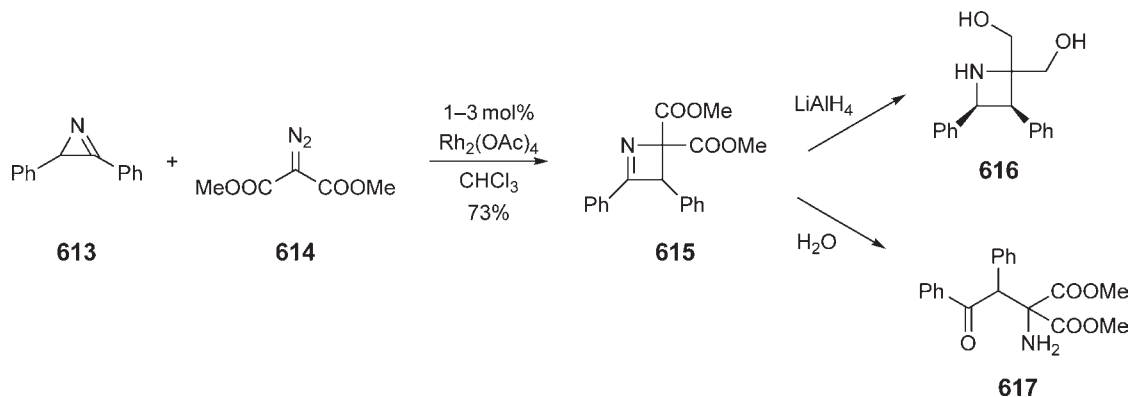


A new reaction of *N*-acyl thiazolidinethione enolates with enolizable aldoxime ethers has been reported to give 2-(thiazolidine-2-thione)-1-azetidines **608** with excellent diastereoselectivity (Equation 235) <2003JA3690>. The absence of either a methoxy or a carbonyl group in the 1-azetidines indicated a complex mechanism rather than a simple addition reaction. The formation of azetines has been rationalized by combination of the oxime and TiCl_4 to give a highly electrophilic trichlorotitanium iminium intermediate **609**, which adds onto enolate **610** to form intermediate **611**, which cyclizes to azetidine **612** (Scheme 81). An irreversible elimination of bis-trichlorotitanium oxide provides the ultimate driving force to produce azetines.



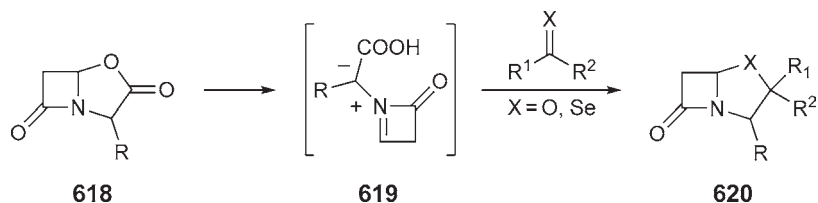
Scheme 81

The reaction of 2,3-diphenylazirine **613** with diazomalonate **614** in the presence of dirhodium tetraacetate afforded 2,3-diphenylazetine-4,4-dicarboxylate **615**, the structure of which was acknowledged through reduction toward azetidine **616** and hydrolysis toward β -amino ketone **617** (Scheme 82) <2004TL6003>.



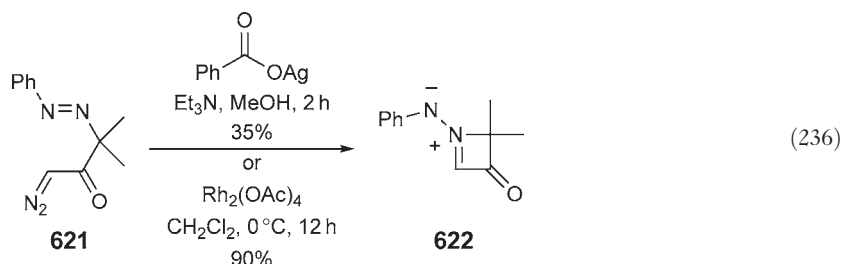
Scheme 82

Thermolysis of 1-oxa-4-azabicyclo[3.2.0]hept-2,5-diones **618** led to an *in situ* generation of azomethine ylides **619**, which added onto the carbon–oxygen double bond of aldehydes or ketones to give oxapenems **620** (Scheme 83) <1999CC249>. A similar strategy has been employed for the synthesis of selenapenems by reaction with different selenoketones <1997CC1897, 1999JHC1365, 2000T5579>.

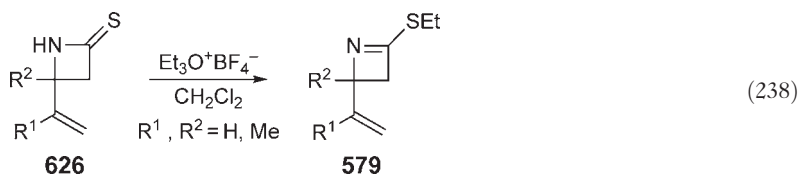
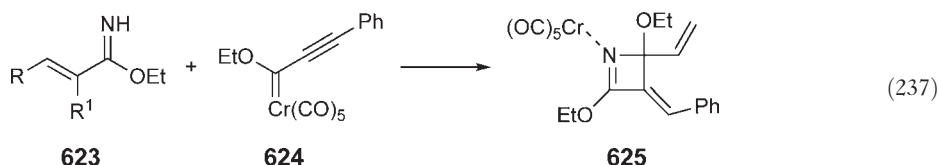


Scheme 83

The reaction of diazoketone **621** with either silver benzoate in methanol or with rhodium acetate in dichloromethane led to the formation of the stable azetinium salt **622**, which was isolated as yellow crystals (Equation 236) <1998AGE2229>.

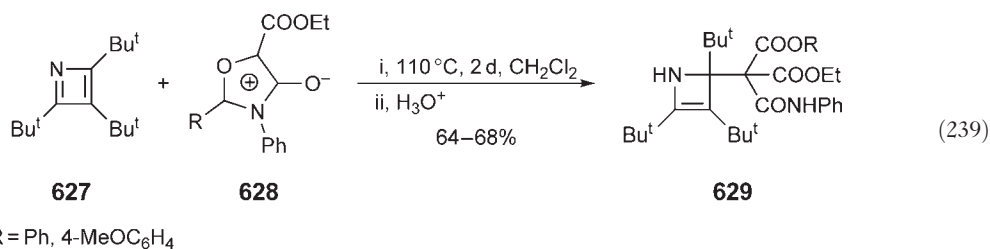


The addition of alkenyl imidates **623** (R , $R^1 = \text{Ph, Me, H}$) to (1-alkynyl)carbene complexes **624** afforded 2,4-diethoxyazetine complexes **625** (Equation 237) <1997OM2571>. Treatment of 2-thioxazetidines **626** with Meerwein's reagent yielded 2,4-disubstituted 1-azetines **579** (Equation 238) <2006TL425>.

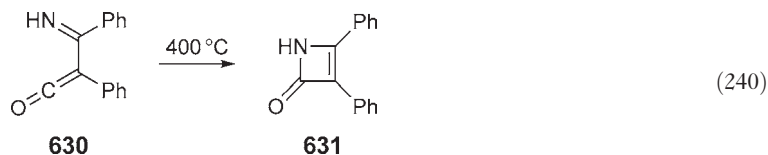


2.01.4.5.2 2-Azetines

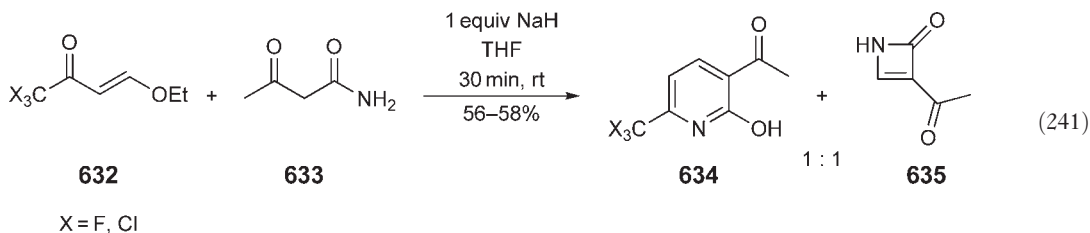
The kinetically stabilized tri-*(t*-butyl)azete **627** and isomünchnone **628** gave 2-azetines **629** after chromatography on acidic silica gel (Equation 239) <1997BSF927>. Thermolysis of the latter azetines afforded 2*H*-pyrazoles.



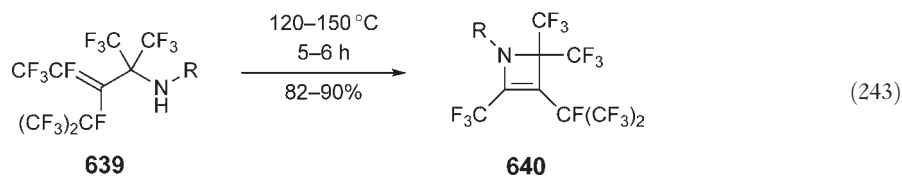
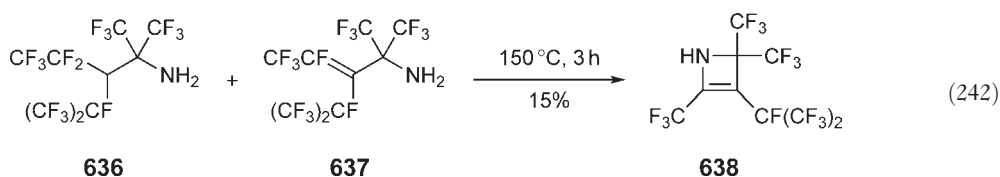
The cyclization of diphenylimidoalkyne **630** toward azetinone **631**, which undergoes a cycloreversion to diphenylacetylene and isocyanic acid, has been observed in the matrix IR spectrum at the mildest flash vacuum thermolysis temperatures, 325–400 °C (Equation 240), and has been rationalized on the basis of theoretical calculations <2004OBC3518, 2004JOC1909>.



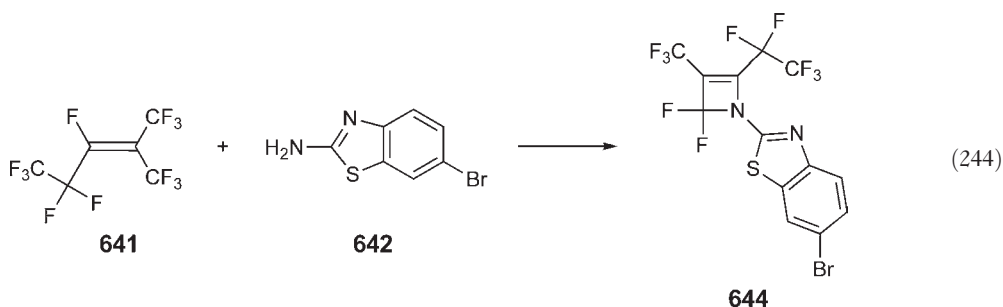
The reaction of the α,β -unsaturated ketones **632** with 2-acetylacetamide **633** and sodium hydride has been reported to give a 1:1 mixture of pyridine **634** and azetinone **635** (Equation 241) <1999S765>.

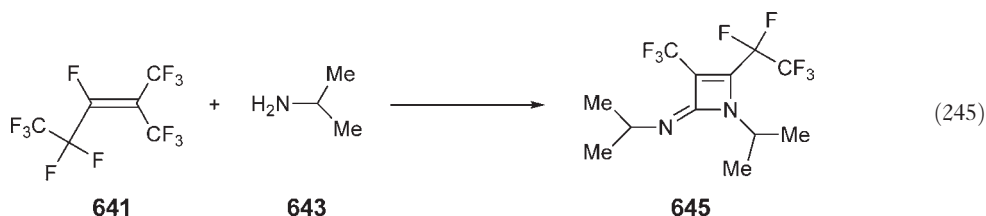


Heating of a mixture of polyfluoro amines **636** and **637** resulted in a mixture in which azetine **638** was present in 15% yield (Equation 242), whereas heating of fluorinated alkenyl amines **639** furnished *N*-alkyl azetines **640** selectively in excellent yields (Equation 243) <1996JFC(79)97>.

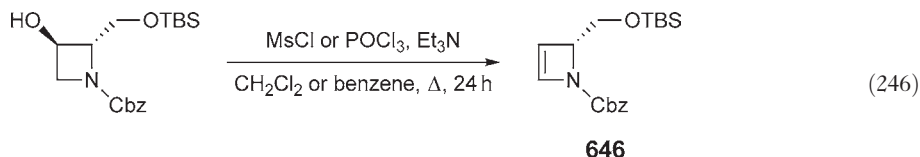


The reaction of perfluoro-2-methylpent-2-ene **641** with 2-amino-6-bromobenzothiazole **642** and with more nucleophilic isopropyl amine **643** afforded 2-azetines **644** (Equation 244) and **645** (Equation 245), respectively <2000RJO99>.



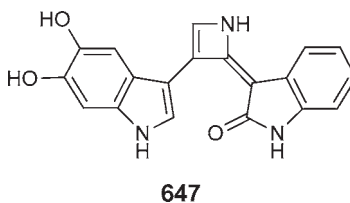


Treatment of *trans*-3-hydroxyazetidine with methane sulfonyl chloride or phosphoryl chloride in the presence of triethylamine afforded 2-azetine **646** (Equation 246) <2006TL6377>. Interestingly, the *trans*-relationship between the hydroxyl group and the alkyl substituent is crucial for effective elimination since the *cis*-3-hydroxyazetidine failed to give the 2-azetine.



2.01.4.6 Important Compounds and Applications

Treatment of violacein with the enzyme HRP-VI afforded azetine **647**, a structural analogue of violacein. This biotransformed violacein exhibited a fourfold lower cytotoxicity, indicating a decrease in antitumor activity as compared to violacein itself <2001JMO463>.



2.01.5 Azetes

2.01.5.1 Introduction

The parent azete (azacyclobutadiene) is a highly reactive and unstable compound. The successful search for cyclobutadienes in the early 1980s stimulated efforts to unravel the chemistry of azacyclobutadienes. However, the chemistry of azetes is still underdeveloped. Although several reports concerning theoretical studies on the parent azete have been published, only a limited number of contributions on practical organic chemistry involving azetes have been reported, all dealing with the remarkably stable tri-(*t*-butyl)azete.

2.01.5.2 Theoretical Methods

Theoretical studies have been performed on the parent azete **4**, for example, regarding the relationship between the preferred site of hydrogen bonding and protonation <2005PCA5509> and concerning the nonadditivity of the static correlation energy of π -electrons in planar molecules as a manifestation of antiaromaticity <2003JPO753>. A computational investigation of the enthalpy of formation (ΔH_f) of the parent azete has been reported to amount $110.7 \text{ kcal mol}^{-1}$ <2000JCP5829>.

2.01.5.3 Experimental Structural Methods

X-Ray crystallography analysis of 2,3-di-*t*-butyl-4-mesitylazete showed longer C(2)–C(3) and N–C(4) single bonds (Figure 4, see CHEC-II(1996)). In addition, normal bonds were observed. The angle between the planes of the aromatic ring and the heterocyclic ring is 70°. The crystal structure analysis of a sandwich complex of 2,3,4-tri-*t*-butylazete with (cyclopentadienyl)-bis(ethylene)-cobalt(I) revealed that the bond lengths in the planar four-membered ring became much more similar as a result of electron delocalization. The IR, NMR, and MS data of selected azetes are described in CHEC-II(1996).

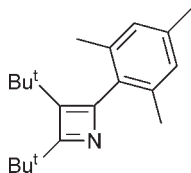


Figure 4

The electrophilicity index for, among others, the parent azete has been tabulated for two different models of the energy-electron number relationships <1999JA1922>. The electrophilicity index in the ground state parabola model ω_{gs} and the electrophilicity index in the valance state parabola model ω_{vs} are reported as $\omega_{gs} = \omega_{vs}/2 = 1.91$.

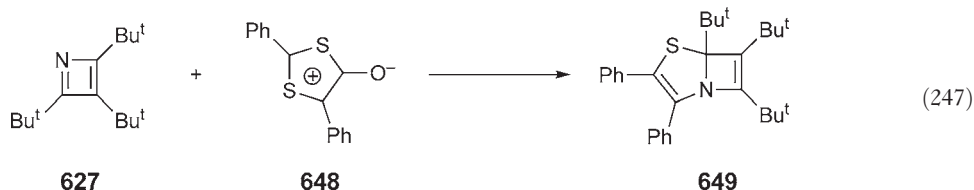
2.01.5.4 Thermodynamic Aspects

It is known that 2,3,4-tri-*t*-butylazete **627** is a remarkable stable, strained, kinetically stabilized heterocyclic compound, which can be distilled (Kugelrohr, bp 60 °C, 0.05 mbar) and has a melting point of 37 °C <1996CHEC-II(1B)507>. The reddish-brown needles are stable for several days at 100 °C, while the compound fragmented at 700 °C (10^{-6} mbar) into di-*t*-butylacetylene and *t*-butylcyanide.

2.01.5.5 Reactivity of Azetes

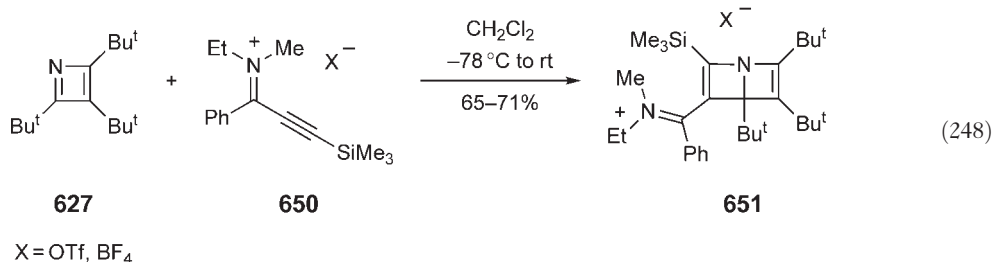
2.01.5.5.1 Hydrolysis and nucleophilic addition

The reaction of tri-(*t*-butyl)azete **627** with isomünchnone **628** to give azetine **629** has been described previously (Equation 239). The reaction of this azete with meso-ionic compound **648** afforded the bicyclic azetine **649** (Equation 247) <1997BSF927>.

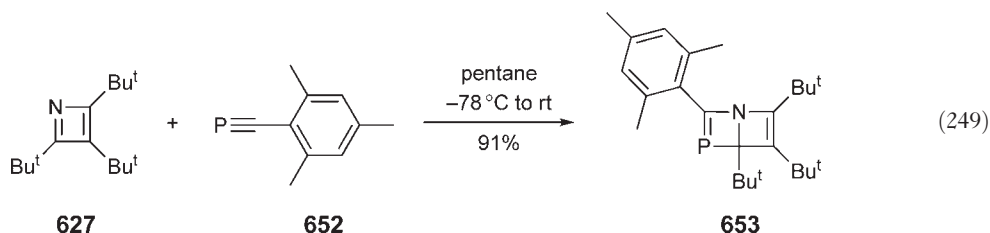


2.01.5.5.2 Cycloaddition reactions

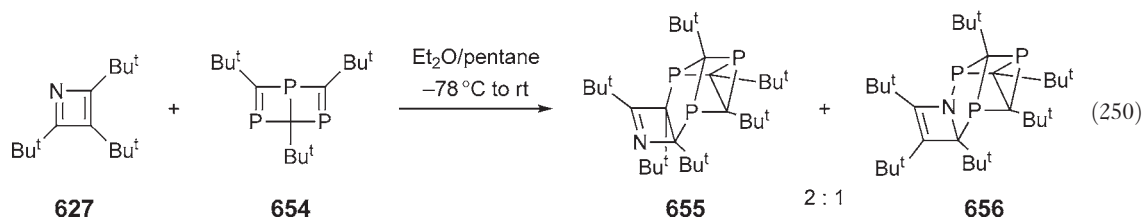
Cycloaddition of iminium salts **650** onto azete **627** afforded the Dewar pyridines **651** in good yields (Equation 248) <2002S497>.



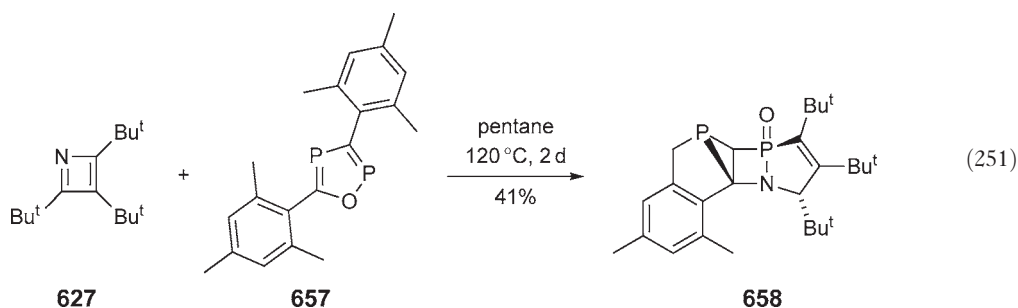
Tri-*t*-butylazete **627** underwent regioselective cycloaddition onto mesitylphosphaacetylene **652** to afford 1,3-azaphosphabenzene **653** in excellent yield (Equation 249) <1998S1305>.



The reaction of triphospha-Dewar-benzene **654** with tri-*t*-butylazete **627** resulted in a mixture of two adducts **655** and **656** in a 2:1 ratio (Equation 250) <1997JOM(529)215>.

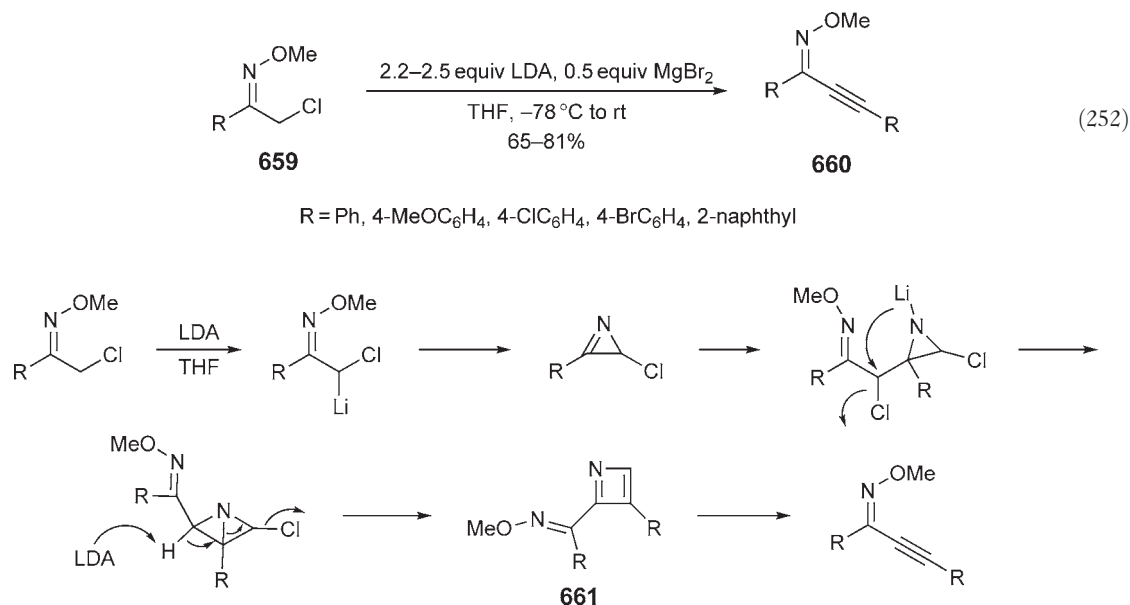


Cycloaddition of tri-*t*-butylazete **627** with 1,2,4-oxadiphosphole **657** afforded compound **658** (Equation 251) as a result of a complex reaction pathway <1999EJO587>.



2.01.5.5.3 [2+2] Cycloreversion reactions

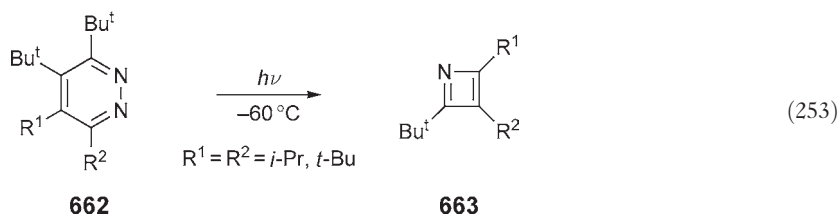
Azetes are known to undergo [2+2] cycloreversion to provide acetylene and hydrogen cyanide <1996JPC1569>. The reaction of chloroacetophenone oxime **659** with LDA yielded another oxime **660** (Equation 252). The formation of this product has been explained by [2+2] cycloreversion of the azetes **661** formed in the reaction (Scheme 84) <2003AGE5613>.



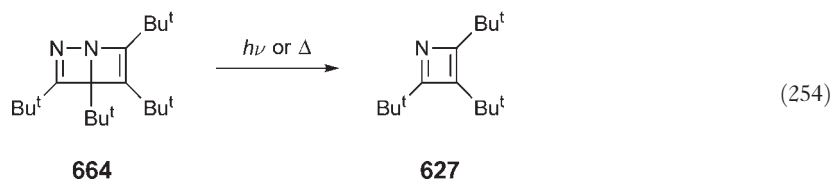
Scheme 84

2.01.5.6 Synthesis of Azetes

Photolysis of pyridazines **662** afforded tri-substituted azetes **663** (Equation 253) <1995LA173>.



Tri-*t*-butylazete **627** has been prepared both by photolysis as well as by thermolysis of Dewar pyridazine **664** (Equation 254) <1995LA169>.



2.01.6 Further Developments

The synthesis of novel azetidine derivatives remains the subject of intensive study. New procedures for the preparation of this class of compounds include, e.g., rearrangement of β,γ -aziridino- α -amino esters <2007OL4399>, copper-catalyzed multicomponent reactions of terminal alkynes, sulfonyl azides, and carbodiimides <2007OL1585>, regioselective addition of 1,3-dicarbonyl dianions to *N*-sulfonyl aldimines <2007T4779>, elaboration of α -amino acids <2007TL2471>, palladium-catalyzed *N*-arylation of azetidines <2007S243> and

intramolecular ring closure of β -amino chlorides <2007ARK71>. The synthetic utility of azetidines as synthons for further elaboration has also been documented, e.g., the Lewis acid-catalyzed regioselective ring opening of azetidines with alcohols and thiols <2007TL5375>, and [4+2] cycloaddition reactions of *N*-tosylazetidines with aldehydes and ketones towards chiral 1,3-oxazinanes and 1,3-amino alcohols <2007TL4373>. The biological relevance of azetidine derivatives was further demonstrated by, e.g., the synthesis of a variety of penaresidin derivatives <2007BMC4910> and the preparation of 2-alkyl-2-carboxyazetidines as scaffolds for the induction of γ -turns <2007TL3689>.

Due to the biological and synthetic relevance of β -lactams, a lot of effort is devoted to the synthesis of novel monocyclic derivatives. A few recent examples involve the use of the Kinugasa reaction under click chemistry conditions <2007SL1585>, the synthesis of spiro- β -lactams by epoxide ring opening <2007EJO3199>, the ionic liquid supported synthesis of β -lactam libraries in ionic liquid batch <2007TL5143>, the solvent-free, one-pot synthesis of β -lactams by the Sc(OTf)₃-catalyzed reaction of silyl ketene thioacetals with imines <2007EJO2865>, the stereoselective synthesis of *trans*-disubstituted β -lactams from *N*-phenylsulfonylimines <2007TL4301>, the synthesis of 1,3,4-trisubstituted 4-carboxy β -lactam derivatives from amino acids <2007OL1593>, the asymmetric synthesis of β -lactams by [2+2] cycloaddition using 1,4:3,6-dianhydro-D-glucitol (isosorbide) derived chiral pools <2007T3380>, the use of *N*-sulfonylimines <2007T3205>, the synthesis of monocyclic and spirocyclic selenoazetidin-2-ones <2007T3195>, and the synthesis and antimicrobial activity of new 2-azetidinones from *N*-(salicylidene)amines and 2-diazo-1,2-diarylethanones <2007ARK80>.

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Biographical Sketch



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2.02

Cephalosporins

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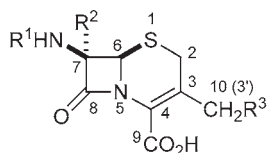
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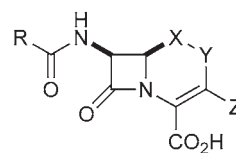
2.02.1 Introduction

2.02.1.1 Structural Types and Nomenclature

The term ‘cephalosporins’ refers to a variety of semisynthetic antibiotics derived from cephalosporin C (CPC), **1**, a natural antibiotic isolated in 1945 from a *Cephalosporium acremonium* strain by Brotzu and which structure was elucidated by Newton and Abraham in 1961. An important structural variant was discovered in the cephamycins (1971), or 7 α -methoxycephalosporins, as cephamycin C, **2**, a natural product from a strain of *Streptomyces clavuligerus*. The 7 α -methoxy group imparts to these molecules excellent stability against β -lactamases, and similarly to cephalosporins, cephamycins can be varied semisynthetically. Cephalosporins contain the 7-aminocephalosporanic acid nucleus (7-ACA), **3**, which consists of a fused β -lactam-dihydrothiazine system, also termed as cephem, with the lowest-numbered position of the double bond being specified by prefixes (cephalosporins are 3-cephems or Δ^3 -cephems). Over the years the term cephem has been expanded to enclose other non-natural nuclear analogues of the general structure **4**, a number of them exhibiting broad spectrum antibiotic activity, a similar pharmacological profile and in some cases greater chemical stability than the parent compounds.



- 1** Cephalosporin C: $R^1 = (R) \text{HO}_2\text{C}(\text{NH}_2)\text{CH}(\text{CH}_2)_3\text{CO}$,
 $R^2 = \text{H}$, $R^3 = \text{OAc}$
2 Cephamycin C: $R^1 = (R) \text{HO}_2\text{C}(\text{NH}_2)\text{CH}(\text{CH}_2)_3\text{CO}$,
 $R^2 = \text{OCH}_3$, $R^3 = \text{OCONH}_2$
3 7-ACA: $R^1 = R^2 = \text{H}$, $R^3 = \text{OAc}$



- 4a** Isocephems: $X = \text{CH}_2$, $Y = \text{S}$
4b Oxacephems: $X = \text{O}$, $Y = \text{CH}_2$
4c Isooxacephems: $X = \text{CH}_2$, $Y = \text{O}$
4d Carbacephems: $X = Y = \text{CH}_2$

The accepted conventional nomenclature based on the cepham (the fused β -lactam-perhydrothiazine system) is used throughout this chapter. Carbon atom bonded to C-3 has been numbered as C-10 (or C-3'). Stereochemistry at C-7 is specified either as absolute configuration R/S , or as α/β depending on the orientation of the substituent, below or above the plane, respectively. The above abbreviated common names and numbering for the cephalosporins should not be confused with the IUPAC systematic nomenclature as used by *Chemical Abstract*, which, for example, designates 7-ACA as (6*R*,7*R*)-3-(acetoxymethyl)-7-amino-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

2.02.1.2 General Overview

The continued popularity and worldwide use of parenteral and oral cephalosporins, is predominantly related to both a proved track record of broad-spectrum antibacterial activity (against several Gram-positive and Gram-negative bacteria) as well as excellent safety during more than 30 years of clinical experience. In this context, there is a continuous battle in the design of new cephalosporin antibiotics to withstand inactivation by the ever increasing diversity of β -lactamases. The introduction of a variety of substituents at different positions of the cephalosporin nucleus has generated a vast array of compounds with differences in the spectra of activity and in various properties such as a better oral availability, stability to hydrolysis by β -lactamases, protein binding affinities, and various other chemical susceptibilities. Besides, several analytical and structural procedures have been reported in the literature for the analysis of cephalosporins in biological and pharmaceutical samples. On the other hand, a variety of synthetic strategies have been used to build polycyclic cephalosporin systems and other nuclear analogues. In addition, some other nonantibiotic applications of cephalosporins in fields ranging from enzyme inhibition to gene activation have also been discovered.

2.02.2 Theoretical Methods

The aim of this section is to extend previous accounts on this subject in CHEC-II(1996) <1996CHEC-II(1B)591>. The last decade and especially the last few years, have witnessed an explosive growth of the field, with new computational and theoretical studies being published at different levels.

It is well known that bacterial resistance to β -lactam antibiotics stems from the expression of a β -lactamase that catalyzes the hydrolytic cleavage of the substrate amide bond. Understanding the mechanisms by which β -lactamases destroy cephalosporins or penicillins is potentially vital in developing effective therapies to overcome bacterial antibiotic resistance. β -Lactamases can be classified into four different classes (A–D) according to structure. Class A, C, and D β -lactamases are serine enzymes, the serine residue acting as the nucleophile in the hydrolysis reaction. Class A β -lactamases are also known as ‘penicillinases’ on account of the ease with which they can hydrolyze penicillins, and class C β -lactamases as ‘cephalosporinases’ by virtue of their increased activity against cephalosporins. Of the four structural classes of this enzyme, metallo- β -lactamases (class B) contain zinc and other divalent cations as cofactors. Although the relative population of the class B β -lactamases is low, their broad substrate specificity and the absence of clinically useful inhibitors make pathogens with genes encoding for this enzyme a hazard to human health. A key process in the reaction mechanism of class A β -lactamases is the acylation of the active site serine by the antibiotic. Three activation processes for Ser70 (Ser, serine-OH) in the acylation mechanism for hydrolysis of cephalosporin antibiotics catalyzed by a class A β -lactamase have been studied and compared using the molecular modeling and quantum mechanics (QM/MM) approaches <2005MI103>. Theoretical results aimed at elucidating the origin of the kinetic preference for penicillins over cephalosporins characteristic of the TEM/SHV subgroup (TEM: Temoniera; SHV: sulfhydryl variable) of class A β -lactamases have been reported <2005JME780>. First, the conformational properties of the cephalosporin cephalothin were studied showing that the C-2-down conformer of the dihydrothiazine ring is preferred over the C-2-up one by ~ 2 kcal mol⁻¹ in solution (0.4–1.4 kcal mol⁻¹ in the gas phase). Second, the TEM-1 β -lactamase complexed with cephalothin was investigated by carrying out a molecular dynamics simulation. The $\Delta G_{\text{binding}}$ energy was then estimated using molecular mechanics Poisson–Boltzmann surface area (MM-PBSA) and quantum chemical PBSA (QM-PBSA) computational schemes. The preferential binding of benzylpenicillin over cephalothin is expressed by the different energetic calculations, which predict relative $\Delta\Delta G_{\text{binding}}$ energies ranging from 1.8 to 5.7 kcal mol⁻¹. The benzylpenicillin/cephalothin $\Delta\Delta G_{\text{binding}}$ energy is most likely due to the lower efficacy of cephalosporins compared to penicillins to simultaneously bind the ‘carboxylate pocket’ and the ‘oxyanion hole’ in the TEM-1 active site. It has been reported that hybrid quantum mechanical/molecular mechanical (QM/MM) simulation of the metallo- β -lactamase CcrA from *Bacteroides fragilis* complexed with the cephalosporin nitrocefin shows that the substrate β -lactam group interacts with active site zinc ions, replacing the apical water molecule upon formation of the Michaelis complex <2005JA4232>. Hybrid Car–Parrinello QM/MM calculations have been used to investigate the reaction mechanism of hydrolysis of a common cephalosporin substrate (cefotaxime) by the monozinc β -lactamase from *Bacillus cereus* <2004JA12661>. The calculations suggest a fundamental role for an active site water in the catalytic mechanism. On the basis of molecular dynamics simulations, the dynamic properties of the cephamycin-resistant dinuclear zinc metallo- β -lactamase from *B. fragilis* and its complex with a biphenyl tetrazole inhibitor, 2-butyl-6-hydroxy-3-[2’-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-3*H*-quinazolin-4-one (L-159061) have been investigated <2005JME1630>. Molecular models for the Henry Michaelis complexes of *Enterobacter cloacae*, a class C β -lactamase, with penicillin G and cephalothin have been constructed using molecular mechanic calculations, based on the assisted model building with energy refinement (AMBER) force field, to examine the molecular differentiation mechanisms between cephalosporins and penicillins in β -lactamases <2003MI442>. Accurate, large-scale mixed *ab initio* QM/MM calculations have been used to study the hydrolysis of acyl-enzyme intermediates formed between cephalothin and the DD-peptidase of *Streptomyces* sp. R61, a PBP, and the *E. cloacae* P99 cephalosporinase, a class C β -lactamase <2004JA7652>. Qualitative and, in the case of P99, quantitative agreement was achieved with experimental kinetics. A 2.6 ns dynamics simulation has been carried out for the complex of the cephalosporin 7 β -[*N*-acetyl-L-alanyl- γ -D-glutamyl-L-lysine]-3-acetoxymethyl-3-cephem-carboxylic acid bound to the active site of the deacylation-deficient Q120L/Y150E variant of the class C AmpC β -lactamase from *Escherichia coli*, which revealed that the peptidoglycan surrogate (i.e., the active-site-bound ligand) undergoes substantial motion and is not stabilized for binding within the active site <2003JA9612>.

The recent increase in resistant bacterial infections has created a critical need to develop novel antibacterial drugs that elude existing mechanisms of resistance. For this reason, many researchers worldwide have been interested in the search and evaluation of novel lead antibacterial compounds. Because the experimental tests (based on ‘trial and error’ screening; especially pharmacological and toxicological tests) are usually expensive and time consuming, the

pharmaceutical industry has reoriented its research strategy during the past two decades to the development of methods enabling rational selection or design of novel agents with the desired properties. Quantitative structure–activity relationship (QSAR) is based on the assumption that the biological activities of a chemical compound are related to, and hence characterizable by, some of its physicochemical parameters such as solubility, lipophilicity, polarity, and steric structure. Quantitative electronic structure–activity relationship (QESAR) analysis is an alternative to the QSAR concept, assuming that the biological activities of a chemical compound can be described by its electronic molecular parameters. If linearity in the dependence of the responses on the predictor variables prevails, linear regression is a simple description of the data, weighs the contribution of each predictor with a single coefficient, and provides a simple method for predicting new observations. However, this assumption of linearity does not always hold in QSAR studies, and thus some nonlinear methods were proposed as their performance was expected to be better than linear regression in such cases. For instance, the projection pursuit regression (PPR) method was applied to interpret and predict the antibacterial activity of pyridinium cephalosporins using semi-empirical quantum mechanical descriptors <1996EJM479>. This method can deal with responses due to interactions of predictors (descriptors) which cannot be completely represented by additive regression models. Based on leave-one-out cross-validation, the best PPR model gave a cross-validated r^2 or q^2 value of 0.711, whereas the traditional method, multiple linear regression, and another additive nonparametric model, alternating conditional expectations, produced the best q^2 values: 0.233 and 0.324, respectively. Its ability to provide models with good predictive ability reveals that PPR is a valuable tool in QSAR studies. The TOpological MOlecular COmputer Design (TOMOCOMD–CARDD) approach has been introduced for the classification and design of antimicrobial agents, including cephalosporins, using computer-aided molecular design <2005BMC2881>. For this purpose, atom, atom-type, and total quadratic indexes have been generalized to codify chemical structure information. In this sense, stochastic quadratic indexes have been introduced for the description of the molecular structure. These stochastic fingerprints are based on a simple model for the intramolecular movement of all valence-bond electrons.

The vast pharmaceutical and biological implications of β -lactam antibiotics have promoted a large number of studies on their chemical reactions. Special attention has been given to nucleophilic substitution reactions of the β -lactam carbonyl with hydroxyl groups; in fact, the magnitude of the kinetic constants of alkaline hydrolysis of these substances was initially used as a measure of the bactericidal power of the antibiotics. The β -lactam carbonyl of cephalosporins can also undergo other nucleophilic substitution reactions with amines, alcohols, and thiols in aqueous solution. Semi-empirical calculations were used to conduct a comprehensive study of the thiolysis of the fundamental core of cephalosporins <2005MI434>. The significance of the intramolecular protonation of the β -lactam nitrogen in the formation and cleavage of the tetrahedral intermediate was examined in two thiols bearing substituents of different basicity in β with respect to the thiol group in the attacking nucleophile, namely 2-mercaptoethanol and 2-mercaptoethylamine. Based on the results, the rate-determining step in the reaction of cephalosporins, which possess an appropriate leaving group at position 3', is the formation of the tetrahedral intermediate, so the desolvation energy of the nucleophile is a major contributor to the overall energy of the process. The theoretical results are consistent with previous experimental data showing that, unlike penicillins, cephalosporins undergo no intramolecular acid catalysis in their thiolysis. A model to predict clathrate formation of molecules with the cephalosporin antibiotic cephradine has been investigated <2001JP2981>. For this purpose, linear discriminant analysis was employed on molecular similarity data of a set of molecules comprising both complexing agents and molecules that do not form a complex with cephradine. The success of this method strongly depends on how the molecular similarity indices are calculated. Furthermore, the amount of similarity data subjected to linear discriminant analysis should not be too large as this may lead to under-determination of the model. This problem can be avoided by using the similarities of the molecules of the data set with a limited number of guiding compounds only. The ultimate result of this study is a simple equation to predict whether a compound will be able to form a clathrate with cephradine or not.

2.02.3 Experimental Analytical and Structural Methods

The aim of the following section is to give some examples of the main analytical and structural methods for the determination of cephalosporins during the last decade. Several procedures have been reported in the literature for the analysis of cephalosporins including high-performance liquid chromatography (HPLC), solid-phase extraction and capillary electrophoresis in biological or pharmaceutical samples. Spectrophotometric techniques, mass spectrometry, X-ray, infrared (IR), and nuclear magnetic resonance (NMR) have also been studied.

2.02.3.1 High-Performance Liquid Chromatography

The determination of cephalosporins has been carried out either by microbiological techniques or by HPLC. The major drawback of bioassays is the lack of specificity, especially when a biotransformation of the cephalosporin molecule leads to active metabolites, or when the antibacterial therapy is based on association with drugs. HPLC methods have been described for the determination of cephalosporins in biological fluids using different stationary phases, mobile phases with different buffer systems, mostly phosphates or ion pairing agents, detection mode, for example, ultraviolet (UV) and electrochemical and sample preparation procedures <1998JCH(A)159, 1998JCH(A)237, 1998JCH(B)145, 1998MI893, 2002MI795>. Reverse-phase separations predominate, with C₁₈ stationary phases being the most common. These separations have generally employed aqueous buffer mobile phases modified with a small percentage of either methanol or acetonitrile, with UV absorbance detection in the 220–280 nm range. All of the cephalosporins and most of their degradation products absorb in this region, and the sensitivity is reasonable.

A rapid, accurate and sensitive method for the quantitative simultaneous determination of four cephalosporins, cephalixin and cefradoxil (first-generation), cefaclor (second-generation), and cefataxim (third-generation) has been developed for pharmaceuticals as well as for human blood serum and urine <2003JCH(B)147>. Detection was performed with a variable wavelength UV-Vis detector at 265 nm resulting in a limit of detection of 0.2 ng for cefradoxil and cephalixin, but only 0.1 ng for cefotaxime and cefaclor per 20 µl injection. A linear relationship has been observed up to 8, 5, 12 and 35 ng µl⁻¹ for cefadroxil, cefotaxime, cefaclor, and cephalixin, respectively. Simultaneous determination of cefotaxime and desacetylcefotaxime in human plasma and cerebrospinal fluid has been described, requiring small volumes of biological fluids <2001JCH(B)171>. The assay involved deproteinization and subsequent separation on a reversed-phase HPLC column, with UV detection at 262 nm. The retention times obtained were 6.8 and 2.2 min for cefotaxime and desacetylcefotaxime, respectively.

2.02.3.2 Capillary Electrophoresis

In recent years, capillary electrophoresis (CE) and micellar electrokinetic chromatography (MEKC) have become important separation techniques owing to its advantageous features, such as extremely high column efficiency, small sample volumes and rapid analysis, in comparison with HPLC. CE is very suitable for analysis of cephalosporins due to their high UV absorption and their very good solubility in water, and therefore, it has been applied intensively during the last decade <1997ANC1364, 1998MI2895, 2000JCH(A)197, 2000JCH(A)439>. The cephalosporins had two UV absorption maxima both at 200 and 270 nm, whereas the plasma components exhibited UV absorption only at 200 nm in that range where the cephalosporins could be determined at 270 nm. Separation and identification of cephalosporins such as ceftiofur, cefuroxime, cefotaxim, and cefodizim have been carried out in both water and plasma <1997JCH(B)321> and have been performed at a pH value of 6. The results of these measurements showed that at pH 6 all four cephalosporins were separated from plasma and detected. MEKC has been applied to evaluate the hydrophobicity of a family of cephalosporins (ceftiofur, ceftiofur, cefazolin, ceftazidim, ceftazidim, cefuroxime, cefotaxim, cephradine, and cephalothin) <2000JCH(A)237>. Partition coefficients of cephalosporins were calculated between a micelle and an aqueous phase from the measurement of the migration time, provided the critical micelle concentration and the phase ratio were known. Thermodynamic quantities such as enthalpy and entropy changes of micellar solubilization were obtained from the temperature dependence on the partition coefficients.

2.02.3.3 Solid-Phase Extraction

The solid-phase extraction technique has been employed in order to identify and quantify cephalosporins in biological samples. This technique is rapid, simple, and generally gives good recoveries of the assessed compounds. However, the degree of polarity of the different cephalosporins varies widely and it is, therefore, difficult to develop a single extraction procedure for all of them. Analytical methods to determine conjugated residues of cephalosporins in milk <2005MI151>, in hospital sewage water <2004MI1479>, in human serum <2004MI483>, and in bovine kidney tissue <2005ANC1473> have been developed using solid-phase extraction and liquid chromatography with tandem mass spectrometry (LC-MS-MS). This technique has been used for the analysis of several cephalosporins in the treatment of urine samples <1998JCC2191>. Cephalixin, cefotaxime, cefazolin, cefuroxime, and cefoxitin have been tested with a 2M Empore extraction disk cartridges packed with octadecyl (C₁₈) bonded silica, providing clean extracts with a single extraction.

2.02.3.4 Clathration of Cephalosporins

Clathration of cephalosporins is an industrially relevant method to remove these antibiotics from aqueous reaction mixtures obtained by enzymatic synthesis from a β -lactam nucleus and a D-amino acid side chain. The complexation efficiencies for a series of guest molecules are explained in terms of both the thermodynamics of the complexation reaction and the structural features of the cephalosporin complexes. In this process, the most important parameter is the complexation efficiency, which expresses the extent to which the cephalosporins can be withdrawn from a solution. In this manner, insight is gained into the subtle relationship between the molecular structure of naphthalene derivatives and the stability of their complexes with the antibiotics <2001J(P2)633>. Zwanenburg and co-workers have studied the clathrate-type complexation of several cephalosporins with a variety of naphthalene derivatives <2001EJO3641> and disubstituted benzene derivatives <2002EJO345, 2001J(P2)981>. Cephalexin, cephradine, cefaclor, and cefadroxil form clathrates with β -naphthol in the presence of water. The crystal structures of these complexes have been determined by single-crystal X-ray diffraction and reveal that the cephalosporin nucleus plays the role of the host, while the β -naphthol is the guest molecule and water acts as a 'cementing' agent and plays an essential role in the interaction between the guest and the host molecules <1999CEJ2163>. The clathrates of cephalexin, cephradine, and cefaclor are isomorphous. Although these three cephalosporins have subtle structural differences, their complexation behavior with β -naphthol is essentially the same. The introduction of a hydroxyl group, as in cefadroxil, has a pronounced effect on the polarity and the hydrophilicity of the molecule. In addition, it has a notable steric influence at that position of the molecule. As a consequence, the cefadroxil/ β -naphthol complex is a clathrate with a different crystal structure of the cephalosporins studied. Although the host framework formed by cefadroxil is very different, the remaining cavities are quite similar, because the same guest molecule can be accommodated. In all types of structures, β -naphthol is hydrogen bonded to a water molecule. Apart from this hydrogen bond, β -naphthol has only Van der Waals interactions with both cephalosporin and water molecules.

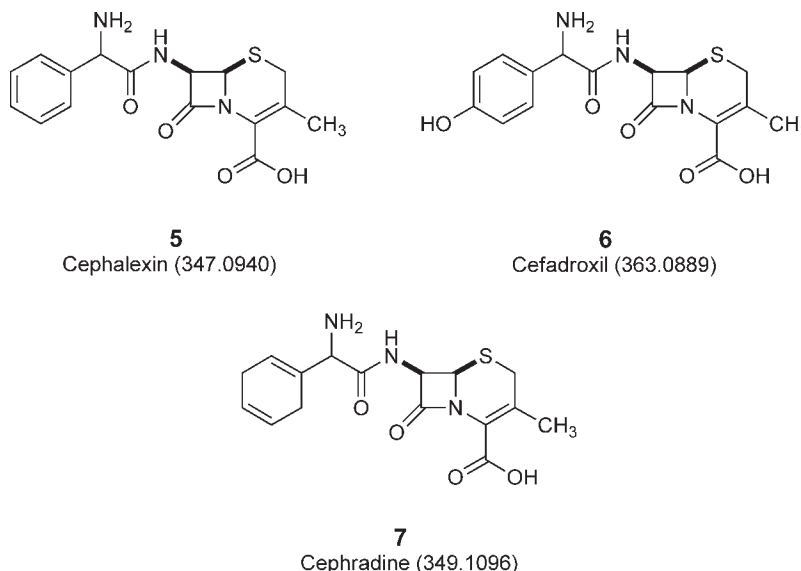
Single-crystal X-ray diffraction has provided information on the structures of four clathrates of cephalosporins (cephalexin, cephradine, cefaclor, and cefadroxil) with β -naphthol <2000J(P2)1425>. The dimensions and shapes of the hosting cavities for these complexes have been compared. The distances between three sulfur atoms, which form three corners of a parallelogram, have been measured. The distance between two sulfur atoms is a measure of the length of the cavity because the line between both sulfur atoms parallels the longest dimension of the guest molecule. The distance d has been defined between two two-dimensional (2-D) hydrogen-bonded layers of cephalosporin molecules. The values of sulfur-sulfur distances, the slip, and the distance d have been calculated. The S^1 - S^2 distance, which is in the first approximation proportional to the size of the cavity, decreases from the large guest 2,2'-bipyridyl to the smaller guests naphthalene, quinoline, and β -naphthol. Apparently, the hosting framework is able to adjust the dimensions of the cavity to match the size of the guest, in order to achieve the most favorable crystal packing. The slip and the distance d are measures for the extent that the hosting framework is using its flexibility to adjust the size and shape of the cavity. For cephradine complexes the distance d between the 2-D layers varies only marginally, 0.10 Å. On the other hand, the slip shows a considerable decrease (1.15 Å) going from the largest to the smallest guest. These observations lead to the conclusion that the adjustment of the size and shape of the hosting cavity mainly takes place by varying the slip rather than the interlayer distance.

2.02.3.5 Spectrophotometric Techniques

Several spectrophotometric and spectrofluorimetric procedures for quantitative determination of cephalosporins in either pure form or in pharmaceutical formulations have been developed. Gazy has described two procedures for the determination of cephalosporins based on the acidic oxidation of these compounds with cerium(IV) at elevated temperature, followed by measurement of the solution spectrophotometrically at 317 nm or fluorimetrically at 256 and 356 nm for the excitation and emission wavelengths, respectively <2000SPL931>. A selective fluorimetric method has also been described for the determination of three α -aminocephalosporins, cephalexin, cefaclor, and cephradine, involving acid-hydrolysis and subsequent alkalization before measurement <1996MII17>. A procedure for the spectrophotometric determination of cefotaxime <1998JCH(B)143> and cephalexin in pharmaceutical and urine samples has been described by derivatization with 1,2-naphthoquinone-4-sulfonate (NQS) in solid-phase extraction cartridges (C_{18}) using UV-Vis detection <1998MII15>.

2.02.3.6 Mass Spectrometry

Cephalosporins have been the subject of mass spectrometry investigations since 1964. The ionization method employed at that time was electron ionization (EI), which required derivatization of the polar groups present in the molecule. With this approach, clear characterization of the cephalosporins under study was achieved and the fragmentation pattern was found to be closely related to the original structure. As observed in the case of the penicillins, cleavage of the β -lactam ring was the main, common, primary fragmentation pathway, together with the side-chain amide bond and the C-3-R bond. The fragmentation pathways of three structurally similar 7 β -amino-3-deacetoxycephalosporanic acid (7-ADCA) derivatives, cephalixin **5**, cefadroxil **6** and cephradine **7**, have been evaluated <2005MI376>.

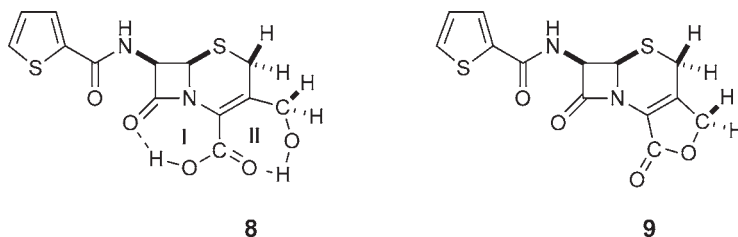


Under electrospray ionization (ESI) conditions, the three cephalosporins produced negative ions in high abundance. This phenomenon has been observed by Tenconi and co-workers in their studies of the free acid of cephradine and four other cephalosporins <1999JMP268>. The preference for negative ion formation may be ascribed to the presence of $[M-H]^-$ ions in the methanol solutions injected into the ESI source as a result of ionization of carboxylic groups. The $[M-H]^-$ ions of cephalixin at 346.0862 produced principal products ions at m/z 312.0984, 302.0932, 268.1087, 233.0381, 189.0664, and 156.0146. The fragment at m/z 189.9664 was postulated to originate from the cleavage of N(5)–C(8) and C(6)–C(7) bonds. The loss of a neutral fragment of mass 33.9878 (from m/z 346.0862 to 312.0984) corresponds to the loss of H_2S and the loss of a neutral fragment of mass 43.9899 (from m/z 346.0862 to 302.0963) corresponds to the loss of CO_2 . The fragment at m/z 156.0146 is common to all three compounds. It is also produced by the cleavage of the N(5)–C(8) and C(6)–C(7) bonds, which occurs for positively charged species of cephalosporins. Another common fragment pathway involves the loss of a neutral fragment of molecular mass 113.048, giving rise to m/z 233.0381, 249.0372, and 235.0546 in compounds **5**, **6**, and **7**, respectively. It has been speculated that this arises from the cleavage of the N(5)–C(8), N(5)–C(6), and S(1)–C(2) bonds.

2.02.3.7 IR and NMR

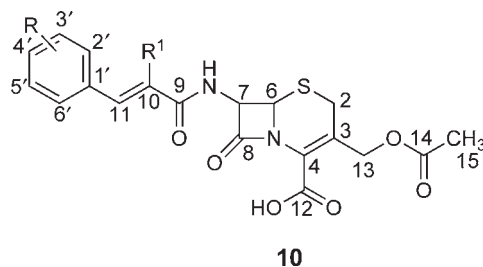
IR and NMR spectroscopy of the cephalosporin nucleus have been discussed in a general way in CHEC-II(1996) <1996CHEC-II(1B)591>. However, in this section we will focus our attention on the study of more specific cephalosporins. Solvent-dependent conformational transitions of metabolites of cephalothin, deacetylcephalothin **8**, and cephalotin lactone **9** have been compared by proton nuclear magnetic resonance (^1H NMR) and IR <1998JMT116>. Solvent effects have been measured in d_6 -DMSO (DMSO – dimethyl sulfoxide), d_6 -acetone, and in mixtures of both solvents. In cephalosporins, the magnetic resonance spectral data of the geminal protons 2- H_2 in position 2 of the dihydrothiazine ring and of protons 3- CH_2 – are a reliable source of structural information. These AB proton systems generally appear in the spectra as degenerated doublets of doublets. The hydroxyl and acidic protons 3- CH_2OH and 4- $COOH$ undergo fast exchange under the conditions applied.

In the ^1H NMR spectra of cephalothin lactone **9**, the geminal protons 2- H_2 , and also 3- CH_2O appear as singlets, unlike the remaining compounds belonging to this class, for which typical doublets of doublets of AB systems occur. This kind of magnetic equivalence in both positions 2 and 3 may be evidence of higher symmetry in this part of the molecule compared with other cephalosporins. For deacetylcephalothin **8**, the chemical shift differences in both geminal systems mentioned above are exceptionally small compared to other cephalosporins. Hence, this could point to some conformational analogies with cephalothin lactone **9**. Thus, an intramolecular hydrogen bond between the 4-carboxyl and the 3-hydroxyl groups (ring II) might be proposed, assuming that instead of the five-membered lactone ring in **9**, a seven-membered ring in deacetylcephalothin **8** is formed. As a result, the molecule could adopt a constrained, more symmetric conformation. It has been observed that in deacetylcephalothin **8**, for a solvent composition of about 12% DMSO in acetone, the 3- CH_2O protons show full magnetic equivalence and probably the highest local symmetry. The spatial dislocation of these protons with respect to the dihydrothiazine ring might be similar to those in the lactone **9**.



The infrared spectra (KBr pellet) gave evidence for the formation of ring I in the solid state. The stretching frequencies of the β -lactam carbonyl were investigated, giving essential information about intramolecular hydrogen bonding (ring I). The shifts of the carboxyl and hydroxyl bands were less specific, originating from groups which easily form both intra- and intermolecular (dimer) bonds. In cephalothin lactone **9**, the β -lactam frequency was 1785 cm^{-1} , whereas in deacetylcephalothin **8** merely 1761 cm^{-1} . The shift of 24 and 17 cm^{-1} toward lower frequencies could point to the formation of a hydrogen bond. It has been concluded that in the solid state, the simultaneous existence of both rings I and II in deacetylcephalothin **8** is conformationally favorable.

The ^1H and ^{13}C spectroscopic data for 7 β -(cinnamoyl-substituted) amino-3-acetoxymethyl-cephalosporins **10** have been fully assigned by a combination of 1-D and 2-D experiments <2005MRC261>. It has been observed that substitution on the cinnamoyl moiety has little effect on the 7-ACA ring protons and the corresponding chemical shifts are typical for cephalosporins. The CH_3 protons of the acetoxymethyl group appear in the narrow range of 2.02–2.05 ppm in all cephalosporins. The two protons on C-2 and C-13 appear in all cases as an AB system, with coupling constants of 18 and 13 Hz, respectively, indicating that these protons are not equivalent. The H-6 proton appears as a doublet at δ 5.14–5.21 ppm, with a coupling constant of 5 Hz, and the H-7 proton appears as a doublet of the doublet located between 5.77 and 5.87 ppm. The substituents on the aromatic ring do not affect the H-7 chemical shift, but the cyano and methyl groups attached to the double bond α -position of the cinnamoyl moiety produce a slight shielding of 0.08 ppm. on the H-7 signal. The signal corresponding to the amide proton (NH) appears as a doublet in the range of 8.73–9.24 ppm, with a coupling constant of 8 Hz. Electron-accepting groups in the 4' position shift this signal downfield by 0.12–0.16 ppm, whereas the 4' electron-donating groups shield the NH signal by 0.07–0.35 ppm. With the exception of the nitro group, which shifts the NH signal downfield, the rest of the substituents have little effect on this signal when they are located at the 2' and 3' positions of the aromatic ring. H-10 appears as a doublet at 6.50–6.96 ppm with a coupling constant of 16 Hz. This J value indicates that in all cases the cinnamoyl moiety is in the *trans* isomeric form. The H-11 signal appears as a well-defined doublet ($J=16\text{ Hz}$) in the range 7.40–7.82 ppm or is overlapped with aromatic protons, depending on the aromatic substitution pattern.



The ^{13}C NMR spectroscopy properties of the 7-ACA ring atoms were little affected by the substitution on the cinnamoyl moiety, and the chemical shifts of these carbon atoms are typical for cephalosporins. The carbonyl carbon of the amide group (C-9) resonates in the narrow range of 164–166 ppm. The α -cyano group produces a ~ 3 ppm upfield shift on the C-9 signal and the α -methyl group shifts the C-9 signal ~ 4 ppm downfield. Electron-accepting groups shift the C-10 signal downfield (3–4 ppm), particularly when the substituent is on the 2' position of the aromatic ring. In contrast, electron-donating substituents shift this signal upfield (~ 3 ppm), especially when they are linked to the 4' position of the aromatic ring. The signal of C-11 is little influenced by electron-accepting groups (1–2 ppm upfield shift) except when they are located on the 2' position (4–5 ppm up field). Electron-donating groups do not affect the resonance of the C-11 signal. The α -substitution on the double bond of the cinnamoyl moiety strongly affects the chemical shifts of C-10 and C-11. The cyano group has little influence on the C-10 signal but shifts the C-11 signal 10 ppm downfield. The methyl group produces a shielding of ~ 7 ppm of the C-11 signal and shifts the C-10 signal ~ 11 ppm downfield.

^{13}C NMR longitudinal relaxation times and nuclear Overhauser enhancements have been measured for two diastereomers of the 1-acetoxyethylester of cefuroxime at two magnetic fields <1998MRC559>. The relaxation parameters of ^{13}C nuclei located in the rigid core of the cefuroxime ester showed inconsistency within the frame of the relaxation model assuming axially symmetric overall reorientation and CH bond lengths derived from the PM3 method. The consistency of relaxation data was restored allowing for the increase in C–H bond lengths reflecting the influence of vibrational corrections. The diastereomers, exhibiting differences in biological activity, differ in the ^{13}C relaxation parameters of the ester moiety of the side chain. This difference has been analyzed with the aid of the model-free approach.

The metal complexation behavior of several cephalosporins has been studied by several physicochemical and spectroscopy methods, along with detailed biological investigations. Dialkyltin(IV) and trialkyltin(IV) complexes of the deacetoxycephalosporin antibiotic, cephalixin, [7-(D-2-amino-2-phenylacetamido)-3-methyl-3-cephem-4-carboxylic-acid] have been prepared and investigated in solution using ^1H , ^{13}C , and ^{19}Sn NMR spectroscopies <2004JIB534>. Another type of complexes with metal(II) salts such as $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$, CoCl_2 , NiCl_2 , CuCl_2 , ZnCl_2 , CdCl_2 , or HgCl_2 have also been obtained <2004JCR1263>. The IR spectra of cephalixin and its complexes are similar; the lactam (C=O) band appears at 1750 cm^{-1} in the spectrum of cephalixin while the amide (C=O) band appears at 1680 cm^{-1} . The complexes show these bands at 1750 and 1640 cm^{-1} , respectively, suggesting that ligand coordination occurs through the oxygen atom from the amide carbonyl group rather than the lactam carbonyl group. The amide carbonyl bands were shifted toward lower frequencies ($30\text{--}40\text{ cm}^{-1}$) relative to the value of the uncomplexed cephalixin while the lactam carbonyl bands were not shifted. The exceptions were the manganese(II) and cobalt(II) complexes, the spectra of which suggest that coordination of the ligand occurs through the lactamic carbonyl group. Comparison of the ^1H NMR spectrum of cephalixin with those of the diamagnetic complexes has shown that there is a downfield shift in the frequency of amino protons, confirming coordination of this group to the metal ions. The absence of the signal assigned to the COOH proton of cephalixin has confirmed deprotonation and has suggested the formation of a COO–metal bond. Unfortunately, due to extremely low solubility of these complexes, ^{13}C NMR spectra were not recorded.

A spectrophotometric method for the analysis of 15 cephalosporins has been developed. The method is based on the charge-transfer complexation reaction between cephalosporins as an electron donor and *p*-chloranilic acid (*p*-CA) or 7,7,8,8-tetracyanoquinodimethane (TCNQ) as a π -acceptor to give highly colored complex species. The formation of cephalosporin-*p*-CA charge-transfer complexes leads to a violet chromogen measured at 520 nm <2003MI281>. The sites of interaction have been confirmed by both IR and ^1H NMR spectroscopy techniques. The majority of IR measurements on charge-transfer complexes have concerned shifts in the vibrational frequencies in a donor or acceptor (or both). Decreases in the vibration frequency of a particular band have been used as evidence for a particular site of a charge-transfer interaction. The IR spectrum of the complexes showed that the β -lactam carbonyl band was shifted by $5\text{--}40\text{ cm}^{-1}$ compared to the spectra of the cephalosporins alone. For example, the β -lactam carbonyl was shifted from 1752 to 1779 , 1725 to 1750 , and 1740 to 1780 cm^{-1} for cefaclor, cefotaxime sodium, and cephaloridine, respectively. In ^1H NMR, generally, the protons of the donor are shifted to a lower field. ^1H NMR spectra of the complexes in $\text{DMSO-}d_6$ showed that only 6H and 7H (but not 2- CH_2) were downfield shifted ($\Delta\delta = 0.1\text{--}0.25\text{ ppm}$). The formation of cephalosporin-TCNQ charge-transfer complexes resulted in the formation of an intensive blue color, causing characteristically long wavelength absorption bands, frequently with numerous vibrational maxima in the electronic spectrum <1999MI975>.

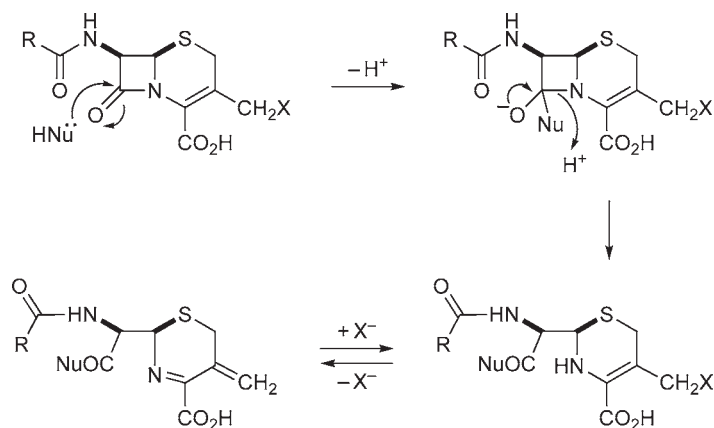
2.02.4 Reactivity of the Bicyclic System

The goal of this section is to update and extend previous accounts on this subject in CHEC(1984) and CHEC-II(1996). In particular, rearrangement and degradation of the cephalosporin core as well as dihydrothiazine ring cleavage, which were not included in CHEC-II(1996) <1996CHEC-II(1B)591> are to be presented herein.

2.02.4.1 β -Lactam Ring Cleavage

The bicyclic system in cephalosporin consists of a four-membered 2-azetidinone ring and a six-membered dihydrothiazine ring. As a result, cephalosporin suffers large angle and torsional strains. Ring opening relieves this strain by cleavage of the more highly strained four-membered lactam ring. The antibacterial effect of cephalosporins is due to their capacity to disrupt bacterial cell wall biosynthesis. β -Lactamase hydrolytic enzymes are the most common, and a growing form of bacterial resistance to their normally lethal action <2004B2664, 2004JA13945, 2004JBC9344, 2005CRV395>. β -Lactamases catalyze the hydrolysis of the strained four-membered β -lactam ring in cephalosporin antibiotics to give the ring-opened and bacterially inert β -amino acid.

The carbonyl group in the β -lactam ring is highly susceptible to nucleophiles and does not behave like a normal tertiary amide which is usually quite resistant to nucleophilic attack. This difference in reactivity is mainly due to the fact that stabilization of the carbonyl is possible in the tertiary amide, but not in the β -lactam nucleus. The β -lactam nitrogen is unable to feed its lone pair of electrons into the carbonyl group since this would require the bicyclic rings to adopt a strained flat system which is impossible. As a result, the lone pair is localized on the nitrogen atom and the carbonyl group is far more electrophilic than one would expect for a tertiary amide. Many cephalosporins bear at the C-3' position a potential leaving group (pyridine, acetate, thiol, etc.), which is expelled during the hydrolysis of the 2-azetidinone nucleus to give an *exo*-methylene cyclic imine (Scheme 1).



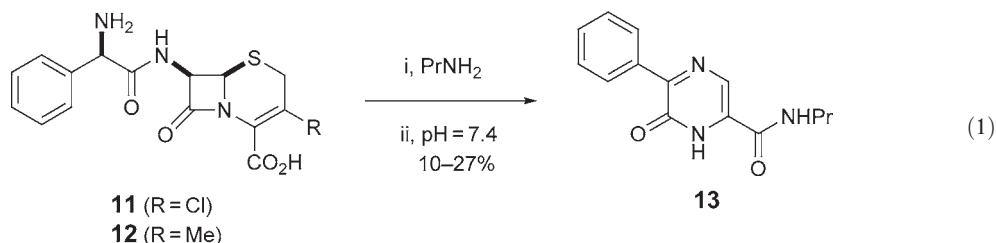
Scheme 1

Experimental observations have led to the conclusion that β -lactam C–N bond fission is not concerted with the departure of the leaving group, and that the tetrahedral intermediate breaks down by proton transfer to generate an intermediate enamine, which subsequently in a separate step expels the leaving group. For example, the rate of aminolysis of cephaloridine by hydroxylamine, unlike other amines, shows only a first-order dependence of the amine concentration <2004OBC651>. The rate enhancement compared to that predicted from a Brønsted plot for other primary amines with cephaloridine is greater than 10^4 which demonstrates that β -lactam C–N bond fission and expulsion of the leaving group at C-3' are not concerted. Exceptionally, the thiolysis of some cephalosporins appears to involve the breakdown of the tetrahedral intermediate by the expulsion of an enamine anion <2004JPO521>. The effect of replacing the β -lactam carbonyl oxygen in cephalosporins by sulfur on their reactivity has been investigated. Thioxo- β -lactams and oxo- β -lactams show a similar reactivity toward nucleophiles. However, regarding reactions of oxo- β -lactams which normally involve rate-limiting breakdown of the tetrahedral intermediate, thioxo- β -lactams may have an earlier rate-limiting step because of the slower rate of reversion of the intermediate back to reactants and so occur at a faster overall rate <2004JOC339>. It has been reported that the hydrolysis product of thioxocephalosporin, a thioacid, inhibits the *B. cereus* metallo β -lactamase competitively with a $K_i = 96 \mu\text{M}$, whereas the cyclic thioxo-piperazinedione, formed by intramolecular aminolysis of thioxocephalexin, has a K_i of $29 \mu\text{M}$ <2004BML1737>.

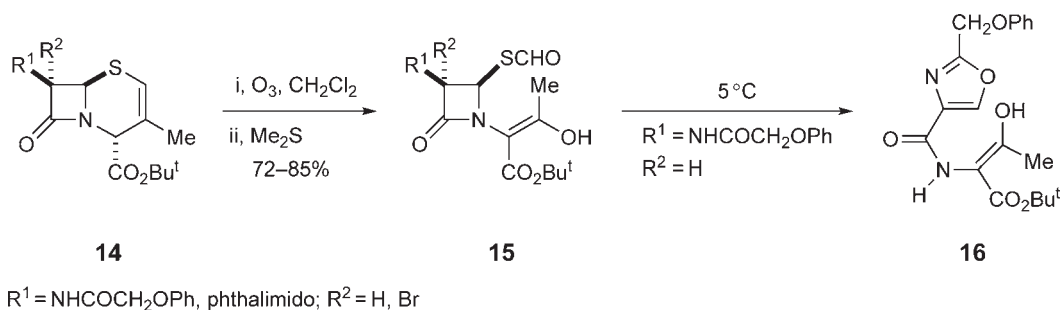
2.02.4.2 Rearrangement, Degradation, and Dihydrothiazine Ring Cleavage

Use of 2-azetidinones as building blocks in organic synthesis is now well established. However, cephalosporins have rarely been used as intermediates for the synthesis of non- β -lactam products. Cephalosporins with an α -amino group on the 7- β -acyl substituent, cefaclor **11** and cephalaxine **12**, have been aminolyzed and the initial, unstable

intermediates have been shown to degrade and finally afford a substituted pyrazinone derivative **13**, albeit in low isolated yields (Equation 1) <2001BML1869>. *In vitro* conjugation of these cephalosporins to amine-containing macromolecules such as albumin and polylysine seems to give the same pyrazinone derivative as a hapten conjugated to the macromolecules. 7 β -BOC-aminocephalosporin sulfone (BOC – *t*-butoxycarbonyl), generated *in situ* from the appropriate 7 β -aminocephalosporin and diazotized in a one-pot reaction in aqueous HClO₄–MeOH–NaNO₂, rearrange exclusively to 1,4-substituted triazoles in a multistep reaction <1998TL3061>. Open-chain aminoacrylic acid derivatives are the products from the degradation of cephalosporins under the influence of mercury(II) trifluoroacetate in methanol <2000OL103>.



The ozonolysis of Δ^2 -cephem derivatives **14** to obtain functionalized 4-(formyl)thio- β -lactams **15** has been described <1996T10205>. It is interesting to note that this ozonolysis was very selective. In fact, only a little amount of the corresponding sulfoxide was isolated, showing that the possible sulfur atom oxidation and double bond isomerization were uncompetitive reactions with the dihydrothiazine ring cleavage under these experimental conditions. Some compounds **15** were stable for only a few days when stored at 5 °C under a nitrogen atmosphere, and the oxazole derivative **16** was the only detectable degradation product (Scheme 2). An unusual nucleophilic ring opening of the 2-azetidinone nucleus and the displacement of the whole (formyl)thio moiety may be important steps in the formation of **16**.

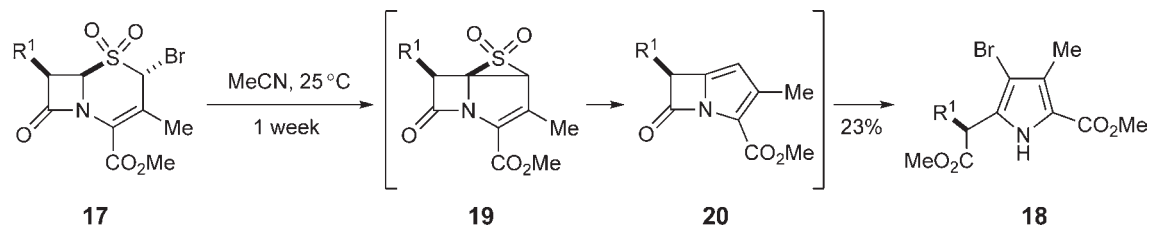


Scheme 2

A sequential reductive ring-opening/recyclization reaction of 3-heterosubstituted Δ^3 -cephems into 2-*exo*-methylene-penams and/or 2-methylpenams was performed by treatment with Al–BiCl₃–AlCl₃ in *N*-methylpyrrolidone (NMP) <1997CL1221>. It is likely that an elimination of the C-3-heterosubstituent with concomitant dihydrothiazine ring cleavage leading to an intermediate allenecarboxylate and then an intramolecular Michael-type addition takes place. A radical rearrangement approach for the conversion of cephalosporins to carbacephems has been reported <2000T5679>. The crucial bond construction in the assembly of the carbacephem framework was accomplished by intramolecular C–C bond formation between an azetidin-2-one-4-yl radical and a pendant diene ester. This reactive intermediate was generated by dihydrothiazine ring cleavage of a cephem-derived radical followed by loss of sulfur dioxide. Chlorinolysis of the dihydrothiazine ring of cephalosporins followed by reconstruction of the isomerically modified skeleton through a ring-closure step has been used for the epimerization of the stereogenic center at C-6 <1999CC253>.

2 α -Bromocephem sulfone **17** exhibited a novel rearrangement in an acetonitrile solution to afford the bromopyrrole derivative **18**, which can possibly be attributed to an unusual Ramberg–Bäcklund-like rearrangement followed by bromination (Scheme 3) <1998T6565>. It is interesting that among the investigated solvents, the formation of **18**

was only observed in acetonitrile solution: SO_2 and HBr elimination instead of electrophilic bromination. A reason for this may lie in the interaction of acetonitrile and the bromonium ion: acetonitrile may interact with the ion and stabilize it to some extent with the aid of its $\text{C}\equiv\text{N}$ π -bonds or the lone pair of the nitrogen. This may decrease the reactivity of the bromonium ion toward the aromatic ring. The resulting ionic transition product may initiate an 'inverse' Ramberg–Bäcklund rearrangement: instead of the usual replacement of the halogen by a β -carbanion, now the anion resulting from the halogenium loss would expel the β -hydrogen. In such a process the hydrogen should leave in the form of a hydride ion, which should be considered very unlikely *per se*. However, the $\text{Br}^+-\text{CH}_3\text{CN}$ complex could facilitate the expelling of the C-6 hydrogen, leading to **19**. Thus, formally a HBr 1,3-elimination takes place. After the SO_2 elimination, the highly strained pyrrole- β -lactam fused ring system **20** cleaves very easily, yielding a monocyclic pyrrole, which, in turn, is brominated to the end product **18**.



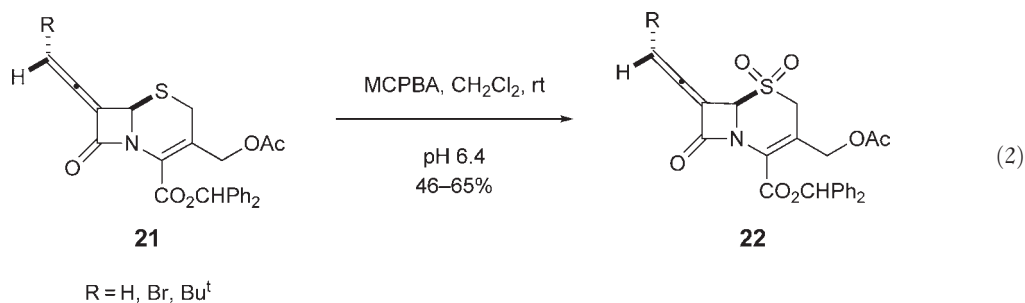
Scheme 3

2.02.5 Reactivity of the Substituents Attached to the Cephalosporin Core

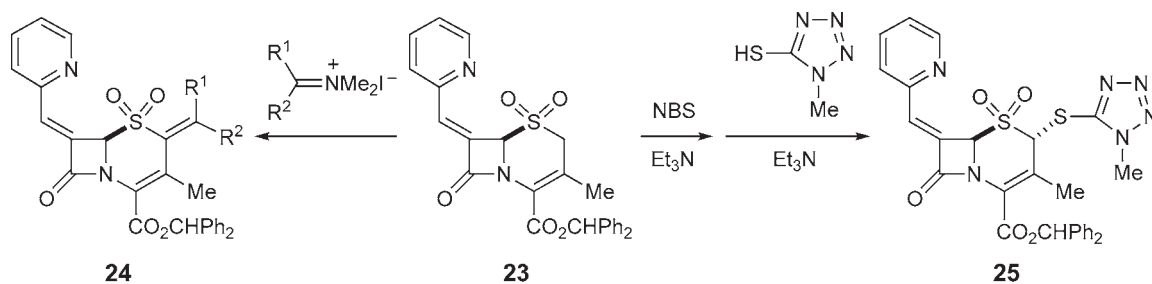
2.02.5.1 S-1 and C-2 Modification

Cephalosporins in the sulfoxide or sulfone oxidation states can easily be obtained by treatment with different oxidants. This sulfur oxidation is usually accomplished for one of the following reasons: (1) sulfoxide formation to obtain reactive intermediates for further transformations; (2) sulfoxide formation with subsequent reduction in cephems to shift the double bond from position 2 to position 3; (3) preparation of sulfones as β -lactamase or elastase inhibitors.

Oxidation of 7-vinylidenecephalosporins **21** with peracids afforded the corresponding sulfones **22** (Equation 2). These 7-vinylidenecephalosporin sulfones, as their benzhydryl esters, have been tested as inhibitors of both porcine pancreatic elastase and human leukocyte elastase <1997JME3423>. 1,1-Dioxo-7 α -methoxy-3-methyl- Δ^3 -cephem-4-yl phenyl ketone, a valuable precursor of potent HLE inhibitors, was obtained from the cheap and commercially available 7-ADCA encompassing smooth sulfide to sulfone oxidation with MCPA among others steps <1998SL319>. 3-Substituted 7-alkylidenecephem sulfones have been prepared and tested as β -lactamase inhibitors <2001OL2953, 2002BML1663>. The lithium diisopropylamide (LDA)-generated anions of cephalosporin sulfoxides may give rise to a mixture of C-2- and/or C-4-substituted products owing to the delocalized nature of the negative charge. Under optimized conditions 2 α -crotonoyl- and 2 α -cinnamoylcephalosporin sulfoxides were obtained in satisfactory yields, and are useful starting materials for cycloaddition reactions leading to novel analogues with β -lactamase or human leukocyte elastase (HLE) enzyme-inhibiting properties <1999J(P1)721, 2003HCA50>.



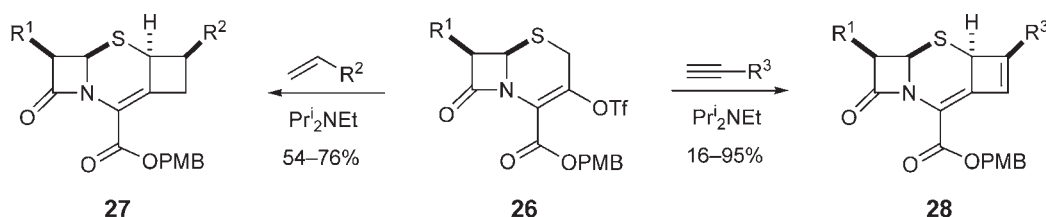
2-Substituted-7-(alkylidene)cephalosporin sulfones **24** and **25** were prepared from 7-(alkylidene)cephalosporin sulfone **23** as is shown below, and evaluated as β -lactamase inhibitors <2000BML847>. Sulfone **23** was treated with Eschenmoser's salt to produce the 2-exomethylidene cephems **24** (Scheme 4). Alternatively, the incorporation of heteroatom substituents at C-2 was accomplished by sequential reactions of compound **23** with *N*-bromosuccinimide (NBS) and 5-mercapto-1-methyltetrazole to afford the thiotetrazolecephalosporin sulfone **25** (Scheme 4). Treatment of 3-methyl-3-cephem sulfone with sodium hydride followed by carbon disulfide and alkyl halides provides an entry to 2-(1,3-dithiolan-2-ylidene)cephem derivatives, which are new potent inhibitors of human sputum elastase (HSE) <1996BML823>. The regiospecific bromination of cephalosporin sulfones at C-2 with cyanogen bromide and subsequent reactions of the corresponding 2 α -bromocephalosporin derivatives have been accomplished <1997SC3395>.



R¹ = H, SMe; R² = H, SMe

Scheme 4

C(2)–C(3) fused polycyclic cephalosporins have received considerable attention as new candidates for β -lactam antibiotics. An access to tricyclic cephalosporins based on metal-promoted alkenylation of 3-trifloxy- Δ^3 -cephem and subsequent Diels–Alder reaction has been published <1996TL5967>. Alternatively, the reaction of a cephalosporin triflate with silyl enol ethers and silylketene acetals has been described to afford tri- and tetracyclic cephalosporins <1996TL7549>. A related process is the formation of fused polycyclic cephalosporins **27** and **28** bearing a wide range of functionalities from the reaction of cephalosporin triflates **26** with unsaturated compounds (alkenes and alkynes) and a base (Scheme 5) <1997JOC4998>. These studies have suggested that the reaction proceeds via the intermediacy of a six-membered cyclic allene which undergoes concerted $\pi 2_s + \pi 2_a$ cycloaddition with alkenes and acetylenes.



R¹ = NHCOCH₂Ph, NHCOPh; R² = H, Bu, cyclopropyl, cyclohexyl, Ph, OEt, OAc, SPh, CN, CO₂Me;
R³ = H, Bu, Ph, CH₂OH, CH₂Br, OEt, SiMe₃, CO₂Me

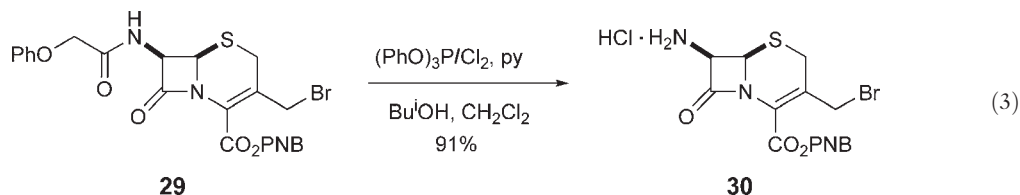
Scheme 5

2.02.5.2 C-7 and 7-Amino Modification

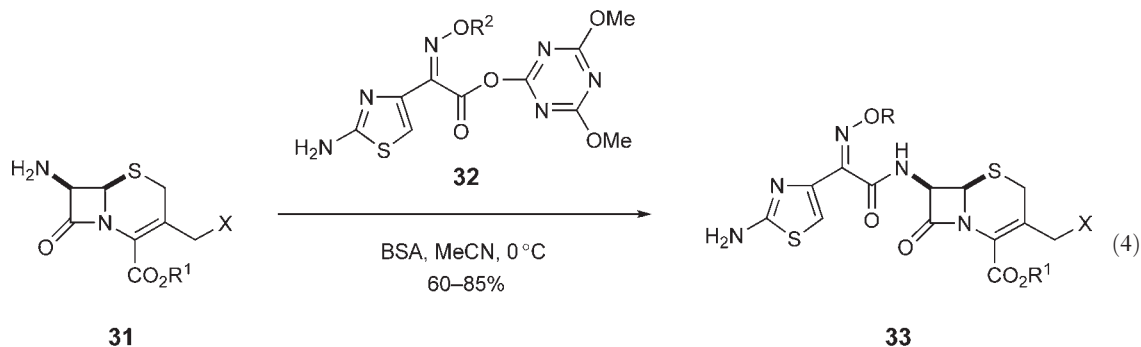
The study of several analogues of CPC with varying side chains at the 7-position has demonstrated that the best activity is obtained if the α -carbon is monosubstituted. Besides, lipophilic substituents on the aromatic ring increase the Gram-positive activity and decrease the Gram-negative activity. However, access to analogues of CPC by variation of the 7-acylamino side chain initially posed a problem. Until recently, it proved impossible to obtain

cephalosporin analogues by fermentation or by enzymatic hydrolysis of CPC <B-2004MI179>, thus preventing the semisynthetic approach analogous to the preparation of penicillins from 6-aminopenicillanic acid (6-APA). Therefore, the reported methods to obtain 7-ACA from CPC rely on chemical hydrolysis which is not an easy task <1996CHEC-II(1B)591>.

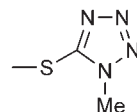
The $(\text{PhO})_3\text{P}/\text{Cl}_2$ reagent, prepared *in situ* by titrating a solution of triphenyl phosphite with chlorine, was used to convert the phenoxyacetamido cephalosporin (cephalosporin V) derivative **29** into the 7-amino derivative **30** (as an easily filterable hydrochloride) in excellent yield (Equation 3) <2004OL3885>. A 7-formamido cephalosporin was deformylated with concentrated HCl to yield the corresponding 7-amino compound <2000BMC2317>.

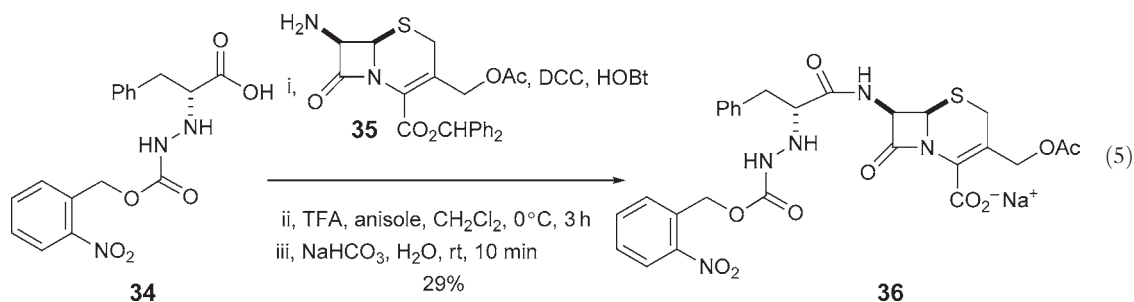


Activated esters obtained from 2-chloro-4,6-dimethoxy-1,3,5-triazine have been documented as new effective and convenient coupling reagents for cephalosporins <1998SC1339>. Treatment of 7-ACA derivatives **31** with these active esters **32** gives the acylated cephalosporins **33** after washing the reaction mixture with dilute acid and then with a sodium hydrogen carbonate solution (Equation 4). Related derivatives were obtained using acid chlorides or carboxylate sodium salts instead of the above activated esters <2000BMC43, 2003BMC591>. It has been described that the coupling of a cinnamoyl moiety to the 7-ACA cephem nucleus provides cephalosporins with selective activity against Gram-positive bacteria <2003BMC265, 2004EJM657>. A variety of cephalosporins bearing carboxylic acid substituents that have different linkers between the dichloroaryl ring and the carboxylate at C-7 have been obtained <2003BMC281>. The synthesis and *in vitro* activity of cephalosporins with hydroxamic acid at the 7-position have been described <1996BML2077>. Incorporation of a basic aminopyridine into the C-7 position of 3-(aminosubstituted arylthio)-3-norcephalosporins afforded high potency against methicillin-resistant *Staphylococcus aureus* (MRSA) and acceptable solubility for intravenous administration <2001BML137>. The synthesis of cephalosporin-type antibiotics by coupling of their β -lactam nucleus and racemic amino acid side chains using a clathration-induced asymmetric transformation has been documented <2001EJO1817>. Dicyclohexylcarbodiimide-promoted coupling between the acid **34** and compound **35**, the diphenylmethyl ester of 7 β -aminocephalosporanic acid, followed by removal of the diphenylmethyl group with trifluoroacetic acid (TFA) resulted in a new type of β -lactam antibiotic, sodium 7 β -[(*R*)-2-(*N*^{*o*}-nitrobenzyloxycarbonyl)hydrazino-3-phenylpropanamido]cephalosporanate **36** (Equation 5), which undergoes light-induced destruction of its β -lactam moiety and hence becomes biologically inactive <2000JME128>. This type of antibiotic holds the promise of self-destruction over a number of hours of exposure to light, so that it would not allow selection of resistance in the environment.

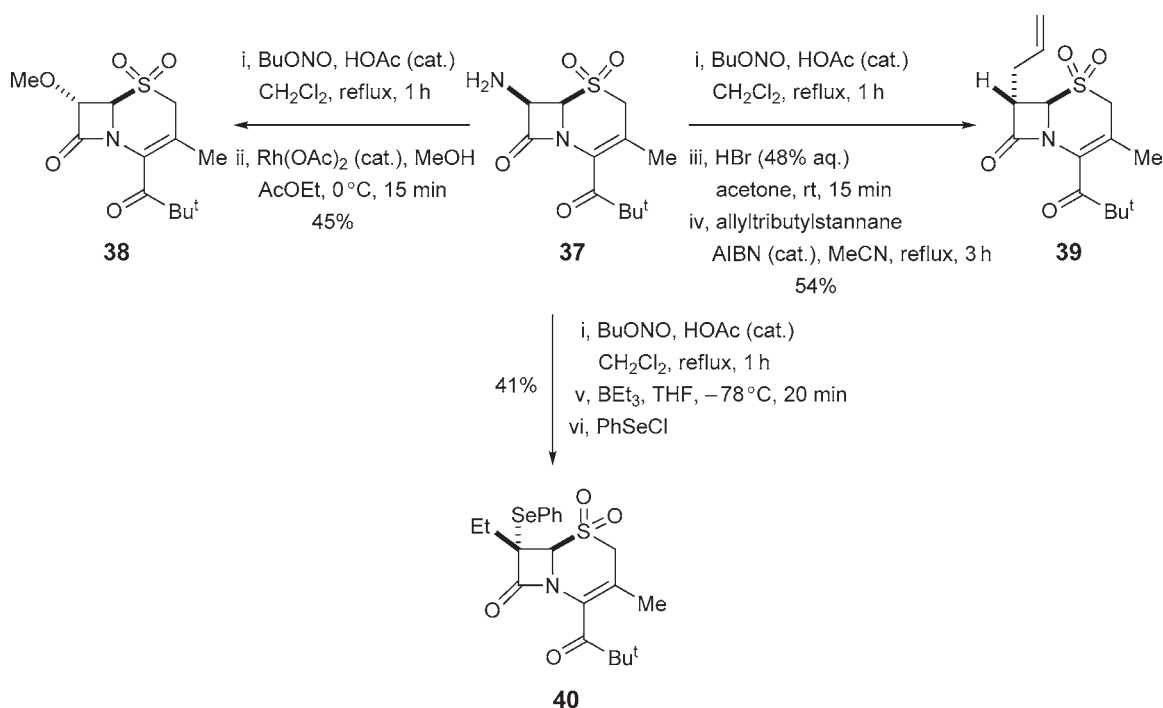


$\text{R}^1 = \text{H, Na; R}^2 = \text{H, Me, CH}_2\text{CO}_2\text{Bu}^t, \text{C}(\text{CH}_3)_2\text{CO}_2\text{Bu}^t; \text{X} = \text{OAc, } -\text{CH}=\text{CH}_2,$



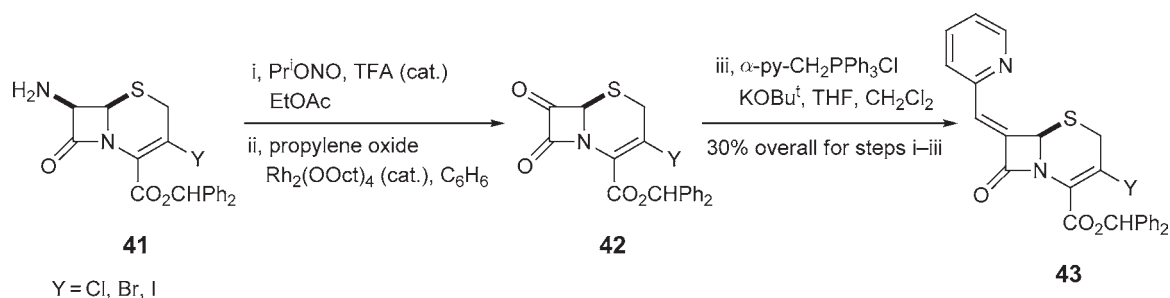


The synthesis and inhibitory activity toward human leukocyte elastase of new 7 α -methoxy and 7 α -chloro (2-acyloxymethyl)cephem derivatives have been reported [<2001EJM185>](#). Starting from 4-(*tert*-butylcarbonyl)-7 β -amino-3-methyl- Δ^3 -cephem 1,1-dioxide **37**, a practical and efficient route leading to the synthesis of 4-(*tert*-butylcarbonyl)-7 α -methoxy-3-methyl- Δ^3 -cephem 1,1-dioxide **38**, a key intermediate in the preparation of potent inhibitors of mammalian serine proteinases, has been reported [<1998SL322>](#). The new synthetic pathway has allowed easy access to an array of 7-substituted cephem derivatives such as **39** and **40** (Scheme 6).

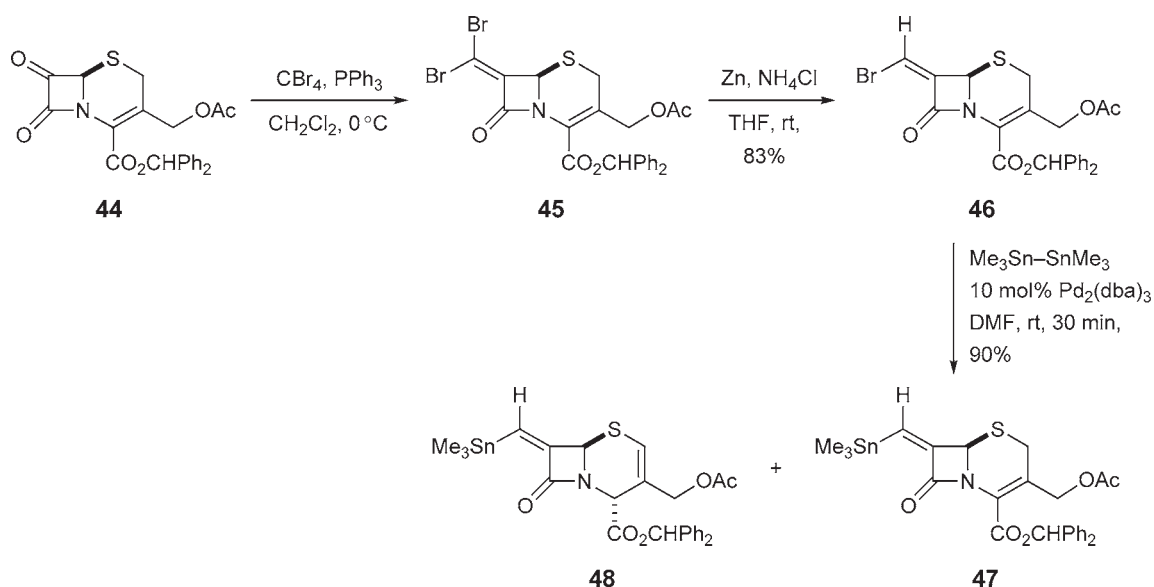


Scheme 6

Amines **41** were converted to the 7-oxocephalosporins **42**, which are direct precursors of C-7 alkylidene cepheams **43** using the Wittig reaction (Scheme 7) [<2000BMC1033, 2001OL2953, 2002BML1663>](#). Ketones **42** are not purified because of their instability [<1998TL4945>](#). Dibromide **45**, which is readily prepared from 7-oxocephalosporanate **44**, reacted with zinc/NH₄Cl to produce *E*-monobromide **46** in 83% yield. 7*E*-Bromomethylidenecephalosporin **46** was then coupled with hexamethylditin to yield the corresponding stannilated *E*-substituted alkylidenes, as shown in Scheme 8 [<1999TL1281, 2000T5709>](#). The reaction was stereospecific, with retention of configuration at the 7'-position. However, it was complicated by a concurrent partial isomerization of the dihydrothiazine double bond from the Δ -3,4 (cephalosporin numbering) to the Δ -2,3 position, forming a separable mixture (3:1) of **47** and **48** as shown in Scheme 8.



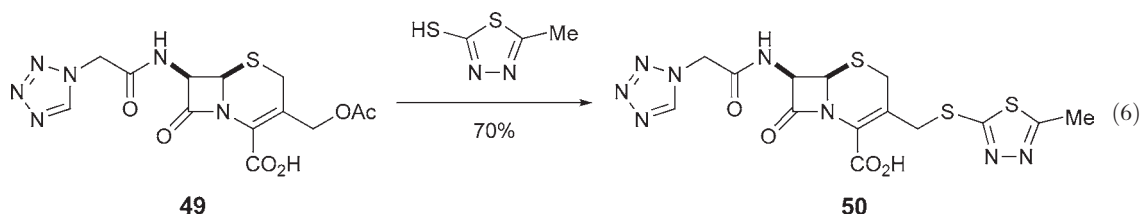
Scheme 7



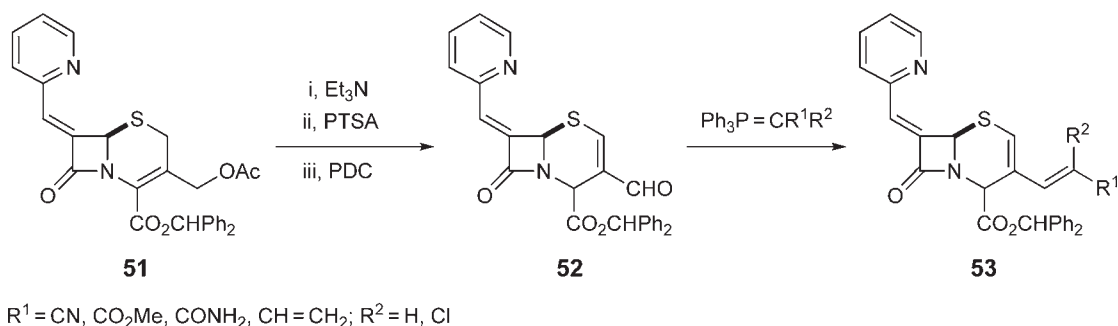
Scheme 8

2.02.5.3 C-3 and C-10 (C-3') Modification

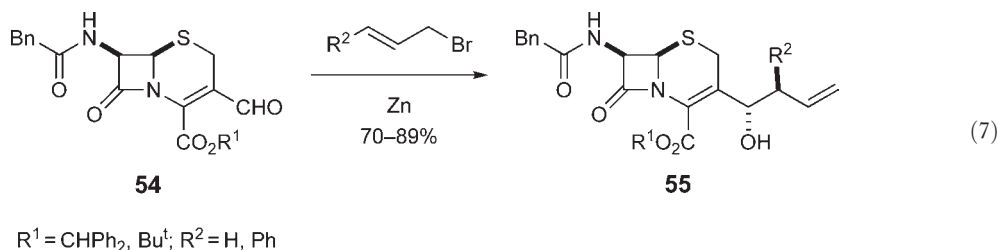
The chemical modifications of the C-3'-substituent have mainly relied on the replacement of the acetoxy group of 7-ACA or the halides of 3-(halomethyl)- Δ^3 -cephems with heteroatom nucleophiles. Transformations of 3-acetoxy-methyl cephalosporins are of central importance <2004MI93>. The first observation which can be made about this area of the molecule is that losing the 3-acetyl group releases the free alcohol group and results in a drop of activity. However, if the correct 7-acylamino group is present, then activity can be retained <B-2001M1>. Diphenylmethyl cephem alcohols were acylated by 2-chloroethyl isocyanate in pyridine to give a mixture of Δ^3 - and Δ^2 -cephems, the Δ^3 -cephem isomer being the major product <1996T5983>. 7-[(1*H*-Tetrazol-1-yl)acetamido]-3-(acetoxy-methyl)- Δ^3 -cephem-4-carboxylic acid **49** was used as an intermediate for the cefazolin **50** synthesis by direct displacement of the 3'-acetoxy group displacement with 2-mercapto-5-methyl-1,3,4-thiadiazole (Equation 6) <1997JOC9099>. Related derivatives having the free C-7-amino moiety have been prepared using a microwave-assisted method <1999CL487>. C-3-Substituted triazolylmethyl cepems can be synthesized by the nucleophilic displacement of the acetoxy group of 7-ACA with various mercapto-1,2,4-triazoles by heating either in an acetone/water mixture or in a phosphate buffer <1996EJM301>.



Oxidation of alcohols obtained from acetate hydrolysis of 3-acetoxymethyl cephalosporins allows preparation of the corresponding 3-formyl or 3-carboxycephalosporins <2001EJO2529>. 3-Formylcephalosporins can suffer further transformations such as the Wittig olefination (Scheme 9) or Barbier-type allylation (Equation 7). Cephalosporanate **51** suffered sequential Δ -3,4 to Δ -2,3 isomer equilibration, acetate hydrolysis, and oxidation to afford aldehyde **52**, which reacted with Wittig reagents to produce the alkenes **53** <2000BML853>. The allylation of 3-formylcephalosporins **54** under zinc-mediated, aqueous Barbier conditions, allowed the obtention of the corresponding homoallylic alcohols **55** in good yields and diastereoselectivities <2003EJO1749>.

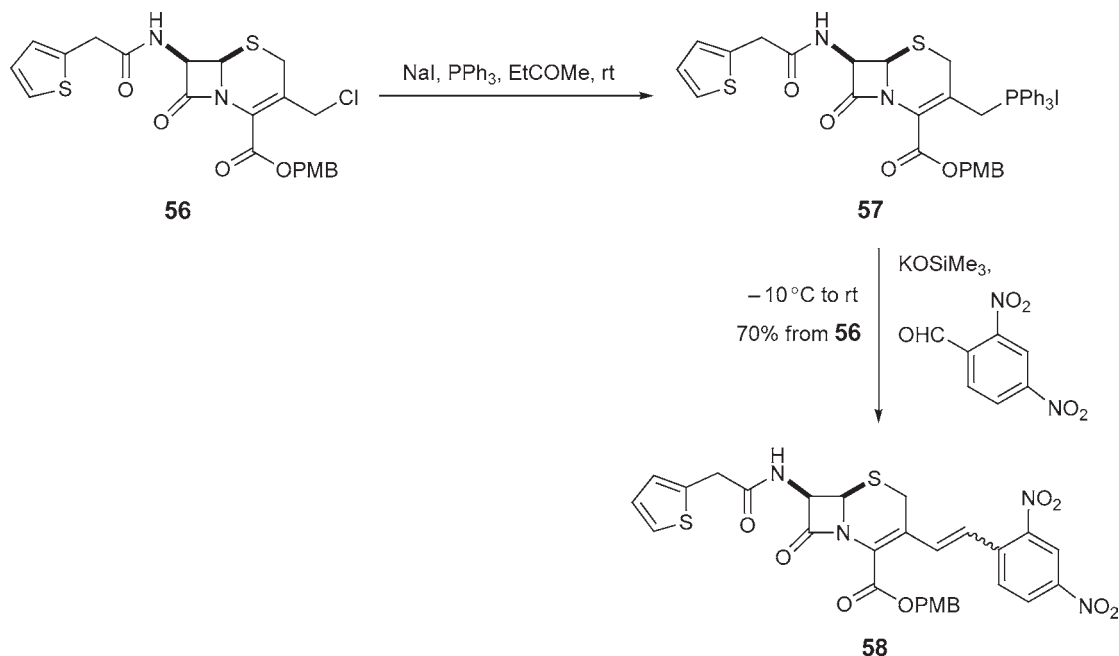


Scheme 9



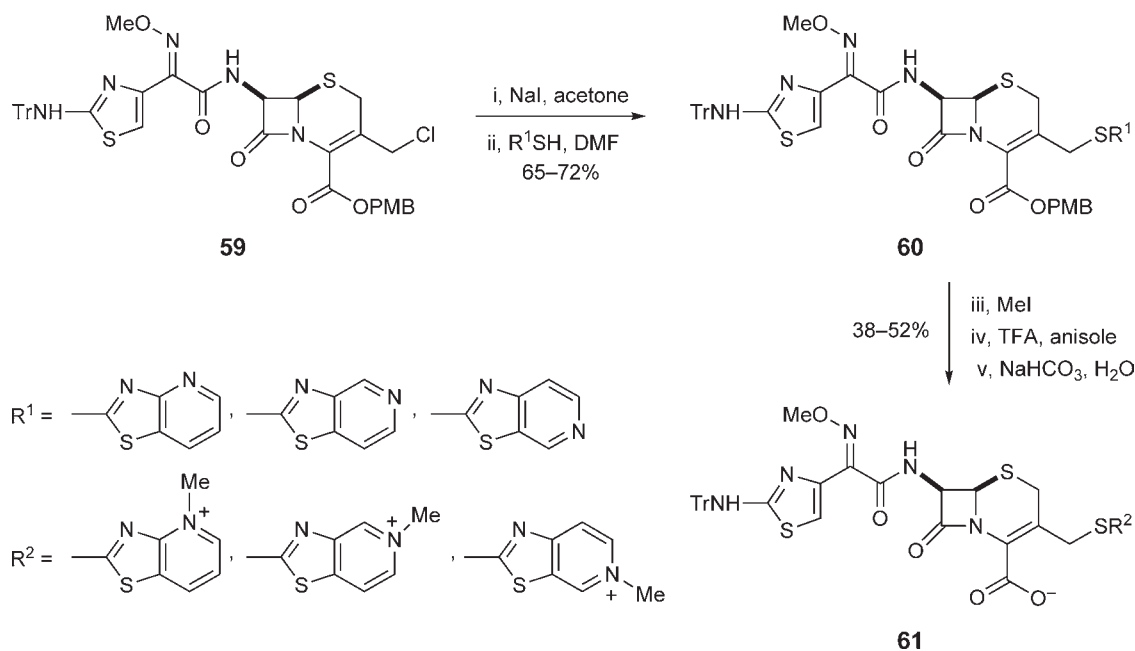
The synthesis of 3-halomethyl cephalosporins can be achieved both via substitution reactions in 3-acetoxy(hydroxy)methyl cephalosporins as well as through halogenation of deacetoxycephalosporins. Bromination at C-3' on *t*-butyl Δ^3 -cephalosporanate was performed, through a radical mechanism, using NBS to produce the corresponding bromide, which due to its instability, was rapidly oxidized to the appropriate bromocephem sulfone <2001EJO3075>. A related photoinduced bromination has been carried out on cephem sulfones <1997BML843>. These 3-halo derivatives usually act as building blocks for more complex derivatives. For example, the 3-chloromethyl cephalosporin **56** has been used for the preparation of nitrocefins <2005JOC367>. The chloro moiety of **56** was converted to the iodo moiety by the Finkelstein reaction, which was allowed to undergo reaction with triphenylphosphine *in situ* to result in **57**. The Wittig reaction of compound **57** with 2,4-dinitrobenzaldehyde was carried out in the presence of potassium trimethylsilanolate (KOSiMe₃) to afford a 7:1 mixture of *Z*:*E* isomers **58** (Scheme 10). A related route for the synthesis of 7-substituted-3-dinitrostyryl cephalosporins and their ability for detecting extended spectrum β -lactamases has been published <2005JAN69>. A 3-chloromethyl cephalosporin

related to **56** has been used for the synthesis of a novel fluorogenic substrate for imaging β -lactamase gene expression <2003JA11146>. The Wittig protocol has been used as well for structural modifications of 3-isoxazolylvinylcephalosporins <2000T5657> and for the preparation of 3-(3-chloropropenyl)cephalosporins <2000JAN1305>.



Scheme 10

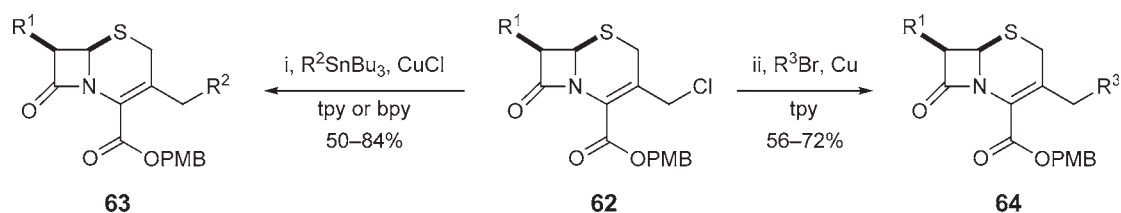
Cephalosporin derivatives bearing a heterocyclic ring, in particular with a quaternary ammonium moiety, at the C-3' position showed enhanced antibacterial activity <1997BML2753, 2001JAN460>. Therefore, considerable effort has been directed toward the preparation of these compounds. Most of these syntheses rely on the nucleophilic displacement of a 3-chloromethyl cephalosporin. Compound **59** has been converted into the sulfides **60** through the corresponding iodide intermediates by substitution with 2-mercaptothiazolo[4,5-*c*]pyridine, 2-mercaptothiazolo[5,4-*c*]pyridine, and 2-mercaptothiazolo[4,5-*b*]pyridine, respectively <1998BMC1641>. These sulfides were subjected to quaternization of the thiazolopyridine group at the 3'-position via methylation with methyl iodide followed by deprotection using trifluoroacetic acid and anisole to afford the final compounds **61** (Scheme 11). Cephalosporin derivatives containing a unique combination of lipophilic C-7 side chains and polar C-3 thiopyridinium groups were synthesized and found to exhibit potent *anti*-MRSA activity *in vitro* and *in vivo* <2000T5687>. The optimum C-7 side chains utilized were 2,5-dichlorophenylthioacetamido and 2,6-dichloropyrid-4-ylthioacetamido. The C-3 thiopyridinium rings were substituted at nitrogen with amino acid and pyruvic acid groups that were designed to confer aqueous solubility as required for IV formulation. A series of cephalosporins bearing a 5,5-fused ring system, an (imidazo[5,1-*b*]thiazolium-6-yl)methyl group, at the C-3 position were synthesized and evaluated for *in vitro* antibacterial activities, showing potent antibacterial activities against Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa* <2000BMC2781>. A set of substituted thiopyridinium cephems exhibiting excellent activity against MRSA *in vitro* and *in vivo* has been synthesized via thiopyridones derived from either acyclic precursors or direct alkylation of 2,6-dimethylpyran-4-one <2001BML797>. The synthesis and *in vitro* antibacterial activity of 7 β -[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido] cephalosporins bearing various 2-alkyl-3-aminopyrazolium groups at the 3-position have been described <1997BMC1685>. Antibacterial activity against MRSA was affected by the nature of the substituent at the 2-position on the 3'-aminopyrazolium groups. A series of novel cephalosporin derivatives, 7 β -[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(*Z*)-ethoxyiminoacetamido]-3-[1-(aminoalkyl)-1*H*-pyrazolo[4,3-*b*]pyridinium-4-yl]methyl-3-cephem-4-carboxylates, showed potent activity against both MRSA and *P. aeruginosa*, and displayed good water solubility <2004BMC4211>. 3-[*N*-Methyl-*N*-(3-methyl-1,3-thiazolium-2-yl)amino]methyl cephalosporin derivatives possessed a well-balanced broad spectrum and potent antibacterial



Scheme 11

activity [<2000BML1143>](#). A broad-spectrum S-3578-related cephalosporin, 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoxyiminoacetamido]-3-[1-(3-methylamino-propyl)-1H-imidazo[4,5-*b*]pyridinium-4-yl]methyl-3-cephem-4-carboxylate sulfate has been regioselectively synthesized in good yield using a diaminopyridine derivative bearing a dimethylformamidinium group [<2004H\(63\)1757>](#).

The reaction of 3-(chloromethyl)-Δ³-cephem **62** with organotin in the presence of copper(I) chloride, and the related copper(0)-promoted coupling reaction of **62** with allyl and benzyl bromides have been investigated [<1997JOC3782>](#). It was found that both reactions could be achieved only in the presence of terpyridine (tpy) or bipyridine (bpy) as a ligand, to afford 3-alkyl-Δ³-cephems **63** and 3-(arylalkyl)-Δ³-cephems **64**, respectively (Scheme 12).

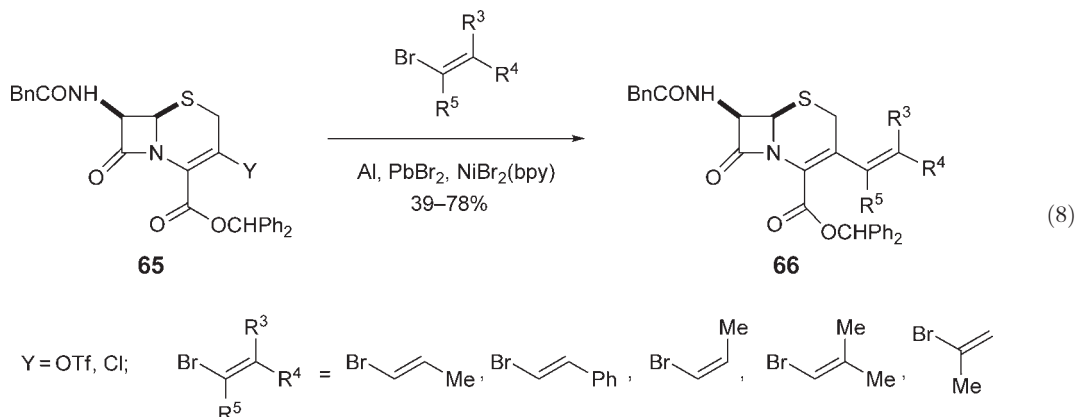


R¹ = BnCONH; R² = allyl, allenyl, styryl, vinyl; R³ = allyl, benzyl, 4-Br-benzyl, 4-NO₂-benzyl

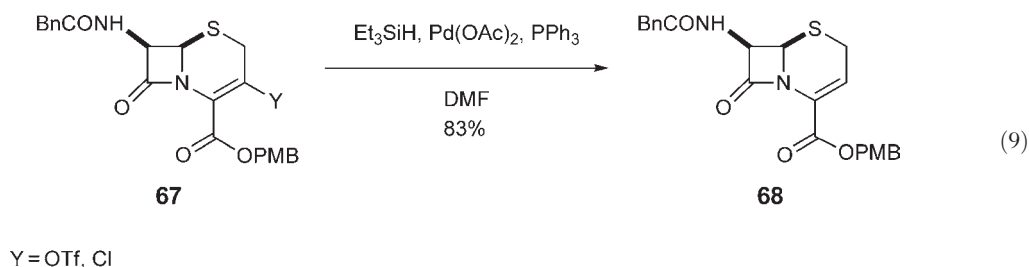
Scheme 12

3-Halo, 3-triflyoxy, or 3-mesyloxy cephem derivatives are key intermediates for further transformations. In particular, they are useful building blocks both for incorporating carbonated side chains at C-3 through cross-coupling reactions, as well as for the introduction of substituents bearing heteroatoms. Displacement of 3-triflyoxy cephem derivatives with LiBr produced the corresponding bromides that could be coupled with pregenerated Burton's reagent (CF₃Cu) to give 3-trifluoromethyl cepheems [<1998BML1261>](#). Several cepheems bearing vinyl sulfoxide and sulfone moieties at C-3 were prepared by the Stille coupling of a 3-triflyoxy cephem with stannanes [<1996BML1613>](#). The cross-coupling between 3-(trifluoromethylsulfonyloxy or chloro)-Δ³-cephem **65** with

alkenyl halides, for example, vinyl bromide, *trans*-1-bromo-1-propene, and *trans*- β -bromostyrene in an Al/cat. PbBr₂/cat. NiBr₂(bpy)/NMP (or DMF) system allowed the synthesis of 3-alkenyl- Δ^3 -cephems **66** <2001JOC570> (Equation 8).



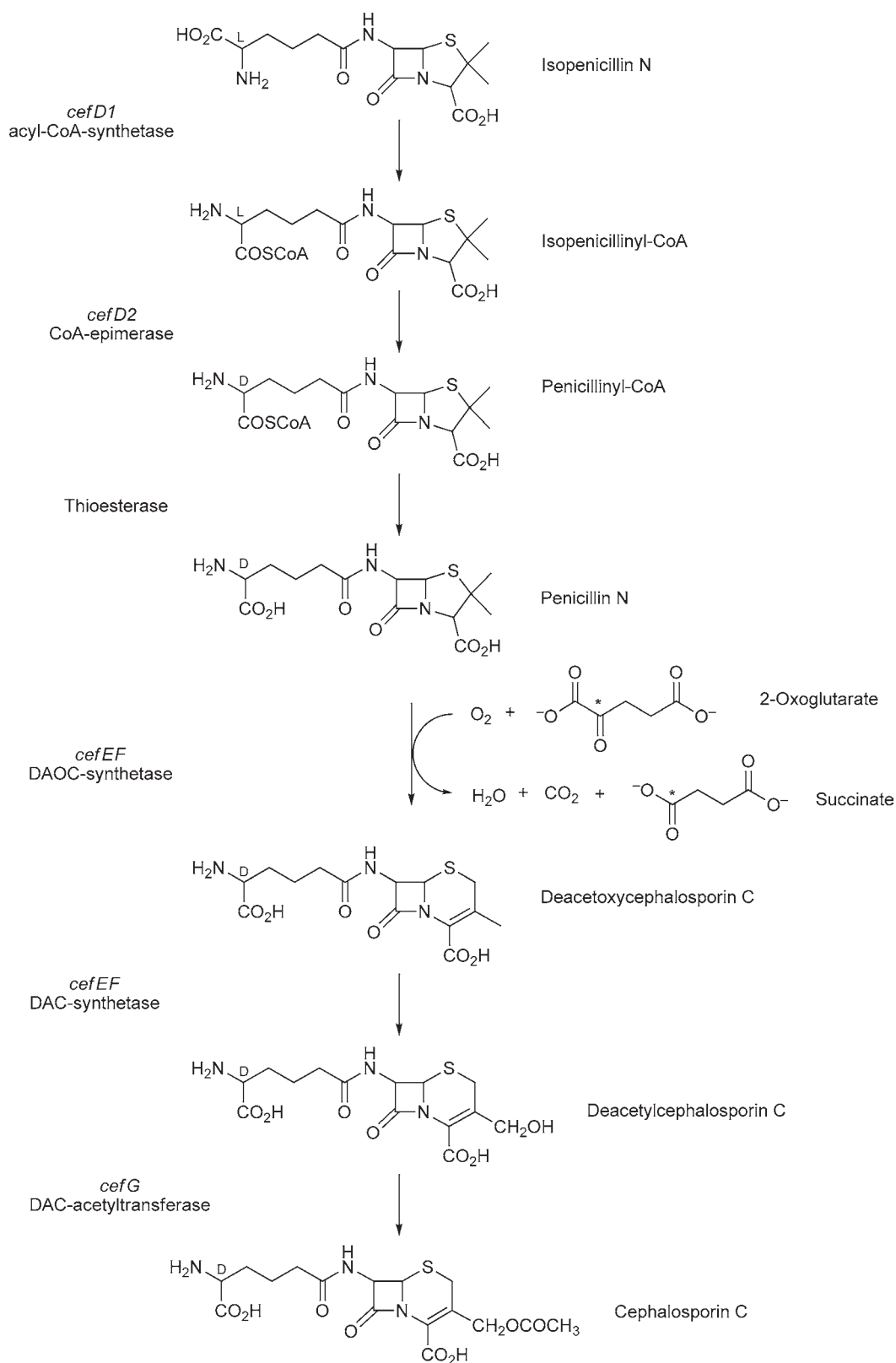
The reduction of 3-chloro or 3-trifloxy cephem derivatives **67** using Et₃SiH as the hydride source and a catalyst generated *in situ* from Pd(OAc)₂ and triphenylphosphine (TPP), allowed a high-yield synthesis of the ceftizoxime key intermediate **68** <1997TL3291> (Equation 9). 3-Heteroarylthio cephalosporins have been prepared from 3-methanesulfonyloxy or 3-trifloxy cephalosporins through the reaction with substituted thiols <1997BML2261, 1999BML3123, 2000BML2123, 2001BMC465, 2004JAN468>. 1,3-Dipolar and Diels–Alder cycloaddition reactions of a 3-(1,3-butadienyl)cephalosporin and the antibacterial activity of the obtained new cephem derivatives have been reported <1996JAN1182>. The Pummerer intermediate generated from a 3-exomethylene-1-oxocephem with trifluoroacetic anhydride has been trapped intermolecularly in the presence of a Lewis acid by some aromatic or olefinic nucleophiles <1996JHC987>. 3-Benzothiopyranthiovinyl cephalosporins which have favorable profiles against MRSA and vancomycin-resistant enterococci (VRE) because of the vinyl-thio linkage, have been prepared from 3-(2-chlorovinyl)cephalosporins <2000JAN546>. The synthesis of carbacephem key intermediate (4-nitrophenyl)methyl-7-amino-1-carba(dethia)-3-chloro-3-cephem-4-carboxylate via chlorination and deacylation at C-3 employing chlorotriphenoxyphosphonium chloride [(PhO)₃P⁺ClCl[−]] has been described <2003OPD758>. The synthesis of cephalosporin derivatives bearing an oxygen atom directly attached to the C-3 position has been accomplished from diphenylmethyl 7 β -formamido-3-hydroxy-3-cephem-4-carboxylates and pyridylcarbinols using a Mitsunobu reaction in the presence of diethyl azodicarboxylate (DEAD) and TPP <2000BMC1159>.



2.02.6 Synthesis of Classical Cephalosporins

2.02.6.1 New Aspects Involved in Cephalosporin Biosynthesis

The biosynthetic pathway for cephalosporins by *Acremonium chrysogenum* has been disclosed in detail previously in CHEC-II(1996), and has also been reviewed during the last years <B-1998MI98, 1998MI1, 1999MI109, B-2004MI1, B-2004MI91>. The following section focuses on the molecular and genetic mechanisms of cephalosporin biosyntheses that have been elucidated in recent years. The currently accepted pathway of CPC biosynthesis from isopenicillin N is shown in Scheme 13.



Scheme 13

The formation of isopenicillin N is the branch point of penicillin and cephalosporin biosynthesis. The epimerization system converting isopenicillin N into penicillin N has been elucidated at the genetic level and the reaction cycle of isopenicillin N synthase (IPNS) has been observed by X-ray diffraction <1999NAT721>. This epimerization reaction is catalyzed by a two-component protein system encoded by the acetyl-CoA-synthetase (*cefD1*) and acetyl-CoA-racemase (*cefD2*) genes that correspond, respectively, to an isopenicillin-CoA ligase and an isopenicillinyl-CoA epimerase. A putative third component thioesterase, named *cefD3*, that later releases penicillin N has not been located so far. The gene designated *cefD1* encodes for a protein with a molecular mass of about 71 kDa which shows a high degree of similarity to long-chain acyl-CoA (CoA – coenzyme A) synthetases. The encoded protein contains all characteristic motifs of the acyl-CoA ligases involved in the activation of the carboxyl moiety of fatty acids or amino acids. The second identified gene designated *cefD2* encodes a protein with a deduced molecular mass of 41.4 kDa.

Based on the identified homology of the *cefD1* and *cefD2* proteins with known eukaryotic enzymes, a mechanism for the *A. chrysogenum* two-component epimerization system which is different from the epimerization found in prokaryotes has been established <2002JBC46216>. Therefore, it was suggested that the cephalosporin biosynthesis pathway begins with the activation of the substrate isopenicillin N to its CoA, followed by an epimerization to the D-enantiomer, namely penicillinyl-CoA. Next, the required hydrolysis of the CoA-thioesters seems to occur in a nonstereoselective manner by different thioesterases. The resulting product, penicillin N, is the direct precursor of all cephalosporins and cephamycins.

The next committed step of the cephalosporin pathway leads to the conversion of penicillin N to deacetoxycephalosporin C by expanding the five-membered thiazolidine ring to the six-membered dihydrothiazine ring. This reaction is catalyzed by deacetoxycephalosporin/deacetylcephalosporin C synthetase (DAOCS/DACS). It catalyzes two oxidative reactions, oxidative ring expansion of penicillin N to deacetoxycephalosporin C, and hydroxylation of the latter to give deacetylcephalosporin C. In order to identify residues within DAOCS/DACS that are responsible for controlling substrate and reaction selectivity, structural models based on DAOCS coupled with site directed mutagenesis have been studied <2004JBC15420>. This work has demonstrated that a single amino acid residue side chain within the DAOCS/DACS active site can control whether the enzyme catalyzes ring expansion, hydroxylation, or both reactions. To improve the substrate specificity of this enzyme on hydrophobic penicillins (e.g., penicillin G, ampicillin, and amoxicillin), different strategies have been recently developed. Biotransformation of penicillin G to deacetoxycephalosporin G by resting *Streptomyces clavuligerus* has been improved by growing the cells in ethanol, eliminating agitation, adding water-immiscible solvents and catalase to the reaction, and using a hybrid strain obtained by direct evolution <2002OPD427>.

Analysis of the amino acid sequence of the DAOCS/DACS synthetase of *A. chrysogenum* revealed a 10-amino-acid region containing a cysteine residue at position 100, which is 50% identical to the corresponding region containing the cysteine residue at position 106 of IPNS. This region is of special interest because the cysteine residue of the IPNS is important for substrate binding and specific activity. Thus, it seems to be possible that the corresponding residue C-100 of the DAOCS/DACS synthetase may either be directly or indirectly involved in substrate binding. The existent sulfanyl groups in the enzyme were apparently essential for both ring expansion and hydroxylation. DAOCS/DACS also contains eight arginine residues within, or close to, its active site that may be involved in catalysis. By structural and mutagenesis studies, Arg258 has been shown to bind the 5-carboxylate of the 2-oxoglutarate <2001JBC18290>. Mutagenesis of this residue to glutamine reduced the 2-oxoglutarate conversion. However, other aliphatic 2-oxo-acids, which are not co-substrates for DAOCS/DACS, had higher levels of activity as they interact more favorably with the mutated cosubstrate binding site (74, 75, 160, 162, 266, 306, and 307) that, together with the crystallographic analyses, support the proposed roles for arginines 160, 162, and 266, and suggest roles for other arginine residues <2002MI2735>.

In the last reaction of the cephalosporin biosynthesis pathway, the transfer of an acetyl moiety from the acetyl coenzyme A to the hydroxyl group on the sulfur containing ring of deacetylcephalosporin C leads to the formation of the final product CPC. This acetylation reaction is catalyzed by the acetyl-coenzyme A (CoA):DAC acetyltransferase, which behaves like a soluble cytosolic enzyme without any known targeting signals or other indications for compartmentalization <1999MI41>. The acetylation reaction of DAC to CPC seems to be very inefficient in most strains of *A. chrysogenum*. The acetyl-CoA/deacetylcephalosporin C acetyltransferase (*cefG*) gene is expressed very poorly when compared with other genes of the pathway. Consequently, the conversion of DAC to CPC seems to be the limiting step in the pathway.

2.02.6.2 Industrial Production of Cephalosporins

The industrial production of cephalosporins was not covered in CHEC-II(1996). However, the current state of the technologies employed for the production of cephalosporins is certainly of interest, focusing on the new and

environmentally safer 'green' routes to these products <2003MI385, B-2004MI179>. Starting with the fermentation and purification of CPC, enzymatic conversion in conjunction with aqueous chemistry will lead to the key intermediate, 7-ACA, which can be converted into the active pharmaceutical ingredient (API). The overall process comprises the following main stages:

1. Fermentation of a high-yielding strain of *A. chrysogenum* to produce a broth containing CPC;
2. Recovery and purification of the fermentation broth to produce an aqueous solution of CPC; and
3. Conversion of cephalosporin C into 7-ACA of the purified aqueous extract to produce an aqueous solution followed by precipitation and isolation of 7-ACA of appropriate purity (*c.* 98%) for use in the preparation of advanced cephalosporin intermediates and/or active pharmaceutical ingredients.

Adding up the times of all steps, an industrial scale production takes roughly 3 weeks, of which 2 weeks are devoted to the fermentation and about 1 week is required for the downstream processing. Derivatization at positions 3' and 7' to yield an API is not included. Starting from 7-ACA, these processes may take 1 day each for the derivatization plus the time for purification, crystallization, and drying. The resulting bulk active cephalosporin can then be sterilized and formulated for marketing.

2.02.6.2.1 Fermentation

The starting point for the synthesis of cephalosporins is CPC obtained as secondary metabolite from large-scale fermentations of the filamentous fungus *A. chrysogenum*. High-yielding industrial production strains are used for production. These strains require continued improvement in both the titer achieved at the end of the fermentation and in their stability. In practice, industrial strains are constantly mutated and re-isolation of best performing strains is conducted routinely, as even prolonged storage of a high-producing strain can occasionally result in the loss of its productivity. Genetic engineering is increasingly being used to improve productivity or to direct the fermentation to new products <1996MI359>. Major fermentation producers of CPC obtain harvest titers in the range of 20–25 g l⁻¹. Production scale fermentations are batch-fed with carbon supplied as simple or complex carbohydrate feeds during the growth phase of the fermentation. As the fermentation progresses, sugar feeds are reduced and are usually replaced by higher energy oils such as soybean oil or peanut oil. Energy conservation from oil as substrate is considerably less efficient and leads to a slower growth, with the vegetative mycelium becoming largely transformed into multicellular arthrospores. The arthrospore stage leads to greater oxygen availability to the organism and results in rapid cephalosporin production. DL-Methionine addition, which also results in the onset of arthrospore formation, is often added to the medium during the early growth phase of the fermentation. The formation of arthrospores is also correlated with improved dissolved oxygen concentration in the broth and is critical for maximal expression of the important biosynthetic cyclase and expandase enzymes.

Organic nitrogen is often supplied as a combination of soybean and cottonseed meals supplemented with ammonium sulfate and ammonia that is also used to help control the pH throughout the fermentation. The pH of the fermentation is maintained between 6.2 and 7.0 and the temperature range is controlled between 24 and 28 °C. Corn steep liquor is also supplied as a cheap nitrogen source and is rich in amino acids, vitamins, organic acids, and trace elements. When the productive fermentation is stopped after approximately 5–7 days, the CPC is isolated rapidly to avoid losses owing to its chemical instability in the broth and due to the action of esterases, which will also increase the level of side products. In this context, the cloning of many of the genes involved in the biosynthesis pathway of cephalosporins has resulted in more productive strains. Basch and Chiang have reported on the use of engineering strategies to reduce the levels of undesirable by-products in CPC fermentations <1998MI344>. They showed that using a recombinant strain of *A. chrysogenum* with an increased copy number of the bifunctional expandase/hydroxylase (*cefEF*) gene resulted in a reduced level of DAOC in large production fermentors. The recovery and purification of these broths and subsequent chemical conversion to 7-ACA resulted in significant reduction of contaminating 7-ADCA.

2.02.6.2.2 Recovery and purification

The purification and recovery of harvest CPC broth begins with the rapid chilling of the active broth to 3–5 °C followed by removal of the mycelial solids either by filtration or by centrifugation. The active broth contains not only the desired CPC component, but also small quantities of the biosynthetic precursors, penicillin N, DAOC, deacetylcephalosporin C, and the degraded CPC product, 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid.

Two major strategies can be used for the recovery and purification of CPC. One strategy involves the use of activated carbon or the use of a nonionic resin. Because of the high selectivity of the resin, CPC is preferentially adsorbed over penicillin N or the contaminating biosynthetic precursor molecules. Most of the penicillin N is removed in the pH 2.0 acidification step. An additional anion- and cation-exchange step usually results in high-quality CPC. A large fraction of the CPC is converted to 7-ACA and derivatized to semisynthetic cephalosporins.

A second purification strategy involves the substitution of the amine moiety on the α -aminoadipyl side chain at C-7. Two substituted derivatives, *N*-2,4-dichlorobenzoyl CPC and tetrabromocarboxybenzoyl CPC, can be crystallized from the acidic aqueous solution. Alternatively, salts can be formed between the *N*-substituted derivatives and an organic base, such as dicyclohexylamine or dimethylbenzylamine, resulting in cephalosporin salts that are solvent extractable. Bristol-Myers Squibb uses a solvent-extractable process resulting in the isochlorobutylformate (ICBF) ester of CPC, termed cephalosporin D. Several extraction steps are usually necessary to achieve the desired final purity. *N*-Substituted CPC salts containing small amounts of contaminants can be effectively converted to 7-ACA.

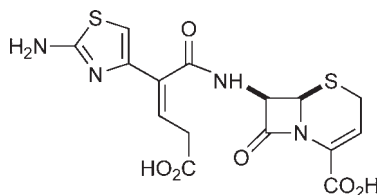
2.02.6.2.3 Conversion of cephalosporin C into 7-ACA

7-ACA represents the key intermediate for the synthesis of the API which is obtained after (bio-) chemical derivatization at position 3' and 7'. Cephalosporin C can be converted to 7-ACA by either a chemical or an enzymatic removal of the 7-amino adipoyl side chain. The chemical transformation of CPC into 7-ACA is shown in [Scheme 14](#). CPC is treated with phosphorus pentachloride in the presence of base after protection of the amino and carboxyl functions. The reaction proceeds to form an imidoylechloride intermediate, which is converted into an iminoether by addition of propanol. Finally, 7-ACA is obtained by hydrolysis of the iminoether. Further improvements have been introduced using silyl protection, which simultaneously blocks the amino and carboxyl functions of CPC and permits the cleavage with PCl_5 to be carried out in the common solvent methylene chloride. While overall yield (64%) and product quality produced are excellent, a major drawback is the need for organic solvents and the production of toxic chemical waste. This has resulted in a gradual replacement of the chemical route to 7-ACA by the environmentally safer enzymatic cleavage of CPC.

Efficient enzymatic processes are now utilized for the conversion of CPC to 7-ACA, which has resulted in a dramatic cost reduction for this important bulk intermediate. Two key genetically engineered enzymes are involved ([Scheme 15](#)). The initial step is the reaction of the α -aminoadipyl group with D-amino acid oxidase (DAO) to produce glutaryl-7-ACA (GL-7-ACA). This reaction proceeds through a keto-7-ACA (KA-7-ACA) intermediate that undergoes an oxidative decarboxylation in the presence of hydrogen peroxide. A glutaryl acylase (GAC) is used to remove the glutaryl side chain to produce 7-ACA.

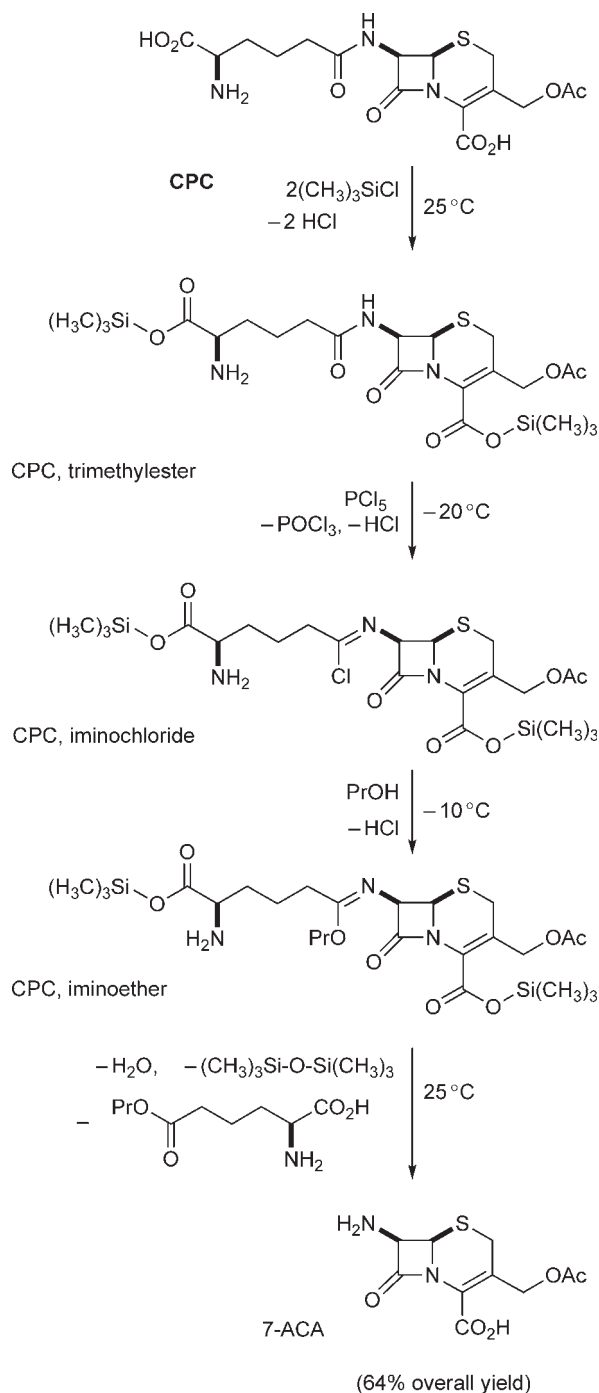
About one-third of the commercial cephalosporins are derived from 7-ADCA. Due to the lower cost of penicillin, 7-ADCA is usually produced from penicillin G by ring expansion of a penicillin sulfoxide ester to yield a cephalosporin ester. The removal of the ester group is followed by cleavage of the phenylacetyl side chain to give 7-ADCA. Two-thirds of the commercial cephalosporins are derived from 7-ACA, that is produced from CPC by either chemical or enzymatic deacylation.

A high-yielding, all-aqueous process for the manufacture of ceftibuten **69** from fermented CPC broth has also been described via enzymatic transformations and electrochemical reduction without isolation of any precursors [\(<2002OPD152, 2002OPD158, 2002OPD169>\)](#).



69

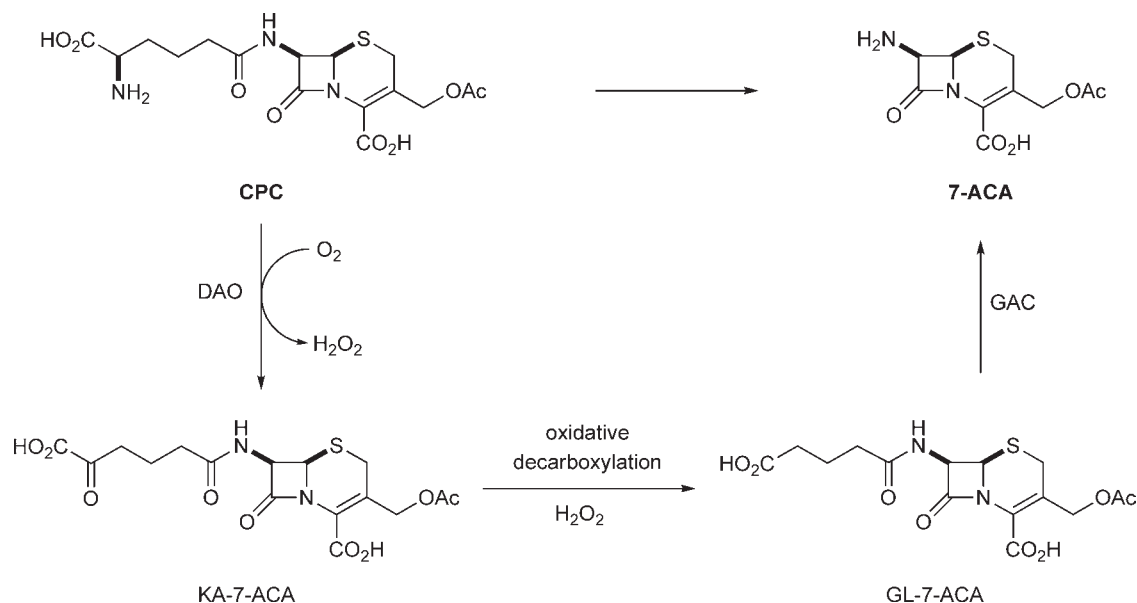
Ceftibuten



Scheme 14

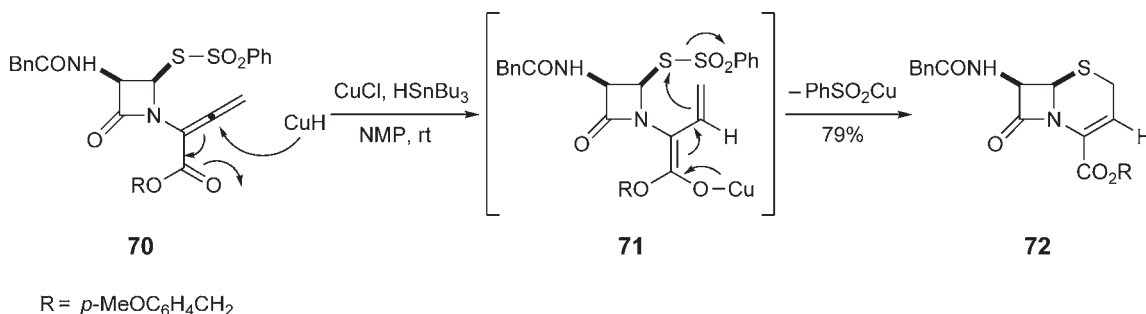
2.02.6.3 Synthesis of Cephalosporins

This section aims to complete the picture on the studies summarized in CHEC-II(1996) on the synthesis of classical cephalosporins, describing the main cephalosporin methodologies developed during the last decade. In CHEC-II(1996), an approach was presented for the formation of the cephalosporin framework bearing various heteroatom and carbon substituents at the C-3 position, which relies on a sequential addition/cyclization of allenolate **70**, derived from penicillin G.



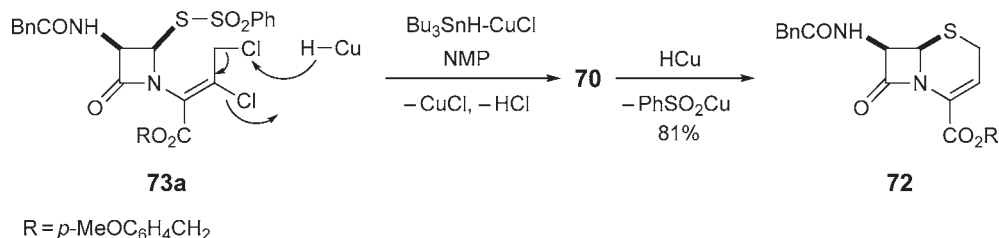
Scheme 15

More recently, the synthesis of 3-norcephalosporin **72** has been performed successfully by reaction of either allenolate **70** or 3,4-disubstituted 2-butenates **73a** and **73b** with copper(I) chloride and tributyltin hydride in NMP [\[1996CC2705, 1999J\(P1\)3463\]](#). Conversion of the allenolate **70** into **72** took place through Michael addition of copper(I) hydride to the central carbon of the allene moiety of **70** and subsequent ring closure of adduct **71**. The sequential reaction could be performed successfully by treatment of **70** with copper(I) chloride and tributyltin hydride in NMP at room temperature, affording **72** in 79% yield without any detectable amount of the Δ^2 -isomer (Scheme 16).



Scheme 16

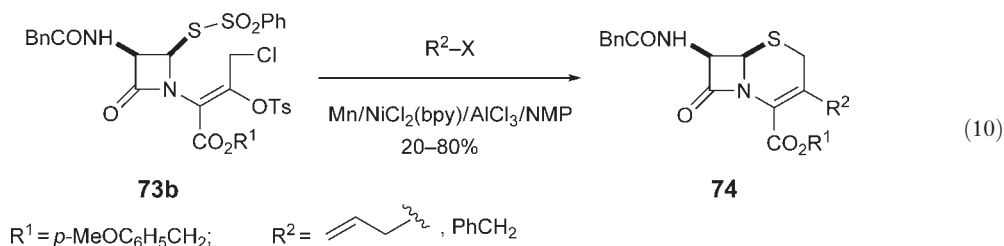
The above procedure must be one of the most straightforward approaches to the 3-norcephalosporin **72**, but is not necessarily satisfactory for practical use because the allenolate **70** is not easy to handle owing to its lability. Dichloroderivative **73a**, which is readily available and stable under ambient conditions, has been found to be a potent synthetic equivalent of the allenolate **70**, and can undergo a similar addition–cyclization, leading to the cephalosporin framework. Reaction of the 3,4-disubstituted 2-butenate **73a** with copper(I) chloride and tributyltin hydride in NMP afforded cephalosporin **72** in 81% yield. The cyclization of the dichloride **73a** to the 3-norcephalosporin **72** was monitored by HPLC showing that during the course of the reaction, the allenolate **70** was formed and finally disappeared. This fact suggests a reductive 1,2-elimination of the vicinal dichloro group of **73a** leading to **70** and subsequent hydride addition to afford the norcephalosporin **72** via the adduct **71** (Scheme 17). It is likely that copper(I) hydride generated from the reaction of tributyltin hydride with copper(I) chloride functions both as the reducing agent for the 1,2-elimination and as a



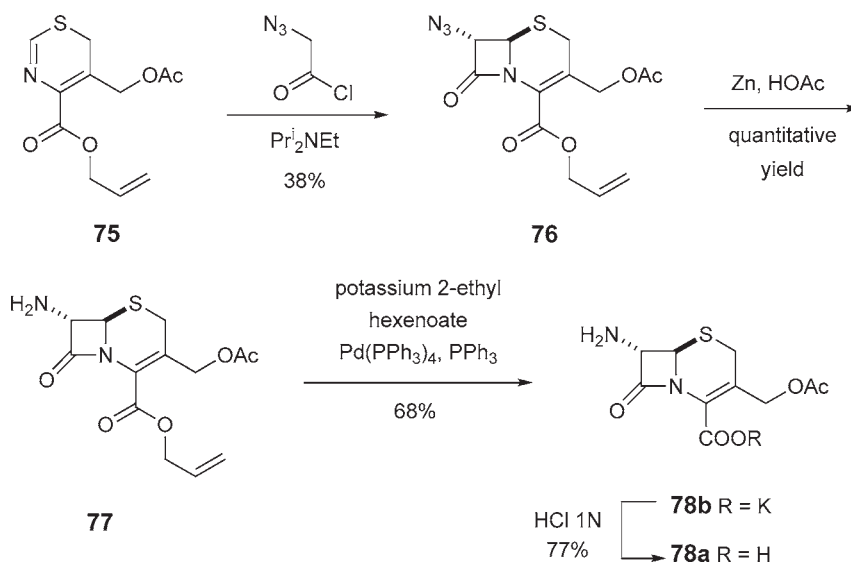
Scheme 17

hydride source of the latter addition–cyclization stage. Construction of a 3-norcephalosporin analogue has been carried out by ring closure of an alleneazetidinone in presence of CuCl and diethylzinc <1998TL8743>.

The same methodology has been adopted for the preparation of 3-allyl- and 3-benzyl- Δ^3 -cephems through reductive addition/cyclization of the allenoate **70** with allyl and benzyl halides in an Al/PbBr₂/NiCl₂(bpy) system <1997J(P1)637>. The transformation of the 3,4-disubstituted 2-butenate **73b** into the 3-alkenyl and 3-benzyl- Δ^3 -cephems **74** through the allenoate **70** via reductive 1,2-elimination of 3,4-disubstituted 2-butenate **73b** and subsequent reductive addition of allyl and benzyl halides proceeded smoothly employing the Mn/NiCl₂(bpy)/AlCl₃/NMP system (Equation 10) <2000H(52)633>. In this context, the synthesis of 3-alkenyl- Δ^3 -cephems has been performed from 3,4-dichloro-[(4-phenylsulfonylethio)-2-oxoazetidin-1-yl]-2-butenate **73a** under the alkenyltributyltin/copper(I) chloride/bpy/NMP conditions <1999SL774>.



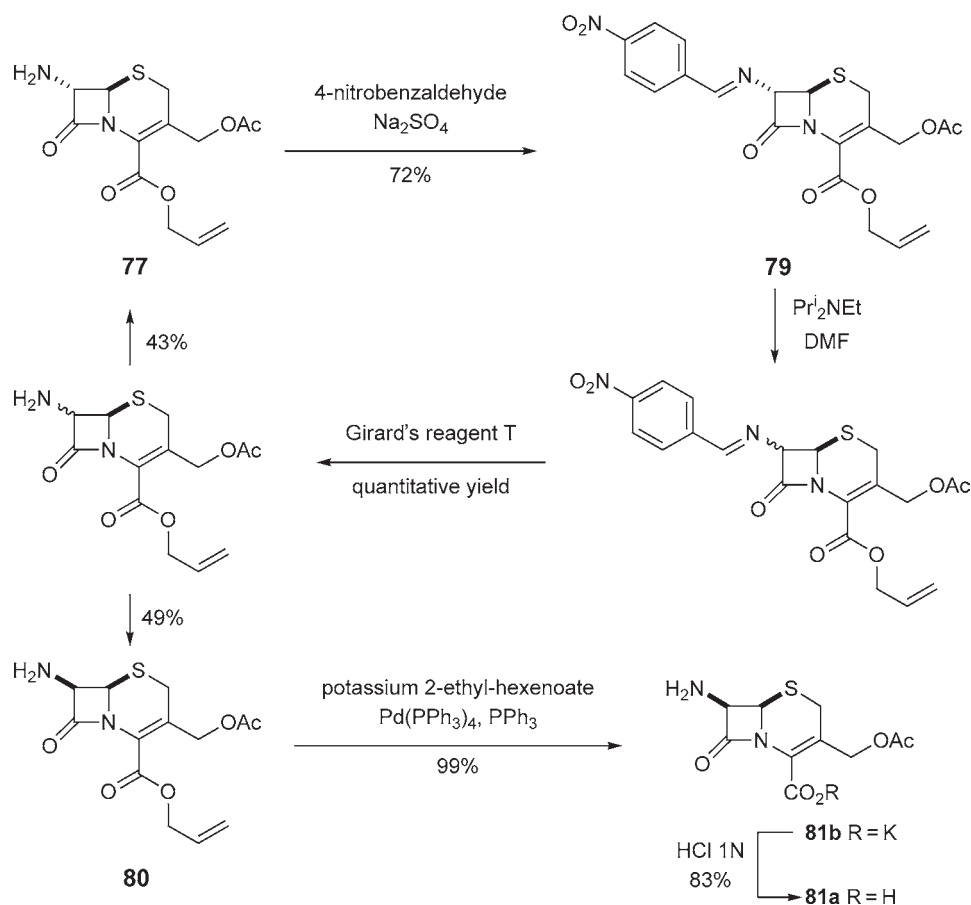
An approach to obtain racemic 7-ACA and its 7-epimer has been achieved employing a Staudinger–Bose ketene–imine cycloaddition to form the β -lactam ring <1996T7691> (Scheme 18). Reaction of azidoacetyl chloride and thiazine **75** in the presence of *i*-Pr₂NEt afforded azidocephem **76** in 38% yield. Compound **76** was reduced to amine



Scheme 18

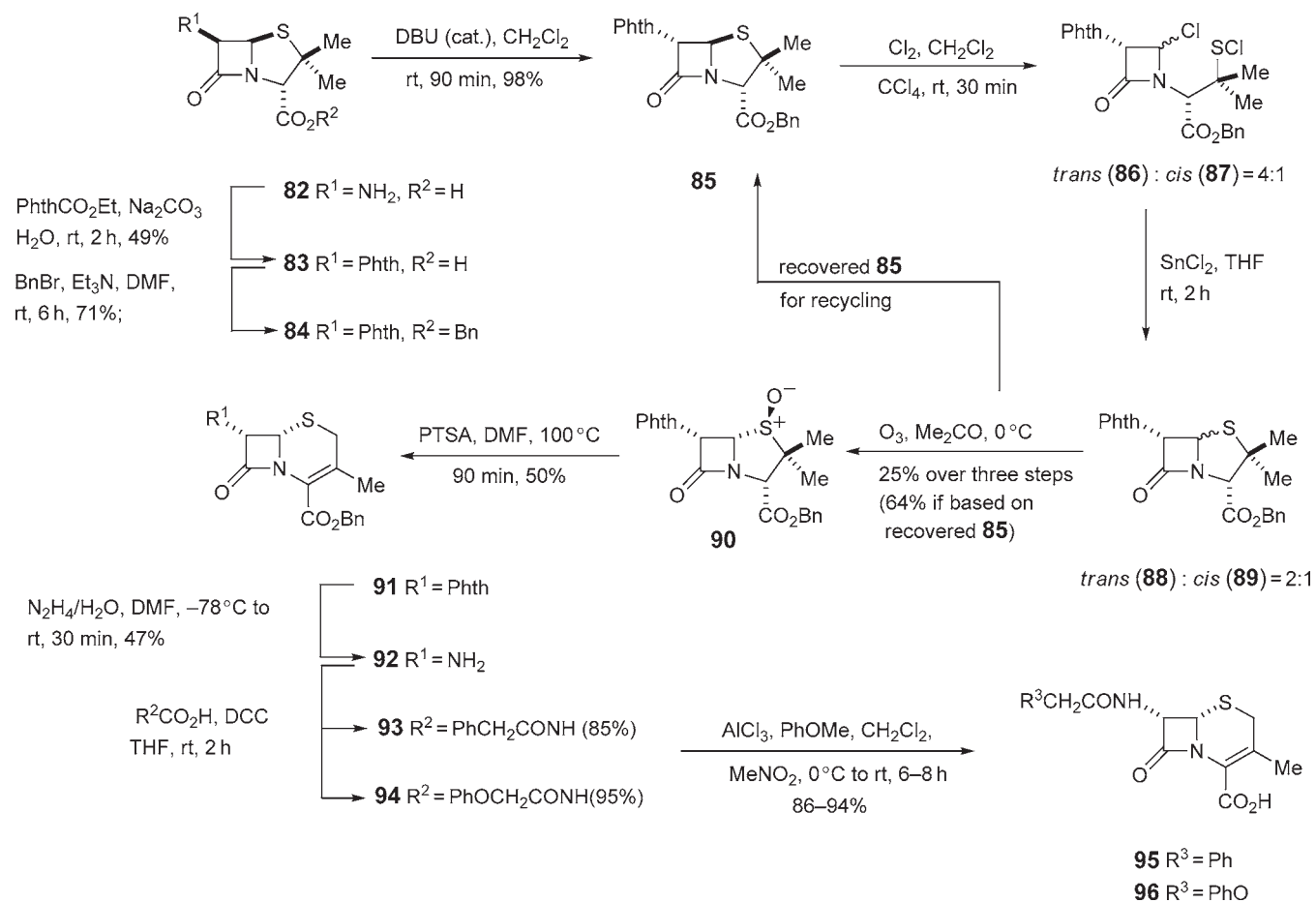
77 with Zn/HOAc in quantitative yield. Due to its instability, **77** was immediately subjected to a Pd(0)-catalyzed cleavage of the allylic ester in the presence of potassium 2-ethylhexanoate, affording compound **78b**. (±)-7-*epi*-ACA **78a** was prepared by neutralization of **78b** with 1 N aqueous HCl.

The synthesis of (±)-7-ACA **81a** is shown in Scheme 19. Reaction of **77** with 4-nitrobenzaldehyde followed by treatment with Hünig's base gave a 2:3 mixture of *cis/trans* isomers of the Schiff base **79**. Compound **79** was therefore cleaved with Girard's reagent T and amines **77** and **80** were obtained after chromatography. Amine **80** was converted to (±)-7-ACA **81a** as outlined below.



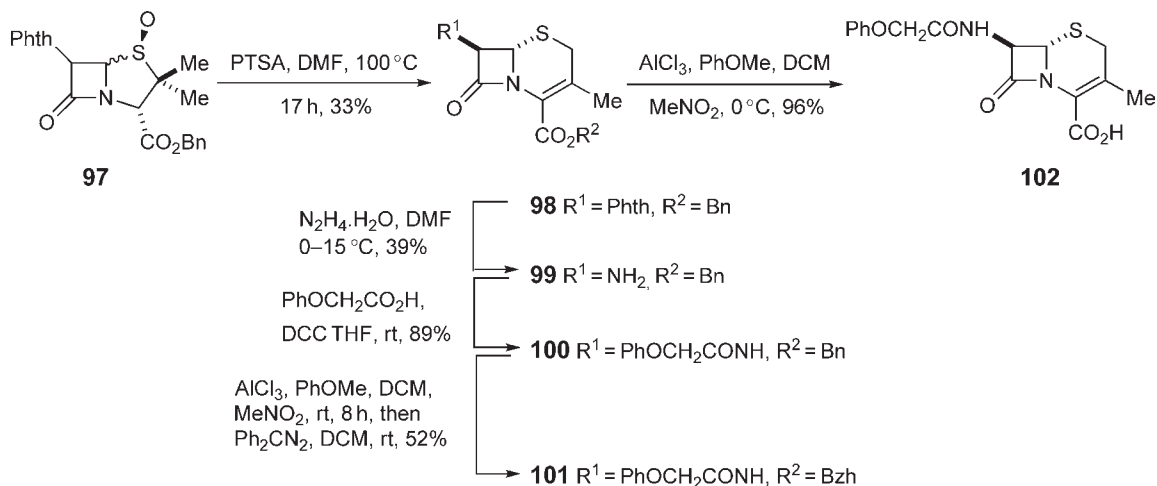
Scheme 19

Two practical routes to (6*S*,7*S*)-cephalosporins from 6-aminopenicillanic acid (6-APA) have been reported [\(<2000T6053>\)](#). In the first, 6-APA was converted to penicillin sulfoxide **90**, which underwent Morin ring expansion to a protected (6*S*,7*S*)-cephem **91**. The sodium salt of **82** was treated with Neffkens' reagent, *N*-carboxyphthalimide, to give acid **83** which was subsequently esterified with benzyl bromide in the presence of triethylamine to afford ester **84**. The base-promoted epimerization of the C-6 position of penam **84** was accomplished readily in excellent yield using a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Subjecting penicillin **85** to the Kuolja protocol furnished a mixture of two diastereomers, the requisite *cis*-penicillin **89** and the parent *trans*-penicillin **88** in ratio of 1:2. Selective oxidation of the mixture of esters **89** and **88** with ozone in cold acetone afforded the desired sulfoxide **90** and only traces of the sulfoxides derived from penicillin **85** could be detected by ^1H NMR. Separation of sulfoxide **90** from sulfide **85** was accomplished by flash chromatography. Cephem **91** was obtained in moderate yield via the Morin rearrangement of sulfoxide **90** in hot dimethylformamide (DMF) in the presence of a catalytic amount of *p*-toluenesulfonic acid. The Ing-Manske dephthaloylation using hydrazine hydrate furnished free amine **92**, which was subsequently acylated with appropriate acids using dicyclohexylcarbodiimide (DCC) as a dehydrating agent to afford amides **93** and **94**, in both cases in excellent yields. Finally, debenzoylation with AlCl_3 produced free acids **95** and **96** in excellent yields Scheme 20.

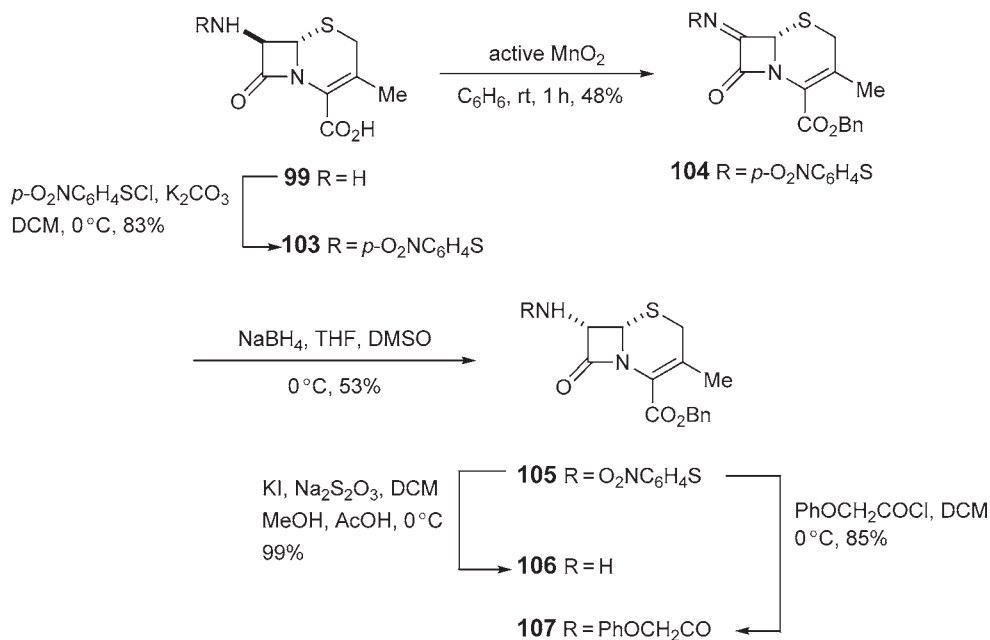


Scheme 20

The second approach to obtain (6*S*,7*S*)-cephems **Scheme 21** relied on the observation that the target compound **96** might be easily obtained from its (7*R*)-epimer **102** by any of the methods devised to convert (6*R*,7*S*)-cephems, available from various total syntheses, to the naturally configured ones. Sulfoxide **97** was obtained by oxidation with *m*-chloroperoxybenzoic acid (MCPBA) of the sulfide precursor. Sulfoxide **97** underwent the acid-catalyzed Morin rearrangement to give cephem **98**. As in the previous approach, dephthaloylation of cephem **98** using hydrazine hydrate afforded amine **99**. DCC-mediated coupling with phenoxyacetic acid gave amide **100** in good yield. Dephenylation with AlCl_3 afforded contaminated acid **102** that was purified as its benzhydryl ester **101**. Final rapid deprotection with AlCl_3 under milder conditions gave pure acid **102**. As shown in **Scheme 22**, amine **99** was converted to (6*S*,7*S*)-cephem derivatives. This transformation involves preparation and subsequent reduction of



Scheme 21



Scheme 22

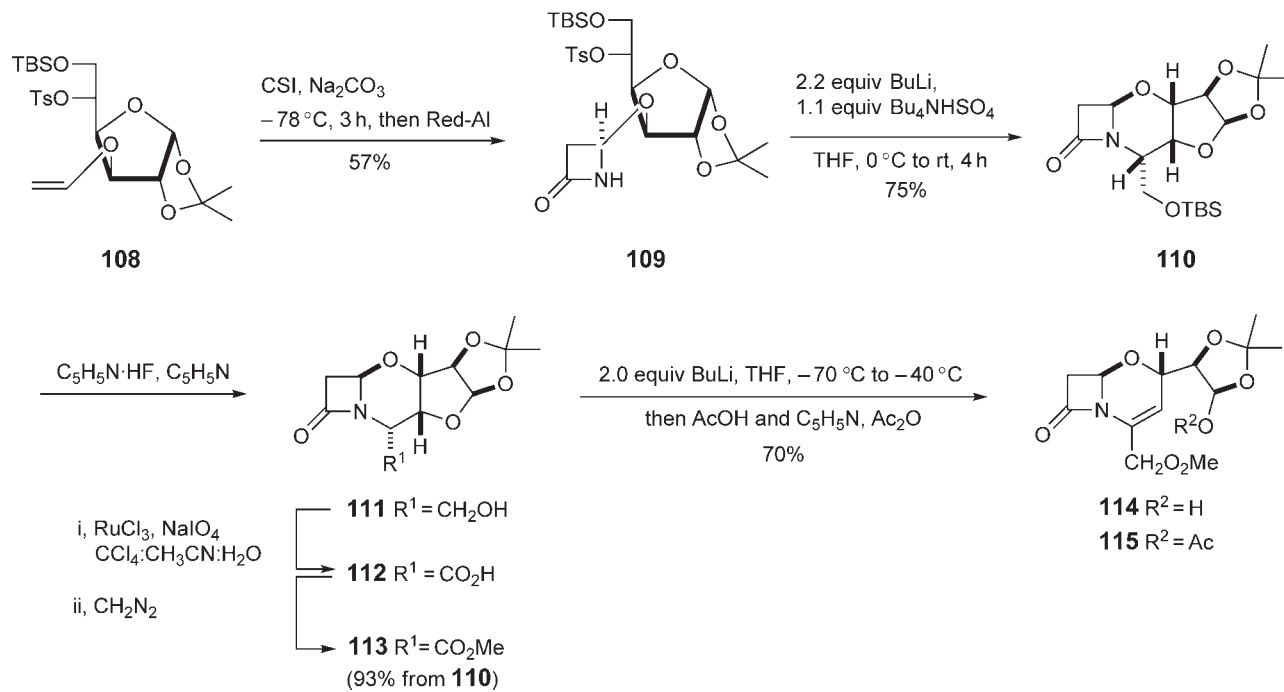
sulfenimines. Thus, treatment of amine **99** with *p*-nitrobenzenesulfonyl chloride in the presence of K_2CO_3 afforded sulfenamide **103** in good yield. Oxidation with active manganese dioxide furnished sulfenimine **104**, which was reduced with $NaBH_4$ to produce sulfenamide **105** as the major product, along with a small amount of the parent sulfenamide **104**. Direct acylation of cephem **105** with phenoxyacetyl chloride afforded amide **107**. It was also possible to reductively cleave of (KI/AcOH/MeOH) the side chain of sulfenamide **105** to form free amine **106**.

2.02.7 Synthesis of Oxacephams and Oxacephems

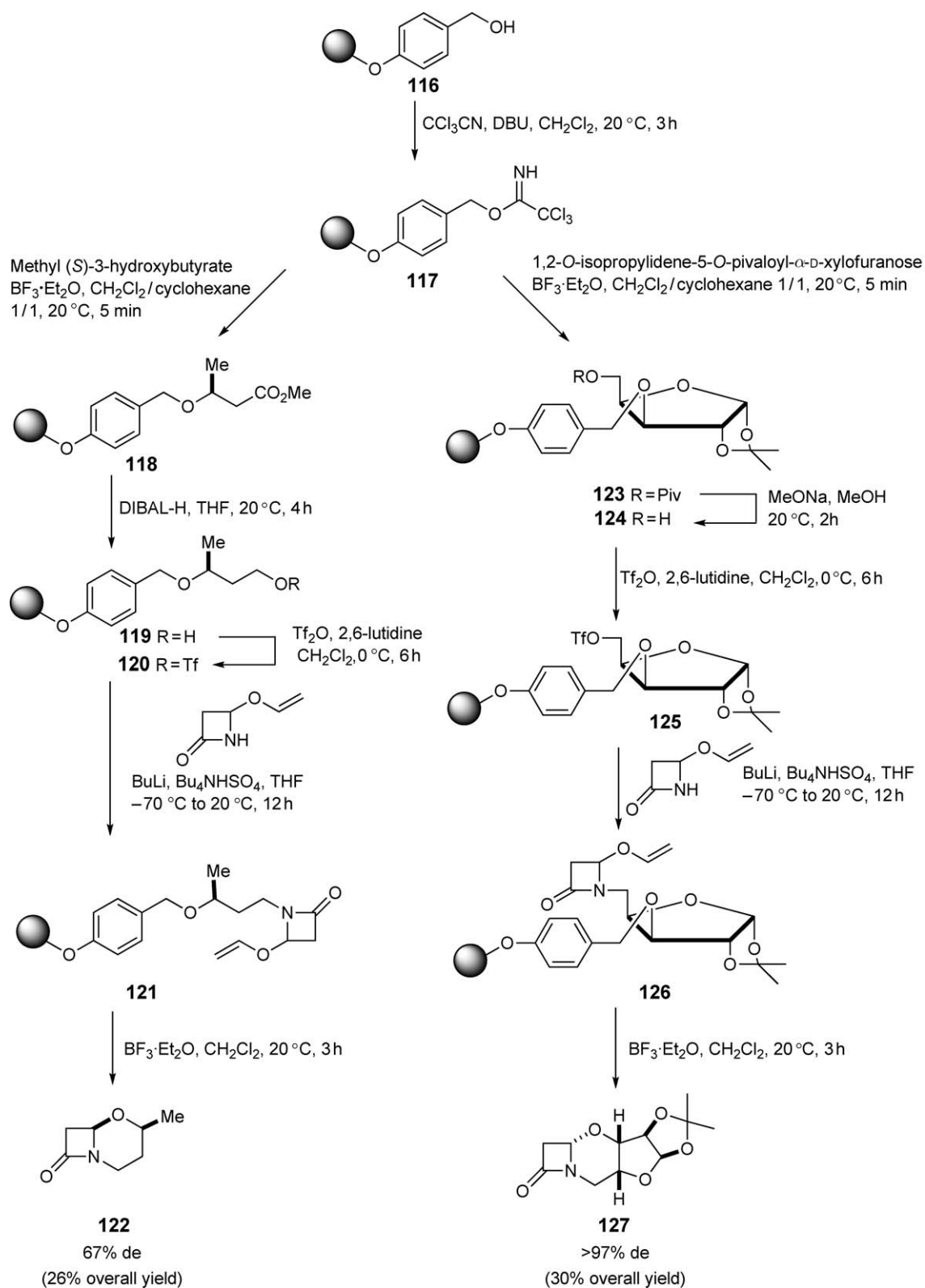
The information gathered on the molecular architecture of naturally occurring β -lactam compounds coupled to the discovery that the biological activity is increased several times when the sulfur atom is replaced by an oxygen <1996CHEC-II(1B)591> made it possible to design new series of non-natural oxacephams and oxacephems. This section has the aim of covering the literature on the use of classical or improved methods and the design and development of new procedures for preparing oxacepham and oxacephem derivatives. The most general strategy for the synthesis of 1-oxa-bicyclic β -lactams involves nucleophilic substitution at C-4 of the azetidin-2-one ring, which can constitute the ring-closure step, or which can be followed by formation of the six-membered ring <2000T5553>. Two general pathways have been developed during this decade: (1) use as starting materials of 3-unsubstituted 4-alkoxyazetidin-2-ones, which can be prepared by [2+2] cycloaddition of chlorosulfonyl isocyanate (CSI) to chiral vinyl ethers having a chiral center next to the oxygen atom <1997JOC3135>, and (2) synthesis of oxacephams employing readily available 4-benzyloxy- and 4-vinylxyazetidin-2-ones <1996SL895, 1997TA2553, 1998TL8349>. The first approach has been applied to the synthesis of oxacephems **114** and **115** by [2+2] cycloaddition of chlorosulfonyl and trichloroacetyl isocyanates to sugar vinyl ethers derived from D-glucose, D-glucuronolactone <1997T5883>, D-arabinal, L-rhamnal <1996CC2689, 1997T14153>, or D-xylofuranoses <1996T6019> followed by intramolecular *N*-alkylation of monocyclic β -lactam derivatives. [2+2] Cycloaddition of CSI to vinyl ether **108** in the presence of base, followed by reduction of the chlorosulfonyl group with Red-Al, gave β -lactam **109** as single diastereomer in moderate yield. Tetracyclic 1-oxacepham derivative **110** was obtained in high yield by intramolecular alkylation in the presence of butyllithium. Deprotection of the silyl ether by hydrogen fluoride in pyridine gave alcohol **111** in quantitative yield. Subsequent oxidation of the hydroxymethyl group gave acid **112**. Treatment of the acid **112** with diazomethane in ethyl acetate yielded 1-oxacepham methyl ester **113**. β -Elimination in the presence of butyllithium at low temperature opened the furanoid ring and introduced a double bond to the six-membered ring affording unstable 1-oxacephem **114** which was characterized as its acetate **115** (Scheme 23).

Construction of 1-oxacephams **122** and **127** has been achieved on a solid-phase synthesis with excellent results from 4-vinylxyazetidin-2-ones <1999AGE1121> (Scheme 24). Transformation of commercially available Wang resin **116** to the corresponding trichloroacetimidate resin **117** was carried out by reaction with trichloroacetonitrile and DBU. Lewis acid-coupling reaction of resin **117** with the optically active methyl (*S*)-3-hydroxybutyrate or with the 1,2-*O*-isopropylidene-5-*O*-pivaloyl- α -D-xylofuranose provided compounds **118** and **123**, respectively. Reduction of the ester group in the resin-bound methyl (*S*)-3-hydroxybutyrate **118** in the presence of diisobutyl-aluminium hydride (DIBAL-H) afforded the expected alcohol **119**. On the other hand, basic cleavage of the pivaloyl ester of the resin-bound sugar derivative **123** yielded the alcohol **124**. Resin-bound alcohols **119** and **124** were subjected to protection with Tf_2O affording the corresponding triflates **120** and **125**. Subsequent *N*-alkylation of 4-vinylxyazetidin-2-one afforded resins **121** and **126**, respectively. The 1-oxacephams **122** and **127** were obtained in good overall yield (26–30%, over six steps) and moderate to excellent diastereoselectivity (67 and 97% de, respectively) by a cyclization/cleavage step of the corresponding resins **121** and **126** with $BF_3 \cdot Et_2O$.

The synthesis of 1-oxacephem derivative **128** exhibiting human chymase inhibitor (HCI) activity ($IC_{50} = 0.25 \mu M$) has been previously published in the literature <2004MI93>. In this context, Aoyama and co-workers have reported the structure–activity relationship by structural modifications at the 3'-, 4-, and 7 β -positions of the 1-oxacephem nucleus of **128** <2000BML2397, 2000BML2403>. Although structural changes at the 7 β -position did not lead to any improvement in activity, changes at the 4-position led to a lowest IC_{50} value of $0.05 \mu M$ in the case of compounds **129a** and **129b**. Alternatively, modifications at C-3' provided two compounds, **130a** and **130b**, showing roughly the same inhibitor potency than **129**. Considering the match–mismatch between 3'-, 4-, and 7 β -substituents, a hybrid compound **131** was prepared, which was 40-fold more active ($IC_{50} = 0.006 \mu M$) than the lead compound **128** as a selective inhibitor, causing weak or no absorption of several other serine proteases. However, its *in vivo* evaluation

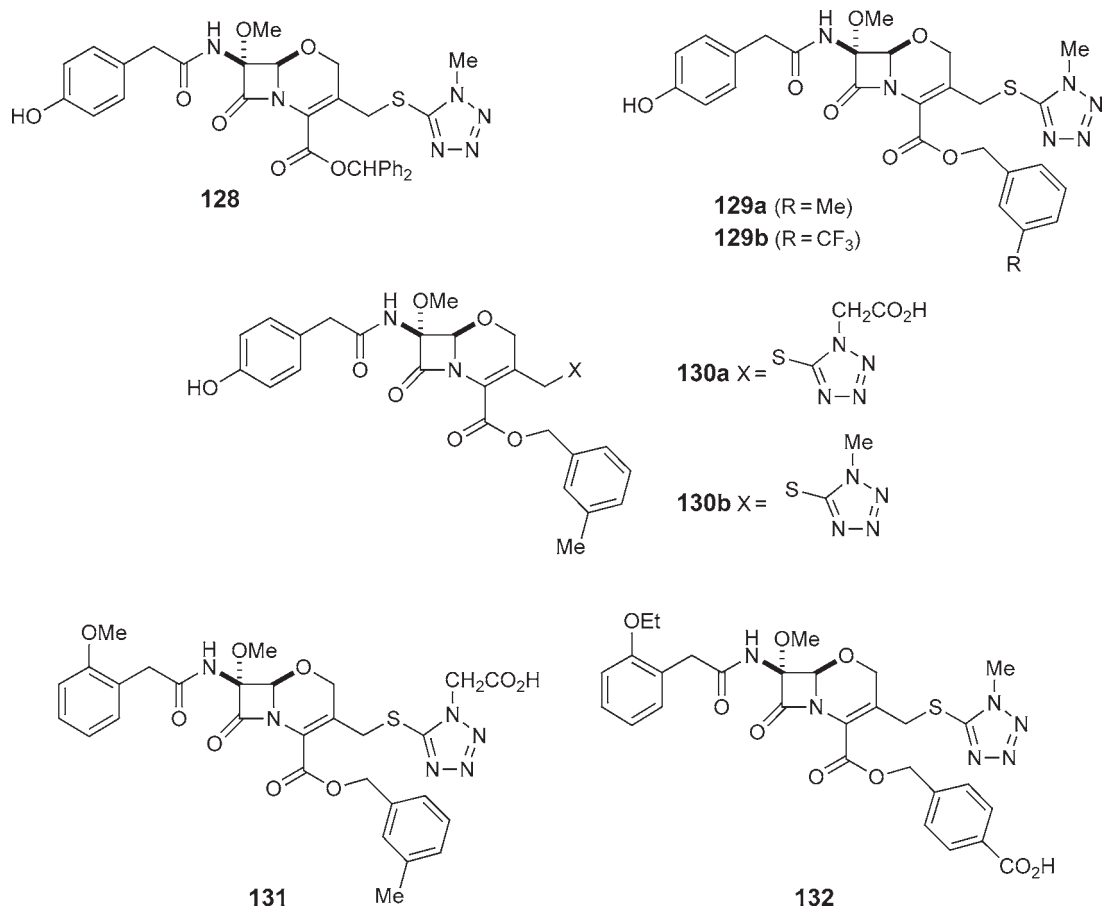


Scheme 23



Scheme 24

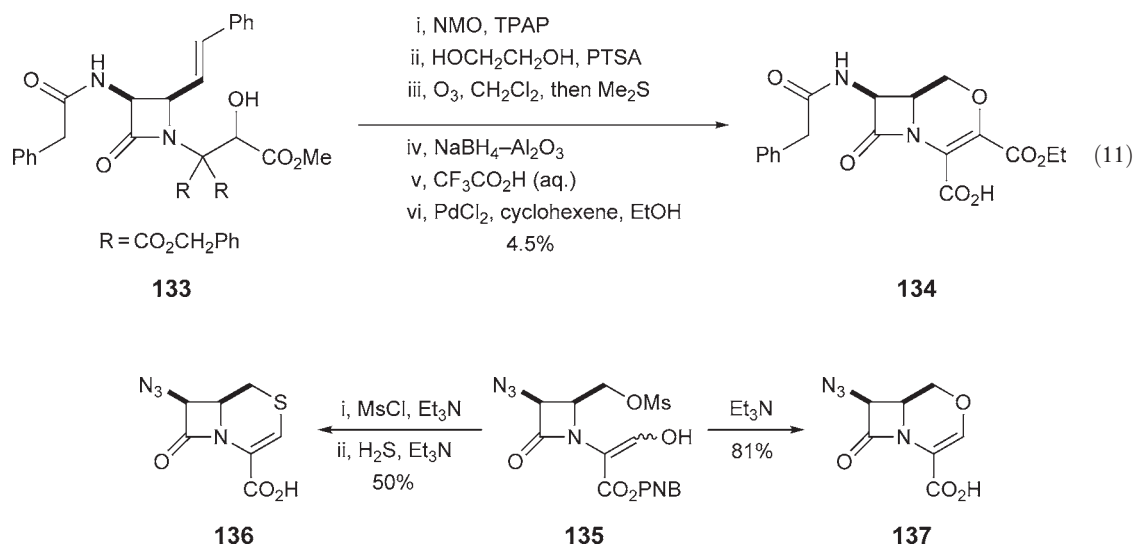
was limited by its lability in human plasma ($t_{1/2} < 10$ min). This problem was addressed by making several other modifications leading to compound **132** having fourfold less inhibition of chymase ($IC_{50} = 0.027 \mu M$) than compound **131** but with high stability in human plasma.



2.02.8 Synthesis of Isocephems and Isooxacephems

Although structure–activity relationship studies of several isocephem and isooxacephem derivatives bearing hydrogen, methyl, and substituted methyl at the C-3 position have revealed potent antibacterial activity, only a few syntheses have been reported during the last few years. Access to this kind of skeletons involves first the formation of the monocyclic β -lactams followed by cyclization.

A family of isocephems and isooxacephems with C-3' catechol-containing (pyridinium-4-thio)methyl groups and isocephems with C-7 catechol related aromatics have been prepared and evaluated for antimicrobial activity <1996BMC2135>. It has been reported that isocephems with a 1,3-dihydroxy-4-pyridone moiety at C-7 or with a catechol moiety have shown strong *in vitro* antibacterial activity against Gram-negative bacteria. Preparation of isooxacephem **134** has been prepared in a six-step synthesis from monocyclic β -lactam **133** (Equation 11) <1996BMC1361>. Compound **134** has been found to possess notable antimicrobial activity against several pathogenic microorganisms *in vitro*, mainly due to the presence of an electron-withdrawing group (e.g., an ester functionality at C-3). Isocephem and isooxacephem analogues have been prepared from enol **135** <1997J(P1)1793>. Treatment of azetidinone **135** with triethylamine afforded 7-azidoisooxacephem **137**. Alternatively, methanesulfonylation of **135** and subsequent reaction with hydrogen sulfide furnished the 7-azido-isocephem **136** (Scheme 25).



Scheme 25

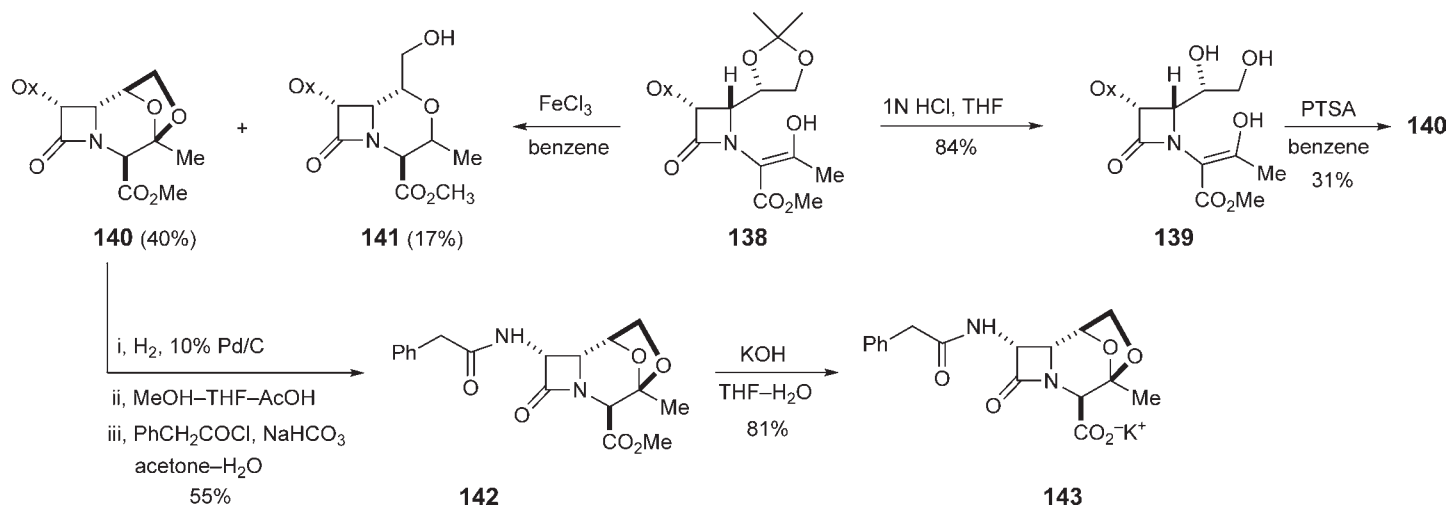
The asymmetric total synthesis of two enantiomeric isooxacephem derivatives has been described from β -lactams **138** and **144** <1996JOC1014>. Hydrolysis of azetidinone **138** in acidic conditions afforded glycol **139**. Refluxing **139** with *p*-toluenesulfonic acid (PTSA) in dry benzene produced tricyclic β -lactam **140** in 31% yield. Furthermore, refluxing acetamide **138** with ferric chloride provided the same product, tricyclic β -lactam **140** in 40% yield, along with isooxacephem **141** in 17% yield. Hydrogenolysis of **140** followed by acylation with phenylacetyl chloride gave the corresponding phenylacetamido compound **142** in 55% overall yield. Tricyclic β -lactam **143** was obtained in 81% yield from **142** by hydrolysis with potassium hydroxide (Scheme 26). Synthesis of the other enantiomer **148**, showing potential inhibitory activity against four typical strains of bacteria, was achieved using the same strategy as it was described for isooxacephem **143** (Scheme 27).

2.02.9 Synthesis of Carbacephems and Other Nuclear Analogues

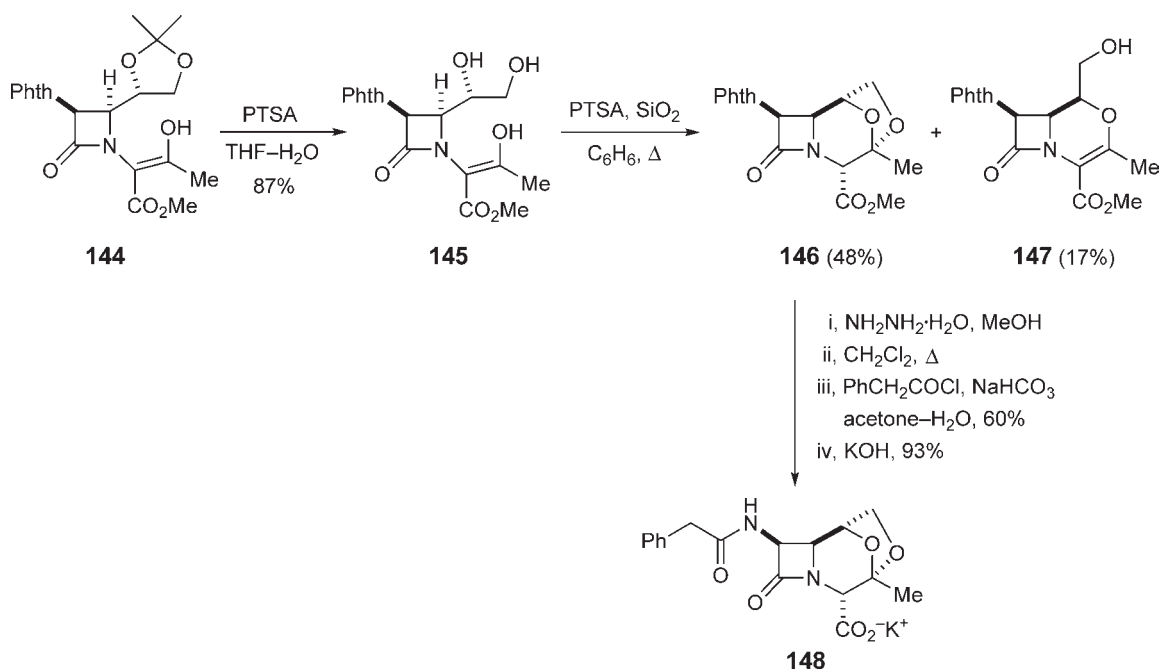
As a consequence of the increased resistance of bacteria to classical β -lactam antibiotics, several strategies devoted to the synthesis of new bi- and polycyclic β -lactam derivatives have been developed, giving rise to a large number of compounds featuring enhanced antibacterial activity or better resistance toward β -lactamases. It is the aim of this section to extend previous accounts on this subject in CHEC(1984) and CHEC-II(1996) and to summarize several recent methodologies concerning the preparation of these fused heterocycles.

2.02.9.1 Synthesis of Carbacephams and Carbacephems

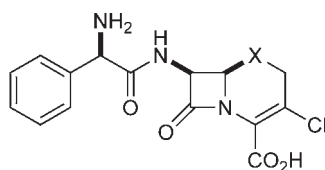
Carbacephems, in which the sulfur atom at position 1 is replaced by a methylene group, have been shown to have comparable activity as the corresponding cephalosporins. An illustrative example is loracarbef **149**, which possesses a spectrum of biological activity similar to cefaclor **150** but is substantially superior in chemical stability. This oral antibiotic is currently on the market and has found specialized use in the treatment of pediatric ear infections. However, unlike their sulfur counterparts which are usually obtained by partial synthesis from either penicillin sulfoxide esters or side chain modifications of natural cephalosporins, carbacephems are currently only available by total or semisynthesis. During the present decade many different syntheses of the carbacephem antibiotic loracarbef have been published. Although there are few examples involving the construction of the six-membered ring first, followed by cyclization to give the bicyclic β -lactam, most of the procedures described in the literature assemble the six-membered ring last, with formation of the C(4)–N(5) and C(3)–C(4) σ -bonds.



Scheme 26

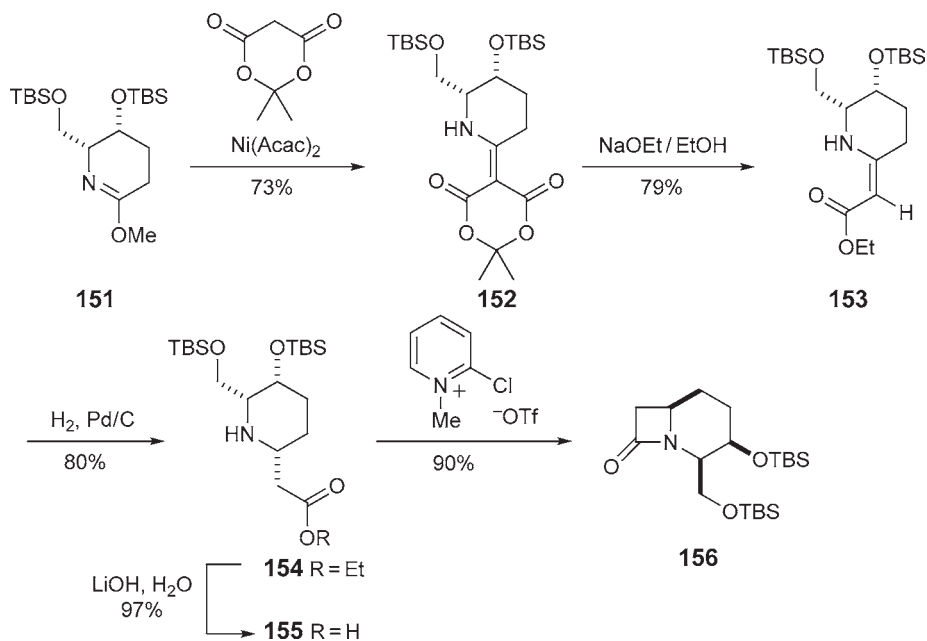


Scheme 27

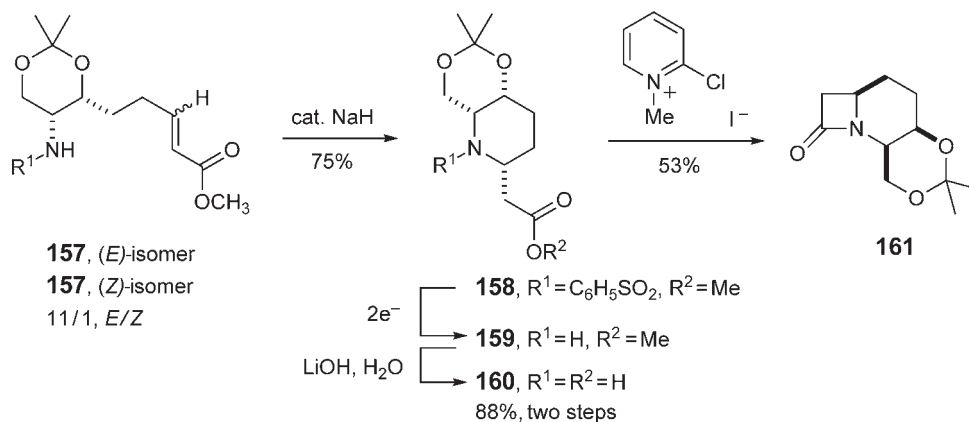


The synthesis of carbacephams **156** and **161** from D-serine has been described by two routes involving initial construction of the six-membered ring followed by cyclization to give the bicyclic β -lactam <1998JOC8170>. First, the preparation of the carbacepham core has been carried out by the lactim ether route (Scheme 28). The lactim route to the carbacepham core relies on the generation of the lactim ether **151**, followed by condensation with Meldrum's acid in the presence of a catalytic amount of Ni(Acac)₂ (Acac – acetylacetonate) giving the 2,2-dimethyl-4,6-dioxo-1,3-dioxanylidene derivative **152** in high yield. Monodecarboxylation using NaOEt/EtOH gave the enamino ester **153**. Subsequent stereospecific hydrogenation using Pt as a catalyst gave the *syn*-diastereomer 6*R*-ethoxycarbonylmethyl-substituted piperidine **154** in 80% yield. Hydrolysis of ester **154** with LiOH and followed by cyclization of the resulting amino acid **155** gave carbacepham **156** in excellent overall yield. Closure of the piperidyl β -amino acid intermediate was accomplished using a modified Mukaiyama reagent where triflate was acting as a counterion.

A more direct alternative to the lactim ether route for the formation of the carbacepham core has also been proposed, using a stereospecific Michael cyclization (Scheme 29). The possibility of using a stereocontrolled Michael cyclization on an amino ester such as (*E*)-**157** or (*Z*)-**157** has been devised to generate the piperidine **158** possessing the *R* stereochemistry of the methoxycarbonylmethyl tether required in the β -lactam. After several attempts in order to obtain compound **158**, the best conditions were found when the reaction was carried out in the presence of NaH at temperatures above 50 °C, yielding compound **158** in 75% yield together with 20–25% recovered starting material. Electrolytical treatment of compound **158** in order to selectively remove the benzenesulfonyl moiety, in the presence of the methyl ester, produced amino ester **159** in 90% yield. Further hydrolysis of the ester **159** with LiOH provided **160** in 98% yield. Although isolation of **160** was difficult, cyclization of the amino acid **160** with *N*-methyl-2-chloropyridinium iodide gave the β -lactam **161** in 53% yield.

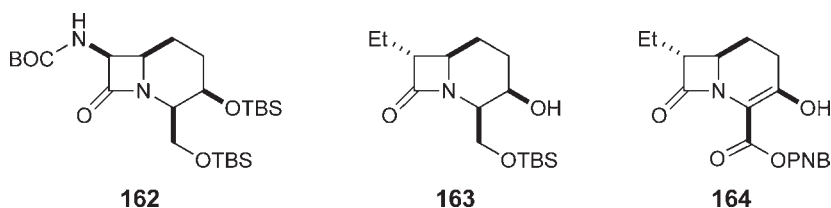


Scheme 28



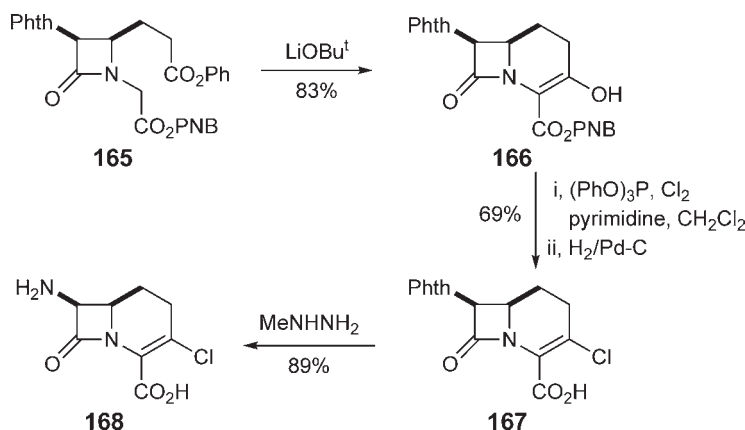
Scheme 29

The resulting carbacepham compounds have been stereospecifically substituted at C-7 with an ethyl or amino functionality to obtain compounds **162** and **163**. Finally, carbacepham **164** can be obtained from carbacepham **163** by sequential oxidation with RuO_4 and Dess–Martin periodinane.



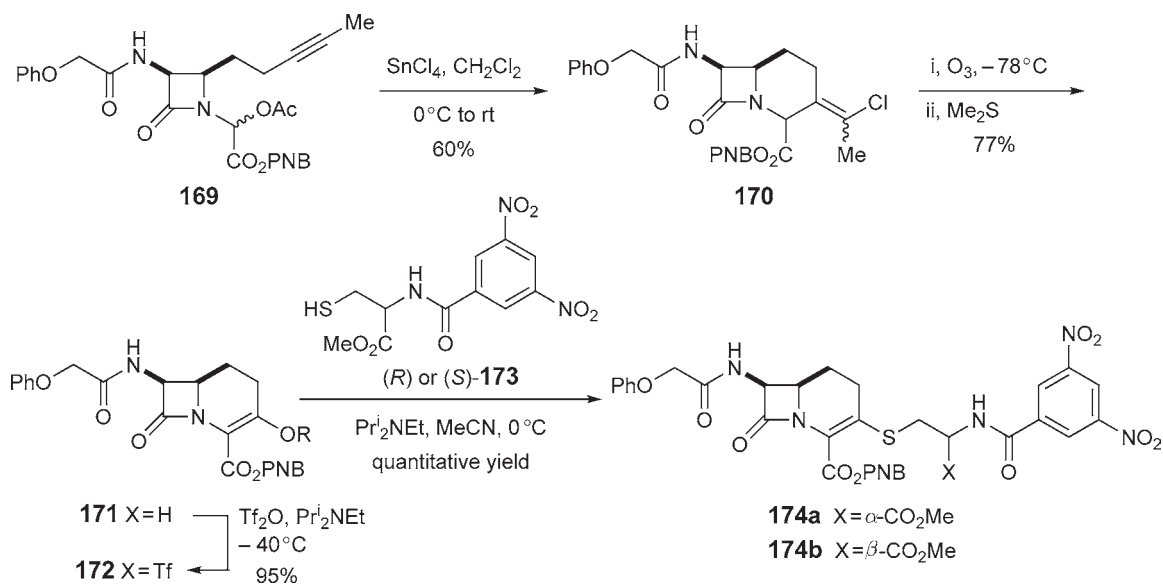
The utilization of the Mitsunobu reaction and Dieckmann condensation has been demonstrated for the highly efficient and enantioselective synthesis of loracarbef, starting from the unnatural amino acid (2*S*,3*S*)-2-amino-3-hydroxy-6-heptenoic acid <2000T5667, 2003TL5991> (Scheme 30). The cyclization step from monocyclic

azetidinone **165** was performed using 3.3 equiv of LiO(*t*-Bu) at low temperature affording enol **166** in 83% yield. Chlorination of the enol followed by deprotection of the ester gave compound **167**. Finally, the loracarbef nucleus **168** was obtained by removal of the phthalimido protecting group using methylhydrazine.



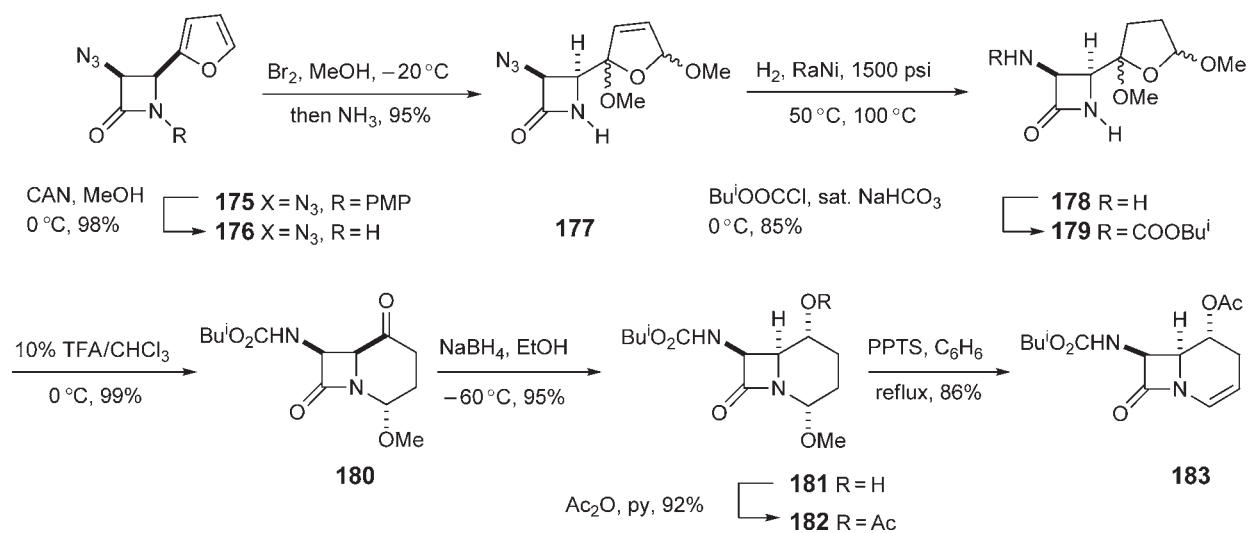
Scheme 30

Overman has developed a new method for constructing carbacephems involving the formation of the C(3)–C(4) σ -bond by a chloride-terminated *N*-acyliminium-alkyne cyclization (**Scheme 31**). Using this approach, exposure of **169** to SnCl₄ followed by allowing the reaction mixture to warm to room temperature provided the desired 3-(1-chloroethylidene)carbacephem **170** in 60% yield [<1997JOC9210>](#). Cleavage of the chloroethylidene group by an excess of ozone followed by treatment with Me₂S provided in 77% yield 3-hydroxy carbacephem **171**, which after treatment with triflic anhydride afforded triflate **172**. Condensation of **172** with the individual enantiomers of protected cysteine **173** gave diastereomeric vinylogous cysteine thioesters **174a** and **174b** in quantitative yield.



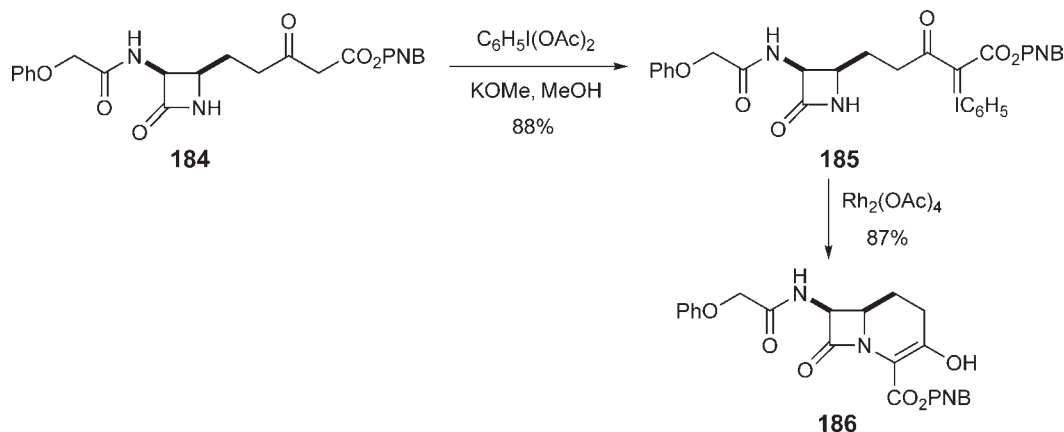
Scheme 31

The synthesis of carbacephems **183** and **186** involving C(4)–N(5) bond formation has been described. Carbacephem **183** has been prepared through aza-Achmatowicz rearrangement of 4-(2-furyl) azetidinones (**Scheme 32**) [<1996CC881, 1998SL105>](#). Azetidinone **175** was obtained by the formal cycloaddition of suitable ketenes with *N*-*p*-anisyl-2-furylimines.



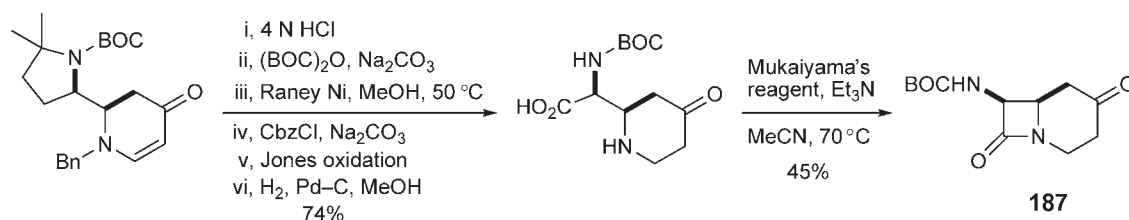
Scheme 32

Oxidative methanolysis of azetidinone **176** followed by hydrogenolysis of compound **177** afforded β -lactam **178**, which was protected to obtain the protected amine **179**. The best conditions for rearrangement of **179** were found using TFA. Conversion of compound **180** to carbacephem **183** was accomplished by ketone reduction, alcohol protection, and elimination of methanol. Synthesis of carbacephem derivative **186** has been performed by rhodium(II)-catalyzed cyclization of iodonium ylide **185** <1997TL6981> (Scheme 33). The iodonium ylide **185** was easily prepared from the corresponding β -keto ester **184** and [(diacetoxy)iodo]benzene in good yield.

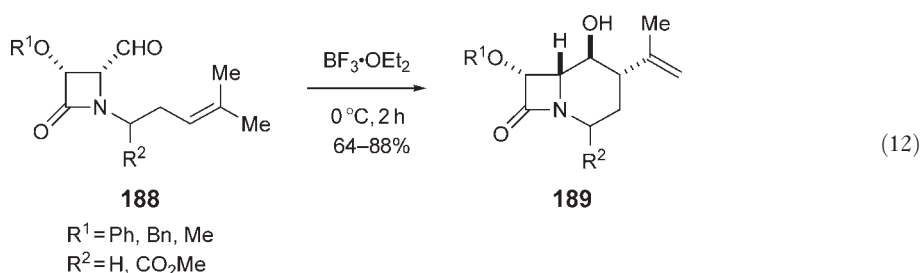


Scheme 33

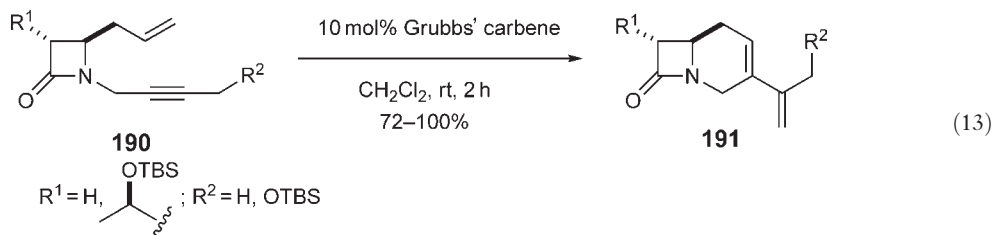
The titanocene(III) chloride-induced cyclization of four enantiomerically pure isomeric *N*-substituted epoxyaldehyde-2-azetidinones has been shown as a stereospecific entry to polyfunctionalized carbacephams <2003JOC2024>. A short asymmetric synthesis of the 2-ketocarbacephem **187** has been described with as the initial step the hetero Diels–Alder reaction of the benzylimine derived from the enantiomer of Garner's aldehyde with Danishefsky's diene for the preparation of the starting piperinone <2002JOC598>. The key cyclization step to form the bicyclic β -lactam system was achieved starting from a β -amino acid precursor using the Mukaiyama's reagent, 2-chloro-*N*-methylpyridinium iodide (Scheme 34). Enantiopure carbacephem derivatives **189** have been prepared in good yields via Lewis acid-promoted carbonyl-ene cyclization of the corresponding 2-azetidinone-tethered alkenylaldehydes **188** <2001OL4205> (Equation 12).



Scheme 34



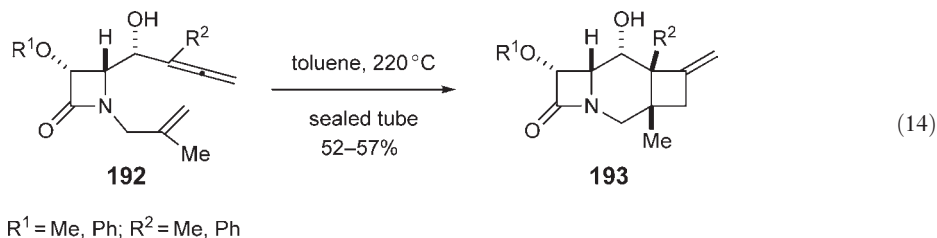
The synthesis of Δ^2 -carbacephems has been accomplished by ring-closing metathesis reaction of monocyclic diene- and enyne- β -lactams <1998JOC7893, 1999J(P1)1695>. The enyne metathesis of compounds **190** afforded bicycles **191** in good yields (Equation 13).



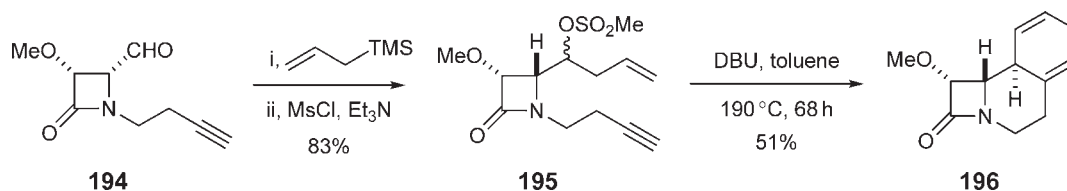
2.02.9.2 Synthesis of Polycyclic Carbacephem Derivatives

During the present decade, a wide variety of polycyclic carbacephem derivatives have been reported starting from readily available monocyclic β -lactams, which after transformation in more functionalized compounds and further cyclization yielded different fused carbacephems. Several approaches for the preparation of fused carbacephem derivatives including cycloaddition reactions such as the [2+2], 1,3-dipolar, and Diels–Alder reactions, as well as transition metal-catalyzed reactions such as the Pauson–Khand and ring-closing metathesis (RCM) reactions have been reported in the literature.

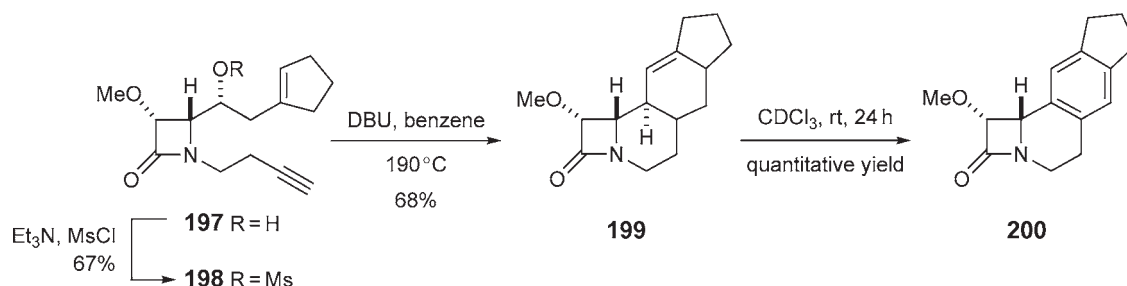
Indium-mediated reaction of 4-oxoazetidine-2-carbaldehydes with a propargyl bomide bearing aliphatic or aromatic substituents at the terminal position regioselectively provided the corresponding α -allenic alcohols **192** in moderate to high yields. Enantiopure strained tricyclic β -lactams **193** containing a cyclobutane ring have been prepared by intramolecular formal [2+2] cycloaddition of 2-azetidinone-tethered enalenols **192** (Equation 14) <2006CEJ1539>. The regioselectivity of this thermal cyclization is determined by the presence of an alkyl substituent at the internal alkene carbon atom, affording compounds **193** as single regio- and diastereomers. The tricyclic structures **193** arise from the formal [2+2] cycloaddition of the alkene with the distal bond of the allene, most likely via a diradical intermediate.



It has been demonstrated that the intramolecular Diels–Alder reaction (IMDA) is a simple and efficient entry to different tricyclic 2-azetidinones, with a six-membered ring fused to the β -lactam nucleus. The reaction of 4-oxoazetidine-2-carbaldehyde **194** with propenylmetal reagents yielded the corresponding homoallylic alcohol in high yield and with good diastereoselectivity. The mesylate of this homoallylic alcohol, **195**, was used for the stereoselective preparation of fused tricyclic 2-azetidinone **196** through a tandem one-pot elimination–intramolecular Diels–Alder reaction (Scheme 35) <1999TL1015, 2000JOC3310>. In similar way, the Lewis acid-promoted carbonyl-ene reaction of the above enantiopure 4-oxoazetidine-2-carbaldehyde **194** with methylenecyclopentane followed by mesylation of the homoallylic alcohol **197** to afford mesylate **198**, elimination, and intramolecular Diels–Alder reaction has allowed the preparation of enantiopure fused tetracyclic β -lactam **199** <2003JOC3106> (Scheme 36). 1,4-Cyclohexadiene **199** is prone to undergo aromatization to afford the tetracyclic β -lactam **200** containing a benzene ring, as illustrated in Scheme 36. Reaction of enallenes or allenynes **201** in the presence of methanesulfonyl

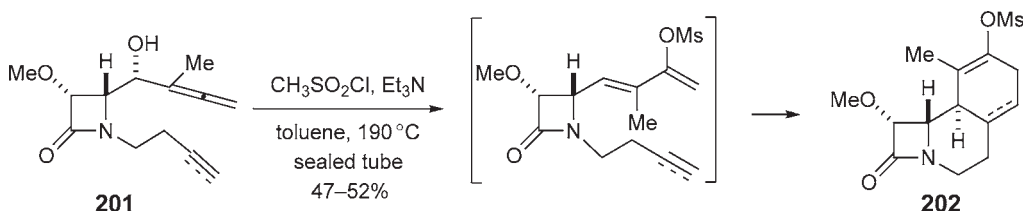


Scheme 35



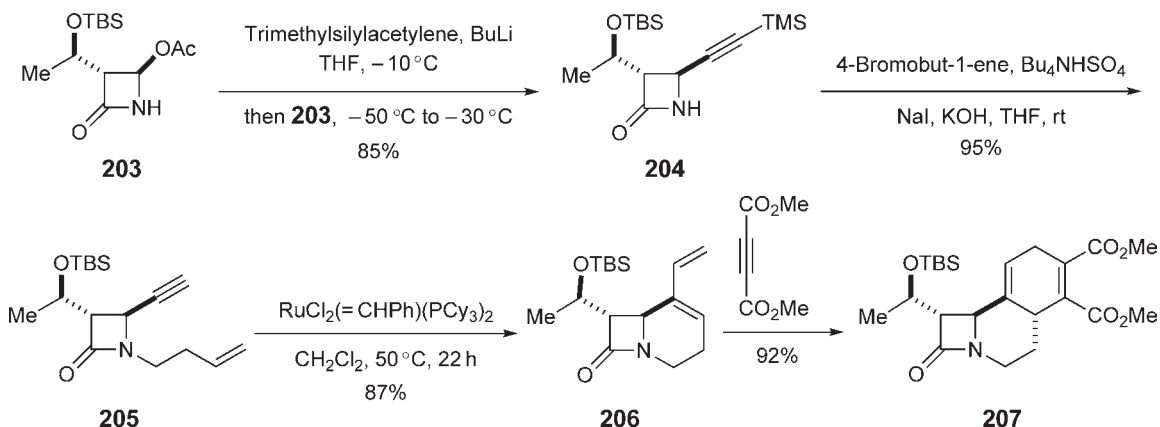
Scheme 36

chloride at 190 °C provided tricyclic azetidinones **202**. These tricycles have been obtained from monocyclic allenols **201**, masked functionalized dienes, via a domino allenol transposition/intramolecular Diels–Alder reaction process (Scheme 37). This transformation has been explained in terms of a migration of the methanesulfonyl group in the initially formed α -allenic methanesulfonate to give the corresponding mesyloxy-diene through a [3,3] sigmatropic rearrangement followed by intramolecular Diels–Alder reaction <2002CC1472, 2005EJO98>.

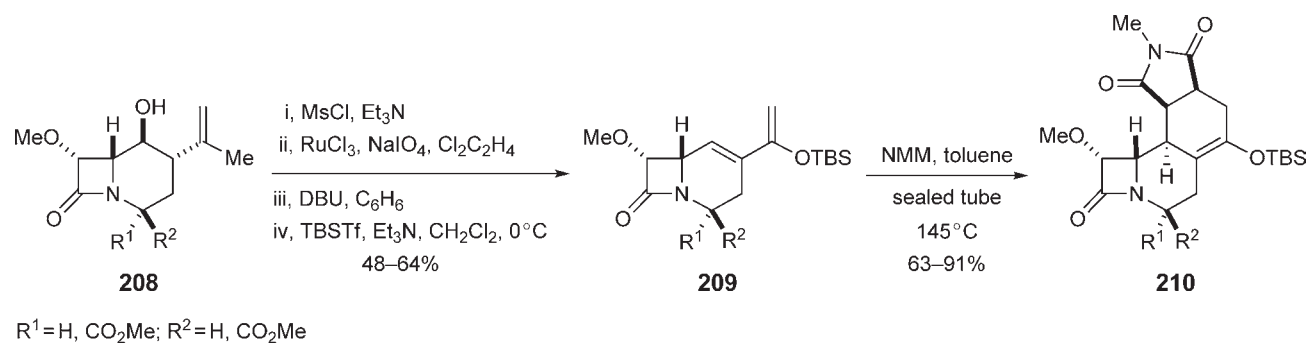


Scheme 37

It has been shown that the combination of ring-closing metathesis and Diels–Alder reaction sequences is a useful synthetic tool for the asymmetric synthesis of novel polycyclic carbacephem derivatives <2001TL2461, 2004EJO4840, 2004S2665>. Reaction of commercially available (3*R*,4*R*)-4-acetoxy-3-[(*tert*-butyldimethylsilyl)-oxy]ethyl-2-azetidinone **203** with lithium trimethylsilyl acetylide gave azetidinone **204** in 85% yield with retention of configuration. Alkylation of **204** under phase transfer conditions led to the desired enyne **205** in high yield. Enyne metathesis afforded bicyclic compound **206**. This diene was then engaged in a Diels–Alder reaction with dimethyl acetylenedicarboxylate as dienophile to obtain tricyclic β -lactam **207** in high yield (Scheme 38). Starting from enantiopure 1-hydroxycarbacephams **208**, the synthesis of inner–outer ring 2-[(*tert*-butyldimethylsilyl)-oxy]dienes **209** with a carbacephem structure and their totally π -facial *endo* selective Diels–Alder reactions to structurally novel polycyclic β -lactams **210** have been reported (Scheme 39) <2004TL7255>.

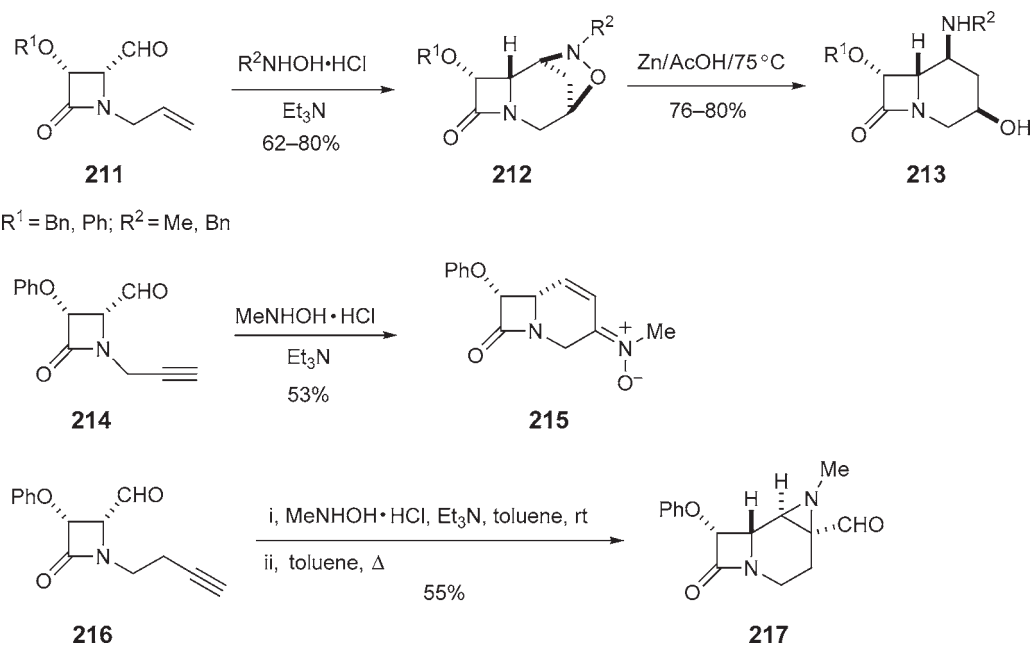


Scheme 38



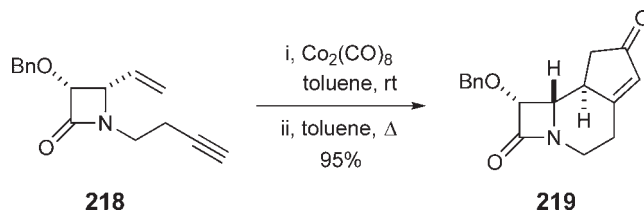
Scheme 39

The intramolecular nitronc-alkene cycloaddition reaction of monocyclic 2-azetidinone-tethered alkenyl(alkynyl) aldehydes **211**, **214**, and **216** with *N*-alkylhydroxylamines has been developed as an efficient route to prepare carbacepham derivatives **212**, **215**, and **217**, respectively (Scheme 40). Bridged cycloadducts **212** were further transformed into 1-amino-3-hydroxy carbacephams **213** by treatment with Zn in aqueous acetic acid at 75 °C. The aziridine carbaldehyde **217** may arise from thermal sigmatropic rearrangement. However, formation of compound **215** should be explained as the result of a formal reverse-Cope elimination reaction of the intermediate α -hydroxyhydroxylamine <1999TL5391, 2000TL1647, 2005EJO1680>.



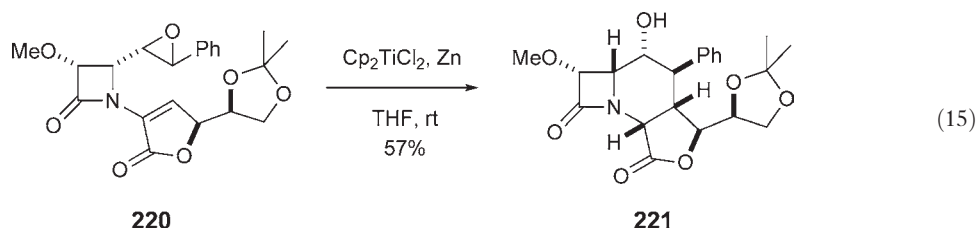
Scheme 40

A synthetic approach to enantiopure-fused tricyclic 2-azetidinone **219** of the carbacepham type has been developed using a Pauson–Khand reaction as the key step <1996TL6901, 1998JOC6786> (Scheme 41). Enyne-2-azetidinone **218** was tested for the Pauson–Khand reaction. Formation of the alkyne- $\text{Co}_2(\text{CO})_8$ complex occurred in quantitative yield. Treatment of such complex with trimethylamine-*N*-oxide afforded the desired tricyclic product **219**. Fused carbacepham derivatives were obtained by intramolecular aldol-type condensation of the corresponding monocyclic β -lactams with hexamethyldisilazane lithium salt (LHMDS) at low temperature, yielding the corresponding tricyclic β -lactams as single diastereomers <1996JOC7125>.

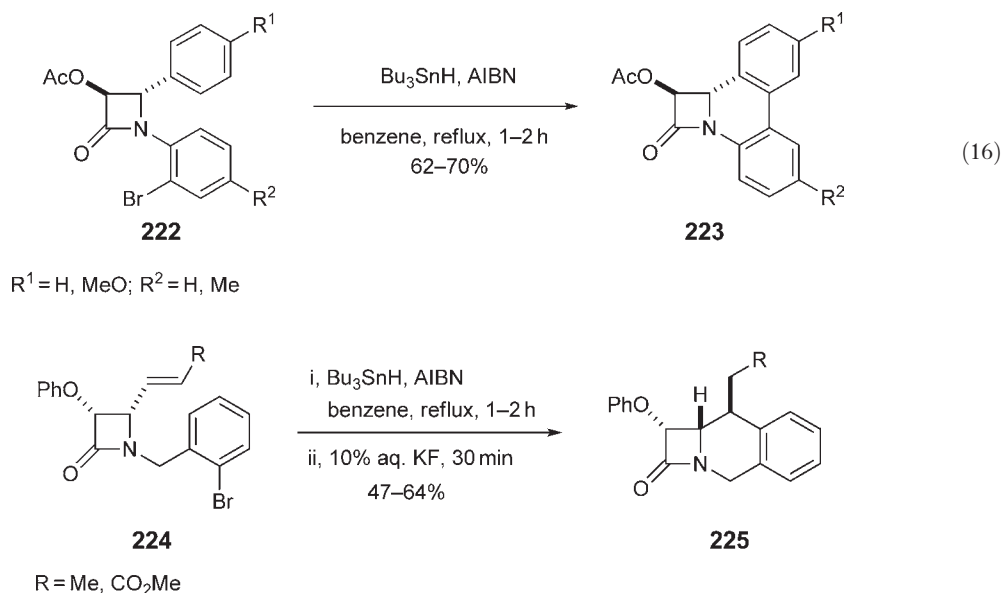


Scheme 41

The reductive opening of epoxy- β -lactam **220** with titanocene(III) chloride gives rise to a radical that can be trapped by intramolecular π -systems to give the tricyclic 2-azetidinone **221** (Equation 15) <2002JOC8243>.



β -Lactam-tethered haloarenes **222** have been used for the regiocontrolled preparation of fused tetracyclic biaryl-2-azetidinones **223** via aryl-aryl radical cyclization (Equation 16) <1998TL6589, 2005T7894>. An alternative synthesis of some β -lactam-biaryl hybrids related to **223** through Staudinger ketene-imine cycloaddition using phenanthridine as the imine component of the reaction has been developed <1999TL2005>. Starting from 2-azetidinone-tethered haloarenes **224**, a regio- and stereoselective preparation of benzocarpacephems **225** via intramolecular aryl radical cyclization has been achieved (Scheme 42) <1996TA2203, 2005T2767>. The preparation of 3,4-benzocarpacephems through lactamization of 1,2,3,4-tetrahydroquinoline-2-acetic acids has also been reported <1998J(P1)1203>.

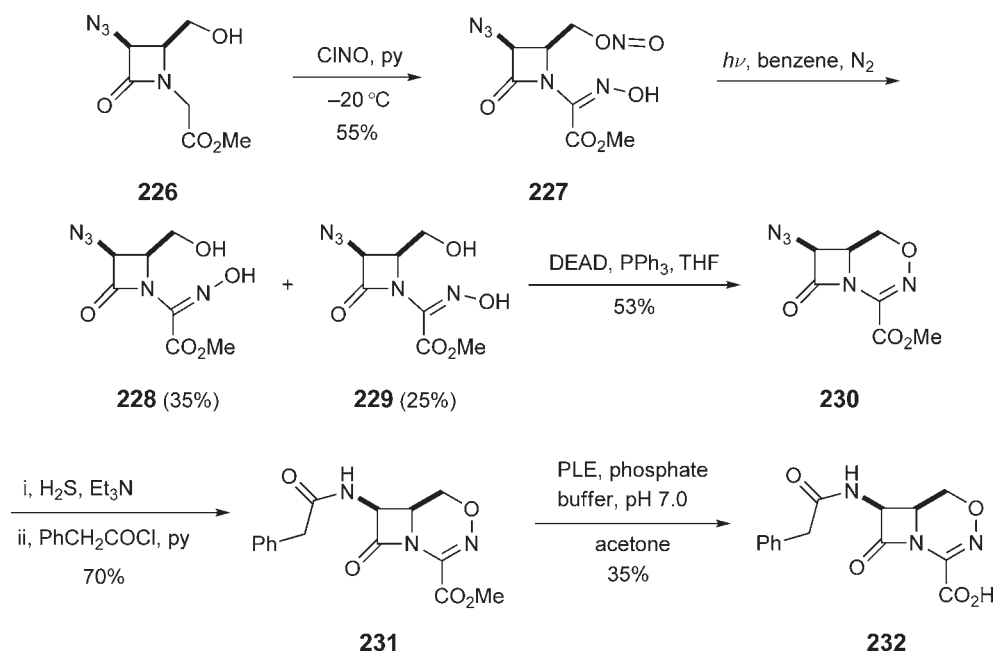


Scheme 42

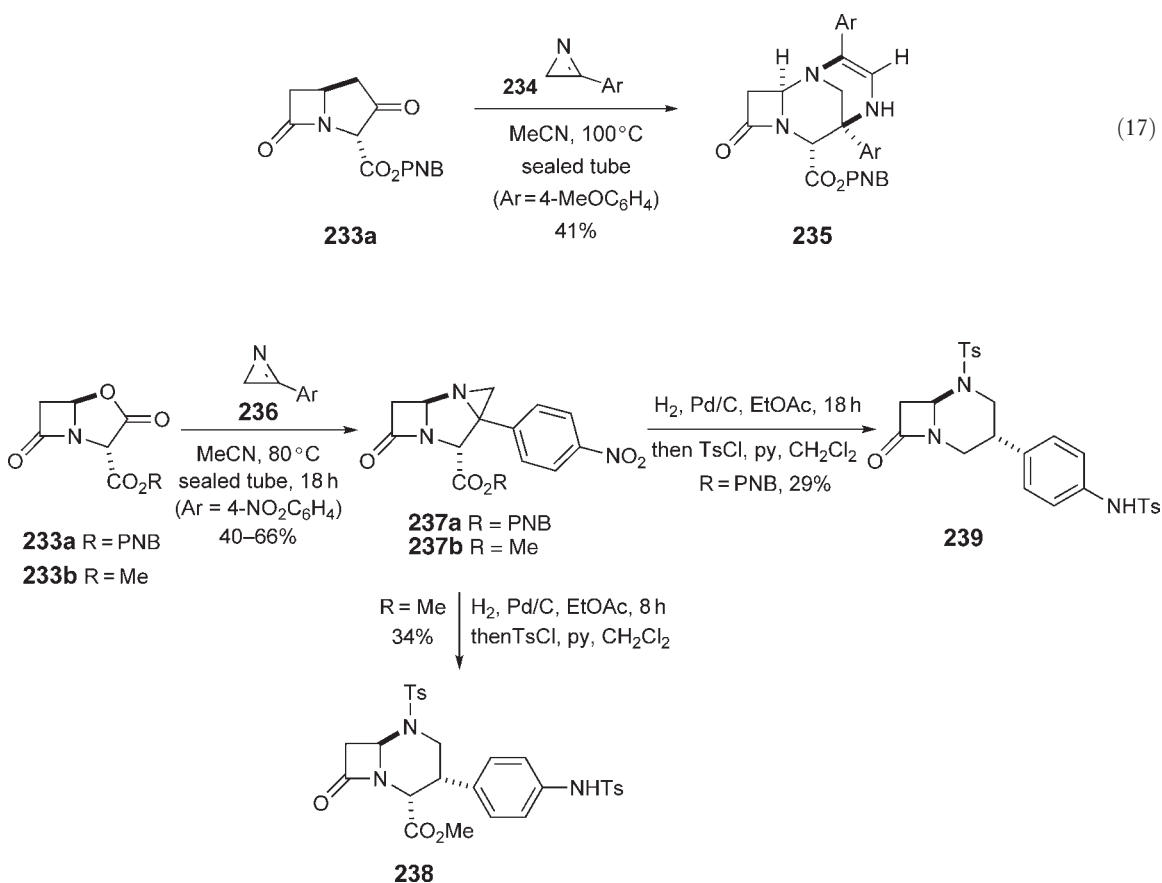
2.02.9.3 Synthesis of Other Nuclear Analogues

A large number of nuclear analogues of cephalosporins containing different heteroatoms (S, O, N) have been described in the literature during the present decade. 7-(Phenylacetamido)-3-aza-1-carba-2-oxacephem **232** was prepared from alcohol **226** as shown in Scheme 43. Alcohol **226** was reacted with nitrosyl chloride to generate nitrite ester **227**. Photolysis of compound **227** afforded two regioisomers, the *anti*-oximino β -lactam **228** and the *syn*-oximino β -lactam **229** <2003OBC2461>. Intramolecular cyclization of *syn*-oximino- β -lactam **229** afforded 7-azido-2-oxa-3-azacephem **230**, which was reduced and acylated. Enzymatic removal of the methyl group from **231** produced carbacephem derivative **232** showing high stability toward β -lactamases of different bacterial species.

The reactivity of 2*H*-azirines **234** and **236** as 1,3-dipolarophiles has been investigated toward β -lactam-based azomethine ylides derived from oxazolidinones **233** <2002J(P1)2014>. The reaction of 3-(4-methoxyphenyl)-2*H*-azirine **234** with oxazolidinone **233a** did not afford the expected cycloadduct; however, compound **235** was isolated as major product in 41% yield (Equation 17). In contrast, by using a nitroaryl moiety at the 3-position of the azirine ring, the initial cycloadducts **237** were prevented from further fragmentation (Scheme 44). Subsequent release (by nitro group reduction and protection) of the corresponding anilide then triggers the desired C–N bond cleavage. It has also been demonstrated that depending on the nature of the ester-protecting group (**237a** vs. **237b**), these conditions lead to either **238** or **239**, both of which are novel azacephem derivatives.

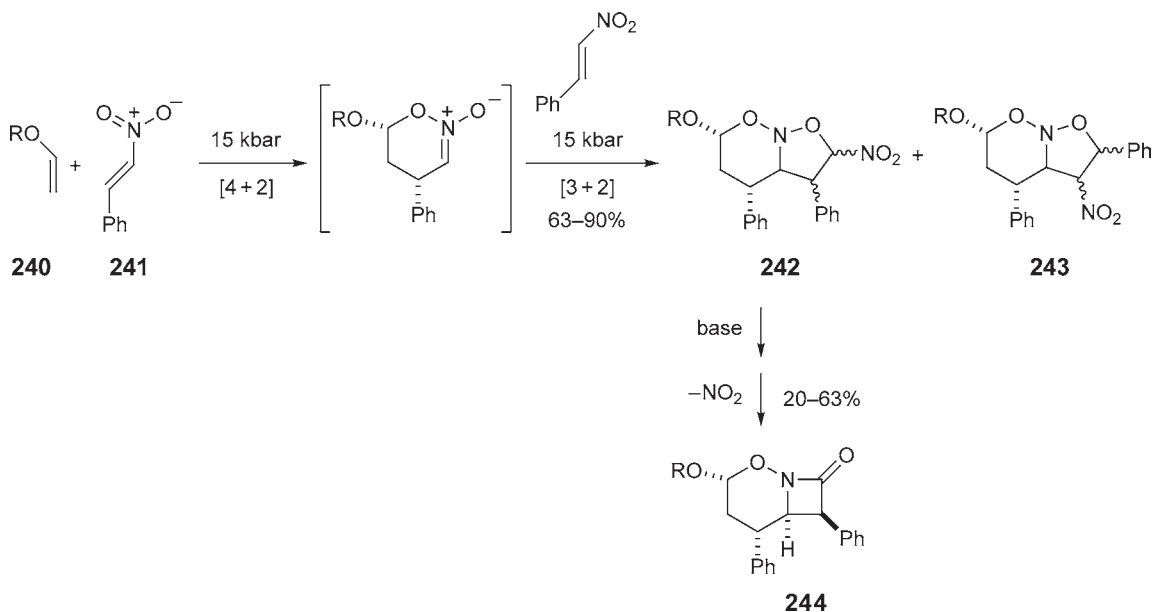


Scheme 43



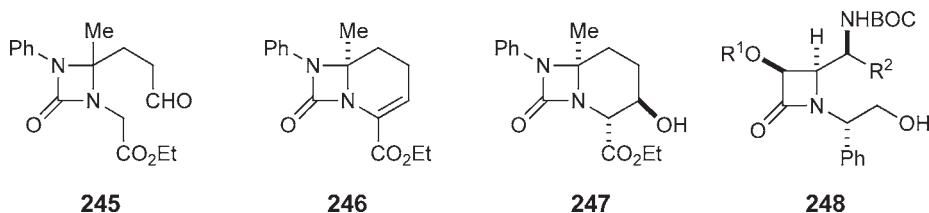
Scheme 44

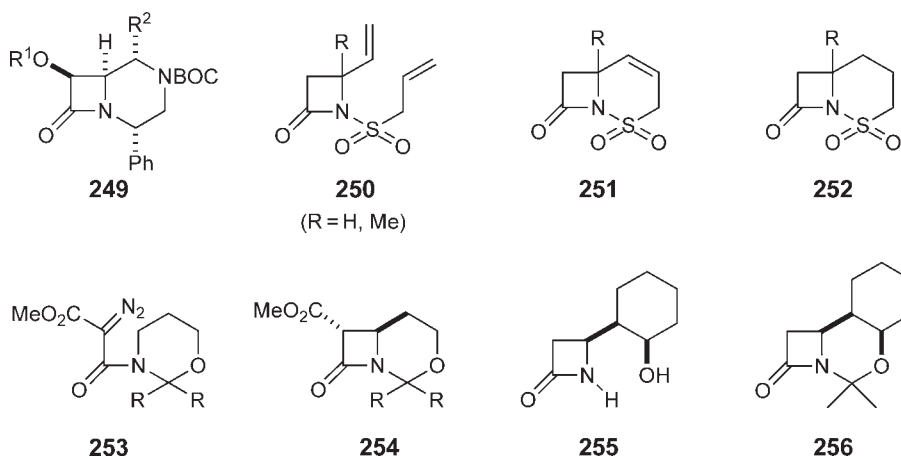
The oxygen atom directly attached to the nitrogen atom makes the β -lactam more susceptible to nucleophilic attack than the corresponding *N*-alkyl- β -lactams. Although polycyclic *N*-oxy- β -lactams, oxamazins, can be considered as attractive targets in the search for new antibiotics only a few articles describing their synthesis have been reported <1996T4225, 2004EJO4397>. A novel synthesis of bi- and tricyclic *N*-oxy- β -lactams has been described by high-pressure-promoted tandem [4+2]/[3+2] cycloadditions of enol ethers and β -nitrostyrene <1999CC855>. Tandem cycloaddition of the enol ether **240** with an excess of β -nitrostyrene **241** formed regioisomers **242** and **243** (Scheme 45). β -Nitrostyrene first reacts as an electron-poor diene in an inverse electron demand Diels–Alder reaction with an electron-rich enol ether, and thereafter as an electron-poor dipolarophile with the *in situ* formed mono adduct through a 1,3-dipolar cycloaddition. Main regioisomer **242** was converted in one step into β -lactam **244**.



Scheme 45

Azacarbacephem **246** and azacarbacephem **247** have been synthesized from formyl ester **245**, and evaluated on the principle that their reactions with the active site of Ser-OH will form a carbamoyl–enzyme intermediate that is sluggish to hydrolysis <1998J(P1)2597>. Synthesis of isoazacephem **249** has been accomplished by cyclization reaction of monocyclic β -lactam **248** <1997TL4643>. Cephalosporin–sulfonamide hybrids **251** and **252** have been prepared by RCM as the key operation from 4-vinyl-azetidin-2-ones **250**, followed by hydrogenation of unsaturated sultams **251** to provide **252** <2004S1696, 2004TL3589>. Construction of 3-oxa-1-azabicyclo[4.2.0]octanes **254** has been achieved by intramolecular C–H insertion of α -methoxycarbonyl- α -diazoacetamides **253** catalyzed by dirhodium(II) complexes <1998CC1517, 1998TL9063>. Lewis acid treatment of monocyclic β -lactam **255** with dimethoxy propane afforded acetone derivative **256** <1996TA2929, 1996TL2467, 1997TA15>.





2.02.10 Practical Use of Cephalosporins and Analogues in Medicine

The following section has two main objectives: first, to summarize the classification of cephalosporins in terms of their spectrum of activity and second, to provide an overview of the new cephalosporin antibiotics discovered in the last decade.

2.02.10.1 Classification and Spectrum of Activity

Cephalosporins are classified into generations based on general features of their antimicrobial activity <2001MI1391>. The early cephalosporins (first-generation cephalosporins) had good activity against a wide range of Gram-positive bacteria, including a number of strains that produce penicillinases. In contrast, they tend to have a very limited activity against Gram-negative bacteria. Cefazolin and cefradine, typical first-generation products, are still widely used in China but generally less and less elsewhere. The therapeutic limitations of the first generation of products led to the development of the so-called ‘second-generation’ products (cefamandol, cefaclor, and cefuroxime). These compounds are characterized by a slightly poorer effect on Gram-positive bacteria but a significantly improved activity against enterobacteria and better resistance toward β -lactamases, especially those from Gram-negative species. The third-generation products (e.g., cefotaxime, ceftriaxone, and cefixime) were designed to have enhanced activity against Gram-negative bacteria, while retaining good activity for Gram-positive bacteria. The newest, fourth-generation, products (cefepime and ceftipime) couple the anti-Gram-negative activity of the third- (and some of the second-) generation products with the anti-Gram-positive activity of the first. Generally, too, the later generation products have better pharmacokinetics and pharmacodynamics than the earlier generation products.

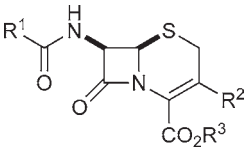
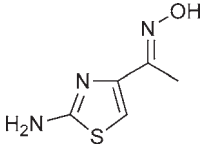
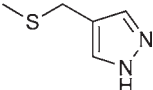
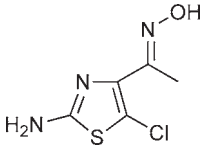
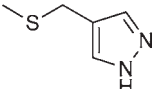
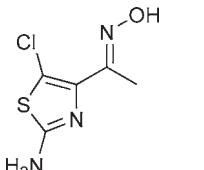
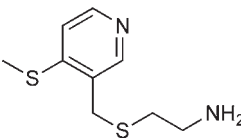
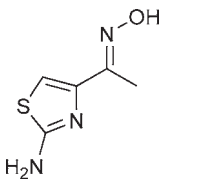
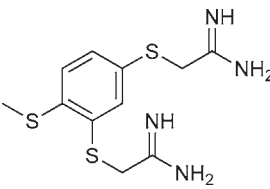
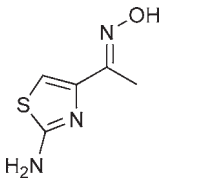
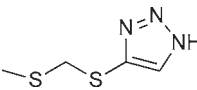
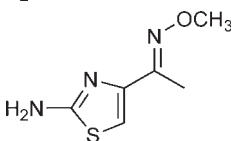
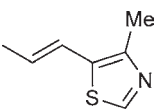
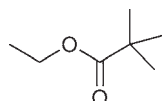
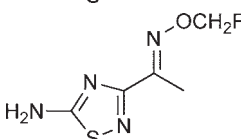
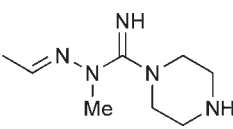
2.02.10.2 New Cephalosporin Antibiotics

Cephalosporins are widely used antibacterial agents, primarily due to their broad spectrum of activity and low toxicity. Several cephalosporin derivatives are already in the market, while a relatively small number of cepems are currently in clinical trials. In addition, many cepems are reported to be in preclinical development. The newer generation cepems have generally focused on two parameters: broadening the spectrum to include resistant pathogens as well as improving the pharmacokinetic properties, whether for oral or intravenous use. Because of their broad spectrum of activity and low toxicity, cephalosporins are excellent choices for initial treatment of many infectious diseases. Determining the specific agent to use depends on the clinical setting, patient factors, and local susceptibility patterns.

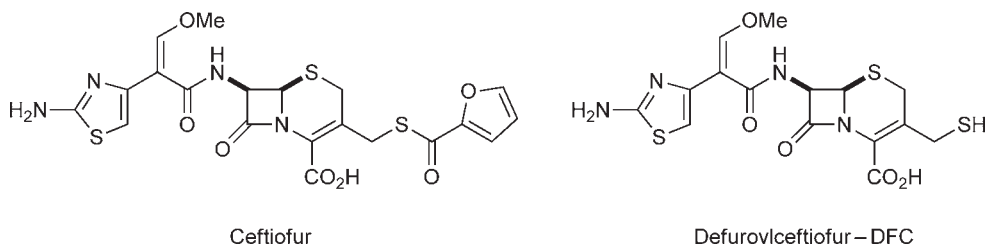
Table 1 summarizes some of the most important cephalosporin antibiotics that have been synthesized and evaluated during the last decade. FK041 and FR192752 (entries 1 and 2, respectively) are new orally active cephem antibiotics exhibiting broad spectrum activity against both Gram-positive and Gram-negative bacteria. While MC-02331 (entry 4) has excellent *in vitro* potency and good *in vivo* efficacy, the compound suffers from low solubility. Replacement of one of the basic group (e.g., a pyridine) resulted in a compound with improved solubility but decreased potency. Use of a primary amine instead of the amidine gave improved potency. Final refinement by addition of the chloro group at C-7 provided MC-02479 (entry 3), which has good solubility and potency in

clinical trials. S-1090 (entry 5), also known as cefmatilen, is an orally active cephalosporin in clinical trials. A key structural feature is the thiomethylthiotriazole moiety at C-3, which confers enhanced Gram-positive bacteria and oral bioavailability compared with other cepheims. On the other hand, cefditoren (entry 6) has shown to have a broad spectrum of activity against many Gram-negative and Gram-positive aerobes and high stability by many common β -lactamases. CB-181963 (entry 7) is a novel parenteral investigational cephalosporin exhibiting a broad antibacterial spectrum, although toxicity and pharmacokinetic/pharmacodynamic studies are being evaluated.

Table 1 New parenteral and oral cephalosporin antibiotics

					
Entry	Name	R ¹	R ²	R ³	References
1	FK041			H	1998JAN683, 1999JAN649
2	FR192752			H	2000JAN1223
3	MC-02479			H	2001CME1775
4	MC-02331			H	2001CME1775
5	S-1090			H	2001CME1775
6	Cefditoren				2001MI1924
7	CB-181963			H	2004AAC4037

Use of cephalosporin antibiotics has not been limited for human use. In this context, a third-generation broad spectrum cephalosporin, ceftiofur, exclusively for veterinary medicine has been developed <2002MI717>. Ceftiofur contains an oxymino aminothiazolyl group as the 7- β amino-acyl substituent of the 7-aminocephalosporin nucleus and a furoic acid thioester at position 3, which is a unique substitution for third-generation cephalosporins. The primary metabolites of ceftiofur, namely defuroylceftiofur (DFC), which result from the hydrolytic cleavage of the thioester bond to liberate furoic acid, and the defuroylceftiofur dimer (DFC-dimer), where DFC condenses with itself, retain the β -lactam ring and the oxymino-aminothiazolyl group of ceftiofur. Thus, ceftiofur and its principal metabolites, DFC and the DFC-dimer, are structurally related to third-generation cephalosporins and thus retain the activity inherent to ceftiofur itself.



2.02.11 Mode of Action and Resistance Development

The aim of this section is to describe some specific resistant mechanisms of bacteria against cephalosporin antibiotics focusing on β -lactamase action and the interaction of cephalosporins with penicillin binding proteins (PBPs).

Cephalosporins, like other β -lactam drugs, exert their antimicrobial effect by interfering with the synthesis of peptidoglycan, a major structural component of the bacterial wall. The three most common mechanisms by which bacteria can resist the effects of cephalosporins are (1) the production of enzymes (β -lactamases) to inactivate the drugs, (2) alteration of the drug target (essential PBPs), and (3) changes in the cell outer membrane that limit the ability of the drug to reach its target. Any combination of these resistance mechanisms can exist in individual bacterial cells <1996MI37>.

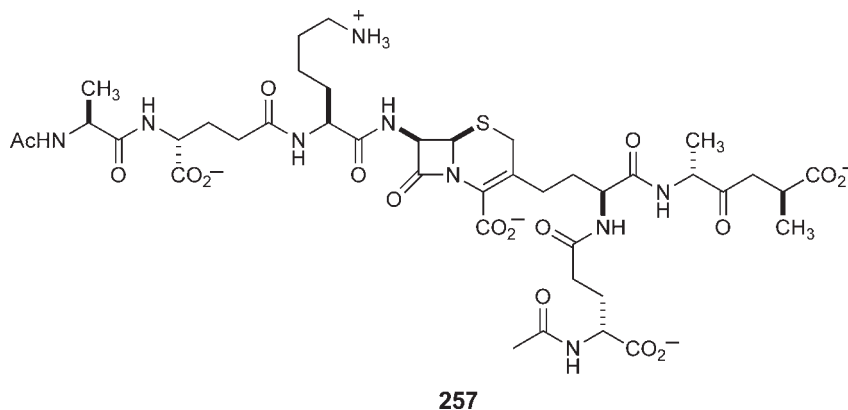
Crystallographic studies <2001B6233, 2004JBC9344>, mutagenic analysis <2001JBC46568>, and chemical complementation <2005CBC2055> among others have helped to shed light on the evolution of the mechanism of resistance in the class C enzymes. In this context, it has been described that ceftazidime is a potent inhibitor of the wild-type (wt) class C enzymes because of the fact that the tetrahedral intermediate formed in the enzyme's acylated state cannot achieve a conformation that is competent for deacylation due to steric clashes between the oxymino side chain and the dihydrothiazine ring of ceftazidime <2001B9207>. It has been proposed that for β -lactamases to become effective as antibiotic resistance enzymes, they should undergo structure alterations such that they would not interact with the peptidoglycan <1998AAC1>. To test this notion a cephalosporin analogue, 7 β -[N-acetyl-L-alanyl- γ -D-glutamyl-L-lysine]-3-acetoxymethyl-3-cephem carboxylic acid, has been conceived and synthesized <2003JA9612>. The X-ray structure of the complex of this cephalosporin bound to the active site of the deacylation-deficient Q120L/Y150E variant of the class C AmpC β -lactamase from *E. coli* has been solved. This complex has revealed that the surface for interaction with the strand of peptidoglycan that acylates the active site, which is present in PBPs, is absent in the β -lactamase active site.

The hydrolysis of cephalosporin β -lactam antibiotics by zinc-dependent metallo- β -lactamases (class B) generates dihydrothiazines which subsequently undergo isomerization at C-6 by C-S bond cleavage and through the intermediacy of a thiol. These thiols can be trapped by the β -lactamase from *B. cereus*, causing inhibition of the enzyme. The rate of production of the thiol corresponds to the rate of inhibition, and the inhibition's constants are in the micromolar range but vary with the nature of the cephalosporin derivative. The structure of the thiols causing inhibition has been identified by NMR studies showing that the thiol binding to the zinc ion perturbs the metal-bound histidines. Inhibition is slowly removed as the thiol becomes oxidized or undergoes further degradation. In particular, the thiol intermediate generated from cephalthrin is a slow binding inhibitor <2005B8578>.

The mechanism of hydrolysis of cefepime by the class A TEM_{pUC19} β -lactamase has been investigated <1996JA7441>. Models for the active-site binding of this antibiotic indicate severe steric interactions between the

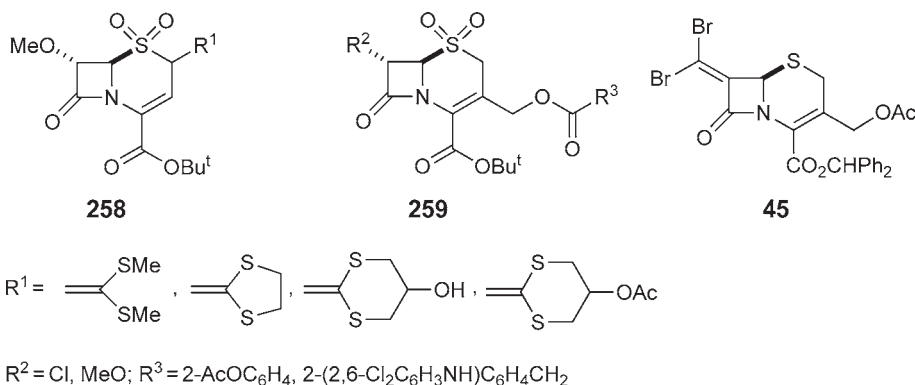
active site of the enzyme and the C_{7β} function of cefepime. Specific interactions with the side-chain functions of Pro-167 and Asn-170, amino acids present in the Ω-loop spanning residues 164–179, have been singled out as important in the interactions with the antibiotic. These interactions displace the hydrolytic water from its preferred position for the deacylation step. These observations have confirmed the experimental evidence that deacylation is the rate-limiting step in the turnover of the cefepime by this β-lactamase.

A cephalosporin derivative **257** with structural features of the peptidoglycan has been conceived as an inhibitor specific for DD-transpeptidases <2003JA16322>. The compound **257** has been synthesized in 13 steps and has been tested with recombinant PBP1b and PBP5 of *E. coli*, a DD-transpeptidase and a DD-carboxypeptidase, respectively. It has been found that compound **257** is a time-dependent and irreversible inhibitor of PBP1b and does not interact with PBP5, neither as an inhibitor (reversible or irreversible) nor as a substrate.



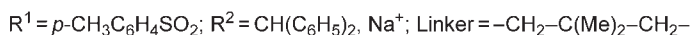
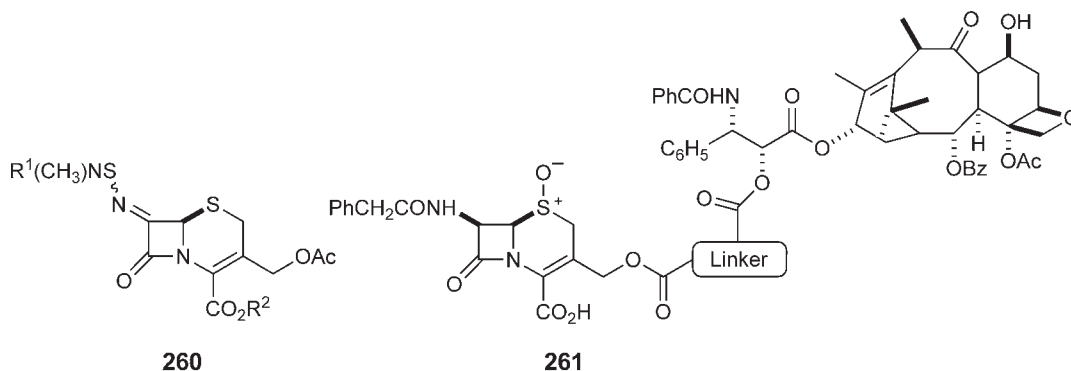
2.02.12 Miscellaneous Applications

During the last decade, chemical modifications of the C-2, C-3, C-4, and C-7 positions of the cephalosporin moiety as well as molecular modeling techniques have been performed with the aim of obtaining potent elastase inhibitors. The synthesis and evaluation of new C-2-substituted cephem sulfones **258** has been undertaken. These compounds have been tested for their elastase inhibitory activity against HSE. The values obtained have indicated that the introduction of 1,3-dithiolan-2-ylidene moiety at C-2 of the cephem sulfone nucleus potentiates the elastase inhibitory activity <1996BML823>. A double hit mechanism of elastase inhibition by the expulsion of carboxylic acid from C-3' acyloxy moiety has been successfully employed in the preparation of anti-inflammatory DACs containing aspirin or ciclofenac attached to the C-3 methylene group of cephalosporanate sulfones **259** <1997BML843>. The discovery of HLE inhibition activity by 7-haloalkylcephalosporanate **45** has stimulated structural variations at C-7 and S-1 positions of the cephem nucleus, thus permitting to reach a desired biological effect <1997JME3423>.

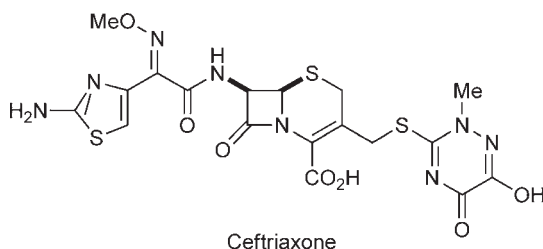


It has been shown that cephalosporin structures bearing an *S*-aminosulfenimine side chain at the 7-position, such as in compounds **260**, are prototypic examples of novel classes of β-lactamase-dependent prodrugs wherein enzyme-catalyzed

cleavage of the β -lactam ring triggers the rapid expulsion of the *S*-amino moiety <1999JOC3132>. This reaction pattern constitutes an enabling technology at the molecular level and has a potential application in antibody-directed enzyme prodrug therapy (ADEPT) and in the further development of β -lactamase-dependent prodrugs for use as antibiotics <2000T5699, 2004JOC7965>. Paclitaxel conjugates of 7-phenylacetamidocephalosporanic acid have also been prepared as prodrugs for site-specific activation by targeted β -lactamases <2003BML539>. In particular, *in vitro* cytotoxicity assays showed that the prodrug **261** was less toxic than the natural product paclitaxel.



A new property of the known third-generation antibiotic ceftriaxone has been documented as a potential neurotherapeutic, modulating the expression of glutamate neurotransmitter transporters, GLT1, via gene activation <2005NAT73>.



2.02.13 Further Developments

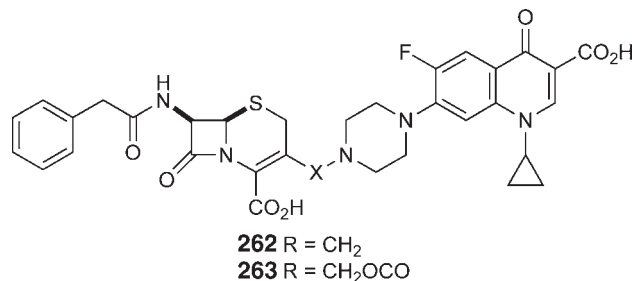
Recent developments have been centered mainly in theoretical, analytical and synthetical aspects of the cephalosporin core. These new achievements are briefly summarized below.

The thermochemistry of some cephams and cephems has been investigated by high-level *ab initio* methods. Particular attention has been paid to estimate the magnitudes of amide resonance and ring strain <2006JPCA10521>. Determination of the kinetic parameters for interactions of three cephalosporins with PBPs has been reported <2006JBC10035>.

A rapid and simple reversed phase HPLC method has been developed and validated for the estimation of ceftriaxone and ceftizoxime. The cephalosporins have been resolved on a reversed-phase C_{18} column utilizing a mobile phase of methanol and water <2006MI3207>. Evaluation of the liquid chromatographic behavior of a series of five cephalosporin antibiotics (cefoperazone, cephacetril, cephalixin, cephapirin, and ceftiofur) in bovine milk has been reported <2006JFA1180>. Analysis of cephalosporins in bronchial secretions by capillary electrophoresis after simple pretreatment has been reported. The lyophilization was found to be a simple but effective pretreatment of these samples to bring them into a form which has been shown suitable for injection to CE <2007JCB355>. An off-line solid phase extraction (SPE) for improving the sensitivity in the CE analysis of four cephalosporins has also been developed. The off-line SPE-CE has been validated for river water <2007MI501>. ^{13}C NMR spectroscopy data for 25 cephalosporin derivatives have been assigned by combination of one- and two-dimensional experiments. The

effect of the substitution at C-3, C-7 and C-4 acid group positions on the chemical shifts of the cephem nucleus has been discussed <2007MRC236>.

The role of nitrogenated compounds in the biosynthesis of cephalosporins and its regulation has been discussed. The most important amino acids from the viewpoint of regulation are lysine, methionine, glutamate and valine <2006MI67>. The syntheses and anti-tuberculosis activity of quinolone-cephalosporin conjugates (262 and 263) have been described. Both derivatives have shown broad-spectrum antibacterial activity and significant anti-tuberculosis activity <2006BMCL5534>.



It has been demonstrated that the [2+2] cycloadducts of chlorosulfonyl isocyanate (CSI) to 2-*O*-allenyl-1,3-benzylidene-L-erythritol are versatile intermediates for the preparation of a wide range of 7-substituted-5-oxa-cephams and for the introduction of the carboxylic function to the C-2 carbon atom <2006T10928>. The synthesis of four *trans*-stereoisomers of 7-(1-hydroxyethyl)-2-isooxacephem-4-carboxylic acids, analogues of thienamycin, has also been reported <2006TA3111>. A polyhydroxylated carbacephem has been designed and synthesized as a potent glycosidase inhibitor <2006TL7923>. A carbacephem derivative has been obtained in excellent yield by intramolecular Horner–Emmons reaction <2007JOC415>. An approach to substituted benzocarba-cephems from epoxy-benzonitrile-2-azetidinones by radical cyclization using titanocene monochloride has been reported <2007SL1243>.

It has also been reported that patients with allergic-like events after penicillin treatment have had a markedly risk of events after subsequent cephalosporin antibiotics. Cross-reactivity is not an adequate explanation for this increased risk and the data obtained indicate that cephalosporins can be considered for patients with penicillin allergy <2006MI354.e11>. Comparisons of parenteral broad-spectrum cephalosporins have been tested against bacteria isolated from pediatric patients. The results have indicated that cefepime has been the most broad-spectrum cephalosporin analyzed and it is a very potent alternative for the treatment of contemporary pediatric infections in North America <2007MI109>. The historical safety of the most commonly used oral cephalosporins has been reviewed <2007MIS67>. The antimicrobial spectrum and *in vitro* potency of the most frequently prescribed orally administered cephalosporins (cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime axetil and cephalexin) has also been reviewed <2007MIS5>.

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Biographical Sketch



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2.03

Penicillins

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2.03.1 Introduction

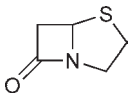
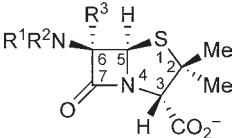
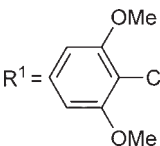
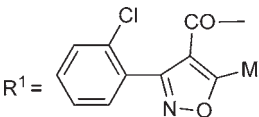
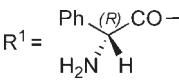
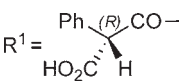
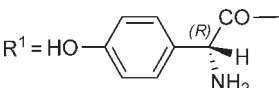
The generic term ‘penicillin’ covers a large family of antibiotics featuring an azetidin-2-one ring (β -lactam) fused to a five-membered ring ([Table 1](#)). The related family named ‘cephalosporin’ involves the azetidin-2-one core fused to a six-membered ring ([Table 2](#)). Both families belong to that so-called ‘ β -lactam antibiotics’ class, an important class of therapeutic agents that also contains several monocyclic azetidin-2-ones ([Table 3](#)). Since the amount of relevant literature concerning β -lactam antibiotics is so abundant, the reader who needs to be introduced to the subject is invited to first consult books of general interest <[B-1972MI1](#), [B-1980MI1](#), [B-1981MI1](#), [B-1985MI1](#), [B-1989MI1](#), [B-1982MI1](#), [B-1983MI2](#), [B-1991MI1](#), [B-1992MI2](#), [B-1992MI3](#), [B-1997MI400](#), [B-2003MI1](#), [B-2006MI1127](#), [B-2007MI\(7\)479](#), [B-2007MI1](#)>.

The first penicillin (penicillin G) was serendipitously discovered by Alexander Fleming in 1928, but its therapeutic potential was recognized later, in the early 1940s, thanks to the works of Florey and Chain. Since the Second World War, a tremendous amount of research has been devoted to the discovery of naturally occurring antibiotics possessing the β -lactam motif, and to the preparation of semisynthetic or totally synthetic analogs <[1998MI589](#), [2002MI125](#), [2004RMC93](#), [B-2005MI113](#), [2005MI319](#)>. The introduction of β -lactam antibiotics into the health care system, about 60 years ago, represents a major contribution to the modern medicine. Today this class still includes the clinically most-widely-used agents and counts for about half of all prescribed antibacterial drugs (cephalosporins: 30%; penicillins: 16%; penems: 5%; macrolides: 18%; quinolones: 19%; others: 12%) <[2006AGE5072](#)>.

The evolution of the penicillin antibiotics’ chemistry is linked to several phenomena:

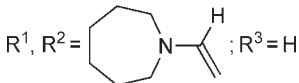
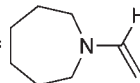
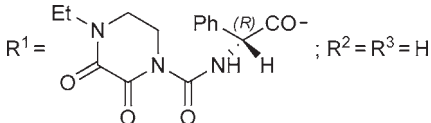
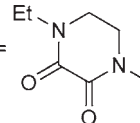
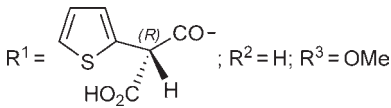
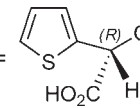
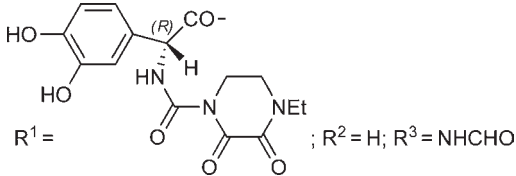
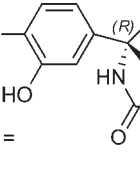
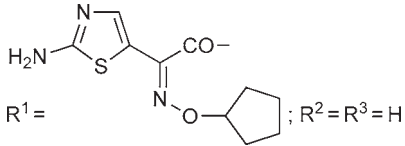
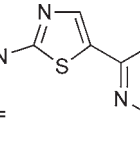
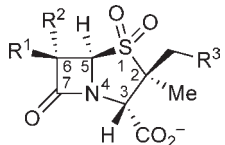
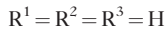
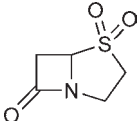
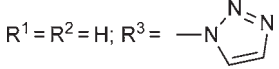
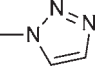
1. The successive discoveries of cephalosporin C (1945), cephamycin (1971), thienamycin (1976), clavulanic acid (1975), nocardicin (1976), sulfazecin (1981), etc.: The structural diversity found in the natural compounds inspired the medicinal chemists for side-chain modifications of the penam and penem cores (see [Section 2.03.11](#)).
2. The industrial production of 6-aminopenicillanic acid (6-APA), the key building block for all semisynthetic variations (1957): 6-APA is readily available from high-producing strains of *Penicillium chrysogenum* by enzymatic cleavage of penicillin G with penicillin acylase (see [Section 2.03.11](#)).
3. The emergence of bacterial resistance against all classes of β -lactam antibiotics as an inevitable consequence of the intensive use of such drugs. The increasing selection for bacteria having acquired resistance mechanisms progressively devaluates our antibiotic arsenal. This provides a strong incentive for continuously developing novel drugs that escape the destruction by β -lactamases (resistance enzymes) (see [Section 2.03.12](#)).
4. The progress made at the molecular biology level in the comprehension of the mechanisms of action of β -lactam drugs, and the mechanisms of bacterial resistance. This now allows the rational design of synthetic drugs, particularly in the field of β -lactamase inhibitors acting as suicide substrates (see [Section 2.03.12](#)).

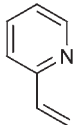
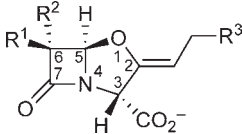
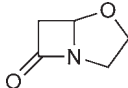
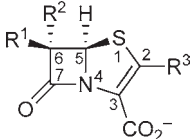
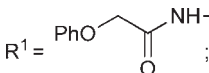
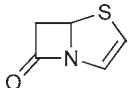
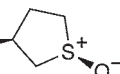
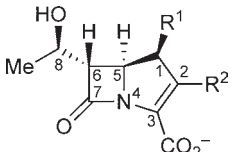
Table 1 The penicillin family

Subfamily, core structure	Atom numbering, absolute configuration	Selected representatives	Date of discovery	Notes and references
Penam		$R^1 = \text{PhCH}_2\text{CO}-; R^2 = R^3 = \text{H}$	1928	Penicillin G, natural product, group I
	 <i>(3S)(5R)(6R)</i>	$R^1 = R^2 = R^3 = \text{H}$ (6-APA)	1957	6-APA, natural product
Antibiotics		$R^1 = \text{PhOCH}_2\text{CO}-; R^2 = R^3 = \text{H}$	1960	Penicillin V, natural product, also produced from 6-APA, group I
		$R^1 = $  $; R^2 = R^3 = \text{H}$	1961	Methicillin, semisynthetic product, group II
		$R^1 = $  $; R^2 = R^3 = \text{H}$	1962	Cloxacillin, semisynthetic product, group II
		$R^1 = $  $; R^2 = R^3 = \text{H}$	1962	Ampicillin (BRL-1341), semisynthetic product, group III _A
		$R^1 = $  $; R^2 = R^3 = \text{H}$	1967	Carbenicillin (BRL-2064), semi-synthetic product, group V
		$R^1 = $  $; R^2 = R^3 = \text{H}$	1970	Amoxicillin (BRL-2333), semisynthetic product, group III _A

(Continued)

Table 1 (Continued)

Subfamily, core structure	Atom numbering, absolute configuration	Selected representatives	Date of discovery	Notes and references
		 $R^1, R^2 = $  $; R^3 = H$	1976	Mecillinam, semisynthetic product, group VI <1976MI14>
		 $R^1 = $  $; R^2 = R^3 = H$	1977	Piperacillin, semisynthetic product, group III _B
		 $R^1 = $  $; R^2 = H; R^3 = OMe$	1981	Temocillin (BRL-17421), semisynthetic product, group IV <1981AAC38>
		 $R^1 = $  $; R^2 = H; R^3 = NHCHO$	1984	Foramidocillin (BRL-36650), semisynthetic product, group IV <1984AAC734>
		 $R^1 = $  $; R^2 = R^3 = H$	1989	BRL-44154, semisynthetic product, group VII
Penam sulfone	 $(3S) (5R)$	 $R^1 = R^2 = R^3 = H$	1978	Sulbactam, synthetic compound
		 $R^1 = R^2 = H; R^3 = $ 	1984	Tazobactam (YTR-830), synthetic compound

	β -Lactamase inhibitors	$R^1, R^2 = $  $; R^3 = H$	1986	Synthetic compound
Oxapenam (clavam)		$R^1 = R^2 = H; R^3 = OH$	1975	Clavulanic acid, natural product
	(3 <i>S</i>) (5 <i>R</i>) β -Lactamase inhibitors			
Penem		$R^1 = $  $; R^2 = H; R^3 = Me$	1976	Synthetic compound designed by R. B. Woodward, combining penam and cephem features, but too unstable for medical purpose
	(5 <i>R</i>) Antibiotics			
		$R^1 = H; R^2 = $  $; R^3 = SEt$	1981	Synthetic compound
		$R^1 = H; R^2 = $  $; R^3 = S- $ 	1988	Sulopenem (CP-70429), synthetic compound <1990JAN422, 1990JOC3670, 1992JOC4352>
		$R^1 = H; R^2 = $  $; R^3 = $ 	1992	Faropenem, antibiotic patented and marketed in Japan
Carbapenem		$R^1 = H; R^2 = S-CH_2-CH_2-NH_3^+$	1976	Thienamycin, natural product

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Table 1 (Continued)

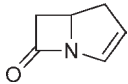
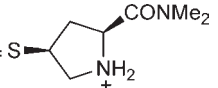
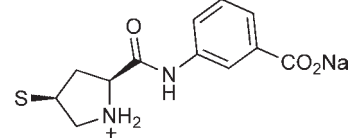
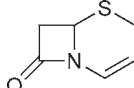
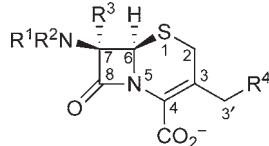
<i>Subfamily, core structure</i>	<i>Atom numbering, absolute configuration</i>	<i>Selected representatives</i>	<i>Date of discovery</i>	<i>Notes and references</i>
	(5<i>R</i>)(6<i>S</i>)(8<i>R</i>) β-Lactamase inhibitors and antibiotics	$R^1 = \text{H}; R^2 = \text{S}-\text{CH}_2\text{CH}_2\text{N}(\text{H})\text{CH}=\text{NH}_2^+$	1983	Imipenem, semisynthetic product
		$R^1 = \text{Me}; R^2 = \text{S}-$ 	1985	Meropenem (SM-7338), synthetic product
		$R^1 = \text{Me}; R^2 =$ 	2002	Ertapenem, synthetic product

Table 2 The cephalosporin family

Subfamily, core structure	Atom numbering, absolute configuration	Selected representatives	Date of discovery	Notes and references
Cephem 	 (6 <i>R</i>) (7 <i>R</i>) Antibiotics	$R^1 = \begin{array}{c} \text{HO}_2\text{C} \\ \\ \text{H}_2\text{N} \end{array} \begin{array}{c} \text{H} \\ \\ \text{CH}_2 \end{array} \text{CH}_2 \text{CH}_2 \text{CO}^-; R^2 = R^3 = \text{H}; R^4 = \text{OAc}$ $R^1 = R^2 = R^3 = \text{H}; R^4 = \text{OAc}$ (7-ACA) $R^1 = R^2 = R^3 = R^4 = \text{H}$ (deacetyl 7-ACA) $R^1 = \begin{array}{c} \text{Ph} \\ \\ \text{H}_2\text{N} \end{array} \begin{array}{c} \text{CO}^- \\ \\ \text{H} \end{array}; R^2 = R^3 = R^4 = \text{H}$ $R^1 = \begin{array}{c} \text{HO}_2\text{C} \\ \\ \text{H}_2\text{N} \end{array} \begin{array}{c} \text{H} \\ \\ \text{CH}_2 \end{array} (\text{CH}_2)_3 \text{CO}^-; R^2 = \text{H}; R^3 = \text{OMe}; R^4 = \text{OAc}$ $R^1 = \begin{array}{c} \text{CO}^- \\ \\ \text{CH}_2 \end{array} \begin{array}{c} \text{S} \\ \\ \text{CH}_2 \end{array}; R^2 = \text{H}; R^3 = \text{OMe}; R^4 = \text{OCONH}_2$ $R^1 = \begin{array}{c} \text{N-OMe} \\ \\ \text{CO}^- \end{array} \begin{array}{c} \text{O} \\ \\ \text{CH}_2 \end{array}; R^2 = R^3 = \text{H}; R^4 = \text{OCONH}_2$ $R^1 = \begin{array}{c} \text{H}_2\text{N} \\ \\ \text{CH}_2 \end{array} \begin{array}{c} \text{N} \\ \\ \text{CH}_2 \end{array} \begin{array}{c} \text{N-OMe} \\ \\ \text{CO}^- \end{array}; R^2 = R^3 = \text{H}; R^4 = \begin{array}{c} \text{Me} \\ \\ \text{N} \\ \\ \text{S} \end{array}$	1945 1962 1962 1967 1971 1973 1976 1981	Cephalosporin C, natural product Key intermediate for hemisynthesis Key intermediate for hemisynthesis <1962JA3400> Cephalexin, first generation <1967MI765> Cephamycin, natural product Cefoxitin, semisynthetic product <1973MI653> Cefuroxime, second generation <1976JAN29> Ceftriaxone, third generation <1981AAC414>

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Table 2 (Continued)

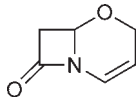
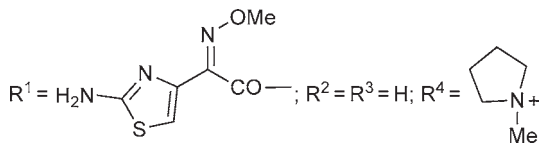
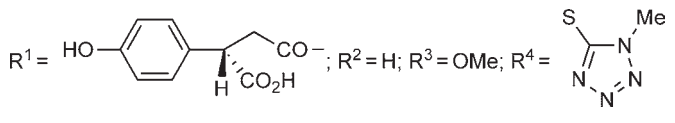
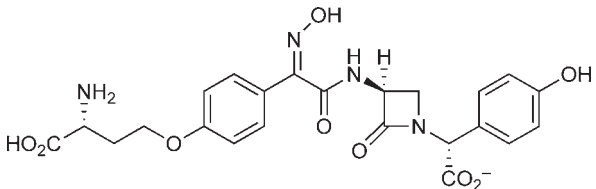
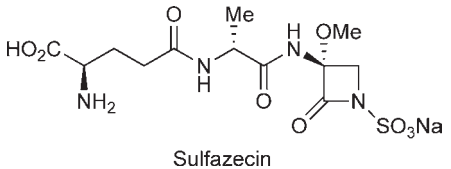
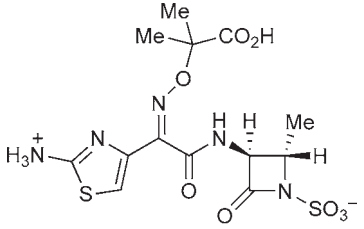
<i>Subfamily, core structure</i>	<i>Atom numbering, absolute configuration</i>	<i>Selected representatives</i>	<i>Date of discovery</i>	<i>Notes and references</i>
Oxacephem 	(6 <i>R</i>) Antibiotics	 $R^1 = \text{H}_2\text{N}-\text{C}_5\text{H}_3\text{N}-\text{C}(\text{N}=\text{OMe})=\text{CO}-;$ $R^2 = R^3 = \text{H};$ $R^4 = \text{C}_4\text{H}_8\text{N}^+\text{Me}$	1984	Cefepime (BMX-28142), fourth generation <1984AAC585>
		 $R^1 = \text{HO}-\text{C}_6\text{H}_4-\text{CH}(\text{H})-\text{CH}_2\text{CO}_2\text{H};$ $R^2 = \text{H};$ $R^3 = \text{OMe};$ $R^4 = \text{C}_4\text{H}_3\text{N}_3\text{S}-\text{Me}$	1981	Moxalactam (latamoxef), synthetic product <1981MI217>

Table 3 The monobactam family

Structure (name)	Date	Notes and references
 Nocardicin A	1976	Natural product with antibiotic activity, but no clinical application <1976JAN492>
 Sulfazecin	1981	Natural product with antibiotic activity, but no clinical application <1981NAT590>
 Azthreonam	1982	Synthetic antibiotic <1982AAC85>

This chapter deals with penam and penem chemistry, that is, azetidin-2-one fused with thiazolidine and thiazoline rings, respectively, and covers the literature from 1995 till 2006. Since CHEC-II(1996) <1996CHEC-II(1B)623>, more than 29 000 papers containing the keywords penicillin, penam, or penem in their title or abstract have been published. Important topics already discussed in CHEC-II(1996) have been recalled and updated with fresh references, as well as a selection of relevant studies from the recent literature has been incorporated in this chapter.

Penam derivatives usually result from semisynthetic approaches, while penem derivatives require enantioselective total synthesis strategies to be constructed. As a consequence, only the most relevant 3(*S*),5(*R*),6(*R*) natural configuration has been considered in the case of penam derivatives, whereas both 5(*R*),6(*R*) and 5(*R*),6(*S*) configurations have been discussed in the case of penem derivatives. Even though two numbering systems can be considered regarding such classes of fused-ring compounds, the common numbering system of penicillins as depicted in **Tables 1 and 2** is used rather than the IUPAC system. Thus the description of chemical disconnection/functionalization for both penam and penem derivatives is approached with respect to that systematic numbering (see **Sections 2.03.5 and 2.03.6**).

During the last 15 years, the chemistry of penicillins has remained relatively classical for the construction of the bicyclic cores and the anchorage of the side chains. However, interesting chemical developments have arisen in the fields of prodrugs for oral administration and dual action drugs designed for targeting antibiotics or using the mechanism of action of β -lactams to deliver other drugs. On the other hand, the major advances are dealing with structural biochemistry, namely the analysis of inhibitor–protein complexes by X-ray diffraction, nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry, which has led to a better understanding of the penicillins' biological activity and, therefore, paved the way to extending the potential therapeutic uses of β -lactams (see **Section 2.03.12**).

2.03.2 Theoretical Methods

Some theoretical works report the geometric features of penams skeleton, considering the strain of the bicyclic system and the bridgehead nitrogen pyramidity (see **Section 2.03.3.1**). For instance, the two possible conformations (axial and equatorial with respect to the C-3 carboxyl group) of the penicillins thiazolidine ring have been localized as two minima by *ab initio* calculations employing several theoretical methods (Hartree–Fock (HF), density functional

theory (DFT), MP2, and MP4) and basis sets (6-31G*, 6-31G**, 6-311G**, and 6-311++G**). The axial conformation was found to be the most stable one and the transition state connecting the two conformers corresponds to a pseudorotation barrier of approximately 2 kcal mol^{-1} <1999JMT(491)177>. A comparative structural study has been carried out on three penem skeletons as well using a 3-21G* level of *ab initio* molecular orbital (MO) and molecular mechanics calculations; results are in good agreement with the crystallographic data <1998BMC367>.

Besides, most of the computational studies have been performed on the reaction mechanism of β -lactam ring opening by hydrolysis, alcoholysis, or aminolysis. Indeed, β -lactam antibiotics activity is directly related to their ability to block penicillin-binding proteins (PBPs) through a covalent bond with a serine residue (see Section 2.03.12.2). The nucleophilic attack on the carbonyl group of the penicillin nuclei, via a tetrahedral intermediate, has been extensively studied, mostly in the gas phase, using different computational methods, including *ab initio* or semi-empirical tools. A lot of publications deal with monocyclic β -lactams, considered as models of penicillins <1996HCA353, 1997PCB3581, 1997HCA739, 1998JA2146, 1998JMT(426)313, 2002CEJ859>. One theoretical study dealing with the gas-phase alkaline hydrolysis of penicillin G, on the assumption of a B_{AC2} mechanism, has been reported <1997JMT(390)255>.

In a recent review, various theoretical methods carried out in solution and enzymatic media are extensively discussed in relation to the biological activity <2006COR805>. The methanol-mediated hydrolysis of penicillin G mimicking the enzymatic pathway has been studied by *ab initio* quantum-mechanical calculations using a polarizable continuum model to estimate solvation effects <1999PCB8628>. Strong correlations have been found between the calculated kinetic, structural, and electronic properties, and the experimental data. Recently, the intrinsic chemical reactivities, in alkaline hydrolysis, of clavulanic and penicillanic acids have been compared <2002JA12042>. Both reactions share a common two-step mechanism of β -lactam ring opening which involves the formation of a tetrahedral intermediate as the rate-limiting step (HO^- addition onto the C-7 carbonyl), followed by the N(4)–C(7) bond breaking with a concomitant intramolecular transfer of the hydroxide proton to N-4. Differences arise in the subsequent cleavage of the five-membered ring, the clavam derivatives being more reactive than the penam derivatives.

Aminolysis of 3-carboxypenam in aqueous solution, explored with the DFT method, reveals a concerted mechanism as the most favored route <2000JA6710, 2001EJO793>. Penicillin haptenation to human serum albumin (HSA) also proceeds through a water-assisted concerted mechanism via the conjugation to the neutral amino group of Lys₁₉₉ <2001JA7574>, with a calculated energy barrier of 38 kcal mol^{-1} , which is in agreement with the experimental reaction kinetics.

The majority of the penicillin-recognizing enzymes (PREs) in bacteria, transpeptidases, and β -lactamases (see Section 2.03.12) are serine proteases, differing mainly in their kinetic behaviors <2006COR805>. However, all PREs share a common mechanism of β -lactam processing which involves the formation of an acyl–enzyme complex. This step has been modeled, by means of quantum-chemical method (PM3, HF level with MINI-1' basis set), on the basis of catalytic site models built by using segments of the most important amino acid residues of the catalytic machinery <2000JMT(504)13, 1999IJQ(73)161>. Usually, a concerted mechanism of nucleophilic attack on the β -lactam carbonyl from the back of the ring (α -face of the penam bicycle) is proposed, along with a proton shuttle. The detailed mechanisms are discussed in Section 2.03.12.2.

2.03.3 Experimental Structural Methods

2.03.3.1 X-Ray Crystallography

The first X-ray crystal structure analysis regarding the penam skeleton was performed on benzylpenicillin in 1949 <B-1949MI310>. From this date until 1996, the structures of 32 penicillin derivatives were elucidated, and, since CHEC-II(1996), 15 novel penam X-ray structures have been reported in the literature. Among them, two penam sulfoxides <1996AXC3142, 1999AXC656>, four lithium, sodium, rubidium, and cesium penicillin V salts <1997JA9793>, a 6 α -chloro penam sulfone <1998AXC242>, the first example of a tricyclic 2'/ β ,6-bridged penam <1998JA6846> (see Section 2.03.7.3), 5(*S*)-penams <2000T6053, 2001J(P1)1897>, and a 6-spirocyclopropyl penicillanate sulfone <2003JME2569>. Besides single crystal X-ray analyses, a recent study performed X-ray powder diffraction on eight β -lactam antibiotics including penicillins <2005ANS833>. The data were tabulated in terms of lattice spacing and relative line intensities, useful for the identification of drugs in illicit preparations.

Thirty years after the disclosure of Fleming's penicillin structure, the Cambridge Crystallographic Data Centre recorded *p*-nitrobenzyl-5(*S*)-pen-2-em-3-carboxylate as the first penem <1979CC665>. As of 2006, only 23 penem X-ray structures have been published. Among them, none is bearing a nitrogen atom at C-6 in the *cis*-configuration

relative to the C(5)—S(1) bond, as found in penams. Since the crystallographic studies of penicillins were described in CHEC-II(1996) (section 1.20.3.1), this chapter highlights the crystallographic differences between penam and penem nuclei. Penamecillin **1**, a prodrug (see Section 2.03.7.2) depicted in Figure 1, represents a recent example of a typical penam antibiotic with the (5*R*,6*R*)-configuration <2004CEJ2977>. Compound **2**, with the (5*R*,6*S*)-configuration along with the 1(*R*)-hydroxyethyl chain at C-6, illustrates a typical penem antibiotic <1999STCI311>. Their most relevant geometrical features are compared in Table 4.

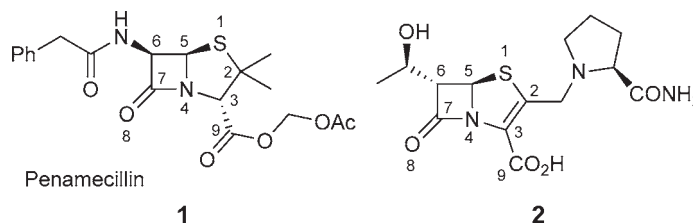


Figure 1 Two representative examples of penam **1** and penem **2**.

Table 4 Bond distances and angles of X-ray structures **1** and **2**

Bond distances (Å)			Bond angles (deg)		
	1	2		1	2
S(1)—C(2)	1.853	1.722	C(5)—S(1)—C(2)	94.89	89.57
C(2)—C(3)	1.571	1.321	S(1)—C(2)—C(3)	105.13	117.96
C(3)—N(4)	1.442	1.417	C(2)—C(3)—N(4)	106.24	110.10
N(4)—C(5)	1.465	1.480	C(3)—N(4)—C(5)	117.24	113.81
C(5)—S(1)	1.818	1.817	N(4)—C(5)—S(1)	105.64	104.91
C(5)—C(6)	1.566	1.539	N(4)—C(5)—C(6)	88.58	89.75
C(6)—C(7)	1.556	1.513	C(5)—C(6)—C(7)	83.95	83.67
C(7)—N(4)	1.383	1.383	C(6)—C(7)—N(4)	92.05	94.66
C(7)—O(8)	1.206	1.224	C(7)—N(4)—C(5)	94.26	90.55
C(3)—C(9)	1.518	1.435	C(6)—C(5)—S(1)	119.11	118.36
C(9)—O(8)	4.378	3.645	C(7)—N(4)—C(3)	125.85	126.28

Source: Cambridge Crystallographic Data Centre.

From Table 4, it appears that penam and penem skeletons possess some differences in their bond angles and bond distances, due to the presence of the double bond in the five-membered ring of **2** and the steric repulsion of the side chains at C-2 for penems <1997BMC1389> and at C-6. As a consequence of the presence of the double bond and its delocalization with the sulfur atom lone pairs in **2**, C(2)—C(3) and S(1)—C(2) distances are shorter than in **1**, and S(1)—C(2)—C(3) and C(2)—C(3)—C(4) angles are bigger. Moreover, as it is known for penicillins, one of the five atoms of the thiazolidine ring is out of the plane defined by the four other atoms, thus conferring to the five-membered ring an envelope shape; this phenomenon can no longer be observed in the penem skeleton due to the n- π overlapping between S-1 and the C=C bond. The slightly twisted shape of the penem five-membered ring is indeed due to the different values of angles C(6)—C(5)—S(1) and C(7)—N(4)—C(3). The same C(7)—N(4) bond distance for both **1** and **2** reveals that the nitrogen N-4 is as pyramidal in penems as it is in penams, making it difficult to overlap its n-orbital with the carbonyl π^* -orbital. Despite its conjugation with the double bond, its pyramidity infers also a poor double-bond character to the C(3)—N(4) bond, 1.417 versus 1.442 Å in **1**. The pyramidity of the bridgehead nitrogen, also known as Woodward's parameter <1980MI239>, is usually defined as the height of N-4 from the plane formed by the three surrounding carbon atoms C-3, C-5, and C-7. However, according to Bruton, the nitrogen pyramidity can also be measured by the torsion angle across the β -lactam amide bond of the carbon atom bearing the carboxyl group. This is expressed as 360° minus the sum of the three contiguous angles around N-4, namely C(7)—N(4)—C(5), C(3)—N(4)—C(5), and C(7)—N(4)—C(3) <1993BML2329>. In the case of **1** and **2**, it is equal to 22.65° and 29.36°, respectively. Another important geometric parameter, also narrowly correlated to bioactivity of such families of

antibiotics (see Section 2.03.12.1), is the Cohen's distance which separates the carboxyl carbon atom C-9 from the β -lactam carbonyl oxygen O-8 <1983JME259> (see Section 2.03.12.1, Figure 13). Empirically, he defines a good bioactivity in the range of 3.0–3.9 Å. From Table 4, compound 2 fits well in this requirement (3.645 Å), whereas 1 doesn't seem to (4.378 Å). In fact, the envelope shape of the thiazolidine ring in penam allows a pseudorotation movement between two different conformations, relatively close in energy (see Section 2.03.2). Thus, the crystallization can occur either in an 'open' shape where the carboxylate occupies a pseudoequatorial position (active form), or in a 'closed' shape with a pseudoaxial orientation of the carboxylate (inactive form). On the contrary, the rigidity of the penem nucleus avoids such a pseudorotating effect.

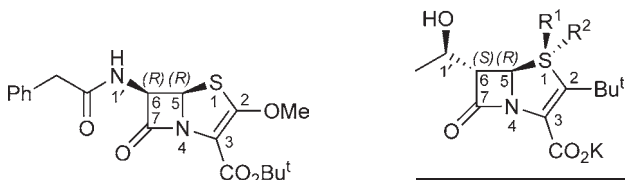
Other crystallographic data can be found in the literature, regarding structural analysis of protein–penicillin complexes where the penam is located in the enzymatic cavity, thus showing the active-site amino acids involved in the catalytic machinery <1992NAT700, 1996JME3712>. Recent studies deal with β -lactamase–penem complexes <2003B13152, 2004AAC4589, 2005JA3262> where the suicide inhibition mechanism can be visualized (see Section 2.03.12.4).

2.03.3.2 NMR Spectroscopy

NMR spectroscopy continues to be the most widely used tool to identify compounds. By solubilizing the sample in a deuterated solvent, it allows easy access to structural and conformational information, based on the magnetic behavior of odd-spin-nucleus atoms, commonly ^1H , ^{13}C , and ^{15}N . NMR experiments can also be performed in the solid state. For instance, a study has been made on a series of penicillin V salt crystals using variable-temperature ^{13}C cross-polarization magic angle spinning (CP/MAS) NMR spectroscopy, combined with X-ray crystallography, and provides qualitative and semiquantitative information about local structures <1997JA9793>. Another study speculates on a relationship between chemical shift values of $^{13}\text{C}/^{15}\text{N}$ sites and β -lactam ring conformation of ampicillin and penicillin V, using a ^{13}C and ^{15}N chemical shift anisotropy (CSA) analysis, which is an association of two-dimensional phase-adjusted spinning sidebands (2-D PASS) and conventional CP/MAS experiments <1998MR144>. The description of typical $^1\text{H}/^{13}\text{C}$ NMR features of penam antibiotics was covered previously in CHEC-II(1996) (section 1.20.3.2) <1996CHEC-II(1B)623> and, as there has been no novelty since then, this section focuses mostly on the NMR features of penem derivatives. Thus, the reader is recommended to refer to CHEC-II(1996) along with this section for a complete overview of NMR specificities of both penam and penem skeletons.

Considering the presence of two side chains at C-2 and C-6, the penem nucleus bears only two hydrogen atoms, located on the azetidinone ring at positions C-5 and C-6. Its steric strain makes these two protons very characteristic and particularly useful for determining the relative configuration *cis/trans* between the substituents linked to C-5 and C-6. The first penems to be synthesized bore a 6-acylamino substituent in *cis*-configuration with the C(5)–S(1) bond, whose NMR spectral data are comparable to those of the penicillin nucleus, namely H-5 and H-6 in the range of 5–6 ppm with $^3J_{5,6} = 4\text{--}5\text{ Hz}$ (Table 5) <1978JA8214, 1980TL3085, 1983TL2563, 1983T2493>. Other (5*R*,6*R*)-penems have been described <1986JOC3413>, as well as 6-unsubstituted penems, whose H-6 *gem*-protons come out in the range of 3.3–3.9 ppm and H-5 in the range of 5.6–5.8 ppm, with $^2J_{6,6'} = 16\text{ Hz}$, $^3J_{5,6\text{ cis}} = 4\text{ Hz}$, and $^3J_{5,6\text{ trans}} = 2\text{ Hz}$ <1979JA6296, 1979JA6301, 1979JA6306, 1981JA4526>. Since the discovery of thienamycin (see Table 1), for chemical stability reasons, the most common configuration encountered in penems remains the 5,6-*trans* one, or (5*R*,6*S*), most of the time with a 6-(1'(*R*)-hydroxyethyl) group. Table 5 shows that 5,6-*trans*-penems differ from 5,6-*cis* ones, and corresponding penams, in the value of the coupling constant between H-5 and H-6, which is around 1.5 Hz

Table 5 ^1H NMR features of a 5,6-*cis*-penem (in CDCl_3) and a 5,6-*trans*-penem (in D_2O) (n = lone pair)

				
		$R^1, R^2 = n$	$R^1 = \text{O}; R^2 = n$	$R^1, R^2 = \text{O}$
H-5 (ppm)	5.79	5.55	5.00	4.83
H-6 (ppm)	5.70	3.82	3.64	3.84
$^3J_{5,6}$ (Hz)	4.0	1.5	3.1	2.9
$^3J_{6,1'}$ (Hz)	8.0	5.9	4.9	4.8

instead of 4.0 Hz. Moreover, the nature of the C-6 substituent induces a change in the H-6 chemical shift; from the acylamino to the hydroxyethyl group, H-6 is notably shielded. Besides, with the sulfur atom oxidation state increasing in penems from sulfur to sulfone, H-5 shifts upfield while $^3J_{5,6}$ doubles and $^3J_{6,1'}$ decreases (Table 5) <1997BML623, 1997BML2217>.

The C-2 side chain of penems has been extensively modified with different substituents for biological purpose; lots of examples along with their ^1H NMR spectral data have thus been described <1985H(23)2255, 1988H(27)49, 1988H(27)1329, 1990H(30)799, 1997BMC1389, 1998BML2793>.

Surprisingly, most of the papers dealing with synthetic aspects of penems restrict the structural assignment to ^1H NMR data. In addition, papers that describe penems' ^{13}C NMR analysis do not usually mention specific assignments. It was not possible to find in the literature any long-range heteronuclear ^1H – ^{13}C NMR experiments on penem derivatives to help discriminating the penem backbone carbon atoms from each other. However, the lactam carbonyl carbon atom C-7 remains one of the less affected atoms of the penem skeleton with variation of side-chain nature, and it shows up in the range 168–175 ppm <1983T2493, 1995JME4244>.

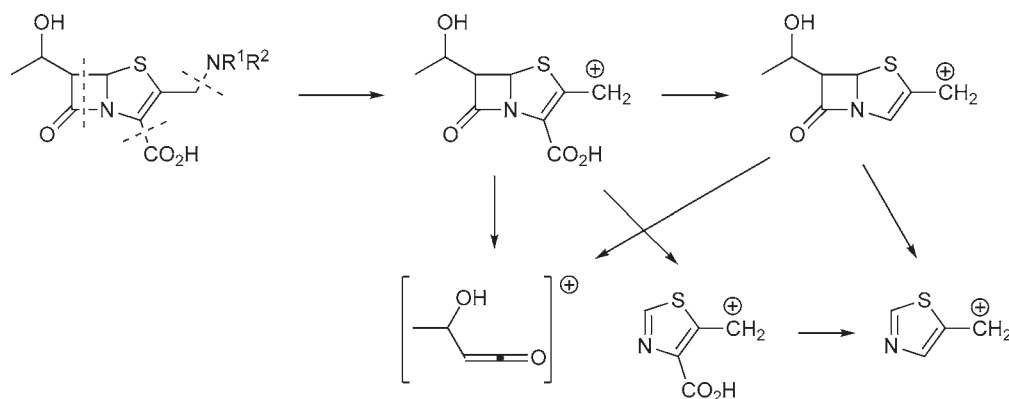
A conformational comparative study has been performed on a penem, a carbapenem, and a 1β -methylcarbapenem, bearing the same C-2 and C-6 side chains, using both NMR and theoretical tools. The corresponding calculations have been performed at the $3\text{-}21\text{G}^*$ level using the *ab initio* MO method, while ^1H NMR measurements and nuclear Overhauser effect (NOE) enhancements were carried out in D_2O solution. It arose from this study that there are conformational differences in the side chains of these three compounds in the physiological environment; in particular, the conformation of the C-6 side chain in the penem appears to be different from that in the carbapenem <1998BMC367>.

From the growing research of anti- β -lactamase compounds (see Section 2.03.12.4), the 6-unsubstituted penam sulfone nucleus has emerged as a basic pharmacophore (see Table 1). In this case, the two geminal H-6 and the H-5 protons give an ABX pattern in the range of 3.0–3.4, 3.5–3.8, and 5.2–5.5 ppm, with $^2J_{6,6'} = 15\text{--}17\text{ Hz}$ and $^3J_{5,6} = 4\text{--}5$ and $1\text{--}2\text{ Hz}$ for the *cis*- and *trans*-coupling, respectively <1996JME3712, 2005BMC2847>.

2.03.3.3 Mass Spectrometry

This section complements CHEC-II(1996) (section 1.20.3.3) <1996CHEC-II(1B)623>, which gave an overview of mass spectrometric behavior of penicillins, in particular their fragmentation patterns under electronic impact (EI) and chemical ionization (CI) conditions <1982JOC4008>, as well as for both positive and negative fast atom bombardment mass spectrometry (FABMS). Electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) methods now appear more convenient <1998RCM1820, 2002JPB1093>. Due to its high sensitivity and its rapid response time, the pyrolysis-negative ion mass spectrometry (Pyr-NIMS) has proven to be a suitable technique for the monitoring of enzymatic hydrolysis of penicillin G to 6-APA and phenylacetic acid <2002JPB569>.

From early studies on mass spectrometric characterization of penems <1988JAN1268, 1991OMS703, 1992RCM712>, a need for soft ionization techniques arose, considering their lower stability compared to penams. A series of penems, bearing both a $1(R)$ -hydroxyethyl group at C-6 and a methylene group at C-2, has been analyzed by collisionally activated dissociation (CAD) triple quadrupole tandem mass spectrometry <1995RCM707>. Penems behave in a quite similar



Scheme 1 General fragmentation pattern of 2-aminomethylene penems.

way toward positive ionization as penams (**Scheme 1**). Besides side-chain elimination, the typical common fragmentation of β -lactams corresponds to a [2+2] cycloreversion cleavage.

Nowadays, soft ionization mass techniques are of particular interest since they can help to elucidate mechanistic aspects of biological events <2001JMP58, 2003MI165, 2004JAM803>. For instance, the mechanism of inactivation of β -lactamases by 6-methylidene penems has been proven using ESI mass spectrometry, through the detection of the corresponding acyl-enzyme complexes <2004JME3674>.

Either coupled or not with chromatographic columns, those gentle mass analysis methods have been useful for antibiotics detection in various applications such as the quality control of milk, bovine tissues, water, and drugs <2001ANC1614, 2003ANA73, 2004JCH(1054)359, 2004JCH(1042)107, 2005JCH(1100)193, 2005ANC1473, 2005CPB172, 2006JCH(1103)83, 2006JCH(830)91, 2006RCM321>, and the monitoring of fermentation processes <1995ANA313, 1996MI485, 2001RCM1229>.

2.03.3.4 Other Spectroscopic Methods

Another spectroscopic value that characterizes penam/penem nuclei is the β -lactam carbonyl stretching frequency of their infrared (IR) spectra. Typically for penicillins, the C=O bond signal comes out around 1780 cm^{-1} , due to the geometric strain of the four-membered ring that diminishes the amide resonance and thus shifts its frequency compared to acyclic tertiary amides. For penems the β -lactam carbonyl signal is slightly higher and in the range $1780\text{--}1800\text{ cm}^{-1}$ <1979TL3777, 1983TL2563, 1992JOC4352, 2004JOC5850>. Besides, with the sulfur atom oxidation state increasing, the β -lactam carbonyl peak shifts toward higher frequencies; hence, penam sulfones see their C=O stretch around 1810 cm^{-1} . As IR spectroscopy is a reliable technique, it has been used to develop a quantitative method of positive qualification or discrimination of β -lactam antibiotics <2006JST(792)110>. A recent study reported vibrational investigations performed on benzylpenicillin potassium salts using in particular Raman spectroscopy <2006JRS318>.

Other analytical methods like ultraviolet (UV) absorption spectroscopy, usually together with complementary analytical techniques (X-ray crystallography, mass spectrometry, theoretical studies), are often helpful to monitor reactions for a better understanding of their mechanisms, for instance, the inhibition mechanisms of β -lactamases <1996JA9198> by inhibitors such as penam sulfones <1996JME3712> or 6-methylidene penems <1999B1547, 2007PCA4720> (see Section 2.03.12.4). Another example is the hydrolysis of penicillin G potassium salt in water and oil-water microemulsions with different charges, which was studied by ultraviolet-visible (UV-Vis) absorption spectroscopy <2003MI253>.

Although circular dichroism (CD) spectropolarimetry was discussed for penicillins in CHEC-II(1996) (section 1.20.3.4) <1996CHEC-II(1B)623>, it is useful to point out the two characteristic peaks which correspond to a positive Cotton effect at 230 nm and a negative Cotton effect at ca. 203 nm <1977T711, 1982J(P1)563>. Lately, this technique has been used to measure the rate of enzymatic hydrolysis of β -lactam antibiotics <1997ABI389>. No CD spectra of penems could be found in the literature; however, they have been studied using polarography, voltammetry, and tensammetry techniques <1990ELA373>. Recently, fast Fourier transformation continuous cyclic voltammetry has been developed as a highly sensitive detection system for ultra trace monitoring of penicillin V <2007ABI175>.

Other surface spectroscopic techniques such as X-ray photoelectron spectroscopy (XPS) and sum-frequency generation (SFG) have been used in a very recent paper for the detection of self-assembled monolayers of a penicillanic acid featuring an anchoring group adapted for gold substrates <2007MI1071>.

2.03.4 Thermodynamic Aspects

2.03.4.1 Thermodynamic Properties

Microcalorimetric analysis constitutes a useful tool to access the thermodynamic parameters of a phenomenon (enthalpy, entropy, Gibbs' free energy), especially when it comes to host-guest chemistry. This technique consists in measuring the heat that accompanies such phenomenon: either it is endo- or exothermic. By this method, Aki has investigated inclusion complexes of ampicillin with β -cyclodextrins in aqueous solution <2004MI423, 2004THE87>. From this work, two different types of complexes (1:1 and 1:2 stoichiometries) were observed whose respective prevalent existence depends on the pH; association constants and thermodynamic parameters for both complexes were accessible from isothermal calorimetric titration curves. Degradation represents another example of a phenomenon that can be monitored by microcalorimetry since it involves heat exchanges; as a matter of fact, differential

scanning microcalorimetry (DSC) has been used to determine the influence of magnesium glutamate on the stability of penicillin G in aqueous solution <2004IJP149>.

Thermodynamic parameters of micelle formation have been investigated on penicillin V in aqueous solution (self-association), using microcalorimetry together with conductivity, density, ultrasound, and static light-scattering techniques <1999L6285, 2002THE39>. A recent study has also reported the thermodynamic parameters of adsorption of penicillin–berberine ion associates at a water/tetrachloromethane interface <2005ANA337>.

2.03.4.2 Solubility and Chromatographic Behavior

The nature of the C-6/C-2 side chains, the sulfur atom oxidation state, and whether the C-3 carboxyl function is protected or not, constitute determining factors that help apprehend penams/penems solubility in organic solvents. Indeed, a free secondary amine function or a hydroxyethyl group at C-6, a sulfone function at S-1, and a free carboxylic acid function at C-3 considerably increase the polar character of the molecule. Thus, 6-APA for instance is hardly soluble in most polar organic solvents (see Section 2.03.11.3). Furthermore, for stability reasons, penicillins and particularly penems are usually isolated in their carboxylate salt form, which makes them soluble in aqueous (physiological) media. Based on that, their chromatographic analyses often require the use of reverse-phased columns. As already described in CHEC-II(1996) (section 1.20.4) <1996CHEC-II(1B)623>, many analytical tools have been developed to easily and reliably determine β -lactam antibiotics purity but also their concentrations in various media, such as biological fluids <2001ANC1614, 2004JCH(1054)359, 2006JCH(830)91, 2007ANA280>, animal tissues <2004JCH(1042)107, 2005ANC1473>, food <2003ANA73>, aquatic environments <2006AGE5158>, etc.; high-performance liquid chromatography (HPLC) is the most used analytical technique for penicillins <2005CPB172, 2006JCH(1103)83>, as well as for penems <1996JCH(685)273, 1998JPB255>. More and more, this chromatographic method is coupled with mass spectrometric analysis <2001ANC1614, 2004JCH(1042)107, 2004JCH(1054)359, 2005ANC1473, 2005CPB172, 2006JCH(830)91, 2006JCH(1103)83> (see also Section 2.03.3.3). Some examples of capillary electrophoresis analysis are also reported on penicillins <2002ELP414> and penems <1995ANC3697>.

2.03.5 Reactivity of the Penam Skeleton

2.03.5.1 Introduction

Penicillins, also called penams, occur naturally and possess a bicyclic skeleton: a β -lactam ring fused with a thiazolidine ring (4-thia-1-azabicyclo[3.2.0]heptan-7-one in IUPAC nomenclature). An important feature of penicillins, closely related to their biological properties, is the absolute configurations of the three chiral centers, which are 3(*S*), 5(*R*), and 6(*R*). Thus, all the chemical transformations made on penam nuclei have to preserve this stereochemistry (see also Section 2.03.7). Recent books have been devoted to penicillins together with other β -lactam antibiotics <B-1997MI400, B-2003MI129, B-2006MI1127, B-2007MI(7)479>.

The following sections discuss chemical aspects of penicillins' reactivity by considering each atom of the skeleton. Since CHEC-II(1996) (section 1.20.5) already described these aspects, and since the penicillins chemistry has not radically changed over the last decades, this chapter merely refreshes the references on the essential points that characterize the penam skeleton. The development of semisynthetic penicillins from 6-APA (see Table 1) is discussed in Sections 2.03.11.3 and 2.03.7.1 <2007JAA3>.

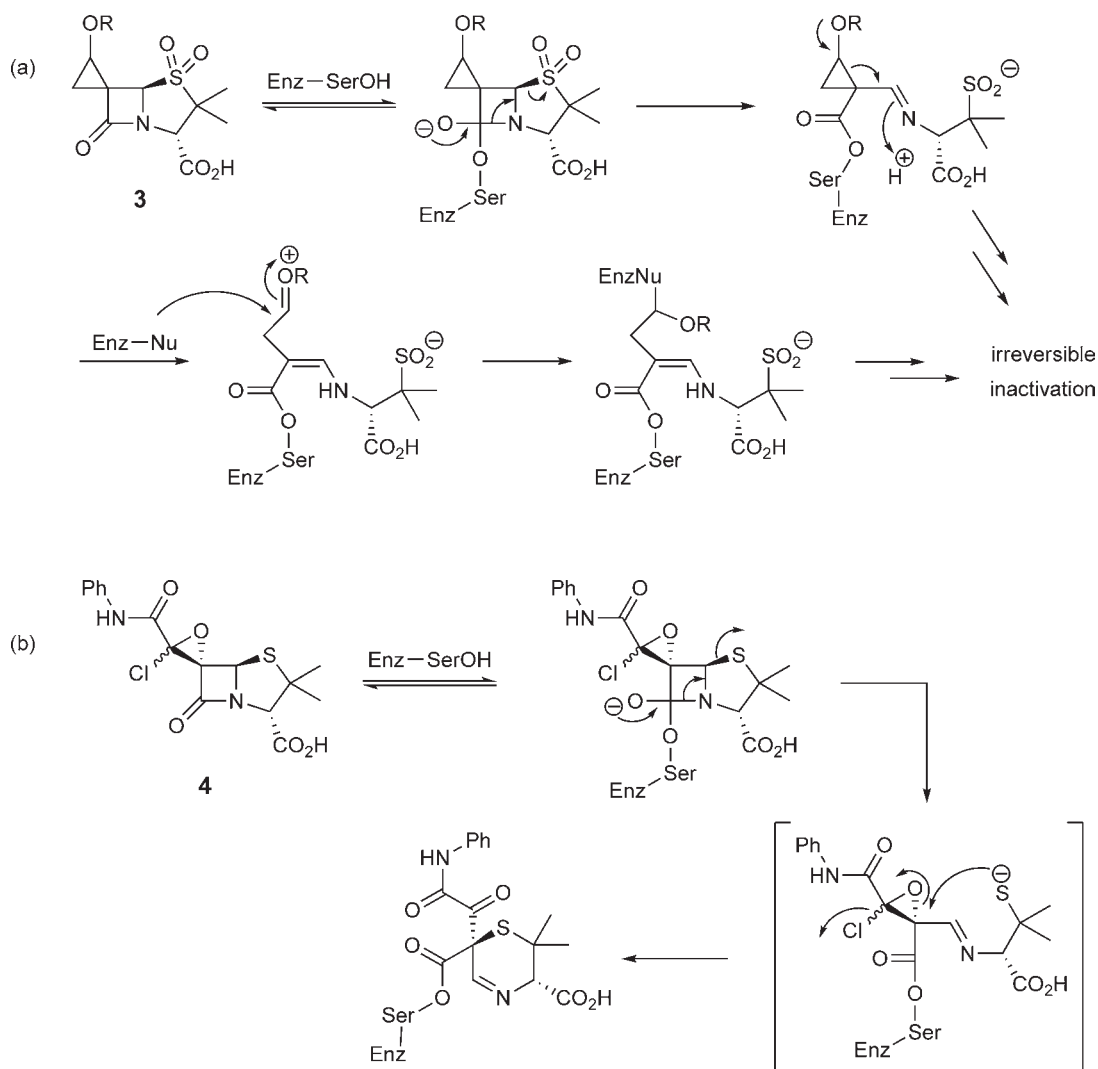
2.03.5.2 Reactivity Associated with the Biological Activity of Penicillins

The biological activity of penicillins involves the β -lactam ring opening via a tetrahedral intermediate; such a process is favored by release of strain energy <1984ACR144, B-1992MI79>. A recent study reviewed the processes of β -lactam ring opening in solution and enzymatic media from a theoretical point of view <2006COR805>. CHEC-II(1996) <1996CHEC-II(1B)623> overviewed that topic, going through, in particular, the aminolysis process and mentioning the influence of transition metal ions on the rate of hydrolysis of penicillins. For this reason, the reader is recommended to refer to CHEC-II(1996) (section 1.20.5.2) along with this section.

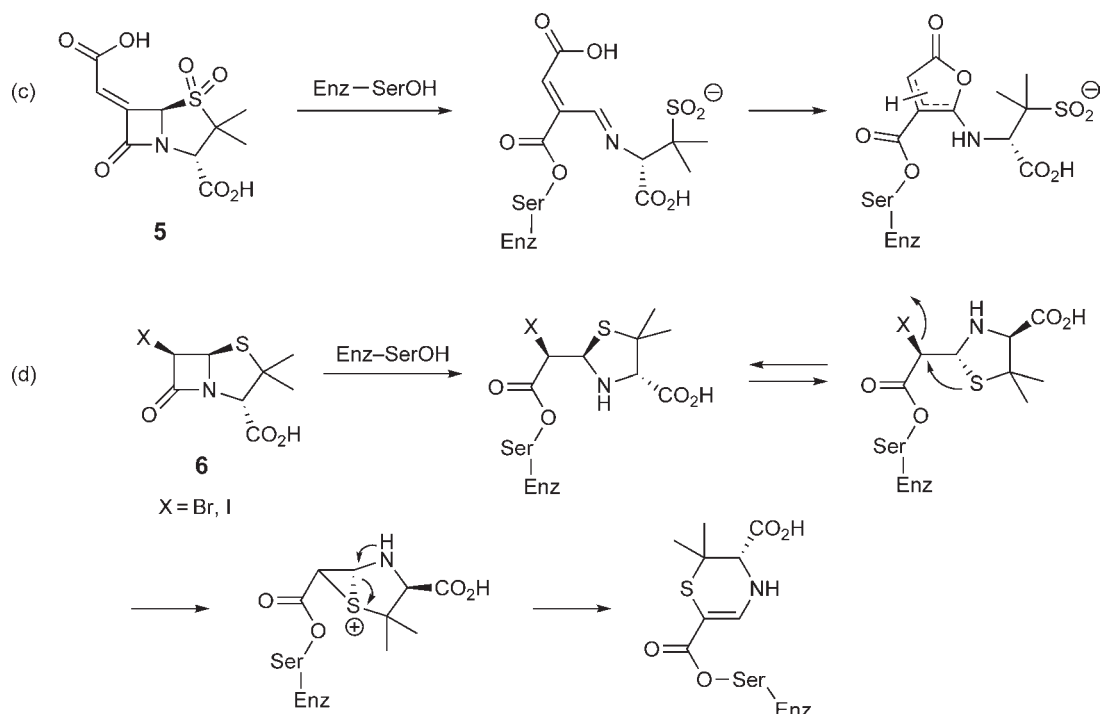
This section will mainly focus on the progress made in the comprehension of β -lactamase inhibition mechanisms <B-1992MI198>, which constitutes the major actual interest to overcome the bacterial resistance issues toward β -lactam-ring-containing antibiotics (see Section 2.03.12). β -Lactamases, naturally produced to remedy bacterial cell wall destruction by antibiotics, efficiently hydrolyze the β -lactam ring of penicillins into their corresponding inactive

penicilloic derivatives. In such a context, the hydrolysis of penams catalyzed by transition metal complexes has been investigated to help to establish how metallo- β -lactamases work [\[1995AAC1211, 1998CC1609, 2005AAC2778, 2006B11012, 2007JA2808\]](#). Recent studies have been reported regarding the hydrolysis of penicillins by mono- and dinuclear zinc(II) complexes as metallo- β -lactamase mimics [\[2000JA6411, 2005CEJ5343, 2006CEJ7797\]](#).

From several publications, it appears that the nature of the C-6 side chain and the oxidation state of S-1 of penams play key roles in their β -lactamase inhibition activity, by strengthening the enzyme link through a sequence of subsequent chemical events, which can lead to irreversible inhibition, also called suicide inhibition. In the case of 6-cyclopropyloxypenam sulfones **3**, after β -lactam ring cleavage, the thus-generated oxycarbenium (aldehyde, R = H) can be unraveled by further cross-linking with other active-site residues of the enzyme (**Scheme 2(a)**) [\[2003JME2569\]](#). 6-Spiroepoxypenamams **4** [\[1988CC274\]](#) also constitute good β -lactamase inhibitors, as the four-membered ring cleavage triggers the thiazolidine ring opening which leads to a 1,4-thiazine, through epoxide ring opening (**Scheme 2(b)**) [\[1988CC1610\]](#). By oxidizing penams into penam sulfones, the thiazolidine ring opening becomes more favorable after initial acylation of the enzyme [\[1999MI141, 2002JA9396\]](#), thus allowing a subsequent intramolecular nucleophilic attack on the generated imine as depicted in **Scheme 2(c)** in the case of **5** [\[2000MI109\]](#), where the (*E*)-stereochemistry of the C-6 side-chain carboxylate favors the 5-*exo-trig*-cyclization. 6 β -Halopenicillanic acids **6** have also been used as specific inhibitors of class A β -lactamases [\[2000MI109\]](#). They yield a 1,4-thiazine through displacement of the halide and formation of a bicyclic sulfonium ion intermediate (**Scheme 2(d)**).



Scheme 2 (Continued)



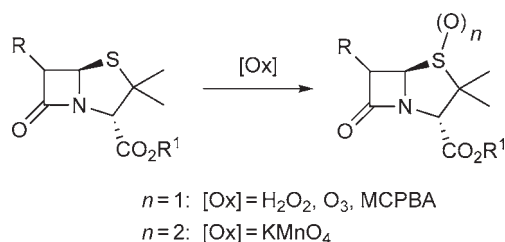
Scheme 2 Suggested pathways for irreversible inactivation of β -lactamases (four examples).

Penicillins bearing an *S*-aminosulfinimine ($R^1R^2NSN=$) side chain at the C-6 position constitute examples of both β -lactamase inhibitors and dual-release prodrugs <1998JOC7600, 1999JOC3132, 2000T5699> (see also Sections 2.03.12.4 and 2.03.12.5).

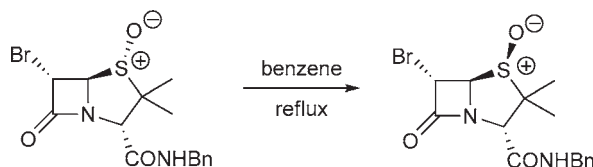
2.03.5.3 Modifications at the S-1 Position

Oxidation reactions on the sulfur atom of penicillins remain the most important reactivity of S-1 encountered in the literature. Penam sulfoxides and sulfones are indeed important compounds as they confer to the skeleton an ease of thiazolidine ring opening by weakening the C(5)–S(1) and S(1)–C(2) bonds (see Section 2.03.5.9) <2004CHE816>. In particular, the former constitute key intermediates in ring-expansion transformations from penams to cepems (see Section 2.03.5.9), while the latter have a special biological interest as β -lactamase inhibitors (e.g., sulbactam, tazobactam; see Sections 2.03.1, 2.03.5.2, and 2.03.12.4). Since CHEC-II(1996) covers all the aspects of these oxidation reactions on the S-1 atom of penicillins, this section focuses on the most relevant recent papers. As there is no particular change in the subject, only a few articles have been released since 1995.

The selective synthesis of either penam sulfoxides or sulfones can be controlled by the strength of the oxidizing agent used (Scheme 3). On the one hand, the mono-S-oxidation, leading to penam sulfoxides, is carried out using mild reagents such as hydrogen peroxide <1999BML997, 2002CCA211, 2005S442>, ozone <2000T6053>, or *m*-chloroperbenzoic acid (MCPBA) <1996CCA1367, 1999TA3893, 1999BML1997, 2002FA273, 2004BML1299, 2004BML147>. On the other hand, the use of potassium permanganate in an acidic medium performs complete oxidation to penam sulfones <1995BML2037, 1996T5591, 1996CCA1367, 1999BML991, 2000OL3087, 2001BMC2113, 2002JA9396, 2003JME2569, 2005BMC2847>. If the concave face (β -face) of penams is not too congested by a bulky 6 β -side chain, oxidation reactions performed with peracids mostly lead to β -sulfoxides, with the aid of a directional effect of the β -lactam carbonyl oxygen. However, the use of other oxidizing agents, such as PhICl_2 or NaIO_4 , helps to reverse the selectivity of the reaction toward α -sulfoxides (see CHEC-II(1996), section 1.20.5.3.1). In addition, a study has described the possibility of S-epimerization of a 6-bromopenicillanate α -sulfoxide into its thermodynamic epimer β at the boiling temperature of dry benzene (Scheme 4) <1996CCA1367>.



Scheme 3 General scheme of S-oxidation depending on the nature of the reagent.



Scheme 4 Epimerization of α -sulfoxide into β -sulfoxide.

Other mild methods consist of using a catalyst along with the oxidizing agent. An example of chemoselective aerobic oxidation of penicillin derivatives, catalyzed by cobalt(III) acetylacetonate, affords the corresponding sulfoxides exclusively <1996T2343>. Encapsulating the Co(III) catalyst by a sol-gel method makes it recyclable for numerous runs without affecting its selectivity or its reactivity <2003JMO271>. Supported polyoxometalates, such as molybdate or tungstate metal salts, can also play the role of heterogeneous catalysts and, associated with hydrogen peroxide, have proved to be an efficient way to oxidize penicillin G potassium salt <1996RTC244>.

The reduction of penam sulfoxides to their corresponding sulfides can be done by treatment with either phosphorus pentasulfide/pyridine in dichloromethane <1993H(36)1529> or trifluoroacetic anhydride/KI in acetone <1998TL8537>.

Beside redox reactions, the S-1 atom of penams can also be alkylated or chlorinated. On the one hand, by using Meerwein's salt or methyl fluorosulfonate, a series of methyl penicillanates have thus been S-methylated and their corresponding sulfonium salts **7** isolated and characterized (Figure 2) <1977TL71>. On the other hand, the use of sulfur chloride in carbon tetrachloride on the 6-unsubstituted methyl penicillanate led to the chlorosulfonium chloride salt **8** <1995AJC1065>.

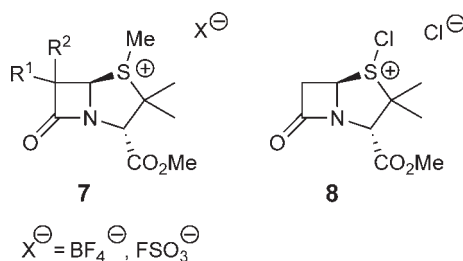
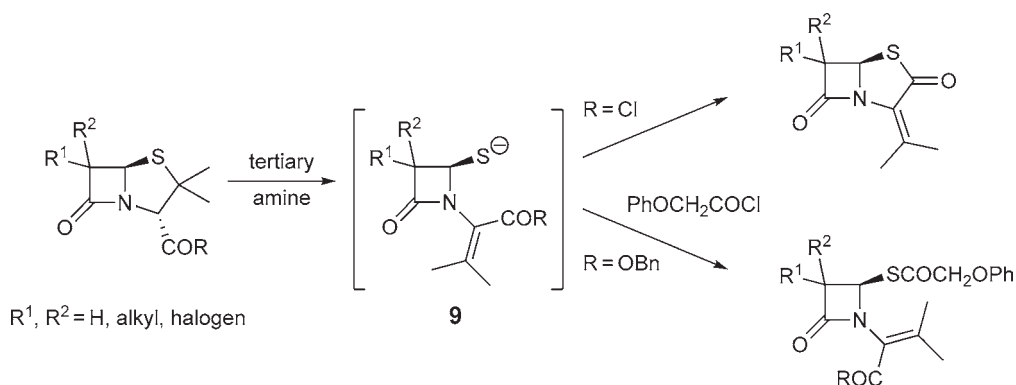


Figure 2 S-Methylated and S-chlorinated penams.

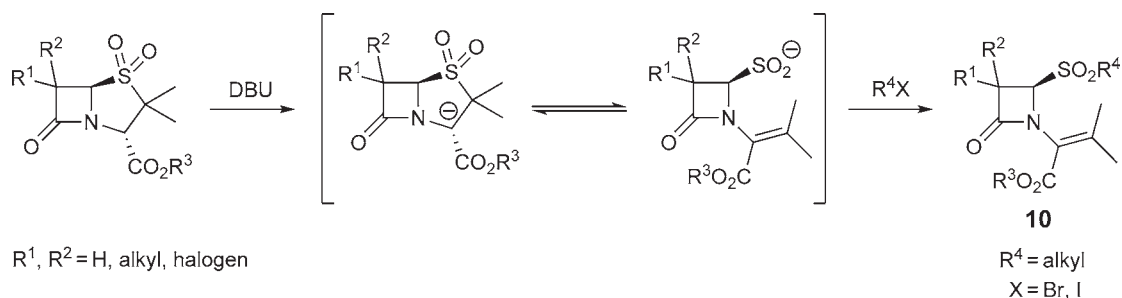
2.03.5.3.1 Reactions involving the S(1)–C(2) bond

Under basic conditions, penams can undergo S(1)–C(2) bond cleavage via generation of the carboxylic enolate which subsequently releases an intermediate thiolate **9** (Scheme 5). The latter can then react with an electrophile in either an inter- <1995T10715, 1995T10723> or intramolecular way <1996TL4431>.

Penam sulfones undergo thiazolidine ring opening through S(1)–C(2) bond cleavage under basic conditions more easily than penam sulfides. Subsequently, the liberated sulfonate can be trapped by a halogenoalkane, giving **10**, as depicted in Scheme 6 <2004BML147, 2004CHE816>.

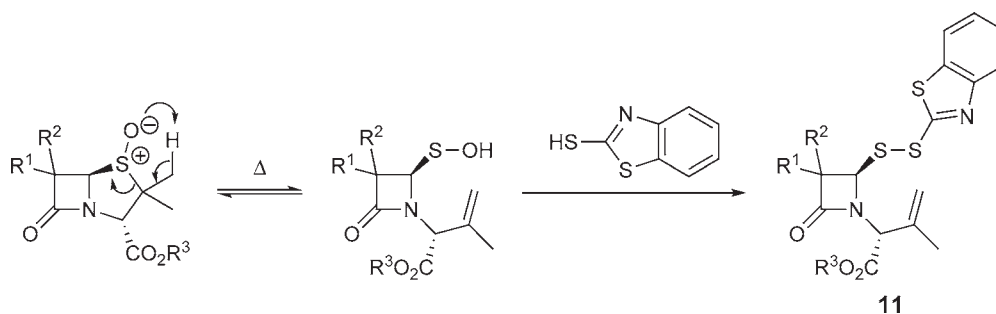


Scheme 5 S(1)–C(2) bond cleavage of penams.



Scheme 6 S(1)–C(2) bond cleavage of penam sulfones.

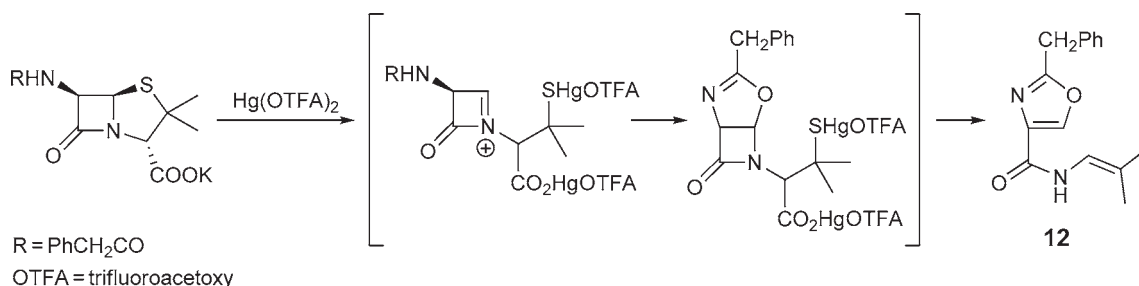
However, the most common way found in the literature to break an S(1)–C(2) bond of a penam consists of putting the corresponding sulfoxide in reaction with 2-mercaptobenzothiazole under heating to afford the disulfide-bridge-containing compound **11** <1995BML2037, 1998JA6846, 1999BML1997, 1999TA3893, 2004BML147, 2005S442>. This reaction goes through a sulfenic acid intermediate resulting from the concerted six-electron pericyclic reaction depicted in **Scheme 7**: a symmetry-allowed sigmatropic [2,3]-shift <B-1977MI167>. In particular, the resulting disulfide constitutes a good precursor for access to 2-substituted penams (see [Section 2.03.5.4](#)).



Scheme 7 S(1)–C(2) bond cleavage of penam sulfoxides.

2.03.5.3.2 Reactions involving the S(1)–C(5) bond

Reactions of mercury salts on penams result in S(1)–C(5) bond cleavage, thus generating an iminium intermediate that reacts subsequently in an intramolecular way with the C-6 amide side chain (**Scheme 8**). Afterward, the bicyclic heterocycle decomposes to the oxazole **12** <2000OL103>.

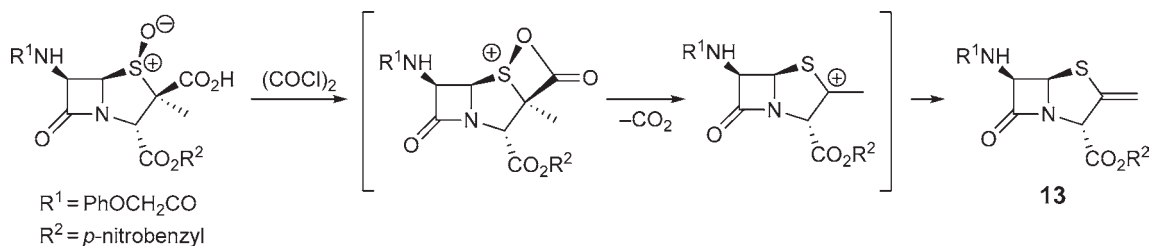


Scheme 8 S(1)–C(5) bond cleavage of penams.

Other reactions involving S(1)–C(2) and S(1)–C(5) bond rupture and leading to ring formation are described in [Section 2.03.5.9](#).

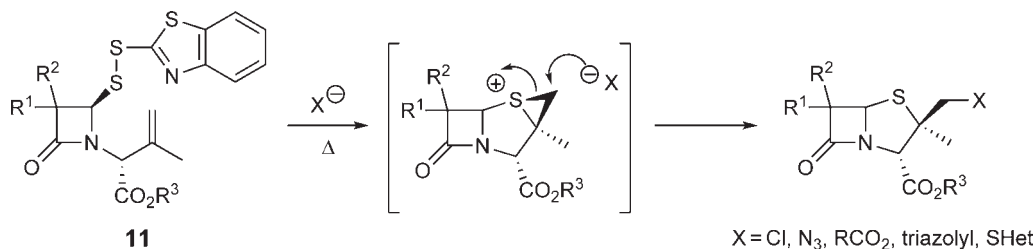
2.03.5.4 Modifications at the C-2 Position

The possibilities of transformations at the C-2 position are relatively poor. Nonetheless, penicillins can be converted into clavulanic-like derivatives [<1983TL2563, 1987TL2283>](#) by changing the hybridization of C-2 from sp³ to sp². Indeed, 2-carboxylate penam β -sulfoxides, readily obtained from penicillin V, enable a decarboxylative Pummerer reaction to provide 2-exomethylene penams **13**, as well as penems, their endocyclic tautomers ([Scheme 9](#)) [<1987CC81>](#). On the other hand, 2-oxo-, 2-thio-, and 2-iminopenams [<1996CCA1367>](#) could be obtained by total synthesis (see [Section 2.03.11.4](#)) and further used for the preparation of 2-heterosubstituted penems (see [Section 2.03.6.4](#)).



Scheme 9 Synthesis of 2-exomethylene penams.

Penam sulfoxides are also known to be good precursors to introduce a substituent at C-2' in a stereocontrolled way, through S(1)–C(2) bond cleavage as shown in [Schemes 7 and 10](#) [<1995BML2037, 1998JA6846, 1999BML1997, 1999TA3893, 1999BML997, 2005S442, 2005BMC2847>](#). For further reactions either involving S(1)–C(2) bond opening or dealing with the reactivity of substituents attached to C-2, [Sections 2.03.5.3.1 and 2.03.7.3](#), respectively, should be consulted.



Scheme 10 Synthesis of 2'-substituted penams.

2.03.5.5 Modifications at the C-3 Position

Besides the typical reactivities belonging to the 3-carboxyl functionality (**Figure 3**), such as reduction to aldehyde **14** <1995J(P2)869> or alcohol **15** <1995BMC95, 1995BML2033, 1998AXC242, 2001BMC2113>, homologation **16** <2005JOC4510>, and transformation to esters or amides (see Section 2.03.7.2), the only modifications reported in the literature regarding the C-3 position of penicillins involve the acidity of the attached proton. In the presence of a non-nucleophilic base, the 3-carboxylic enolate is generated, especially when it comes to penam sulfoxides and sulfones, thus inevitably leading to the five-membered ring opening through S(1)–C(2) bond breaking (see Section 2.03.5.3.1). A similar reactivity can be observed in the presence of a leaving group at C-3', affording 3-exomethylene penams **17** (**Scheme 11**) <1995BMC95, 1996CCA1367>. It is noteworthy that 6-bromo-*N*-benzylpenicillamide sulfoxides can undergo a dehydrating rearrangement to afford the 3-exomethylene sulfide **18** in the presence of triethyl phosphite at the boiling point of dry benzene <1996CCA1367>.

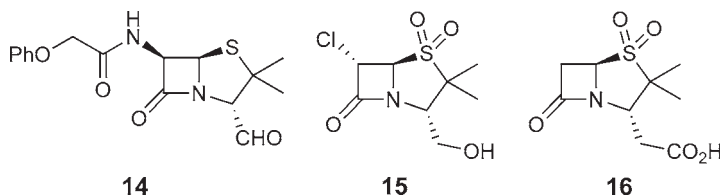
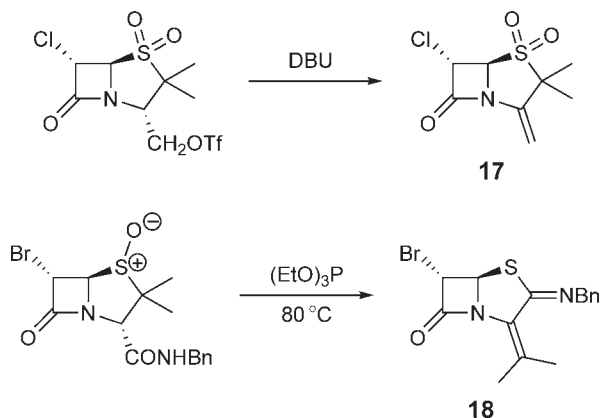


Figure 3 C-3 carboxylic acid transformations.



Scheme 11 Syntheses of 3-exomethylene penams.

2.03.5.6 Modifications at the C-5 Position

Most of the reactions taking place at the C-5 position of penicillins involve the rupture of the C(5)–S(1) bond (see Section 2.03.5.3.2). The 5-epimerization reaction constitutes such an example, accompanied by the five-membered ring opening; unfortunately, no further report has appeared since its description in CHEC-II(1996) (section 1.20.5.5).

In addition, CHEC-II(1996) mentioned an example of a direct copper-mediated substitution at C-5 yielding **19** (**Figure 4**), which is also reported in a more recent paper <1995AJC1065>.

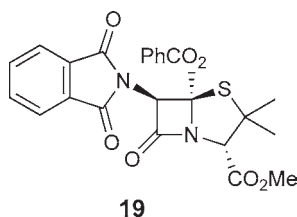
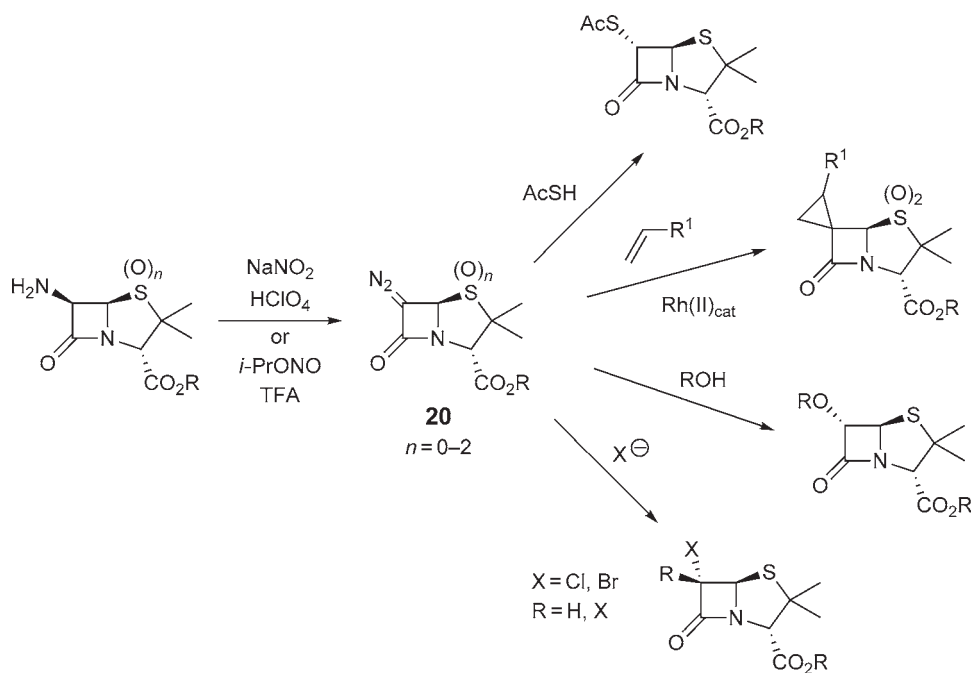


Figure 4 C-5-substituted penam.

2.03.5.7 Modifications at the C-6 Position

The C-6 position of penicillins remains the most versatile one and consequently lots of examples have been reported during the last decades. The variations of the nature of the C-6 side chain fit indeed in the context of finding new broad-spectrum antibiotics <1995J(P1)1483, 2004JA8122> and potential β -lactamase inhibitors (see Sections 2.03.5.2, 2.03.5.9, and 2.03.12.4). CHEC-II(1996) (section 1.20.5.6) <1996CHEC-II(1B)623> fully overviewed the possible transformations at C-6 and, in particular, the synthesis and reactivity of 6-diazo- and 6-halopenicillanates, which constitute key intermediates for access to various 6-substituted penicillins. Therefore, this section only intends to refresh references on that matter.

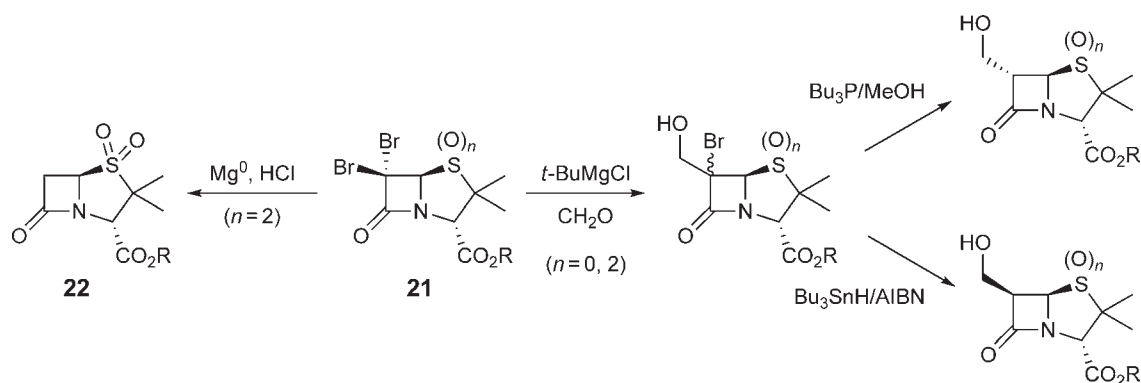
The diazotation of esters of 6-APA can be performed with either sodium nitrite <1995BML2033, 2003JME2569> or isopropyl nitrite <1999JCM270> together with a Brønsted acid to afford the corresponding 6-diazopenams **20** (Scheme 12). From the latter, sulfur <2004BML1299>, oxygen <1995BML2033, 1995T10715, 1995T10723, 1996JBS285, 2004BML1299>, and halogen <1996JBS285, 2005JOC4510> 6-substituted penicillanates are accessible by nucleophilic displacement of nitrogen, with approach on the less-hindered face, thus giving products of 6 α -stereochemistry. The mono- <1995BML2033, 1995T10723, 1996BML2289, 1999JCM270, 2005S442> or dihalogenation reaction <2000OL3087, 2004BML1299, 2005JOC4510> is controlled by the amount of halide used. Another example is the rhodium-catalyzed cyclopropanation of 6-diazopenicillanate sulfones to their corresponding 6-spirocyclopropyl derivatives <2003JME2569>.



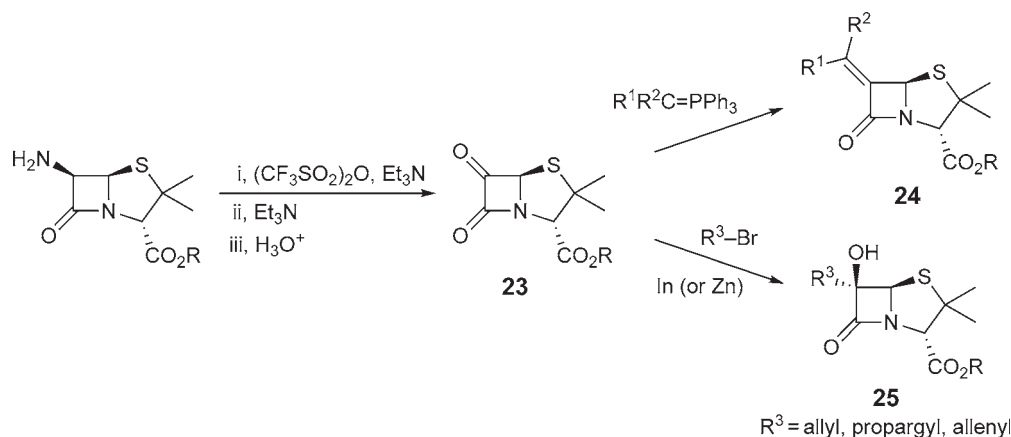
Scheme 12 Synthetic versatility of 6-diazopenicillanates.

6-Halogenated penicillins **21**, either mono- or bis-, are usually utilized as intermediates, for they allow easy access to various C-6 side chains (Scheme 13). Basically, they can be reduced into 6-unsubstituted penicillins **22** <2005S442, 2005JOC4510>, as well as turned into Grignard reagents to react with electrophiles <1999BML997, 2004BML1299>. Stereoselective reduction can be performed by using a phosphine <1996CCA1367, 1999BML991, 2000OL2889> or tributyltin hydride <1995T10723, 1999BML997, 2000OL3087, 2001BML997>.

6-Oxopenicillanate derivatives **23** are also of particular attention as they give access to 6-methylidene penams **24** and 6 β -hydroxy penams **25**, via Wittig reaction <2002FA273, 2004BML147> and indium- (or zinc-) mediated Barbier-type reaction <1999TL1725>, respectively. Besides, they are easily synthesized from esters of 6-APA (Scheme 14) <1999JCM270>. 6-Methylidene penicillins can be obtained from 6 α -monobrominated penicillins as well <2004JOC5850>.

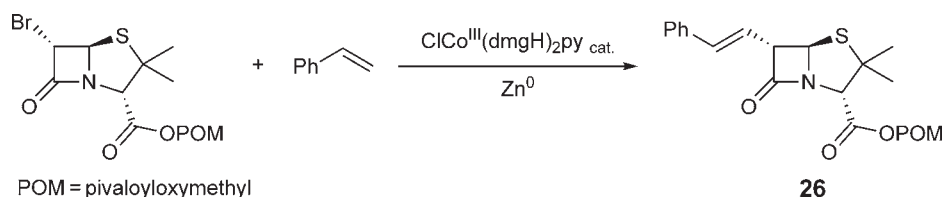


Scheme 13 6,6'-Dibromopenicillin derivatives' reactivity.



Scheme 14 6-Oxopenicillin derivatives' reactivity.

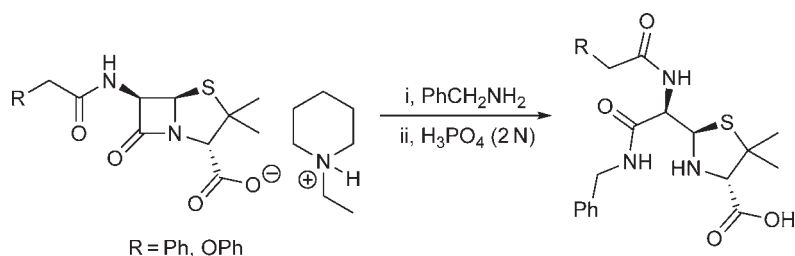
The introduction of a styryl group at the C-6 position of penams finds its application in the intrinsic β -lactamase inhibition activity of 6-vinyl penicillins **26** (see Sections 2.03.5.9 and 2.03.12.4). Its incorporation can be performed via a cobaltoxime-mediated radical cross-coupling reaction between a 6-bromopenicillanate and styrene (**Scheme 15**) <1996BML2289>.



Scheme 15 Cobaltoxime-mediated radical cross-coupling reaction.

2.03.5.8 Modifications at the C-7 Position

In most cases, transformations at the C-7 position involve the β -lactam ring opening due to the geometric strain it represents and its limited amide resonance <B-1992MI79>. Except from a biological point of view, where the β -lactam reactivity finds its interest (see Sections 2.03.5.2 and 2.03.12), it is mainly the nucleophilic attack that leads to opened carboxylic derivatives, as in the aminolysis shown in **Scheme 16** <2006TL1737>.



Scheme 16 A recent example of penam aminolysis.

In CHEC-II(1996) (section 1.20.5.7) <1996CHEC-II(1B)623>, a Wittig olefination reaction <1987J(P1)1369> has been reported on the carbonyl function of penicillins, affording **27**, but has not been exploited since then. A recent study has been developed on the thionation of bicyclic β -lactam compounds using Lawesson's reagent <2005ARK282>, although compound **28** has been isolated in poor yield (**Figure 5**).

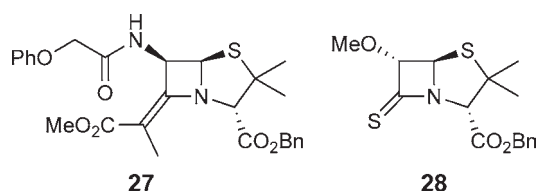
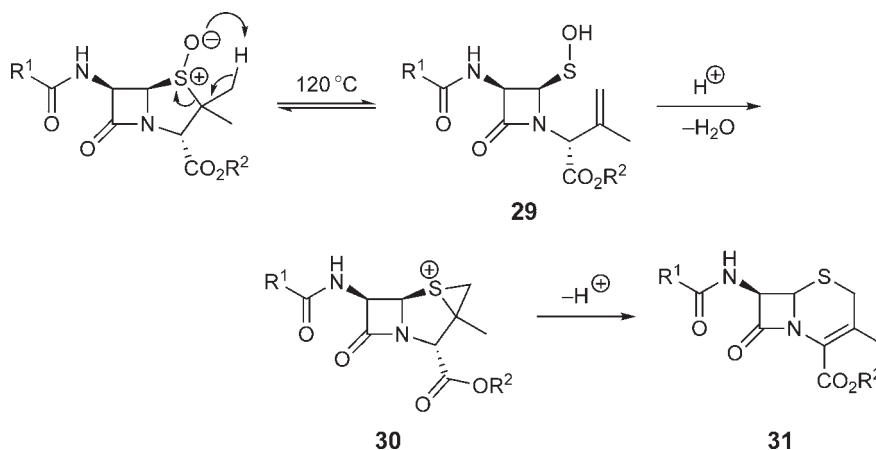


Figure 5 C-7-modified penams.

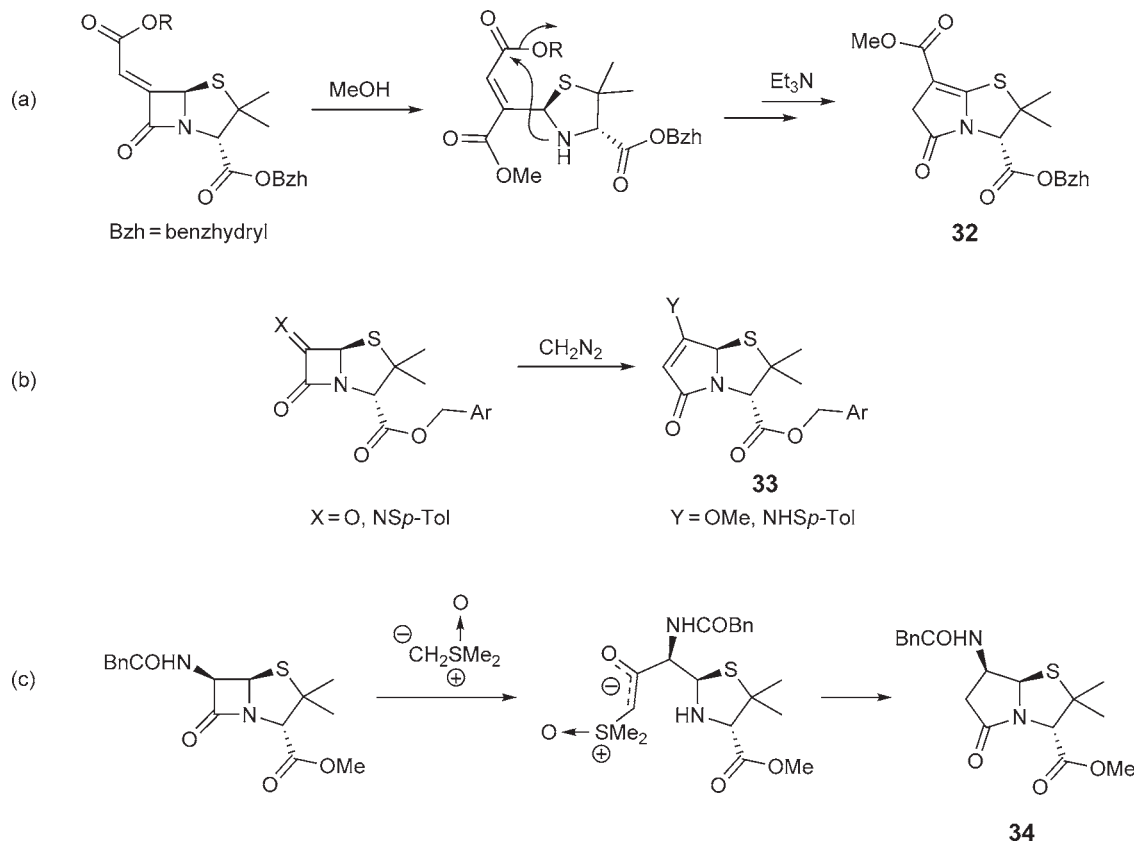
2.03.5.9 Rearrangement Reactions Involving the Penam Skeleton

The most studied rearrangement regarding the penam skeleton remains the ring enlargement of penicillins into cephalosporins **31** <2000T6053, 2001CJC1238, 2002T8313>. As it is of particular importance (CHEC-II(1996), section 1.20.5.8), its mechanism is shown in **Scheme 17**, even though it has already been partially described in Sections 2.03.5.3.1 and 2.03.5.4. Basically, it starts with a thermal rearrangement of a penam sulfoxide to afford a sulfenic acid **29** <B-1977MI167>, which leads, under acidic conditions (in the absence of any reagent able to quench this unstable species), to cephems **31** via an episulfonium intermediate ion **30** (**Scheme 17**).



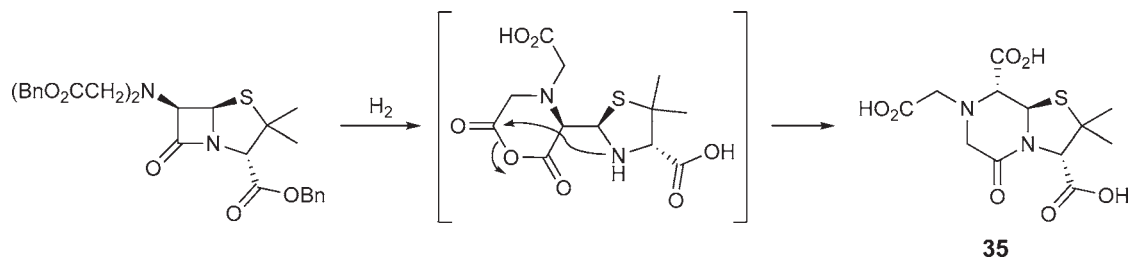
Scheme 17 Ring expansion of penam sulfoxides into cephems.

Some examples of ring expansion of penicillins to homopenicillins are depicted in **Scheme 18**; they can be either β,γ -unsaturated **32** <2004CC2332>, α,β -unsaturated **33** <1983TL3419, 2007OBC160>, or saturated **34** <1988CC110> bicyclic compounds.



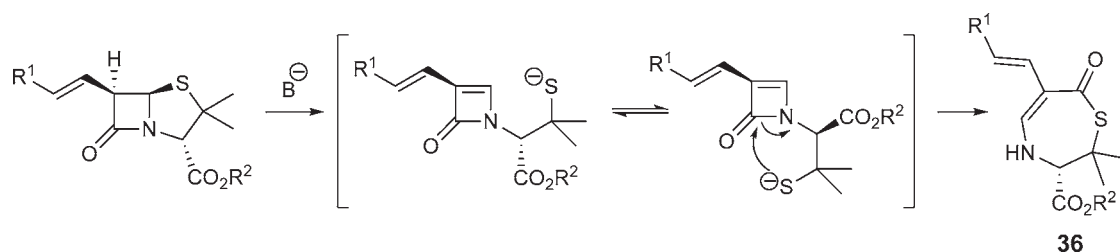
Scheme 18 Ring expansion of penicillins to homopenicillins (three examples).

The possibility of ring expansion of the penicillin β -lactam ring to a fused-ring piperazinone **35** is also worth mentioning (**Scheme 19**) <1995TL9313>.



Scheme 19 β -Lactam ring expansion into six-membered ring.

The presence of a styryl group ($R^1 = \text{Ph}$) at C-6 confers to penicillins a β -lactamase inhibition activity (see **Section 2.03.12.4**) by acidifying H-6, which provokes the C(5)–S(1) bond cleavage (see **Section 2.03.5.3.2**) toward the formation of 1,4-thiazepin-7-ones **36** (**Scheme 20**) <1996BML2289>.



Scheme 20 Rearrangement of 6-vinyl penicillins into 1,4-thiazepin-7-ones.

2.03.6 Reactivity of the Penem Skeleton

2.03.6.1 Introduction

The need to develop new antibiotics with a broad spectrum to overcome the bacterial resistance issues, contributed to the conception of the non-natural penem ring system (4-thia-1-azabicyclo[3.2.0]hept-2-en-7-one in the IUPAC nomenclature), born from the naturally occurring penam and cephem nuclei <1988FA1075, 2003MI105>. As their name betrays, penems possess the skeleton of the former and the double bond of the latter (Figure 6). The first penems were synthesized by Woodward in the mid-1970s and bore the parent penam side chain, namely a 6-acylamino group in a (5*R*,6*R*)-configuration <B-1977MI167, 1978JA8214, 1980MI239, B-1992MI334>. Then the discovery of the broad-spectrum carbapenem thienamycin (see Table 1, Section 2.03.1), with a high β -lactamase stability <1978JAN1, 1978JA6491>, influenced chemists to introduce on penems a 6-(1*R*-hydroxyethyl) side chain in a (5*R*,6*S*)-configuration to enhance both their chemical stability and potent antibacterial activity <B-1981MI330, B-1981MI349, B-1989MI222, 1988MI393, 1995MI705, 2005MI319, 2006BP1085>. The reader should also refer to other monographs for further information on penems <B-1980MI100, B-1982MI315, B-1991MI1, B-1992MI3>.

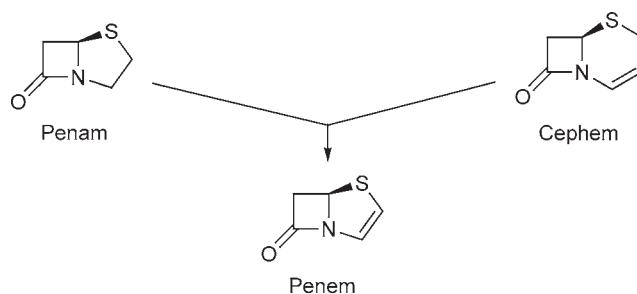


Figure 6 The origin of penem antibiotics.

Within the penem family, five subcategories can be distinguished depending on the nature of the C-2 side chain (Table 6), the determining factor for the pharmacokinetic and toxicological properties of the molecules.

Table 6 Penems classification

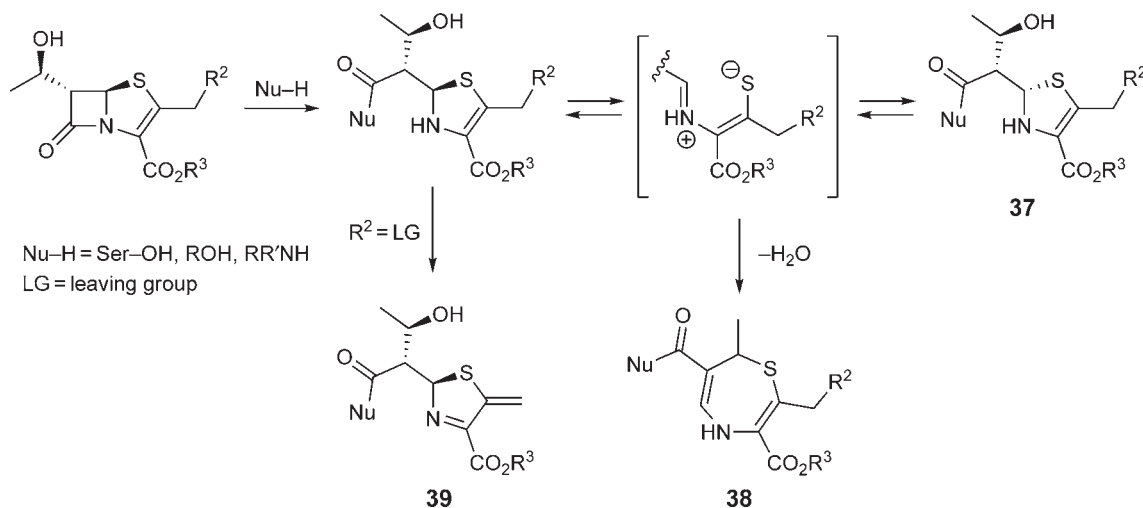
<i>R</i> = <i>Alkyl</i>	<i>R</i> = <i>Aryl</i>	<i>R</i> = <i>N</i>	<i>R</i> = <i>O</i>	<i>R</i> = <i>S</i>
Alkylpenems	Arylpenems	Aminopenems	Oxypenems	Thiopenems

The presence of the double bond, which differentiates penems from penams, allows enamine resonance which renders the bridgehead nitrogen atom less basic and weakens the C(7)–N(4) bond, and hence facilitates β -lactam hydrolysis. As a consequence, they are more labile than the penams, and such instability issues narrow the range of chemical reactivity of the penem skeleton.

As the penem nucleus was not described in both CHEC-II(1996) and CHEC(1984), the following sections go through aspects of the systematic reactivity of penems in a qualitative way since their first synthesis, considering each atom of the skeleton.

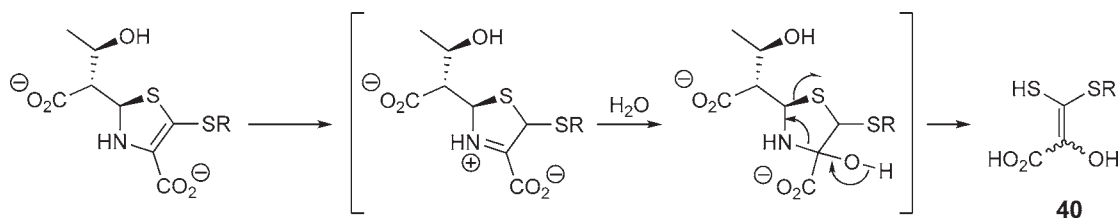
2.03.6.2 Reactivity Associated with the Biological Activity of Penems

In β -lactam chemistry, the strain induced by the four-membered ring geometry and the reduced amide resonance makes the carbonyl carbon atom C-7 more electrophilic than in any normal amide <B-1992MI79>. Thus, the reactivity of the carbon atom C-7 in penems is about nucleophilic attacks that tend to release the azetidinone ring strain via a tetrahedral intermediate. Thus the hydrolytic metabolism of a penem by a PBP (penicillin-binding protein) is nothing but an acyl-enzyme complex formed upon β -lactam ring cleavage; some studies highlight such complexes by crystallization within active sites <1998NAT186, 2003S1732>. Compared to penams, the hydrolysis (alcoholysis, aminolysis) of penems is faster due to the enamine resonance (see Section 2.03.6.1). Moreover, the subsequent five-membered ring opening via C(7)–N(4) and C(5)–S(1) bond cleavage is more favored in penems due to the stabilization by delocalization of the thus-generated thiolate negative charge (Scheme 21). The latter can lead to either the 5-epimer **37** or the 1,4-thiazepine **38** by the attack of the thiolate on the iminium cation <1990JAN901> or substitution of the hydroxyl group on the side chain, respectively <1992H(33)859>. If a leaving group is present on the side chain at C-2', the formation of an exomethylene thiazoline **39** is favored over the five-membered ring cleavage <1986JAN1351, 1988JAN984>.



Scheme 21 Chemical patterns of penems under nucleophilic conditions.

A study reported the mechanism of the turnover of a 2-thiopenem by a class A β -lactamase <1993JA4962>; the resulting detected metabolite is a ketene dithioacetal **40** as shown in Scheme 22.

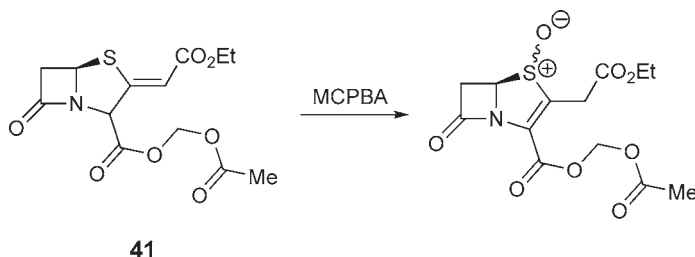


Scheme 22 Degradation of penems by a β -lactamase.

6-Methylene penems constitute good β -lactamase inhibitors as their hydrolytic metabolism leads to the formation of 1,4-thiazepines, strengthening the thus-formed acyl–enzyme complex link (see Sections 2.03.6.9 and 2.03.12.4). However, compared to penams, penem sulfones are not as good β -lactamase inhibitors as their half-lives of hydrolysis are too short, making them labile under physiological conditions <1997BML2217>.

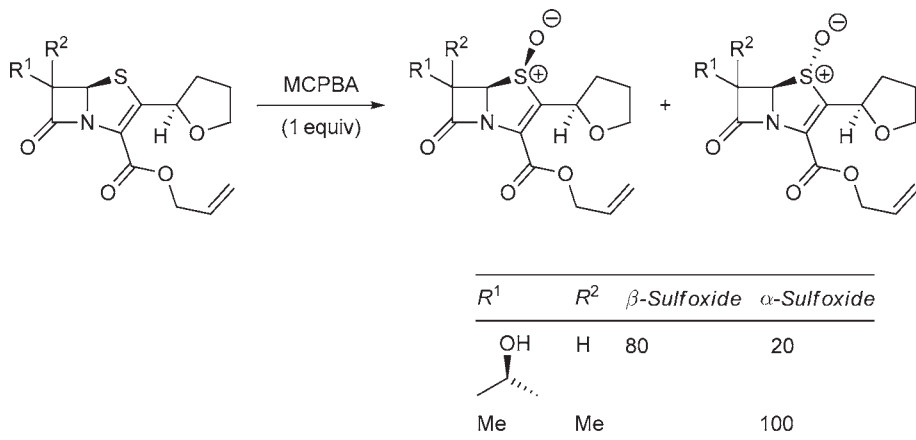
2.03.6.3 Modifications at the S-1 Position

In a trend to develop new antibiotics and β -lactamase inhibitors, comparable to that for the penam, the synthesis of new penem structures and their oxidation reactions on the S-1 atom have been jointly investigated during the last three decades. The first isolated penem sulfoxide was reported in 1979 <1979TL3777>. However, its synthesis was not performed by direct oxidation of a penem but a 2-exomethylene penicillanate **41** (1-thioclavulanic ester), involving a migration of the double bond to afford the penem nucleus (Scheme 23).



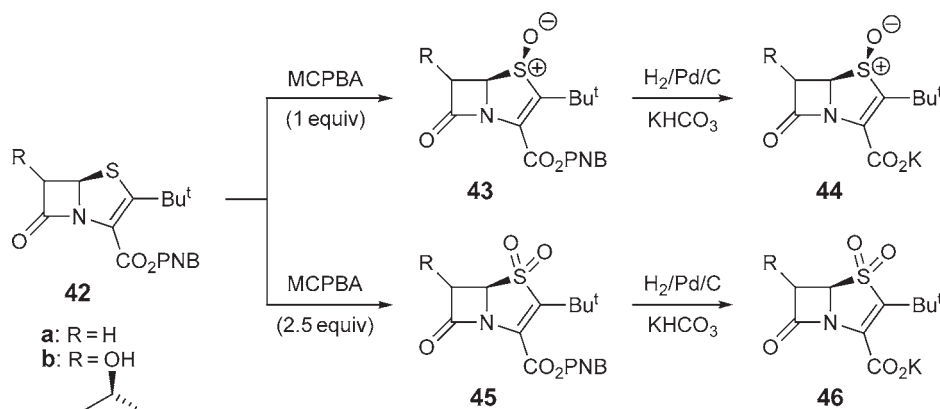
Scheme 23 Synthesis of the first penem sulfoxide.

So far only few S-oxidized penems have been described, mainly due to the fact that their instability increases with their sulfur atom oxidation state. Hence, the most successful oxidation reactions were carried out on the most stable penems, typically those bearing a 1-(*R*)-hydroxyethyl group at C-6 in a *trans*-configuration with the C(5)–S(1) bond (Schemes 24 and 25). Ishiguro and co-workers have reported a study on the high stereoselectivity observed in the peracid oxidation of the sulfur atom in the penem nucleus into its sulfoxide <1990CC853>. Regardless of the steric and hydrogen-bonding effects of 6 β -substituents, they indeed justify the favorability of the β -side (concave face) oxidation by a directional effect of the β -lactam carbonyl oxygen on the peracid attack. Once a 6 β -substituent bulkier than hydrogen is introduced, the selectivity is no longer governed by the β -lactam carbonyl oxygen assistance, but by steric effects (Scheme 24).



Scheme 24 Side-chain effects on the selectivity of the mono-S-oxidation of penems.

Pfaendler's study deals with the preparation of both penem sulfoxides **43** and sulfones **45** from **42** using the required amounts of *m*-chloroperbenzoic acid (MCPBA) as depicted in **Scheme 25**. In a second step, **43** and **45** were converted into their respective potassium salts **44** and **46**. However, catalytic hydrogenation on **45a** resulted in product decomposition, as **46a** was too labile to be isolated <1997BML2217>.



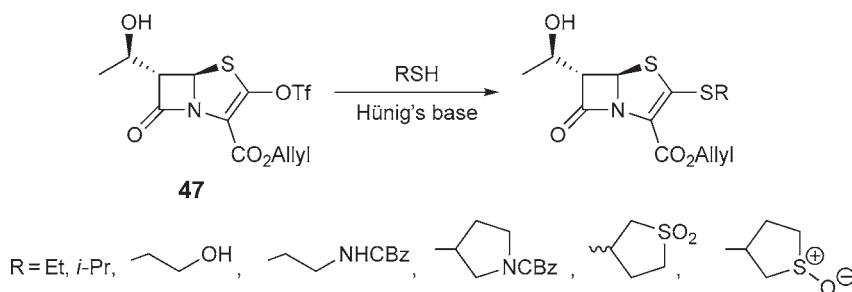
Scheme 25 Oxidation of penems (PNB = *p*-nitrobenzyl).

No reports describing penem S-oxidation with oxidizing agents other than MCPBA, or articles dealing with different S-1 reactivity besides oxidation reactions, have been found.

2.03.6.4 Modifications at the C-2 Position

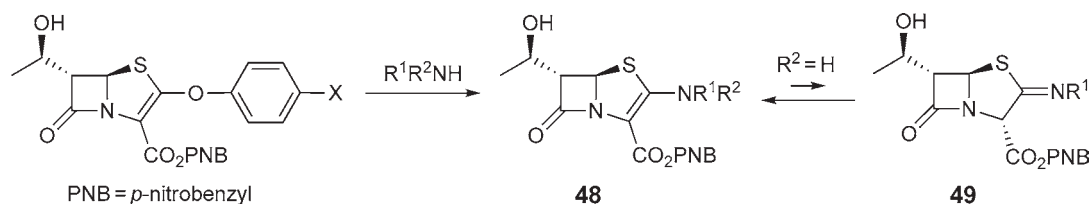
The C-2 position in penems is the most versatile one for substituents variation <B-1992MI96>. Thus, a large number of penem derivatives have been reported bearing 2-substituents bonded via sulfur (e.g., sulopenem; see Section 2.03.12.3) <1980HCA1093, 1981TL3485, 1981TL3489, 1982TL3535, B-1985MI266, 1987CC691, 1987H(25)123, 1992JOC4352>, oxygen <1983CC1005, B-1985MI100, 1988AAC1090, 1998BML2793, 2000T5621>, nitrogen <1983TL2563, 1986JAN1187, 1987TL2283, 1987JAN217>, and carbon atoms (e.g., ritipenem, faropenem; see Section 2.03.12.3) <1984JAN685, 1985H(23)2255, 1988H(27)49, 1988H(27)1329, 1990H(30)799, 1995JME4244, 1997BML623, 1997BMC1389>. For an overview of the reactivity of the substituents attached to C-2, the reader should refer to Section 2.03.7.3. Herein, only the reactivity of the C-2 atom is discussed.

Compared to penams, the presence of the double bond in the five-membered ring of penems confers the specific reactivity to C-2. Its conjugation with the 3-carboxyl function makes the C-2 a Michael-like position. However, due to the double-bond delocalization through S-1 and N-4 as well, the presence of a leaving group at C-2 as driving force is required to help the nucleophilic attack. An illustration of the displacement of a triflate by thiols of a previously synthesized 2-*O*-triflylpenem **47** is summarized in **Scheme 26** <1990TL3291>.



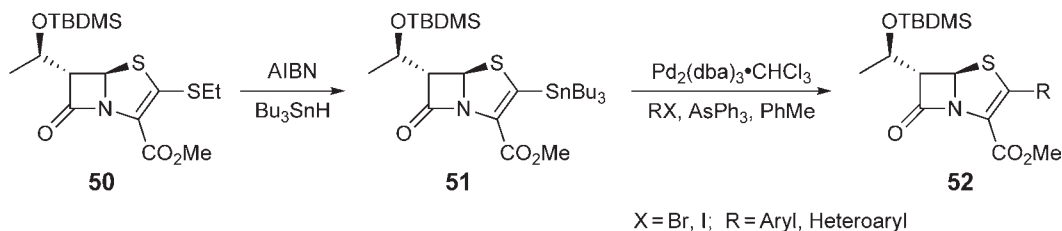
Scheme 26 Addition of thiols on a 2-activated penem.

A general route to various substituted 2-aminopenems **48** via displacement of phenol leaving groups by aliphatic primary and secondary amines is described in [Scheme 27](#) <1987TL2283>. When it comes to primary amines ($R^2 = H$), a minor amount of the corresponding 2-iminopenam tautomers **49** is also formed. Ghosez and co-workers have previously observed such a tautomeric equilibrium on 2-aminopenems <1983TL2563>.



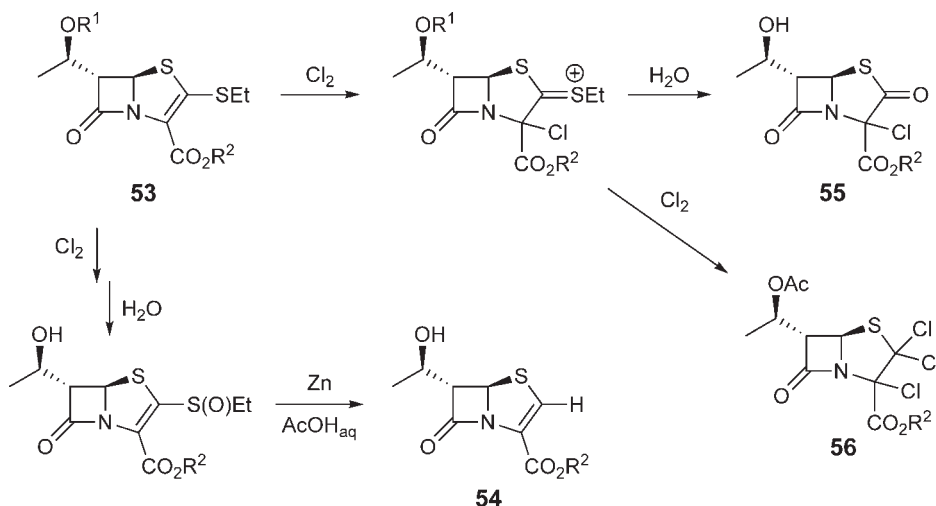
Scheme 27 Reaction of 3-aryloxyopenems with amines.

The exocyclic C(2)–S bond of a 2-thiopenem **50** can undergo radical reactions. As depicted in [Scheme 28](#), its desulfurative stannylation reaction with azobis(isobutyronitrile) (AIBN) and tributyltin hydride leads to a penem stannane **51** <1995TL775>. The latter allows subsequent palladium(0)-mediated cross-coupling reactions with halogenated (hetero)aryl reagents to afford 2-(hetero)aryl penems **52**.



Scheme 28 Palladium(0)-mediated reactions of 2-stannyl penems.

Since the 2-ethylthiopenem **53** could readily be synthesized from the commercially available acetoxyazetidinone <1982JA6138>, it has become a starting material of choice for further modification at the C-2 position of penems. In the following example ([Scheme 29](#)), it allows the access to 2-unsubstituted penems **54** via an oxidation/reduction sequence, and to 2-oxo- **55** and 2,2-dichloropenams **56** <1987CC691>.

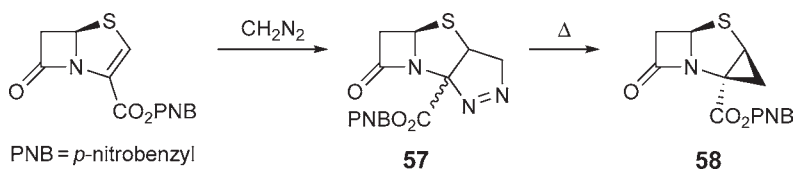


Scheme 29 C-2 modifications from 2-ethylthiopenem.

The C(2)–C(3) double bond can react with diazomethane through a 1,3-dipolar cycloaddition process and thus lead to fused tricyclic species (see [Section 2.03.6.5](#)).

2.03.6.5 Modifications at the C-3 Position

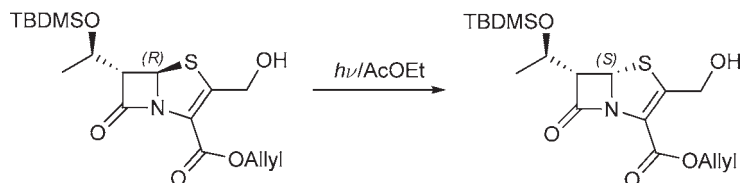
Besides the fact that the C-3 carbon atom in penems can move from sp^2 to sp^3 hybridization by tautomerism, depending on the nature of the substituent at the C-2 position [<1983TL2563, 1987TL2283, 1987CC81, 1988H\(27\)49>](#), so far only two reports concerning the reactivity of C-3 have been found. One deals with the 3-chlorination of a 2-alkylthiopene **53** with dichlorine ([Scheme 29](#)) [<1987CC691>](#), and the other is an example of a pericyclic reaction [<1993TL1799>](#). The C(2)–C(3) double bond can indeed undergo a 1,3-dipolar cycloaddition with diazomethane to afford two tricyclic stereoisomers **57** ([Scheme 30](#)). The subsequent thermolysis of the major isomer gives the corresponding fused 2,3-cyclopropyl penam **58** by extrusion of nitrogen gas [<1993TL1799>](#).



Scheme 30 Synthesis of a 2,3-methylene penam.

2.03.6.6 Modifications at the C-5 Position

So far, no 5-substituted penem has been reported. Two possible absolute configurations exist for the bridgehead carbon atom C-5, (*R*) remaining the most encountered one as 5(*S*)-epimers are inactive [<1980MI239>](#). However, the epimerization reaction from 5(*R*) to 5(*S*) can be readily performed via photochemical irradiation in ethyl acetate ([Scheme 31](#)) [<2003S1732>](#).



Scheme 31 Photochemical epimerization at C-5.

A study also revealed the possibility of a thermal equilibrium between 5-epimers of a protected penem ([Scheme 32](#)), the ratio of which depends on the temperature and the duration of heating [<1981TL3485>](#).



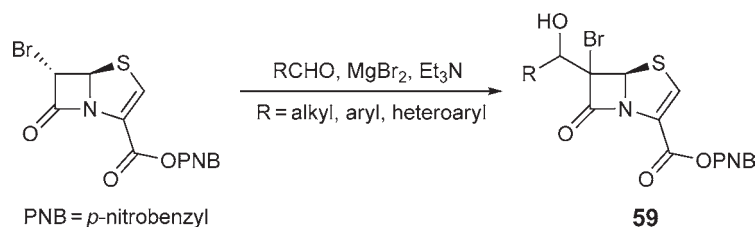
Scheme 32 Thermal 5-epimeric equilibrium of penems.

For further reactivity involving the rupture of the C(5)–S(1) bond, the reader is invited to look at [Section 2.03.6.9](#).

2.03.6.7 Modifications at the C-6 Position

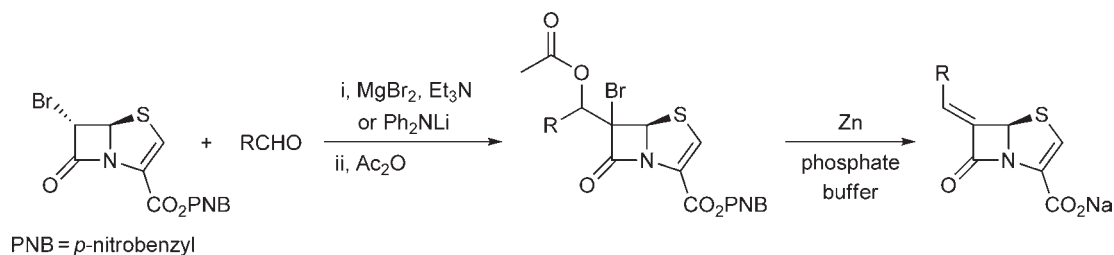
The variations of the C-6 side chain of penems have been extensively investigated as it constitutes an important factor for both their chemical stability and their antimicrobial activity. Because the penem skeleton is a hybrid of penam and cephem, the first penems to be synthesized by the mid-1970s were bearing an acylamino side chain in a 'penicillin-like' configuration <1978JA8214, 1980TL3085>, or were 6-unsubstituted penems <1979JA6296, 1979JA6301, 1979JA6306, 1981JA4526>. After the discovery of thienamycin (see Table 1) <1978JAN1, 1978JA6491>, penem derivatives featuring the 5,6-*trans*-configuration with a 1-(*R*)-hydroxyethyl group at C-6 were synthesized and it was found that they showed an improved chemical and biochemical stability together with similar antibacterial activities to those of the carbapenems <1980JA2039, 1996MI1034, 2007BMC392>. Usually, 6-substituents, and in particular the 1-(*R*)-hydroxyethyl group, are introduced at the beginning of the penem synthesis by choosing a well-substituted azetidinone as starting material; afterward, the penem synthesis ends by the five-membered ring closure (see Section 2.03.11.5). Sometimes, because of the penems' chemical instability, the 6-substituent is introduced on penems starting from the corresponding penicillin, whose thiazolidine ring is opened to afford the intermediate substituted azetidinone, and finally the desired penems by five-membered ring closure (see Section 2.03.10) <1995T10715, 1995T10723>. In addition, most of the variations of the C-6 side chain do not even involve the C-6 carbon atom but just the reactivity of functional groups on the side chain (see Section 2.03.7.1).

However, as the C-6 position is a α -carbonyl position, the preparation of various penem-based antibiotics becomes easily accessible with the aid of enolate reactivity. The example depicted in Scheme 33 is a mild and efficient method for the preparation of 1-hydroxyalkyl(aryl) penems **59** from 6 α -bromopenems <2004JOC5850>.



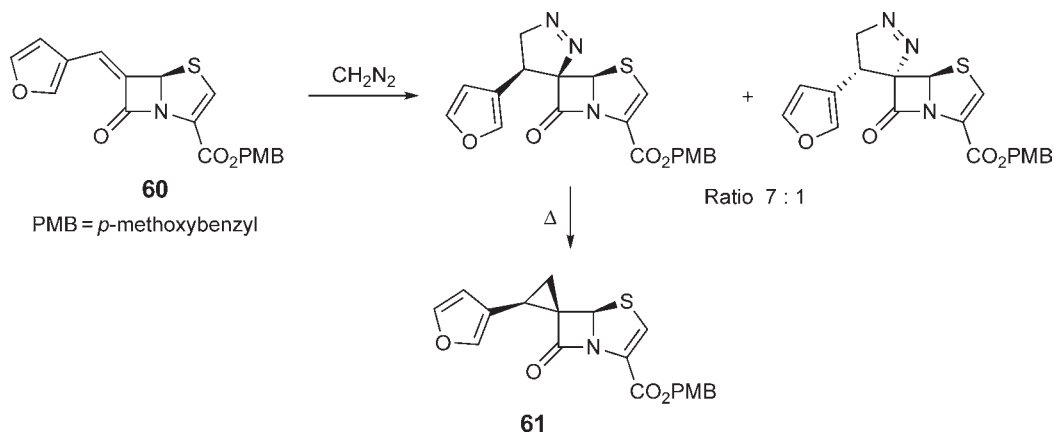
Scheme 33 $\text{MgBr}_2/\text{Et}_3\text{N}$ -promoted aldol-type condensation of a 6-bromopenem with aldehydes.

Later, 6-methylene penems were synthesized and showed interesting anti- β -lactamase properties due to the presence of their exocyclic double bond <B-1989MI247>, which constitutes a driving force for the five-membered ring opening and the subsequent seven-membered ring formation (see Section 2.03.6.9). These substituents can be introduced starting from 6-bromopenems via an aldol/reduction two-step sequence (Scheme 34). The method allows the introduction of a large variety of lateral chains R (R = alkyl, aryl, heteroaryl, bis(tris)heterocyclic) <2004BMC5807, 2004JME3674, 2004JME6556, 2006JME4623>. As an example, the 6-methylene penem BRL 42715 (R = 1-methyl-1,2,3-triazolo-4-yl) presents an effective inactivation activity of β -lactamases <1995JA4797>.



Scheme 34 Synthesis of 6-methylene penems from 6-bromopenems.

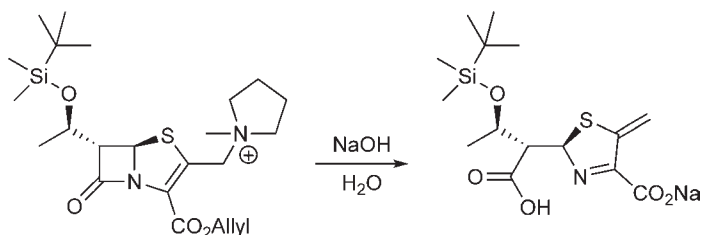
The reaction of diazomethane with the (*E*)-fur-3-yl-methylene penem **60** gives a mixture of two stereoisomers, corresponding to 6-spiropyrazolanyl penems, via a 1,3-dipolar cycloaddition (Scheme 35) <1993TL1799>. The major isomer results from the approach of diazomethane to the sterically most hindered β -face – the opposite of the stereochemistry observed in the carbapenem series where α -face attack predominates <1986J(P1)421>. Its subsequent thermolysis in ethyl acetate at reflux yields the corresponding 6-spirocyclopropyl penem **61**. Although the cyclopropane ring often exhibits double-bond properties, in the 6-spiro position of penems it shows a bioisosterism with the 6-spiroepoxide function rather than with a 6-alkylidene double bond <1988CC274, 1988CC1610>.



Scheme 35 6-Spiropenems synthesis from 6-methylene penems.

2.03.6.8 Modifications at the C-7 Position

Since penems are labile compounds, no particular reactivity at C-7 has been described apart from nucleophilic attack that leads to the β -lactam ring opening. Under basic aqueous conditions, penems are hydrolyzed via a tetrahedral intermediate <1981JA4526>. The additional presence of a leaving group on the side-chain at C-2' constitutes a driving force for the β -lactam ring opening (Scheme 36) <1986JAN1351>.

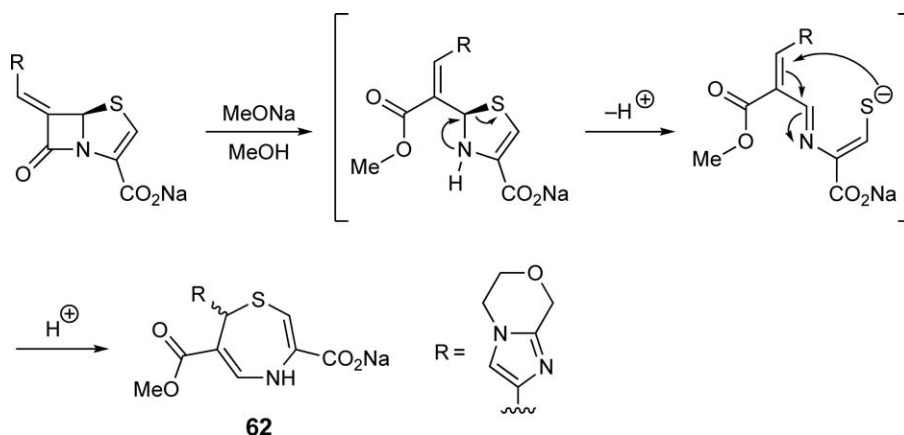


Scheme 36 Penem hydrolysis.

The products arising from cleavage of the azetidinone ring of bioactive penems are of particular interest in the comprehension of an acyl–enzyme complex formation with the target enzymes (see Section 2.03.6.2).

2.03.6.9 Rearrangement Reactions Involving the Penem Skeleton

Under nucleophilic conditions, 6-exomethylene penems readily transform into 1,4-thiazepines **62** as illustrated in Scheme 37 <1994JAN945, 1995JA4797, 2000MI109, 2004JME3674, 2007PCA4720>. This process is triggered by the consecutive four- and five-membered ring opening.



Scheme 37 Rearrangement of 6-exomethylene penems.

2.03.7 Reactivity of Substituents Attached to the Ring Carbon Atoms

2.03.7.1 Substituents Attached to the C-6 Position

Semisynthetic penicillins are constructed by side-chain coupling on the amino function at the C-6 position of the penam nucleus (see [Section 2.03.11.3](#) <1995J(P1)1483, 2000T7601>, and the search for ‘perfect penicillin’ is still pursued <2004JA8122>. For instance, new antibiotics **63** against Gram-negative bacteria including a siderophore moiety have been devised ([Figure 7](#)) <2002JME3032, 2006T7799>; a one-pot protocol for the acylation of 6-APA with $\text{Ph}_3\text{P}=\text{C}=\text{C}=\text{O}$ and an aldehyde allowed the expeditious coupling of bis-catechol hydroxamate chelators <2005TL1127>.

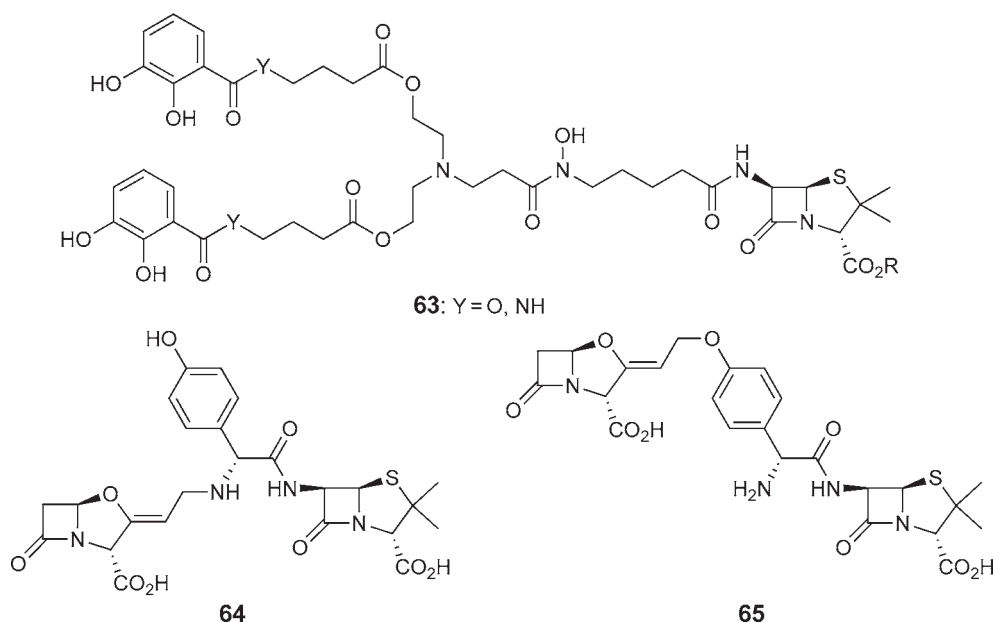


Figure 7 Penicillins with particular C-6 side chains.

The C-6 side-chain functions of antibiotics have been used to develop the pro-dual-drug concept <2002BMC3489>. Compounds **64** and **65**, combining clavulanic acid and amoxicillin, show a notable activity against β -lactamase-producing microorganisms.

The construction of biotechnological tools relies on the fixation of labels on the C-6 side chain <1994BJ141>. In this field, trapping of phage-displayed β -lactamase enzymes by the penam sulfone derivative **66** has been reported <B-1995MI149, 1994JMB415, 1994MI175, 1996BML789>. The anti- β -lactamase activity of 6-sulfonamidopenicilanic acid sulfones has been established <1994JAN1041>, before incorporating this motif into the biotinylated label **66** <1995BMC907, 1996T5591>. Similarly, catalytic single-chain antibodies possessing β -lactamase activity have been selected from a phage-displayed combinatorial antibody library using a penam sulfone inhibitor **67** (Figure 8) <1999TL8063>.

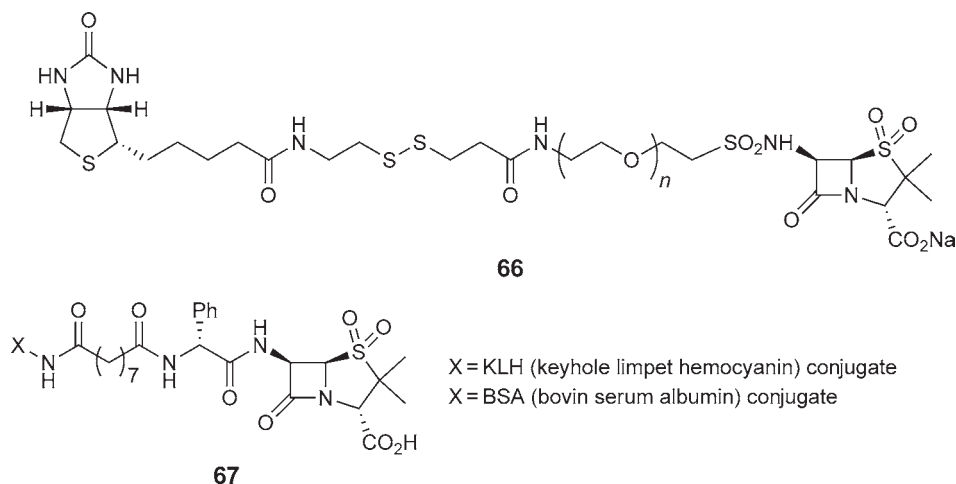
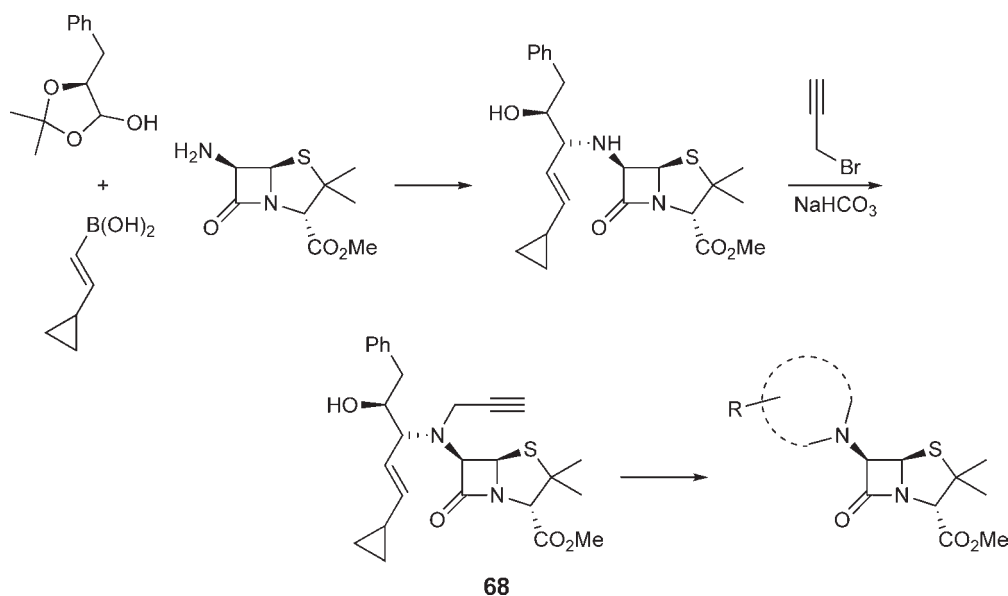


Figure 8 Biotechnological tools derived from penam sulfones.

An American team developing short syntheses toward nitrogen-containing heterocycles from primary amines has exemplified the methodology with methyl 6-aminopenicillanate. They used the Petasis three-component, boronic acid Mannich reaction followed by an amine propargylation to yield the β -amino alcohol **68** (Scheme 38). This methodology allows further cyclization reactions, thus leading to 6-(pyrrolidin-1-yl)-, 6-(*N*-morpholino)-, and even more sophisticated 6-polyheterocyclic penam derivatives <2006AGE3635>.



Scheme 38 Functionalization of the primary amine function of 6-APA.

2.03.7.2 Substituents Attached to the C-3 Position

The acid function of the C-3 position in penams (and penems) can be used for the preparation of esters as prodrugs (**Figure 9**), such as pivampicillin **69a**, talampicillin **69b**, bacampicillin **69c**, and KB-1585 **69d** (doloxate ester) <B-1985MI32>. Their hydrolysis is catalyzed by serum proteases, and tailored ester prodrugs (such as **69e**) for ampicillin intracellular accumulation have been designed <1997BML3107>.

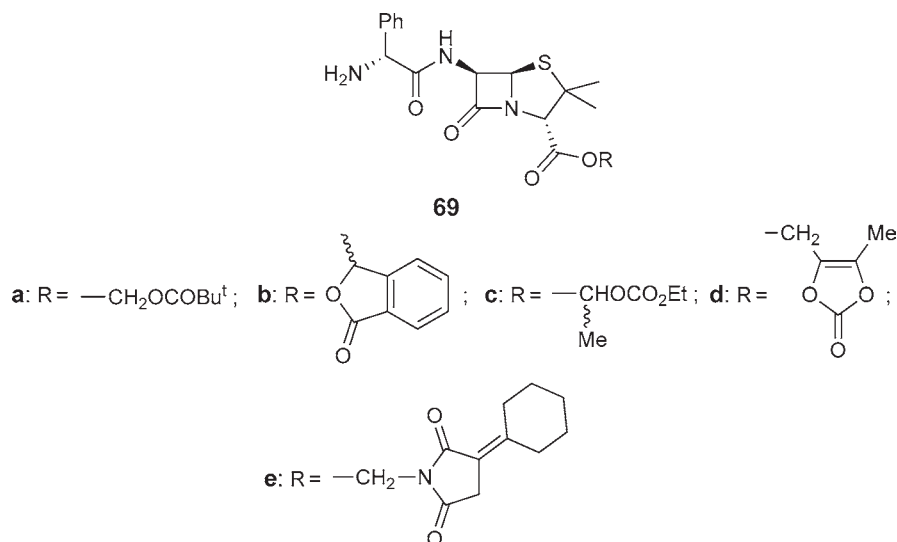


Figure 9 Penicillins' prodrugs.

2.03.7.3 Substituents Attached to the C-2 Position

In the penam series, the starting materials for the functionalization of one of the C-2 methyl groups are the chloro-**70a**, bromo- **70b**, or oxycarbonyl **70c** derivatives, obtained from the usual penam sulfoxide chemistry (**Figure 10**) (see Sections 2.03.5.4 and 2.03.5.9).

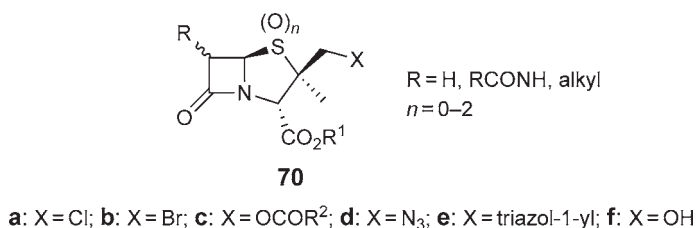
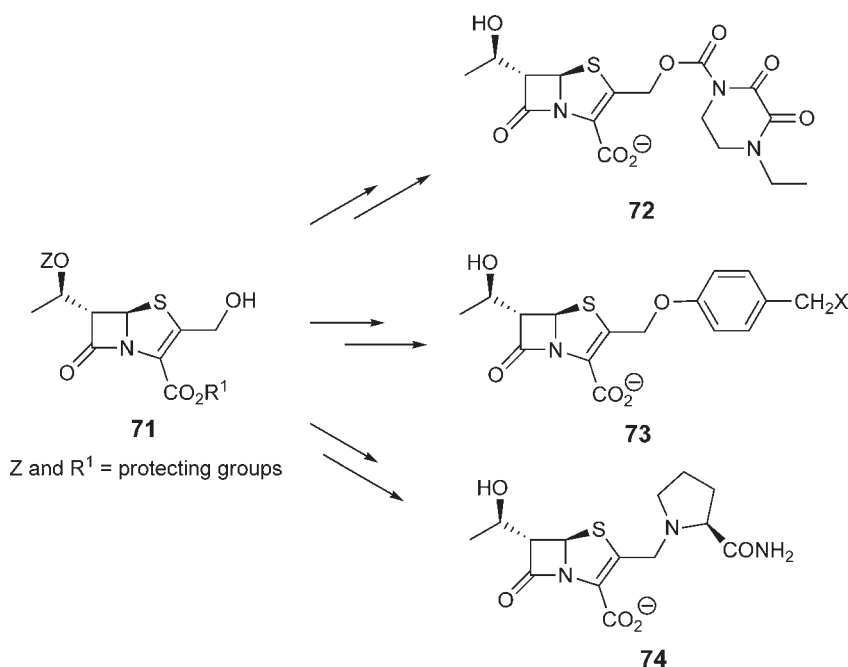


Figure 10 Precursors of C-2' penam derivatives.

Nucleophilic substitution of **70a/70b** by an azide ion produces the intermediate **70d**, precursor of triazoles through 1,3-dipolar cycloadditions <1986S292>. Tazobactam **70e** (R = H, n = 2) represents an example of 2'-β-triazolylpenam sulfone that is an efficient inhibitor of class A β-lactamases <1993AAC851> (see Section 2.03.12.4). Besides, deprotection of **70c** furnishes the alcohol **70f**, which can be acylated again <2006JA13235> or oxidized to an aldehyde and then transformed into Schiff bases <1997BML11>. 2β-Alkenylpenam sulfones, acting as anti-β-lactamases, can be obtained from **70f** via a Swern/Wittig reaction sequence <1996JME3712>. Also, synthesis of 2',6-bridged penams **124** in quite moderate yields (see **Figure 12**, Section 2.03.11.6) by an intramolecular nucleophilic substitution reaction between the C-2 and C-6 side chains of the free 6-amino-substituted penicillin **70c** (R² = CH₂Cl) is worth mentioning. The cyclization is indeed allowed due to the relatively close proximity of the two β-side chains on the concave face of this system <1998JA6846>.

In the penem series, 2-(heteroatom-substituted)-methyl derivatives have been similarly prepared via the 2-(hydroxymethyl) key intermediate **71**. Some examples of this C-2 functionalization are illustrated in [Scheme 39](#) <1990H(30)799, 1995JME4244>. The reactions involved are O-acylation **72**, O-arylation **73** by Mitsunobu coupling, and substitution by nitrogen nucleophiles **74** after OH activation by mesylation.



Scheme 39 Synthesis of C-2' penem derivatives.

2.03.8 Reactivity of Substituents Attached to the Ring Heteroatoms

In penams and penems, the ring heteroatoms S-1 and N-4 do not bear any exocyclic substituents with the exception, however, of penam sulfoxides, which can rearrange into sulfenic acids (see [Sections 2.03.5.3.1, 2.03.5.4, and 2.03.5.9](#)).

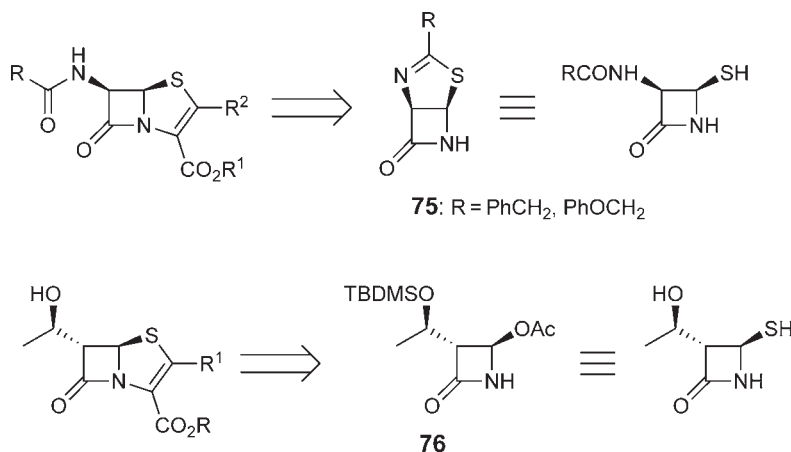
2.03.9 Ring Synthesis from Acyclic Compounds

The oldest approaches to the penam skeleton from acyclic precursors were based on the azetidinone ring closure from β -amino acid precursors (one-bond cyclization) and the [2+2] cycloaddition of ketenes or enolates to imines (two-bond cyclization). These methods have been discussed previously (CHEC-II(1996), section 1.20.6.5) <1996CHEC-II(1B)623>. Nowadays, most of the total syntheses of non-natural penams and penems make use of chiral preformed β -lactams featuring appropriate side chains and substituents, for fused ring cyclization with the right stereochemistry. The methods of β -lactam ring construction have been reviewed <B-1992MI257, B-1992MI295, 2003T7631, 2004ACR592>.

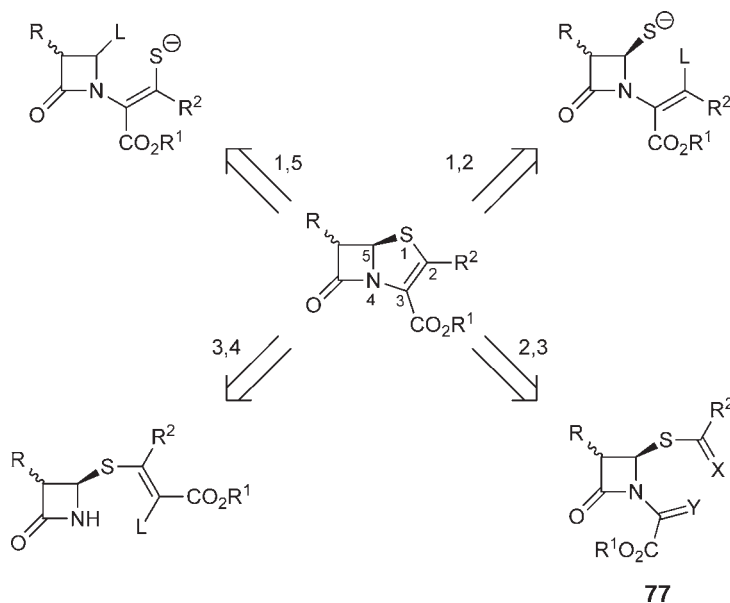
The two chirons **75** and **76** are of particular interest for the preparation of fused-ring β -lactams bearing a penicillin side chain (G and V) or the thienamycin side chain at C-6, respectively. On the one hand (1*R*, 5*R*)-3-Phenyl(oxy)methyl-4-thia-2,6-diazabicyclo-[3.2.0]hept-2-en-7-one **75** is prepared from natural penicillins <1970JA2575, 1972JA1021, 1976J(P1)447>, but is also accessible by total synthesis <2000S289>. On the other hand, (3*S*,4*S*)-4-acetoxy-3-[(*R*)-1'-((*t*-butyldimethylsilyl)-oxy)ethyl]-2-azetidinone **76** results only from enantiocontrolled synthetic approaches ([Scheme 40](#)) <1996T331, 1996TA1241, 1996TL5565, 2004JOC3194, 2006EJO3755>.

The use of precursor **75** is illustrated in [Section 2.03.11.5](#). Recent research concerns mainly the thienamycin-like penems for which the four possible disconnections have been explored ([Scheme 41](#)) <1987PAC467, B-1981MI281, B-1981MI349, B-1985MI100, B-1985MI266, B-1989MI222, B-1989MI259, 2000T5621, 1988MI393, 1988FA1075>. However, only the C(2)–C(3) bond-forming strategies are of preparative interest. Various precursors **77** for C(2)–C(3)

double-bond ring closure have been considered with X being an oxygen or a sulfur atom, and Y being PPh_3 (Woodward's pioneering strategy of Wittig reaction) <1995TL4493> or an oxygen atom <1995TL4487, 1995TL771, 1997BML623, 1997JME2126, 1998BML2793>. In this latter case, the phosphate-mediated cyclization conditions developed by workers at Schering <1982JA6138> and Sankyo <1983CPB768> can be applied (see Section 2.03.11.5).

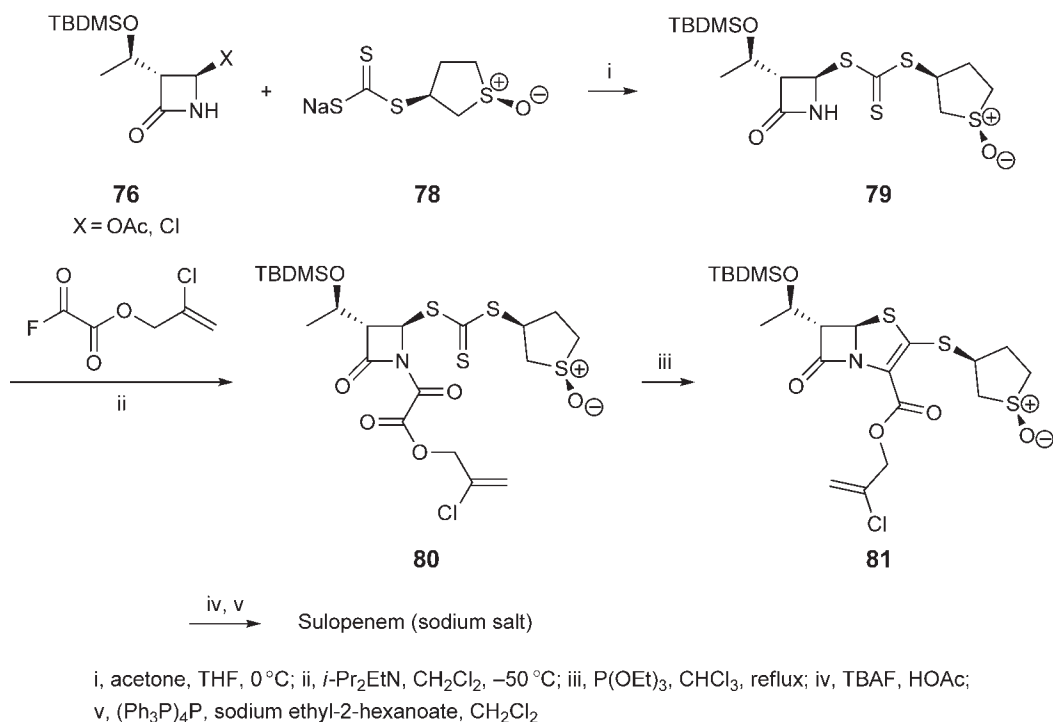


Scheme 40 Two chirons for the synthesis of penems related to penicillins and thienamycin, respectively.



Scheme 41 Four possible disconnections of the penem five-membered ring.

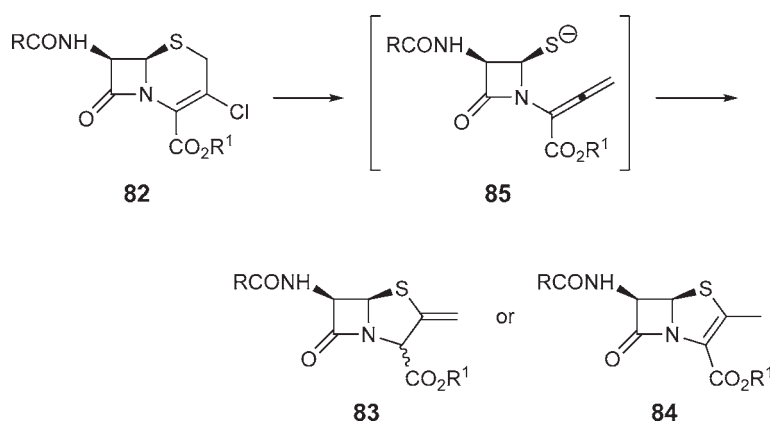
Sulopenem (CP-70429; see **Tables 1 and 7**) has been prepared via this reaction as the key step ($\text{C}=\text{O}/\text{C}=\text{S}$ reductive coupling). The total synthesis utilizes L-aspartic acid to generate the chiral precursor **78** of the C-2 side chain, a modified chiron **76** ($\text{X}=\text{Cl}$) to improve the preparation of the trithiocarbonate intermediate **79**, a chemoselective oxalofluoride-based azetidinone N-acylation to give **80** (a procedure that avoids sulfoxide O-acylation), and mild final deprotection conditions of hydroxyl and carboxyl functions. In particular, the chloroallyl ester **81** has been selected, owing to its smooth cleavage by a palladium-mediated transesterification procedure (**Scheme 42**) <1992JOC4352>.



Scheme 42 Synthesis of sulopenem.

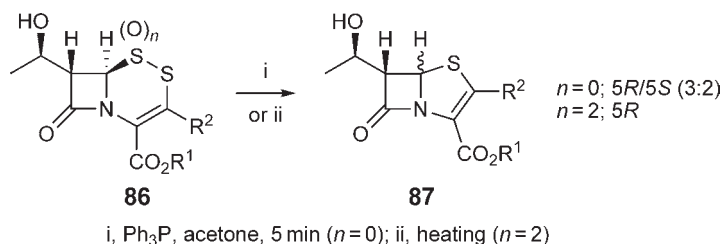
2.03.10 Ring Synthesis by Transformation of Another Ring

Rearrangement reactions involving the penam skeleton are generally directed toward the transformation of natural penicillins (sulfoxides) into cephalosporin derivatives (see Section 5.03.5.9). Ring contraction of cephems into penams (or penems) is synthetically less useful and therefore poorly documented. However, an interesting method has been reported by Torii <1997CL1221>: treatment of 3-chloro-cephem **82** with $\text{Al}/\text{BiCl}_3/\text{AlCl}_3$ led to 2-exomethylene penam **83** or penem **84**, depending on the experimental conditions and the solvent used. It seems likely that the intermediate could be the allene **85**, formed by reductive elimination (**Scheme 43**).



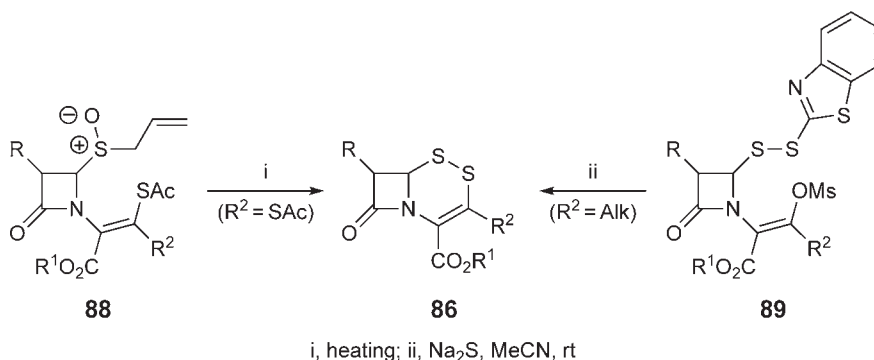
Scheme 43 Synthesis of penams and penems by a ring-contraction approach.

The ring-contraction approach toward penems has been successfully exploited by Farmitalia's group: the targets are generated by sulfur or sulfur dioxide extrusion from 2-thiacephems **86** or their 1,1-dioxides, respectively <1988FA1075>. In the first case, the method produces a 3:2 mixture of 5(*R*)/5(*S*)-stereoisomers of **87**, but in the second case only the 5(*R*)-isomer is recovered (**Scheme 44**) <1983TL1631, 1986JOC3413>.



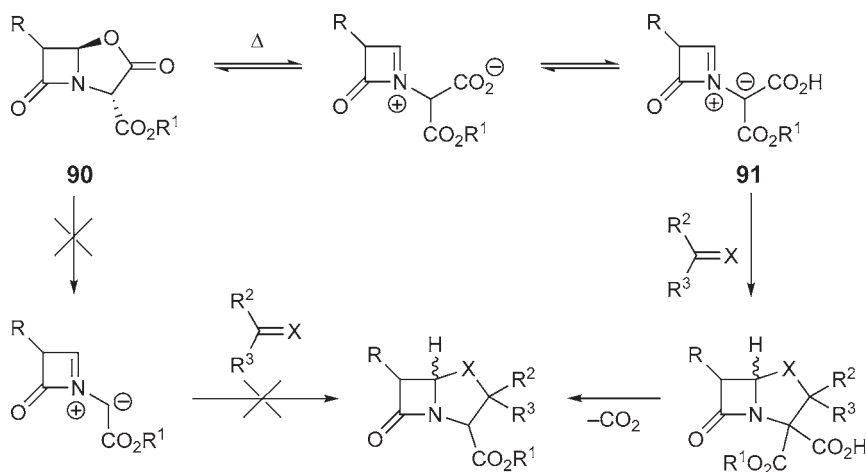
Scheme 44 Synthesis of penems by S or SO_2 extrusion from 2-thiacephem precursors.

The precursors **86** ($n=0$) are accessible from purposely substituted monocyclic β -lactams **88** and **89** by fused ring cyclization (see [Section 2.03.9](#)), in agreement with Baldwin's rules ([Scheme 45](#)) <1982CC1119, 1984TL4171, 1987PAC467>.

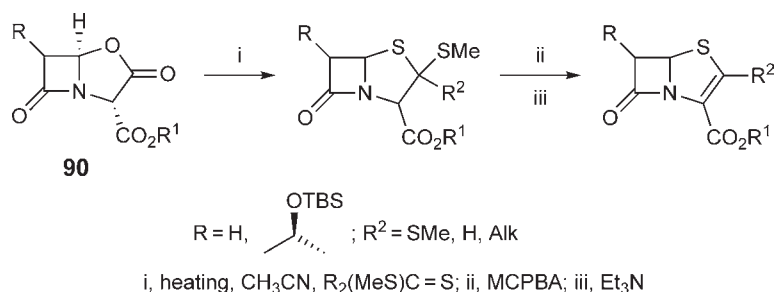


Scheme 45 Synthesis of 2-thiacephem.

Gallagher and co-workers <1997JOC3438, 2001J(P1)1270, 2001J(P1)1281, 2004OL2781, 2005PAC2033> have recently published the direct transformation of oxazolidinones **90** into penams (and penems) via the carboxylated azomethine ylide intermediates **91** (and not via CO_2 extrusion), which react *in situ* with a variety of 1,3-dipolarophiles ([Scheme 46](#)). The precursors **90** are readily available from clavulanic acid <1984J(P1)635> or other approaches <1977CC748, 1981H(16)1487>. Under thermolysis conditions of **90**, the ylides **91** can be trapped by $\text{C}=\text{S}$ -containing 1,3-dipolarophiles, for instance, to furnish 2-heterosubstituted penams that are precursors of penems ([Scheme 47](#)) <2005PAC2033>.



Scheme 46 Azomethine ylide strategy for penam synthesis.



Scheme 47 Synthesis of penems via Gallagher's method.

2.03.11 Synthesis of Particular Classes of Compounds

2.03.11.1 Biosynthesis

In terms of both therapeutic use and annual volume of production, penicillins remain the most important antibiotics. Their industrial production involves aerobic submerged cultivation of microorganisms (filamentous fungi) in an aqueous medium <1998MI483, 1998MI547>. The fermentation types and processes have been already described in CHEC-II(1996) (section 1.20.6.1) <1996CHEC-II(1B)623>. *Penicillium notatum* (Fleming's original strain) is no longer used, but today *P. chrysogenum* (NRRL 1951) represents the basic strain for a high production of penicillin G: the titer has increased from 2 U ml^{-1} in Fleming's original isolate (1 U corresponds approximately to $0.6 \mu\text{g}$) to $7 \times 10^4 \text{ U ml}^{-1}$ and above in modern isolates <1998MI483>. Accordingly, penicillin G is a bulk product costing about $\text{US\$ } 20 \text{ kg}^{-1}$. This production optimization is based on remarkable achievements in classical mutation, selection techniques of production strains, and the considerable advances in the understanding of molecular genetics and the biochemistry of the penicillin-biosynthetic pathway achieved over the past 15 years <1999MI1181, 2000JBC2423, 2000AMB212, 2000MI2355, 2000AMB238, 2001MI812, 2004MI45, 2006MI85, 2006MI618>. Studies of the regulation of gene expression and the cell biology of penicillin biosynthesis in *Aspergillus nidulans*, a genetic model organism closely related to *P. chrysogenum*, actually provide the best tool for a rational approach of penicillin-production improvement <1999AEM5222, 2002JMB425, 2003MI1178, 2003MI186, 2006AEM2957>.

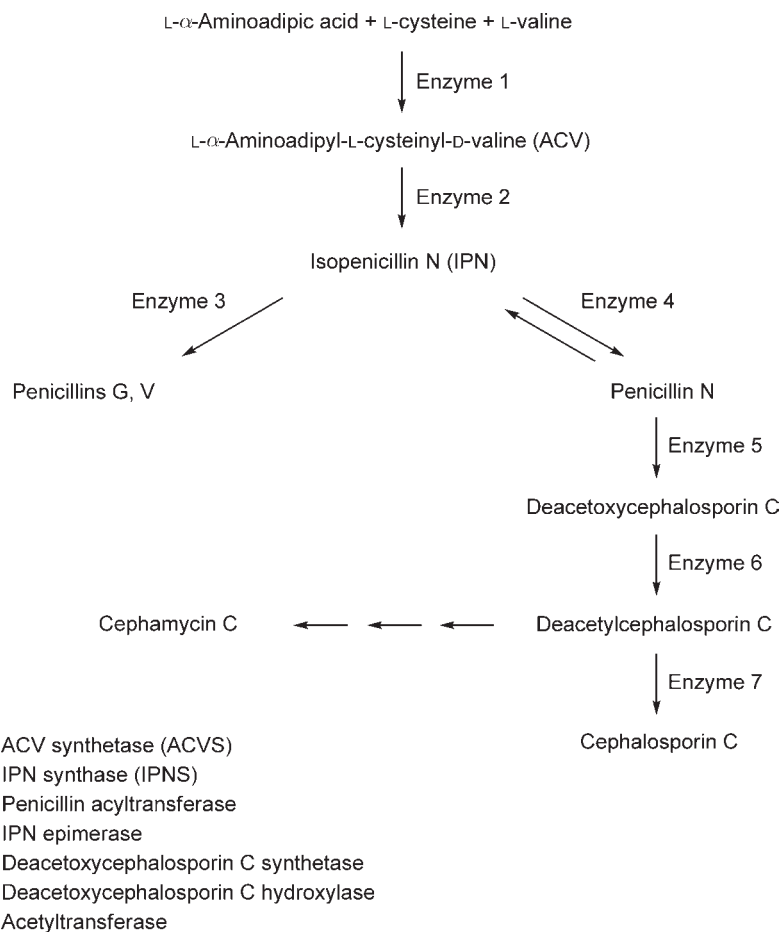
The addition of suitable precursors (e.g., phenylacetic acid, phenoxyacetic acid) in the fermentation medium of *P. chrysogenum* allows the formation of specific penicillins (G, V, F, K, X) with nonpolar side chains <1995JAN1195, 1998MI2001, 1999MI173>. Penicillins are the only β -lactam products formed, while fermentation of *Cephalosporium acremonium* produces penicillin N (D- α -aminoadipyl side chain) together with cephalosporin derivatives (CHEC-II(1996), section 1.20.6.1) <1996CHEC-II(1B)623>.

In strains producing high levels of a secondary metabolite (e.g., penicillin), competition exists between growth and product formation for common precursors, cofactors and energy, delivered by the primary metabolism <2001MI185>. Metabolic flux analysis shows that there are potential bottlenecks in primary metabolism, regarding penicillin production, around the cofactor NADPH supply/regeneration and not around the supply of carbon sources <2000MI602>. Using theoretical models, the calculated maximum yield of penicillin G is about 0.5 mol per mol of glucose; this is 8–10 times higher than the overall yields observed in batch-fed cultures <2004MI45>. Thus, it should still be possible to improve the fermentation process of penicillin G production.

Research on the regulation of the biosynthesis of β -lactam antibiotics is continuing, but the exact technologies applied to industrial production remain highly confidential or protected by the firms <2001MI25, 2002MI1553, 2003MI119, 2004MI119, 2004MI394, 2005MI167, 2005MI53, 2006IEC8299, 2006MI185>.

2.03.11.2 Mechanism of the Biosynthesis of Penicillins

The mechanism by which penicillins are formed during the fermentation of *P. chrysogenum* and *C. acremonium* has been reviewed <B-1992MI1, B-1996MI36>. **Scheme 48** depicts the biosynthetic pathways linking penicillins and cephalosporins via isopenicillin N (IPN) <2000T7601> as common intermediate <1997MI857>. Condensation of three amino acids, namely L- α -aminoadipic acid, L-cysteine, and L-valine, leads to the tripeptide ACV, with configurational inversion of valine. This first step is catalyzed by a single multifunctional cytosolic enzyme, δ -(L- α -aminoadipyl)-L-cysteinyl-D-valine synthetase (ACVS) <2000JMB395, 2002MI49>. The nonproteinogenic amino acid L- α -aminoadipate defines the biosynthetic branch-point of L-lysine and the penicillin biosynthesis in filamentous fungi <2003MI209, 2005MI272>.



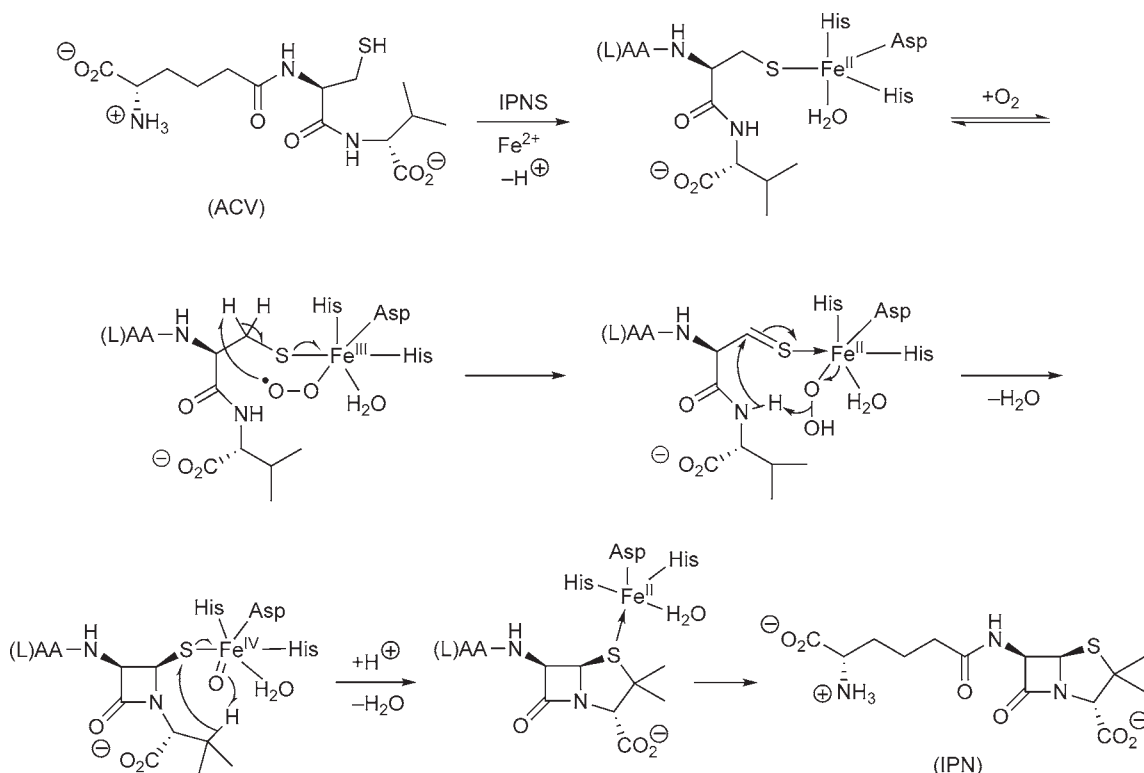
Scheme 48 Biosynthetic pathways of penicillins and cephalosporins.

Oxidation of the ACV tripeptide leads in a two-stage bicyclization reaction to IPN. This second step, catalyzed by isopenicillin N synthase (IPNS), represents a unique biochemical transformation that uses the full oxidizing potential of a single dioxygen molecule and has no precedent in synthetic organic chemistry <1998CHE1237>. IPNS is a non-heme iron(II)-dependent oxidase whose structure and function have been extensively studied <1995NAT700, 1996T2515, 1996T2537, 1997NAT827, 1998CBO229, 1999NAT721, 2001CBO1231, 2003OBC1455, 2003BJ687, 2004BJ659, 2005B6619, 2006MI351>. Due mainly to Baldwin's studies, the mechanism of ACV processing by IPNS is presently elucidated at the molecular level (Scheme 49). Coordination at the ACV thiolate to Fe^{2+} primes the binding of O_2 to iron followed by the irreversible removal of the pro-(*S*)-hydrogen from the cysteinyl β -carbon atom. The iron-bound thioaldehyde intermediate then reacts stepwise to produce first the β -lactam ring and second the thiazolidine ring.

The biosynthesis of IPN (Schemes 48 and 49) is common to the production of penicillins and cephalosporins. In some organisms, exchange of the L- α -aminoadipoyl side chain of IPN results in the formation of the hydrophobic penicillins (mainly G and V); this step is catalyzed by a penicillin acyltransferase. In others, epimerization of the IPN L-configured side chain to the D-configured side chain of penicillin N <2000T7601>, catalyzed by IPN epimerase, followed by oxidative ring expansion leads to the cephalosporin family <B-1992MI1>.

2.03.11.3 Semisynthetic Penicillins

Except for penicillin G (phenylacetyl side chain) and penicillin V (phenoxyacetyl side chain), which can be industrially produced by fermentation, the other penicillins are obtained by coupling the required side chain to 6-APA (see Table 1). 6-APA is an important industrial intermediate produced on a large scale by enzymatic cleavage



Scheme 49 Mechanism of ACV processing by IPNS.

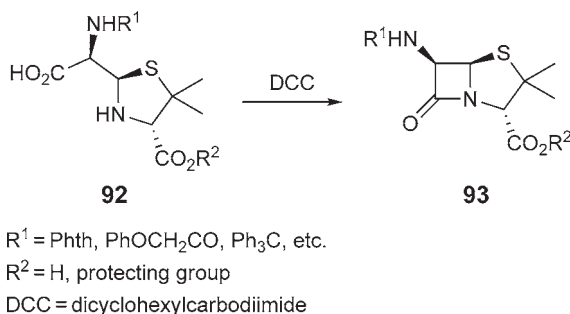
of penicillin G(V) side chain with a penicillin amidase, in solution or with immobilized enzymes <2000MI191, 2000MI345, 2000MI173, 2002MI271, 2002MI395, 2003BTL397, 2003AMB385, 2006MI571, 2006MI213>. The penicillin G side chain can also be cleaved selectively by a chemical process that has been carried out industrially (see CHEC-II(1996), section 1.20.6.3.1) <1996CHEC-II(1B)623>, but nowadays does not fulfill the green chemistry requirements. Acylation of 6-APA is readily performed using the classical methods of peptide synthesis, that is, protection of the 6-APA carboxyl function and activation of the side-chain carboxyl function for selective coupling to the 6-APA amine function (see CHEC-II(1996), section 1.20.6.3.2). In industrial processes for production of ampicillin, amoxicillin, etc. (see Table 1), the 6-APA carboxyl is protected *in situ* as the trimethyl silyl ester (see CHEC-II(1996), section 1.20.6.3.2) to make it soluble in polar organic solvents; to do so, *N,O*-bis(trimethylsilyl)acetamide is usually the reagent of choice <1966JA3390, 1991TL2683>. In a typical way, the following acylation reaction of the free amine function can thus be done under homogeneous conditions with the use of activating agents such as mixed anhydrides <1996FA535>, carbodiimides <2000T7601>, benzotriazoles <2004JA8122>, and triazines <1998SC1339, 2002CBO971>.

Enzymatic processes also exist for acylating 6-APA and some research has been devoted to the production of penicillin acylases, which are enzymes that are able to cleave the penicillin G side chain <B-1997MI400, 2001MI239, 2002MI1176, 2002MI1458, 2002MI992, 2003AMB507, 2003MI689, 2004MI349, 2005MI119, 2005MI367, 2006MI344, 2006MI617, 2006MI1518, 2006AMB953, 2006MI299>.

Penicillins bearing a 6 α -substituent, such as OMe in Temocillin and NHCHO in foramidocillin (see Table 1), require chemical modifications at the C-6 position of 6-APA before side-chain coupling (see Section 2.03.5.7).

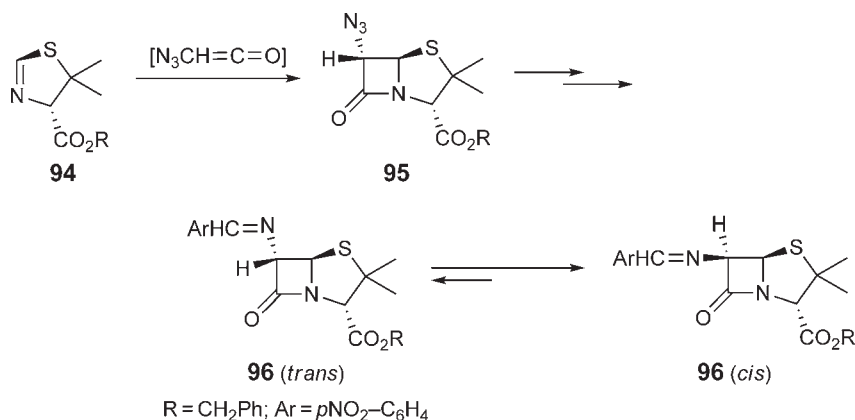
2.03.11.4 Total Synthesis of Naturally Occurring Penicillins

The first total synthesis of natural penicillin (penicillin V) was performed by Sheehan and Henery-Logan in 1957, which was about 30 years after Fleming's discovery <1957JA1262, 1959JA3089, 1976JOC2556>. Their strategy was based on β -lactam ring formation as the last step, a method also suitable for the preparation of *N*-trityl-6-APA (Scheme 50) <1962JA2983>.



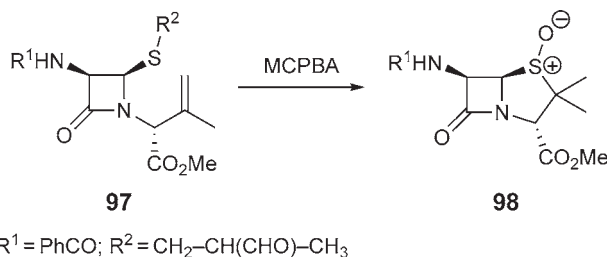
Scheme 50 Last step of Sheehan's total synthesis of penam derivatives.

This synthesis requires the separation of the diastereoisomers of **92** (obtained from D-penicillamine). An attempt to control the stereochemistry was developed by the Merck group in 1974, in a total synthesis based on the [2+2] cycloaddition of the ketene derived from azidoacetyl chloride and the chiral thiazoline **94**. The reaction only gives the *trans*-penam derivative **95**, which could be epimerized via the Schiff base **96** (*cis/trans* ratio = 2:1) (**Scheme 51**). The separated *cis*-isomer has been transformed into synthetic penicillin G [\[1974JOC437\]](#).



Scheme 51 Merck's total synthesis of penams.

The first highly stereocontrolled total synthesis of a natural penicillin was reported 2 years later by Baldwin *et al.* [\[1976JA3045\]](#). In this case, the methodology relies on the formation of the β -lactam ring before the thiazolidine ring closure, via the sulfenic acid intermediate **97** ($\text{R}^2 = \text{OH}$), which gives electrophilic attack on the double bond to produce a penam sulfoxide **98** (see [Section 2.03.5.3](#)) (**Scheme 52**). A similar route has been developed independently by Kishi for the total synthesis of 6 α -methoxy penicillin derivatives [\[1975JA5008\]](#).

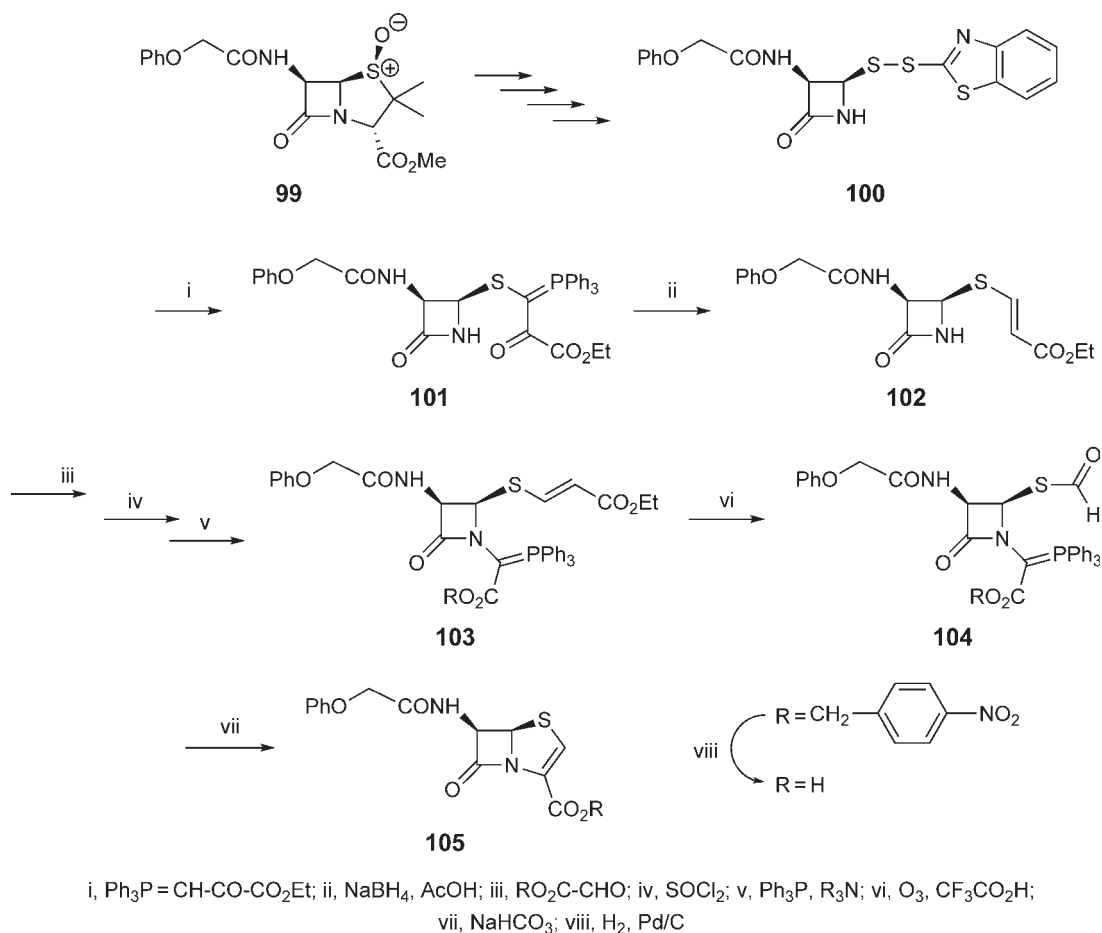


Scheme 52 Last step of Baldwin's total synthesis of penam derivatives.

Starting from 4-acetoxy-2-azetidinones, penam derivatives have been constructed by sequential functionalization of the positions C-4, C-3, and N-1, allowing further thiazolidine ring closure (see Section 2.03.9). All the methods summarized in this section have been reviewed previously (CHEC-II(1996), section 1.20.6.4) <1996CHEC-II(1B)623>. From an academic point of view, they are of interest for the discovery of new reagents and methodologies, but are not exploited for industrial production of penams. These antibiotics are more conveniently and economically produced by fermentation and semisynthesis <1991FA565, 1991MI234>. Since it is not the case for penems (non-naturally occurring compounds), the synthetic efforts of the 15 last years have been mainly devoted to this class of antibiotics (see following section).

2.03.11.5 Total Synthesis of Penems from Penams

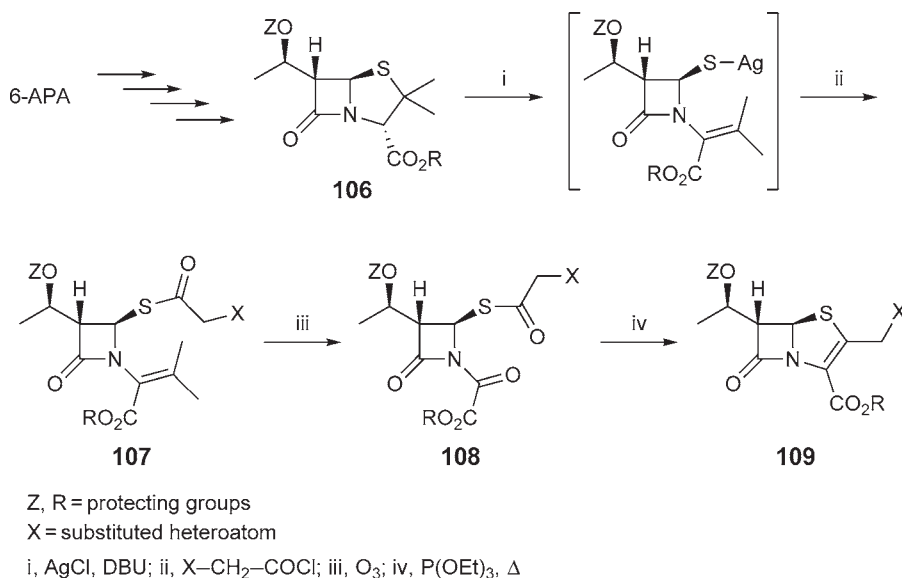
The original Woodward synthesis is a remarkable illustration of the thermal [2,3]-sigmatropic rearrangement of penam *S*-oxide, as a general strategy for transforming natural penicillins into other biologically active β -lactams (see Section 2.03.5.9). Thus, penicillin V sulfoxide **99** was transformed into the (3*R*,4*R*)-monocyclic β -lactam **100**; reaction with ethyl triphenylphosphoranylidene pyruvate resulted in the cleavage of the S–S bond with formation of phosphorane **101**; borohydride reduction gave thioacrylate **102** (Scheme 53). N-Functionalization was readily obtained by condensation with glyoxylate ester and treatment with thionyl chloride and then with triphenylphosphine in the presence of base to furnish phosphorane **103**. Ozonolysis in acidic medium produced the aldehyde intermediate **104**, which cyclized under mild basic treatment into **105**, via an intramolecular Wittig reaction. Finally, PNB ester deprotection (catalytic hydrogenation of the *p*-nitrobenzyl group) afforded the final homochiral penem derivative <1978JA8214, 1979JA6296, 1979JA6301, 1979JA6306, 1980MI239>. The Woodward strategy has been



Scheme 53 Woodward's penem synthesis from a penicillin precursor.

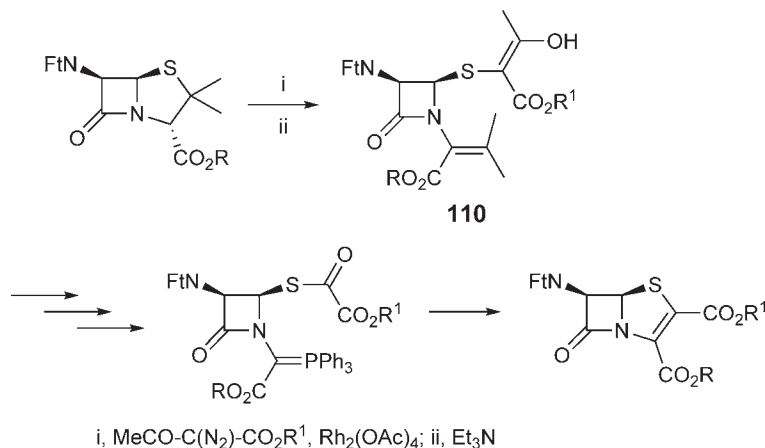
further extended to the synthesis of 2-alkylthiopenems from azetidinone-4-trithiocarbonates <1981TL3489>; in this case, alternative acid-protecting groups have to be employed in order to avoid problems associated with hydrogenolysis (see Section 2.03.9).

Efforts have been devoted to produce oxalimido thioester intermediates (see Section 2.03.9) by chemo- and stereocontrolled degradation of the penicillin thiazolidine ring at different levels of sulfur oxidation <1988FA1075, 1988MI393>. However, the direct β -elimination of penams, in the presence of a thiophile heavy metal (Ag^+), followed by *in situ* S-acylation, provided the best way toward **108**, after ozonation of intermediate **107** (Scheme 54). In particular, penems bearing the thienamycin side chain at C-6 have been prepared from 6-APA via 6,6'-dibromopenicillanic acid (see Section 2.03.5.7); intermediate **108** is readily and directly cyclized by a formal deoxygenative dicarbonyl coupling reaction performed in the presence of 2 equiv of trialkylphosphite. This reaction, developed in parallel by the Farmitalia Carlo Erba's group and the Schering-Plough Corporation's group, represents an interesting large-scale production of 6-(hydroxyethyl)penems <1988FA1075, 1988MI393>.



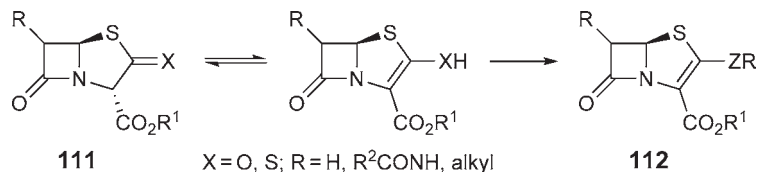
Scheme 54 Dicarboxyl reductive coupling for penem synthesis from a penam precursor.

The total synthesis of penems from penams reported by Kametani <1986JOC624> is based on thiazolidine ring opening with an α -diazoacetate catalyzed by rhodium(II) as the key step to furnish **110** (Scheme 55). Further reactions allowed the fused ring cyclization via Woodward's strategy.

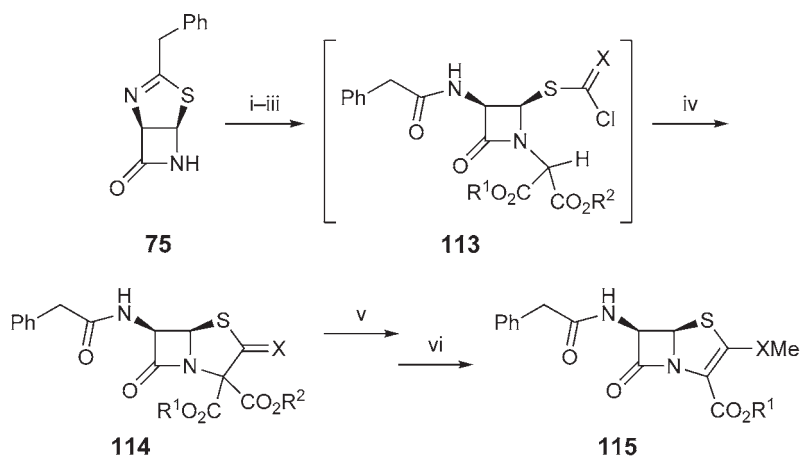


Scheme 55 Kametani's penem synthesis from a penam precursor.

2-Oxopenams and 2-thioxopenams **111** are precursors of penems **112** by direct O- and S-alkylation. Activation of their enol tautomers (as sulfoxides, sulfonates, or phosphonates) gives intermediates suitable for nucleophilic substitution with various sulfur, nitrogen, or carbon nucleophiles (**Scheme 56**) <1980TL3085, 1982TL3535, 1983T2505, 1984H(22)375, 1986JAN1551, 1987TL2283, 1990TL3291>. Precursors **111** with an acylamino side chain at position C-6 are synthesized from the chiral thiazoline azetidinone **75** (see **Section 2.03.9**). The malonate intermediates **113** are readily obtained in three steps, involving N-alkylation with bromomalonates, thiazoline hydrolysis, and S-acylation of the resulting thiol with phosgene (X=O) or thiophosgene (X=S). Precursor **113** spontaneously cyclized to **114** and malonate-selective deprotection afforded 2-oxo (X=O) or 2-thioxo (X=S) penams **111**. Alkylation with diazomethane or methyl iodide produced the penems **115** (**Scheme 57**) <B-1981MI269, 1983T2493, 1983TL2563>.



Scheme 56 Penem synthesis from enolizable penam precursors.



i, $\text{BrCH}(\text{CO}_2\text{R}^1)\text{CO}_2\text{R}^2$, base; ii, H_3O^+ ; iii, $\text{Cl}_2\text{C}=\text{X}$, Et_3N ; iv, Et_3N ; v, $\text{R}^2=\text{PNB}$, H_2 , Pd/C ; vi, $\text{X}=\text{O}$, CH_2N_2 ; $\text{X}=\text{S}$, CH_3I , Et_3N

Scheme 57 The malonate route for C(2)–C(3) thiazolidine(thi)one ring closure.

Nowadays, all the therapeutically relevant penems are equipped with the 1(*R*)-hydroxyethyl side chain, characteristic of the thienamycin (carbapenem) family (see **Table 1**). Accordingly, they are prepared by hemisynthesis from the chiral acetoxyazetidinone **76**, which is industrially produced on a large scale by chemical methods (see **Section 2.03.9**). This chiron plays a similar role as 6-APA for the synthesis of semisynthetic penicillins, but here for the synthesis of non-natural penems and carbapenems <1996T331>.

2.03.11.6 Synthesis of Related Compounds

Isopenams **116** and **117** <1999CEJ2705> and nonconventionally fused bicyclic β -lactams **118–121** have been prepared (**Figure 11**) <1995JOC4980, 1997TL8647, 1998JOC8898, 2000T5571>. Such compounds retain some biological activities.

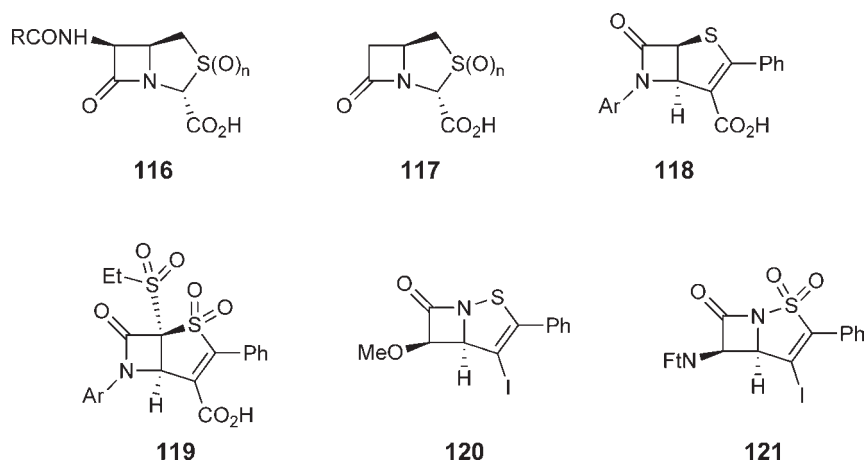


Figure 11 Non-natural bicyclic azetidinones.

A recent review covers the nonclassical polycyclic β -lactams synthesized with the aim of discovering new lead compounds in the field of antibacterial agents <2000T5743>. Selected compounds 122–127 related to penam or penem structures are shown in Figure 12.

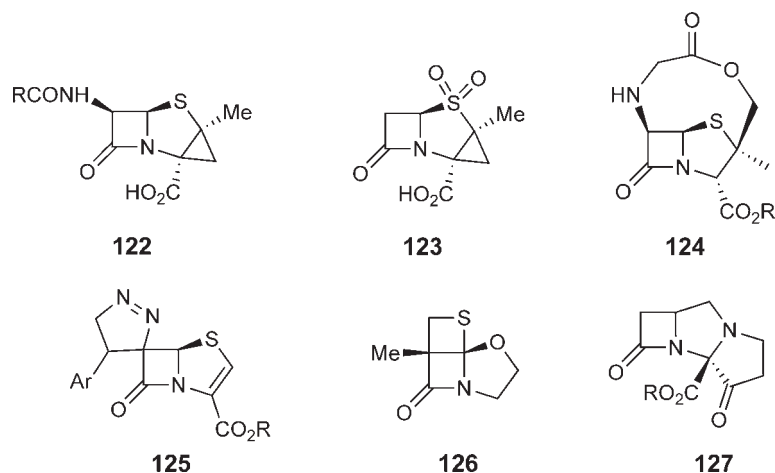


Figure 12 Polycyclic azetidinones.

The approaches toward polycyclic β -lactams mainly use methodologies previously refined for bicyclic β -lactams. Despite the impressive number of prepared structures, this has resulted in little utility in terms of antibacterial/anti- β -lactamase activities.

2.03.12 Applications

The treatment of bacterial infections developed during the twentieth century relies upon tremendous efforts for the discovery of active natural products and synthetic drugs. Considering all classes of antibiotics in human clinical use (β -lactams, tetracyclines, aminoglycosides, erythromycins, glycopeptides, sulfonamides, fluoroquinolones, oxazolidinones), only four targets are addressed: bacterial cell wall biosynthesis, bacterial protein biosynthesis, DNA replication and repair, and folate coenzyme biosynthesis <2005CRV391>. The β -lactams family targets transpeptidase

enzymes that catalyze the final step of cell wall biosynthesis, that is, the peptidoglycan cross-linking. Today, this class remains the most widely used in antibiotherapy due to the comparatively high effectiveness, low cost, ease of delivery, and minimal side effects induced by β -lactams. These beneficial characteristics arise from the facts that the target enzymes are easily accessible and specific to bacteria, with no functional or structural counterpart in the human host <2005MI525>.

2.03.12.1 Mechanism of Antibacterial Activity

Peptidoglycan is the constitutive polymer of the wall surrounding the cytoplasmic membrane of bacterial cells and protecting them against osmotic pressure variations. The cell wall is thus responsible for the preservation of bacteria shape and rigidity. Long polysaccharide chains of *N*-acetylglucosamine and *N*-acetylmuramic acid, cross-linked by short peptides, are forming this rather rigid macromolecule. Gram-positive bacteria are characterized by a pentapeptide linker of the L-Ala-D- γ -Glu-L-Lys-D-Ala-D-Ala type, while in Gram-negative bacteria L-Lys is replaced with *meso*-diaminopimelic acid. Gram-positive and -negative bacteria differ also by their amount of peptidoglycan: the cell wall is 50–100 molecules thick in the former, but only 1–2 molecules thick in the latter organisms. Numerous studies report on the peptidoglycan structure and biosynthesis, and the relation with bacterial morphology <1998MI110, 2001MI99, 2001MI625, 2003MI571, 2004MI5978, 2006PNA4404, 2007SCI1402>.

The dynamic structure of peptidoglycan is continuously regulated by two complementary systems: transglycosylase (for elongation) and transpeptidase or acyltransferase (for reticulation or cross-linking) activities on the one hand, and endopeptidase, carboxypeptidase, or glycosidase activities (for hydrolysis) on the other hand <2003MI594>. These reactions of peptidoglycan synthesis and remodeling are principally catalyzed by PBPs; most of these are membrane-bound proteins, called PBPs because of their capacity to form stable covalent complexes with antibiotics of the penicillin type.

The individual peptidoglycan units, produced inside the cell, are cross-linked outside the cytoplasmic membrane. This reaction is catalyzed by D-Ala-D-Ala transpeptidases (called DD-peptidases): a peptide bond is formed between the penultimate D-Ala on one chain and the free amino end of an L-Lys residue (Gram-positive bacteria) or a diaminopimelic acid (Gram-negative bacteria) on the other chain. The cross-linking reaction causes the cleavage of the terminal D-Ala. DD-peptidases are serine enzymes involving acyl–enzyme intermediates in their catalytic mechanism. The low molecular weight (LMW) DD-peptidases (subclasses A, B, and C) seem to be involved in the bacterial morphology, but are not essential for cell survival <1991ARM37, 2001MI99, 2001MI595, 2003JBC52826, 2003B14614>.

The high molecular weight (HMW) DD-peptidases feature two domains one of which is ‘penicillin binding’ (PB). The subclass A contains bifunctional enzymes (transglycosylases and transpeptidases), and the subclass B, mono-functional enzymes (transpeptidases). Both the classes A and B of HMW DD-peptidases are essential for cell survival <1991ARM37, 1998MI1079>. Proteins of subclass C are involved in β -lactamase synthesis induction (see Section 2.03.12.2) <1998AAC1>.

By mimicking the terminal D-Ala-D-Ala section of the pentapeptide of peptidoglycan strands (Figure 13), the penicillin-type antibiotics are able to covalently bind to DD-peptidases (formation of penicilloyl–enzyme intermediates), where the 3-carboxylate function of the former constitutes a key enzyme recognition parameter <B-2007MI(7)479>. In the early 1980s, to apprehend penicillins bioactivity, Cohen introduced a model based on the distance d between the β -lactam carbonyl oxygen atom and the carbon atom of the carboxyl function (Figure 13). He empirically defined a good antibacterial activity for β -lactam antibiotics when d is in the range of 3.0–3.9 Å <1983JME259, 1993BML2329>.

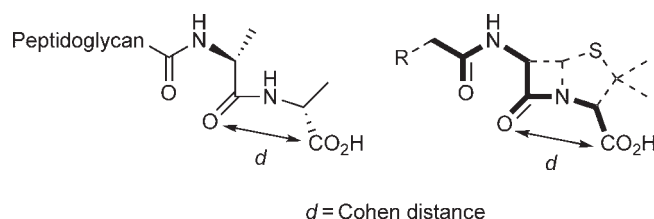
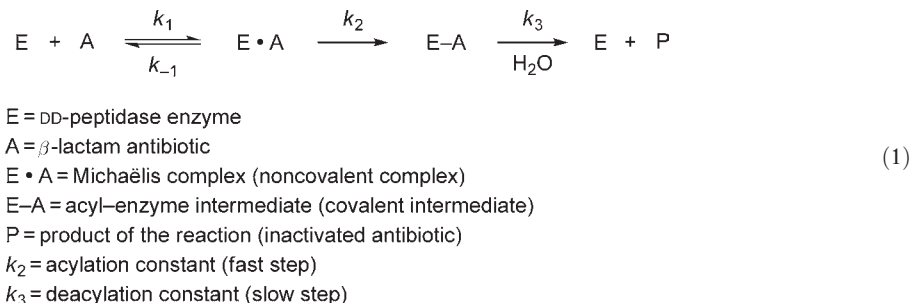


Figure 13 Structural analogies between peptidoglycan-CO-D-Ala-D-Ala and penicillins.

The three-step mechanism of serine enzyme action is usually described as in Equation (1) <B-1992MI148>. Even though the enzyme is recovered in the end, the deacylation step remains slow enough to lead to inhibition of the bacterial cell wall biosynthesis, resulting ultimately in cell lysis by activation of endogenous autolytic mechanisms <B-1996MI1>.



Inactivation of DD-peptidases thus depends on a rapid and nearly quantitative accumulation of E–A intermediate resulting, jointly, from its stability (k_3 is very low, of the order of 10^{-4} – 10^{-6} s $^{-1}$), and its rapid formation. The factor governing the rate of acyl–enzyme formation is k_2/K' , where $K' = (k_{-1} + k_2)/k_1$ (value of the order of 10^3 – 10^6 M $^{-1}$ s $^{-1}$).

The contribution of crystallography appears more and more essential to elucidate enzyme mechanisms. The first data concerning PBPs have been recorded with soluble model proteins, the *Streptomyces* R61 and K15 DD-peptidases <1986NAT378, 1986SCI1429, 1989JMB281, 2003BJ949, 2003B2895>. Crystallization of membrane-bound proteins is rather difficult and few data are available for such PBPs. Nevertheless, acyl–enzyme complexes have been visualized in the case of penams <2002MI1223, 2003B12835> and penems <1998NAT186>.

Since the target enzymes of penicillins are membrane-bound proteins, an essential condition of antibacterial activity is that the antibiotic must be able to penetrate the outer spheres of the bacterial cell and reach its target in an active form. This problem is closely linked to the phenomenon of bacterial resistance (production of β -lactamases), and justify the development of semisynthetic penicillins varying in the nature of the acylamino side chain at position C-6, and more recently the development of totally synthetic penems related to thienamycin (see Section 2.03.12.3).

2.03.12.2 Mechanism of Bacterial Resistance

The resistance phenomenon is the bacterial response to the selection pressure exerted by the β -lactam antibiotics widely utilized for treatment of infections. Nowadays, the accelerated dispersion of the resistance mechanisms across the bacterial kingdom dramatically increases the selection for bacteria having acquired these mechanisms <1997AAC2321>. The production of enzymes that degrade the antibiotic before it can reach its targets (i.e., the cell wall biosynthesizing enzymes) represents the most common mechanism of resistance. Such defense enzymes are called β -lactamases. The other mechanisms are the alteration of cell wall transpeptidases (called resistant PBPs <1998MI332, 2006MI673>) such as PBP2a from methicillin-resistant *Staphylococcus aureus* (MRSA) <2002MI870>, the reduced permeability of the bacterial outer membrane to β -lactams (via the deletion of porin proteins), and the increased β -lactam efflux from bacterial cell (via the activation of exporter proteins) <1992SCI1064, 2003MI525, 2005MI525, 2005CRV395>.

β -Lactamases are excreted in the outside medium by Gram-positive bacteria and in the periplasm by Gram-negative bacteria. They are divided into four classes (A, B, C, and D) on the basis of sequence similarities. Enzymes of classes A, C, and D utilize an active-site serine and perform their catalytic cycle by means of an acylation/deacylation pathway like the DD-peptidases. However, in the case of β -lactamases, both the acylation and deacylation steps are extremely rapid (rates close to the diffusion speed of small molecules); consequently, the β -lactam antibiotics are swiftly hydrolyzed. Class B β -lactamases are metalloenzymes working with zinc atom(s) in their active site <2007JA2808>. A water molecule (ligand of Zn $^{2+}$ together with three His residues) acts as a nucleophile to hydrolyze the β -lactam antibiotic <B-1992MI198>. Metallo- β -lactamases are classified by sequence homology into three subclasses: B1, B2, and B3 <2005AAC2778>.

Important progress has been made in the knowledge of β -lactamases' structure and function, mainly owing to crystallographic, NMR and mass spectrometry studies, and theoretical calculations. Class A β -lactamases, historically named penicillinases for their capacity to better hydrolyze penicillins than cephalosporins <1991BJ269>, are the most studied enzymes <1998BJ581> with conserved amino acid residues forming the catalytic site (Ser $_{70}$, Lys $_{73}$,

Ser₁₃₀, Lys₂₃₄, Glu₁₆₆, etc.) <1987SCI694, 1991B9503>. Ser₇₀ is the active serine and Glu₁₆₆ plays an important role in the proton transfer, via a conserved water molecule, during the catalysis of both the acylation and deacylation steps <1990BJ613, 1991BJ213>. But, the involvement of Lys₇₃ in the catalytic machinery of acylation has also been proposed <1991JBC3186, 1992NAT700, 1996PNA1747, 1997JBC5438, 2005JA15397>. Two amide bonds of the backbone (Ser₇₀ and Ala₂₃₇) constitute the oxyanion hole which stabilizes the negatively charged oxygen atom of the β -lactam linkage <1995BBA109>. The role played by other amino acid residues in proton transfer, water molecule activation, substrate specificity, binding and good positioning of the substrate, stabilization of the tetrahedral intermediate, and maintenance of the active site geometry has been pointed out <1992JBC20600, 1994BJ555, 1994JBC23444, 1996B16475, 1998AAC2576, 1999BBA132>.

Class C β -lactamases are considered as cephalosporinases. They process β -lactams similarly to the class A enzymes, except that in the deacylation step, the hydrolytic water molecule attacks the acyl-enzyme intermediate from the β -face and not from the α -face <1993PNA11257>. Recent studies discuss the catalytic role of Ser₆₄, Lys₆₇, Lys₃₁₅, and Tyr₁₅₀, corresponding respectively to Ser₇₀, Lys₇₃, Lys₂₃₄, and Ser₁₃₀ of class A β -lactamases <1990NAT284, 1994B8577, 2003BJ175, 2003PSC1633, 2004JA7652, 2005PCB16153, 2006B439>.

Class D β -lactamases show specificity toward oxacillins and are therefore named oxacillinases. In this class, the catalytic serine is activated by an N-carboxylated lysine <2001PNA14280, 2003PSC82>.

Class B β -lactamases operate similarly to zinc metalloproteases <1999MI614, 2007JA2808>. They are characterized by the presence of two binding sites for Zn²⁺, whose respective roles are not fully understood <2004MI2827>. These bacterial defense enzymes possess an extremely broad substrate specificity that includes not only the penicillins and cephalosporins, but also the carbapenems (usually β -lactamase resistant). Their inhibition requires totally different strategies regarding the classes A, C, and D of β -lactamases because a covalent acyl-enzyme intermediate is no more involved in the mechanism of action. Accordingly, the clinical application of the entire arsenal of β -lactam antibiotics (and β -lactamic anti- β -lactamases) is severely compromised in bacteria producing metallo- β -lactamases.

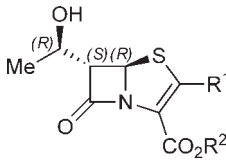
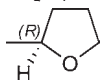
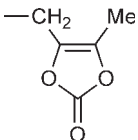
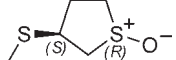
2.03.12.3 Therapeutic Use of Penams and Penems

The penicillins differ regarding the side chain attached at position C-6 of the penam nucleus; they are classified in seven groups of antibacterial agents recently reviewed <B-2005MI113>. The evolution of the penicillin structures, from benzylpenicillin (group I) to oximinopenicillins (group VII), has been governed by the following requirements: (1) stability in acidic medium (for oral administration); (2) stability versus enzymatic hydrolysis (β -lactamases); (3) improved activity against MRSA strains responsible of nosocomial infections in hospitals; and (4) improved activity against Gram-negative bacilli. All the major drugs were discovered between 1960 (penicillin V) and 1989 (BRL-44154) (see Table 1). The parallel developments of cephalosporins and monobactams (see Tables 2 and 3) inspired the most recent modifications of penams, namely the introduction of an additional substituent at C-6 ($R^3 = \text{OMe}$, temocillin (1981); and $R^3 = \text{NHCHO}$, foramidocillin (1984)), which followed the discovery of cephamycin (1971) and the synthesis of cefoxitin (1973) on the one hand, and the introduction of an oximino motif into the aminoacyl chain (BRL-44154 (1989)), which followed the discovery of nocardicin A (1976) and the synthesis of ceftriaxone (1981) and cefepime (1984), on the other hand. CHEC-II(1996) (section 1.20.7.1.2) <1996CHEC-II(1B)623> should be consulted for a previous discussion of penicillins in therapeutic use. Further reading of specialized monographs is also recommended <B-2006MI1127, B-2007MI(7)479>. Nowadays, certain 'old penicillins' (ampicillin, amoxicillin <2002JAA130, 2006BP1085>) are delivered in combination with a β -lactamase inhibitor (see Section 2.03.12.4). During the last 15 years, efforts have been dedicated to the penem class in view of their potential clinical use as potent broad-spectrum antibacterial agents, endowed with very low toxicity levels <B-1993MI1>.

Since the description of the first penem by Woodward in 1976 (see Table 1), a great number of molecules have been synthesized by varying first the C-6 side chain (1*R*)-hydroxyethyl chain in α -orientation instead of the acylamino chain of penicillin in β -orientation) and then the C-2 substituent (being sulfo, sulfonyl, oxy, amino, alkyl, or aryl groups) <1990H(30)799, 1995JME4244, 1998BML2793>. Some representatives have been considered for development (SCH-29482 and SCH-34343), but as yet no drug has been introduced in medical practice. The main reason is the low stability of penems under physiological conditions. For instance, SCH-34343 is stable for 24 h in phosphate buffer at 37 °C, but its activity decreases to 87% in the presence of 50% serum <2005MI319>. More stable compounds, such as faropenem <2003MI581, 2007MI185>, ritipenem <1999AAC2534>, and sulopenem <1992JOC4352> (Table 7), have been studied in Phase II and III trials for clinical use. As a matter of fact, the half-life of ritipenem between pH 4 and 7 is greater than 100 h <2005MI319>. Faropenem is inactivated by only 6%

in aqueous solution at 37 °C and neutral pH after 24 h <2002AAC2327>. Faropenem, which is orally bioavailable, is in clinical use in Japan (as the sodium salt) and is in the preregistration phase in the US (as doloxate ester, SUN A 0026) <2006BP1085>.

Table 7 Penems for clinical use

			
Name ($R^2 = H$)	R^1	Name (ester)	R^2
SCH-29482 SCH-34343 Faropenem	SC ₂ H ₅ SC ₂ H ₄ OCONH ₂ 	SUN A 0026	 —CH ₂ Me O O O
Ritipenem Sulopenem	CH ₂ OCONH ₂ 	Ritipenem acoxil CP 65207	CH ₂ OCOCH ₃ CH ₂ OCOC(CH ₃) ₃

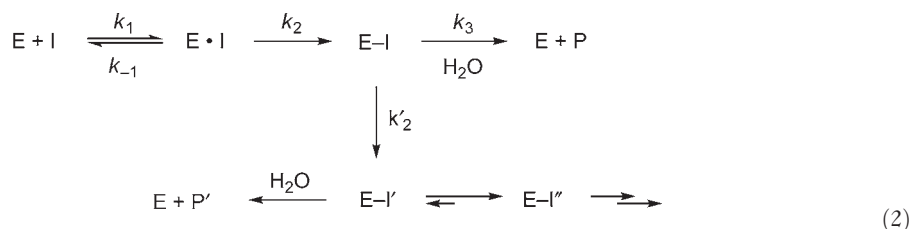
Like carbapenems, penems are stable against hydrolysis by β -lactamases, and may also inhibit the activity of some of them <2006BP930>. Nevertheless, the therapeutic development of penems is handicapped by their rapid degradation by human renal dehydropeptidase (HRDP). This enzyme is the sole metabolite of penem and carbapenem antibiotics in mammals, presently known <2002JMB177>. Cilastatin, an inhibitor of HRDP coadministered with carbapenems, has allowed the effective clinical use of imipenem (see **Table 1**) <1983MI1>. The same strategy should be applied in the future for penem antibiotics. But it has been shown that the presence of a quaternary ammonium moiety on the C-2 side chain increases the stability of carbapenems <2007BMC392> against hydrolysis by HRDP (meropenem, ertapenem; see **Table 1**). This line of research has also been explored in the case of penems <1992JAN500, 1995JME4244, 1995BML555, 1998JAA321, 2003MI105>. Another advantage of penems possessing at C-2 a polar (charged) side chain is that their binding to plasma proteins is diminished <1990JAN422>. The currently available penems are administered parenterally; the oral route is also possible after esterification. The corresponding prodrugs (labile esters) are described in **Table 7** <1995MI705, 2005MI319>. In this context, the enzymatically labile (5-methyl-1,3-dioxol-2-on-4-yl)methyl group is claimed to release nontoxic metabolites *in vivo*, but requires particular storage conditions due to daylight degradation <1995TL4633>.

2.03.12.4 β -Lactamase Inhibitors

Current commercial inhibitors of β -lactamases include clavulanic acid (an oxapenam; see **Table 1**), sulbactam, and tazobactam (two penam sulfones; see **Table 1**). They are effective only against the class A serine β -lactamases and they are administered in the form of antibiotic/inhibitor combinations <2006BP930>: Augmentin™ (amoxicillin/clavulanic acid), Timentin™ (ticarcillin/clavulanic acid), Unasyn™ (ampicillin/Sulbactam), Zosyn™ (piperacillin/tazobactam).

Since the discovery of clavulanic acid and the elucidation of its mode of action <1981B3214, 1992JMB1103, 1993JA4435, 1996B12421>, the search for synthetic inhibitors of serine β -lactamases has been directed toward β -lactam compounds acting similarly as mechanism-based irreversible inactivators (see **Sections 2.03.5.2 and 2.03.5.9**). Molecules are designed to operate through the formation of hydrolytically stabilized acyl-enzyme intermediates **Equation (2)**. This stabilization may result from electronic factors (resonance interactions improving the stability of the ester bond), from covalent bonding to a second nucleophilic residue in the active site (the first nucleophile being the active serine residue), or from modification of the positioning of the bound inhibitor in the active site that precludes water attack <2006BP930>. β -Lactamic inhibitors of β -lactamases are typically also

substrates of their target enzymes which partition the turnover/inhibition processes at the acyl-enzyme stage; the ratio of substrate/inhibitor activity ranges from 10 to 10^4 , depending on the anti- β -lactamase structure.



E = serine β -lactamase enzyme

I = β -lactam inhibitor

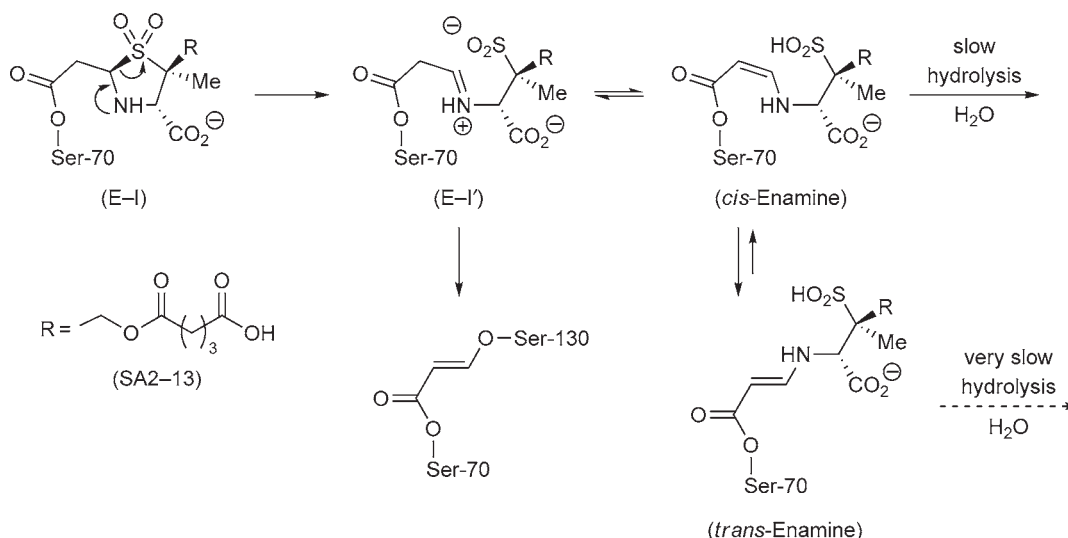
E-I = hydrolyzable acyl-enzyme intermediate

E-I', E-I'' = more stable acyl-enzyme intermediates

k'_2 = inhibition route

k_2 and k_3 = substrate route

6-Unsubstituted penam sulfones constitute the first family of β -lactamase inhibitors. Besides sulbactam and tazobactam <1994B5728, 2004B843, 2004JBC19494>, other inhibitors have been reported, varying the substitution at the C-2' position <1996JME3712, 1997AAC475, 2005JOC4510>. Rational design allows improvement of the (irreversible) inhibition pathways. For instance, the penam sulfone SA2-13 (Scheme 58) forms a stable *trans*-enamine intermediate into the active site of *wt* SHV-1 β -lactamase, because additional interactions can occur between the C-2' side chain and Lys₂₃₄ (salt bridge), Ser₁₃₀ and Tyr₂₃₅ (H-bonds) <2006JA13235, 2007B8689>. Thus the acyl-enzyme intermediate formation with Ser₇₀ is followed by the cleavage of the C(5)-S(1) bond to give the iminium intermediate E-I'. These can be hydrolyzed (recovery of active enzyme) or react with Ser₁₃₀ (irreversible inhibition), as well as tautomerize into *cis*-enamine and *trans*-enamine. Stabilization of the *trans*-enamine intermediate dramatically decreases the rate of deacylation.



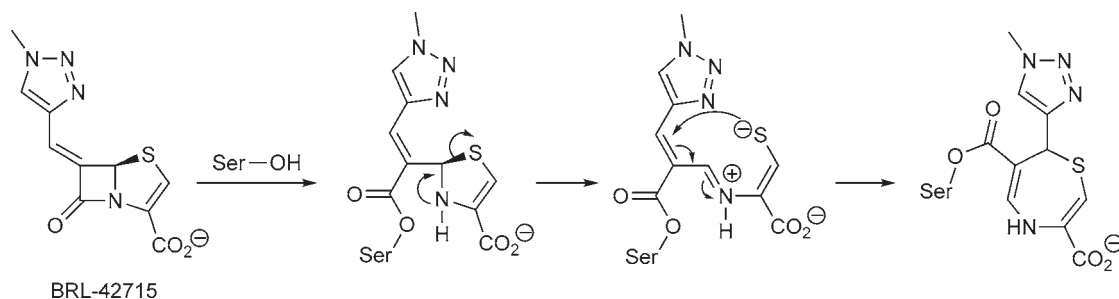
Scheme 58 Inhibition pathways of class A β -lactamases by sulbactam, tazobactam, and SA2-13.

The family of penam sulfones has been extended to a variety of C-6-substituted inhibitors <1986TL3449, 1994JAN1041, 1999BML991, 1999BML997, 1999BML1997, 1999TL8063, 2000OL3087, 2001BML997, 2004BML1299>, including mostly an exomethylene motif.

Carbapenems having a 6 α -hydroxyethyl side chain <2007BMC392> are both broad-spectrum antibiotics and competitive inhibitors (or poor substrates) of serine β -lactamases. This particular side chain may play a role in the

positional movements of the acyl–enzyme intermediate, and subsequently in the displacement of the hydrolytic water molecule ($k_3 \approx 0$). Thus, incorporation of similar C-6 side chains has been extensively investigated in penam, penam sulfone, and penem derivatives, but without remarkable success <2006BP930>.

On the other hand, penem derivatives with a heterocyclic substituent at C-6 connected via a methyldiene linkage are potent β -lactamase inhibitors, active against both class A and class C enzymes <B-1988MI247, 1995JA4797, 2004AAC4589, 2004BMC5807>. The mechanism of action of some representatives has been elucidated by X-ray diffraction analysis of their stable covalent adducts to class A and class C β -lactamases, as shown in **Scheme 59** <1995JA4797, 2003B13152, 2004JME6556, 2004BMC5807, 2005JA3262, 2006JME4623, 2007PCA4720>. The presence of the exocyclic double bond acts as a driving force for the five-membered ring opening, as it undergoes the subsequent nucleophilic attack of the thus-generated thiolate, leading to a dihydro-1,4-thiazepine ring. The formation of the seven-membered ring has been proven by mass spectrometry <2004JME3674>.



Scheme 59 Inhibition of class C β -lactamase via the formation of dihydro-1,4-thiazepine ring.

Recently, prodrugs have been constructed in which amoxicillin (antibacterial agent) and clavulanic acid or cephalosporin 1-oxide (β -lactamase inhibitors) are covalently linked. All these compounds show better antibacterial activity than Augmentin™, comparable anti- β -lactamase activity, and better solubility properties <2002BMC3489>.

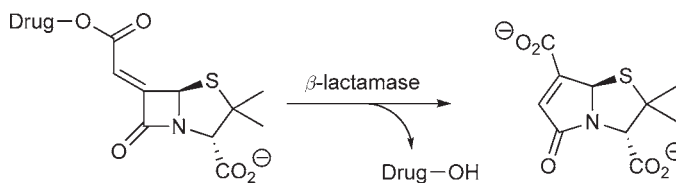
2.03.12.5 Other Applications

Penicillins have been considered for the inhibition of other bacterial serine enzymes than the DD-peptidases and β -lactamases. For instance, bacterial signal peptidases (SPases) are essential for cell viability and therefore represent nowadays a class of novel antibacterial target <1998NAT186>. SPases are involved in protein translocation through the cytoplasmic membrane in the final step of the bacterial protein secretion pathway <1997PSC1119>. 5(*S*)-Stereoisomers of penems have been found to inhibit SPases <1995BML443>. The most potent inhibitors are 5(*S*)-tricyclic penems <2003S1732>.

Since the pioneering discovery by Merck's scientists that cephalosporin derivatives are able to inactivate human leukocyte elastase (HLE) <1990JME2529, 1993BML2277, 2002CRV4639>, other bicyclic β -lactams have been designed as potential HLE inhibitors. Penem <1993BML2277> and penam sulfone derivatives have been reported in this context <1993BML2283, 1996JBS285, 2001BMC2113>, but without development for clinical use in connective tissue diseases. Penam and penam sulfone derivatives also exhibit promising inhibition activities against cathepsins L, K, and S <2002BML3417>. In general, β -lactams have been systematically examined as potential inhibitors of many classes of serine and cysteine proteases: HLE, porcine pancreatic elastase (PPE), *E. coli* signal peptidase, prostate-specific antigen (PSA), cathepsin G, chymotrypsin, thrombin, trypsin, plasmin, chymase, human neutrophil elastase (HNE), human cytomegalovirus protease (hCMV), poliovirus, human rhinovirus 3C proteases, papain <2002CRV4639>.

Penicillin derivatives are also involved in the construction of biochemical tools for *in vitro* selection of catalytic activities. The selection of β -lactamases displayed on phage with a biotinylated 6-sulfonamidopenicillanic acid sulfone inhibitor has been reported <1994JMB415, 1994MI175, 1995BMC907, 1996T5591, 1997BML239, 1997BML479, 2000JMB527>. The selection of β -lactamase displayed on ribosome with a biotinylated ampicillin sulfone inhibitor has been recently described <2002JA9396>.

A promising strategy for drug targeting in which a C-6-modified penicillin liberates the desired compound under processing by a β -lactamase (see [Section 2.03.5.9](#)) is currently being explored; this system illustrated in **Scheme 60** is called a ' β -lactamase-dependent prodrug' <2007OBC160>.



Scheme 60 β -Lactamase-dependent prodrug.

2.03.13 Conclusion

A major success in human therapeutics in the twentieth century was indisputably the discovery of antibiotics that dramatically reduced the death rates from infections. Clearly, the β -lactam family has been, and still remains, the clinically most used agents and accounts for about 50% of all antibacterial drugs prescribed. Two complementary research lines proved fruitful: the isolation of natural products <2007MI608>, usually from microbial sources, and the chemical hemi- or total synthesis of structurally related compounds. This led to a tremendous amount of effort and contributed to significant discoveries in organic synthesis and mechanism elucidation in chemical and biochemical pathways. Strained bicyclic β -lactams, the common structural features shared with all members of the class, provided a very attractive playground for medicinal chemists for more than 60 years. However, due to the onset of bacterial resistances, the golden age of penams is over, and cepheids (see Chapter 2.02) and carbapenems (see Chapter 2.04) represent nowadays the most-sold β -lactam antibiotics. Nevertheless, penams remain useful drugs when dispensed in combination with β -lactamase inhibitors. The discovery of penams, by a synthetic rational approach, also gave new impetus to this old class of antibiotics, although penams are chemically more unstable than the corresponding penams, and inaccessible via short hemisynthetic processes. But the fine comprehension of how (natural) antibiotics work, and why they stop working, appears more and more crucial to rapidly define strategies toward new antibacterial drugs, a real challenge of the twenty-first century.

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2.04

Other Fused Azetidines, Azetines and Azetes

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2.04.1 Introduction

2.04.1.1 Historical Perspectives

This review of developments in the chemistry and applications of fused azetes, azetines, and azetidines should be read in conjunction with the earlier articles in CHEC(1984) <1984CHEC(7)341> and CHEC-II(1996) <1996CHEC-II(1B)659>. As was noted therein, much of the research effort has gone into attempts to develop more effective therapeutic agents, and this work has centered on compounds having a bridgehead nitrogen atom. The coverage of the literature in this chapter and the earlier chapters in this volume on penicillins and cephalosporins follow the pattern of CHEC-II(1996) in that the chapter on cephalosporins describes bicyclic compounds which have the azetidine ring fused to a six-membered ring, whether that ring contains sulfur or not (Chapter 2.02), while the chapter on penicillins is limited to the chemistry of the penicillin nucleus (Chapter 2.03). Other compounds having an azetidine, azetine, or azete nucleus fused to another ring are described in this chapter. The discovery that the sulfur atom of the thiazolidine ring is not essential for antibacterial activity has produced a big growth in the search for useful compounds. These compounds include those where the second ring does not contain another heteroatom and also where the second ring contains heteroatoms other than sulfur. Success in this area, particularly the useful antibiotic activity of the carbapenems, and carbacephems, has encouraged further developments. The chapter in CHEC-II(1996) was written at about this point in the historical development of the subject. This chapter deals with developments of these ideas including the addition of further fused rings to the bicyclic systems. This too brought success, and trinems, first called tribactams, containing three fused rings are developments from carbapenams. Tricyclic β -lactams have been under intense investigations during the last decade following the discovery of their especially valuable therapeutic properties <1996BML1683, 1997MI86, 2000T5743>. These compounds are inhibitors of β -lactamases.

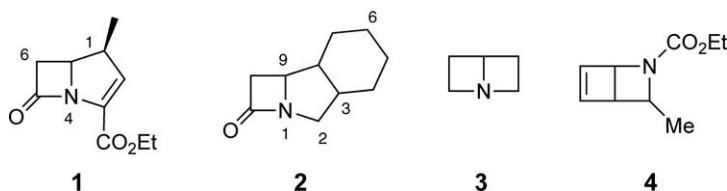
A remarkable feature during the past decade has been the burgeoning of compounds containing three, four, or five fused rings – so much that we have introduced separate sections of this chapter to deal with aspects of progress over the last decade. The finding that fused azetidines have uses in medicine in addition to their function as antibiotics, and the increasing requirement to find therapeutic agents capable of killing organisms which have acquired resistance to the present range of antibiotics, make it appear likely that work in this area will continue apace.

The other general type of fused azetidine, where the nitrogen is not at the bridgehead, is not neglected in this chapter and there have been developments here too. Again a notable feature is the increased number of fused rings in the compounds reported. This brings in its wake increasingly complex stereochemistry and in turn the increasing importance of sophisticated nuclear magnetic resonance (NMR) spectroscopy techniques to establish the relative stereochemistry and X-ray crystallography and circular dichroism (CD) to provide absolute stereochemical assignments for selected examples.

A number of review articles describe developments in the use and availability of β -lactam antibiotics <1999MI5, 2004RMC69, 2004RMC93>. Wide-ranging reviews on the biosynthesis, chemistry, and biochemistry of β -lactams have been published <1995MI330, 1997MI281, 1999MI335>. The development of carbapenem chemistry and structure–activity relationships (SARs) from the discovery of thienamycin in 1976 have been discussed <1996YGK761, 2001H(54)497>, and the use of ruthenium- and palladium-carbene-catalyzed cyclizations (ring-closure metathesis, RCM) leading to carbapenams have been described <2003YGK1065>. Methods used to obtain nonclassical fused β -lactams have been reviewed <2000T5743, 2004CME1921>. Reviews considering the antimicrobial activity, acquired resistance and β -lactamases, pharmacokinetics, toxicity and side effects, and clinical use of β -lactam antibiotics, such as carbapenams, carbapenems, clavams, and trinems, have been published <B-1997MI306, 1997ACR162, 1997MI673, 1997MI1814, 1999MI919, 1999MI3497, 2000MI5, 2000MI1, B-2001MI151>. The following reviews mention examples of fused azetidines as part of a broader coverage of chemistry: <2003AHC71, 2004H(62)877, 1996PHC(8)66, 1997PHC(9)64, 1998PHC(10)70, 1999PHC(11)87, 2000PHC(12)77, 2001PHC(13)71, 2002PHC(14)75, 2003PHC(15)100, 2004PHC(16)82, 2004H(64)577, 2004CME1837>. One review describes polymer-supported and combinatorial syntheses of β -lactams <2006RMC109>. A review on photochemical conversion of 2-pyridones to bicyclo[2.2.0]hexanones is available <B-1999MI(5)85>. Stereoselective synthesis of trinems <B-1999MI347> and nonclassical polycyclic β -lactams (excluding trinems) have been reviewed <2000T5743> as has the formation of tricyclic systems not containing a bridgehead nitrogen atom <2004H(64)577>. The application of the Kinugasa reaction to the synthesis of fused β -lactams has been discussed <2004AGE2198>. One issue of *Tetrahedron* is devoted to β -lactam chemistry <2000T5553>.

2.04.1.2 Nomenclature

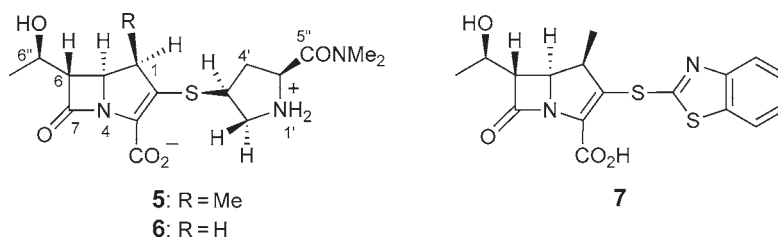
The nomenclature most frequently used for the compounds discussed in this chapter can vary with the type of compound, in particular whether the compound is a β -lactam with a bridgehead nitrogen atom or not. If the compound has a bridgehead nitrogen atom that is part of the β -lactam system, the compound is often named following the system used for penicillin or cephalosporin. Thus, compound **1** is ethyl 1 β -methylcarbapenem-3-carboxylate. The application of this idea to molecules containing more than two fused rings becomes difficult and the systematic type of nomenclature is then adopted as shown in compound **2**. A systematic naming and numbering system is used for compounds which do not contain a β -lactam group, for example, 1-azabicyclo[2.2.0]hexane **3**, or have a nitrogen atom which is not at the bridgehead, for example, 3-methyl-*N*-ethoxycarbonyl-2-azabicyclo[2.2.0]hex-5-ene **4**.



2.04.2 Theoretical Methods

This section updates the information given in CHEC-II(1996) from the year 1995. The conformations of meropenem **5** and desmethyl meropenem **6** have been studied by MM3* calculations. The torsional angles, ϕ_2 and ϕ_3 , of meropenem **5** in its most stable conformers are different from that of desmethyl meropenem **6**. The distances H(1)–H(3'), H(1)–H α (2'), and H(1)–H β (2') were also different. The preferred conformation of meropenem **5** in aqueous solution was relatively linear compared with desmethyl meropenem **6** due to the steric interaction between the 1 β -methyl and the pyrrolidine substituent <1996BML1881>.

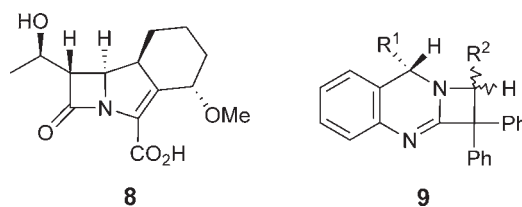
Analysis of energy-minimized conformations generated using a 1000-step Monte Carlo conformational search with the AMBER force field by use of a MacroModel (version 3.5) demonstrates that both the benzothiazole ring and the carboxylic acid moieties of carbapenem **7** could be overlapped with those of 3-benzothiazolethiocephem <1997BMC601>.



A study of the favorable values of the Woodward h factor and the Cohen c number for antibiotic activity has been made from the crystal structures in the Cambridge database. Data for penams, cepems, clavams, penems, carbapenems, oxapenems, carbacepems, and oxacepems were included. It was found that the value for h that corresponded with antibiotic activity was in agreement with that generally accepted but that the corresponding value for c should be revised from 3.0–3.9 to 3.0–4.5 Å. The h parameter is a characteristic of the molecular structure while c is related to the conformational properties of the molecule. Predictions based on h or c alone about the effectiveness of a compound as an antibiotic may give results contrary to experimental findings. A better correlation of structure with biological activity was obtained from a joint analysis of the h and c parameters, though this procedure is still essentially empirical. The convolution of h and c defines a third and more significant parameter, which is shown to be an overall shape factor that is quantified as torsional angle around a nonbonded vector. Active compounds with high h and high c or low h and low c values are able to adopt a nearly similar conformation in the β -lactam- C -carboxylate region of the molecule, while inactive compounds with either high h and low c or low h and high c show much spatial variations in that region of the molecule. It is deduced that the receptor cavity in penicillin-binding protein has a well-defined geometry and that recognition of the drug molecule, without induced fit, is an important prerequisite for binding of β -lactams before they can exert their antibiotic activity. The importance of the overall shape of the β -lactam and the receptor cavity being complementary is shown by the diagonal on an h - c scatter plot which is well populated by the active compounds <1996J(P2)943>.

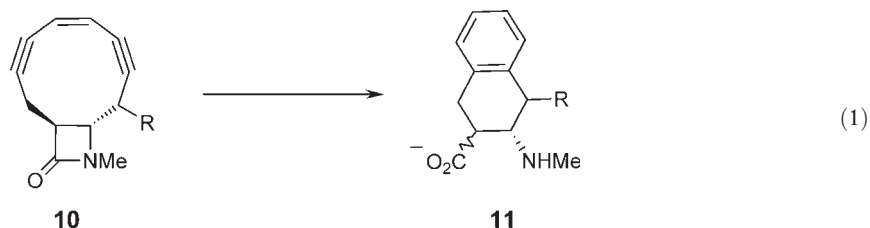
Theoretical calculations for the trinem antibiotic sanfetrinem **8** GV104326, for the isomer with *cis*-protons in the β -lactam ring, and for the methoxy inversion isomer have been performed by *ab initio* molecular orbital (MO) calculations using the GAUSSIAN 94 program package at the CRAY-T3E system. The geometries were fully optimized at the levels up to HF/6-31+G* by *ab initio* Hartree-Fock (HF) method. The vibrational frequencies, the infrared intensities, the Raman activities, and the thermochemical parameters have also been calculated. The structures of *cis*- and *trans*-isomers are different due to the proton change in the β -lactam ring and the methoxy inversion isomer is almost similar in shape to the *trans*-isomer. The bond lengths for the two isomers of protons are similar, except for the C(3)–C(5) length where the *trans*-isomer is 0.0082 Å shorter than the *cis*-isomer. The bond angles and dihedral angles are, however, significantly different. The three isomers have similar pyramidal structures at the β -lactam ring N-atom. The *cis*-isomer is the most pyramidalized of the three isomers. The carboxyl group at C-10 shows a pseudoequatorial conformation <2003JMT265>. The alkaline hydrolysis of compound **8** has been investigated by a RHF/6-31+G**/RHF/6-31+G* theoretical study and two pathways for hydrolysis have been investigated <2005HCA774>.

Computational studies have been carried out on the highly stereocontrolled intramolecular [2+2] cycloadditions between ketenimines and imines to give 1,2-dihydroazeto[2,1-*b*]quinazolines **9**. The calculations were performed using either the GAUSSIAN 94 or 98 series of programs with the 3-21G* and 6-31G* basic sets. Electron correlation was estimated by means of density functional theory using the hybrid method denoted by B3LYP. The study has shown that the source of stereocontrol is a chiral carbon atom adjacent either to the iminic carbon or to the nitrogen atom. However, when a chiral aldehyde is used as the chiral template, the stereocontrol is dictated by the preferential *anti*-disposition between the new σ -bond and the C–X σ -bond present in the reactant, X being an electronegative atom <2000JOC3633>.



Semi-empirical and *ab initio* studies have been used to examine the stereospecificities of adducts from the Ru-catalyzed $[2\pi+2\pi]$ cycloaddition of 5-azabicyclo[2.2.0]hex-2-en-6-one as a dienophile with cyclobutadiene and cyclopentadiene. The study was conducted at the semi-empirical (AM1 and PM3) and *ab initio* (STO-3G-21G, 6-31G*, MP2/6-31G*) levels of theory employing the SPARTAN program version 4.1.1. The predictions made by *ab initio* calculation were in agreement with the experimental results <1997SL38>.

The *trans*-fused 'lactendynes' **10** (R = H) were expected to highly disfavor a cycloaromatization to **11** (R = H) because of the steric strain in the transition state. This idea was in agreement with the results of molecular mechanics calculations. However, for the derivative with a methoxyl group **10** (R = OMe), molecular mechanics calculations predicted a remarkable increase in the tendency toward the formation of compound **11** (R = OMe) via a diradical (Equation 1) <1997T3249>.



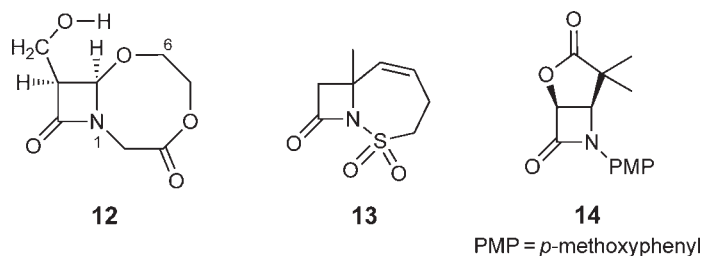
2.04.3 Experimental Structural Methods

CHEC(1984) and CHEC-II(1996) should be consulted in addition to the present updated account to get a complete overview.

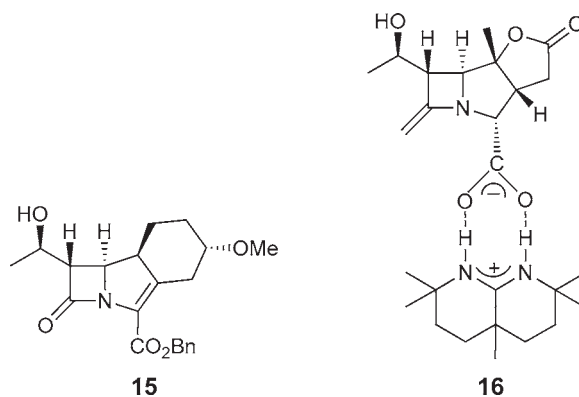
2.04.3.1 X-Ray Studies

X-Ray crystallographic studies have been increasingly necessary during the last decade in order to establish the absolute configuration of β -lactams as the number of rings has increased. This procedure provides reference compounds of known absolute stereochemistry to which other compounds can be related.

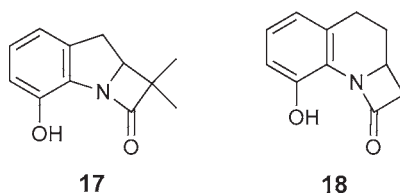
The crystal structure of the lactone **12** shows that the N–C(10) bond is long and the C(10)–O bond is short. These features occur in biologically active β -lactams of the penicillin and cephalosporin type and in lactone **12**, the sum of the bond angles around the N atom is 359.9° . The stereochemistry about C-8 and C-9 is *cis* and the hydrogen atoms are on the α -side of the ring. The hydroxymethyl group is folded back due to its hydrogen bonding with the O-7 oxygen atom <1997T14153>. X-Ray crystallography of a single crystal of ϵ -sultam **13** showed an sp^2 -hybridized nitrogen atom with the sum of the angles around the nitrogen being 359.1° and a C(O)–N bond length of 1.393 Å <2004TL3589>. The bicyclic lactone **14** was isolated from a mixture after bakers' yeast reduction, lipase resolution, and chiral phase high-performance liquid chromatography (HPLC), and was shown to have the absolute stereochemistry by X-ray crystallography <2005CJC28>.



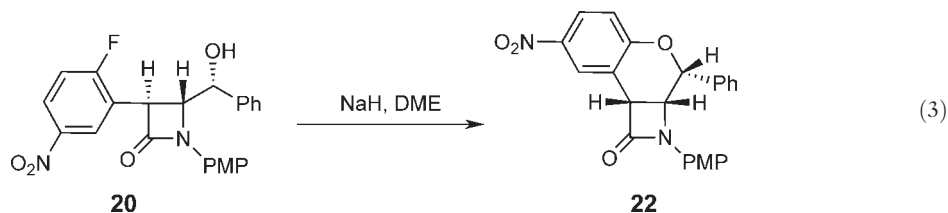
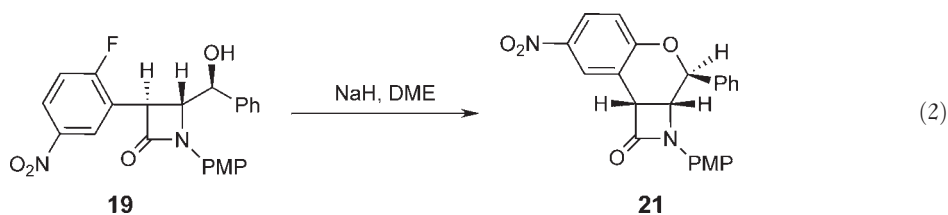
The absolute stereochemistry of the trinem **15** has been established and its debenzylated derivative shown to have interesting biological activity in contrast to its 5 β -methoxy epimer <1995BML2535>. The absolute stereochemistry of the amidinium salt **16** was established by X-ray crystallography. This technique of salt formation has been used by several workers to obtain suitable crystalline derivatives from carboxylic acids <1999T3427>.



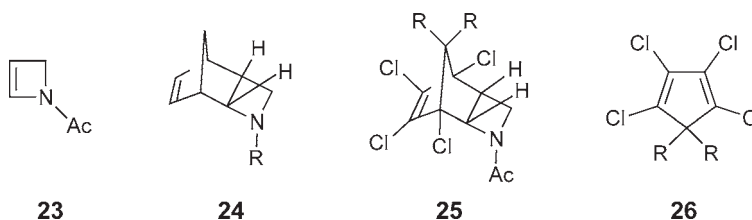
The indolenine **17** and the 3,4-dihydroquinoline derivative **18** have been prepared and comparative studies made. In the case of compound **18**, there is hydrogen bonding between the hydroxyl and the carbonyl groups but this does not occur in compound **17** <1998J(P1)1193, 1998J(P1)1203>.



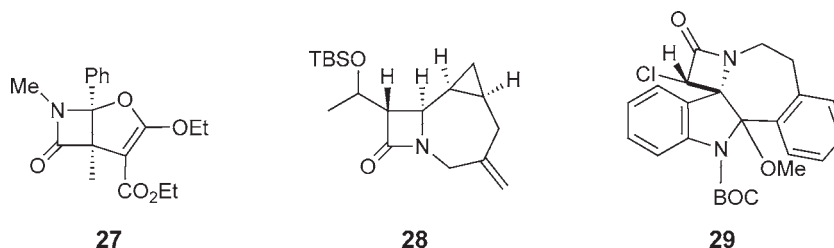
Intramolecular aromatic substitution of the alcohols **19** and **20**, brought about by the action of sodium hydride in dimethoxyethane Equations (2) and (3), provided a single isolated product in each case. These products both showed coupling constants for the bridgehead hydrogen atoms which indicated a *cis*-configuration for both compounds **21** and **22**. This unexpected result was confirmed by X-ray diffraction studies of a single crystal of **19**. This means that the ring-closure steps involve *trans*- to *cis*-isomerization of the β -lactam <2003T5259>.



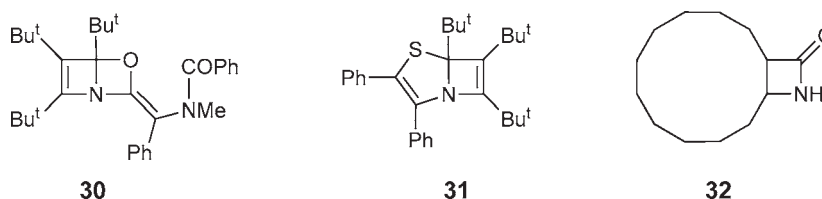
The Diels–Alder addition of cyclopentadiene to *N*-acetyl-2-azetine **23** occurs by *endo*-addition as shown by single crystal X-ray analysis of the *p*-nitrobenzenesulfonamide **24** (R = 4-O₂NC₆H₄SO₂). X-Ray studies of crystals of adducts **25** (R = OMe and R = Cl) obtained by reaction of **23** with **26** (R = OMe and R = Cl) showed that these products were also formed by *endo*-addition. Similarly, the reaction of diphenylisobenzofuran with azetine **23** also gave the *endo*-adduct <1999TL443>.



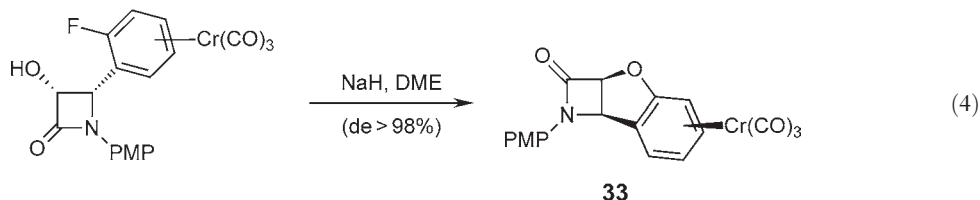
An unusual photochemical rearrangement provided the bicycle **27** whose structure was proved by X-ray crystallography <2003TL9247>. The structures **28** and **29**, and some compounds closely related to **29**, have been studied by X-ray crystallography <2000TL10347>.



The unusual bicyclic azetines **30** and **31** have been studied by X-ray crystallography. The ring strain is reflected in the bond lengths: for example, in structure **30**, the N(1)–C(4) bond length is stretched to 1.531 Å (from the average N–C bond length of 1.469 Å) and the double bond is stretched to 1.365 Å. The folding angle between the two four-membered rings is 114.6° <1997BSF927>. *trans*-13-Azabicyclo[10.2.0]tetradecan-14-one **32** displays a unique example of isostructurality differing only in the orientation of an intermolecular N–H...O hydrogen bond which gives rise to crystal polymorphism <2004CC2114>.



X-Ray studies of the enantiomerically pure reaction product **33** showed that the tricarbonylchromium derivatives are capable of controlling the absolute stereochemistry of the cyclization product which has the inorganic unit on the opposite side to the hydrogen atoms at the bridgehead (Equation 4) <2000TA1927>.

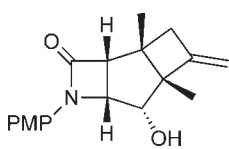
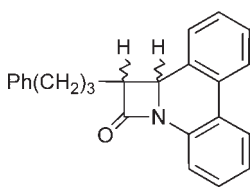
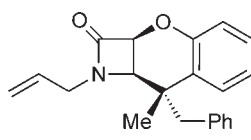
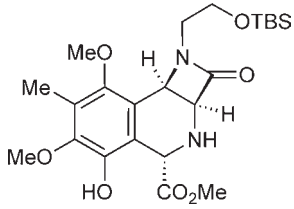
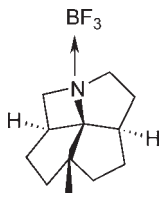
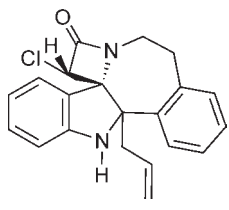


Additional examples of compounds where X-ray crystallography data are available are given in Table 1.

2.04.3.2 NMR Studies

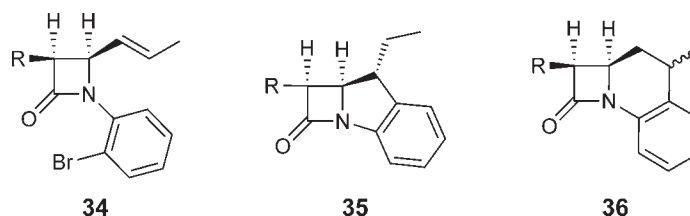
Proton and carbon NMR spectroscopy have played an increasingly important part in the development of the chemistry and especially the stereochemistry of the compounds considered in this chapter. As the molecules have tended to have more fused rings and substituents, the problems associated with the understanding of the stereochemistry have increased. Sophisticated NMR spectroscopy techniques have been a major tool in uncovering these

Table 1 Tricyclic and polycyclic compounds whose X-ray crystallography data are available

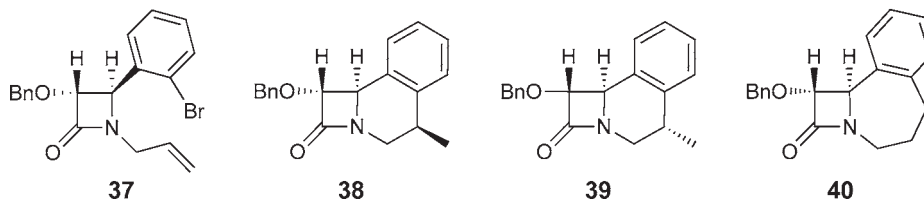
<i>Formula</i>	<i>Reference</i>
	2006CEJ1539
	1998TL7431
	1997M1149
	2001TL543
	2005AGE3732
	2003TL4141

details. Unless there is a relevant reference compound of known absolute stereochemistry, the deductions about stereochemistry made from NMR data are of relative stereochemistry, and unfortunately this is not always made clear. Sometimes, it is possible to convert this relative stereochemistry to absolute stereochemistry by use of X-ray crystallographic data for a key compound.

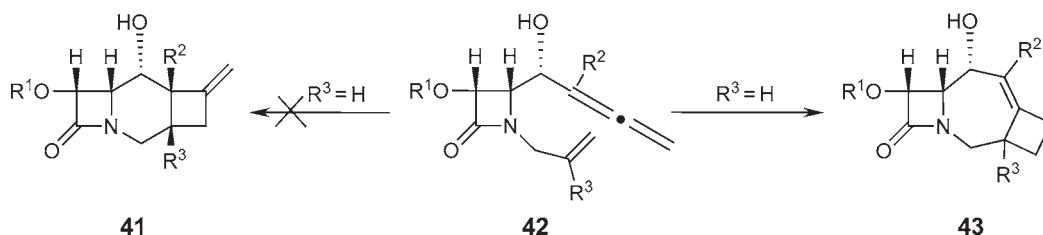
Cyclization of bromoarenes **34** gave the benzocarapenems **35** and benzocarpacephems **36**, which were obtained as single stereoisomers. The process is remarkably independent of the nature of the substituent at C-3 of the azetidinone ring and measurements of $J_{5,6}$ in the carapenem showed that the relative stereochemistry present in the monocyclic azetidinone is retained in the cyclized product (also see Chapter 2.01). Nuclear Overhauser effect (NOE) experiments showed that the ethyl group in the carapenem at C-1 had a *syn*-configuration with H-5 so that H-1 must have the *anti*-configuration <1996TA2203>.



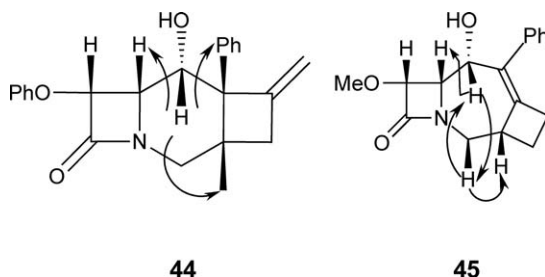
Radical cyclization of bromoarene **37** gave two products **38** and **39** formed by *exo*-ring closure and also isomer **40** by *endo*-reaction. The ^{13}C -NMR spectra of **38** and **39** showed methyl group signals at 18.42 and 23.62 ppm, respectively, and the stereochemistries of the compounds have been tentatively assigned. The compound **40** did not show a methyl group signal and had a spectrum consistent with the seven-membered ring <1996TL1363>.



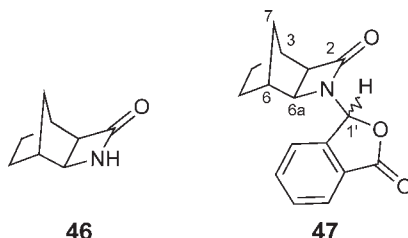
A novel tandem cyclization process gave tricyclic fused azetidinones **41** from *N*-alkenyl- and allenyl-disubstituted azetidinones **42** ($\text{R}^3 = \text{H}$) (Scheme 1). The structure of **41** depended upon whether a formal [2+2] cycloaddition process had occurred on the internal or external double bond of the allene. The regioselectivity of the process was determined by the pattern in the ^1H NMR spectrum of the vinylic protons which appeared as two sharp singlets at δ 4.95–4.99 and 4.97–5.01 ppm. In addition, a doublet or multiplet at δ 2.54–2.82 indicated the presence of a methylene group in the cyclobutane ring. This evidence pointed to the formation of product **41**. However, similarly substituted azetidinones **42** but with $\text{R}^3 = \text{Me}$ gave exclusively products whose ^1H NMR showed no vinylic protons. Their ^1H NMR spectra showed the presence of two methylene groups in the cyclobutane ring and so they were assigned structure **43** ($\text{R}^3 = \text{Me}$) based on evidence from one- and two-dimensional NMR techniques. The relative stereochemical relationships were deduced from vicinal proton coupling constants and qualitative NOE difference spectra as illustrated in structures **44** and **45** <2006CEJ1539>.



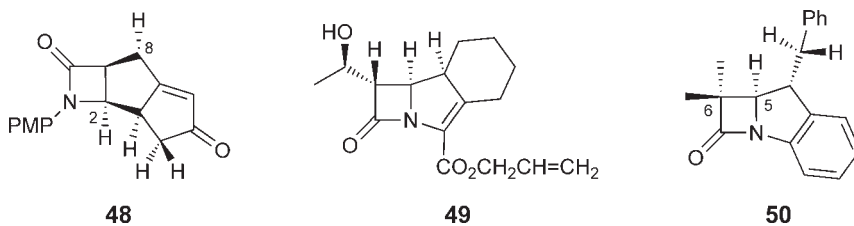
Scheme 1



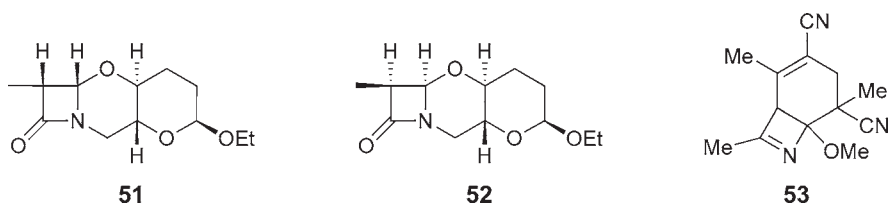
The ratio of diastereoisomers is often revealed by the NMR spectrum [<2004TL587>](#). The reaction of *dioxo*-norbornaneazetidinone **46** with *o*-carboxybenzaldehyde gave two diastereomeric isobenzofuranone-N-substituted 3-azatricyclo[4.2.1.0^{2,5}]nonan-3-ones **47** which showed almost identical ¹H and ¹³C NMR spectra: differences ≤ 0.06 for ¹H (except H-6, -6a, and -7 (*endo*)) and <1.0 ppm for ¹³C. It is thought that the configuration about C-1' must be different in the two diastereoisomers. Saturation of the H-7 (*endo*) signal gave an NOE enhancement of the H-1' signal in one diastereoisomer showing that the H-1' and H-7 (*endo*) atoms are close in that isomer. In the other isomer, an NOE effect was not found between the H-1' and H-7 (*endo*) atoms, but instead NOE was found between H-6a and H-1' showing that these atoms are close. In agreement with this there is an upfield shift of the C-3, C-6, and C-6a lines in the ¹³C NMR spectrum relative to that in the first isomer showing that the second isomer has a more crowded structure with strong steric interaction between the norbornane and isobenzofuranone groups [<1999JT63>](#).



Products from the radical cyclization of 1-alkynyl-4-alkenyl-2-azetidinones have been investigated using a variety of NMR techniques. The structures of the fused bicyclic azetidinone products have been established by use of distortionless enhancement by polarization transfer (DEPT), heteronuclear correlation (HETCOR), and correlation spectroscopy (COSY) techniques and the relative stereochemistry deduced from vicinal proton coupling constants and NOE experiments [<2001JOC1612>](#). Similarly substituted azetidinones have given tricyclic products by reaction with cobalt octacarbonyl and the relative stereochemistry has been deduced from NOE experiments. For instance, the tricyclic compound **48** showed NOE enhancements of H-3 and H-8 upon irradiation of the H-2 signal and enhancement of the H-4 upon irradiation at H-3 showing that all these hydrogen atoms are close due to the relative stereochemistry [<1996TL6901>](#). NMR spectroscopy has played a major role in the elucidation of the structure of trinem antibiotics obtained from 4-substituted azetidinones. Gradient COSY NMR spectra enabled the assignment of chemical shifts and coupling constants to all the axial and equatorial protons in compound **49**. ¹³C NMR signals were assigned using heteronuclear multiple quantum correlation (heteronuclear multiple quantum correlation (HMQC) or ¹H-¹³C COSY or HETCOR) and gradient heteronuclear single quantum correlation (gHSQC). Stereochemistry was deduced from NOE experiments [<1997J\(P1\)463>](#). Similar techniques have been used to determine the structure and ascribe the relative stereochemistry of other trinems [<2003T241>](#), other tricyclic systems [<1999TL5391>](#), and tetracyclic and pentacyclic systems containing the β -lactam nucleus [<2003TL1827, 2004TL7255>](#). The relative stereochemistry of other trinems obtained through radical cyclization processes have been deduced from NOE experiments. For instance, irradiation of the H-5 hydrogen in compound **50** gave enhancement of the signals of the methylene group proton at lower field, the phenyl group and the methyl at lower field in line with configuration **50**. This procedure relates signals from specific atoms or groups with particular relative stereochemistry [<2005T2767>](#).



The two stereoisomers of a tricyclic oxacepham were separated by chromatography and NOE experiments allowed the relative stereochemistry of isomers **51** and **52** to be assigned. These structures were supported by evidence from CD experiments [<2002CAR2005>](#). The structure of the fused bicyclic azetine **53** was established by use of ¹H and ¹³C NMR spectroscopy [<1996CC1349>](#).



Meropenem **5** was the first carbapenem antibiotic that did not require the coadministration of another drug to counter the degrading effects of renal dehydropeptidase-1 (DHP-1) on the antibiotic. A variety of biological effects due to a 1β -methyl group on a carbapenem nucleus were reported and it was unlikely that these could be explained by a simple steric effect of the methyl group. In order to understand the underlying effect, both molecular modeling calculations and studies by NMR spectroscopy were made on meropenem **5** and desmethylmeropenem **6**. The chemical shifts of $5'$ -, $4'\alpha$ -, and $4'\beta$ -H of meropenem **5** were different from those of desmethylmeropenem **6** but other parts of the spectra were very similar. NOE difference spectra for meropenem showed enhancement for 1α -H- $3'$ -H and 1α -H- $2\alpha'$ -H but there was no detectable similar interaction observed between the carbapenem proton and the pyrrolidine ring protons in desmethylmeropenem **6**. These results suggested that the conformations of the carbapenem and pyrrolidine rings were not changed in the two compounds but that the relative spatial arrangement of the two nuclei were different. The chemical shifts and coupling constant for the two compounds are available <1996BML1881>.

The strain at the carbon of the carbonyl group in fused bicyclic β -lactams having a bridgehead nitrogen atom and different sizes of the fused ring can be seen from the effect on the ^{13}C chemical shift of that atom (Table 2) <2004EJO4840>.

Table 2 ^{13}C NMR data

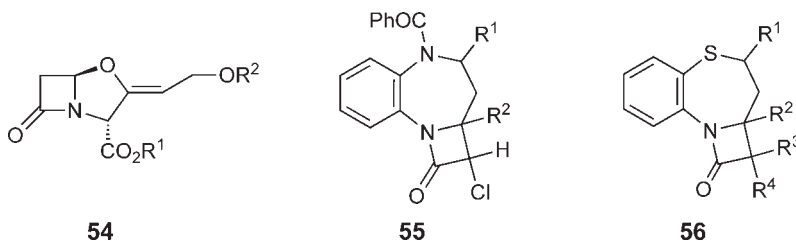
Size of fused ring	$\delta^{13}\text{C}$ (ppm)
0	166.7
5	180.1
6	170.3
7	167.8

2.04.3.3 Mass Spectrometry

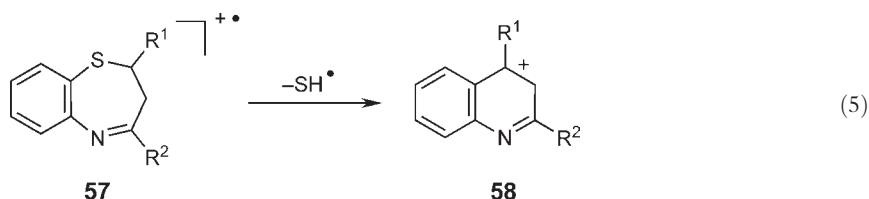
The electrospray ionization mass spectrometry (ESI-MS) analysis of the incubation between porcine pancreatic elastase (PPE) and the *tert*-butylammonium salt of clavulanic acid **54** ($\text{R}^1 = \text{R}^2 = \text{H}$) at time points of between 3 min and 5 h revealed that there were no mass increments relative to PPE. However, when the benzyl derivative **54** ($\text{R}^1 = \text{Bn}$, $\text{R}^2 = \text{H}$) was used, a peak was observed at 26 187 Da after 3 min, which corresponded to the formation of an initial acyl-enzyme complex. The intensity of the peak decreased significantly and two clear additional peaks at 25 968 and 25 967 Da appeared after 5 min, which corresponded to adducts with mass increments at 77 and 88 Da, respectively. The intensities of both peaks decreased after 60 min and almost disappeared after 5 h. The corresponding *p*-nitrobenzyl ester **54** ($\text{R}^1 = \text{CH}_2\text{PhNO}_2$, $\text{R}^2 = \text{H}$) showed similar results except that the formation of adducts appeared slightly faster <2000T5729>.

The electron impact (EI) mass spectral fragmentation patterns of tricyclic β -lactams **55** has been studied. The compounds showed a tendency to yield $[\text{M}-\text{Cl}]^+$ and $[\text{M}-\text{PhCO}]^+$ as the major ions. These ions could further lose a benzoyl radical or benzoylamide and undergo a rearrangement to form 1-benzoozocine-2(1*H*)-one ions. The $[\text{M}-\text{PhCO}]^+$ ions could eliminate NH to produce 2*a*,4-disubstituted 2,2*a*,3,4-tetrahydroazeto[1,2-*a*]quinolin-1-one ions, which could further eliminate chloroketene, CO, and/or hydrogen chloride <2000RCM633>. Xu *et al.* have also made a detailed study of the mass spectra of substituted 2,2*a*,3,4-tetrahydro-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-ones **56**. The fragment ions have been studied by mass-analyzed ion kinetic energy (MIKE) spectrometry and accurate mass measurements under EI ionization. The initial fragmentation pathway is considerably dependent upon the nature of the substituent R^4 . For instance, when $\text{R}^4 = \text{Cl}$, all compounds studied show a tendency to eliminate a

chlorine atom or the chloroketene, $\text{ClR}^3\text{C}=\text{C}=\text{O}$ <2000RCM637>. When $\text{R}^4 = \text{phthalimido}$ and $\text{R}^3 = \text{H}$, the initial fragmentations include elimination of a CO molecule, a phthalimido radical, or a phthalimide molecule <2000RCM2373>.



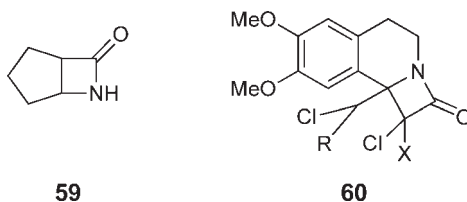
In the case of $\text{R}^4 = \text{phenyl}$ and $\text{R}^3 = \text{H}$, all the compounds investigated eliminate a phenylketene molecule and the fragment ion **57** formed, then lose a thiol radical to give the cation **58** (Equation 5), which is also formed by loss of phenylketene and a thiol radical from the molecular ion <2005PS2779>.



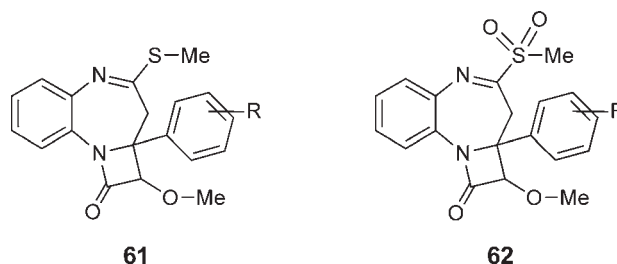
2.04.3.4 Infrared Spectroscopy

Infrared spectra play an important part in the confirmation of the formation of a β -lactam ring. These spectra are measured for samples as KBr discs, Nujol mulls, or in solution, depending on the state of the compound under investigation. Compound **59** has an NH stretching vibration at 3214 cm^{-1} and a sharp peak of $\text{C}=\text{O}$ at 1730 cm^{-1} . Carbonyl stretching frequencies for bicyclic systems containing β -lactam rings fused at the C(3)–C(4) bond is slightly lower than that of systems which are fused at the N(1)–C(2) bond. N-Benzoylation of the secondary amido group of a bicyclic β -lactam was confirmed by the disappearance of the peak at 3214 cm^{-1} and the appearance of peaks at 3017 , 1495 , and 1440 cm^{-1} <2005BML1371>.

The carbonyl stretching vibration for monocyclic β -lactams occurs in the region of 1730 and 1760 cm^{-1} , whereas for the 1-carbapenem series of olivanic acids, it is in the range 1750 – 1770 cm^{-1} <1977JAN770, 1979JAN961>. However, a shifted absorption peak of the β -lactam carbonyl is observed at 1698 – 1660 cm^{-1} for azeto[2,1-*a*]isoquinolin-2-ones **60** ($\text{R} = \text{Me}$ or Cl ; $\text{X} = \text{H}$, Me , Cl), which is lower than for traditional β -lactam antibiotics. In the derivative **60** ($\text{R} = \text{X} = \text{Cl}$) the $\text{C}=\text{O}$ stretching frequency is at 1660 cm^{-1} , which is probably due to the electronegativity of the chlorine atoms <1998JHC77>.



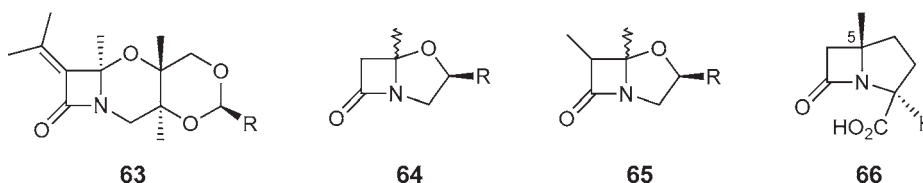
The tricyclic system 1,2,2a,3-tetrahydro-2-methoxy-4-(methylthio)-2a-phenylazeto[1,2-*a*][1,5]benzodiazepin-1(2*H*)-ones **61** has the $\text{C}=\text{O}$ stretching at 1747 – 1766 cm^{-1} , which is similar to the conventional bicyclic β -lactam systems. The carbonyl stretching frequency of the oxidation product **62** is exhibited at 1753 – 1770 cm^{-1} together with a band at 1371 – 1379 cm^{-1} assignable to the sulfonyl group <1996JHC271>.



2.04.3.5 Photoelectron Spectroscopy and Circular Dichroism

CD measurements have been successfully applied and developed as a means by which the absolute configuration of fused bicyclic β -lactams may be established. Chmielewski and co-workers have made significant contributions in this area. They have established that a positive CD band at around 220–240 nm correlates with an (*R*)-configuration and a negative band in the same region correlates with an (*S*)-configuration at the junction of the β -lactam ring with a six-membered ring <2000TA3131, 2002ENA107>. This rule can be extended to include oxacephems **63** having an exocyclic double bond on the β -lactam ring though in this case the CD bands are shifted bathochromically by approximately 10 nm <2005EJO429>.

The sign of the Cotton effect for the band due to $n\text{--}\pi^*$ -transitions at about 220 nm has been used to assign the absolute configurations of the bridgehead carbon atom of families of clavam isomers **64** and **65** <2004BMC405>. Some years before, Bycroft *et al.* reported the structure of a naturally occurring *trans*-carbapenem to have the absolute configuration **66** <1987CC1623>. More recently, Tanaka *et al.* have questioned the assigned configuration for **66** <2002TL93>. The Bycroft group has now confirmed that the original assignment was correct using a stereoselective synthesis of (3*S*,5*S*)-carbapenam-3-carboxylate **66**. The CD curves of the *p*-nitrobenzyl esters from the synthetic and natural sources were superimposable <2003TL973>.



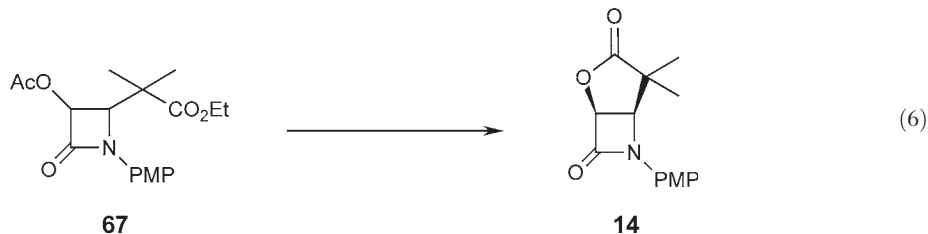
2.04.4 Thermodynamic Aspects

Aromaticity is not a concern for the compounds considered here but chromatography, conformation, and tautomerism have been discussed in CHEC-II(1996) and both previous editions of CHEC should be consulted for a complete overview.

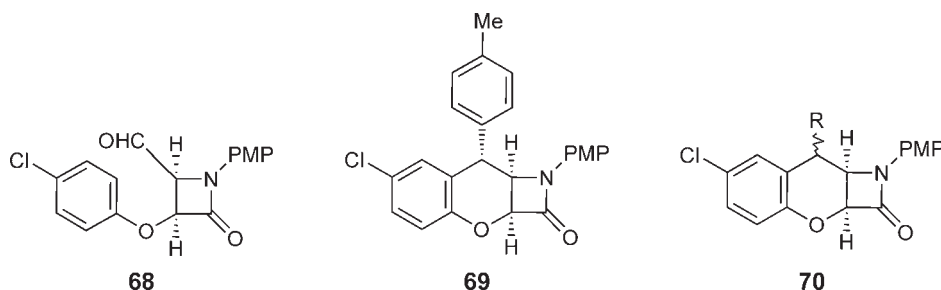
2.04.4.1 Chromatography

Clavulanic acid **54** ($R^1 = R^2 = H$) has been purified by ion-pair adsorption chromatography using commercial hydrophobic matrices in combination with quaternary ammonium salts (QASs). The mechanism of the interaction between **54**, the matrix, and QAS were studied. The presence of **54** caused a significant concentration-dependent shift in the loading of QAS on the matrix. At high concentration of **54** the total capacity of the system was higher than expected from a mechanism based purely on ion-pair interactions. On the basis of electrostatic theory, the surface potential will decrease due to the simultaneous decrease in the concentration of adsorbed QAS and increase in the concentration of adsorbed **54**. The mutual equilibrium shift for **54** and for QAS under different conditions for batch and column configurations is an indication that the formation of a complex **54**–QAS in the liquid phase is an important phenomenon in the ion-pair chromatography. At the normal conditions used in preparative chromatography, the interaction between **54** and the matrix and between **54** and QAS in the liquid phase have an important contribution to the capacity and affinity of the stationary phase for the absorbate and cannot be neglected <1996JCH185>.

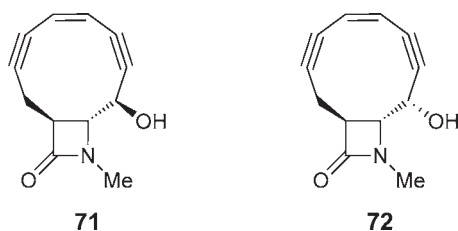
Lipase reduction of the derivative **67** gave the bicyclic β -lactam **14** (Equation 6) along with a mixture of three products which were separated by chiral phase HPLC and their stereochemistry was assigned on the basis of ^1H NMR coupling constants and NOE results. The stereochemistry was later confirmed by X-ray crystallography <2005CJC28>.



Thin-layer chromatography (TLC) is often used to monitor the progress of a reaction and sometimes provides information about the mechanism of the process. The aldehyde **68** in the presence of aluminium chloride in toluene gave **69** where a solvent molecule has been incorporated into the molecular architecture of the product. The same product is obtained when concentrated sulfuric acid in toluene is used to bring about the cyclization. When the progress of the reaction in the presence of aluminium chloride was followed by TLC, it became apparent that two intermediates are first formed and are subsequently transformed into product **70**. These intermediates have the same R_f values as the two epimers of **70** ($R = \text{OH}$) and were thought to be formed by hydrolysis on the TLC plates of the expected epimeric aluminium chloride complex reaction intermediates **70** ($R = \text{OAlCl}_3$). Under these conditions there seems to be no equilibrium between the two epimers **70** ($R = \text{OH}$), because they were formed and destroyed at different rates, and one cannot be converted into the other under the conditions used to bring about the cyclization process <1998T15227>.



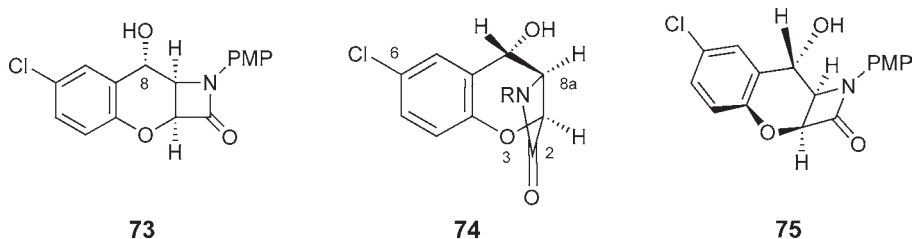
Successful gas chromatography–mass spectrometry (GC–MS) analysis at 200 °C of the epimers **71** and **72** showed their thermodynamic stability. Their separation by chromatography on silica gel and ready conversion to methyl ethers and acetate esters showed the chemical stability produced by the *trans*-ring junction <1997T3249>.



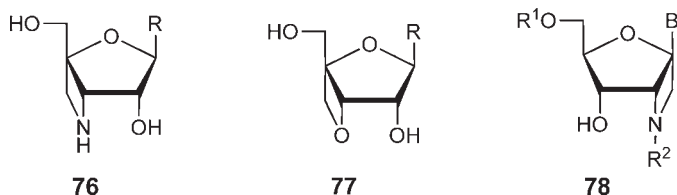
Other examples where fused ring β -lactams have been purified or studied by chromatography have been reported <1997M1149, 2006CC2992>. Selected examples showing the applications of a range of chromatographic techniques are: the use of flash chromatography to separate diastereoisomers of tricyclic compounds <1998JOC6786>, prevention of the occurrence of hydrolysis during chromatography on silica gel by silylation of the gel <1997BSF927>, the use of a gravity flow column, and HPLC to separate polycyclic β -lactams <1997SL38, 2002JOC7004>.

2.04.4.2 Conformation and Tautomerism

Two conformations are possible for compound **73**: one a compact folded structure (**74**: R = PMP) and the other a more extended molecule **75**. In **74** (R = PMP), the H(8a)–C(8a) bond is in the flagpole position of a boat-shaped six-membered ring and is almost perpendicular to the plane of the fused benzene ring. Evidence from NMR spectroscopy shows that this form is the dominant or exclusive conformer present in solution <1998T15227>.



NMR spectroscopy data on derivative **76** (R = thymidyl, X = NH) show that the bridged nucleic acid derivative is conformationally restricted to the *S*-form which is a similar finding to that for the oxygen analogue **77** (X = O). Honcharenko *et al.* have made related compounds with the fused azetidine ring across the 1,2-positions of the furanose ring **78** (R¹ = PhOCH₂CO, B = pyrimidine base). Results from both NMR spectroscopy and theoretical simulation studies show that azetidine **78** has puckering amplitudes and phase angles similar to those observed with the analogous oxetane modified nucleosides. The relatively lower electronegativity of a nitrogen compared to an oxygen atom means that the strength of the restraints of the four-membered ring on the sugar conformation are smaller in the case of the azetidine and the *P* fluctuation amplitude is almost 30% greater for the nitrogen analogue. The azetidine-modified nucleosides may be better candidates for *in vivo* or *in vitro* applications such as binding to mRNA in order to arrest its translation to proteins <2006JOC299>. Some further aspects of conformation are considered in Section 2.04.3.5.



2.04.5 Reactivity of Fully Conjugated Rings

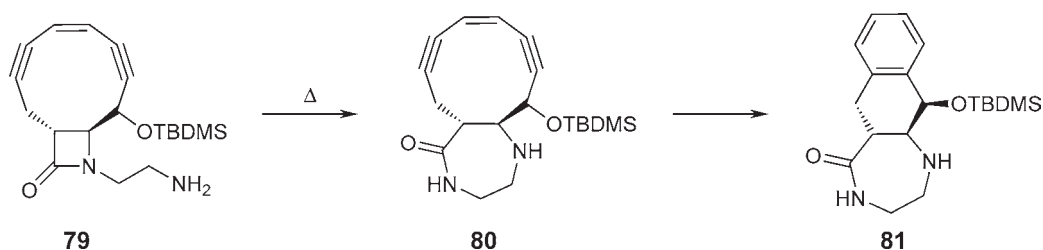
No examples of fully conjugated fused systems have been found.

2.04.6 Reactivity of Nonconjugated Rings

This section was discussed in some detail in CHEC(1984) and CHEC-II(1996), and the present account adds to the information given previously.

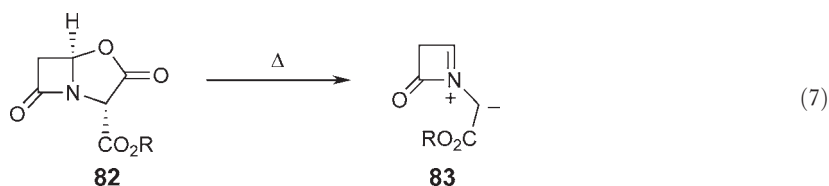
2.04.6.1 Thermal and Photochemical Reactions

Thermal reaction of the lactenediyne **79** in tetrahydrofuran (THF) in the presence of 1,4-cyclohexadiene undergoes cyclization via the intermediate **80** to give the tricyclic product **81** (Scheme 2). The reaction proceeds by the intramolecular opening of the β -lactam ring to a larger seven-membered ring <2003EJO1319>.



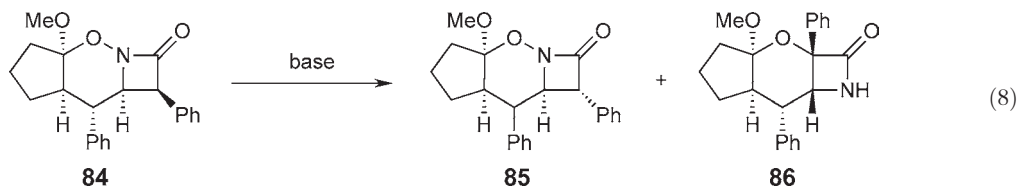
Scheme 2

Thermolysis of oxazolidinone **82** gives the reactive azomethine ylide **83** (Equation 7) which readily takes part in 1,3-dipolar cycloaddition reactions (see Section 2.04.6.3).

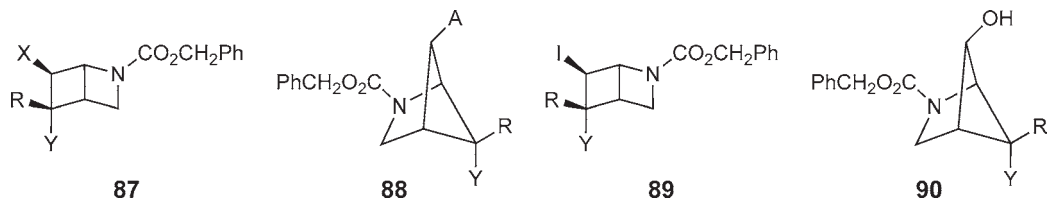


2.04.6.2 Isomerization

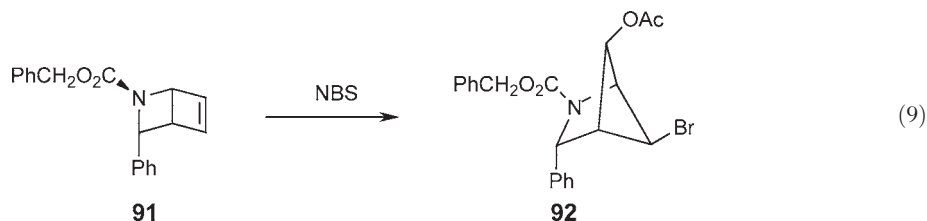
The β -lactam **84** with a bridgehead nitrogen atom is isomerized in the presence of base to its stereoisomer **85** and to a rearranged tricyclic β -lactam **86** without a bridgehead atom in 34% and 61% yield, respectively (Equation 8). A mechanism for the process is proposed <2004EJO4397>.



Salts of silver(I) and mercury(II) with the anions A^- ($\text{A} = \text{F}, \text{Cl}, \text{OH}, \text{OAc}$) catalyze the rearrangement of 6-*exo*-iodo(or bromo)-*N*-benzyloxycarbonyl-2-azabicyclo[2.2.0]hexanes **87** ($\text{R} = \text{H}$ or Me ; $\text{X} = \text{Br}$ or I ; $\text{Y} = \text{OH}$ or F) to yield *N*-benzyloxycarbonyl-5,6-disubstituted-2-azabicyclo[2.2.1]hexanes **88** ($\text{A} = \text{F}, \text{Cl}, \text{OH}, \text{OAc}$). The iodo compounds give a higher yield (37–74%) than the bromo compounds <2003OL2739>. Similar results are obtained when the salts are replaced by SelectfluorTM in aqueous acetonitrile. For example, the 2-azabicyclo[2.2.0]hexanes **89** ($\text{R} = \text{H}$, Me ; $\text{Y} = \text{F}, \text{Cl}, \text{OH}$) are converted into the 2-azabicyclo[2.2.1]hexanols **90** <2004OL1669>.

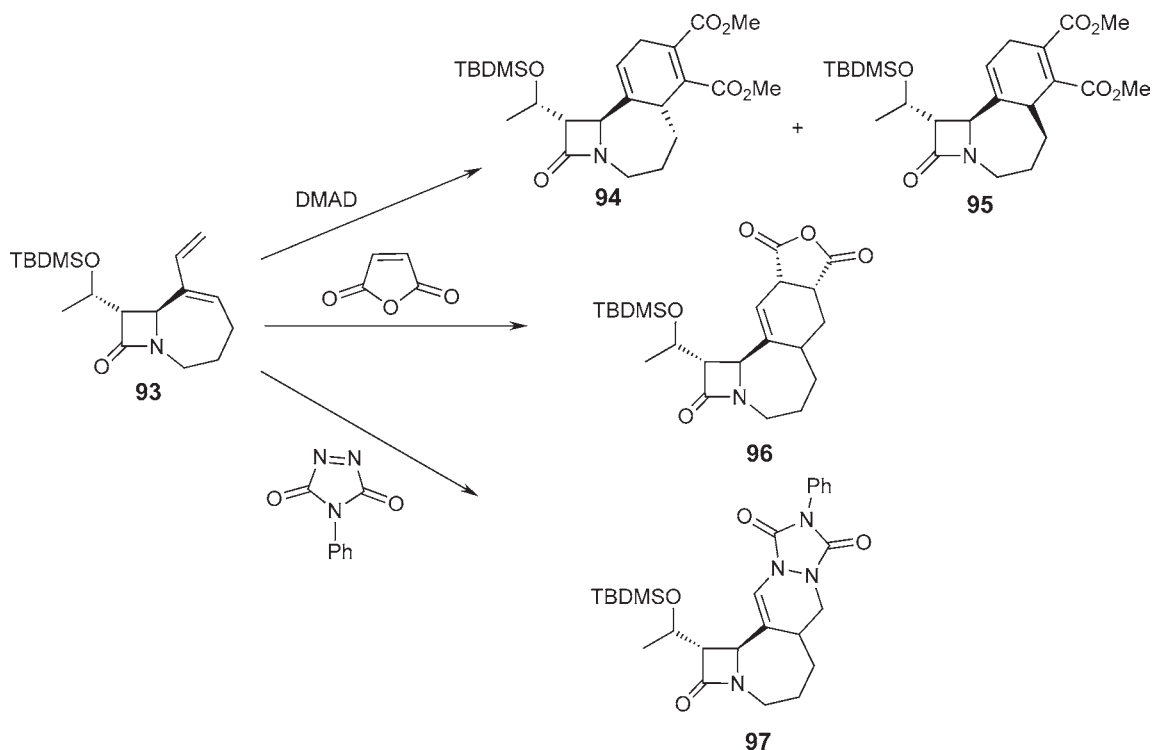


The bicyclic azetidine **91** is converted into **92** by the action of NBS in a mixture of acetic anhydride and acetic acid (Equation 9) <2005JOC590>.



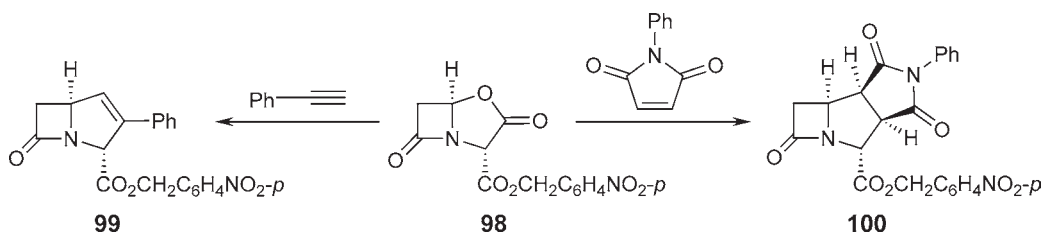
2.04.6.3 Cycloaddition Reactions

Diels–Alder reaction of **93** with dimethyl acetylenedicarboxylate (DMAD), maleic anhydride, or 4-phenyl-1,2,4-triazoline-3,5-dione gives the tri- and polycyclic products **94–97** in 57–95% yield (Scheme 3) <2004S2665>.

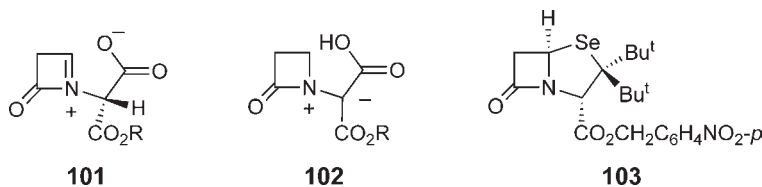


Scheme 3

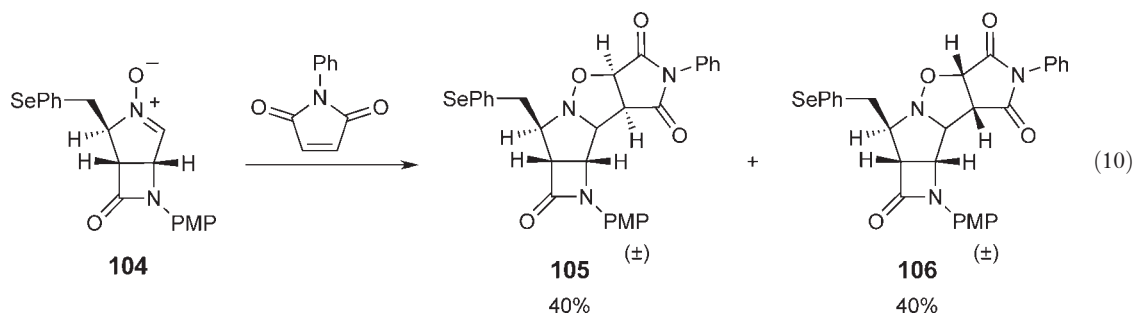
Reaction of **98** at 100 °C with alkenes or alkynes gives fused systems via 1,3-dipolar cycloaddition of a reactive azomethine ylide intermediate (see Section 2.04.6.1, Equation 7). For example, the reactions with phenylethyne and *N*-phenylmaleimide give the bicycle **99** and tricycle **100** products, respectively (Scheme 4). The reaction with *N*-phenylmaleimide shows second-order kinetics and first order with respect to **98** and the dipolarophile. However, surprisingly, in the absence of the dipolarophile, **98** does not lose CO₂, but undergoes racemization. A mechanism for the process has been proposed and involves the initial formation of the ylide **101** and proton transfer to give ylide **102** which reacts with the dipolarophile. Selenopenams **103** have been synthesized by this method <1999JHC1365>.



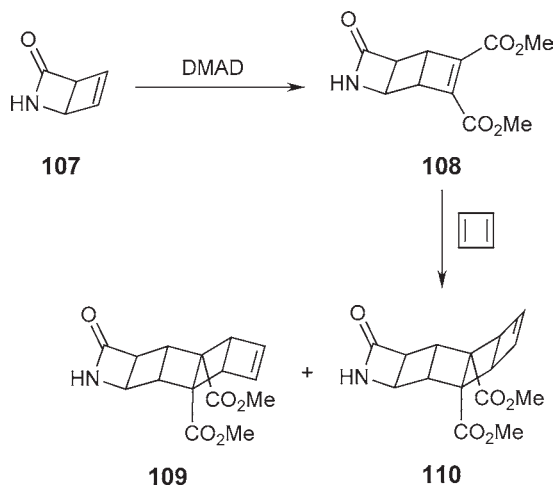
Scheme 4



The reaction of nitrene **104** with *N*-phenylmaleimide yielded the racemic 1,3-dipolar cycloadducts **105** and **106** (Equation 10) in the ratio of 1:1; these were easily separated by gravity flow chromatography <2002JOC7004>.



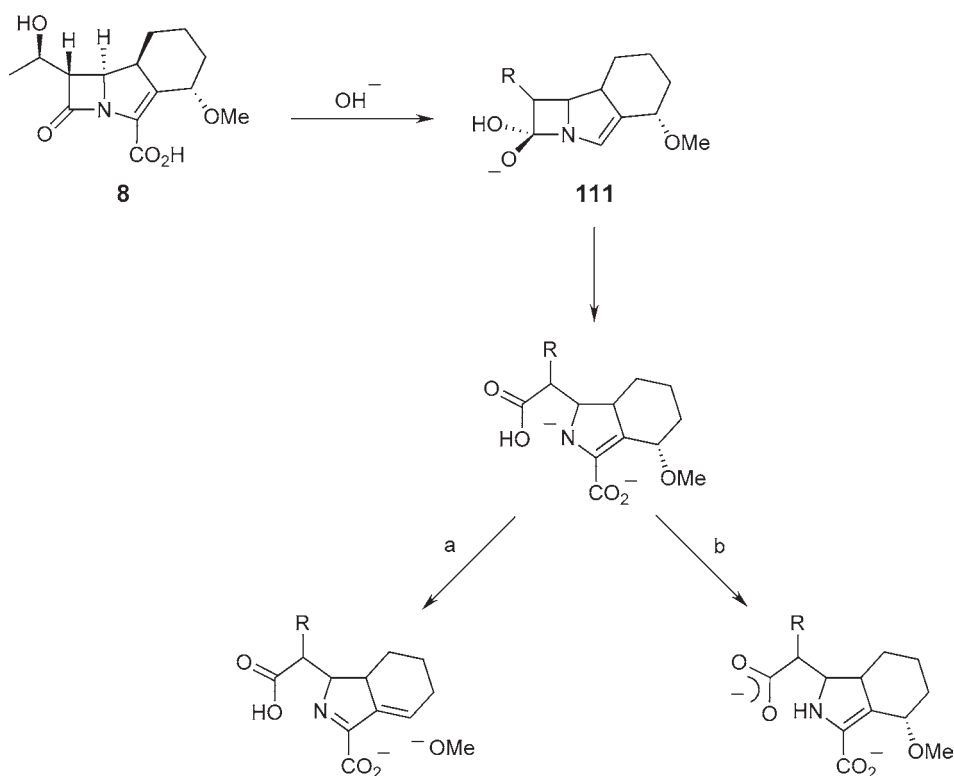
Cycloaddition of aza[2]ladderane **107** with DMAD in the presence of a ruthenium catalyst $\text{RuH}_2\text{CO}(\text{PAr}_3)_3$ ($\text{Ar} = \text{Ph}, p\text{-FC}_6\text{H}_4$) yielded the *exo*-fused aza[3]ladderane diester **108**, which underwent further cycloaddition with cyclobutadiene through the dienophilic cyclobutene π -bonds of **108** to yield a mixture of stereoisomers **109** and **110** in a ratio of 3:2 (Scheme 5). The two isomers were separated by HPLC. The reaction of **107** with cyclopentadiene has also been studied both experimentally and theoretically <1997SL38>.



Scheme 5

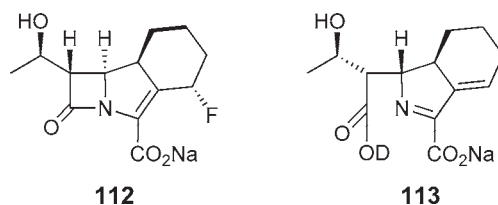
2.04.6.4 Opening of the Four-Membered Ring

A theoretical study of the alkaline hydrolysis of sanfetrinem **8** (see Section 2.04.2) compares two possible pathways. The rate-limiting step is nucleophilic attack on the carbonyl group to give intermediate **111** ($R = \text{CH}(\text{OH})\text{CH}_3$). The isolation of the hydrolysis products having an opened four-membered ring where the methoxyl group is absent confirms that pathway (a) is important (Scheme 6) <2005HCA774>.

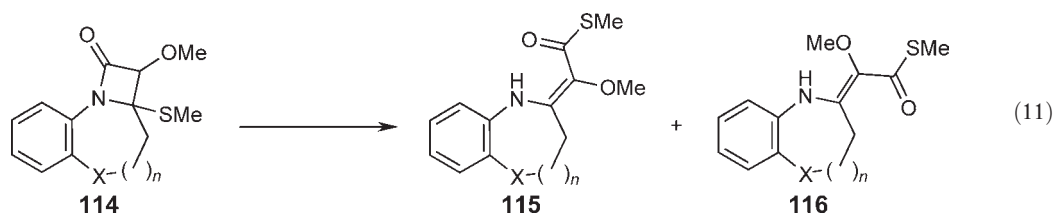


Scheme 6

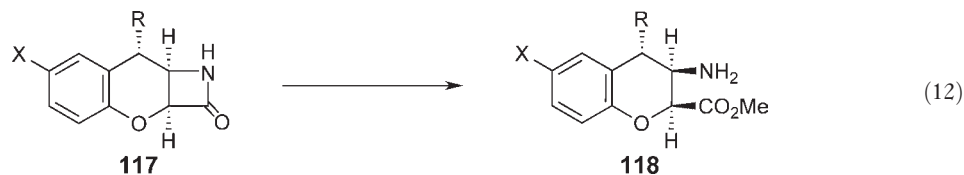
Hydrolysis of the 4-fluorotrinenim **112** in D_2O gave the ring-opened, nonfluorinated, and demethoxylated product **113** in accord with mechanism (a) in Scheme 6 <1996T263>.



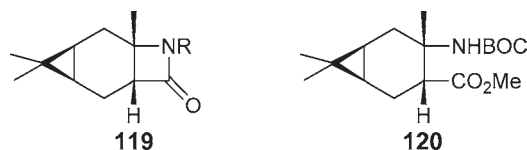
β -Lactams with a methyl sulfide group at the bridgehead undergo an unusual hydrolysis process in the presence of trifluoroacetic acid (TFA). Compounds **114** ($n = 0, 1$; $X = \text{O}, \text{S}$) are hydrolyzed to yield the unsaturated thioesters **115** ($n = 0, 1$; $X = \text{O}, \text{S}$) and **116** ($n = 0, 1$; $X = \text{O}, \text{S}$). Evidence is provided that methanethiol is produced by elimination from **114** as a first step and the thiol then attacks the carbonyl group to give the ring-opened thioesters (Equation 11) <1997T8439>.



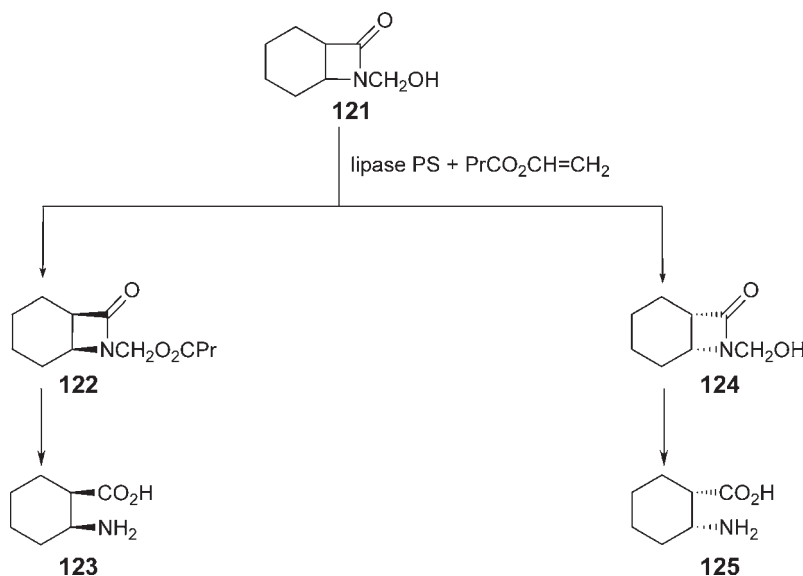
Ring opening of a bi- or tricyclic β -lactam, which does not have a bridgehead nitrogen atom and whose relative stereochemistry is known, gives β -amino acid derivatives where the relative stereochemistry is also known. This idea has been used extensively. For instance, methanolysis of the tricyclic β -lactams **117** gave a series of 3-amino-4-substituted chromane-2-carboxylic esters **118** (Equation 12) whose relative stereochemistry is known <1999T5567>.



Similar results have been obtained by utilizing a β -lactam **119** (R = H) from the homochiral terpene, ($\pm$)-3-carene, but initial attempts using acid-catalyzed ring-opening procedures failed to give clean products. It was necessary to protect the nitrogen atom with a butoxycarbonyl group **119** (R = *t*-butoxycarbonyl (BOC)) and to use basic conditions (sodium methoxide/methanol) to obtain the β -amino ester derivative **120** <2003TA3965>.

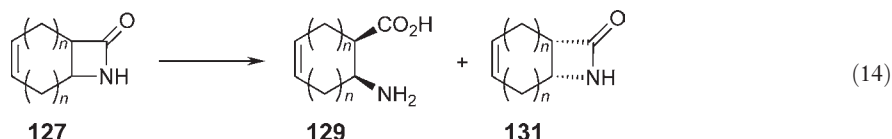
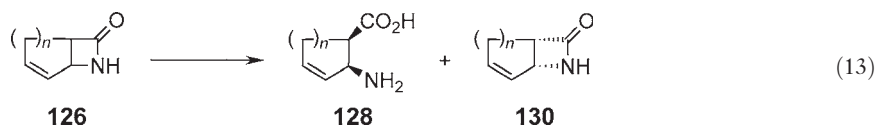


Lipase-catalyzed acylation of one isomer of *N*-hydroxymethyl β -lactam **121** by vinyl butyrate in acetone yielded the ester **122**, which afforded **123** after acidic hydrolysis and ion-exchange chromatography (Scheme 7). The unesterified alcohol **124** gave the β -amino acid **125**. Similar reactions yielded 2-aminocyclohex-3-en-1-carboxylic acid and 2-aminocyclohex-4-ene-1-carboxylic acid from 1-azabicyclo[4.2.0]oct-3-en-8-one and 1-azabicyclo[4.2.0]oct-4-en-8-one, respectively <2000TA1593>.

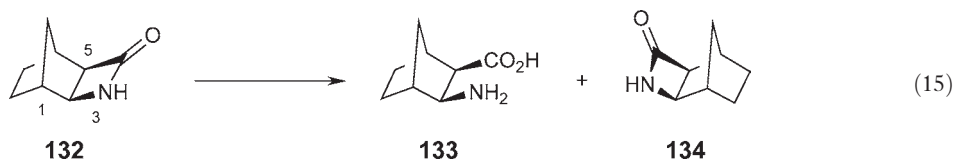


Scheme 7

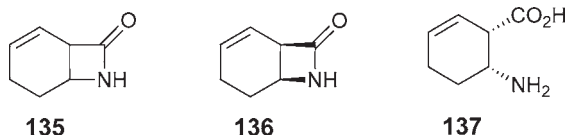
A more direct method for the enantioselective ring opening of unactivated bicyclic β -lactams has been reported. When lipolase (modified lipase B from *Candida antarctica* adsorbed on a macroporous resin) was allowed to interact with racemates **126** ($n = 1$ or 2) and **127** ($n = 1$ or 2) in aqueous diisopropyl ether at 70°C for 4.5–7 h, the products were the enantiomerically pure ring-opened unsaturated alicyclic β -amino acids **128** ($n = 1$ or 2) and **129** ($n = 1$ or 2), and the bicyclic β -lactams **130** ($n = 1$ or 2) and **131** ($n = 1$ or 2) in 45–48% yield with ee 95–99% (Equations 13 and 14) <2004TA2875>.



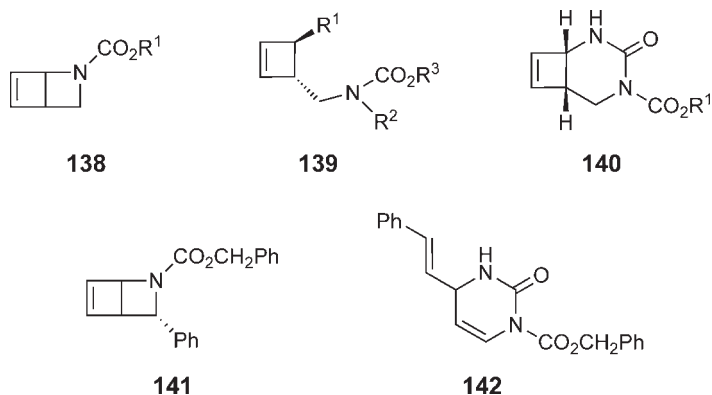
The same supported enzyme under the same reaction conditions, with the exception that the reaction time was much longer (96 h), has brought about the enantioselective ring opening of the β -lactam of racemic *exo*-3-azatricyclo[4.2.1.0^{2,5}]nonan-4-one **132** to give the enantiomerically pure **133** (46% yield) and the bicyclic β -lactam **134**, both with ee 99% (Equation 15) <2004TA573>.



The racemate **135**, an isomer of **127** ($n = 1$), has also been resolved into **136** and a ring-opened product **137** by a lactamase present in the whole cells of *Rhodococcus globerulus* at pH 7 for 24 h. These β -amino acids have been used in the syntheses of potential medicinal chemicals <2003C248, 2004T717>.

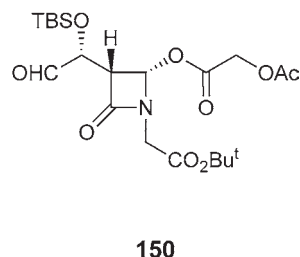
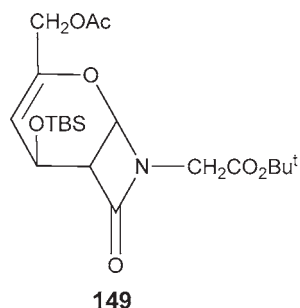


The action of *N*-chlorosuccinimide, or a source of positive fluorine such as SelectfluorTM, in aqueous acetonitrile on the alkene **138** ($\text{R}^1 = \text{Me}$) is to open the azetidine ring by attack at the allylic position to yield the cyclobuten-3-ol **139** ($\text{R}^1 = \text{OH}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Me}$) <2003JOC5292>. Chlorosulfonyl isocyanate (CSI) reacts with **138** ($\text{R}^1 = \text{Et}$) to give both a chlorobutene **139** ($\text{R}^1 = \text{Cl}$; $\text{R}^2 = \text{CONH}_2$; $\text{R}^3 = \text{Et}$) and the bicyclic reduced pyrimidone **140** ($\text{R}^1 = \text{Et}$). However, the action of CSI on the more substituted 2-azabicyclo[2.2.0]hex-5-ene **141** provided the reduced monocyclic pyrimidone **142** <2003JOC1626>.

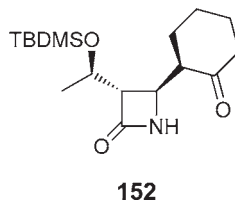
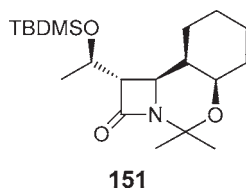


2.04.6.5 Opening of the Fused Ring

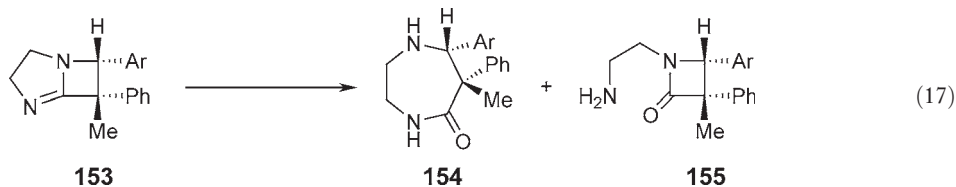
Opening of the fused ring of a bicyclic azetidinone has sometimes been used as a method of obtaining a monocyclic β -lactam of known stereochemistry. Ozonolysis of the unsaturated α -D-glucopyranosylamine **149** yielded a β -lactam **150**, which was useful in the synthesis of carbapenems and carbacephems <2000PJC1243>.



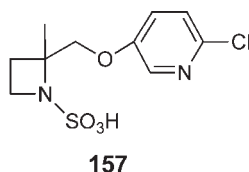
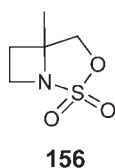
The acetone **151** is available from a 4-substituted azetidinone in three steps and is converted into the 3,4-disubstituted azetidinone **152** by the action of pyridine chlorochromate in the presence of a catalytic amount of Jones' reagent. The disubstituted β -lactam is a suitable starting material for the synthesis of trinems <1996TL2467>.



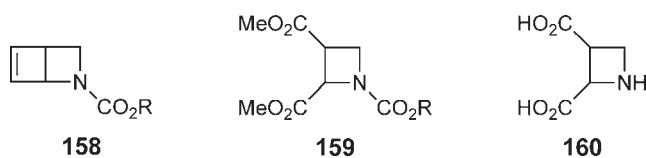
Hydrolysis of the 1,4-diazabicyclo[3.2.0]hept-4-ene **153** gave two products which were readily separated by chromatography. In all three cases investigated, the major product (42–59%) was the *cis*-1,4-diazepin-5-one **154** accompanied by the *cis*-*N*-(2-aminoethyl)-2-azetidinone **155** (16–22%) as the minor product (Equation 17) <2005T1531>.



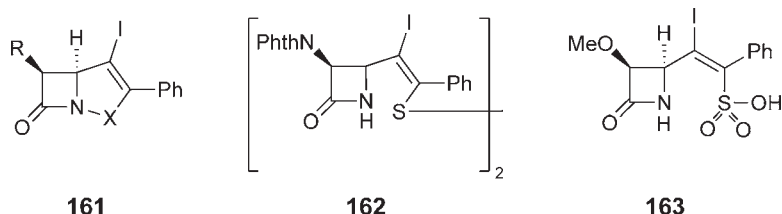
Similar general procedures have been used to prepare azetidines. For instance, the sulfamidate **156** on treatment with 2-chloro-5-hydroxypyridine in the presence of sodium hydride gave the azetidine **157** <2005BML1637>.



Oxidation of the *N*-alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-ene **158** with ruthenium tetroxide followed by esterification with diazomethane affords the *cis*-2,3-diester of azetidine **159** (R=Me) in 67% overall yield. The *N*-protecting group can be easily removed from the diacid by acidic hydrolysis to give acidic amino acid **160** in 85% yield. Strangely, the 2,3-diester **159** (R=Me) upon acidic hydrolysis failed to give any of the amino acid. This approach to azetidines is useful because **158** is readily available from pyridine in three steps <2003CPB96>.



The nitrogen–sulfur bond in **161** ($X = S$, $R = NPhth$; $X = SO_2$, $R = OMe$) is easily broken under certain conditions. For instance, attempts to obtain a palladium-catalyzed carbonylation reaction with the iodide gave only the ring-opened disulfide **162** and the sulfonic acid **163**, presumably by reductive cleavage of the N–S bond by the triphenylphosphine in the reaction mixture <2000T5571>.



An unusual example where both the four-membered ring and the fused ring are opened has already been mentioned in Section 2.04.6.4 <2003JOC4179>.

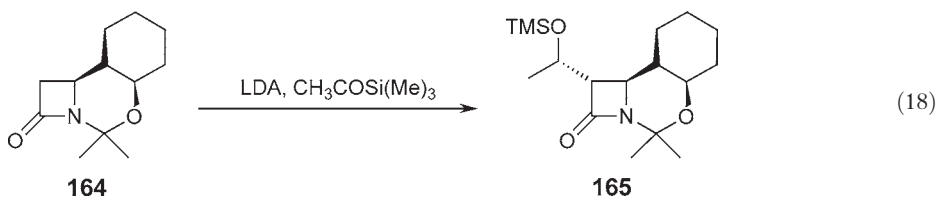
2.04.6.6 Reactions at a Carbonyl or Thiocarbonyl Group of the Fused Ring

The important 2-alkylthio-2-arylthio-carbapenems are usually prepared by nucleophilic displacement of the ester group from the enol ester derived from 2-oxocarbapenem. This procedure is discussed in more detail in Section 2.04.7.2. An account of the procedure and an example of the reactivity of a thiocarbonyl group are given in CHEC-II(1996) <1996CHEC-II(1B)659>. No new examples of the reaction of a thiocarbonyl group in fused β -lactams have been found.

2.04.6.7 Miscellaneous

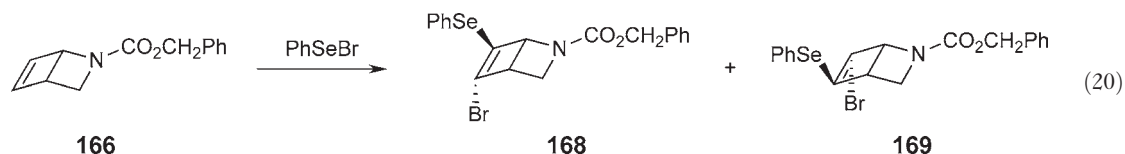
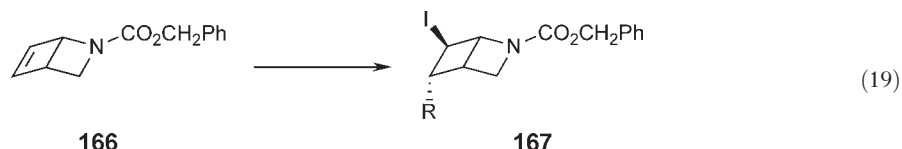
A high-yielding (84–90%) method for the N-alkylation of fused bicyclic β -lactams uses cesium carbonate supported on silica gel in the absence of a solvent at room temperature for relatively short times (1–8 h). The procedure gives higher yields than conventional techniques and in a shorter time <2005MI367>.

The methylene group adjacent to the carbonyl group in a β -lactam is weakly acidic and compound **164** was alkylated to give **165** by the action of lithium diisopropylamide (LDA) and acetyl trimethylsilane (Equation 18) <1996TL2467>.

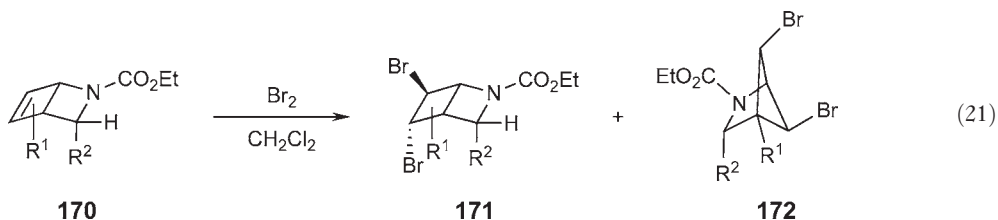


Sometimes addition of electrophiles to the unsaturated group in 2-azabicyclo[2.2.0]hexane occurs regio- and stereo-selectively in good yield. The reaction of the alkene **166** with NBS in aqueous dimethyl sulfoxide (DMSO) or acetic acid gives **167** ($R = OH$ and $R = OAc$), respectively, in 90% and 91% yields (Equation 19). Both iodination and fluorination occur when **166** is treated with iodine and mercury(II) fluoride in a mixture of aprotic solvents to give **167** ($R = F$), though a lower yield (68%) is obtained. The reaction of **166** with phenylselenenyl bromide in methylene chloride is less regioselective and gives both **168** and **169** in a total yield of 83% (Equation 20). In a more polar solvent mixture of

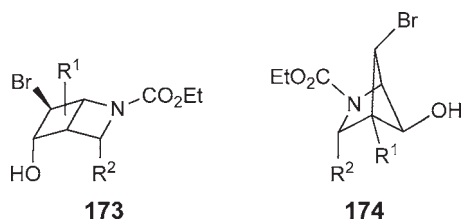
nitromethane and methylene chloride the ratio of regioisomers is altered and the total yield increased to 90%. This seems to imply that the solvent plays a significant part in the regioselectivity of the reaction process [<2003OL2739>](#).



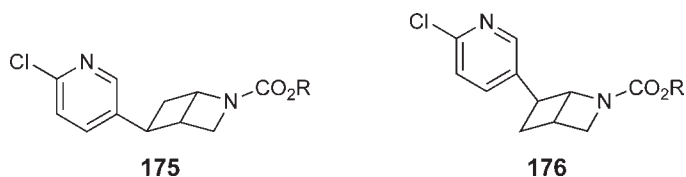
Bromination of *N*-ethoxycarbonyl-2-azabicyclo[2.2.0]hex-5-enes **170** gave a more complicated result which depended upon the nature of substituents in the 4- (or 5-) and 3-positions. When there were no substituents **170** ($R^1 = R^2 = H$), addition of bromine occurred *trans* to give **171** ($R^1 = R^2 = H$) and also a rearranged product **172** ($R^1 = R^2 = H$) which was formed in slightly lower yield. However, when a 5-methyl group was present **170** ($R^1 = 5\text{-Me}$, $R^2 = H$), only the 5-methyl-5,6-dibromo-2-azabicyclo[2.2.0]hexane was isolated, though in relatively low yield (48%). In contrast, when a 3-substituent was present **170** ($R^1 = H$, $R^2 = \text{Me}$), the only product was the rearranged dibromo-2-azabicyclo[2.1.1]hexane **172** ($R^1 = H$, $R^2 = \text{Me}$), which was formed in very high yield (99%) (Equation 21). The authors give mechanistic explanations for these findings [<1998JOC8558, 2001JOC1811>](#).



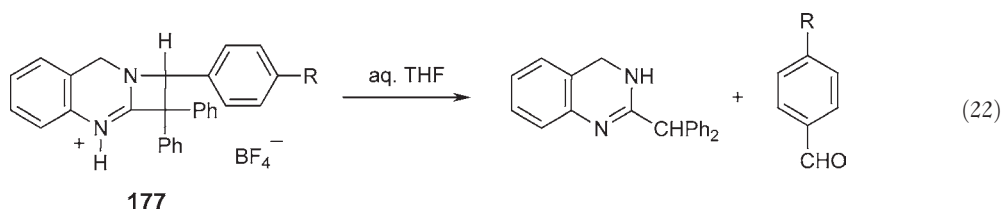
Addition of hypobromous acid follows a similar pattern. Addition to the unsubstituted compound **170** ($R^1 = R^2 = H$) gave the *trans*-bromohydrin **173** ($R^1 = R^2 = H$) and the rearranged product **174** ($R^1 = R^2 = H$). The presence of a 5-methyl group gave mainly the corresponding 5-bromo-6-hydroxy-2-azabicyclo[2.2.0]hexane in 76% yield, while the presence of a 3-substituent, for example, **170** ($R^1 = H$, $R^2 = \text{Me}$), gave only the rearranged product **174** ($R^1 = H$, $R^2 = \text{Me}$) [<1998JOC8558, 2001JOC1805>](#).



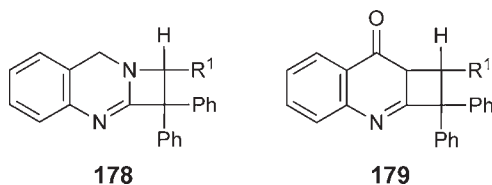
Reduction of *N*-alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-ene with hydrogen and palladium on charcoal catalyst gave the corresponding bicyclo[2.2.0]hexanes [<2003JOC1626>](#). Reductive arylation occurred when *N*-alkoxycarbonyl-2-azabicyclo[2.2.0]hexane was treated with 2-chloro-5-iodopyridine in the presence of palladium(III) acetate, triphenylphosphine, piperidine, formic acid, and dimethylformamide (DMF) to give mainly **175** and **176** but in moderate and variable yields (28–58%) [<2000T9233>](#).



An unusual reaction of an azetidine occurs when **177** ($R = \text{NO}_2$) is hydrolyzed in aqueous THF to give the 4-substituted benzaldehyde and a 3,4-dihydroquinazoline (Equation 22) <1997T13449>.



The azeto[2,1-*b*]quinazolines **178** ($R = \text{OMe}$ or NO_2) in solution in chloroform or dichloromethane undergo slow oxidation, which is accelerated by light, to the quinazolines **179** ($R = \text{OMe}$ or NO_2). The quinazolones are obtained more efficiently by oxidation of **178** by activated manganese dioxide <1997T13449>.



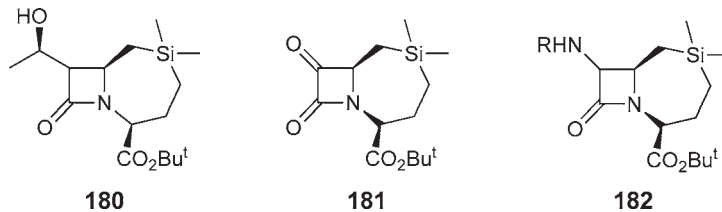
Ring-enlargement reactions of azetisoquinolines and azeto[1',2':1,2]pyrido[3,4-*b*]indole give eight-membered ring compounds which are useful intermediates <1999COR1>.

2.04.7 Reactivity of Substituents Attached to Ring Carbon Atoms

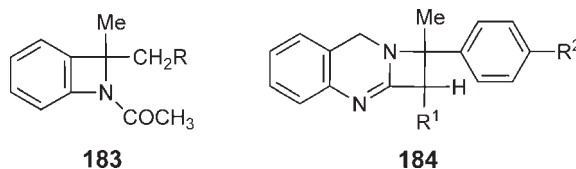
Earlier examples of reactions of substituents on the four-membered and fused rings and on deprotection reactions can be found in CHEC(1984) (Section 6.02.3.3, p. 350) and CHEC-II(1996) (Section 1.12.7, p. 676).

2.04.7.1 Substituents Attached to the Four-Membered Ring

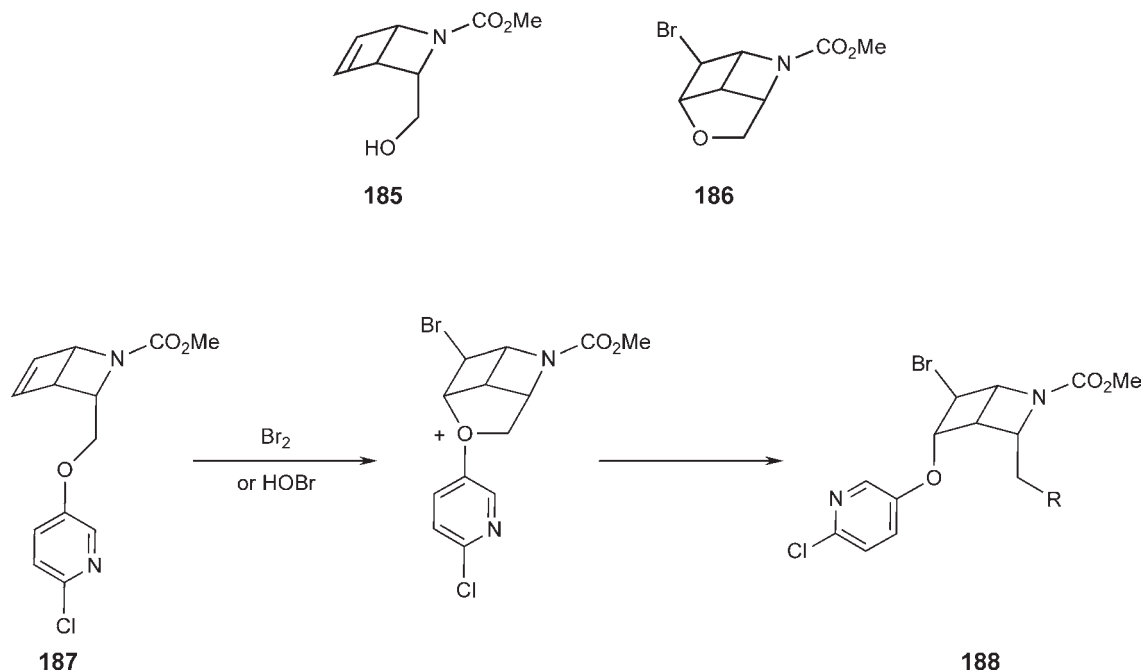
During the period 1996–2006 there has been a paucity of examples of the reactions of substituents attached to the carbon atoms of the four-membered ring of a fused β -lactam. This is in part due to the shift in emphasis from acylation of an amino group at the 3-position of an azetidinone ring to the use of the 3-(1-hydroxyethyl) substituent in trinems and larger ring systems. In one case the secondary alcohol substituent in derivative **180** is removed by mesylation followed by oxidation with osmium tetroxide and periodate to give the ketone **181**, which is then converted to the amine **182** ($R = \text{H}$) by preparation of the oxime and its reduction. The amine is acylated to give the phenoxyacetyl derivative **182** ($R = \text{PhOCH}_2\text{CO}$) <1995JOC8403>.



Reactions of substituents on azetidines include the replacement of the iodine in **183** ($R = \text{I}$) with the phenylthio group **183** ($R = \text{SPh}$) by the action of sodium benzenethiolate <2005BCJ886>. Chromatography on a silica gel column of the trimethylsilyl derivative **184** ($R^1 = \text{Me}_3\text{Si}$; $R^2 = \text{OMe}$ or NO_2) caused protonolysis of the silyl group to afford **184** ($R^1 = \text{H}$; $R^2 = \text{OMe}$ or NO_2) <1997T13449>.

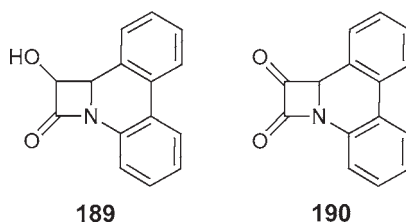


In certain cases, a substituent on the four-membered azetidine ring can attack the fused ring (neighboring group participation). For instance, treatment of the unsaturated alcohol **185** with NBS in aqueous DMSO gives the tricyclic ether **186**. It is suggested that the intermediate bromonium ion in the bromination process activated the fused ring to attack. When the ether **187** is treated with either bromine or hypobromous acid a nucleophilic substitution at the methylene group of the ether ring occurs to give ethers **188** ($R = \text{Br}$ or OH) (**Scheme 8**) <2002OL1259>.



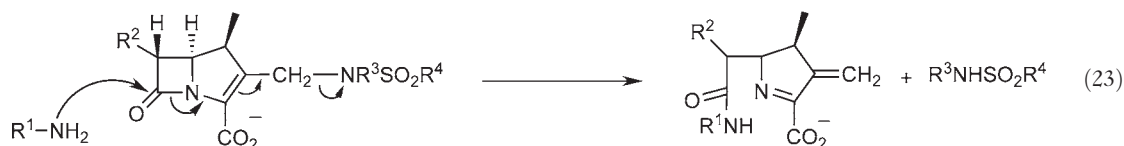
Scheme 8

Oxidation of the secondary alcohol **189** with phosphorus pentoxide in DMSO gives the ketone **190** <1999TL2005>.

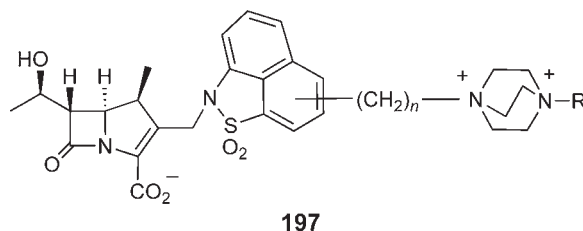


2.04.7.2 Substituents on the Fused Ring

The enol phosphate **191** ($R \neq \text{H}$) has been widely used in the preparation of a large number of carbapenems having a 2-allyl- or aryl-thio substituents. The reaction is promoted by the presence of base and the choice of solvent is important. Diisopropylamine or dicyclohexylamine tend to give better results than tertiary amines and nonnucleophilic bases such as

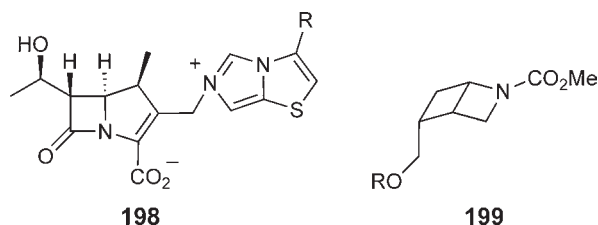


Later, the same group reported the preparation and *in vitro* antibacterial activity of a range of naphthalene derivatives in which the sulfonamide group was part of a ring. A dicationic substituent on the naphthalene nucleus **197** was introduced in order to make the carbapenem more water soluble <1999BML679, 1999BML1559, 1999JA11261, 1999TL427>.



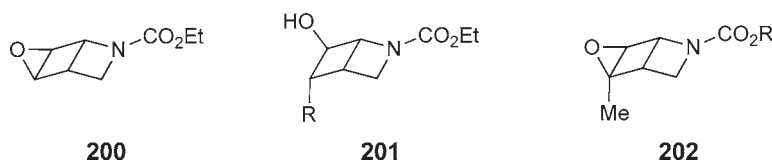
Another example of the Mitsunobu reaction with the hydroxymethyl carbapenem uses 2-mercapto-1,2,4-thiadiazole as the reactant to provide a $-\text{CH}_2\text{S}-$ link between the heterocycles <1998H(48)2287>. A somewhat similar idea has been reported by Aihara *et al.*, but they used the diphenylphosphate of the 2-hydroxymethyl carbapenem and its Mitsunobu reaction with substituted imidazo[5,1-*b*]thiazoles to obtain **198** <2003BML3475>.

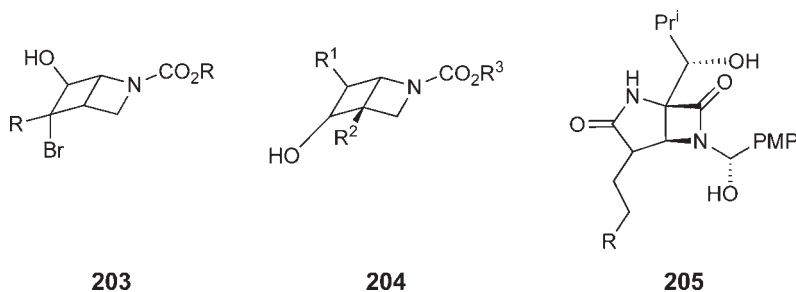
The hydroxymethyl derivative of 2-azabicyclo[2.2.0]hexane **199** (R = H) has been converted into the 2-chloropyridin-5-yl ether **199** (R = 2-ClC₅H₃N) by Mitsunobu reaction with 2-chloro-5-hydroxypyridine <2000T9227>.



Regioselective ring opening of the epoxide in **200** occurs in the presence of bromine and triphenylphosphine to give the bromohydrin **201** (R = Br), which on treatment with azobisisobutyronitrile (AIBN) and tributyltin hydride gives the *exo*-6-hydroxy-2-azabicyclohexane **201** (R = H) <2001JOC1811>. The 5-substituted derivatives of alcohol **201** (R = Me or Ph) are obtained by treatment of **200** with lithium dimethylcopper or lithium diphenylcopper <2004OL1669>.

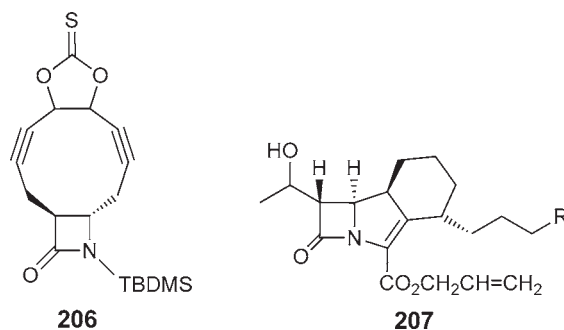
When the 5-*endo*-methyl epoxide **202** was treated with bromine and triphenylphosphine, the bromohydrin **203** (R = Me) was obtained together with the bromomethyl derivative **203** (R = CH₂Br) <2001JOC1811>. The analogous 3-*endo*-methyl epoxide under similar reaction conditions gave a rearranged product. Reductive debromination of the bromohydrins **204** (R¹ = Br; R² = H or Me) occurs to give the *endo*-alcohol **204** (R¹ = H; R² = H or Me) <2001JOC1811>. Replacement of the hydroxyl group in **205** (R = OH) occurs on treatment with dichlorotriphenylphosphorane to give the chloroethyl derivative **205** (R = Cl) <2005JA15386>.



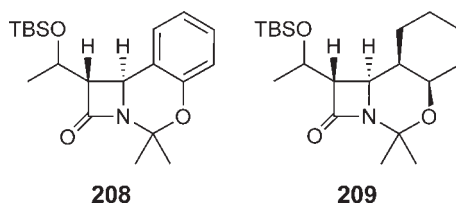


The Corey–Winter procedure was used to obtain the cyclic thiocarbonate **206** from the corresponding vicinal diol [<2000EJO939>](#).

Reactions of substituents on the six-membered ring of the tricyclic compound **207** include the formation of the azide **207** ($R=N_3$) in a one-pot two-step reaction of the alcohol **207** ($R=OH$) with carbon tetrabromide and triphenylphosphine, followed by sodium azide in DMF. After deprotection of the carboxylic acid, the azide was hydrogenated in the presence of palladium on calcium carbonate to give the corresponding primary amine [<1996BML2025>](#).



Reduction of **208** was eventually achieved using hydrogen in the presence of ruthenium(III) chloride as catalyst and Aliquat 336 to give a 65–70% yield of the required single isomer **209** [<1999EJO3067>](#).



2.04.7.3 Deprotection Reactions

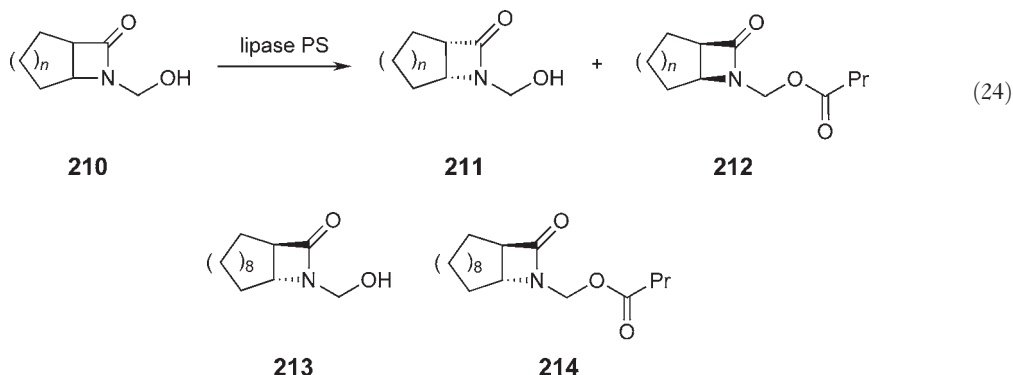
Protection and deprotection reactions were extensively reviewed in CHEC-II(1996) [<1996CHEC-II\(1B\)659>](#) and a reference was given to a book where the topic is discussed. Little has changed since then. The allyl esters appear to be the preferred way to protect carboxylic acid functions, perhaps especially when syntheses of tricyclic systems are intended. Deprotection may be brought about by the action palladium(0) tetrakis(triphenylphosphine) and 5,5-dimethyl-1,3-cyclohexanedione or potassium 2-ethylhexanoate which provides the potassium salt of the acid [<1996BML491, 1996BML1683, 1996BML2019, 2000CJC772, 2000T5649>](#). Sodium *p*-toluenesulfonate has been suggested to be advantageous for the removal of the allyl ester group [<2003JA15746>](#). Sometimes benzyl esters are used and less commonly fluorenyl groups. One advantage of using these groups in the same molecule is that both can be removed by catalytic hydrogenation [<1995BML2535, 1997BML1857, 2000T5649>](#). A nucleophilic nitrogen atom is often protected by use of butyl-, allyl-, or benzyloxycarbonyl groups [<1995TL8693, 1996BML1683, 2000T5649>](#) which are removed in acidic media. Removal of silyl groups from protected alcohols is usually achieved by use of tetrabutylammonium fluoride or the bromide plus potassium fluoride [<1996BML1683, 1997BML1857>](#).

2.04.8 Reactivity of Substituents Attached to Ring Heteroatoms

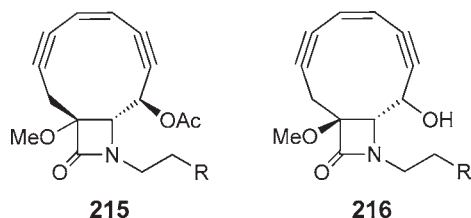
This subject was covered previously in CHEC(1984) (Chapter 6.02) and a dedicated section in CHEC-II(1996) (vol. 1B, Section 1.21.8). The present discussion is an extension from 1995.

2.04.8.1 At Nitrogen

Rarely is the substituent on nitrogen modified but there are occasional examples. The racemic bicyclic β -lactams having medium to large rings have been resolved using enzymes. Lipase PS in the presence of vinyl butanoate converted (48%) racemic *cis*- β -lactams **210** ($n = 3$) in dry acetone into resolved *cis*-alcohol **211** ($n = 3$) and the *cis*-ester **212** ($n = 3$) with ee 97% (Equation 24). A better result was obtained for racemic *cis* β -lactam **210** ($n = 5$ and 8) when vinyl butanoate, was replaced by 2,2,2-trifluoroethyl butanoate, but the ee for **212** ($n = 5$) was 82% and the ee value for **212** ($n = 8$) could not be determined. A similar reaction with racemic *trans*- β -lactam ($n = 8$) required the use of CAL-B (a lipase from *C. antarctica*) and vinyl butanoate, and the ee value for the *trans*-alcohol **213** was 85% but the value for the ester **214** could not be determined <2003TA3805>.



The *N*-substituent in **215** was subjected to a number of chemical changes while the enediyne system remained intact. This showed the stability of the unsaturated ring when *trans*-fused to the β -lactam. The protected alcohol **215** (R = TBDMSO) was converted to the alcohol by hydrofluoric acid in aqueous acetonitrile in 96% yield and the alcohol **215** (R = OH) was converted into the azide **215** (R = N₃) via the methanesulfonyl ester **215** (R = OMs). Changing the azide to the primary amine proved to be a challenge and was eventually accomplished by allowing the azide to react with triphenylphosphine and water followed by protection of the amine to give **215** (R = NHBOC). The ester group was then hydrolyzed to give the alcohol **216** (R = NHBOC) and the amine protecting group removed with TFA to give **216** (R = N⁺H₃) <2002EJO3745>.

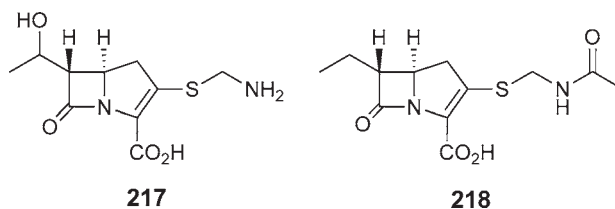


2.04.9 Synthesis of Fused Systems Containing a Four-Membered Ring

Synthetic routes to bicyclic fused systems are discussed in this section. Tricyclic and polycyclic compounds are considered in Section 2.04.11. Synthetic approaches up to 1995 were covered in CHEC(1984) and CHEC-II(1996). Approaches to the synthesis of bicyclic β -lactams have been reviewed <1993MI637, 1995MI330, 1996YKG761, 1997MI281, 1999MI335, 2003YKG1065, 2004H(64)577, 2004RMC69, 2004RMC93, 2004CME1921, 2006RMC109>.

2.04.9.1 From Acyclic Compounds

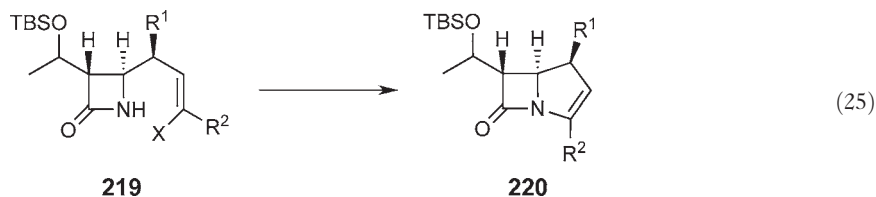
A formal total synthesis of the early carbapenem antibiotics thienamycin **217** and PS-5 **218** from an acyclic amino acid derivative has been reported <1996JOC2413>. For a cycloaddition process from acyclic compounds, see Section 2.04.9.7.



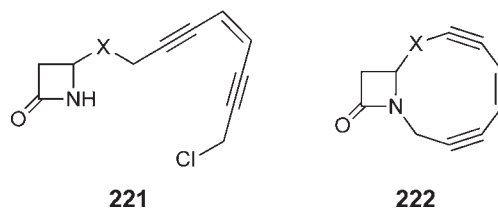
2.04.9.2 Closure to N-1 of the Four-Membered Ring

A number of examples of this type of approach to fused-ring azetidines and azetidinones were given in CHEC-II(1996) (Section 1.21.9.2).

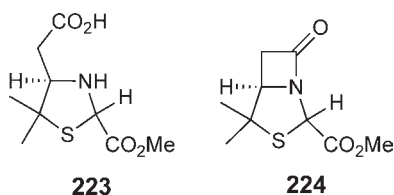
Treatment of the vinyl bromides **219** ($X = \text{Br}$, $R^1 = \text{H}$, $R^2 = \text{CH}_2\text{OTBS}$) with palladium complexes gave products **220** ($R^1 = \text{H}$, $R^2 = \text{CH}_2\text{OTBS}$) but the yields ranged from a trace to 96% depending on the complex employed to bring about the C–N bond-forming process. In this case, palladium(II) acetate in the presence of DPEphos and cesium carbonate was the most active system (Equation 25). However, when the vinyl bromide carried an ethoxycarbonyl group **219** ($X = \text{Br}$, $R^1 = \text{H}$, $R^2 = \text{CO}_2\text{Et}$), the same conditions afforded no product. When the vinyl bromide carrying a β -methyl substituent and an ethoxycarbonyl group was used (**219**: $X = \text{Br}$, $R^1 = \beta\text{-Me}$, $R^2 = \text{CO}_2\text{Et}$), the cyclized product was obtained in 59% yield. It was expected that the iodide **219** ($X = \text{I}$, $R^1 = \beta\text{-Me}$, $R^2 = \text{CO}_2\text{Et}$) would give a better yield than the corresponding bromide but only a 20% yield of product was obtained. Next, the vinyl halide was added to the palladium compound in toluene and briefly heated together until the catalyst had dissolved, and only then was the base added at 0 °C before the mixture was heated to promote reaction. This process gave the products in high yields of 90% and 74% from the iodide and bromide, respectively <2003JOC3064>.



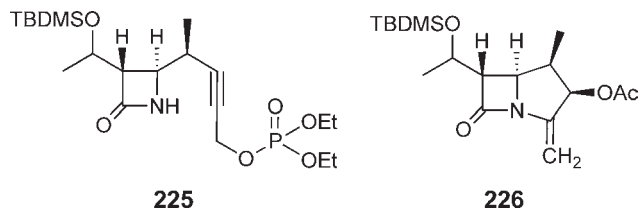
Cyclization of the enediynes **221** ($X = \text{O}$ and CH_2) in DMF were brought about by potassium carbonate and potassium iodide. The thermal stability of the cyclized products **222** ($X = \text{O}$ and CH_2) was evident and the occurrence of a radical intramolecular cyclization process at higher temperatures was shown <1996CC749>.



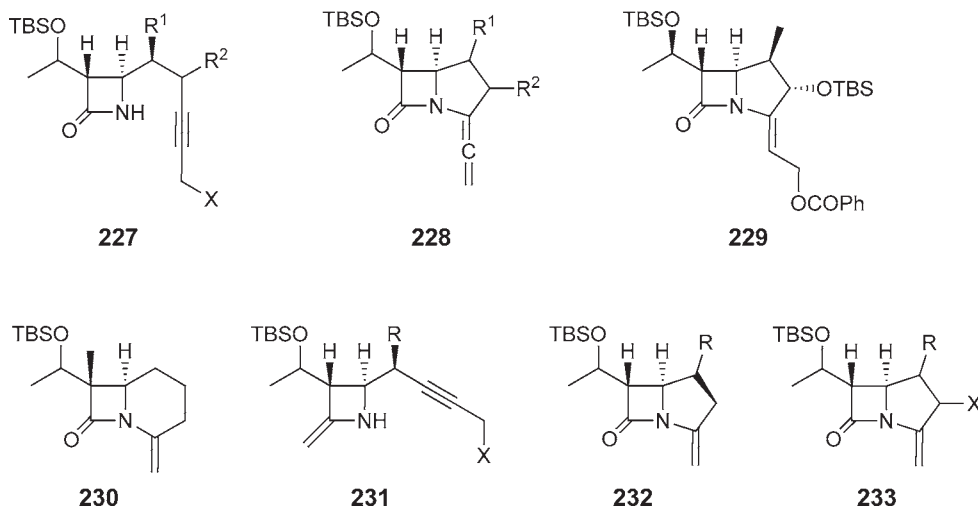
Cyclization of thiazolidinylacetic acids **223** in the presence of bis(2-pyridyl)disulfide and triphenylphosphine yielded isopenams **224**. One isopenam was selectively epimerized to an *exo*-configured precursor of isopenicillin G <1999EJO2433>.



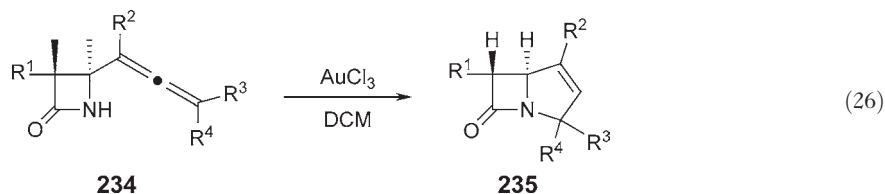
When the propargyl phosphate **225** was heated in the presence of $\text{Pd}_2(\text{DBA})_3 \cdot \text{CHCl}_3$ and sodium acetate in THF, the central sp carbon atom of the σ -allenylpalladium complex, formed from the propargyl alcohol ester and Pd(0), was attacked by the lactam nitrogen atom to yield the carbapenam **226** with an exocyclic methylene group <2001TL4869>.



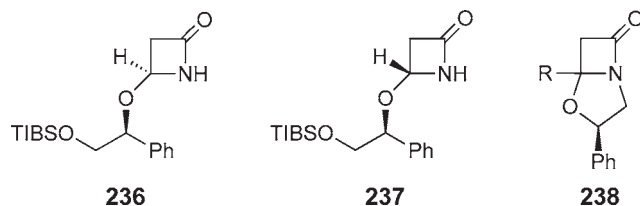
Similar work using the palladium complex was later reported but using β -lactams with an extra methylene group in the 4-substituent and a wider group of esters including carbonate, benzoate, and *p*-methoxybenzoate. Compounds of type **227** ($\text{R}^1 = \text{R}^2 = \text{H}$; $\text{X} = \text{OCOMe}$, OCOPh , $\text{OCOC}_6\text{H}_4\text{OMe-4}$) gave the allene **228** ($\text{R}^1 = \text{R}^2 = \text{H}$) but in low yields (6–57%) in the presence of cesium carbonate and tris(*o*-tolyl)phosphine in toluene. When a methyl group and a protected secondary alcohol group were present and the benzoyl ester was used **227** ($\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{OTBS}$; $\text{X} = \text{OCOPh}$), the allene **228** ($\text{R}^1 = \text{Me}$; $\text{R}^2 = \alpha\text{-OTBS}$) was obtained in 55% yield together with the ester **229**. When a monodentate ligand, such as tris(cyclohexyl)phosphine was used with **227** ($\text{R}^1 = \text{R}^2 = \text{H}$; $\text{X} = \text{OCOPh}$) the allenes **228** were obtained but, if a bidentate ligand was used, the product was a carbacephem **230** but in variable and generally low yield. A higher yield of the carbacephem was obtained with a shorter reaction time. The palladium complex catalyzed reaction of **231** ($\text{R} = \text{H}$, $\text{X} = \text{OCOPh}$) in the presence of a bidentate ligand, and sodium benzoate in THF gave two products **232** and **233** ($\text{R} = \text{OCOPh}$) in yields of 23% and 32%, respectively. When the methyl-substituted alkyne **231** ($\text{R} = \text{Me}$, $\text{X} = \text{OP}(\text{O})(\text{OEt})_2$) was used under the same conditions but with a short reaction time of 5 h, the major product **233** ($\text{R} = \beta\text{-Me}$, $\text{X} = \text{OCOPh}$) was obtained in 71% yield. It is clear that a range of reaction conditions play a part in determining the outcome of these reactions <2003JOC8068>.



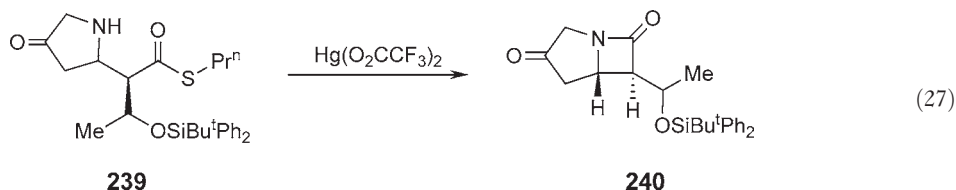
The use of gold catalysts is becoming more important in preparative organic chemistry and several examples have been provided where 4-allene-substituted β -lactams **234** are cyclized in a short time and in high yield in the presence of gold(III) chloride to the carbapenam **235** ($\text{R}^3, \text{R}^4 = \text{H}$ or $\text{R}^3, \text{R}^4 \neq \text{H}$) Equation (26) <2005AGE1840>.



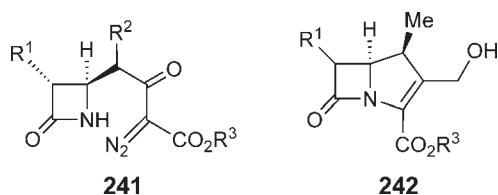
Intramolecular N-alkylation under phase-transfer conditions (PTCs) of **236** and **237** having the triisopropylbenzenesulfonyl (TIBS) protecting groups give the corresponding clavams **238** where R = α -H and β -H, respectively <2004BMC405>.



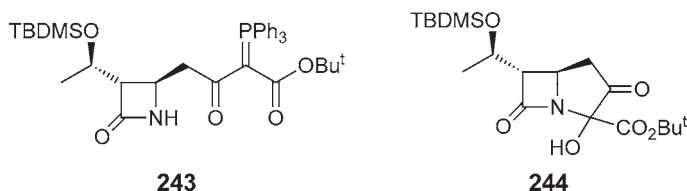
Mercury(II) trifluoroacetate causes cyclization of the thioester **239** to give the carbapenem **240** in 79% yield (Equation 27) <1999AGE1116>.



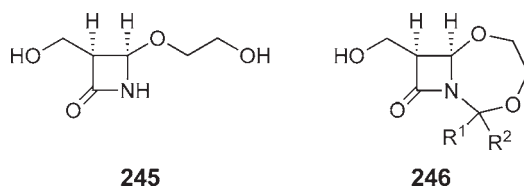
In CHEC-II(1996), carbene insertion reactions into the N-H bond to form a fused-ring azetidinone warranted a separate section. In the last decade, the popularity to this approach to bicyclic systems seems to have markedly declined. Nevertheless, dirhodium tetraacetate and rhodium octanoate were used to generate the corresponding bicyclic compounds from the diazo compounds **241** (R² = H and β -Me), respectively, via the carbene intermediates. In the latter case, the produced enol was esterified and then the ester group replaced with a hydroxymethyl substituent to give derivatives **242** in a one-pot process <2001JCM166, 1999TL427>.



Ozonolysis of the stabilized ylide **243** gave **244**, presumably via the 2,3-dioxoester <2000T5621>.

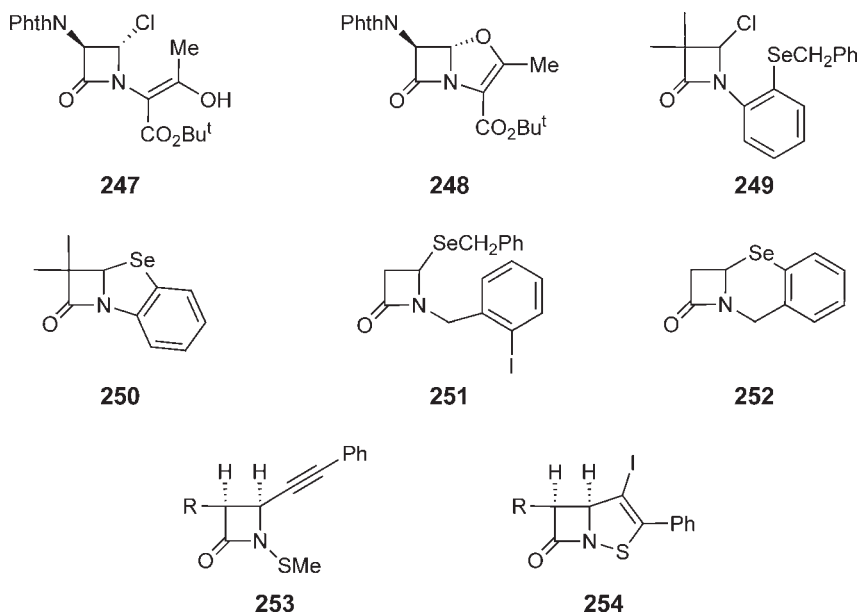


Alcohols of the type **245** undergo reactions with ketones (R¹COR²) or aldehydes (ArCHO) to give **245** and **246** (R¹ = H; R² = Ar), respectively <1997T14153>.

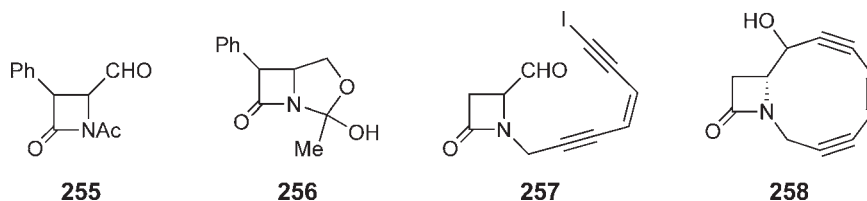


2.04.9.3 From a 1,4-Disubstituted Four-Membered Ring

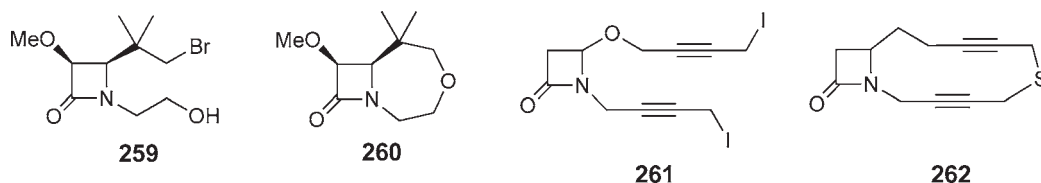
The 4-substituent may be an atom or group which activates the 4-position to nucleophilic attack. The chloro derivative **247** undergoes a cyclization reaction in the presence of triethylamine to give **248**, though only in 36% yield <1996T10205>. On further activation of the chloro compound **249** by reaction with sodium iodide in dry acetone, spontaneous cyclization occurred with elimination of the benzyl group to yield **250**. A similar cyclization process occurred when the *N*-(2-iodobenzyl) derivative **251** was used to afford **252** <2004OBC2612>. Addition of iodine to the alkyne **253** gave concomitant ring closure to provide **254** (R = PhthN or MeO) <2000T5571>.



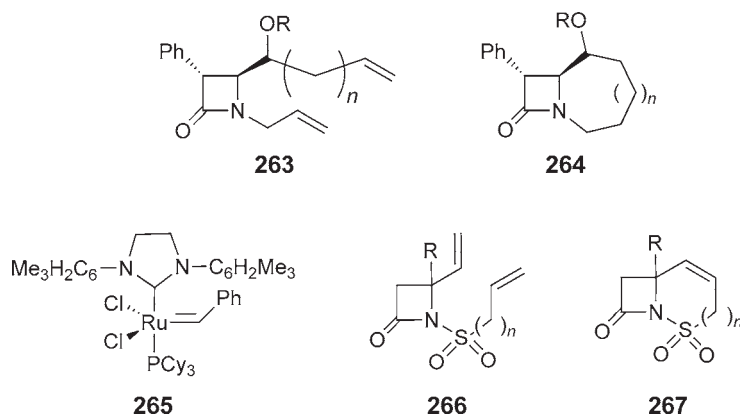
The two substituents on the four-membered ring may be short carbon chains; selective reduction of the aldehydes **255** with sodium borohydride produced the cyclic hemiketalamine **256** <1995TL7771>. One chain may be longer. For instance, the aldehyde **257** was cyclized by a mixture of chromium(II) chloride and nickel(II) chloride in THF to the racemic alcohol **258** <1998EJO1543>.



The two substituents on the β -lactam can be longer and either saturated or unsaturated alkyl groups. The bromo alcohol **259** undergoes cyclization in the presence of base (triethylamine was found to give the best result) to yield the cyclic ether **260** <2005PAC2061>. The unsaturated diiodide **261** yields **262** upon reaction with sodium sulfide <1995TL7913>.

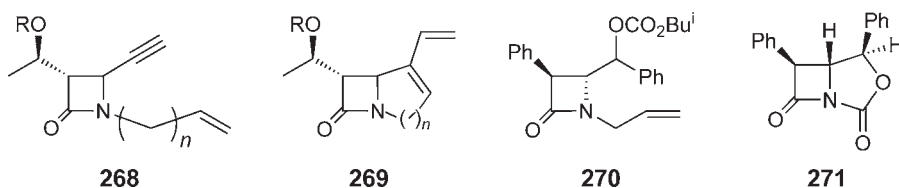


Perhaps one of the most significant changes in the approach to fused azetidines has been the realization that the metathesis catalysts developed by Grubbs and Schrock are of great potential value. The RCM route to carbapenams has been reviewed [\[2003YGK1065\]](#). The potential of this method is being vigorously and extensively exploited. The Grubbs' carbene catalyst, $\text{Cl}_2(\text{Cy}_3\text{P})_2\text{Ru}:\text{CHPh}$, caused RCM of **263** to give **264** ($n=0-2$) in 50–88% yield. Two olefinic carbon atoms are eliminated as ethylene in the course of the RCM process [\[2004H\(63\)2495\]](#). Similar RCM reactions of 1,4-dialkenylazetidinones having terminal alkene groups are brought about by the same catalyst in uniformly high yields [\[2000JOC3716\]](#). A second generation of Grubbs' catalyst **265** is available and is even more active. This catalyst will accept the presence of a heteroatom in the alkenyl substituent. For instance, the sulfonamides **266** ($n=1-3$) undergo RCM in high yields to afford the cyclic sultams **267** [\[2004S1696\]](#). Interestingly, compound **266** ($n=0$) does not undergo cyclization [\[2004TL3589\]](#). 1,4-Disubstituted azetidinones with *N*-allyl substituents or 4-allyl groups have been cyclized using the Schrock molybdenum carbene $[(\text{CF}_3)_2\text{MeCO}]_2\text{Mo}:(\text{CHCMe}_2\text{Ph})(\text{NC}_6\text{H}_3-2,6-\text{Pr}_2^i)$ [\[1996CC2231, 1998JOC7893\]](#).



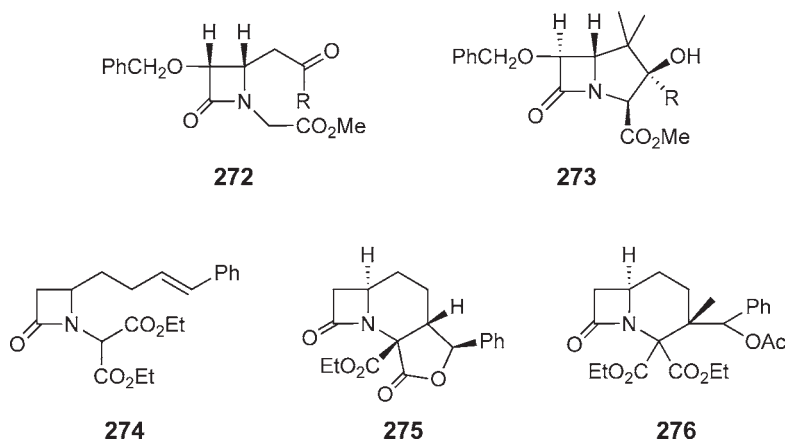
Azetidinones having a 4-ethyne substituent **268** ($n=1$ or 2) undergo cyclization to give a 1,3-diene system **269** ($n=1$ or 2) but the fused five-membered ring compound is formed in poor yield (29%). These dienes undergo cycloaddition reactions with dienophiles to give tri- or tetracyclic fused ring systems (see [Section 2.04.11](#)) [\[2001TL2461, 2004S2665\]](#).

An unexpected reaction occurred when the carbonate **270** was treated with Grubbs' catalyst and the product was **271**, presumably formed by initial *N*-dealkylation [\[2002TA2619\]](#).



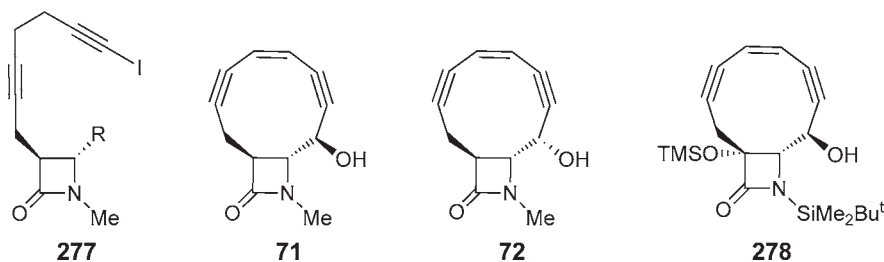
Intramolecular aldol condensation reaction of **272**, brought about by the action of lithium hexamethyldisilazene on the acidic methylene group, produced the carbapenam **273** where *cis-trans*-isomerization of the β -lactam component has occurred [\[1996JOC7125\]](#).

Oxidation of the malonic acid diester **274** with manganese(III) triacetate afforded both **275** and **276** but only in 35% overall yield [\[1995JOC6176\]](#).

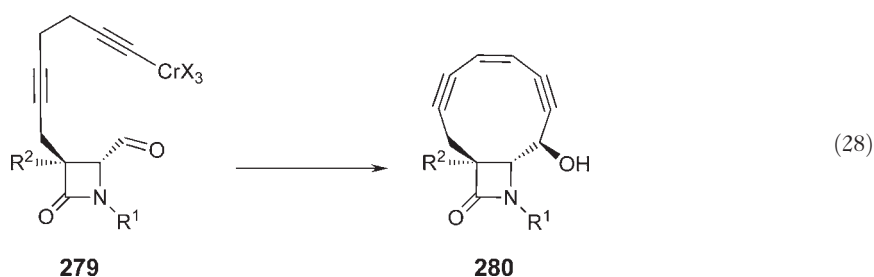


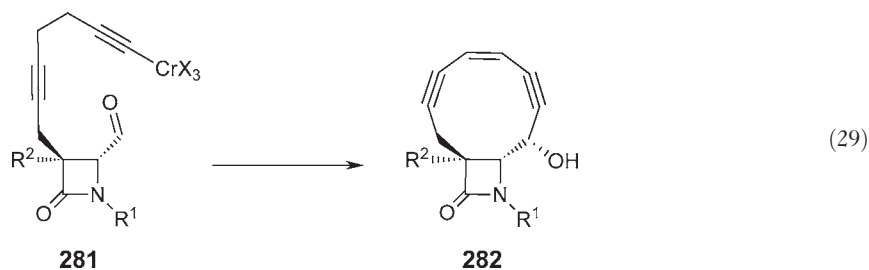
2.04.9.4 From a 3,4-Disubstituted Four-Membered Ring

Banfi and Guanti have used Swern oxidation of the alcohol **277** ($R = \text{CH}_2\text{OH}$) to the aldehyde **277** ($R = \text{CHO}$) as a step on the way to the bicyclics **71** and **72**. Ring closure was obtained by the intramolecular version of the Nozaki–Hiyama–Kishi coupling using a mixture of chromium(II) chloride and nickel(II) chloride as reagent which gave **71** and **72** in good yield and in a ratio of 55:45. Success in the coupling reaction depended upon the aldehyde being freshly chromatographed through silica gel and azeotropically dried immediately prior to use. The two bicyclic isomers were easily separated by silica gel chromatography and no evidence was found of epimerization at the ring junction [<1995AGE2393, 1997T3249>](#). The same general approach to the cyclization of the enediyne chain on to the β -lactam has been successfully applied in the preparation of more highly substituted and more usefully protected bicyclic enediynes **278** [<2002EJO3745, 2002TL7427>](#).

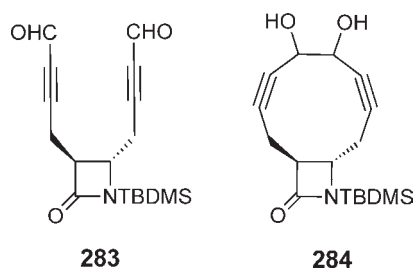


It is interesting to note that only one isomer of the bicyclic product was detected in the last case. A likely explanation is that the stereoselectivity in the cyclization step is controlled by the steric size of the substituents. Cyclization on to the 'outside' carbonyl group in **279** favors formation of **280** and the cyclization with the 'inside' carbonyl group of **281** yields **282** (Equations 28 and 29). The bulky N-protecting group on the aldehyde precursor of **278** favors the formation of the 'outside' configuration of the carbonyl group. However, the evidence adduced supports the view that the steric size of R^2 in **279** is much more important than R^1 in determining the configuration of the aldehyde [<1997T3249, 2002TL7427>](#).

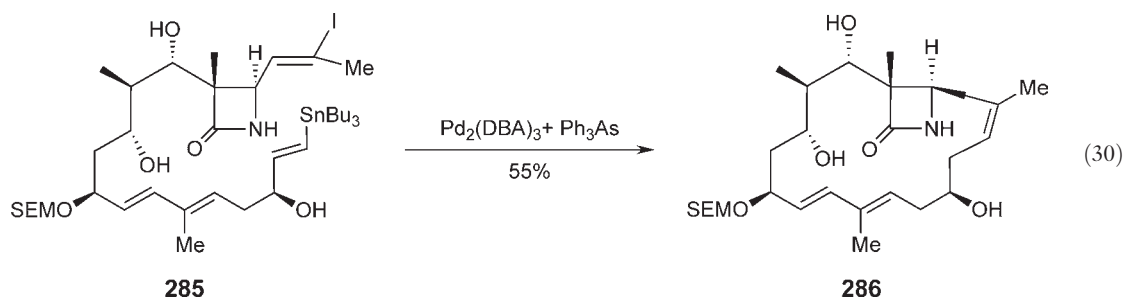




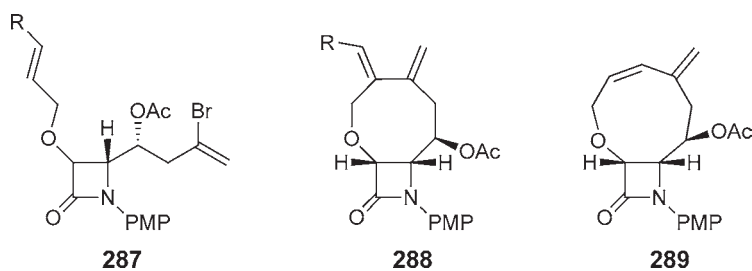
The same group of workers has developed a method for the closure of the 3,4-bis(but-2-ynal)azetidinone **283** using Pedersen vanadium(II)-mediated pinacol coupling to give the *vic*-diol **284** from which it was possible to get the bicyclic enediyne in two steps and 63% overall yield from the diol <2000EJO939> (see Section 2.04.7.2).



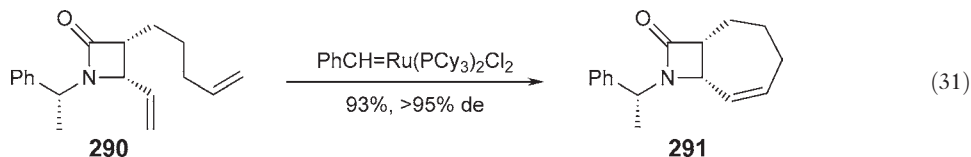
Another example of the exploitation of the effectiveness of inorganic or organometallic reagents is in bringing about ring closure of **285** to **286** through a coupling reaction. The intramolecular Stille reaction requires the use of bis(dibenzylidene)acetone palladium, Pd₂(DBA)₃, and triphenylarsine (Equation 30) <2001TL1251>.



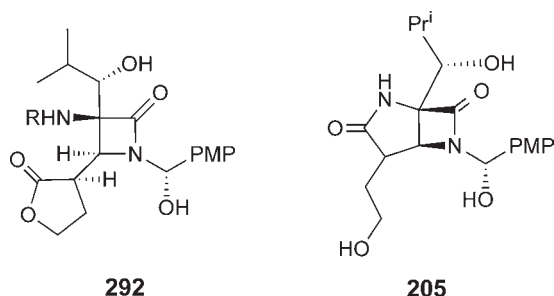
Stereocontrolled access to bicyclic β -lactams has been achieved by application of the Heck reaction to bromoalkenes. Cyclization of the 3,4-disubstituted azetidinone **287** (R = H) was achieved using palladium(II) acetate, triphenylphosphine, and potassium carbonate in DMF but two products **288** (R = H) and **289** were obtained in 21% and 27% yield, respectively. When the allyloxy group had a methoxycarbonyl substituent in **287** (R = CO₂Me) only one product **288** (R = CO₂Me) was produced in 47% yield <2005JOC2713>.



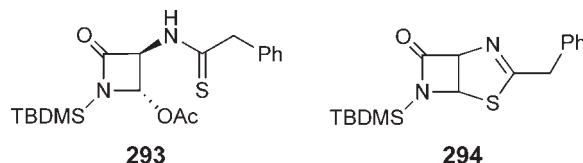
RCM reactions have been little used with 3,4-disubstituted azetidines or azetidinones, in contrast to their enthusiastic use with the corresponding 1,4-disubstituted compounds (see Section 2.04.9.3). However, the 3,4-disubstituted β -lactam **290** has been converted to the bicyclic β -lactam **291** in 93% yield with >95% de by the action of the ruthenium carbene (Equation 31) <2003T3253>.



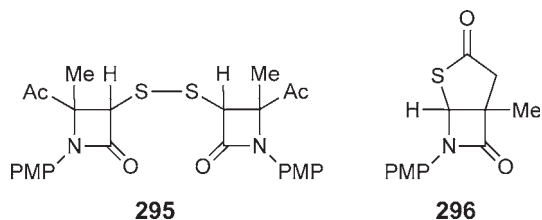
The primary amine in derivative **292** (R=H) reacts with the lactone function in the presence of triethylamine trihydrofluoride in THF to give the bicyclic **205** in 86% overall yield from the protected amine **292** (R=BOC) <2005JA15386>.



In the presence of triethylamine, the sulfur atom in **293** displaces the acetoxy function to afford the bicyclic **294** in 98% yield <2000S289>.



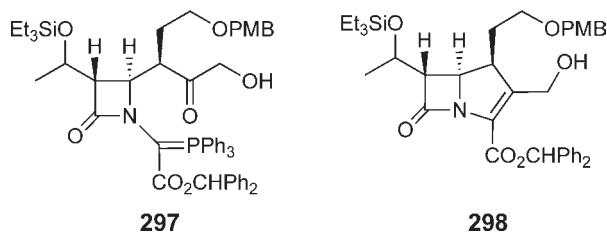
When a mixture of stereoisomers of the disulfide **295** was kept at room temperature under argon at pH 9, the bicyclic azetidinone **296** was obtained in 76% yield <1999CCC190>.



2.04.9.5 By Wittig-Type Reaction

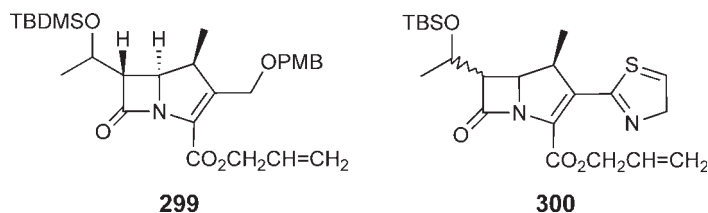
All the bicyclic β -lactams included in this section have a bridgehead nitrogen atom and are formed from 1,4-disubstituted azetidinones, so this section can be considered as an extension of Section 2.04.9.3. In addition, the Wittig reaction has been extensively employed in the preparation of tricyclic and tetracyclic β -lactams and its use is referred to in Section 2.04.11. The main use of the reaction to form bicyclic compounds has been to produce 2-substituted carbapen-2-ems.

Sometimes the phosphorane is isolated and the cyclization step is achieved by heating the compound in an inert solvent such as toluene. In this way carbapenems with useful 2-hydroxymethyl substituents (see Section 2.04.7.2) can be prepared. For example, the phosphorane **297** has been cyclized to compound **298** <1998H(48)2287>.

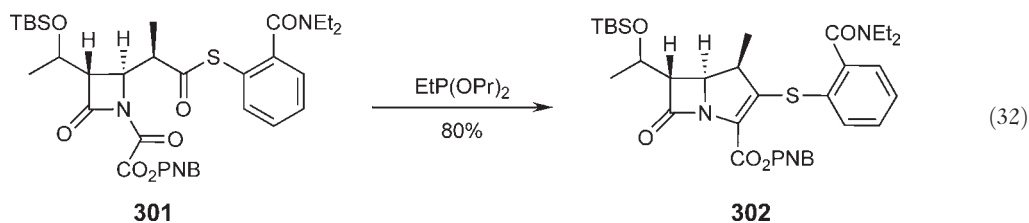


In a similar way, the 1 β -methylcarbapenem **299** was obtained in 95% yield from the corresponding phosphorane <1998JOC1719>.

In other cases, the phosphorane may have the carbonyl group activated by being directly bonded to a heterocycle having an electron-withdrawing nitrogen atom, as when a thiazol-2-yl group is bonded to the carbonyl function. In such an example, the fused ring of the bicyclic β -lactam is directly bonded to the appended group as shown in compound **300** <1998BKC1294, 1999BML2893>.



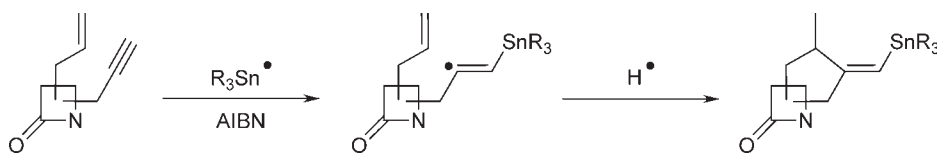
In many examples, it is not necessary to prepare the phosphorane. Instead, the dicarbonyl compound is heated with a trialkyl or triaryl ester of phosphorus acid or, less commonly, with a diester of a phosphonous acid (RP(OH)₂, where R is an organic group). For example, when the thioester **301** is heated with dipropyl ethylphosphonite the 2-substituted carbapenem **302** is produced in 80% yield (Equation 32) <1997CPB1439>. This general method has been used to prepare 2-sulfide-substituted 1 β -methylcarbapenems <2000CPB126, 2001SC587> and O-protected 2-hydroxymethyl derivatives <1999JA11261>.



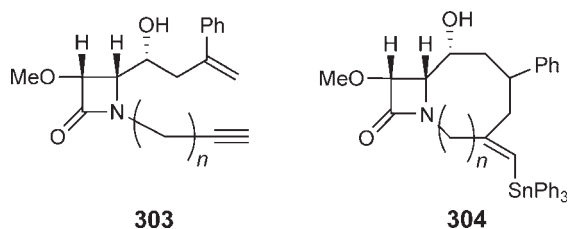
2.04.9.6 Radical Cyclization Processes

This route to bicyclic azetidines and azetidinones was discussed in detail in Section 1.21.9.6 of CHEC-II(1996) <1996CHEC-II(1B)659> and reviews were cited. In the past decade, Alcaide *et al.* have been particularly active in developing new and improved routes to bi-, tri-, and polycyclic fused azetidinones by these techniques. Two types of reagents are used widely to bring about radical formation leading to a cyclization reaction: (1) a chemical reagent such as a trisubstituted tin hydride in the presence of a radical initiator such as AIBN or (2) a source of energy such as light or a high temperature.

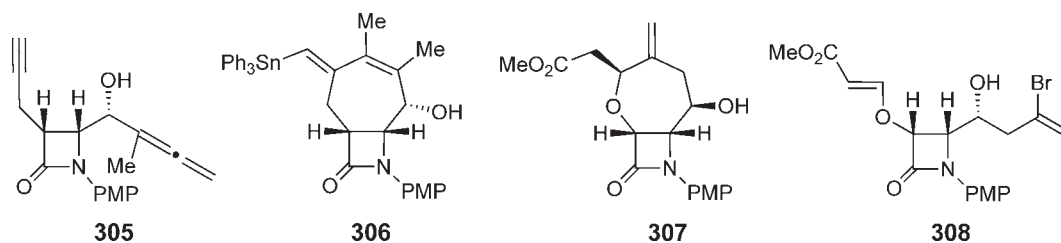
An azetidinone carrying vicinal alkene and alkyne groups, one of which may be an N-substituent, on the four-membered ring may be cyclized in the presence of a trisubstituted tin hydride at elevated temperature (Scheme 9) <1999JOC5377, 2003JOC3106>. In this way, the 1,4-disubstituted β -lactams **303** were converted into the fused bicyclics **304** in moderate yield.



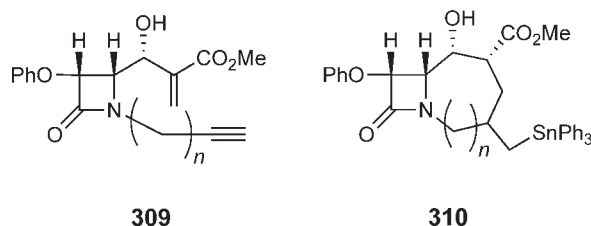
Scheme 9



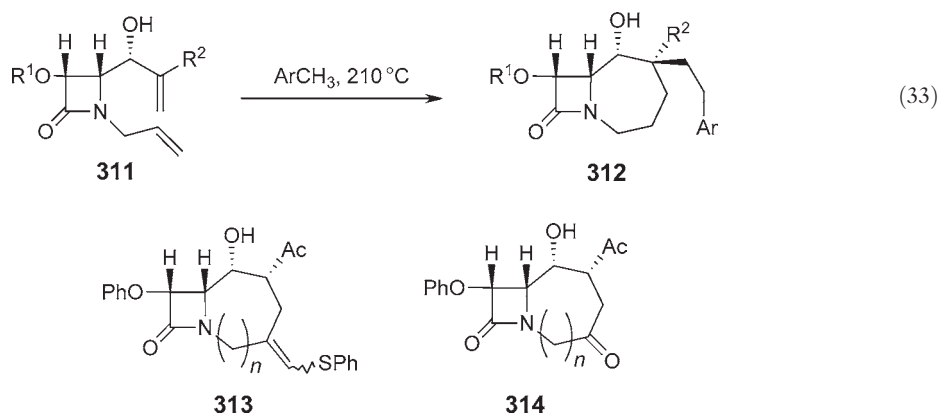
3,4-Disubstituted β -lactams react in a similar way to give fused bicyclics without the bridgehead nitrogen atom. It is possible to use an allene in place of an alkene, for example, **305**, and so obtain an unsaturated fused ring, for example, **306** [<2003OL3795>](#). If the olefinic chain in the starting material contains a bromine atom and is a homoallylic alcohol, treatment with triphenyltin hydride gives a fused ring with an exocyclic methylene group directly. In addition, if the other unsaturated substituent of the azetidinone contains a heteroatom, then the product of radical cyclization is a bicyclic system with the heteroatom in the fused ring, for example, **307** in 46% from **308** [<2005S2335>](#).



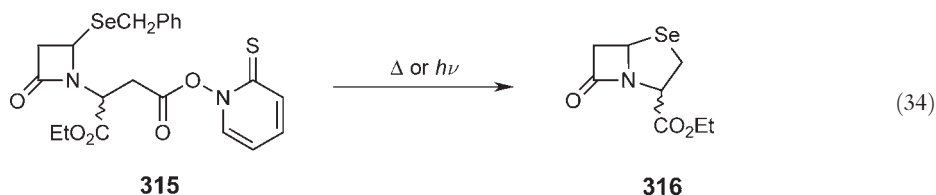
2-Azetidinones with a 4-allyl alcohol substituent, for example, **309**, which are readily available from β -lactam 4-aldehyde by the Baylis–Hillman reaction, are converted by triphenyltin hydride plus AIBN without racemization in good yield to fused ring systems, **310** ($n = 1-3$).



Remarkably, thermolysis of the Baylis–Hillman adducts **311** ($R^1 = \text{alkyl or aryl}$; $R^2 = \text{Ac, CN, CO}_2\text{Me}$) in toluene at 210°C in a sealed tube gave stereoselectively the cyclized product (+)-**312**, which included incorporation of the elements of the solvent and, when $R^2 = \text{Ac}$, a single isomer was obtained (Equation 33). The yields were moderate (37–56%) and when $R^2 = \text{CN}$ and CO_2Me some racemization occurred. Similar results were obtained when either *p*-xylene or mesitylene was used but no reaction occurred when chlorobenzene or anisole was used. Unsaturated rings are obtained in similar yields and stereoselectivity if the N-substituent is an alkyne. In addition, benzene thiol reacted in boiling benzene in the presence of AIBN to give **313**, which on ozonolysis yielded the cyclic ketones **314** ($n = 1-3$) in 52–70% yield [<2001JOC1612>](#).



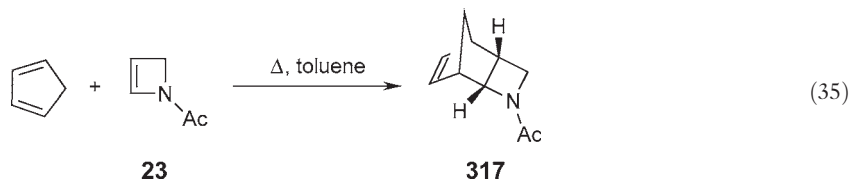
Thermolysis or photolysis of the benzyl selenide **315** gave the selenapenam **316** (Equation 34) <2004OBC2612>.



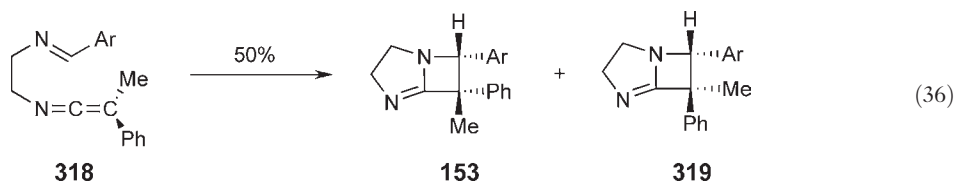
These methods for the synthesis of fused ring β -lactams have been extensively applied to the synthesis of tricyclic or polycyclic fused ring systems and Section 2.04.11 should be consulted for more details.

2.04.9.7 By Cycloaddition Reaction

The intermolecular [4+2] cycloaddition of cyclopentadiene and *N*-acetyl-2-azetine **23** occurs when they are heated in toluene in a sealed tube to give a good yield (83%) of the Diels–Alder adduct **317** (Equation 35). Similar high-yielding addition reactions occur with substituted cyclopentadienes and 1,3-diphenylisobenzofuran to give *endo*-adducts <1999TL443>.



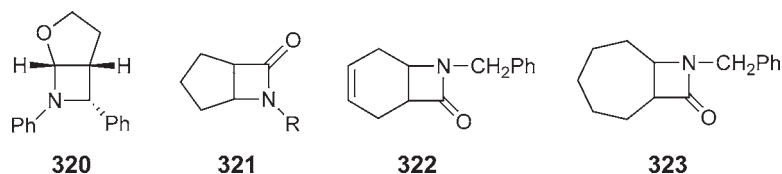
Bicyclic amidines were obtained when the keteneimine **318** was heated in toluene solution to produce a formal [2+2] cycloaddition between the imine group and the $\text{C}=\text{C}$ bond to give an approximately equal mixture of the diastereoisomeric azeto[1,2-*a*]imidazoles **153** and **319** in about 50% overall yield (Equation 36) (see Section 2.04.6.5) <2005T1531>.



The [2+2] cycloaddition of (*E*)-benzylideneanilines and 2,3-dihydrofurans to give 6,7-diaryl-2-oxa-7-azabicyclo[3.2.0]heptanes is promoted by pressure and elevated temperature. The reaction occurs with both regio- and

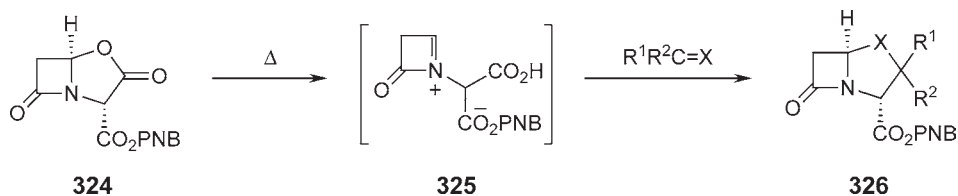
stereoselectivity and when (*E*)-PhCH=NPh is used, product **320** is obtained in 66% yield and with 87% stereoselectivity. A zwitterionic mechanism is favored by the authors <1997MI1253>.

The addition of CSI to cyclic alkenes has been used extensively to yield bicyclic azetidinones with an N-substituent that is readily removed. The addition of the isocyanate to cyclopentene yielded **321** (R=SO₂Cl), which yielded the unsubstituted compound **321** (R=H) on hydrolysis with aqueous sodium sulfite. Similarly, **322** and **323** were prepared among a range of other bicyclic azetidinones <2005BML1371>.



Dehydrohalogenation of substituted acetyl chlorides via tertiary organic bases and the stereoselective construction of an azetidinone ring from an imine (the Staudinger reaction) has played an important part in the development of azetidinone chemistry, which has been reviewed <1993MI637>. The use of bicarbonates in the presence of a crown ether at -10 °C has been suggested as an economical alternative to tertiary amines <2003SL1937>.

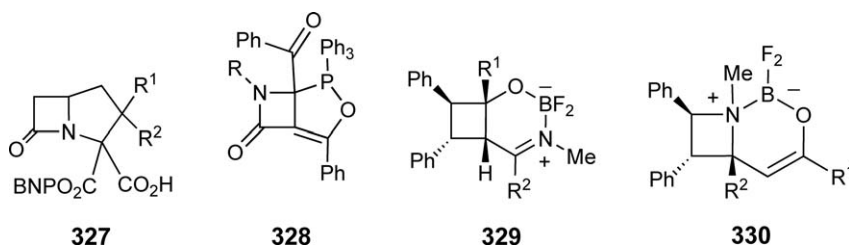
Thermolysis of lactones yielded reactive species either by loss of carbon dioxide or, in the case of the oxazolidone **324**, by ring opening to the azomethine ylide **325**. If the thermolysis of oxazolidone **324** is carried out in the presence of R¹R²C=X, a formal 1,3-dipolar cycloaddition occurs to give racemic oxapenams **326** (Scheme 10) in poor to moderate yield <1999CC249, 2001J(P1)1281>.



Scheme 10

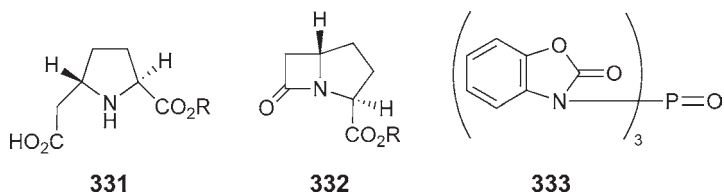
When an alkene is the dipolarophile it is thought that the intermediate **327** is formed and this then undergoes decarboxylation. The cycloaddition step is concerted, rate determining, and stereospecific. A detailed discussion of the investigations of the mechanism of the process is available <2001J(P1)1270>.

Cycloaddition reactions have been used to obtain bicyclic azetidinones and azetidines. Dibenzoylacetylene, an isocyanate, and triphenylphosphine react at room temperature to give a high yield (70–95%) of product **328** <2004S237>. Photocyclization of boron complexes of the type F₂B(OCR¹:CH:CR²:NMe) with arylalkenes gave low to good yields of **329** and **330** <2004HCA292>.

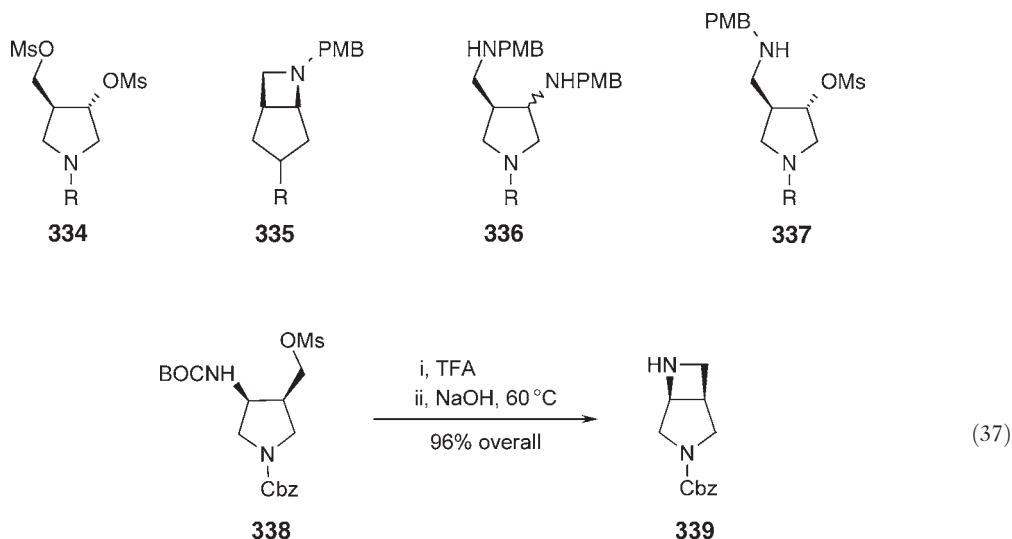


2.04.9.8 From a Five-, Six-, or Seven-Membered Ring

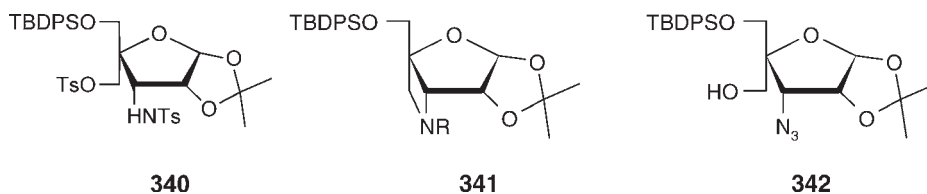
A range of reagents and conditions failed to cause the cyclization of the pyrrolidine β -amino acid **331** ($R = \text{CH}_2\text{Ph}$) to **332** ($R = \text{CH}_2\text{Ph}$) in satisfactory yield but a yield of up to 70% was achieved when the reaction was mediated by tris(1,3-dihydro-2-oxobenzoxazolin-3-yl)phosphine oxide **333** and triethylamine. The same conditions caused the cyclization of **331** ($R = \text{Me}$) to **332** ($R = \text{Me}$) but in only 45% yield <2003TL973>.



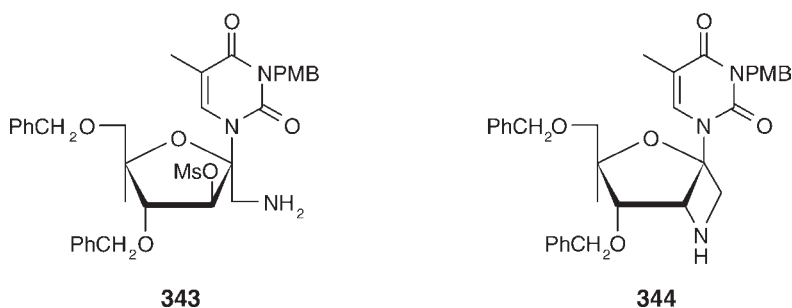
Attempts to achieve reaction of the trisubstituted pyrrolidine **334** with *p*-methoxybenzylamine to yield the bicycle **335** gave disappointing results largely due to the formation of the diaminopyrrolidine **336** rather than the required intermediate **337**. A successful cyclization reaction was eventually achieved when the starting material with the amine nitrogen atom bonded directly to the pyrrolidine nucleus was used and the protecting groups were changed. The trisubstituted pyrrolidine **338** was treated with TFA to remove the *t*-butoxycarbonyl group and then the amine salt was cyclized in the presence of base to give *N*-benzyloxycarbonyl bicyclic azetidine **339** in 96% yield from the salt (Equation 37) <2005PAC2041>.



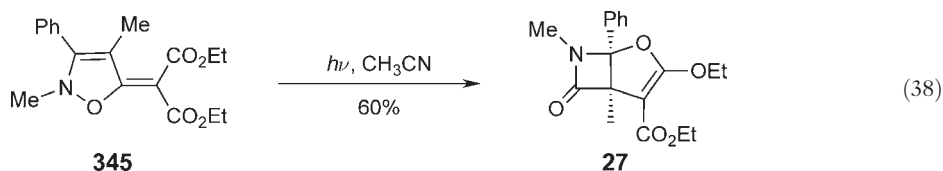
Cyclization of the furanose derivative **340** was mediated by the action of sodium hydride to afford **341** ($R = \text{Ts}$) in 90% yield. The amine **340** had been obtained from the azide **342** and it was later found that thermolysis of this 1,3-azido alcohol under Staudinger reaction conditions (triphenylphosphine in *o*-xylene) gave the azetidine **341** ($R = \text{H}$) directly in 99% yield <2003TL5267>.



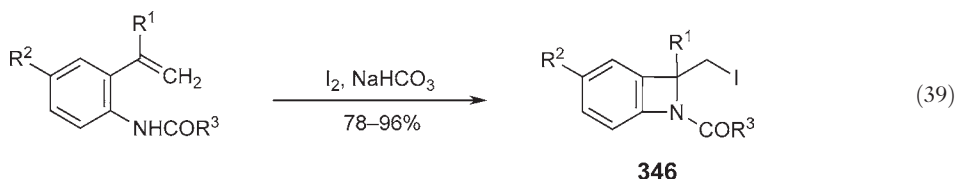
The 1-aminomethyl derivative of pyrimidine nucleoside **343** undergoes cyclization in the presence of a mixture of triethylamine and pyridine at 90 °C with concomitant demesylation to yield **344** but a variety of other bases and conditions failed to produce the required intramolecular nucleophilic attack <2006JOC299>.



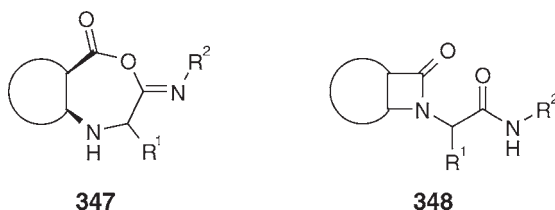
Photochemical rearrangement of the readily prepared isoxazolinone anhydrobase **345** yielded the novel bicyclic 4,5-dihydrofuroazetidinone system **27** (Equation 38). A mechanism for the rearrangement has been proposed <2003TL9247>.



Intramolecular iodoamination of *o*-(acylamino)styrene derivatives gives benzazetine derivatives **346** in high yield (Equation 39). This method is particularly attractive because of the ready availability of the starting materials <2005BCJ886>.



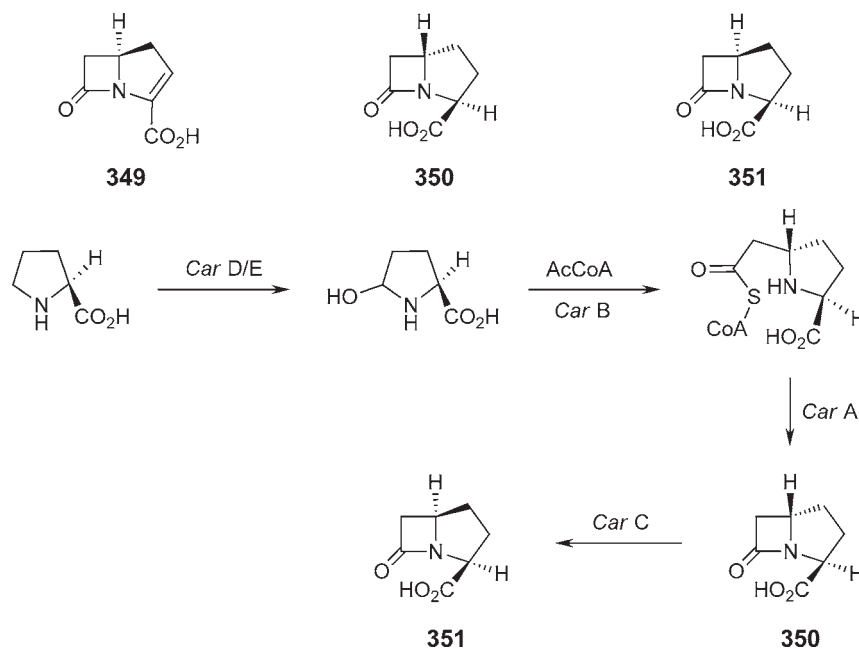
The traditional Ugi reaction is the condensation of a carboxylic acid, an amine, an aldehyde, and an isocyanide in a one-pot process to give α -amino acid derivatives. This four-component reaction is known as U-4CR. If two of the functional groups are on one component, the system becomes one of a four-center but three-component reaction (U-4C-3CR). When an alicyclic β -amino acid is used as one component together with the aldehyde ($R^1\text{CHO}$) and isocyanide ($R^2\text{NC}$), the reaction proceeds through formation of a bicyclic system containing a seven-membered ring **347**. The heterocycle then undergoes a ring contraction to give the bicyclic azetidinone **348**. In this way, 5 sets of 20 seven-membered combinatorial libraries have been prepared by U-4C-3CR reactions with *cis*-2-aminocyclopentane carboxylic acid and *cis*-4-aminocyclohexene 5-carboxylic acid <2003JHC951>.



2.04.9.9 Biosynthesis

Aspects of the natural occurrence, biosynthetic pathways, and preparation by biosynthesis of carbapenams, carbapenems, oxapenams, trinems, and related compounds have been reviewed <1997MI281, 1999MI335, 2004RMC69>. References to earlier reviews are given in CHEC-II(1996) <1996CHEC-II(1B)659>.

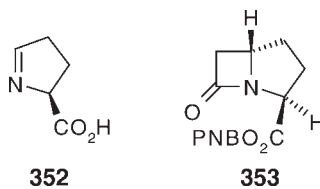
The genes encoding the acetate unit (or an equivalent) and L-glutamate in the biosynthesis of the acids **349–351** have been mapped, sequenced, and analyzed <1996MI145, 1997MI545>. Genes essential to the pathway have been designed *Car* A–E, and the products of these genes are suggested to mediate the sequence of steps shown in Scheme 11 <1998MI203, 2000JA9296>.



Scheme 11

Unfortunately, the absolute stereochemistry of the acid **350** was reversed in a 1998 review [\[1998MI203\]](#). The confusions in the literature about the signs of rotation and absolute configuration have been resolved [\[2003JA8486\]](#). Experimental evidence is available to support the view that *Car C* is an α -ketoglutarate-dependent, non-heme iron oxygenase that mediates the oxidative conversion of **350** and causes the stereo inversion giving **349**. In order to obtain more information about the inversion process, L-proline doubly labeled at C-5 with either tritium or deuterium was administered to *Serratia marcescens* and converted into **350** bearing one labeled atom per molecule at the bridgehead but **351** and **349** formed in the biosynthesis process had no labeled atoms. These results and others have led to the suggestion that L-proline is oxidized to pyrroline-5-carboxylic acid **352** prior to uptake into the biosynthetic pathway [\[2003JA8486\]](#). Evidence has been adduced that **351** is an intermediate in the biosynthetic pathway to **349** and that α -ketoglutarate is essential for *Car C* to carry out the oxidation [\[2003JA15746\]](#).

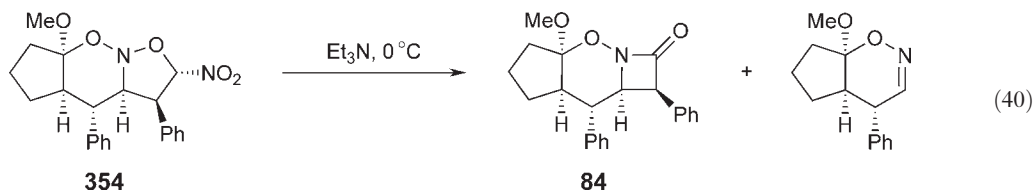
Enzymatic hydrolysis of the methyl ester of **350** with pig liver esterase on Eupergit gave the unstable **350** which was then esterified at pH 8 in a one-pot process with 4-nitrobenzyl bromide in the presence of a phase-transfer catalyst and dichloromethane to give **353** [\[2003TL973\]](#).



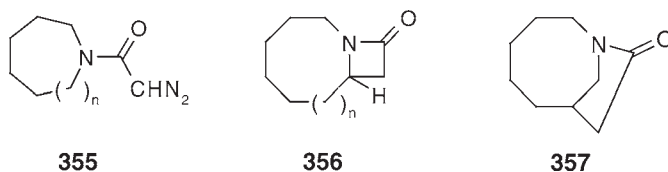
The use of biosynthetic methods to stereoselectively acylate *N*-hydroxymethyl substituents on some bicyclic β -lactams has been mentioned in [Section 2.04.8.1](#) [\[2003TA3805\]](#).

2.04.9.10 Miscellaneous

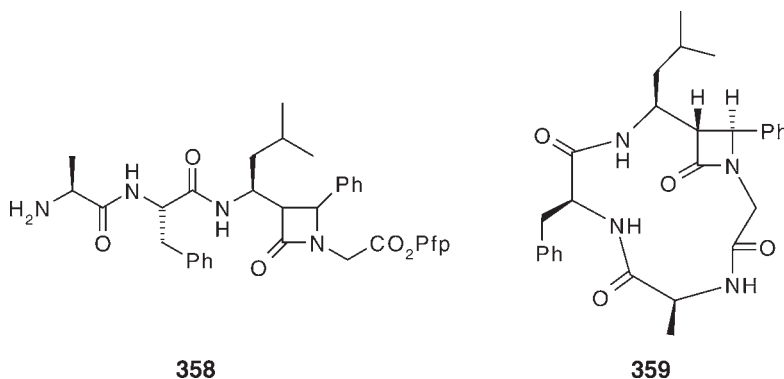
The isomerization of **84** in the presence of a base to provide β -lactams with a bridgehead nitrogen atom **85** and a major product where the nitrogen atom is not at a bridgehead (**86**) has been mentioned (see [Section 2.04.6.2](#)). The starting material for the isomerization was formed by treatment of a fused nitroisoxazolidine **354** with triethylamine at 0°C ([Equation 40](#)) [\[2004EJO4397\]](#).



Carbene insertion into N–H bonds was an important route to fused β -lactams in the last decennial review (CHEC-II(1996) <1996CHEC-II(1B)659>), but no examples have been found for inclusion in this chapter. A carbene insertion into a C–H bond has been reported, however, and this was enantioselective when catalyzed by chiral dirhodium(II) carboxamides. For instance, the *N*-diazoacetylazacycloheptane **355** ($n=1$) gave the β -lactam **356** ($n=1$) in 68% yield and 92% ee. In contrast, the analogous azacyclooctane **355** ($n=2$) in the presence of the same chiral catalyst (dirhodium(II) tetrakis-[methyl 2-oxazolidinone-4(*S*)-carboxylate]) gave both the fused β -lactam **356** ($n=2$) and the 1,3-fused pyrrolidone **357** <1995SL1075>.

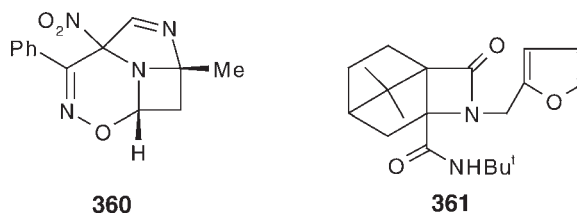


Cyclization of 1,4- and 3,4-disubstituted azetidiones are commonly used routes to β -lactams and have been discussed (Sections 2.04.9.3 and 2.04.9.4), but cyclization of 1,3-disubstituted azetidiones is very unusual and one example can be included here. The β -lactam **358**, carrying an N-terminal dipeptide chain, reacts with the pentafluorophenyl (Pfp) activated ester to give the cyclic peptide **359** containing a β -lactam moiety in 93% yield <2004EJO4379>.



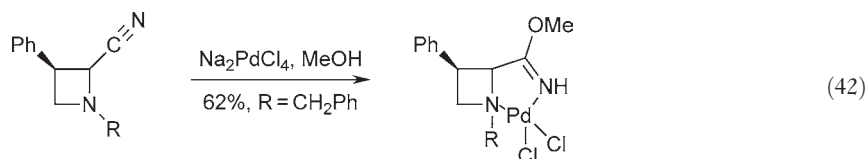
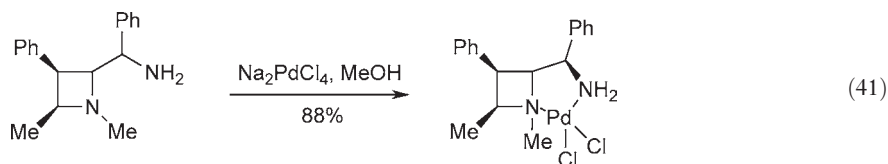
A remarkable fused tricyclic azetidine **360** is formed by reaction of benzonitrile oxide and 2-methyl-5-nitro-1-vinylimidazole but only in 3% yield <2005S2695>.

The use of the Ugi reaction to assemble libraries of fused ring β -lactams has already been mentioned (Section 2.04.9.8). The reaction of β -keto acids, amine, and isocyanide is accelerated in water by the presence of salts (e.g., lithium chloride) or glucose. In this way, even highly strained ring-fused β -lactams, such as **361** (63% yield), have been obtained. Surprisingly, in some of these reactions, a higher temperature (25 °C) gave a lower yield than was obtained at 4 °C <2004SL1425>.

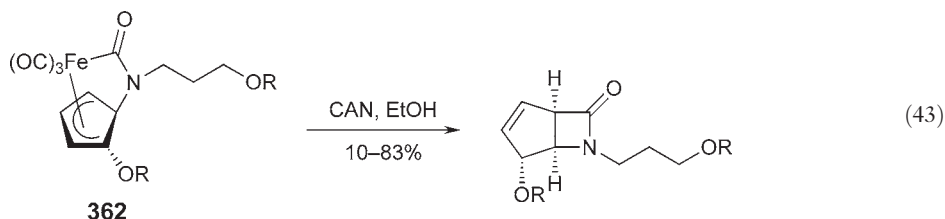


The synthesis of fused alicyclic β -lactams by the four-center three-component Ugi reaction (U-4C-3CR) on a solid support has been reported. Also, resins have been used as scavengers in the purification of fused β -lactams prepared in the solution phase <2004MI215>.

Some fused ring azetidines having a palladium atom in a five-membered ring have been prepared from 2-amino-methyl-1-methylazetidines (Equation 41) and cyano-1-substituted azetidines (Equation 42) <2005JOM2306>.



The bicyclic iron complex **362** on oxidative decomplexation with ceric ammonium nitrate (CAN) affords the *cis*-fused cyclopenteno- β -lactam (Equation 43) <1997HCA121>.



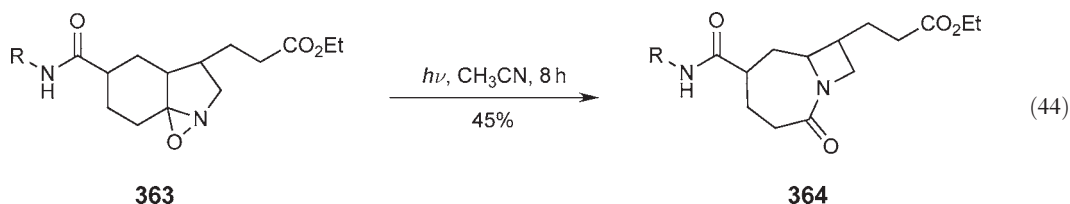
2.04.10 Ring Syntheses by Transformation of Another Ring

There are fewer examples of synthesis by this method as compared to CHEC-II(1996) <1996CHEC-II(1B)659>. Earlier volumes of CHEC(1984) and CHEC-II(1996) should be consulted for other examples.

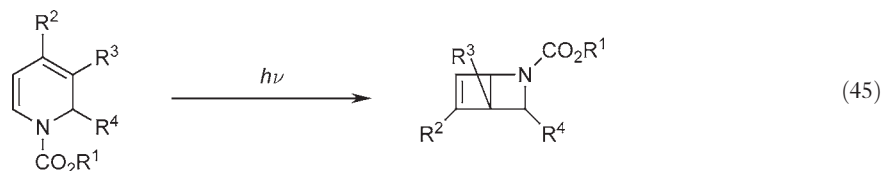
2.04.10.1 Ring Contraction Reactions

Synthesis of 2-azabicyclo[2.2.0]hex-5-enes and 2-azabicyclo[2.2.0]hexanes has been reviewed <2004H(64)577> as has the photochemical conversion of 2-pyridones to bicyclo[2.2.0]hexane lactams <B-1999MI(5)85>.

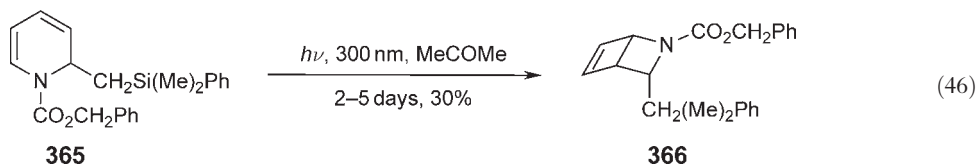
Photolysis is an important method for the synthesis of fused four-membered N-containing rings. Photochemical rearrangement of **363** in acetonitrile afforded the fused azetidine **364** in a reasonable yield (Equation 44). The substituents on the rings did not seem to have influenced the photorearrangement <2003BML1561>.



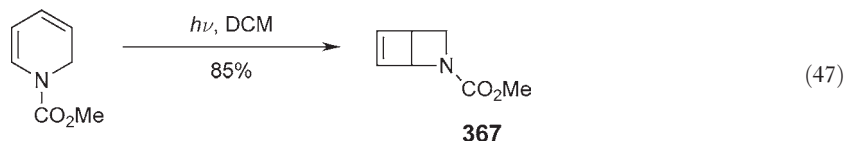
Ring contraction of 1,2-dihydropyridines is a useful route to 2-azabicyclo[2.2.0]hex-5-enes. Because of the difficulty of purifying 1,2-dihydropyridines, they are irradiated in a crude form to synthesize 2-azabicyclo[2.2.0]hex-5-enes in low to medium yields (Equation 45) <2001JOC1805, 2001JOC1811, 2005JOC590>.



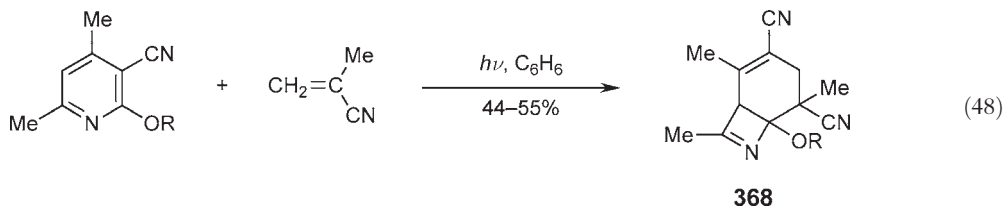
Irradiation of crude 1,2-dihydropyridine **365**, obtained by the reaction of pyridine and a Grignard reagent prepared from chloromethyldimethylphenylsilane, at 300 nm in acetone gave the substituted 2-azabicyclo[2.2.0]hex-5-ene **366** in 30% overall yield (Equation 46). The low yield in the photocyclization step could be due to the competitive aromatization and/or electrocyclic ring opening of the 1,2-dihydropyridine <2005JOC590>.



Another example of the photocyclization of 1,2-dihydropyridine is the synthesis of methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate **367** in 85% yield (Equation 47), which is a useful synthon for azetidines (see Section 2.04.6.5) <2003CPB96>.



Photocycloaddition of 2-alkoxy-3-cyanopyridines with methylacrylonitrile yields a bicyclic [2+2] cycloadduct intermediate followed by rearrangement to give **368** in 44–55% yield along with 3-acetyl-4-amino-1,5-dicyano-2,5-dimethylcyclohexa-1,3-diene (15–17%). Equimolar quantities of reagents have to be used for the formation of **368** (Equation 48) <1996CC1349>.



2.04.10.2 Ring Expansion Reactions

Since 1996 <1996CHEC-II(1B)659>, no examples of the synthesis of relevant compounds by expansion of rings were found.

2.04.11 Synthesis of Tricyclic and Polycyclic Azetidines, Azetines, and Azetes and a Critical Comparison of the Various Routes Available

This section is devoted to tricyclic and polycyclic fused azetines, azetidines, and azetidinones. Since the publication of CHEC-II(1996), there has been a marked increase in activity in this area and a wide variety of different types of compounds have been studied. Other examples of these compounds are mentioned in CHEC(1984) and CHEC-II(1996), and should be consulted in addition to this section.

The ring systems are categorized by the position of the four-membered ring nitrogen atom, the absence or presence of other heteroatoms, and the size of the fused rings starting from the four-membered ring followed by the number of

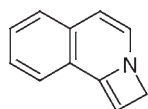
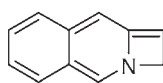
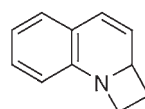
atoms in each subsequent ring in the order they occur in the molecule. A synthetic route which appears in several sections obviously has wide applicability in one sense though the method may, for instance, only provide access to one ring size.

Fused tricyclic β -lactams have been reviewed <1996BML1683, 1997MI86, B-1999MI347, B-2000MI(746)182, 2000MI15, 2000T5743, 2004H(64)577, 2004CME1921, 2004CME1837>. The syntheses of some fused azetidine tricyclic compounds have also been reviewed <1996MI1, 1999COR1, 2003AHC71>. The use of the Kinugasa reaction to obtain fused tricyclic β -lactams has been reviewed <2004AGE2198>.

2.04.11.1 Tricyclic Compounds Having a Bridgehead Nitrogen Atom

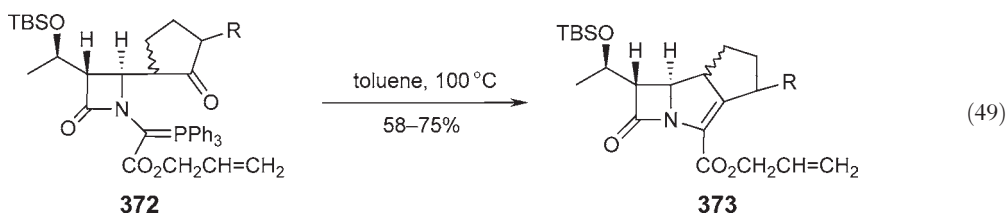
2.04.11.1.1 No additional heteroatoms

Synthesis of tricyclic compounds has attracted a great deal of interest in the last decade and there have been significant advances in the different synthetic routes to trinems (formerly known as tribactams). Reviews on the synthesis of fluorinated <B-2000MI(746)182>, piperidine-condensed <2004CME1837>, alkoxy and amino trinems <1997MI86>, and stereoselective synthesis of trinems <B-1999MI347> are available. Syntheses of azeto[2,1-*a*]isoquinolines **369** and azeto[2,1-*b*]isoquinolines **370** <1999COR1> and azeto[1,2-*a*]quinolines **371** <2003AHC71> have been reviewed. Novel methodologies for the synthesis of tricyclic β -lactams have been surveyed <2004RMC69>.

**369****370****371**

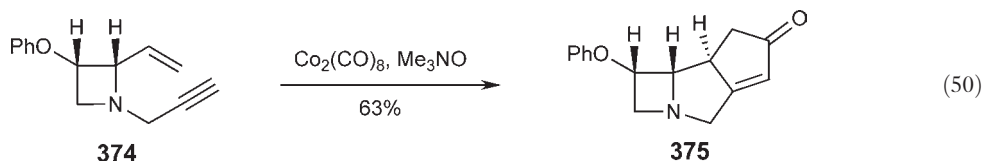
2.04.11.1.1(i) 4/5/5 Ring system

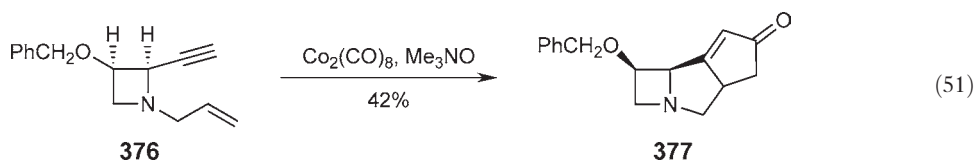
Application of the Wittig route through thermolysis of phosphorane **372** yields the trinem analogue **373** in low to moderate yield (Equation 49) <1996BML525>.



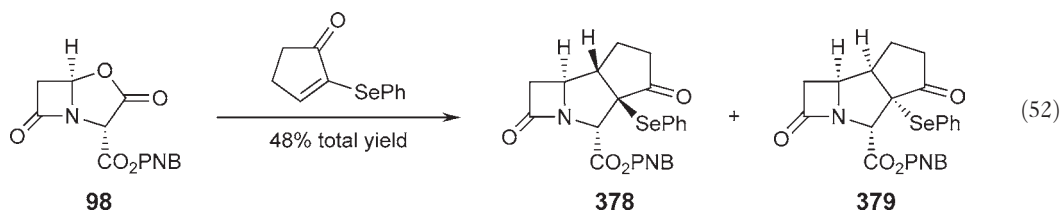
The 1-propargyl-4-vinylazetidine derivative **374** undergoes Pauson–Khand cyclization at room temperature when reacted with cobalt octacarbonyl and trimethylamine *N*-oxide (TMANO) to give the tricyclic azetidine **375** (Equation 50). But when 1-allyl-4-ethynylazetidine **376** is used, product **377** is obtained (Equation 51). In both cases, moderate yields with the formation of a single isomer of the products is achieved <1996TL6901, 1998JOC6786>.

The Pauson–Khand approach to tricyclic fused systems has the advantages of producing a functionalized terminal ring, being a one-step process from readily available disubstituted azetidinones or azetidines, and giving, apparently, only one isomer. The main disadvantage is that only a terminal five-membered ring is formed. Other examples of the use of this reaction are given in Sections 2.04.11.1.1(iii), 2.04.11.2.1(ii), and 2.04.11.2.1(vi).



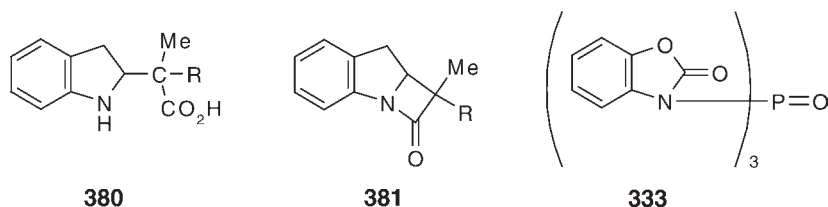


Cycloaddition under thermolytic conditions is another route to tricyclic β -lactams. The 1,3-dipolar cycloaddition of oxazolidinone **98** with *N*-phenylmaleimide to give **100** has been described (see Section 2.04.6.3). In a sealed tube at 100 °C the oxazolidinone **98** reacts with a cyclopentenone derivative to give the tricyclic isomers **378** and **379** in the yield ratio of 4:1 (Equation 52) <1999JHC1365>.

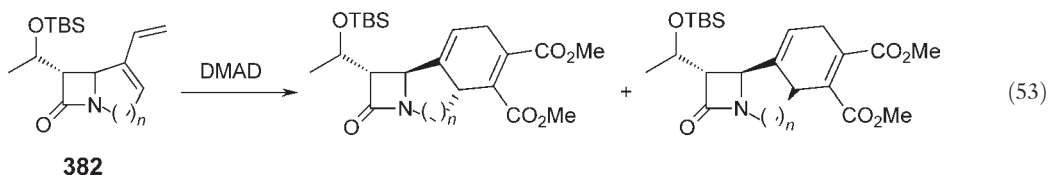


2.04.11.1.1(ii) 4/5/6 Ring system

Cyclization of the α -indolinyllactic acids **380** ($R = H$ and Me) in the presence of triethylamine gave the benzocar-bapenems **381** ($R = H$ and Me), which were more stable than the corresponding unsubstituted compounds. In this last case, the best yield (37%) was obtained from cyclization of α -indolinyllactic acid in the presence of tris(2-oxobenzoxazolin-3-yl)phosphine oxide **333** but the unsubstituted benzocar-bapenem decomposed within a few hours in the presence of air at room temperature. However, the parent compound can be kept below 0 °C with little decomposition. The relative stereochemistry of the monomethyl carbapenems was assigned <1995TL8693, 1998J(P1)1193>.

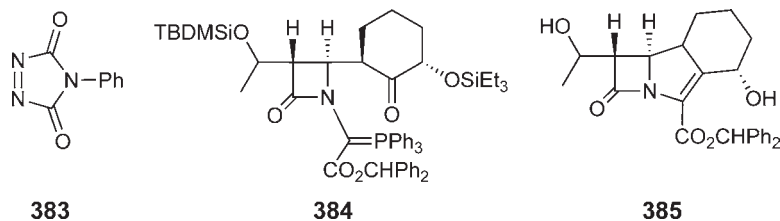


Enyne metathesis of vicinal disubstituted β -lactams is a good route to bicyclic carbapenems carrying a vinyl substituent. It is reported that the second generation of Grubbs' catalysts are advantageous in producing a 4/5 ring fused product. Such a compound, for example, **382** ($n = 1$), is expected to undergo a Diels–Alder reaction to provide access to tricyclic systems from acyclic dienophiles (Equation 53). However, the 4/5 fused system **382** ($n = 1$) reacted readily only with cyclic and highly dienophilic 4-phenyl-1,2,4-triazoline-3,5-dione **383**. The best conditions found for reactions to produce the 4/5/6 fused system were either in ether in the presence of lithium perchlorate or by use of butylmethylimidazolium hexafluorophosphate ionic liquid as solvent when yields of 89% and 84% were obtained, respectively. Similar vinyl-substituted fused β -lactams with larger rings, for example, **382** ($n = 2$ or 3), reacted much more readily with dienophiles. It seems likely that this combination of RCM reaction followed by a Diels–Alder reaction will be exploited in the future because of the relatively easy access to the starting materials <2004EJO4840>.



A route to 4/5/6 fused tricyclic systems that is already well explored is via the Wittig reaction or its derivatives (see Section 2.04.9.5). In this case, the final step in forming the tricyclic system is the reaction to produce the middle ring

<1996BML525, 1996BML2589>. The phosphorane may be isolated and used as the starting material in this final step. Thus, the triprotected phosphorane **384** was first desilylated and the resulting dihydroxy phosphorane was cyclized by thermolysis in toluene solution to yield **385** <1998H(48)2287>.



More usually, and often more conveniently, the monocyclic β -lactam starting material has *vic*-substituents carrying suitably arranged carbonyl groups so that cyclization can be achieved through the action of triethyl phosphite or a similar ester. For example, the N-unsubstituted β -lactam **386** (R = H) reacts with allyloxalyl chloride to afford **386** (R = COCO₂CH₂CH=CH₂) and is then cyclized in refluxing xylene in the presence of triethyl phosphite to yield **387** in 44% overall yield <1996BML2025>.

Other workers have used a similar approach using an allyl group protection of the ester <1996T263, 2000T5639>. A similarly mediated cyclization of a diketone, but with a benzyl group protection of the ester, has been applied more widely <1995BML2535, 1996JA9884, 1996J(P1)2029, 1997BML1857>. Sometimes a fluorenyl ester was used <2000T5649>. This general method has been used to obtain derivatives of the trinem **388** as shown in Table 3. These procedures have the advantages that the disubstituted β -lactam is usually easily prepared and the carboxylic acid group in the product is readily obtained. Other examples of applications of Wittig-type reactions leading to the synthesis of tricyclic compounds are given in Sections 2.04.11.1(i) and 2.04.11.2(iv).

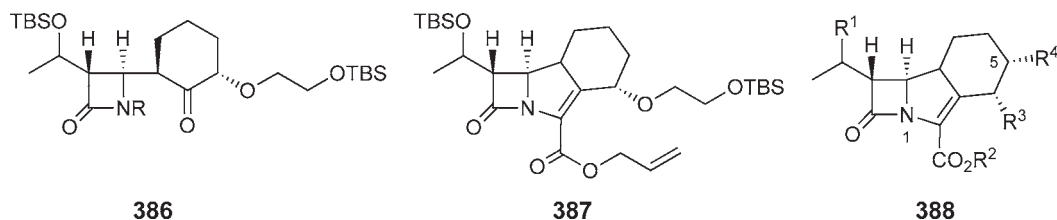
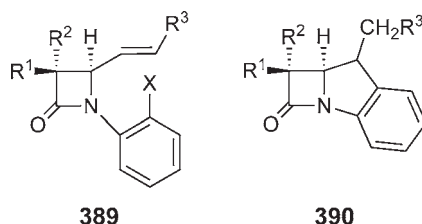


Table 3 Derivatives of trinem **388**

R^1	R^2	R^3	R^4	Reference
OH	CHPh ₂	OH	H	1998H(48)2287
OH	Na	F	H	1996T263
OH	H and Na	OMe	H	1996JA9884
PhCH ₂ COO	PhCH ₂	OMe	H	1996J(P1)2029
OH	CO ₂ H	NMeCH=NH	H	2000T5649
OH	CH ₂ Ph	H	(CH ₂) ₂ OH	1997BML1857 ^a
OH	CH ₂ Ph	H	OMe and OH	1995BML2535 ^a
OH	CH ₂ CH=CH ₂	CH ₂ OH	H	2000T5639
OH	Na	O(CH ₂) ₂ NH ₂	H	1996BML2025
OH	Na	O(CH ₂) ₃ NH ₂	H	1996BML2025

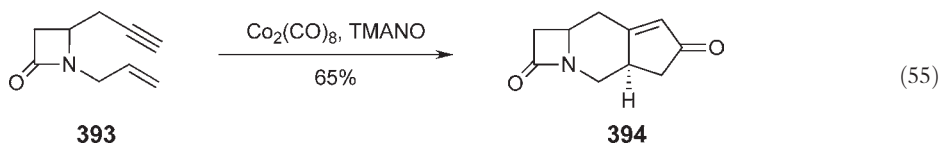
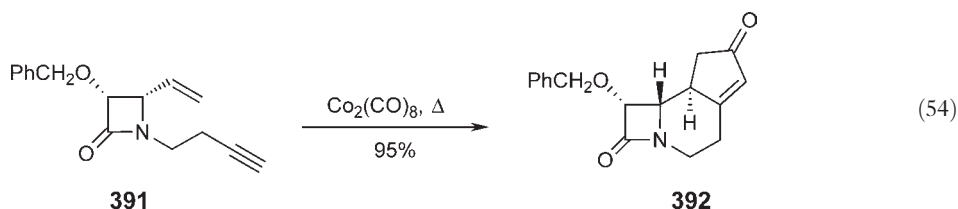
^aThe 5 α -substituted acids formed by debenzoylation were isolated as their salt with 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]dec-1-ene.

The readily available 4-alkenyl-*N*-(2-halogenophenyl)- β -lactams **389** (X = Br or I) have been used in tributyltin hydride-mediated radical cyclizations to give generally good yields of benzopenems **390** <1996TA2203>. Sanfetrinem **8** labeled with ¹⁴C at the metabolically stable 2-position has been reported <1995MI667>.

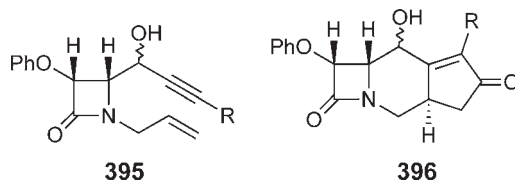


2.04.11.1.1(iii) 4/6/5 Ring system

Pauson–Khand cyclization of *vic*-enynes derivatives of β -lactams gave good yields of fused tricyclic compounds. The 1,4-disubstituted 2-azetidinone **391** and cobalt octacarbonyl gave the alkyne–cobalt carbonyl complex, which on thermolysis gave the tricycle **392** in 95% yield (Equation 54). When the complexes of **393** with cobalt octacarbonyl were treated with TMANO, a lower yield (65%) of **394** was obtained (Equation 55). A single diastereoisomer was formed in each case <1996TL6901>.



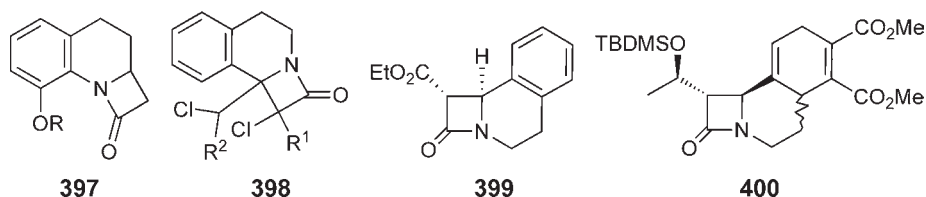
Other workers, apparently unaware of the earlier report, have reported the reactions with **391** and **393** and obtained identical results. Exploration of the effects of substituents gave a variety of results. When **395** (R = H) as a diastereomeric mixture was treated in a similar way, the yield of **396** (R = H) was 95%, but no product was obtained from **395** when R = TMS <1998JOC6786>.



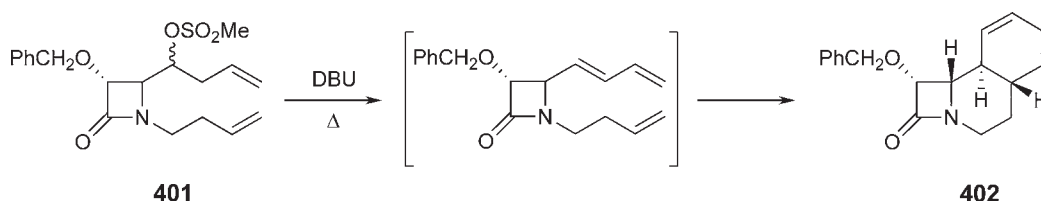
2.04.11.1.1(iv) 4/6/6 Ring system

The tetrahydroquinoline derivatives **397** (R = Prⁱ and H) have been obtained from the corresponding 3,4-dihydroquinolines, and intramolecular hydrogen bonding between the hydroxyl and carboxyl groups has been demonstrated <1998J(P1)1203>. A series of tetrahydroisoquinoline derivatives **398** have been reported together with their ¹H and ¹³C NMR data <1998JHC77>. 3,4-Dihydroisoquinoline *N*-oxide has been reacted with ethyl propiolate in the presence of copper(I) iodide in the Kinugasa reaction to give **399** in 56% yield <2003IJB1508>.

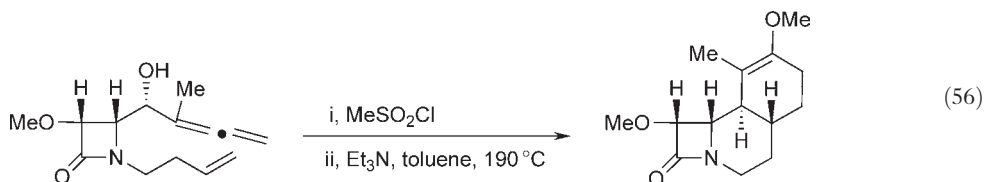
The synthetic route using a Diels–Alder reaction with a 1-vinylcarbacephem has been used to obtain compound **400** <2001TL2461>.



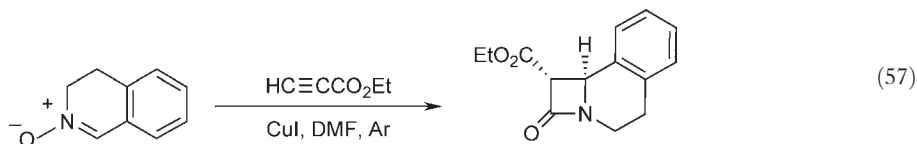
Treatment of the δ -methanesulfonate of an alkene with a non-nucleophilic base gives a 1,3-diene system. If a β -lactam having such a substituent also has an adjacent substituent containing an olefinic group, it is possible for an intramolecular Diels–Alder reaction to occur. Thus treatment of dialkene **401** with base in refluxing toluene gave a high yield of **402** by a stereoselective tandem one-pot elimination–intramolecular Diels–Alder reaction ([Scheme 12](#)) <1999TL1015>. The procedure can be used to provide substituted and functionalized tricycles ([Equation 56](#)). Alcaide *et al.* have developed this approach to tricyclic and polycyclic compounds. An inconvenience is that the method often requires a sealed system and a high temperature <2005EJO98>. Other examples of the method are given in [Sections 2.04.11.2.1\(iii\), 2.04.11.2.2\(iv\), and 2.04.11.3](#).



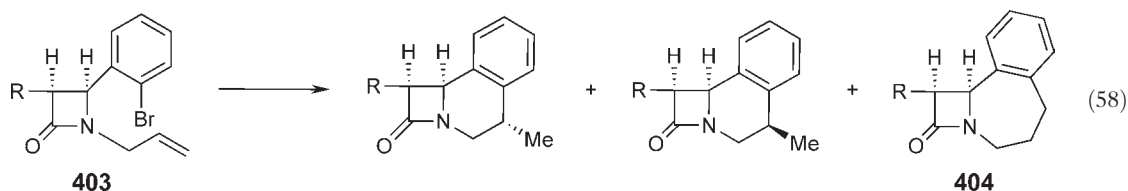
Scheme 12



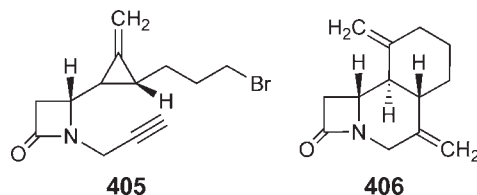
A novel tricyclic β -lactam has been obtained using the Kinugasa reaction to form the four-membered ring ([Equation 57](#)). This procedure has the advantage that relatively simple starting materials are required and that the β -lactam ring is the last to be formed <2003IJB1508>. Other examples are given in [Sections 2.04.11.1.1\(iv\) and 2.04.11.2.1\(vii\)](#).



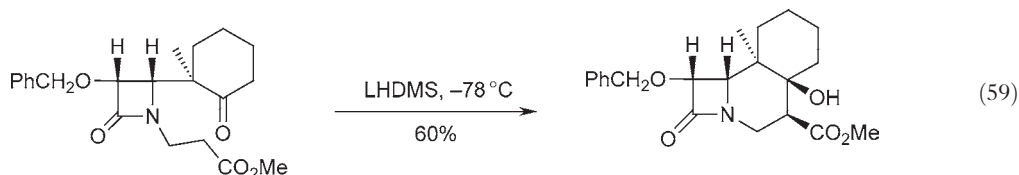
Tributyltin hydride-mediated radical cyclization of alkenes **403** ($R = \text{OPh}$ or OAc) led to three types of product ([Equation 58](#)). The yields of the 4/6/6 ring system were low and the ratio of the isomers varied with the nature of R but the major product was **404** in each case <1996TL1363>.



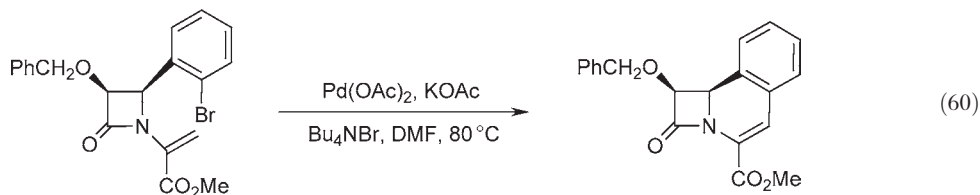
Radical cyclization of **405** led to the dimethylene tricyclic β -lactam **406** in a cascade sequence of steps. Radical procedures have been used extensively and have the advantages of stereoselectivity in the cyclization step from relatively simple starting materials. A disadvantage is the sometimes relatively low yield <1999TL5391, 2000TL10347>. Other examples of the use of radical cyclization processes are given in Sections 2.04.11.1(ii), 2.04.11.2.2, 2.04.11.3, and 2.04.11.4.



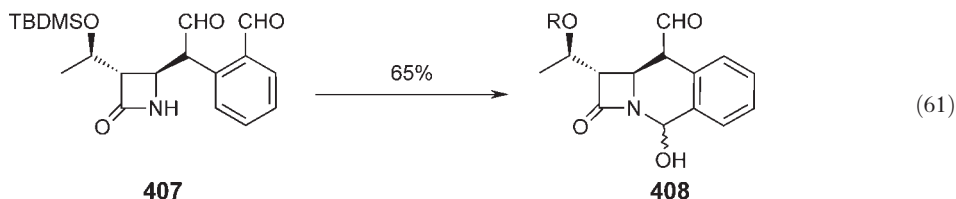
The intramolecular aldol condensation route to fused tricyclic β -lactams has been explored. The methylene group of an *N*- ω -methoxycarbonyl alkyl chain is sufficiently acidic to react with a carbonyl group when treated with lithium hexamethyldisilazane (LHMDS) in THF at -78°C . Reaction times are short and yields high (Equation 59) <1996JOC7125>.



Palladium(II)-mediated cyclizations have been little used in the synthesis of the tricyclic structures under consideration here but one example does show that the approach is feasible (Equation 60) <1998EJO2913>.

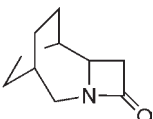
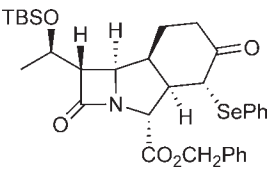
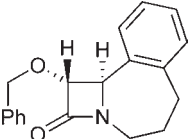
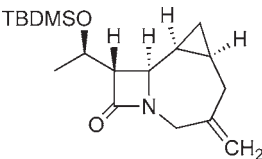
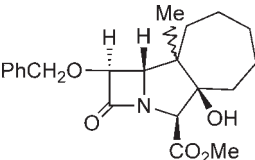


Formation of the middle ring by alkylation of a reactive group on a 4-substituent of the β -lactam is a simple preparative approach. The benzaldehyde derivative **407** formed by ozonolysis of a protected 4-(1-indanyl)azetidinone spontaneously cyclized to yield one stereoisomer of the tricyclic **408** ($\text{R} = \text{TBDMS}$) which was then deprotected to yield **408** ($\text{R} = \text{H}$) (Equation 61) <2000T5621>. Other examples of routes to these tricyclic β -lactams are given in Table 4.



More information on these types of compounds is given in Sections 2.04.2, 2.04.3.1, 2.04.3.2, 2.04.3.4, 2.04.6.3, and 2.04.6.4.

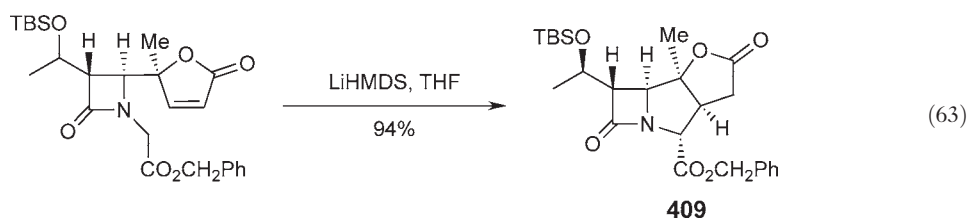
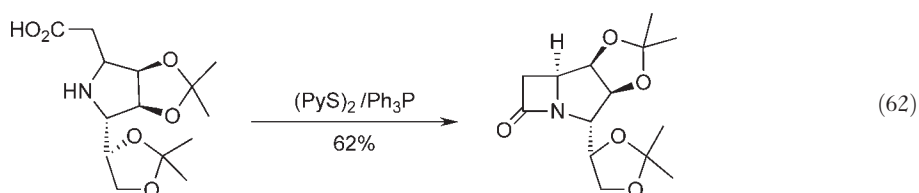
Table 4 Miscellaneous examples

<i>Formula</i>	<i>Method of synthesis</i>	<i>Reference</i>
	Carbene insertion into C–H bond	1995SL1075
	Michael reaction and phenylselenation	1995BML2535
	Radical cyclization	1996TL1363
	Radical cyclization	2000TL10347
	Intramolecular aldol condensation	1996JOC7125

2.04.11.1.2 Additional heteroatoms

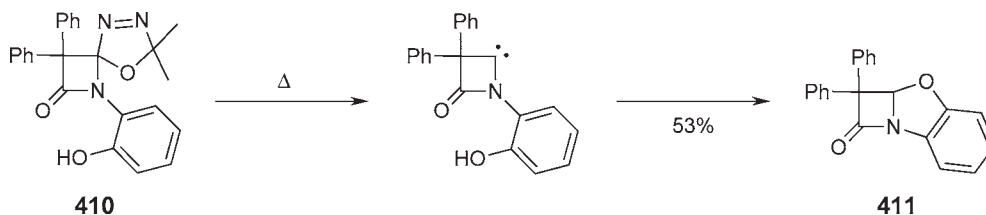
2.04.11.1.2(i) 4/5/5 Ring system

The fused 4/5/5 system has been obtained by ring closure forming the lactam ring on a bicyclic pyrrolidine (Equation 62) <1998JOC8170>. Michael addition to an unsaturated lactone was used to form the middle ring of compound **409** (Equation 63) <1999T3427>.



2.04.11.1.2(ii) 4/5/6 Ring system

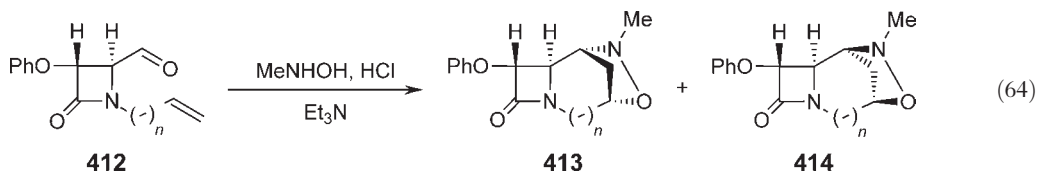
An infrequently used potential route to tricyclic fused β -lactams was demonstrated by the thermolysis of **410** in benzene at 100 °C to yield the product **411**, presumably through the intermediacy of a β -lactam carbene (**Scheme 13**) <1998CJC241>.



Scheme 13

2.04.11.1.2(iii) 4/6/5 Ring system

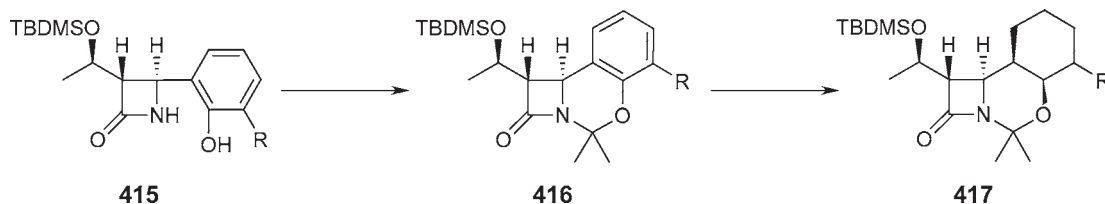
An unusual tricyclic β -lactam system was obtained when the reaction of 1-allyl-4-formyl-2-azetidinone **412** ($n=1$) with *N*-methylhydroxylamine gave the 4/6/5 bridged cycloadduct **413** ($n=1$) in excellent yield (**Equation 64**). Compounds with larger middle rings **413** and **414** ($n=2$ or 3) were also obtained in good yields from appropriate starting materials. The stereochemistry of the β -lactam starting material has a large influence on the stereoselectivity without affecting the regioselectivity of the cycloaddition. The *cis*-isomer gave the higher de (90–100%) and the isomers **413** and **414** in the ratio 3:1 <1999TL5391, 2005EJO1680>.



2.04.11.1.2(iv) 4/6/6 Ring system

The biggest group of tricyclic compounds having a bridgehead nitrogen atom and extra one or more heteroatoms is the fused 4/6/6 system. Two main routes have been adopted for their synthesis: either cyclization onto the nitrogen atom of a β -lactam or by a cycloaddition process. Each of these routes can be achieved by either an intermolecular or an intramolecular reaction.

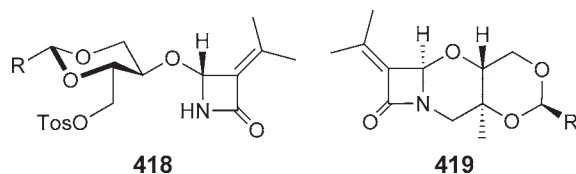
Cyclization of the phenol **415** ($R=H$) in the presence of 2,2-dimethoxypropane and boron trifluoride etherate gave the acetone **416** ($R=H$) and this was reduced in the presence of ruthenium(III) chloride and Aliquat 336 to provide **417** ($R=H$) as a single isomer in 65–70% yield (**Scheme 14**). Although the corresponding 5-methoxy tricyclic compound **416** ($R=OMe$) was obtained, it could not be converted to the corresponding fully reduced ring system <1999EJO3067>.



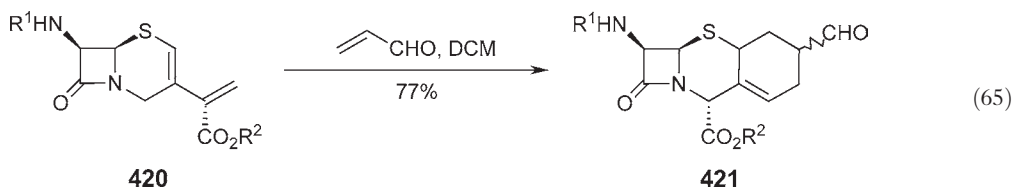
Scheme 14

Chmielewski and co-workers have done extensive work on the synthesis of the bi-, tri-, and tetracyclic oxacephams from β -lactams carrying a carbohydrate derivative on a substituent in the 4-position <1998T14065, 2002CAR2005>.

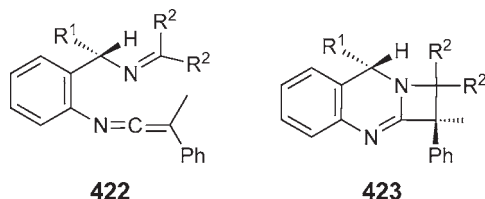
Chiral alkoxy allenes derived from 1,3-alkylidene-L-erythritol and -D-threitol have been used in cycloaddition reactions to provide the 4-substituted β -lactams **418** (R = Me, Ph). Intramolecular alkylation at nitrogen was achieved by the action of potassium carbonate and tetrabutylammonium bromide in dry acetonitrile. The absolute stereochemistry of the product **419** (R = Me, Ph) was assigned on the basis of the CD helicity rule (see Section 2.04.3.5) and NMR spectroscopy. The [2+2] cycloaddition of CSI to threitol vinyl ethers was found to have low stereoselectivity in contrast to the findings with erythritol derivatives <2004CH414, 2005EJO429>.



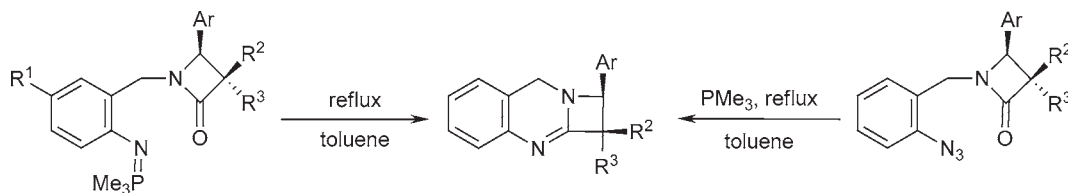
The second major route to tricyclic β -lactams with a bridgehead nitrogen atom and extra heteroatom(s) is through cycloaddition reactions. Again, these may be of the intermolecular or intramolecular type. Diels–Alder reaction of acrolein and the cepheids **420** gave **421** as the major products (Equation 65) <1996TL5967>.



Intramolecular [2+2] cycloaddition reactions leading to highly stereocontrolled formation of 1,2-dihydro-azeto[2,1-*b*]quinazolines have been investigated both by experiment and through theoretical studies. Ketenimine **422**, formed in an aza-Wittig reaction and not necessarily isolated, yielded **423** in good to moderate yields depending upon the substituents <2000JOC3633, 2000JOC7512>. An electronic conference report on this reaction to give azeto[2,1-*b*]quinazolines is available <1996MI1>.

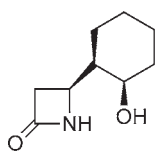


The aza-Wittig reaction and aza-Wittig-type reactions from azaphosphoranes by thermolysis and by the reaction of azides and trimethylphosphine have been used to obtain azeto[2,1-*b*]quinazolines (Scheme 15) <1998MI1, 1998SL1288>.

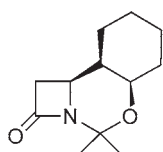


Scheme 15

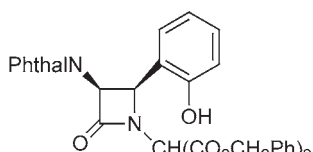
Intermolecular cyclization of **424** with dimethoxypropane in the presence of boron trifluoride afforded the acetone **425** (84%) <1996TL2467>. Chlorination of the reactive methane group in **426** with trifluoromethanesulfonyl chloride and treatment of the product with triethylamine gave the tricyclic azetidinone **427** <1999T8039>.



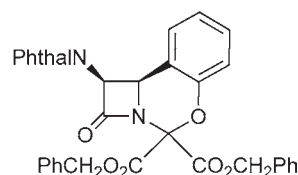
424



425



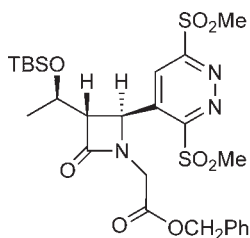
426



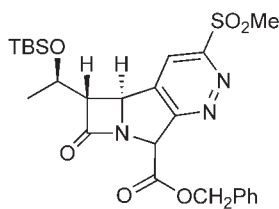
427

2.04.11.1.2(v) 4/7/6 Ring system

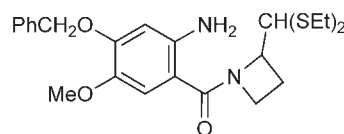
Treatment of the disulfone derivative of pyridazine **428** with 2 equiv of lithium hexamethyldisilazane at -78°C gave the closed ring, monosulfone **429** in 67% yield as a single diastereoisomer [<1997TL5913>](#). Cyclization of **430** by mercury(II) chloride and calcium carbonate afforded azetidine **431** after debenzoylation [<1997TL5839>](#). A number of other examples of the 4/7/6 system **432–436** are known and usually they have been prepared by Staudinger-type addition to an azine bond in the appropriate bicyclic system [<1996JHC271, 1999CCL23, 1999CCL447, 2000H\(53\)557, 2004EJO535>](#).



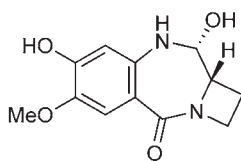
428



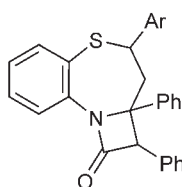
429



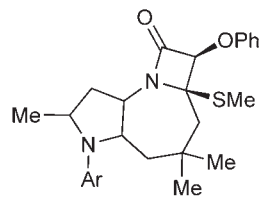
430



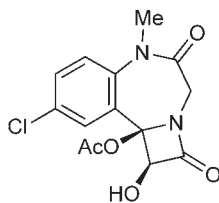
431



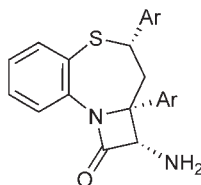
432



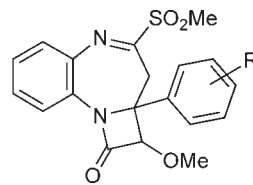
433



434

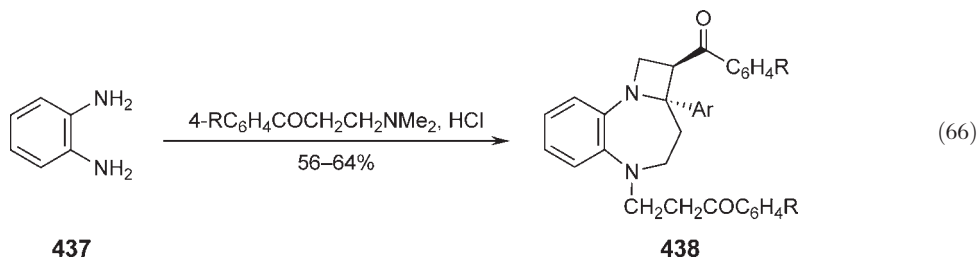


435

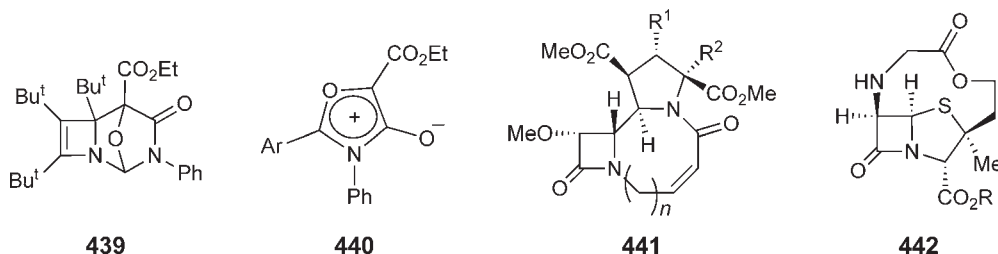


436

An unexpected product was obtained when the *o*-phenylene diamine **437** was reacted with an excess of the Mannich base, *p*-substituted 3-dimethylaminopropiophenone hydrochloride. A product, whose relative stereochemistry was determined by NMR, was shown to have structure **438** (Equation 66) [<2000EJO1973>](#).



More unusual products include **439** formed by reaction of tri(*tert*-butyl)azete with the mesoionic isomunchone **440** <1997BSF927>, and larger ring compounds, such as **441** ($n = 1-3$) and **442** formed by RCM reactions and alkylation of the amino group, respectively <1998JA6846, 2001SL773>. Interestingly, compound **441** formed only as the *cis*-isomer when $n = 1$ or 2 but the *trans*-isomer was obtained for $n = 3$ (a diazacinone ring). Other examples of these types of compounds are reported in Sections 2.04.2, 2.04.3, 2.04.6.2–2.04.6.5, 2.04.6.7, and 2.04.9.10.



2.04.11.2 Tricyclic Compounds Having Only Carbon Atoms at the Bridgehead

2.04.11.2.1 No additional heteroatoms

2.04.11.2.1(i) 4/4/3 and 4/4/4 Ring systems

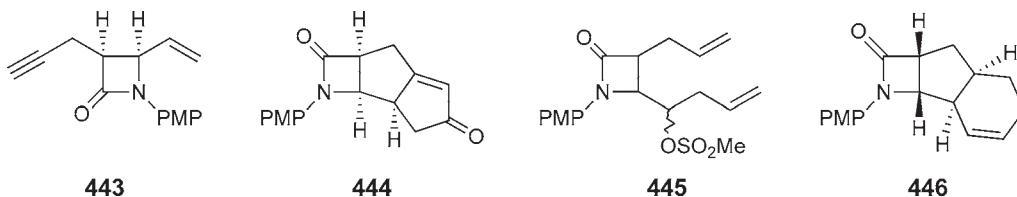
Linear tricyclic systems have been obtained from intramolecular photocyclization of 1,2-dihydropyridin-2-one to give an olefinic bicyclic product and subsequent Diels–Alder reaction with an acyclic dienophile to give the tricyclic compound. Reactions of this type have been mentioned in Sections 2.04.6.3 and 2.04.7.2.

2.04.11.2.1(ii) 4/5/5 Ring system

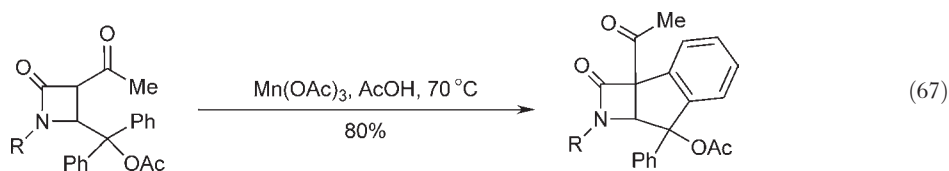
The Pauson–Khand reaction has been used to obtain 4/5/5 systems from β -lactams having unsaturated 3,4-substituents. Thus, the reaction of **443** with cobalt octacarbonyl in the presence of TMANO gave **444** in 80% yield <1996TL6901, 1998JOC6786>.

2.04.11.2.1(iii) 4/5/6 Ring system

Suitably substituted β -lactams carrying methanesulfonate ester groups, for example, **445**, underwent tandem elimination/intramolecular Diels–Alder reactions provided 4/5/6 fused tricyclic systems, for example, **446** <1999TL1015, 2000JOC3310>.

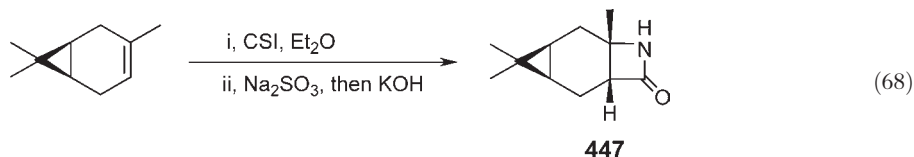


Similar tricyclic compounds but with an aromatic nucleus have been obtained by radical aromatic substitution and 4-*exo-trig*-cyclization (Equation 67) <1997T13129, 2000TL3261>.



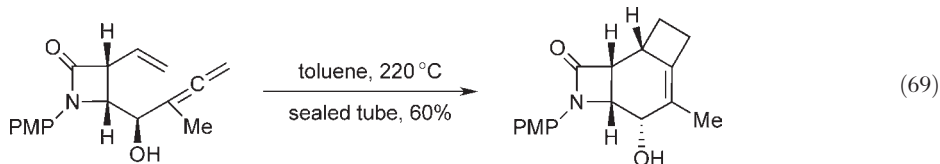
2.04.11.2.1(iv) 4/6/3 Ring system

Commercially available (+)-3-carene undergoes cycloaddition with CSI at room temperature to give the unusual 4/6/3 system **447** in a regio- and stereoselective process in good yield (76%) (Equation 68) <2003TA3965>.



2.04.11.2.1(v) 4/6/4 Ring system

The unusual 4/6/4 system has been obtained by an intramolecular [2+2] cycloaddition reaction of 2-azetidine-tethered enallenols by thermolysis in toluene solution at 220 °C in a sealed tube (Equation 69) <2006CEJ1539>.

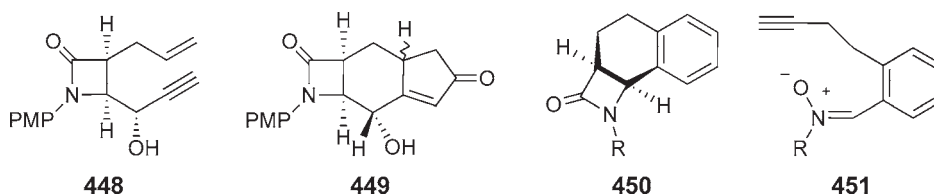


2.04.11.2.1(vi) 4/6/5 Ring system

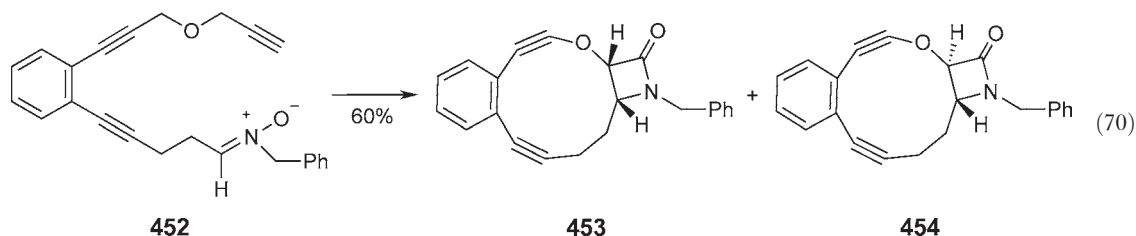
The Pauson–Khand reaction provides a route to the 4/6/5 system from 3,4-disubstituted β -lactams having both alkenyl and alkynyl groups, and will allow the presence of some functional groups on the substituents. The reaction of cobalt octacarbonyl and TMANO with **448** furnished **449** in 55% yield as a mixture of diastereoisomers in a ratio of 70:30 <1998JOC6786>.

2.04.11.2.1(vii) 4/6/6 Ring system

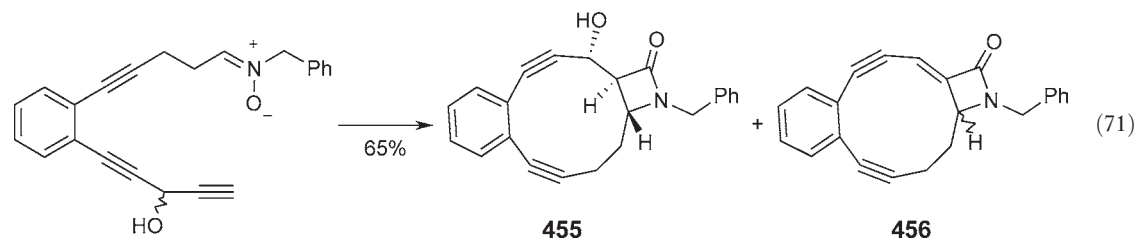
The Kinugasa reaction has emerged as a useful route to β -lactams and its use has been reviewed <2004AGE2198>. The reaction has been used as a method by which the 4/6/6 system **450** was obtained from **451** with high ee <2004AGE2198>.



Compounds containing larger rings such as β -lactam-fused cyclic enediynes have been prepared by intramolecular Kinugasa reaction. The nitron **452** when subjected to the Kinugasa reaction in the presence of cuprous iodide and triethylamine at room temperature gave **453** and **454** which were isolated by chromatography over silica gel in the ratio of 1:3, respectively (Equation 70) <2006CC2992>.



Similarly, the 11-membered enediyne systems **455** and **456** were obtained from the nitrone, which was prepared in 10 steps (Equation 71) <2006CC2992>.

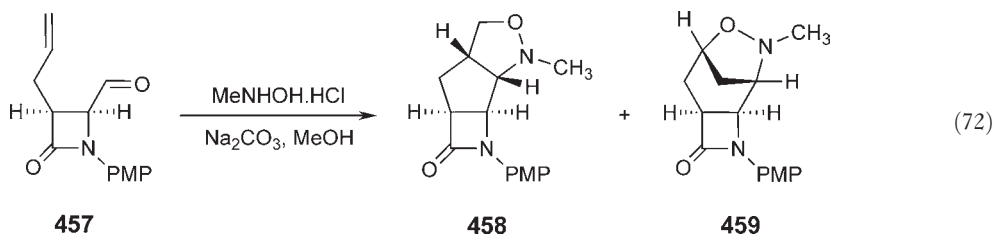


Further examples are mentioned in Sections 2.04.3.1–2.04.3.3, 2.04.6.3, and 2.04.6.4.

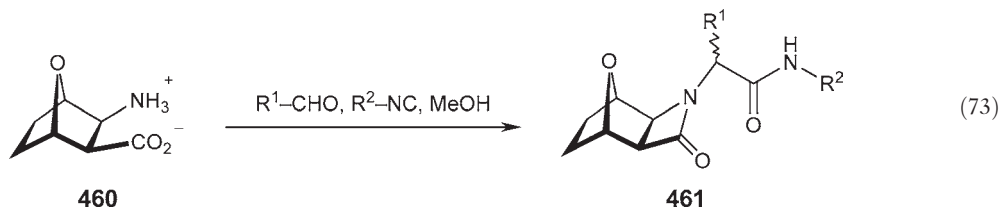
2.04.11.2.2 Additional heteroatoms

2.04.11.2.2(i) 4/5/5 Ring system

When 3,4-disubstituted β -lactam **457** was treated with methylhydroxylamine hydrochloride in the presence of sodium carbonate in methanol, a quantitative yield of an isomeric mixture of fused adduct **458** and bridged isoxazolidine **459** in a 15:1 ratio, respectively, was obtained (Equation 72) via a nitrone intermediate <1999TL5391>.

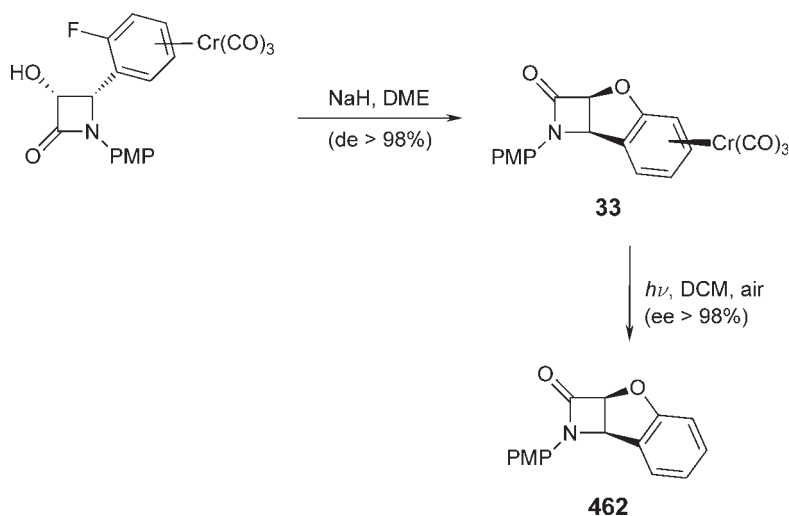


The β -amino acid derivative **460** undergoes Ugi reaction with aldehydes and isocyanides to give **461** in quantitative yields (Equation 73). However, the diastereomeric ratios were disappointingly not higher than 42% <2004TL587>.



2.04.11.2.2(ii) 4/5/6 Ring system

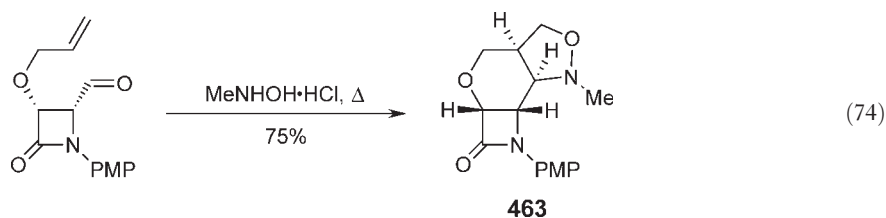
Intramolecular nucleophilic aromatic substitution of a tricarbonyl chromium derivative in the presence of sodium hydride and dimethoxyethane gave **33** which on photolysis yielded bicyclo[3.2.0]hept-3-en-7-one derivative **462** with ee > 98% (Scheme 16). The mechanistic pathways of the reaction have been discussed <2000TA1927, 2005TA971>.



Scheme 16

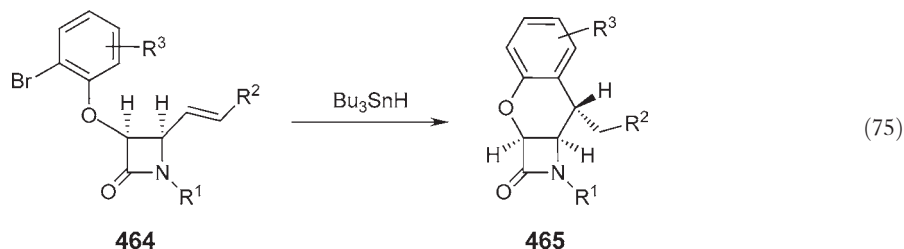
2.04.11.2.2(iii) 4/6/5 Ring system

The nitron route has been used to obtain **463** from 3,4-disubstituted β -lactam in the presence of triethylamine and benzene (Equation 74) <1999TL5391, 2005EJO1680>.

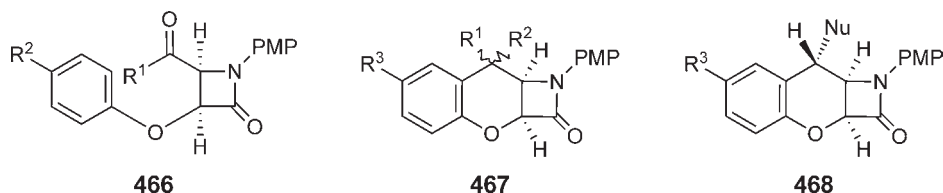


2.04.11.2.2(iv) 4/6/6 Ring system

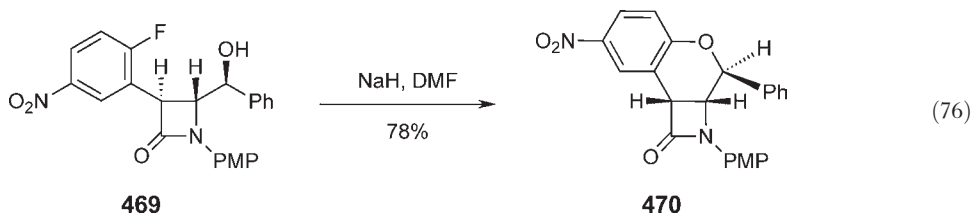
Intramolecular radical cyclization of haloarenes **464** ($R^2 = \text{CH}=\text{CHPh}$, $\text{CH}=\text{NCH}_2\text{Ph}$, $\text{CH}=\text{CHCO}_2\text{Me}$, $\text{CMe}=\text{CHPh}$) in the presence of tributyltin hydride gave the fused tricyclic β -lactams **465** in reasonable yields (Equation 75) <1997M1149, 2005T2767>.



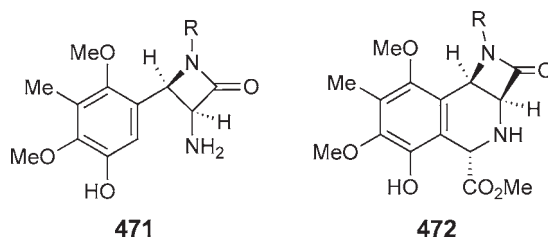
The azetidinone derivatives **466** ($R^1 = \text{H}$ or Cl ; $R^2 = \text{Cl}$ or F) in the presence of Lewis or Bronsted acids in nonaromatic solvents or nitrobenzene afforded the corresponding dihydrochromeno[3,2-*b*]azetidin-1(1*H*)-ones **467** ($R^1 = \text{H}$, $R^2 = \text{OH}$, $R^3 = \text{Cl}$ and F , $R^1R^2 = \text{O}$, $R^3 = \text{Cl}$ and F). In the presence of a nucleophile (Nu^-) the alcohol gave **468** ($R^1 = \text{Cl}$ or F) through a highly diastereoselective reaction which involved a carbocation at the 8-position. The alcohol **467** ($R^1 = \text{H}$, $R^2 = \text{OH}$) was also obtained by sodium borohydride reduction of the ketone **467** ($R^1R^2 = \text{O}$) <1998T15227, 1999T5567>.



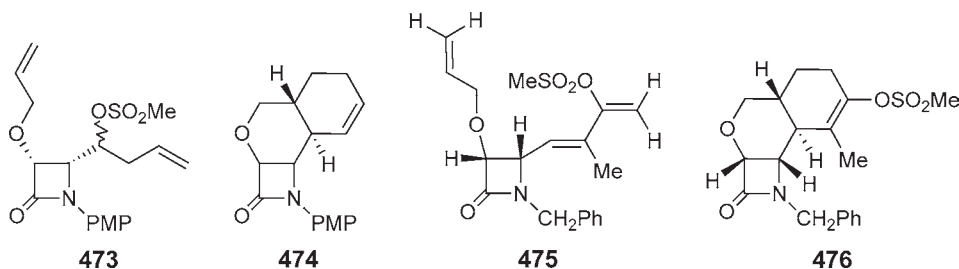
Nucleophilic displacement of fluorine from the activated aromatic nucleus in **469** gave **470** (Equation 76) <2003T5259>.



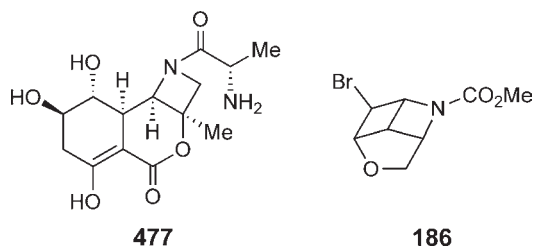
Reaction of the amine **471** with methyl glyoxylate produced electrophilic attack on the activated aromatic ring to yield **472** as a single stereoisomer in good yield <2001TL543, 2003OL2095>.



A tandem one-pot elimination–intramolecular Diels–Alder reaction occurs when the mesylate of 4-homoallylic azetidinone having a *vic*-alkene or alkyne substituent is heated in a sealed tube in the presence of an equimolecular quantity of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The method has been used to produce derivatives of oxacepham. In a similar way, the 3,4-disubstituted azetidinone mesylate **473** afforded an 88% yield of **474**. The method can be further elaborated through the introduction of a novel [3,3]-sigmatropic rearrangement of α -allenic mesylates: thus, **475** yielded **476** on thermolysis <1999TL1015, 2000JOC3310, 2005EJO98>.



The fused azetidine derivative of bactobolin **477** has been prepared <1998JAN184>. The azatricycle **186** has been synthesized by an intramolecular nucleophilic cyclization (see Section 2.04.7.1) <2002OL1259>.

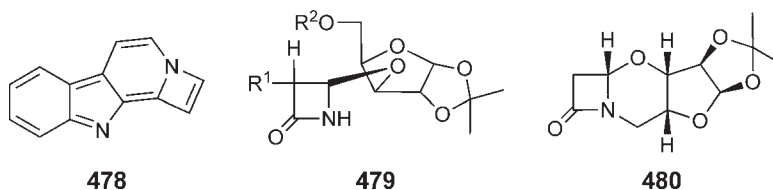


Other examples of these types of compounds are described in Sections 2.04.3.1, 2.04.4.1, 2.04.4.2, 2.04.6.2, 2.04.6.4, 2.04.7.1, and 2.04.7.2.

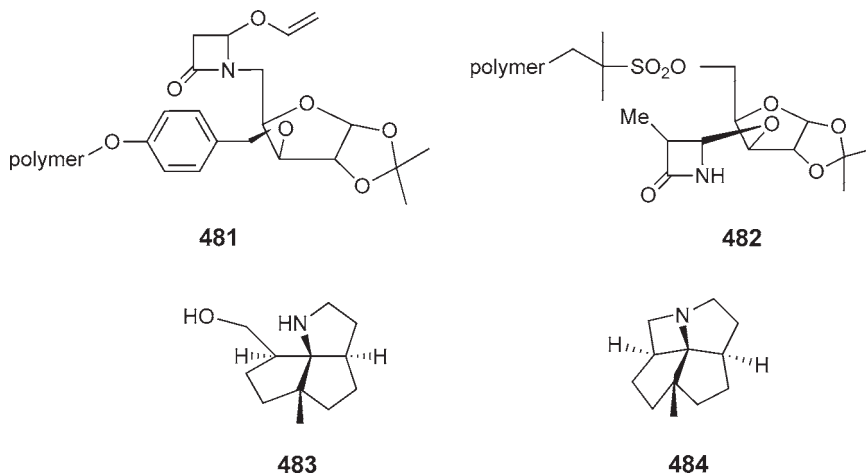
2.04.11.3 Polycyclics with Bridgehead Nitrogen Atom

The term 'polycyclic' is used here to denote compounds having four or more fused rings in the molecule. Wide-ranging reviews which include coverage of polycyclic structures include 'Cephems, Oxacephems, Penams and Subbactams' <2004RMC93> and 'Non-classical Polycyclic β -Lactams' <2000T5743>. A review of the syntheses and transformations of azeto[2,1-*a*]- and azeto[2,1-*b*]-isoquinolines and azeto[1',2':1,2]pyrido[3,4-*b*]indoles **478** describes the ring enlargement of the latter to give an eight-membered ring tricyclic compound <1999COR1>.

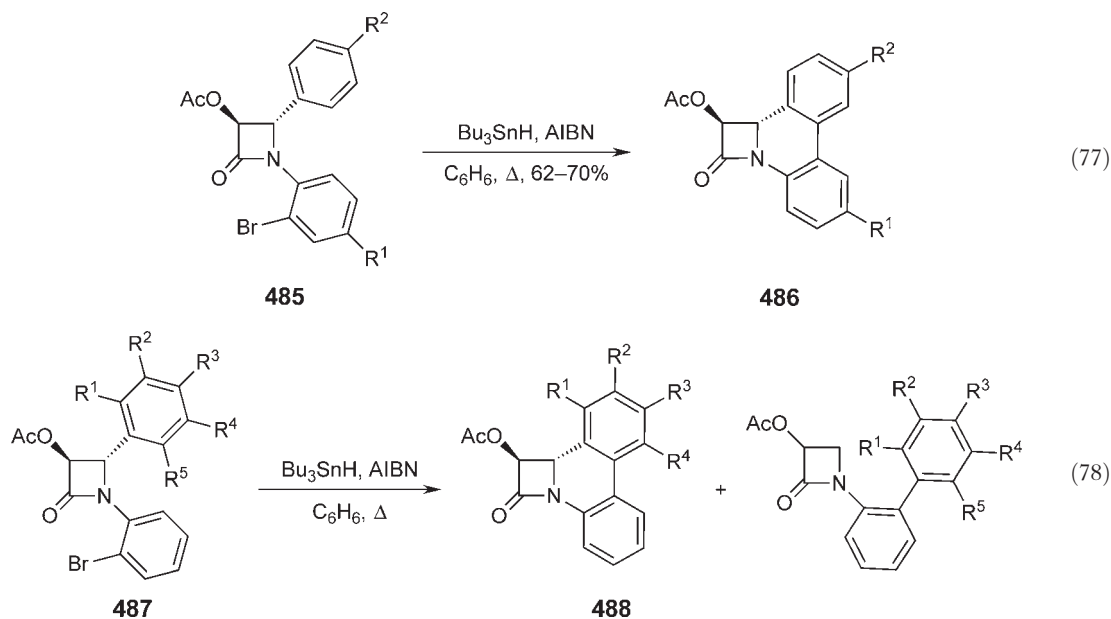
In addition to their work on tricyclic systems, Chmielewski and co-workers have used monosaccharides to obtain polycyclic derivatives of oxacepham. For instance, cyclization of **479** (R^2 = Tos or TIBS) in a two-phase system including a phase-transfer catalyst and potassium carbonate gave **480** in 65–90% yields. The protecting group R^1 was lost if it was a silyl group, for example, TMS, TBDMS <1998T14065>.



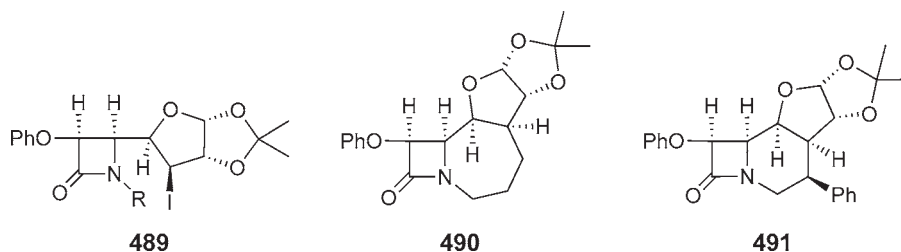
Resin-based chemistry has been used to construct **480** from **481** by use of boron trifluoride to mediate both the cyclization and cleavage steps <1999AGE1121>. When the monosaccharide was bound to the polystyrene resin (Merrifield and MPP type) by an alkylsulfonfyl linker **482** and cyclization was mediated by 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine, the reaction had low stereoselectivity and the products included tricyclic oxetanes and oxiranes <2004EJO4177>. The Mitsunobu reaction was used to obtain intramolecular N-alkylation of **483** and formation of **484** <2005AGE3732>.



Tin(IV) hydride-induced aryl–aryl coupling of *vic*-diarylazetidinones has been extensively investigated as a route to polycyclic β -lactams. The 3,4-*trans*-1,4-diaryl β -lactams **485** afforded **486** in 62–70% yield (Equation 77), but the corresponding 3,4-*cis*-isomer did not provide a tetracyclic product. Radical cyclization of the 3,4-*trans*-1,4-diarylsubstituted β -lactams carrying two substituents **487** (two of R^1 – R^4 = Me or OMe; R^5 = H, OMe, or Me) gave two products: the expected tetracyclic β -lactam **488** and a 1-biaryl β -lactam in 51–58% total yield with **488** being the major product in each case (Equation 78) <2005T7894>.

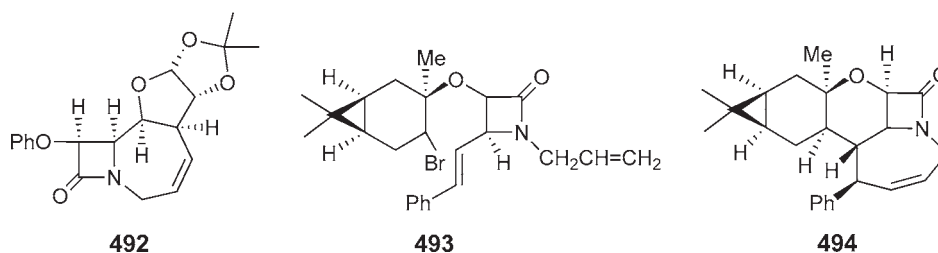


Deshmukh *et al.* have used *endo-dig*-tandem radical cyclization of the iodinated acetone from glucose **489** ($R = \text{CH}_2\text{CH}=\text{CH}_2$) to obtain the tetracyclic **490** in 61% yield. When the *N*-allyl group was replaced by *N*-cinnamyl **489** ($R = \text{CH}_2\text{CH}=\text{CHPh}$), the reaction occurred by an *exo-trig*-cyclization route to give **491**. The other diastereoisomer of the β -lactam **489** gave a 1:1 diastereoisomeric mixture of *exo-trig*-cyclized products [<2004S2965>](#).

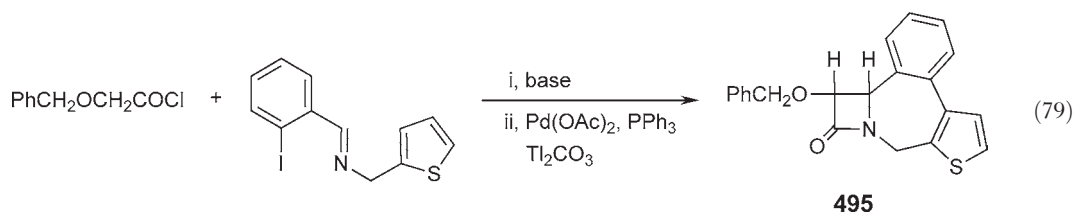


When the *N*-substituent was propargyl, the radical cyclized products were the unsaturated analogues of those obtained with an *N*-allyl substituent, for example, **489** ($R = \text{CH}_2\text{C}\equiv\text{CH}$) yielded **492** [<2004SL1249>](#).

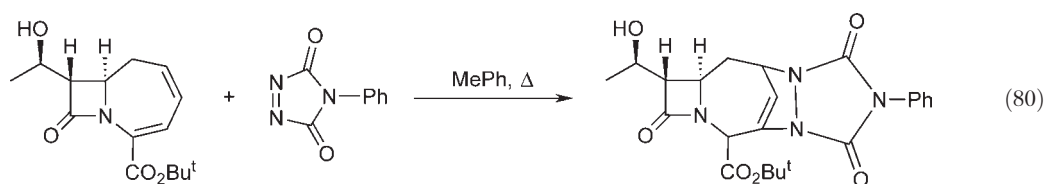
Fused pentacyclic systems have been produced by this approach from suitably substituted β -lactams. For instance, **493** on treatment with tributyltin hydride afforded **494** in 44% isolated yield as a pure diastereoisomer [<2003TL1827>](#).



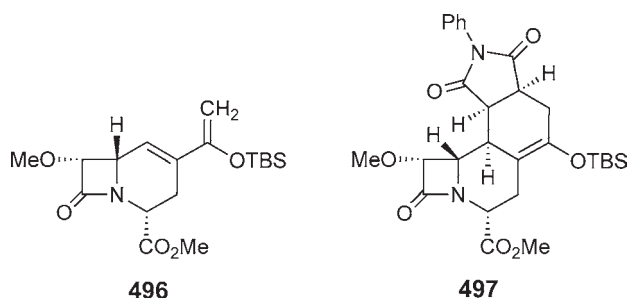
Cyclization of halogenoaryl-substituted β -lactams can be mediated by palladium(II) derivatives. The formation of the lactam from a ketene-imine addition and subsequent cyclization of the product can be carried out as a one-pot process. As an example, *in situ* generation of the ketene from the acid chloride and formation of the β -lactam followed by addition of palladium(II) acetate, triphenylphosphine, and thallium carbonate gave **495** in 54% yield (Equation 79) [<1995TL9053>](#).



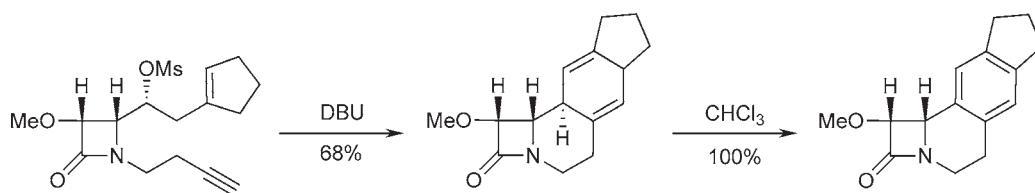
Cycloaddition reactions, in particular the Diels–Alder reaction, provide a convenient way to increase the number of fused rings by two with high stereoselectivity if a monocyclic dienophile is used [<2004S2665>](#). An early example of this approach to polycyclic β -lactams used a diene system that was entirely within a ring ([Equation 80](#)) [<2000JOC3716>](#).



A more versatile approach uses an inner–outer ring diene system such as compound [496](#), which reacted with *N*-methylmaleimide in toluene at 145 °C in a sealed tube to give cycloadduct [497](#) in 91% yield [<2004TL7255>](#). Similar procedures with different electrophiles have been reported by other workers who were able to combine consecutively the preparation of the inner–outer diene by RCM reaction (see [Section 2.04.9.3](#)) and the Diels–Alder reaction in a one-pot process, which gave increased yields in most cases for the polycyclic compounds when compared with the two-pot approach [<2004S2665>](#).



Alcaide *et al.* have used their methanesulfonate route to fused β -lactams in a cascade sequence of reactions, including an intramolecular Diels–Alder reaction to obtain tetracyclic compounds ([Scheme 17](#)) [<2003JOC3106>](#).



Scheme 17

Oxidation of certain *N*-methoxyphenylazetidinones gave tetracyclic products. The action of CAN on triazole **498** gave **499** and lead tetraacetate reacted with tetrazole **500** to yield **501** <1999T8457, 2003JCM759>. Other routes to polycyclic β -lactams are listed in Table 5.

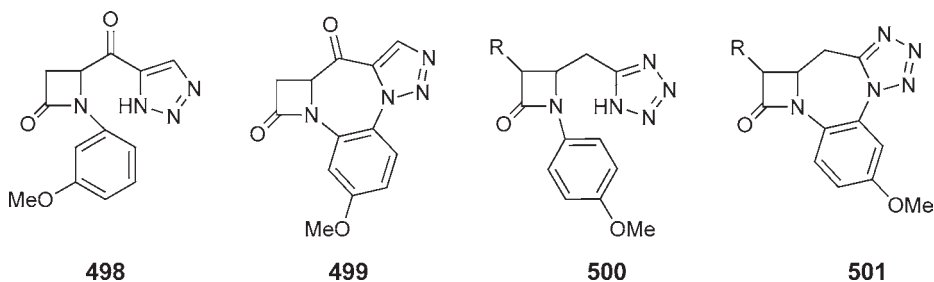
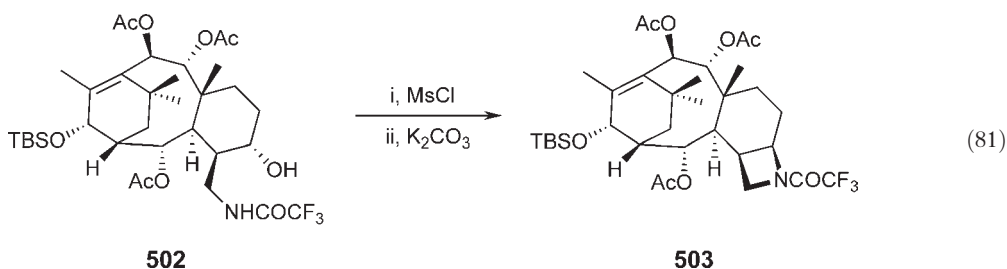


Table 5 Polycyclic β -lactams

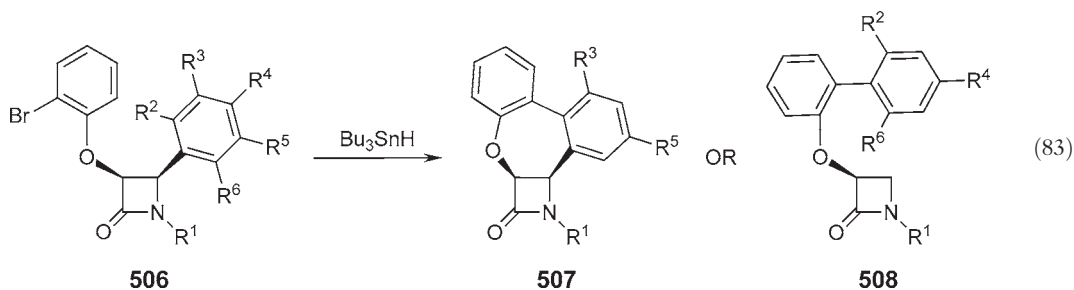
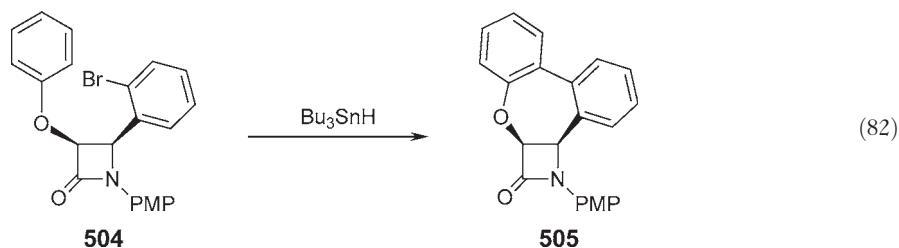
Formula	Method of synthesis	Reference
	Staudinger type; PhCH ₂ OCH ₂ COCl/base	1999TL2005
<i>cis</i> and <i>trans</i>	Staudinger type; Ph(CH ₂) ₃ COCl/base	1998TL7431
	Staudinger type; ClCH ₂ COCl/base	2003TL4141
	Wittig type	2000CJC772

2.04.11.4 Polycyclics with Carbon Atoms at the Bridgehead

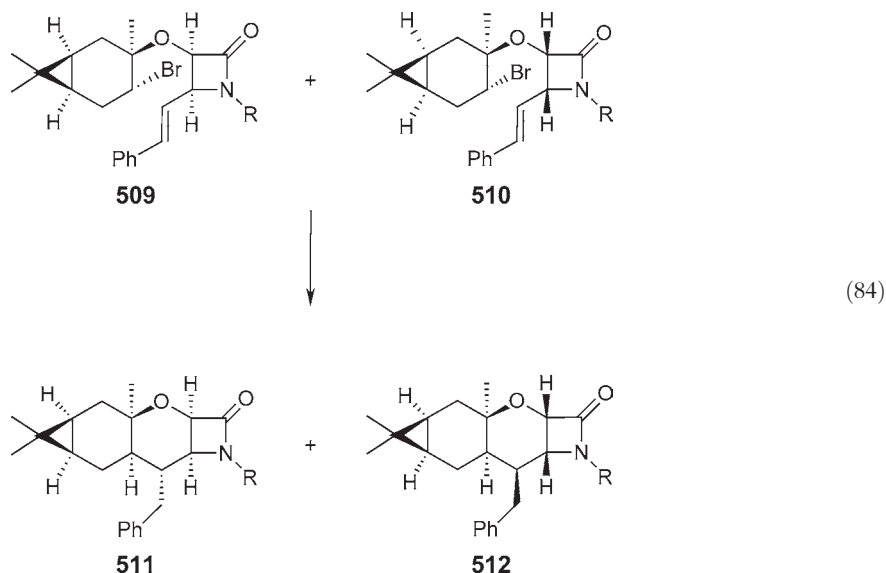
There are fewer examples of polycyclics with a carbon rather than a nitrogen at the bridgehead. The synthesis of novel azetidine paclitaxel analogues has been reported. The azetidine ring was formed after the activation of the hydroxyl group of compound **502**. A key intermediate **503** for the synthesis of paclitaxel analogues has been prepared by mesylation of the hydroxyl group of **502** followed by treatment with a base (Equation 81) <2003BML1075>.



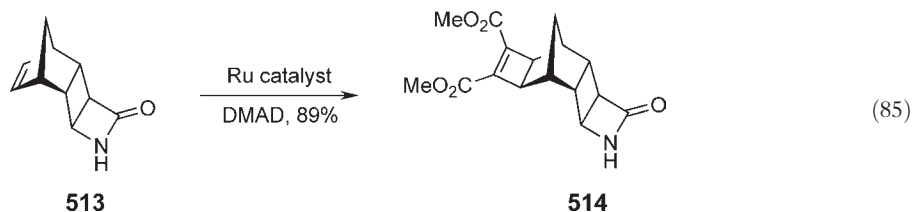
Fused tetracyclic biaryl-2-azetidinones have been prepared by the radical cyclization of aryl β -lactam-tethered haloarenes. Azetidin-2-one **504**, having an extra radical acceptor on C-3, underwent radical cyclization with tributyltin hydride to give the biaryl-2-azetidinone **505** in a low yield, with debrominated 3-phenoxy-4-phenyl-1-(*p*-methoxyphenyl)-2-azetidinone as the main product (60% yield) (Equation 82). But when the azetidinones **506** ($R^2 = R^6 = H$) bearing an extra link (O) on the radical precursor at C-3 or N-1 of the β -lactam ring were treated with tributyltin hydride, the expected cyclization products **507** were obtained. If azetidinones **506** ($R^2 = OMe$, or Me; $R^6 = H$, OMe, or Me) were treated in the same way then the tetracyclic azetidinones **508** were produced (Equation 83) <2005T7894>.



The diastereospecific synthesis of novel [3.6.6.4.7]-fused pentacyclic β -lactams via a novel 6-*exo-trig*,7-*endo-dig*-tandem radical cyclization has been reported. The use of this method for the construction of a polycyclic system fused to an azetidin-2-one template has been very little exploited. The mixture of β -lactams **509** and **510** ($R = -CH=CH_2$, $-CH=CHCH_3$) in their racemic forms on treatment with tributyltin hydride gave diastereomeric mixtures of tetracyclic **511** and **512** in the same ratio as in the starting materials (Equation 84) <2003TL1827>.

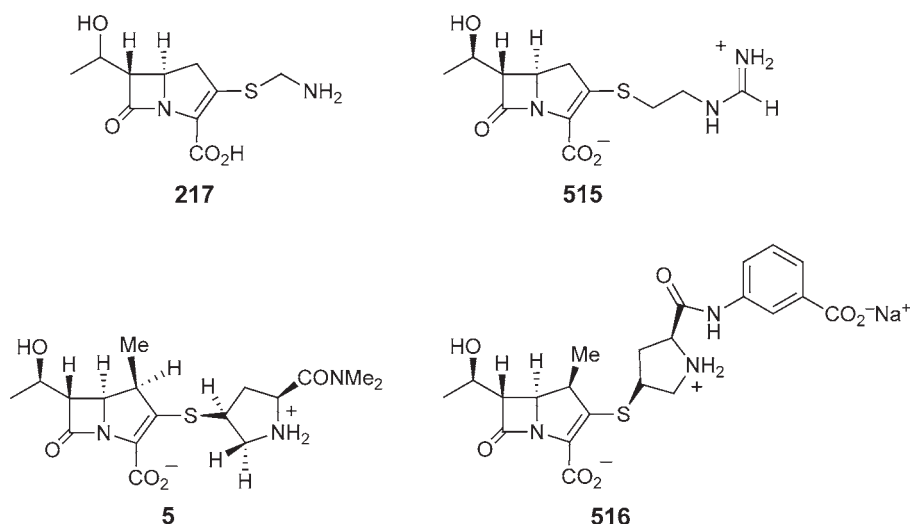


The synthesis of aza[*n*]adderanes and azahomo[*n*]adderanes (*n* = number of fused rings) containing β -lactams at the terminus has been reported for the first time (see Section 2.04.6.3). Cycloaddition of DMAD to the norbornene π -bond of **513** in the presence of a ruthenium catalyst yielded [5]homoladderane **514** in 89% yield (Equation 85) <1997SL38>. Other examples of these types of compounds are reported in Section 2.04.6.3.

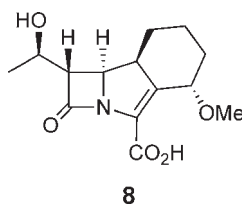


2.04.12 Applications

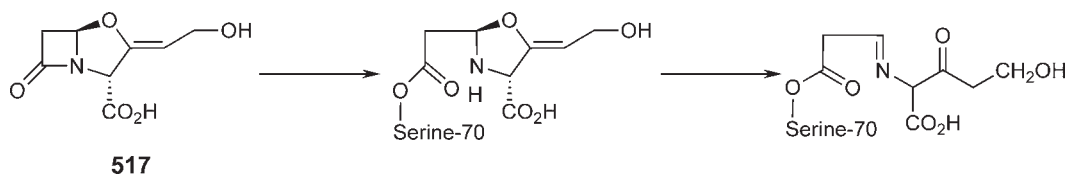
In CHEC-II(1996) (Section 1.21.12), mention was made of the potential importance of the announcement of antibacterial activity found in naturally occurring thienamycin **217**. This compound was too unstable for clinical use and although more than 50 naturally occurring carbapenems have been isolated, none have been found to be superior to thienamycin <2001H(54)497>. Synthetic compounds were essential. By the end of the 1980s, routes to the carbapenem nucleus had been established. Imipenem **515** was developed but had to be administered in conjunction with cilastatin, which inhibited deactivation by DHP-1 and also decreased the nephrotoxicity of the drug. A big leap forward was made in the 1990s with the development of meropenem **5** with a weakly basic side chain (in contrast to the strongly basic substituent in imipenem) and a 1 β -methyl substituent which allowed the administration of an adjuvant drug unnecessary and decreased both the nephro- and neurotoxicity <B-1997MI306, 1997MI673, 1997MI1814, 2000MI5, 2000MI1, B-2001MI151>. In the past decade, much effort has gone into the development of new carbapenems, particularly by modification of the 2-substituent, often by the procedures mentioned in Section 2.04.7.2 <2005JOC7479>. Many compounds have been prepared and the SARs evaluated usually for carbapenems with a 6-(1-hydroxyethyl) substituent and a 1 β -methyl group <2003EJM841>. Meropenem has been applied widely in clinical use though several doses are required per day. Developments are leading to compounds gaining approval for use, for example, ertapenam **516** having an improved pharmacokinetic profile and once-daily administration <2003BML4399, 2005JOC7479>. It is presumed that the sodium carboxylate group is responsible for the enhanced DHP-1 stability and pharmacokinetic profile <2005BML231>.



A major development was the announcement by GlaxoWellcome of their studies of synthetic tricyclic carbapenems in the early 1990s <1991EPP0416953A2, 1996BML491, 1999MI3497, 2001MI553>. These tricyclic compounds (formerly known as tribactams but now known as trinems, for example, sanfetrinem **8**) are stable to β -lactamases and dehydropeptidases and have a good range of potency and spectrum of action <1996BML491>. Studies of tetracyclic carbapenems followed but without so much success in uncovering useful properties. A review of non-classical β -lactams, which includes tri- and tetracyclic compounds with and without the bridgehead nitrogen atom, has been published <2000T5743, 2004RMC69>.



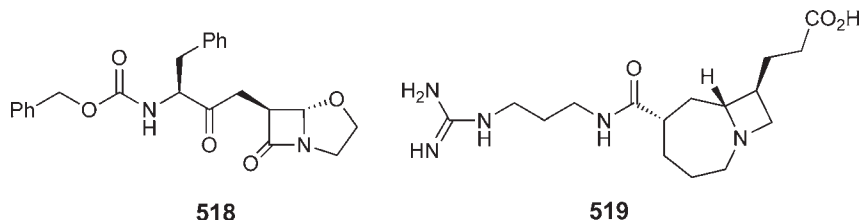
An important use of β -lactams is in the prevention of class A serine β -lactamases from catalyzing the hydrolysis of medically important β -lactams to give biologically inactive ring-opened products. Clavulanic acid **517** itself possesses insufficient antibacterial activity to be important as an antibiotic but it does possess the very important property of inhibiting the serine β -lactamases in a process by which both the four- and five-membered rings are opened (Scheme 18). Clavulanic acid is administered in combination with an antibiotic in order to increase the effectiveness of the drug. β -Lactams have also found applications as inhibitors of elastase, which is a member of the chymotrypsin subfamily of serine proteases. Esters of clavulanic acid, but not the acid, inhibit PPE <2000T5729>.



Scheme 18

Cysteine proteases, cathepsin B, L, K, and S, may be involved in a variety of pathogenic conditions including rheumatoid arthritis, osteoporosis, and cancer metastasis, and are important targets for the development of inhibitors. The 4-oxa-1-azabicyclo[3.2.0]heptan-7-one **518** is an excellent inhibitor of cathepsin L and K *in vitro* <2002BML3413>.

It is suggested that the bicyclic diastereoisomeric *trans*-azetidine **519** is a convenient nonpeptidic framework which mimics the β -turn topology of the Arg-Gly-Asp (RGD) tripeptide portion of the extracellular matrix protein, fibronectin, involved in cell adhesion <2003BML1561>.

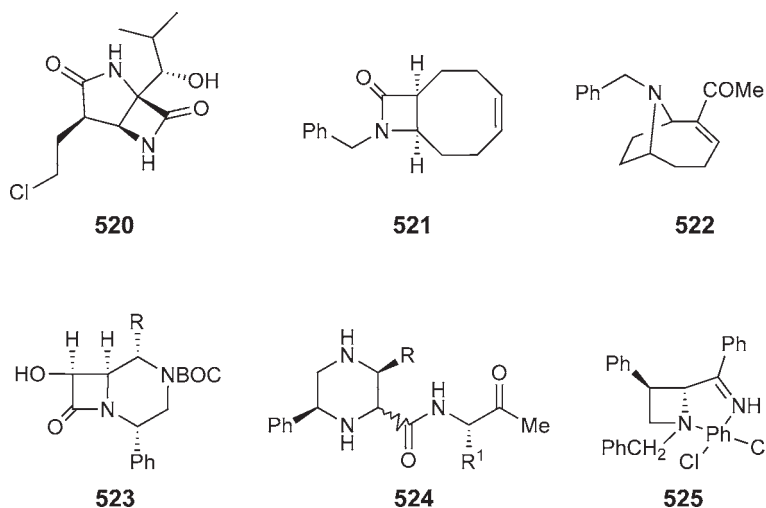


In addition to their role as antibiotics, another use of β -lactams under investigation is their potential as a trigger when fused with a cyclic enediyne system <2006CC2992>. It is envisaged that the trigger event of opening of the four-membered ring can be promoted by a suitable endogenous enzyme predirected to the target tumor site in procedures such as antibody-directed enzyme-prodrug therapy (ADEPT) or the analogous gene-directed approach (GDEPT) <2002EJO3745> (see Sections 2.04.9.3 and 2.04.11.2.1(vii)).

The fused bicyclic β -lactones salinosporamide A and omuralide are potent selective inhibitors of proteasome function. Unfortunately, they have short half-lives in serum; otherwise, they might be interesting candidates for use as anticancer agents. The fused bicyclic β -lactam **520**, which has similar but not identical molecular architecture to salinosporamide A, shows proteasome inhibition *in vitro* and 'indefinite' stability in neutral aqueous solution. It is thought that **520** acts by acylation of the hydroxyl group of threonine in a proteolytic β -subunit of the proteasome <2005JA15386>.

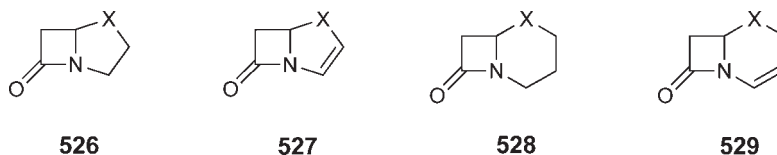
Much effort has been devoted to the development of stereoselective, or ideally stereospecific, routes to fused ring β -lactams of known relative or absolute stereochemistry. These compounds are now being used to obtain the corresponding β -amino acids by opening of the four-membered ring (see Section 2.04.6.4) <2004TA573, 2004TA2875, 2005BML1371>. More widely, some fused ring β -lactams have been used as synthons in routes to other heterocycles, for example, the synthesis from **521** of the natural product **522** <1996T11637> and the conversion of **523** to **524** <1997TL4643>. Routes to β -lactams and their use as synthons have been reviewed <2004CME1921>.

Bicyclic complexes containing an azetidine ring and a palladium atom **525** have been shown to be effective catalysts in Suzuki coupling reactions with bromobenzenes and with the generally less reactive chlorobenzenes. The catalyst was stable in air for several months without loss of activity and the catalyst loading in the reaction could be lowered to 0.1% without a decrease of yield in the reactions studied <2005JOM2306>.



2.04.13 Further Developments

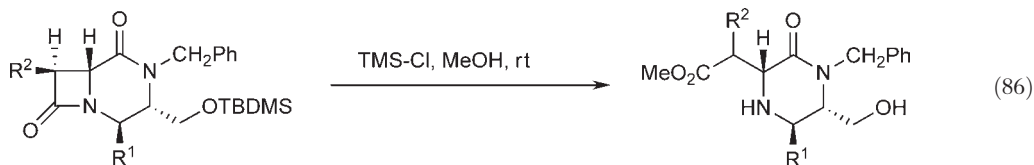
High level *ab initio* calculations performed with the Gaussian 03 program using the multistep G3/B3LYP method to calculate the ring strain energies (RSE) and amide resonance energies (ARE) of the β -lactam rings in the penam, penem, and cepham type nuclei **526–528**, respectively, have shown that the RSE destabilization is greater than the stabilization due to ARE when X = S, O, or CH₂ (see Section 2.04.2). In the cephem type nucleus **529** (X = S, O, or CH₂) the converse is true, though the difference between the two opposing effects is small. The lactam nitrogen atom is more pyramidal in the penam and penem nuclei than in the cepham and cephem nuclei. Delocalization of π -electrons into the six-membered ring in cephems makes the ring more rigid. This delocalization effect does not occur in the penem nucleus. Changing the nature of the atom or group X does not lead to pronounced discernible trends in RSE or ARE <2006JPC(A)10521>.



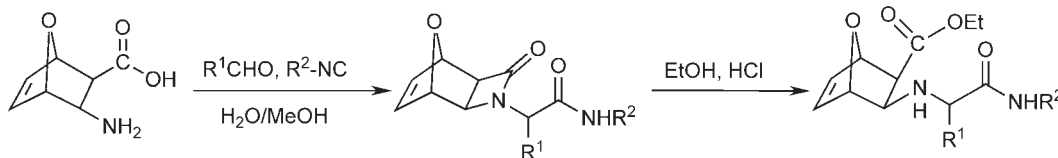
Lipase-catalyzed enantioselective ring cleavage of racemic *cis*- and *trans*-13-azabicyclo[10.2.0]tetradecan-14-one has given enantiopure β -aminoacids and β -lactams (see Section 2.04.6.4) <2006TA3193>.

Structural studies of clavulanic acid dehydrogenase, which catalyzes the biosynthesis of clavulanic acid **54** (R¹ = R² = H) from clavulanate-9-aldehyde, have provided a deeper understanding of the mechanism of the reduction process <2007B1523>.

Enantiopure fused oxopiperazino- β -lactams have been produced by application of the Staudinger reaction with 5,6-dihydropyrazin-2-(1*H*)-ones and the β -lactams were converted to the 2-oxopiperazine-3-acetic acid esters in good yield with no epimerization (Equation 86) <2006TL8911>. Fused β -lactams have been formed from macrocyclic imines by use of the Staudinger reaction (see Section 2.04.9.7). When phenoxyacetyl chloride and triethylamine were used, the best yields (45–52%) of the fused β -lactams were obtained with dry dichloromethane as solvent <2006TL8855>.

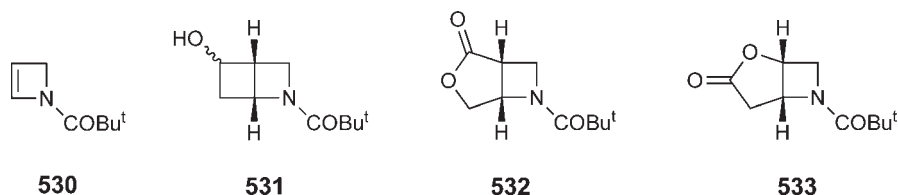


Further work on the use of the Ugi reaction to convert β -amino acids into fused β -lactams (see Section 2.04.9.8) followed by opening of the β -lactam ring to obtain derivatives of the original β -amino acid has been reported (see Section 2.04.11.2.2) (Scheme 19). In general, distilled water was found to be a better solvent than methanol and careful adjustment of the concentration of reactants for each individual reaction produced precipitation of the products and acceleration of the reaction <2006TL9113>.

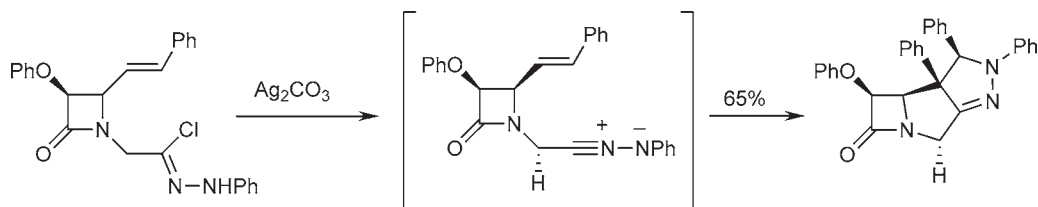


Scheme 19

The cycloaddition of 2-azetine **530** and dichloroketene gave the alcohol **531** in three steps which, in two further steps, gave the lactones **532** (mainly) and **533** <2006TL6377>.



Intramolecular 1,3-dipolar cycloaddition (see Section 2.04.9.7) has been used to obtain racemic and enantiopure azeto[2',1':1,2]pyrrolo[3,4-*c*]pyrazoles from nitrilimine intermediates (Scheme 20). The relative configuration of the products was established from the NOE enhancements in the ^1H NMR spectra (see Section 2.04.3.2) <2006TA1319>.

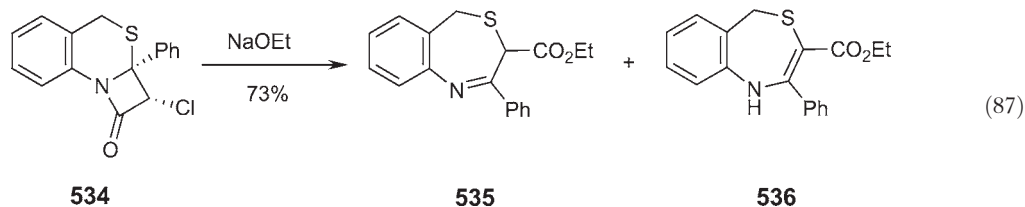


Scheme 20

A better understanding of the role of substituents in the photochemical rearrangement of 5-alkylidene-2,5-dihydroisoxazoles has been obtained (see Section 2.04.9.8, Equation 38) <2007T1583>.

Alcaide's group has reported further work on the radical cyclization of alkenyl or alkynyl substituted 4-allenynol- β -lactams (see Section 2.04.9.6) <2007JOC1604>. Titanocene monochloride mediated reductive radical cyclization of 1-cyanoalkyl-4-(epoxy-2-phenylethyl)-2-azetidinones yielded bi- or tri-cyclic β -lactams, the latter having an aryl group fused to a seven membered ring <2007T3017>.

Treatment of the tricyclic β -lactam **534** with sodium ethoxide in ethanol gave the tautomeric 4,1-benzothiazepines **535** and **536** in an isolated yield ratio of 3:1, respectively (Equation 87) <2006TL5665>.



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Biographical Sketch



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Lina Mehta obtained B.Sc., M.Sc., and Ph.D. degrees in India before moving to the Chemistry Department at Brunel University in 1989 as a postdoctoral research fellow. Her work has been centered mainly in synthetic organic chemistry associated with anticancer research in collaboration with Cancer Research UK, Gray Cancer Research Trust, and Royal Marsden Hospital in the UK, and with several other research institutes in the USA and Australia. The Chemistry Department at Brunel finally closed in 2000 and Dr. Mehta moved into the Centre for the Environment and subsequently into the Institute for the Environment at Brunel. Her main area of research at present is on the synthesis and application of ionic liquids to environmental problems. She has published numerous research papers in various journals and co-authored reviews on aspects of heterocyclic chemistry for several well-known series of books.

2.05

Oxetanes and Oxetenes: Monocyclic

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2.05.1 Introduction

Oxetanes are an important group of four-membered cyclic ethers that undergo a wide range of chemical transformations. The corresponding carbonyl-substituted systems are known as oxetanones: one well-known group is 2-oxetanones, the β -lactones. Oxetenes are unsaturated oxetanes. The synthesis and study of oxetane, oxetanones, and oxetenes are of significant research interest since, like their three-membered ring analogues, the epoxides, oxetane ring systems have a high degree of ring strain, making them ideal monomers for polymerizations. They can also be used in synthesis as equivalents for the α^3 -synthon, and undergo a wide range of chemical transformations. The oxetane ring structure is found in many natural products, and exhibits a range of biological activities.

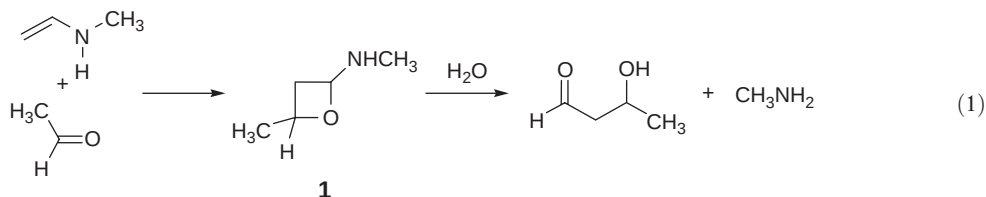
Oxetanes and oxetanones were covered in CHEC(1984) and CHEC-II(1996) <1984CHEC(7)363, 1996CHEC-II(1)721>. This chapter covers the literature for the period 1996–2007, is intended to update and complement the previous chapters in CHEC(1984) and CHEC-II(1996), and covers major new preparations, reactions, and concepts. At the beginning of each main section is a sentence explaining the major advances since the publication of the earlier chapters. It will also be of benefit to the reader to read this chapter together with CHEC-II(1996) and CHEC(1984) for an in-depth coverage of the area. Other recent reviews, published since 1995, that may be of interest include the polymerization of heterocyclic monomers in 1998 <1998PPO919>, and the formation of four-membered heterocycles constructed via electrophilic heteroatom cyclizations in 2002 <2002EJO3099>.

2.05.2 Theoretical Methods

2.05.2.1 Structure and Synthesis

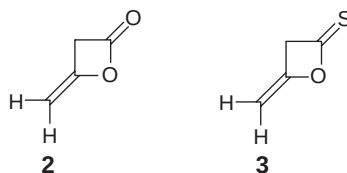
A few theoretical studies of oxetanes and oxetanones have been reported since CHEC-II(1996). Building upon a study of the oxetane $\cdots$ HCl complex studied by rotational spectroscopy, MP2 calculations were used to investigate the axial and equatorial HCl arrangement, and to try and explain why for oxetane $\cdots$ HCl only one conformer was observed <2001CPL250, 2002CPL123>. The amine-catalyzed aldol reaction via enamine intermediates has been explored using density functional theory (DFT) (B3LYP/6-31G*) and conductor-like polarizable continuum model

(CPCM) solvation, to study the mechanisms and stereochemistries of this important synthetic reaction. Interestingly, from these calculations, it was concluded that secondary enamine-mediated aldols have high activation energies if there is no proton source, and oxetane intermediates such as **1** can be formed (Equation 1) <2001JA11273>.

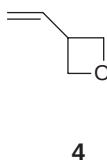


2.05.2.2 Stability and Reactivity

The theoretical infrared (IR) spectra of diketene 4-methylene-2-oxetanone isomers (e.g., **2**) and mono- and disulfur analogues such as **3** have been calculated at the MP2/6-311++G** level to provide data on whether new analogues could potentially be prepared <2001JST433>.



Compared to oxetane or alkyloxetanes, 3-vinyloxetane **4** undergoes a fast thermal fragmentation. To explore this observation, a theoretical study was undertaken with MP2 and quadratic configuration interaction with single and double excitations (QCISD) *ab initio* theories using the 6-31G(d) basis set <2003PCA2919>. Transition states for the chemical reactions involved were characterized and, for the direct fragmentation of **4** to formaldehyde and butadiene, synchronous and asynchronous concerted paths were predicted. However, the asynchronous path gave the most favorable reaction channel and could explain the increased fragmentation rate in **4**.



The cycloreversion of oxetanes and cleavage of two bonds can be achieved using electron-transfer photosensitizers, and this general process is important since it is involved in the photorepair of DNA <2002AGE767>. The cycloreversion of oxetane radical ions has been studied theoretically at the UB3LYP/6-13G* level <2005PCA2602>. DFT calculations indicated that C–C bond breaking of the transition state is more advanced than O–C cleavage, and that cycloreversion is via a concerted asynchronous mechanism. The thermal decomposition of 2-oxetanone and 2-azetidinone has been studied and compared using DFT calculations and photoelectron spectroscopy to explore the cycloreversion pathways. Theoretical calculations indicated that the cycloreversion of 2-oxetanone to ethene and CO₂ is probably a concerted asynchronous process and has the lowest free energy and activation barrier of the two compounds <2000CPL433>.

The influence of substituents on the energetics of the uncatalyzed Mukaiyama aldol reaction was studied using *ab initio* molecular orbital calculations at the G3(MP2) level <2005JOC124>. For the reaction between formaldehyde and trihydrosilyl enol ether, a concerted pathway via a six-membered transition state was favored over a stepwise pathway and an oxetane intermediate.

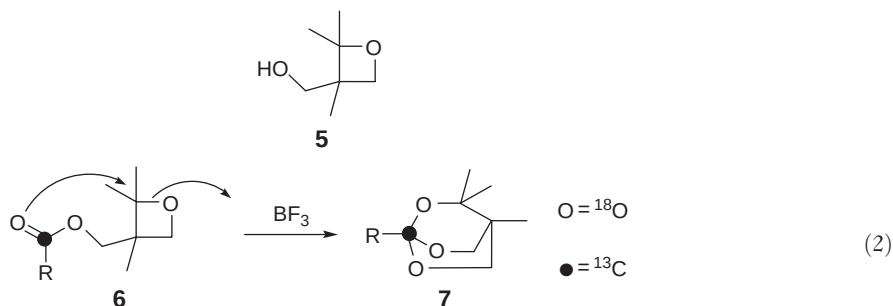
2.05.3 Experimental Structural Methods

2.05.3.1 Nuclear Magnetic Resonance Spectroscopy

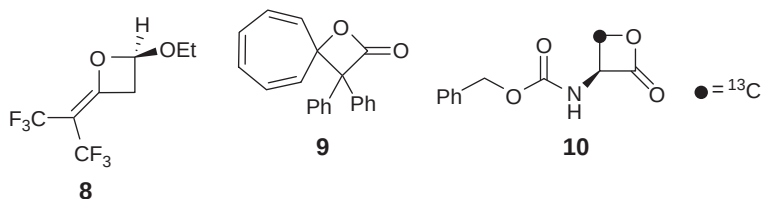
Key references prior to 1993 on ^1H and ^{13}C nuclear magnetic resonance (NMR) shifts for oxetanes are found in CHEC(1984) <1984CHEC(7)363>. Further references on ^{13}C NMR coupling constants and chemical shifts, and ^{17}O NMR data on oxetanones are in CHEC-II(1996) <1996CHEC-II(1)721>. Since 1995, several NMR spectroscopy studies of oxetanes have been used for the structural identification of novel natural products (see Sections 2.05.11 and 2.05.12).

The hydrogen-bonded complexation of 3,3-pentamethyleneoxetene, oxetane, 3-phenyloxetane, and 3-(4-nitrophenyl)oxetane with nitric acid and trifluoroacetic acid (TFA) have been measured by ^1H NMR spectroscopy <1996J(P2)2073>. The proton signals on the carbon adjacent to the oxygen were monitored and the complexation related to the basicities of the oxetane oxygens. Complexation with trifluoroacetic acid indicated that with this acid, oxetane was a stronger hydrogen-bonding base than tetrahydrofuran (THF). A detailed NMR study has been reported on the ^1H , ^{13}C , and ^{19}F NMR spectra of a variety of fluorinated oxetanes with fluorine either on or in close proximity to the ring <2000JFC219>. These data will be particularly useful for those investigating the regio- or stereochemistry of [2+2] photochemical reactions between fluorinated alkenes and carbonyl compounds. The effect of ring substituents on the chemical shifts and coupling constants are described for over 50 fluorinated oxetanes.

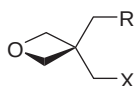
Several mechanistic studies using NMR spectroscopy have been reported on oxetanes or 2-oxetanones. The protection of carboxylic acids toward nucleophiles and strong bases through conversion to the orthoester is known. The orthoester is typically prepared via the Lewis acid-catalyzed rearrangement of the corresponding oxetanyl esters. Recently the dimethyl oxetanyl alcohol **5** has been reported <2005OL499>. Rearrangement of its oxetanyl ester **6** to the orthoester **7** using BF_3 etherate was studied using ^{18}O labeling (Equation 2). The position of the label was determined using ^{13}C NMR spectroscopy, which indicated that attack of the ester carbonyl on the oxetane ring occurred at the most substituted position.



The mechanism for the Staudinger ketene–alkene cycloaddition to give cyclobutanones has been studied using low-temperature ^1H , ^{13}C , and ^{19}F NMR spectroscopy, which indicated that an α -methyleneoxetane **8** was initially formed <2003JA14446>. Low-temperature NMR studies of the reaction between tropone and ketenes also led to the characterization of the β -lactone intermediate **9** from a [2+2] cycloaddition, which was subsequently isomerized to the γ -lactone product isolated <2005HCA1519>. Investigations into proteinase inhibition have been carried out using heteronuclear multiple quantum correlation (HMQC) NMR studies and ^{13}C -labeled **10**. Irreversible enzyme inactivation was determined to be due to nucleophilic attack by a cysteine thiol residue at the β -position (^{13}C labeled) of the oxetanone ring <2002JOC1536>.



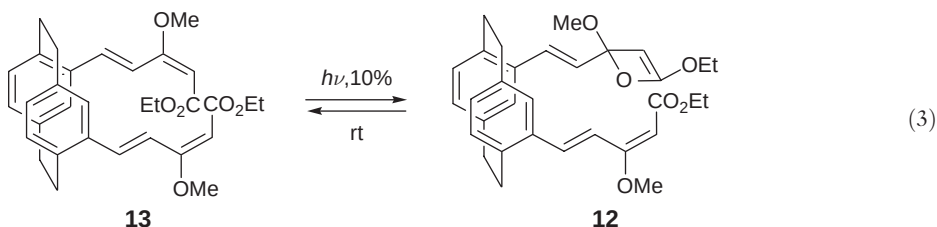
Functionalized oxetanes **11**, with R = indenyl or fluorenyl and $\text{X} = \text{PR}_2$, have been prepared and studied in detail by ^1H , ^{13}C , and ^{31}P NMR spectroscopy <2001EJI949>. They were then converted into tripod ligands via a nucleophilic ring opening for complexation to metal ions.

**11**

R = indenyl, fluorenyl

X = PR₂

Recently, a novel oxetene **12** has been isolated from the irradiation of crystals of a vinyllogous cinnamophane **13** (Equation 3) <2005EJO558>. The structure was elucidated by NMR spectroscopy and mass spectrometry and interestingly, for a thermodynamically unstable compound, was isolated at room temperature after column chromatography. The cycloreversion of **12** to **13** was also observed at ambient temperature.



2.05.3.2 IR Spectroscopy

There are few further fundamental IR spectroscopy studies since 1995. A high-resolution far-IR spectrum of oxetane from 50–145 cm⁻¹ has been recorded (at 203 K since the spectrum was not resolved at room temperature), and the rotation ring-puckering spectrum of oxetane was observed for the first time <2001JST1>. In further studies, Ritz assignment and Watson fits of the high-resolution ring-puckering spectrum of oxetane were described <2003JSP152>. Fourier transform infrared (FT-IR) spectrometry has also been used to study the 1:1 hydrogen-bonded complexes of methanol and a range of ethers including oxetanes to assess the hydrogen-bond basicity of the sp³ oxygens <1998EJO925>.

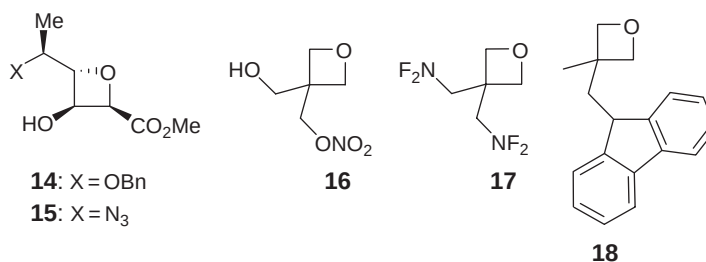
2.05.3.3 Mass Spectrometry

The fragmentation patterns of oxetanes have been described in previous studies including CHEC-II(1996). Mass spectrometry has been used together with other spectroscopic techniques for the structure elucidation of new 2-oxetanone natural products and this is covered in Section 2.05.11.

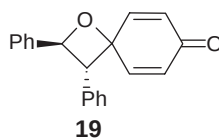
2.05.3.4 X-Ray Crystal Structure

The X-ray crystal structure of oxetane was reported in 1984 and is mentioned in CHEC-II(1996) <1996CHEC-II(1)721>. Notably, the carbon–oxygen bond length was longer than that in THF and dioxane, and the ring was puckered with symmetry *C_s*. Substituted oxetanes were reported where the oxetane ring was puckered at an angle ranging from ca. 5° to 23° <1984CHEC(7)363>.

More recently, other crystal structures of substituted oxetanes have been reported including methyl 2,4-anhydro-6-deoxy-5-*O*-benzyl-*L*-altrionate **14**, methyl 2,4-anhydro-5-azido-5,6-dideoxy-*L*-altrionate **15**, and 3,3-bis(hydroxymethyl)-oxetane mononitrate **16**. X-Ray crystallographic analysis was used to confirm the structure of the benzyl ether **14**, an intermediate in the synthesis of oxetane *cis*-β-amino acids <2001TL4247>. In related work, the azido analogue **15** was prepared <2004AXE1609> and the crystal structure determined. A procedure has been reported to synthesize the mononitrate **16**, and X-ray crystallography indicated that the oxetane ring was virtually planar <2003RCB1859>, as has previously been reported for the corresponding dinitrate. In 3,3-bis(difluoroaminomethyl)oxetane **17**, a new energetic material, the difluoroamine groups showed no signs of disorder and the molecule occupied a position on a twofold axis <2003AXE2032>. The X-ray crystal structure of the fluorenyl oxetane **18** has also been reported <1999EJI2187>.



The [2+2] cycloaddition of stilbenes and chloranil to give oxetanes has been investigated using photoinduced electron transfer (PET) <1999JOC2250>. X-Ray crystallography indicated that *trans*-oxetanes such as **19** were generated selectively in high yields. The mechanism of this photoinduced cycloaddition, the Paternò–Büchi reaction, was also studied using time-resolved spectroscopy, which revealed that the singlet ion-radical pair [stilbene^{•+}, chloranil^{•-}] was formed as the primary reactive intermediate.



2.05.3.5 Microwave and Photoelectron Spectroscopy

Several microwave spectroscopic studies of oxetanes have been carried out since 1995. Fourier transform microwave spectroscopy was used to observe the rotational spectrum of the van der Waals complex of oxetane–argon <1998CPL272>. The conformation behavior of the hydrogen bond in oxetane···HX has also been investigated. The rotational spectrum of oxetane–hydrogen fluoride was studied using molecular beam Fourier transform microwave spectroscopy which indicated a *C_s* symmetry with the HF lying in the symmetry plane, and little oxetane structural changes on complexation <2001CPL31>. The complex oxetane···HCl generated in a supersonic jet was analyzed using Fourier transform microwave spectroscopy, and again indicated a *C_s* symmetry <2001CPL(334)250>. The rotational spectrum of the 3,3-dimethyloxetane···HF complex was studied and only the axial conformer was detected <2005PCP1157>. *Ab initio* computations were carried out to rationalize why an equatorial conformer was not observed. An identical study was also carried out with 3,3-dimethyloxetane···HCL complex where again only a single axial conformer was observed <2005CPL259>.

The interaction between oxetane and water has also been investigated by measuring the rotational spectrum of the 1:1 oxetane–water complex <2004CEJ538>. The rotational spectra of oxetane with H₂O, D₂O, DOH, HOD, and H₂¹⁸O were studied and quantum-chemical calculations also performed. The water molecule was found to lie in the plane of symmetry of oxetane with the oxetane ring slightly nonplanar.

2.05.4 Thermodynamic Aspects

Thermodynamic aspects of oxetanes related to stabilities and cycloreversions have been discussed in Sections 2.05.2 and Section 2.05.3.1. Mechanistic studies involving thermolysis or photolysis are in Section 2.05.6.2.

2.05.5 Reactivity of Fully Conjugated Rings

No reports have been published during the period 1996–2006.

2.05.6 Reactivity of Nonconjugated Rings

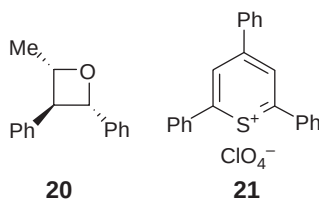
2.05.6.1 General

Oxetanes can undergo a range of synthetically useful transformations. The basicity of the ring oxygen makes them readily susceptible to electrophilic attack. Where the electrophile is a Lewis acid, the oxetane ring is activated allowing nucleophilic attack and subsequent ring opening. Oxetanes can also be cleaved under reductive conditions to afford carbanions. Leaving groups that are directly attached to the oxetane ring can be substituted by various nucleophiles while leaving the ring intact. Oxetanes have also been extensively used as monomers for the synthesis of both branched and linear polyethers by cationic or anionic processes. Other useful transformations include thermal decomposition, photolysis, and cycloaddition.

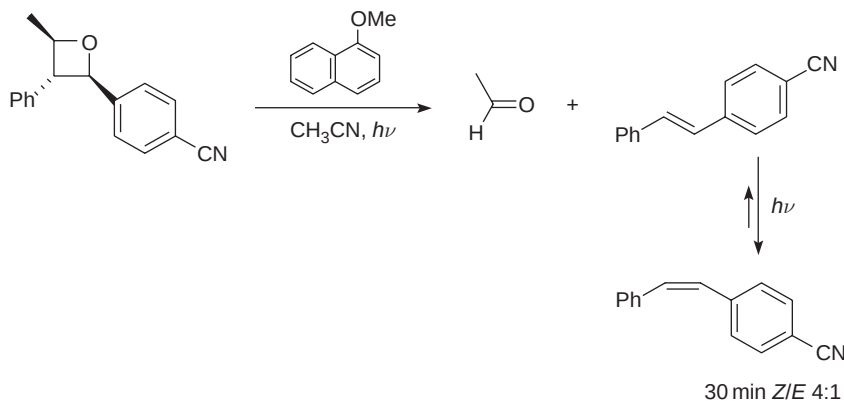
The high susceptibility of oxetanones to ring cleavage limits the number of transformations when the ring remains intact. However, there are examples of nucleophilic addition at the carbonyl carbon. They can also undergo thermal decomposition by loss of carbon dioxide, as well as a range of acid-catalyzed transformations.

2.05.6.2 Thermolysis and Photolysis

The photolytic cleavage of oxetanes was described in CHEC-II(1996), including the photochemical fragmentation of 2,2-diaryloxetanes with electron-transfer photosensitizers <1996CHEC-II(1)721>. Such photochemical fragmentations are of interest because it is the reverse of the Paternò-Büchi photocycloaddition used to generate oxetenes. A more recent study has investigated the cycloreversion of oxetane **20** using a thiapyrylium salt **21** as the electron-transfer photosensitizer <2001OL1965>. The use of laser flash photolysis detected the radical cation of *trans*-stilbene as an intermediate, and although previous studies have indicated that the cycloreversion goes through the photosensitizers' singlet state, here it was concluded that the reaction takes place from the triplet excited state.

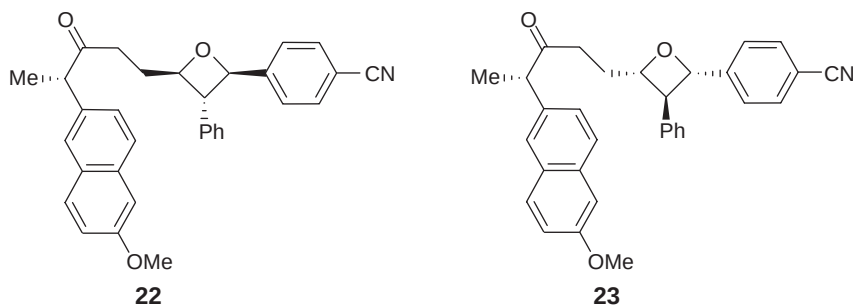


Cycloreversion of oxetanes by PET has also attracted interest, because it is analogous to the repair of (6-4) photoproducts <2003JOC10103, 2005JOC1376>. These DNA lesions are formed by a Paternò-Büchi reaction between dipyrimidine sites, followed by rearrangement of the oxetanes formed, and can cause mutagenic, carcinogenic, and other lethal effects. To this end, the cycloreversion of 2-(*p*-cyanophenyl)-4-methyl-3-phenyloxetane was studied, using 1-methoxynaphthalene as the electron-transfer photosensitizer <2003JOC10103>. Rather than giving the expected Paternò-Büchi photoproducts, β -methylstyrene and *p*-cyanobenzaldehyde, irradiation at 300 nm led to the formation of acetaldehyde and *p*-cyanostilbene (with the *cis*-isomer as the major isomer in a ratio of 4:1 after 30 min) by cleavage of the O-C(2) and C(3)-C(4) bonds in the radical anion (Scheme 1).



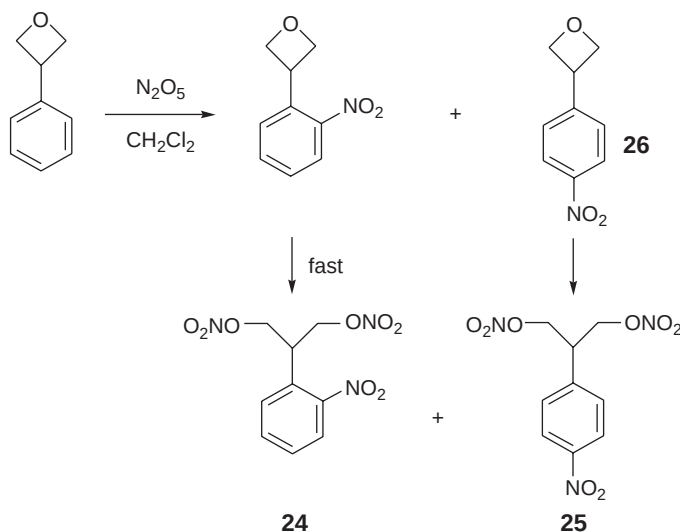
Scheme 1

A comparative study of cycloreversion was carried out between oxetane stereoisomers **22** and **23**, in both acetonitrile and chloroform at a λ_{max} of 300 nm with oxetanes being cleaved in the same fashion as the previous example <2005JOC1376>. For both oxetanes, photoreactivity was found to be higher in acetonitrile. Cycloreversion was faster for oxetane **23** than oxetane **22** in both solvents, although this difference in reactivity was more significant in chloroform. The higher reactivity of **23** was attributed to the folded conformation which it can adopt, allowing interactions between the methoxynaphthalene chromophore and the *p*-cyanophenyl group.



2.05.6.3 Reactions with Electrophiles

The basicity of oxetanes makes them susceptible to attack by electrophiles, which is usually followed by attack from a nucleophile and ring cleavage. Examples given in CHEC(1984) and CHEC-II(1996) include the reaction of oxetanes with reagents such as thioesters, dimethylboron bromide, or oxides of nitrogen <1984CHEC(7)363, 1996CHEC-II(1)721>. The latter reaction, which is used to generate acyclic dinitrate products, is still widely applicable. As part of a mechanistic study, 3-phenyl oxetane was reacted with dinitrogen pentoxide under various conditions (Scheme 2) <1998J(P2)243>. It was shown that aromatic nitration is overwhelmingly preferred over nitration of the oxetane ring, so this always occurs prior to the ring-opening reaction. Both *ortho*-**24** and *para*-**25** products were formed, with a significant preference for *para*-aromatic nitration. However, the *ortho*-nitrated oxetane intermediate was converted into **24** much more rapidly than the *para*-nitrated intermediate **26** was converted to **25**. Reaction conditions were adjusted to enable the formation of the *para*-nitrophenyl oxetane **26** in 93% yield with only 7% of **24** formed.



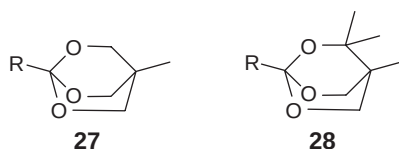
Scheme 2

2.05.6.4 Acid-Catalyzed Transformations

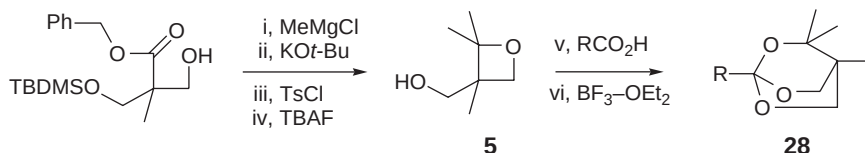
CHEC(1984) and CHEC-II(1996) discuss the acid-catalyzed transformations of oxetanes including ring expansion to THFs and formation of cyclic orthoesters <1984CHEC(7)363, 1996CHEC-II(1)721>. They also include many examples of the use of oxetane monomers in cationic polymerization reactions, giving ready access to polyethers.

2.05.6.4.1 Oxetane rearrangement

The mechanism of orthoester formation, discussed in CHEC-II(1996), includes the nucleophilic ring opening of an oxetane by an oxygen nucleophile <1996CHEC-II(1)721>. More recent examples of acid-catalyzed, intramolecular ring opening and expansion of oxetanes by oxygen and other heteroatom nucleophiles are discussed in Section 2.05.6.5. Orthoesters are typically formed by a reaction between a carboxylic acid and an oxetane and this provides a protecting group for the carboxylic acid, the most common being [2.2.2]-bicyclic (OBO) orthoesters, **27**, which are stable toward nucleophilic attack and basic enolization. Recently, work in this area of protecting group strategies has focused on developing related orthoesters that are formed at a faster rate and are more stable to hydrolysis <2003JOC10079>. The dimethyl-substituted OBO (DMOBO) orthoesters, **28**, are formed 85 times faster (from the corresponding esters) than OBO orthoesters and they are 36 times more stable to acidic hydrolysis <2005OL499> (see Section 2.05.3.1). Also, compared to the [3.2.1]-bicyclic orthoester protecting group ABO which is prepared via the rearrangement of an oxirane ester, the formation of DMOBO requires harsher reaction conditions but it is more stable to hydrolysis.

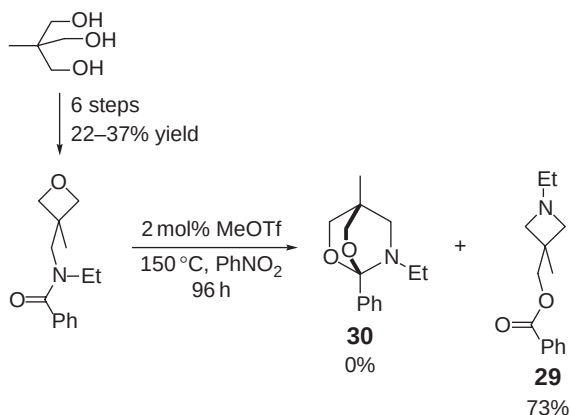


One potential disadvantage is that the synthesis of the precursor **5** is via a four-step synthetic sequence from the benzyl ester TBDMS ether of 2,3-bis(hydroxymethyl)propionic acid (Scheme 3), and investigations are currently underway to develop a more efficient synthesis.



Scheme 3

An unusual example of an acid-catalyzed rearrangement of oxetanes is the reaction of *tert*-amide-substituted oxetanes with MeOTf at high temperatures to give ester-substituted azetidines (e.g., **29**; Scheme 4) <2000JOC2253>. The tertiary amide oxetanes can readily be prepared using a six-step sequence from trimethylolethane.

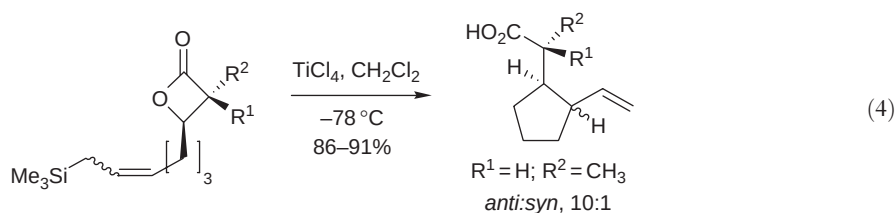


Scheme 4

This rearrangement proceeds via a bicyclic acetal (e.g., **30**), and therefore it is a double isomerization involving a ring expansion followed by a ring contraction. It was shown to be most effective using benzamide or pivalamide derivatives and the ratio of the ester to the bicyclic acetal was dependent on the reaction conditions used; for example, with 5 mol% of MeOTf at 130 °C in chlorobenzene, 53% of **29** and 14% of **30** was formed.

2.05.6.4.2 Ring expansion of 2-oxetanones

Prior to 1995, 2-oxetanones were shown to be converted to butyrolactones by a dyotropic rearrangement using magnesium bromide <1996CHEC-II(1)721>. A more recent example of an acid-catalyzed ring expansion is the stereoselective conversion of α -methyl- β -lactones to a cyclopentane (Equation 4) <2002OL3231>. This transformation was utilized as a key step in the synthesis of (+)-brefeldin A, a fungal metabolite with a range of potent pharmaceutical properties. A model reaction is shown in Equation (4) and studies indicated that the highest yields were achieved when the Lewis acid TiCl_4 was used. The stereochemistry of the β -lactone was shown to have an effect on the stereoselectivity of the reaction, with *trans*- β -lactones generally giving higher *anti:syn* ratios (10:1) and the opposite diastereoselectivity compared to *cis*- β -lactones (*anti:syn*, 2:3). The geometry of the allylsilane was found not to influence the stereochemical outcome of the reaction.

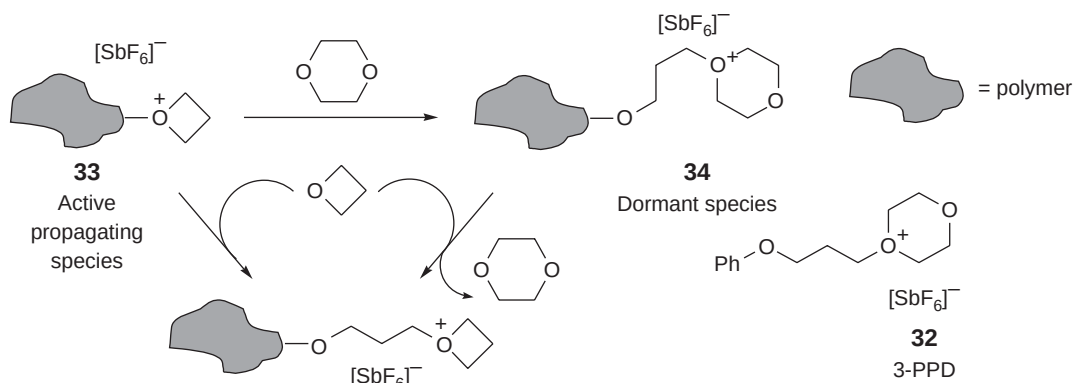


2.05.6.4.3 Cationic polymerization reactions

Cationic polymerization of cyclic ethers is the most commonly used method of synthesizing polyethers. A Lewis acid catalyst is generally used to initiate the cationic polymerization reaction by activation of the oxetane ring oxygen, allowing nucleophilic attack from the ring oxygen atom of a second oxetane molecule and ring opening. Branched polyethers can be formed by intramolecular chain transfer and the prevalence of branched units can be increased by using monomers with pendant hydroxyl groups <1999MARC369, 2001MM5112, 2002MI155, 2003PIN1595>. When such monomers are used, branching can arise from chain transfer to hydroxyl groups or by active monomer propagation reactions between the protonated oxetane ring and a hydroxyl group <2003PIN1595>. However, intramolecular chain transfer to hydroxyl groups is also responsible for the formation of cyclic fragments, leading to polyethers of limited molecular weight (1000–2000 g mol⁻¹) <2001MM5112>. Where 3-ethyl-3-(hydroxymethyl)oxetane **31** was used as a monomer, neither the molecular weight nor degree of branching were successfully controlled by polymerization conditions, although copolymerization with a dihydroxymethyl-functionalized monomer did lead to an increase in the number of branched units <2003PIN1595>.



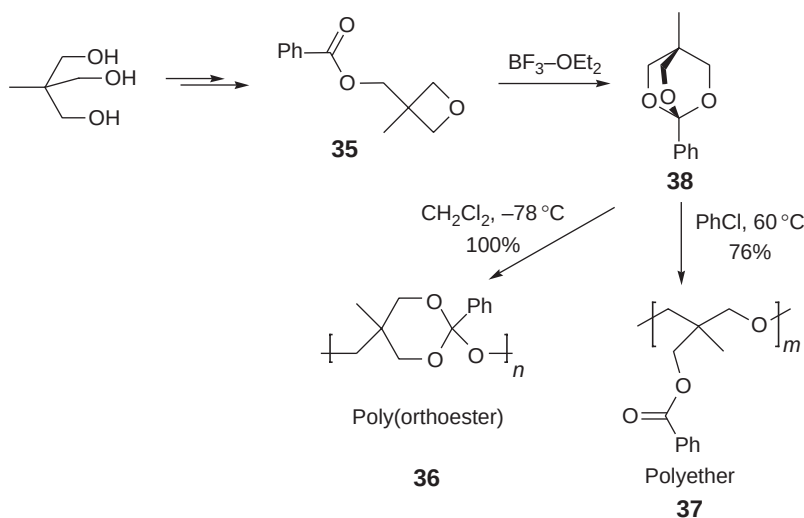
It is well known that so-called ‘living polymerization’ can be used to control the molecular weight and polydispersion of polymers formed by this method. The name refers to a polymerization process whereby there is a dynamic equilibrium between an active and an inactive species, with the rate of conversion being much higher than the rate of propagation. ‘Living polymerization’ in the cationic ring-opening polymerization of oxetanes has been demonstrated using 3-phenoxypropyl 1,4-dioxonium hexafluoroantimonate (3-PPD) **32** as a fast initiator in 1,4-dioxane <2005CC3870>. Here, the active propagating species **33** is capped in the form of a tertiary oxonium ion **34** giving a species that is inactive or dormant due to the lack of ring strain (Scheme 5). The rate of activation of **34** was influenced by its concentration and that of the monomer oxetane, since **34** can be reactivated by a monomer addition reaction. Using this method, well-defined oxetane polymers were achieved with low polydispersion.



Scheme 5

Photoinitiated cationic polymerization, using onium salts to generate very strong acids, has been successful for many classes of monomers. However, in the case of oxetane monomers, this type of initiation gives a long induction period followed by rapid conversion of the monomer [\[2004PSA1630\]](#). This is thought to be due to the high stability of a tertiary oxetanium ion intermediate. It has since been shown that the induction period can be minimized by increasing the reaction temperature, copolymerization with more reactive epoxides monomers, or by the use of free-radical photoinitiators [\[2005PSA3205\]](#).

When oxetane monomers with phthalimide, maleimide, succinimide, or glutarimide pendant groups in the 3-position were treated with an acid catalyst, there was initially a rearrangement reaction to give bicyclic acetals [\[2001MAC2489\]](#). The polymerization which followed was temperature dependent, with temperatures below room temperature giving polyacetals and temperatures of 120–130 °C giving polyethers. Oxetanes with 3-ester substituents (e.g., **35**) were reacted in a similar fashion using BF_3 etherate, to give either poly(orthoesters) such as **36** (through a single ring opening) or polyethers **37** (with a double ring-opening polymerisation) via a bicyclic orthoester **38** (Scheme 6) [\[2002MAC511\]](#).



Scheme 6

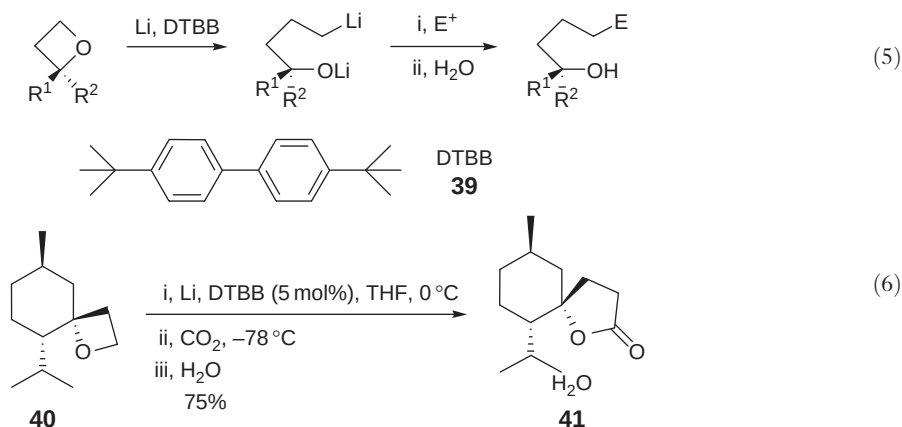
2.05.6.5 Reactions with Nucleophiles

Oxetanes are generally much more stable to nucleophilic attack than the more strained three-membered ring oxiranes. However, activation of the oxygen atom by a Lewis acid increases the electronegativity of the adjacent carbon atom and renders oxetanes susceptible to attack from a nucleophile accompanied by subsequent ring opening.

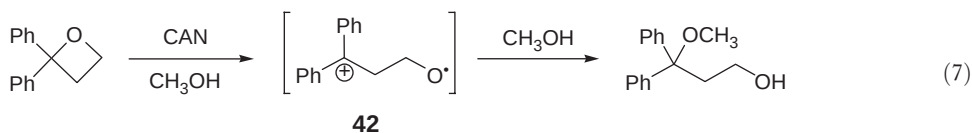
Where the nucleophile is a second molecule of oxetane, a chain reaction occurs leading to the formation of polymers, as discussed in [Section 2.05.6.4.3](#). However, oxetanes can also be ring-opened by a wide range of alternative nucleophiles, and reactions of this nature make oxetanes an important synthetic intermediate.

2.05.6.5.1 Ring cleavage by oxidation or reduction

Oxetanes can be reduced to acyclic products by strong reducing agents such as lithium aluminium hydride. CHEC(1984) describes the regiochemistry of these reactions and CHEC-II(1996) discusses further reductive cleavages of oxetanes to give lithioalkoxide ions [<1984CHEC\(7\)363, 1996CHEC-II\(1\)721>](#). A similar reaction has been reported more recently using lithium and 4,4'-di-*tert*-butyldiphenyl (DTBB) **39** as the electron carrier in the reductive ring opening of chiral oxetanes ([Equation 5](#)) [<1997TA2633>](#). The lithium dianion formed can then be reacted with a range of electrophiles (e.g., D₂O, Bu^tCHO, PhCHO, Me₂CO, CO₂) and after workup lead to a range of products. An interesting example is shown in [Equation \(6\)](#), with reaction of the chiral oxetane **40** with Li and DTBB and then the addition of CO₂: after an acidic workup, the spirolactone **41** was isolated in 75% yield.



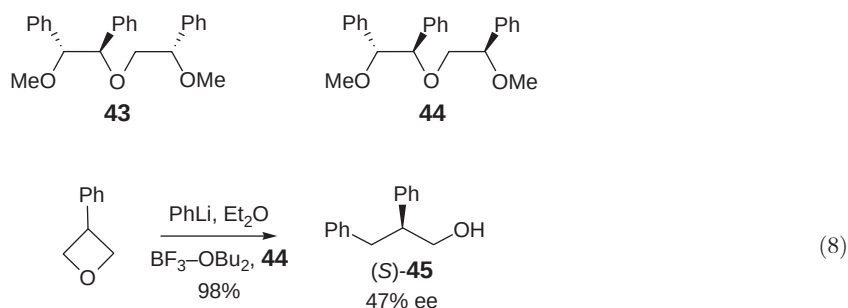
The ring opening of 2,2'-diphenyloxetane has been achieved using cerium(IV) ammonium nitrate (CAN) as a redox catalyst ([Equation 7](#)) [<2003TL4585>](#). The first step involves oxidation of the oxetane by Ce(IV) to a cyclic radical cation. Equilibration to the ring-opened distonic version **42** with a stabilized cation, then quenching of the cation with methanol and reduction of the alkoxide radical by Ce(III) to the anion, completes the catalytic cycle.



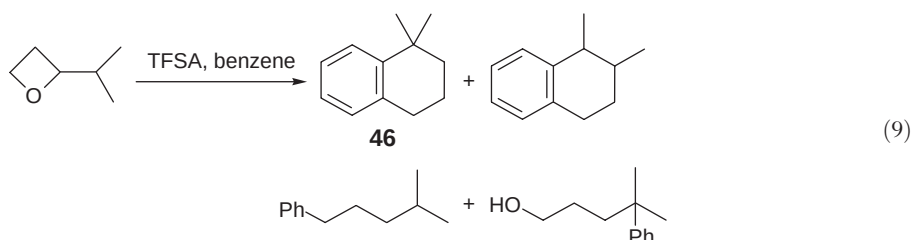
2.05.6.5.2 Reactions with carbon nucleophiles

CHEC-II(1996) discusses reactions between oxetanes and a variety of organometallic or enolate carbon nucleophiles [<1996CHEC-II\(1\)721>](#). It has since been demonstrated that such reactions with carbon nucleophiles are also successful where the substrate has a hydroxyl group attached to the oxetane ring [<1998EJO2161>](#). Hence 3-isopropyl-2-phenyl-3-oxetanol was reacted in a clean regioselective fashion (at the C-4 position) with a range of organolithium reagents (RLi; R = Ph, Me, ⁿBu). Two equivalents of the organometallic species were required for a successful reaction, the first of which deprotonated the hydroxyl group.

Attempts have been made to influence the stereoselectivity of the Lewis acid-catalyzed oxetane ring opening by carbon nucleophiles using chiral ligands [<1996TA2483, 1997T10699>](#). To this end, chiral ligands **43** and **44** were synthesized, from 1,2-diphenylethane-1,2-diol as a starting material, and tested in the Lewis acid-catalyzed ring opening of 3-phenyloxetane with phenyllithium to form the chiral alcohol **45** ([Equation 8](#)). Ligand **43** had little effect, and an essentially racemic mixture was generated. However, the use of ligand **44** favored the formation of (*S*)-**45** in 47% ee.

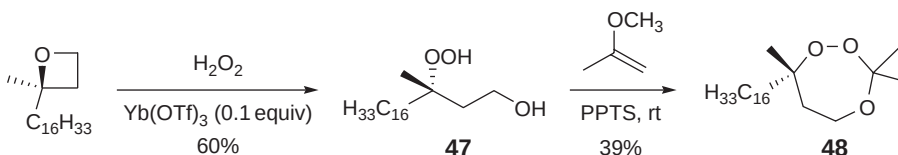


Oxetanes have also been used as alkylating agents in the Friedel–Crafts reaction; for example, 2-isopropoxyxetane was reacted with benzene in superacidic trifluoromethanesulfonic acid (TFSA) to give a mixture of alkylated aromatic products (Equation 9) <2003CAL1>. The main product of the reaction was the tetralin derivative **46** which could be isolated in up to 75% yield. Other notable side products are shown, resulting from monoalkylation or other skeletal rearrangements.



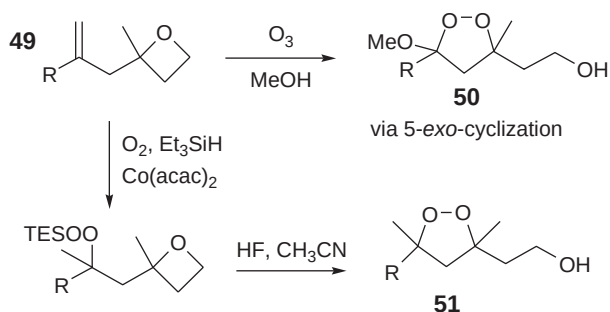
2.05.6.5.3 Reactions with oxygen nucleophiles

The reaction between β -lactones and alkoxides has been extensively reviewed in CHEC(1984) and CHEC-II(1996) <1984CHEC(7)363, 1996CHEC-II(1)721>. Recently, there has been an interest in the stereoselective synthesis of 1,2-dioxolanes and 1,2-dioxanes, which are found in peroxide natural products, and this has given rise to further examples of reactions between oxetanes and oxygen nucleophiles. It has been demonstrated that oxetanes will react with hydrogen peroxide in the presence of a Lewis acid (e.g., TMSOTf, Yb(OTf)₃, Sc(OTf)₃), to give hydroperoxyalkanol products that can be used as in the synthesis of 1,2-dioxolanes (Scheme 7) <2002OL4591>. This regioselective reaction also has moderate to good stereoselectivity (up to 90% inversion observed) and moderate yields (29–60%). Oxetanes were synthesised from 1,3-diols that were enantiomerically enriched (>80% ee), and these enantiomerically enriched oxetanes were then reacted with hydrogen peroxide to give the first general method for the asymmetric synthesis of 3-hydroperoxyalknols such as **47** in 60% yield (Scheme 7). The ketalization of these in the synthesis of 1,2,4-trioxepanes (e.g., **48**) was also demonstrated.



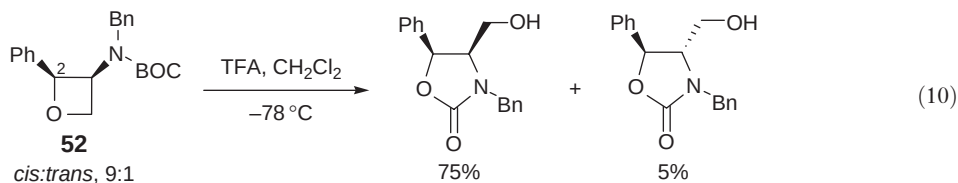
Scheme 7

Several successful methods have been reported for the synthesis of 1,2-dioxolanes and 1,2-dioxanes that involve intramolecular attack of an oxetane by an oxygen nucleophile <2005OL4333>. These include a 5-*exo*-ring opening of **49** by hydroperoxides, generated in solution using ozone, to give **50** as a mixture of *cis*- and *trans*-diastereoisomers. Another method is the deprotection of silyl-protected hydroperoxyacetals, formed by a reductive dioxxygenation of **49**, which can undergo a 5-*exo*-nucleophilic attack to generate the 1,2-dioxolane **51** (Scheme 8).

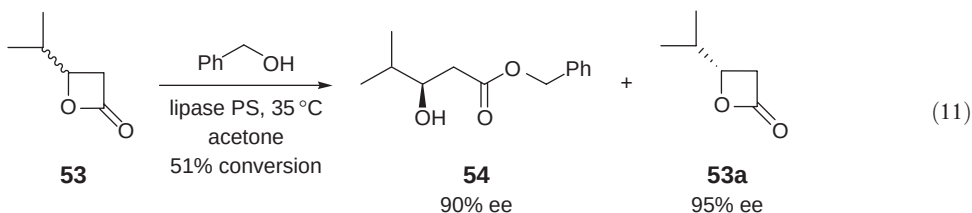


Scheme 8

A further example of intramolecular attack and ring opening of an oxetane by a variety of heteroatom nucleophiles has been reported [\[1996JOC7642\]](#). Where the heteroatom nucleophile was an alkoxide, a six-membered cyclic ether was successfully synthesized (see an analogous amine reaction in [Section 2.05.6.5.4, Equation 12](#)). Treatment of *N*-*t*-butoxycarbonyl-substituted 2-phenyl-3-aminooxetanes **52** (the *cis*-isomer is the major diastereoisomer) with TFA leads to the formation of oxazolidinones, with inversion of configuration at the C-2 position ([Equation 10](#)) [\[1997TL3707\]](#). The mechanism is thought to involve a nucleophilic attack on the more substituted α -position of the protonated oxetane, followed by elimination of the *t*-butyl group. This stereospecific reaction gives access to precursors of *anti*-1,2-amino alcohols. However, attempts to form cyclic carbonates with inversion of configuration by an analogous reaction gave nonstereospecific products [\[1998JOC1910\]](#).

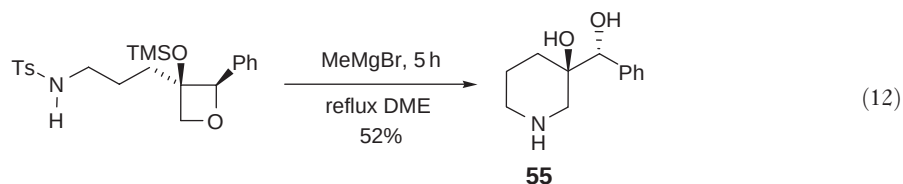


β -Lactones have been ring-opened by an alcohol in a lipase-promoted asymmetric transesterification reaction [\[2000JP171\]](#). A kinetic resolution of racemic 2-oxetanones was achieved using Lipase PS (*Pseudomonas* sp. lipase) on a range of substrates. For example, as shown in [Equation \(11\)](#), oxetane **53** was readily converted into the (*S*)-3-hydroxy-4-methylpentanoate **54** with high ee, leaving the unreacted (*R*)-stereoisomer **53a**. For the majority of reactions with 4-alkyl, 3-alkyl, and 3,4-dialkyl β -lactones, lipase PS, rather than porcine pancreatic lipase (PPL), was shown to give transesterified products with the highest ee's.

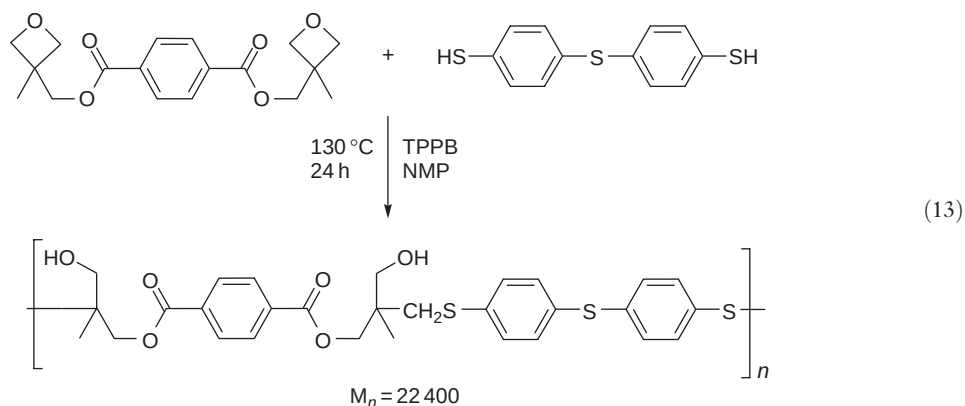


2.05.6.5.4 Reactions with other heteroatom nucleophiles

The intermolecular ring opening of oxetanes by nitrogen nucleophiles has been widely reported. Reactions of this type are often Lewis acid catalysed and are highly regioselective, with the nucleophile attacking the least substituted α -carbon of the oxetane. The analogous intramolecular reaction has been reported for nitrogen and other heteroatom nucleophiles in recent years as a method of forming heterocycles of various sizes [\[1996JOC7642\]](#). These reactions were both regioselective, with the heteroatom attacking the least-substituted α -carbon, and stereospecific with no epimerization. An example is shown in [Equation \(12\)](#) with the reaction of a diastereomerically pure oxetane to give piperidine **55**. Instead of an $-NTs$ group, analogous reactions were also carried out with oxetanes possessing a terminal OPiv or SAc moiety to give the corresponding tetrahydropyrans and thiotetrahydropyrans.

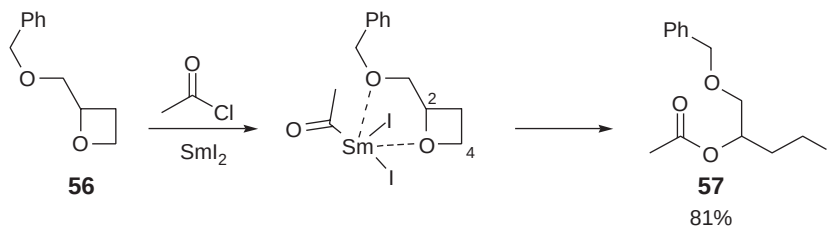


The nucleophilicity of thiols has been exploited in a polymerization reaction between bisoxetanes and dithiols (Equation 13) <1998PSA2873>. This polymerization reaction afforded products with high molecular weights (up to $M_n = 22\,400$), and also water-soluble polymers possessing pendant hydroxyl groups. Rather than being acid-catalyzed, the reaction was accelerated by using neutral catalysts, either quaternary onium salts (e.g., tetraphenylphosphonium bromide (TPPB)) or crown ether complexes (e.g., 18-crown-6/KBr), and *N*-methyl-2-pyrrolidine (NMP) was used as a typical reaction solvent. No cross-linked gel products were observed, indicating that side reactions between the polymer pendant hydroxyl groups and monomer oxetane groups did not occur.



2.05.6.5.5 Reactions with halides

4-Dimethylaminopyridine (DMAP) reacts with POCl_3 or PCl_3 to form a complex and liberate a chloride ion. It has been shown that when this reaction is carried out *in situ* in the presence of an oxetane, a ring-opening reaction proceeds to give chlorohydrins in good yields and under relatively mild conditions <2002TL15>. The reactions can also be highly regioselective for asymmetric oxetanes, particularly when using POCl_3 , with chloride attack at the carbon with either the most favorable electronic effects or the least steric hindrance. Conditions have been developed for the ring opening of oxetanes, with ether moieties at C-2, in a highly regioselective fashion <2002JOC9488>. The reaction between samarium diiodide and acyl chloride or anhydride gives a reagent which can form a bidentate chelate with oxetanes (e.g., **56**), making the addition of iodide to the unsubstituted α -carbon (C-4 rather than C-2) far more favorable (Scheme 9). Although some alkyl- or ether-substituted oxetanes showed moderate regioselectivities, one regioisomer only (**57**) was formed when there was a CH_2OBn moiety at C-2.



Scheme 9

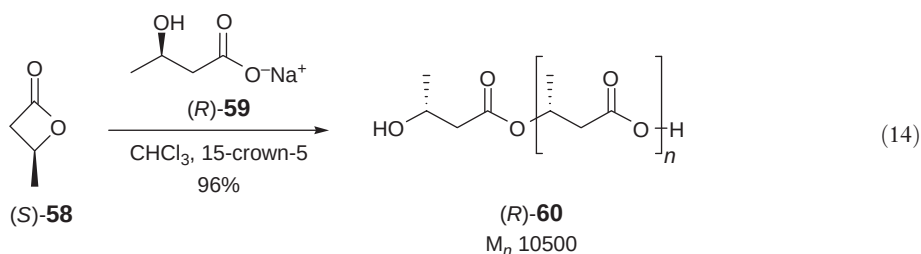
2.05.6.5.6 Anionic polymerization reactions

Reports of anionic polymerization reactions of oxetane monomers are less common in the literature, than the generally applied cationic method. While unsubstituted oxetanes have been successfully converted to their corresponding

polyethers using initiator systems consisting of bulky nucleophiles and hindered Lewis acids, there can be unfavorable interactions between the pendant functional groups and nucleophilic species when substituted oxetanes are used.

It has recently been reported that substituted oxetanes, such as 3'-(4-bromobutoxymethyl)-3-methyl oxetane, can be converted to the corresponding polyethers by anionic/coordination polymerization with aluminium benzyl alcoholate bis(2,6-di-*tert*-butyl-4-methylphenolate) (BnOAD). This reaction can also be accelerated by addition of the hindered Lewis acid methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenolate) (MAD) <2004PSA4570>. Unlike cationic polymerizations of oxetanes with boron trifluoride etherate, no linear or cyclic oligomer by-products are formed in this reaction and molecular weights are significantly higher. Also, oxetanes with pendant hydroxyl groups have been converted to hyperbranched polyethers in good yields, using potassium *tert*-butoxide as the initiator with 18-crown-6 <2003POJI88, 2004POJ413, 2004PSA3739>. These polyethers contain an oxetane moiety, as well as many hydroxyl end groups, and postpolymerization under the same conditions affords higher-weight polyethers.

The use of metal alkoxides as activators in the synthesis of polyhydroxyalkanoates (PHAs), such as poly(β -hydroxybutyrate), has been widely studied in recent years <1996PIN479, 1996MM3773, 1998MM3473, 1998MM6718, 2001BMM623, 2002PSA2184, 2002JA15239, 2004T7177>. These reactions can proceed by different mechanisms: a coordination–insertion mechanism or an anionic mechanism. The choice of initiator and reaction conditions can be used to determine the mechanistic outcome and thus the stereochemistry of the polymer formed, and explain the formation of side products that may be generated. The ring-opening polymerization of (*S*)- β -butyrolactone ((*S*)-**58**) initiated by the sodium salt of (*R*)-3-hydroxybutyric acid ((*R*)-**59**), in the presence of a crown ether, led to the formation of poly-(*R*)-3-hydroxybutyrate (PHB) ((*R*)-**60**) by the anionic mechanism (Equation 14) <1998MM6718>. PHB is a natural biopolymer produced by many microorganisms. The polymerization proceeded regioselectively, with inversion of configuration of ((*S*)-**58**) to generate PHB with an almost identical structure to natural PHB. Notably, this synthetic approach avoided the synthesis of PHB with acetoxy end groups associated with the coordination–insertion mechanism, which are not present in naturally occurring poly-(*R*)-3-hydroxybutyrate (see Section 2.05.12.2). The initiator **59** has also been used for the synthesis of completely atactic poly-(*R,S*)-3-hydroxybutyrate, using a racemate of β -butyrolactone as the starting material <2002PSA2184>.



2.05.6.6 Enolates Derived from 2-Oxetanones

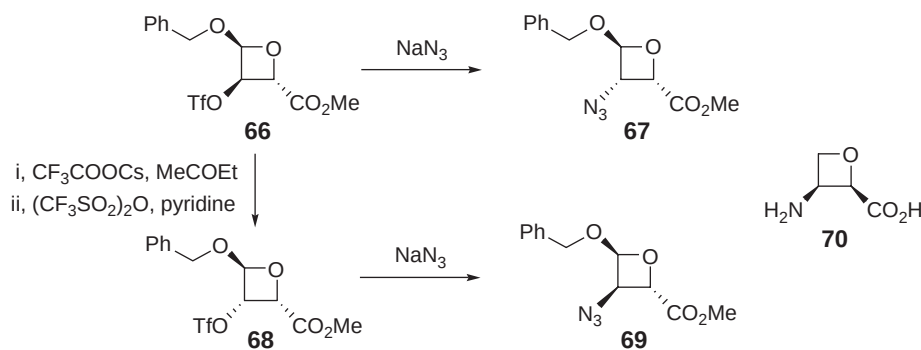
The scope for forming 2-oxetanone enolates is limited because oxetanones have a high affinity toward reacting with nucleophiles. Past examples are discussed in CHEC(1984) and CHEC-II(1996); however, no notable examples have been published since 1996 <1984CHEC(7)363, 1996CHEC-II(1)721>.

2.05.6.7 Reactions with Radicals and Carbenes

Limited examples of reactions between oxetanes and radicals are found in CHEC(1984) and CHEC-II(1996) <1984CHEC(7)363, 1996CHEC-II(1)721>. In recent years, no reactions of this nature have been reported.

2.05.6.8 Cycloaddition Reactions

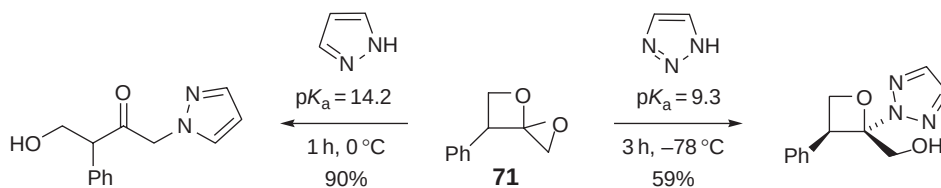
It has long been known that oxetane can be reacted with isocyanates and carbodiimides to give 1,3-oxazin-2-ones and 1,3-oxazin-2-imines, respectively, and CHEC(1984) and CHEC-II(1996) give examples of these and analogous reactions <1984CHEC(7)363, 1996CHEC-II(1)721>. Previously, reactions of this nature have required high temperatures (100–200 °C); however, it has been reported that vinyl oxetanes such as **61** can be reacted with these species at room temperature in the presence of a palladium catalyst to form 1,3-oxazines in good yields (e.g., Scheme 10) <1999JOC4152>. Thought to proceed via a π -allylpalladium intermediate, these reactions were completely regio- and stereoselective to give heterocycles **62** and **63** in good yield.



Scheme 12

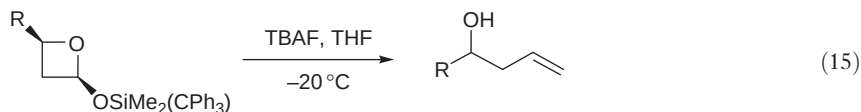
give the *cis*- β -azido ester **67**. Alternatively, **66** could be reacted with cesium trifluoroacetate, again with inversion of configuration, to give the *cis*- β -hydroxy ester, which was converted to the triflate ester **68**. Reaction with sodium azide as before gave the corresponding *trans*- β -azido ester **69**. Subsequent hydrolysis of the ester and reduction of the azide enabled access to unnatural amino acid analogues of oxetin **70**, which could be coupled to form peptides (see Section 2.05.11.2).

Epoxides directly attached to the oxetane ring in 1,5-dioxaspiro[3.2]hexanes (e.g., **71**) can be ring-opened by certain nucleophiles without attack on the less-strained oxetane ring [<1999OL825, 2003JOC1480>](#). However, such reactions can alternatively lead to the formation of α -substituted- β' -hydroxyketones. It was reported that the pK_a of the nucleophile generally determines the reaction outcome ([Scheme 13](#)).



Scheme 13

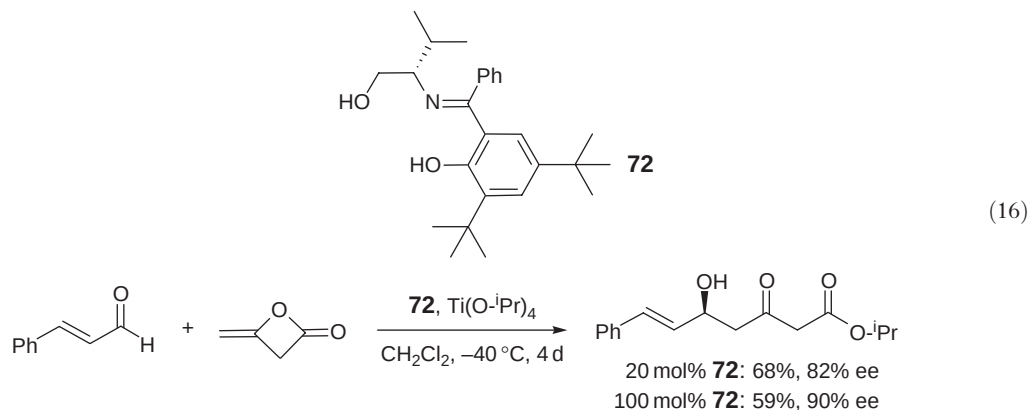
Silylmethyl oxetanes were converted to allylic alcohols when added to a solution of tetrabutylammonium fluoride (TBAF) in THF ([Equation 15](#) [<1998JOC5517>](#)). Treatment with TBAF is a commonly known method of removing silyl protecting groups. In this case, attack of the fluoride ion on the silica atom lead to elimination of the silyl group and ring opening of the oxetane.



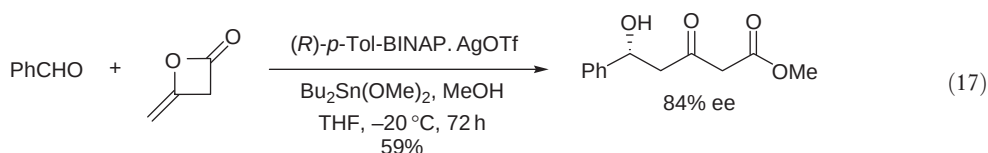
2.05.7.3 Reactions of Methylene-Substituted 2-Oxetanones

The chemistry of methylene-substituted 2-oxetanones, and in particular diketene, has attracted a vast amount of research over the years, so other alkylene-substituted oxetanes and oxetan-2-ones, including methylene oxetanes, are discussed separately in [Section 2.05.7.4](#). Diketene is also known as 4-methylene-2-oxetanone and a notable difference between this and other 2-oxetanones is that it undergoes thermal decomposition by a cycloreversion reaction to give ketene, rather than forming allene and CO₂. CHEC-II(1996) refers to a series of comprehensive reviews of the chemistry of this compound [<1996CHEC-II\(1721\)>](#).

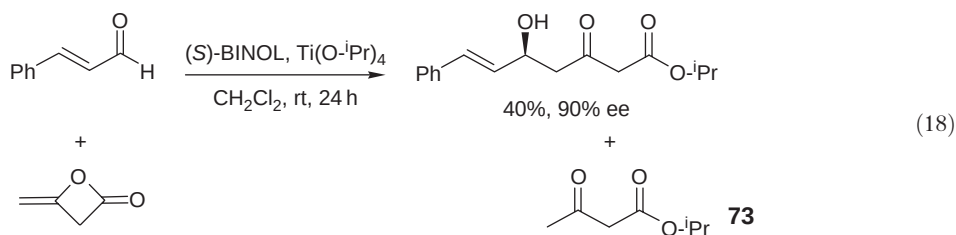
Recently, diketene has been employed in a range of enantioselective reactions. For example, a series of enantioselective aldol-type reactions between diketene and aldehydes have been reported [<1998SL601, 1999JA892, 2004SC4487>](#). The use of a chiral Schiff base **72** and $\text{Ti}(\text{O}^i\text{Pr})_4$ to promote this reaction gave the product in good yield and high ee ([Equation 16](#)) [<1998SL601>](#).



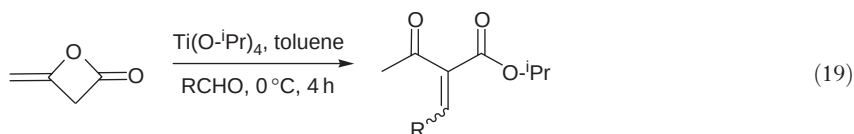
An alternative system for this reaction that gave the product in a comparable yield and similar enantioselectivities has been reported, and uses trialkyltin methoxide and a BINAP–silver(i) catalyst (BINAP = 2,2-bis(diphenyl-phosphanyl)-1,1'-binaphthyl; [Equation 17](#)) [<1999JA892>](#).



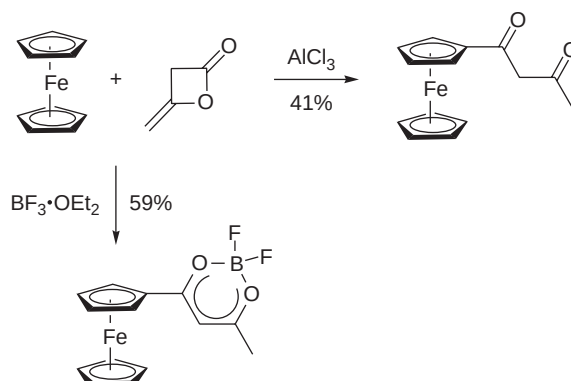
High enantioselectivities were also achieved using $\text{Ti}(\text{O}^i\text{Pr})_4$ and (*S*)-BINOL ([Equation 18](#)) [<2004SC4487>](#). Here, the yield was much lower than with the previous examples (up to 40% only). This was thought to be due to strong coordination of the oxo-functionalized product to the titanium center, as well as the formation of a by-product **73** due to hydrogen abstraction. The use of a proton sponge led to an improved yield, but the enantioselectivity was dramatically reduced, giving an almost racemic mixture of products.



Diketene has also been used as a C-4 unit in a Knoevenagel-type reaction [<2004T6777>](#). Reaction between diketene and $\text{Ti}(\text{O}^i\text{Pr})_4$ generated a titanium enolate, which then reacted with a series of aldehydes ([Equation 19](#)). Aliphatic aldehydes were found to be generally more reactive than aromatic aldehydes. However, reactions with aromatic aldehydes were much more regioselective, with the (*E*)-isomers formed predominantly. This regioselectivity in reactions with aromatic aldehydes is not observed in the conventional Knoevenagel reaction. A further interesting observation was that the reaction took place under mildly acidic conditions, whereas the conventional method proceeds under basic conditions.

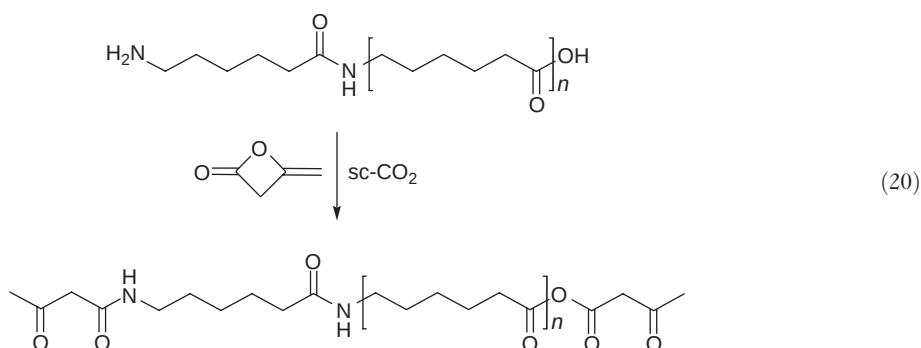


Other interesting reactions with diketene include its use in a Friedel–Crafts-type acetoacetylation of ferrocene (**Scheme 14**) and a 1,1'-diphosphaferrocene <2001OM4448>. When boron trifluoride was used as the Lewis acid, BF₂ chelates of the acetoacetylated metallocenes were formed.

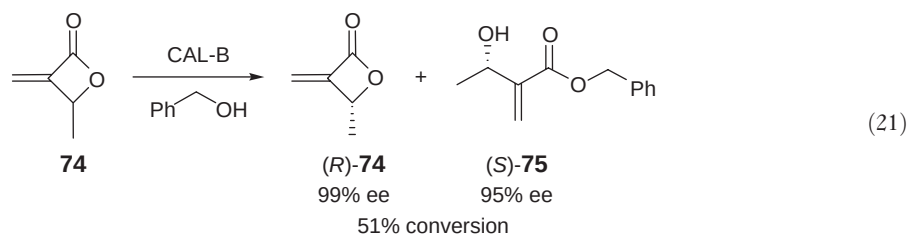


Scheme 14

The end group modification of a polyamide with diketene in supercritical carbon dioxide has also been reported (**Equation 20**) <2004MI75>.

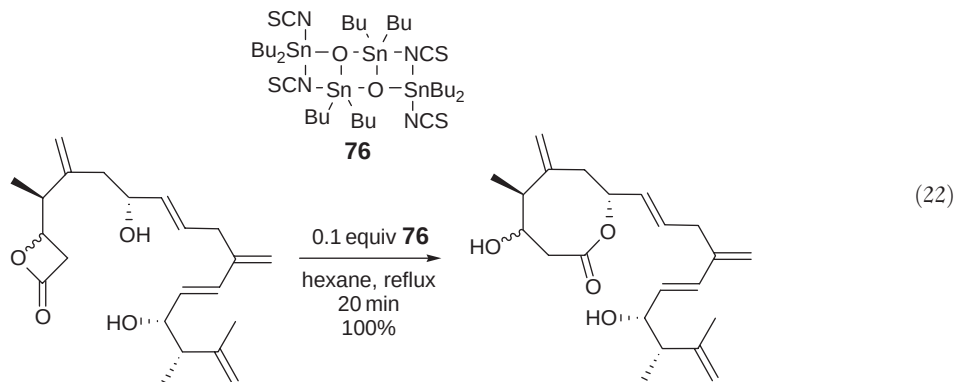


While diketene remains a very important synthetic precursor, there has been increasing interest in the chemistry of α -methylene- β -lactones, 3-methylene-2-oxetanones. However, unlike diketene, which can be readily synthesized by the dimerization of aldehydic ketenes, there are few methods for the synthesis of α -methylene- β -lactones in the literature. Recent strategies for the preparation of the compounds are discussed in **Section 2.05.9.2**. The kinetic resolution of racemates of alkyl-substituted α -methylene- β -lactones has been carried out via a lipase-catalyzed transesterification reaction with benzyl alcohol (**Equation 21**) <1997TA833>. The most efficient lipase tested for this reaction was CAL-B (from *Candida antarctica*), which selectively transesterifies the (*S*)-lactone. At 51% conversion, the (*R*)- β -lactone, (*R*)-**74**, and (*S*)- β -hydroxy ester, (*S*)-**75**, were formed in very high enantioselectivities (up to 99% ee).

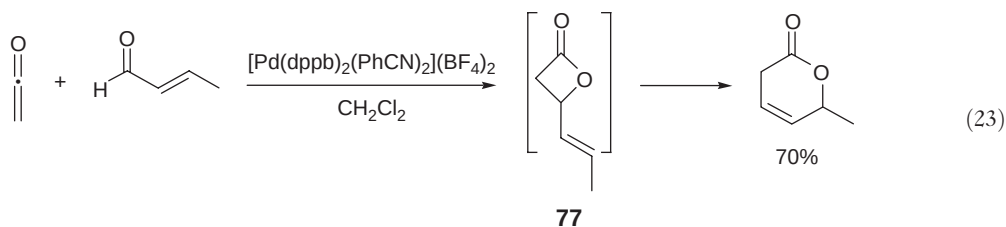


2.05.7.4 Reactions of Alkylene-Substituted Oxetanes and 2-Oxetanones

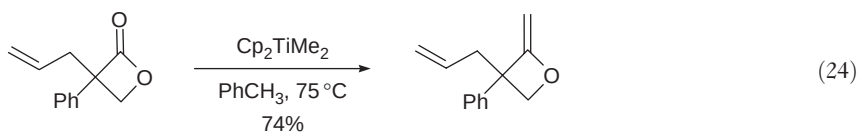
Alkylene-substituted β -lactones are important members of certain classes of natural products. An example of a biologically active compound with this type of structure is the β -lactone enzyme inhibitor (–)-ebelactone A <2002OL2043> (see Section 2.05.11.1). Alkylene-substituted β -lactones have also been utilized as intermediates in the synthesis of natural products, due to their potential for undergoing ring expansion. An example of this is discussed in Section 2.05.6.4.2, where an alkylidene-substituted β -lactone was converted into a cyclopentane as a key step in the synthesis of (+)-brefeldin A <2002OL3231>. The ring expansion of a 3-alkylene-substituted 2-oxetanone was also reported as part of the total synthesis of amphidineolide P (Equation 22) <2005JA17921>. Here, the β -lactone was converted to an eight-membered lactone by treatment with Otera's catalyst, **76**.



Another ring expansion of an alkylene-substituted 2-oxetanone was observed during the [2+2] cycloaddition of ketene with certain aldehydes <2000CC73>. This reaction, which is catalyzed by palladium(II) complexes $[\text{PdL}_2(\text{PhCN})_2](\text{BF}_4)_2$, can be used as a general method for forming β -lactones and is discussed further in Section 2.05.9.2. However, when the oxetanones formed were 4-vinyl substituted (e.g., **77**), these intermediates were isomerized to give 3,6-dihydro-2*H*-pyran-2-ones in reasonable yields, as long as the reaction was carried out at high dilution and the aldehyde and ketene were added portionwise (Equation 23).

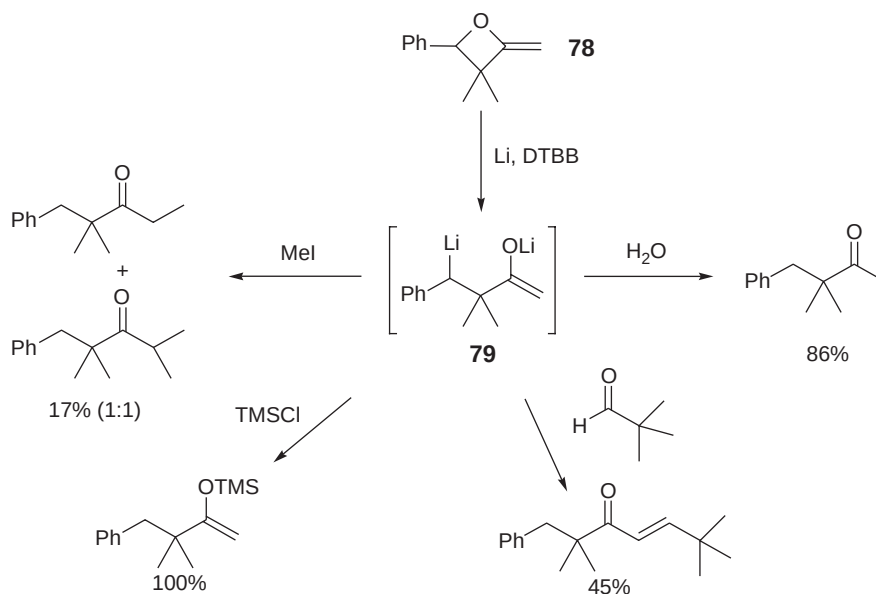


2-Methylene oxetanes are a related class of compounds that have attracted increasing interest in recent years. Again, the use of these compounds was initially limited due to the lack of a general method for their preparation. Problems associated with the synthesis of 2-methylene oxides by the Paternò–Büchi method are discussed in Section 2.05.9.2. However, since 1996, it has been demonstrated that these compounds can be synthesized via the methylation of β -lactones using dimethyltitanocene (Equation 24), providing a method which is applicable to a wide range of β -lactone substrates <1996JOC7248, 1999JOC7074>.



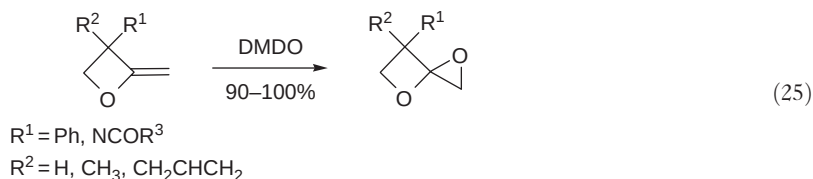
The reaction is highly chemoselective and can be carried out in the presence of unprotected alcohols, alkenes, and carbonyl moieties. This method was also used for the synthesis of a series of 3-alkylidene, 2-methylene oxetanes <2003OL399>. These compounds have been shown to be susceptible to a range of useful transformations <1998JOC6098, 1998JOC6782, 1999TL7051, 2000TL1855>. The most widely applicable of these is ring opening by a nucleophile, followed by a reaction of the enolate formed with an electrophile. For example, 3,3-dimethyl-2-methylene-4-phenyloxetane **78** was reductively ring-opened with lithium and 4,4'-di-*tert*-butylbiphenyl (DTBB) to

give the dianion **79** *in situ* (Scheme 15) <2000TL1855>. This was then reacted with a range of electrophiles or the enolate could be trapped with trimethylsilyl chloride.

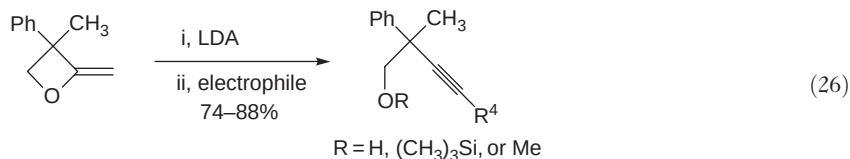


Scheme 15

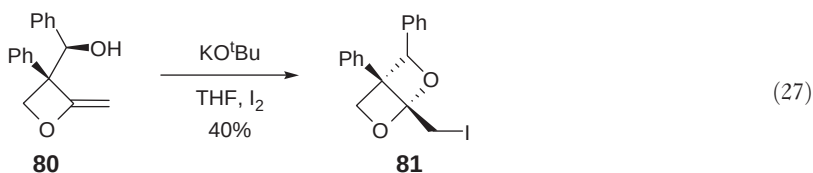
2-Methylene oxetanes have been used as substrates for the synthesis of 1,5-dioxaspiro[3.2]hexanes. Epoxidation of the methylene group was achieved using dimethyldioxirane (DMDO), often in quantitative yield (Equation 25) <1998JOC6098>.



Upon treatment with lithium diisopropylamide (LDA) followed by the addition of an electrophile (water, trimethylsilyl chloride, or methyl iodide), 2-methylene oxetanes were converted into homopropargylic alcohols, in good yields (Equation 26) <1998JOC6782>.



Electrophile-mediated intramolecular cyclization of a 2-methylene oxetane functionalized with a pendant hydroxyl group, **80**, gave 1-iodomethyl-3,4-diphenyl-2,6-dioxobicyclo[2.2.0]hexane **81** (Equation 27) <1999TL7051>. This was particularly notable for being the first reported example of a [2.2.0]-fused ketal.



2.05.8 Reactivity of Substituents Attached to Ring Heteroatoms

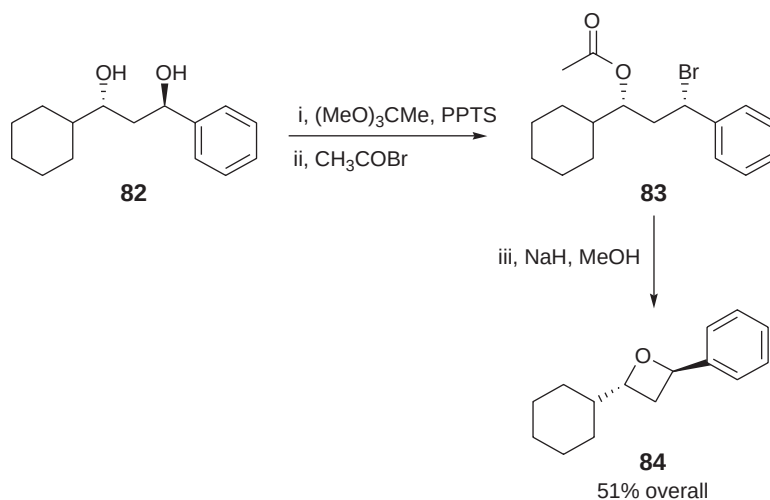
CHEC-II(1996) discusses reaction between carbenes and the oxetane oxygen, and subsequent Stevens rearrangement or β -elimination of the oxygen ylide formed in this reaction <1996CHEC-II(1)721>. However, no relevant literature on the reactions of substituents attached to the oxetane ring heteroatom have been published since 1995.

2.05.9 Ring Synthesis Classified by Number of Ring Atoms

2.05.9.1 Oxetane Synthesis by Single C–O Bond Formation

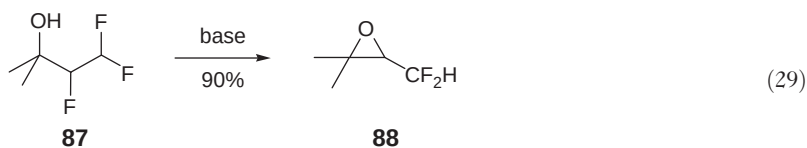
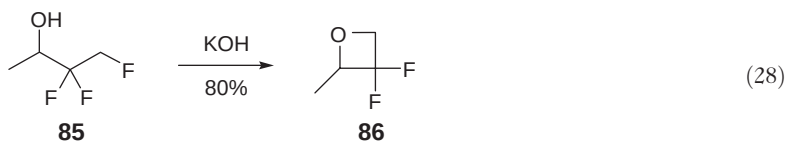
A common method of oxetane formation is by intramolecular attack of an alcohol in a 1,3-relationship with a good leaving group or electrophilic intermediate. CHEC(1984) discusses this type of intramolecular cyclization with a variety of leaving groups including halides and sulfonic acid esters, and the competing formation of formaldehyde and an alkene in these reactions <1984CHEC(7)363>. In addition to intramolecular substitution reactions, CHEC-II(1996) gives examples of the cyclization of homoallylic alcohols, via an electrophilic intermediate <1996CHEC-II(1)721>. More recent examples of both types of reaction are given in this section.

With an S_N2 mechanism, oxetane synthesis by intramolecular cyclization will result in an inversion of stereochemistry, as the oxygen nucleophile will attack from the opposite face to the leaving group. In order to retain the overall configuration of the starting diol in the oxetane product, the *anti*-diol **82** was first converted to an orthoester, followed by treatment with acetyl bromide to give the *syn*-1,3-bromoacetate **83**, with an inversion of configuration (Scheme 16) <1999TL8679, 2000J(P1)711>. Treatment of **83** with base and methanol resulted in deprotection and an intramolecular cyclization, accompanied by a second inversion of configuration, to give the corresponding oxetane **84**, with an overall retention of stereochemistry in 51% yield.

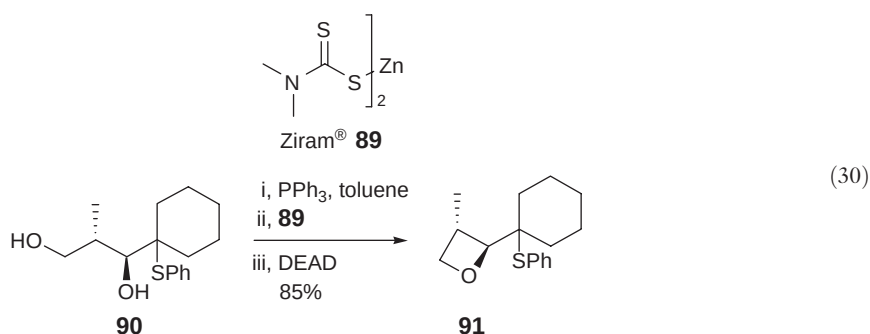


Scheme 16

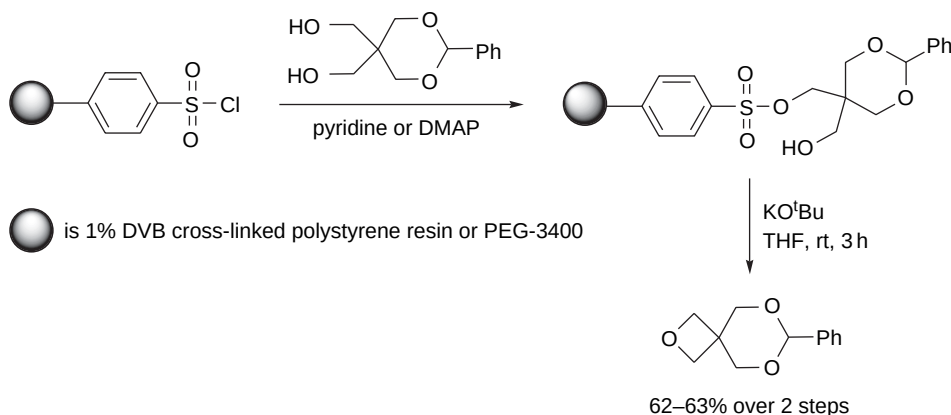
Hydroxytrifluoroethene adducts with terminal CH_2F moieties, such as **85**, were converted into a fluorinated oxetane **86** by alkoxide formation and cyclization in high yield (Equation 28) <2000JFC53>. This type of cyclization was unusual for polyfluorinated alkoxides, and the nucleophilic displacement of a fluorine atom to give an oxetane was only possible when the terminal carbon was monofluorinated. By comparison, in hydroxytrifluoroethene adducts with terminal CHF_2 sites, such as **87**, cyclization again proceeded with displacement at the CH_2F site to give the corresponding epoxide **88** (Equation 29). Fluorinated oxetanes, including **86**, were then used as monomers in the synthesis of perfluoropolyethers.



In an attempt to replace a hydroxyl group with an *N,N*-dimethyldithiocarbamate moiety using triphenylphosphine, diethyl azodicarboxylate (DEAD), and Ziram® **89**, unexpectedly the 1,3-diol **90** was converted to the corresponding oxetane product, **91** (Equation 30) <2001J(P1)2983>. This represented a new Mitsunobu-style cyclization of 1,3-diols, with triphenylphosphine oxide acting as the leaving group.

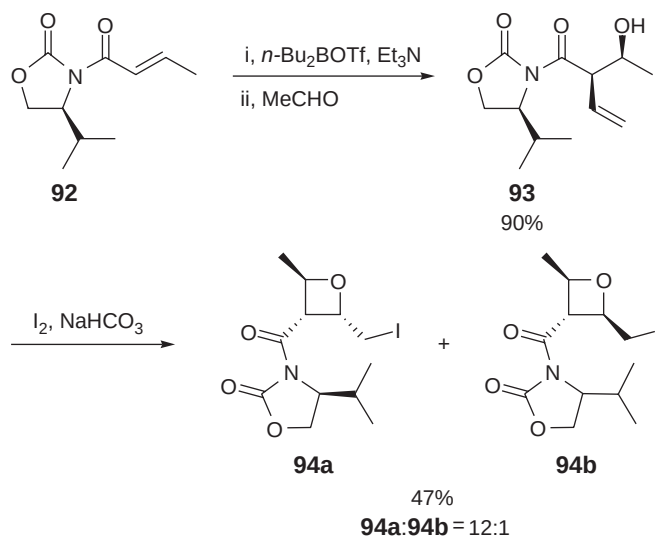


Oxetanes have also been synthesized by the immobilization of 2,2'-disubstituted 1,3-diols with polymer-bound sulfonyl chloride, followed by intramolecular cyclization/cleavage from the solid support (Scheme 17) <2005TL643>. One percent divinylbenzene (DVB) cross-linked polystyrene and polyethylene glycol (PEG) (average M_n 3400) were used as polymer support in this reaction, and in both cases the properties of the polymer support allowed rapid purification of the intermediate. Intermediates on the insoluble cross-linked polystyrene support could be washed with a range of organic solvents to remove insoluble impurities, whereas the soluble PEG supported products could be purified by recrystallization from isopropanol. This is thought to represent the first reported polymer-supported synthesis of oxetanes.



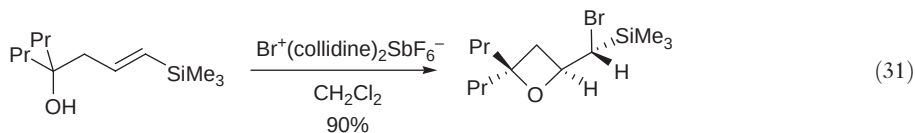
Scheme 17

It has been demonstrated that optically active oxetanes can be formed from oxazolidinone **92**, a crotonic acid moiety functionalized with Evans' chiral auxiliary (Scheme 18) <1997JOC5048>. In this two-step aldol-cyclization sequence, the use of **92** in a deconjugative aldol reaction, with boron enolates and ethanal, led to formation of the *syn*-aldol **93**. This product was then converted to the corresponding oxetanes, **94a** and **94b**, via a cyclization with iodine and sodium hydrogencarbonate. This reaction sequence was explored with other aldehydes to yield optically active oxetanes in similar yields. Unlike previous experiments using the methyl ester of crotonic acid, in an analogous reaction sequence rather than the oxazolidinone, there was no competing THF formation.

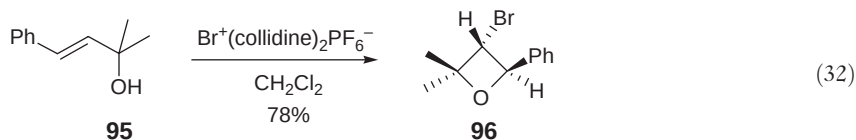


Scheme 18

Homoallylic alcohols with a silyl group attached to the terminal alkene carbon were cyclised to oxetanes in high yields by reaction with bis(*sym*-collidine)bromine(i) hexafluoroantimonate (e.g., Equation 31) <2001TL2481>. This reaction exclusively gave the four-membered cyclic ether, with the silyl group directing formation of the electrophilic intermediate for the subsequent 4-*exo-trig*-cyclization. When the carbon β to the silyl group on the double bond was unsubstituted, the reaction was diastereospecific.



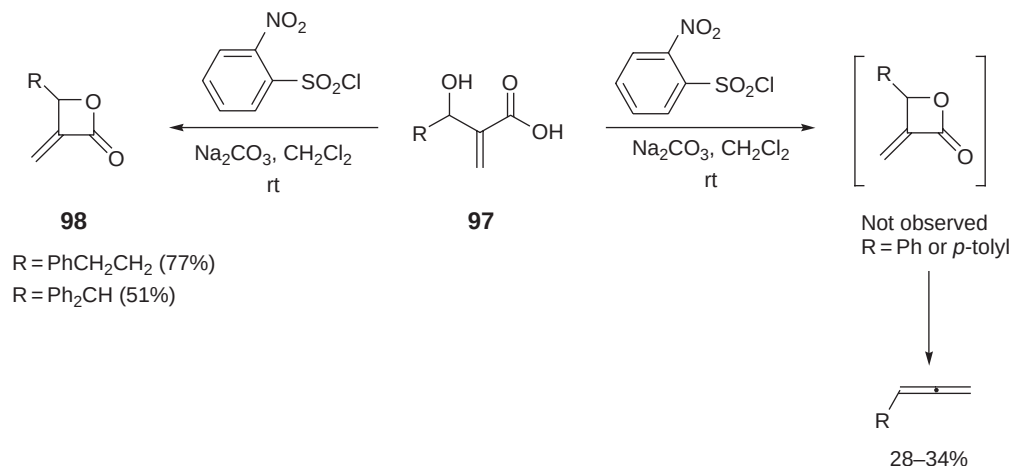
Cinnamyl alcohols such as **95** were converted to the corresponding oxetane **96** by reaction with bis-(collidine)bromine(i) hexafluorophosphate (Equation 32) via a 4-*endo-trig*-electrophilic cyclization <1999JOC81, 2001TL2477>. High yields of oxetanes (up to 88%) were only achieved with tertiary alcohols, with secondary alcohols giving mainly degradation products.



2.05.9.2 2-Oxetanone Synthesis by Lactonization

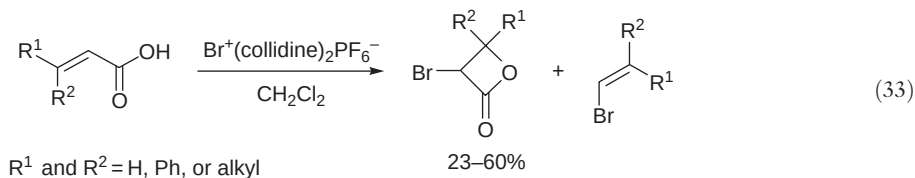
The classical method of synthesizing 2-oxetanones is by the cyclization of β -halocarboxylate and was first reported in 1883. Prior to 1996, a number of alternative methods were developed (see CHEC(1984) and CHEC-II(1996)), with

the most common being the treatment of 3-hydroxycarboxylates with benzenesulfonyl chloride in pyridine <1984CHEC(7)363, 1996CHEC-II(1)721>. A sulfonate ester promoted cyclization was also utilized in the two-step synthesis of α -methylene- β -lactones from propargyl alcohols <1996JMO51>. The first step involved the hydrocarboxylation of propargyl alcohols by carbon monoxide under phase-transfer conditions with a nickel cyanide catalyst. The α -methylene-3-hydroxypropanoic acid derivatives formed were then cyclized by treatment with mesyl chloride. This type of cyclization reaction has more recently been employed for the preparation of α -alkylene- β -lactones from α -alkylene-3-hydroxypropanoic acid derivatives **97** by treatment with *o*-nitrobenzenesulfonyl chloride (nosyl chloride) (Scheme 19) <2003OL399>. These reaction conditions gave the desired lactones **98**, when R was PhCH₂CH₂ and Ph₂CH. Attempts to make simple phenyl- or 4-aryl-substituted α -methylene- β -lactones by this method instead led to the direct formation of allenes in low yield.

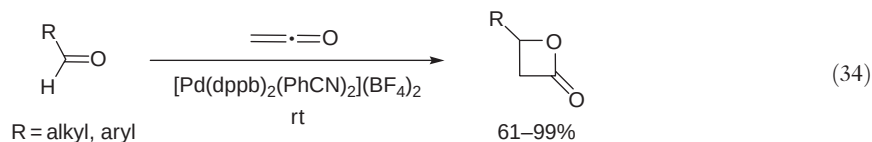


Scheme 19

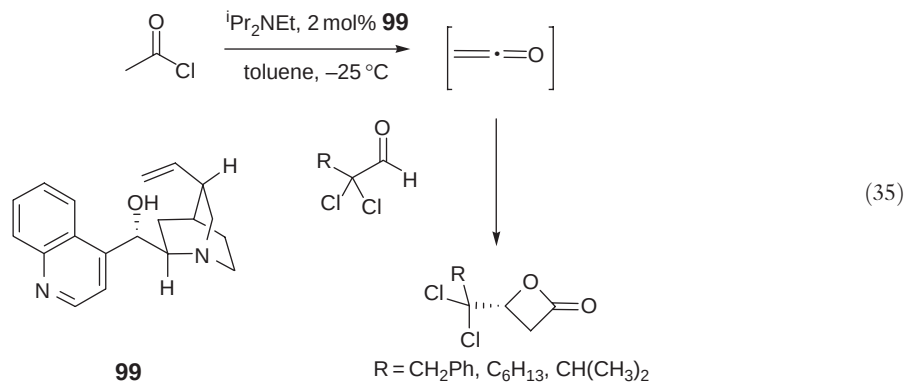
It has been reported that reaction of α,β -unsaturated carboxylic acids with bis(collidine)bromine(i) hexafluorophosphate leads to the formation of 2-oxetanones in moderate yields (Equation 33) <1999JOC81>. As with the related reaction of cinnamyl alcohols (discussed in Section 2.05.9.1), this 4-*endo*-cyclization occurs via an electrophilic intermediate. The cyclization reaction was diastereospecific; single (*E*)- or (*Z*)-isomers were reacted to give single stereoisomeric products. Lactonization was favored by substrates that were β -dialkyl-substituted, or α -alkyl/aryl-, β -aryl-substituted on the C–C double bond. α -Monoalkyl/aryl, β -unsubstituted substrates gave either polymeric products or exclusive vinyl bromide formation.



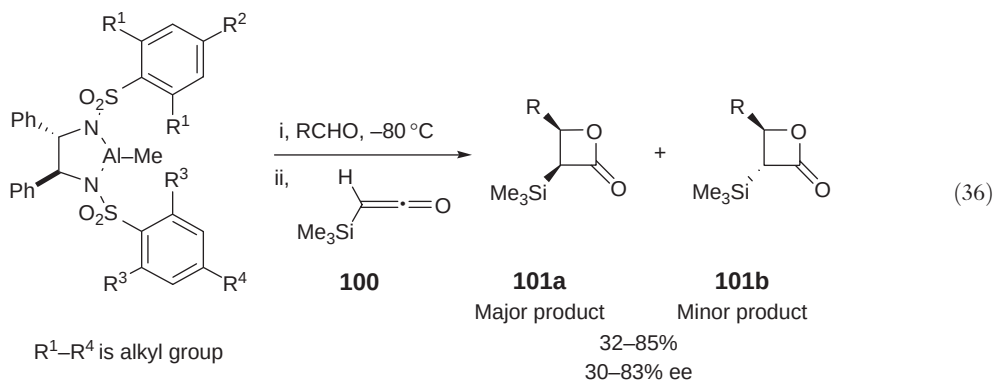
Various methods have been explored for the synthesis of lactones by cycloaddition reactions. The most common of these types of reaction is the [2+2] cycloaddition of aldehydes and ketene. Palladium(II) complexes, [Pd(dppb)₂(PhCN)₂](BF₄)₂, have been shown to be efficient catalysts for this reaction (Equation 34) <2000CC73>.



One major drawback of this reaction is that ketene is inherently unstable and this can have a detrimental effect on the yields of these reactions, particularly at higher temperatures <2000JOC7248>. One way to overcome this problem is to generate ketene *in situ*. Using such a procedure, dichlorinated aldehydes were converted into 2-oxetanones with up to 98% ee by treatment with acetyl chloride, quinidine **99**, and Hünig's base in toluene (Equation 35) <2000JOC7248>. Quinidine acted as the nucleophilic catalyst, generating ketene from the acetyl chloride. The choice of solvent was important; toluene could effectively precipitate the chloride salt of Hünig's base, allowing it to effectively regenerate the quinidine catalyst. This reaction gave the highest yields when carried out at lower temperatures (-25°C), as higher temperatures (0 – 25°C) led to the degradation of the ketene formed *in situ*.

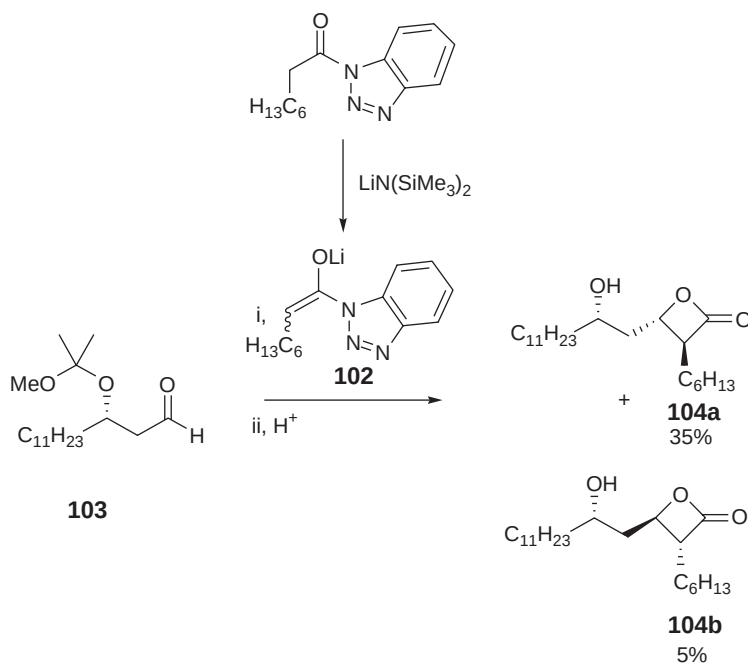


More stable alternatives to ketene that have been used in 2-oxetanone synthesis are (trimethylsilyl)ketenes **100** <1996CC1053>. Using methylaluminoimidazolines as catalysts, with aldehydes and **100**, 3-(trimethylsilyl)oxetan-2-ones (**101a** and **101b**) were generated with up to 83% ee (Equation 36).

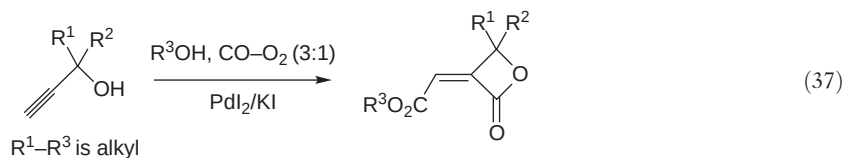


Another interesting synthesis of 2-oxetanones was carried out by a one-step tandem aldol lactonization of the amide enolate **102**, with aldehyde **103** (Scheme 20) <1999JOC5301>. Enolate **102** was readily generated from 1-octanoylbenzotriazole and lithium hexamethyldisilazide. This reaction was used as a key step in the formation of (3*S*,4*S*)-3-hexyl-4-[(2*S*)-2-hydroxytridecyl]oxetane-2-one **104a**, the major product, which is an important intermediate in the synthesis of enzyme inhibitors tetrahydrolipstatin and tetrahydroesterastin (see Section 2.05.11). Diastereoisomers **104a** and **104b** were readily separated using flash chromatography and recrystallization methods.

Propynyl alcohols have been converted into (*Z*)- α -(alkoxycarbonyl)methylene β -lactones by dialkoxycarbonylation in alcoholic media, under a carbon monoxide–air (3:1) atmosphere, using a PdI_2/KI catalyst (Equation 37) <1997J(P1)147>. The (*Z*)-stereochemistry of the products was attributed to the *syn* nature of the carbon monoxide insertion. Substitution at the α -alkyl position was essential to generate the lactone products in good yields. When the propynyl alcohols were α -alkyl-unsubstituted, no β -lactone formation was observed; instead, a maleic diester and its cyclic isomer were the predominant products. Where substrates were mono- α -alkyl-substituted, yields of the β -lactone were low, unless the alkyl group was sufficiently sterically bulky.



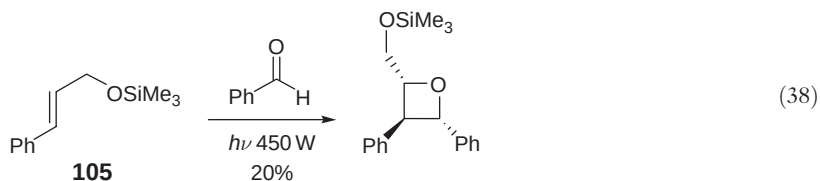
Scheme 20



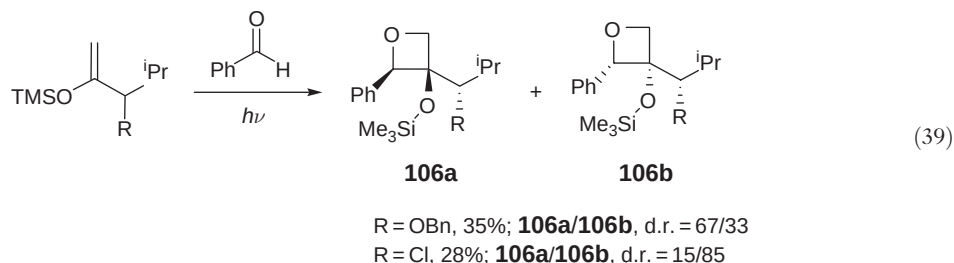
2.05.9.3 Photochemical Cycloaddition

First reported in 1909, the photochemical [2+2] cyclization between alkenes and carbonyl compounds, known as the Paternò-Büchi reaction, is one of the most commonly used methods of synthesizing oxetanes. The scope of the reaction is however limited and only occurs readily between electron-rich alkenes and electron-poor carbonyls. The importance of the reaction is that, with careful selection of alkenes and carbonyl compounds, high regio- and stereoselectivities can be achieved (see CHEC(1984) and CHEC-II(1996) for previous examples) <1984CHEC(7)363, 1996CHEC-II(1)721>.

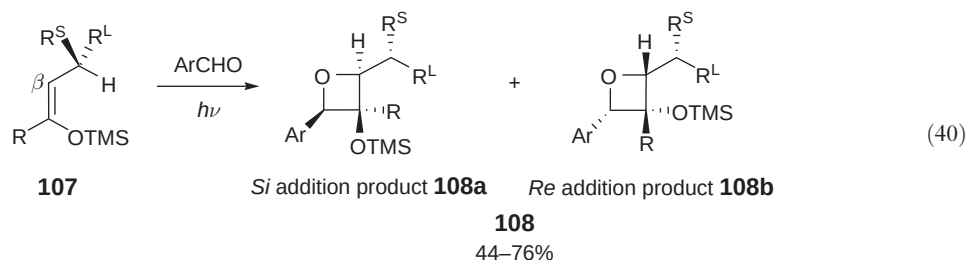
In recent years, there has been an increasing focus on the ability of substituent groups of Paternò-Büchi-type reagents to control both the regio- and stereoselectivity of the cycloaddition reaction. For example, the photocycloaddition between benzaldehyde and trimethylsilyl cinnamyl ether **105** proceeded to give the corresponding *all-trans*-oxetane as the only cyclic adduct in a 20% isolated yield (Equation 38) <1997TL5407>. By comparison, the reaction between benzaldehyde and styrene under the same conditions led to the formation of 2,3-*trans*- and 2,3-*cis*-oxetane isomers in a 3:1 ratio. The much higher stereoselectivity in the former reaction is likely to be due to a favorable interaction between the silyl group of the ether and the carbonyl oxygen, with the phenyl groups held *trans* to each other for steric reasons.



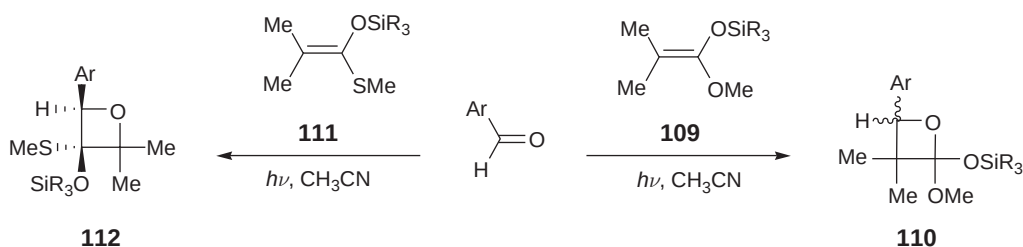
Bach *et al.* have also carried out a series of investigations into the effect of alkene substituents on the stereoselectivity of the photocycloaddition with benzaldehyde <1996T10861, 1997JA2437, 1998T4507, 1999JOC1265>. When using silyl enol ethers as substrates, a chiral center at the α -position to the alkene exerted a significant degree of control on the facial diastereoselectivity of the reaction (Equation 39) <1996T10861>. For a silyl enol ether with a benzyl ether at the α -position, oxetane **106a** was the major stereoisomer, but for a silyl enol ether with a chloro group in this position, the facial diastereoselectivity was reversed and oxetane **106b** was the major product.



Further investigations showed that for reactions of silyl enol ethers that were disubstituted (with small R^S and larger R^L groups) at the γ -carbon to the silyl enol ether **107**, a more favorable diastereoisomeric ratio between products **108a** and **108b**, up to 95/5, was achieved with large (e.g., R^L = Bu^t, SiMe₂Ph) and polar (R^L = OMe) substituents (Equation 40) <1997JA2437>.



A comparative study between the Paternò–Büchi reaction of aromatic aldehydes with silyl *O,O*-ketene acetals, **109**, and *O,S*-ketene acetals, **111**, has highlighted sulfur atom effects on both regio- and stereoselectivities (Scheme 21) <1996TL5901, 1998J(P1)3253, 1998J(P1)3261, 2000JA4005>. Cycloadditions with **109** were not stereoselective and gave 2-siloxyoxetanes **110**. By contrast, reactions with **111** favored the formation of *trans*-3-siloxyoxetanes, **112**.

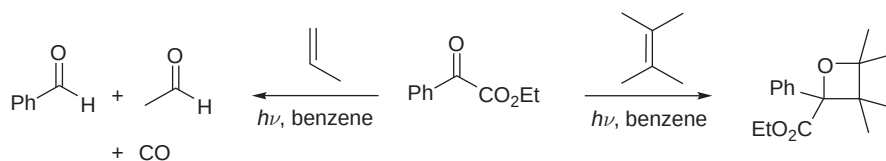


Scheme 21

The regiochemistry of the latter reaction was thought to be due to the stability of the 1,4-diradical intermediate and interaction between the electrophilic oxygen of the aldehyde and the C-2 nucleophilic carbon of the *O,S*-ketene acetal. The stereochemistry of this reaction was attributed to sulfur effects controlling the approach of the electrophilic oxygen of the triplet $n\pi^*$ aldehyde to the nucleophilic alkene.

A recent example of this reaction is the photo-irradiation of mixtures of benzaldehyde and substituted enamines to give 3-amino oxetanes with very high diastereoselectivities in favor of the *cis*-product <1999JOC1265>. High regio- and stereoselectivity were again achieved in reactions between monosubstituted benzils and 2-morpholinopropenenitrile

<2004M425>. Here the selectivity was only low with respect to the site of addition, which could be either the benzoyl or 4-substituted benzoyl group. Phenyl glyoxylates can also be successfully utilized as reactive carbonyls in the Paternò-Büchi reaction as demonstrated by Hu and Neckers <1997JOC564>. Oxetanes were formed in very high yields with electron-rich (e.g., polyalkylated) alkenes, but with monosubstituted alkenes there was no oxetane formation due to the prevalence of Norrish II type hydrogen abstraction (Scheme 22).

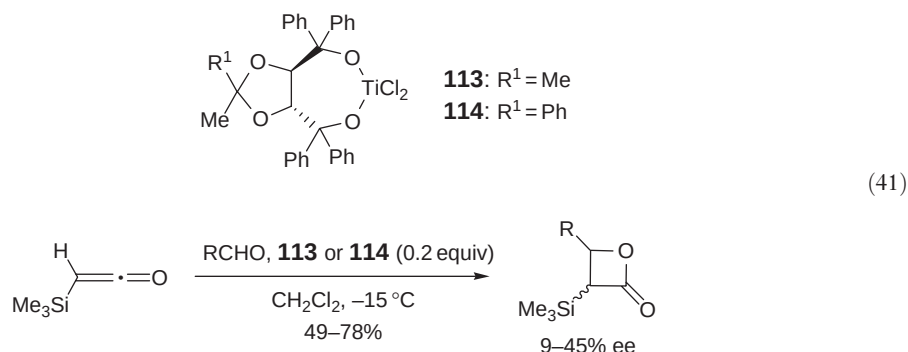


Scheme 22

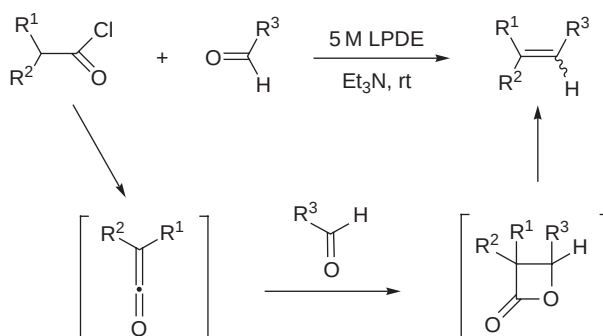
2.05.9.4 Thermal and Lewis Acid-Catalyzed [2+2] Cycloaddition

It has been long established that Lewis acid-catalysed [2+2] cycloaddition of ketenes and carbonyl compounds provides access to 2-oxetanones. In the development of this reaction prior to 1996, there has been a specific focus on controlling the stereochemistry of the β -lactone product and cycloadditions have been achieved between trimethylsilylketene and aldehydes with up to 90% stereoselectivity, as discussed in CHEC-II(1996) <1996CHEC-II(1)721>. CHEC(1984) and CHEC-II(1996) also discuss examples of the Lewis acid-catalyzed, nonphotolytic [2+2] cycloaddition of electron-rich alkenes with aldehydes or ketones <1984CHEC(7)363, 1996CHEC-II(1)721>. While this method can have some advantages over the photolytic reaction in terms of regioselectivity, no examples of this reaction have been reported in recent years.

Romo *et al.* have used Lewis acids to catalyze the formation of α -silyl- β -lactones in their synthesis of potential inhibitors of yeast 3-hydroxy-3-methyl glutaryl-coenzyme A (HMG-CoA) synthase <1998BMC1255>. In addition to various Lewis acid catalysts, a chiral promoter based on the chiral diol (1*R*,2*R*)-2-[(diphenyl)hydroxymethyl]cyclohexan-1-ol was introduced to the reaction in an attempt to improve the stereoselectivity. A variety of chiral 2-oxetanones were formed, with enantioselectivities ranging from 22% to 85%. Dichlorotitanium–TADDOL catalysts **113** and **114** have also been used in an attempt to encourage the stereoselective [2+2] cycloaddition of silyl ketenes and aldehydes (TADDOL = (–)-*trans*-4,5-bis(diphenyl-hydroxymethyl)-2,2-dimethyl-1,3-dioxolane), although this method only afforded 2-oxetanones in moderate yields and optical purity (Equation 41) <1998TL2877>.



This type of methodology has been used to synthesize 2-oxetanones as intermediates in the synthesis of β -hydroxy esters <1999TL6535>. Here aldehydes were reacted with acyl halides, with a hindered tertiary amine base required to abstract the halide and form the ketene, in the presence of an Al(III)-catalyst. The mixture of stereoisomers formed was separated by column chromatography, and lactone alcoholysis of the optically pure product gave the corresponding ester. A reaction between acyl chlorides and aromatic or α,β -unsaturated aldehydes, with a tertiary base in lithium perchlorate diethyl ether (LPDE), has been reported to give substituted alkenes at room temperature, via 2-oxetanones generated *in situ* (Scheme 23) <1996TL7143>. The reaction is thought to proceed via a thermal decarboxylation of the 2-oxetanone intermediate.

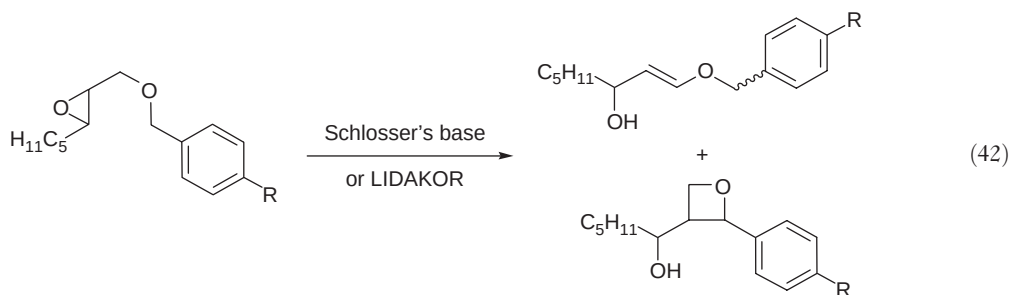


Scheme 23

2.05.10 Ring Synthesis by Transformation of Another Ring

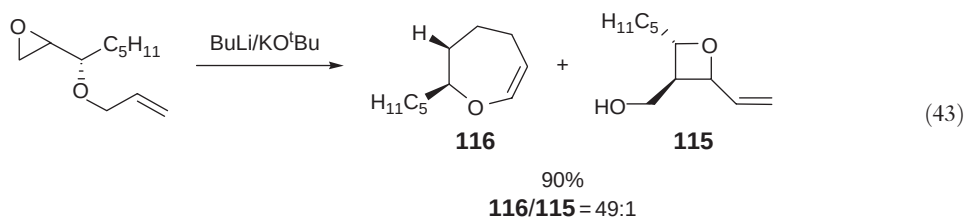
2.05.10.1 Three-Membered Ring Transformations to Oxetanes or Oxetanones

CHEC-II(1996) discussed various methods for the ring expansion of functionalized epoxides into oxetanes, with the most common being the treatment of *cis*-epoxy alcohols with a base <1996CHEC-II(1)721>. Another generally applicable method discussed previously was the treatment of epoxides with sulfur ylides or sulfonimidamides. In recent years, Mordini and co-workers have extensively explored the formation of oxetanes by the base-promoted isomerization of oxiranyl ethers, including allyl, benzyl, and propargyl ethers <2001T8173>. Upon treatment with either Schlosser's base (butyllithium/potassium *tert*-butoxide) or lithium diisopropylamide/potassium *tert*-butoxide (LIDAKOR), aryl oxiranyl ethers derived from primary alcohols were converted to either a 2-aryl-3-(hydroxyalkyl)oxetane or a benzyl vinyl ether (Equation 42) <1996JOC4374>. Alkyl substituents had some control over which product was formed, with electron-donating groups shifting the equilibrium toward vinyl ether formation, whereas electron-withdrawing groups lowered the reactivity leading to a mixture of products. Where the oxetane product was formed, it was obtained as a single diastereoisomer.



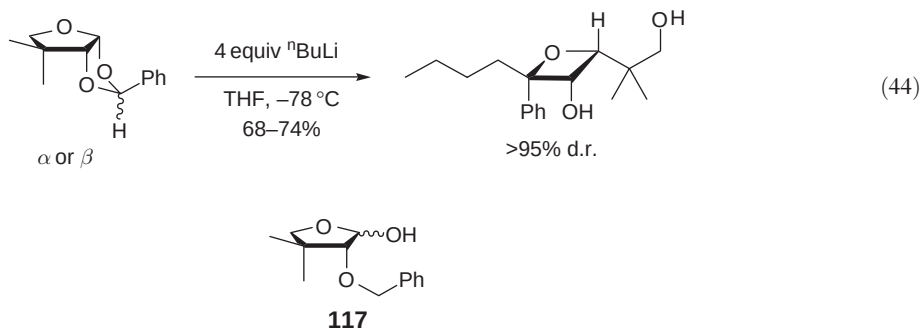
Interestingly, when aryl oxirane ethers derived from secondary alcohols were reacted under the same conditions, the corresponding oxetanes were formed exclusively [<1996JOC4466>](#). This was again a highly stereoselective reaction, forming trisubstituted oxetanes with four stereocenters.

Base-promoted isomerism was shown to be applicable for oxiranyl ethers derived from amino acids, including valine, leucine, and serine, providing access to amino alcohols bearing an oxetane moiety, which are potentially useful building blocks for the synthesis of peptide isosteres [<1997JOC8557>](#). When the oxiranyl starting material had an allyl vinyl ester substituent, oxetane formation [115](#) was disfavored and treatment with Schlosser's base gave the seven-membered tetrahydrooxepines [116](#) as the main product (Equation 43) [<2001JOC3201>](#).



2.05.10.2 Ring Contractions of Butanolides

CHEC-II(1996) discusses the base-induced ring contraction of both arino-lactone triflate and ribono-lactone to give functionalized oxetanes <1996CHEC-II(1)721>. A more generally applicable oxetane synthesis can be achieved by the anionic ring contraction of cyclic acetals fused to butanolides, using organolithium reagents (Equation 44) <2004SL651>. This stereoselective reaction was also successful for the ring contraction of the pantolactol-derived benzyl ether **117**.

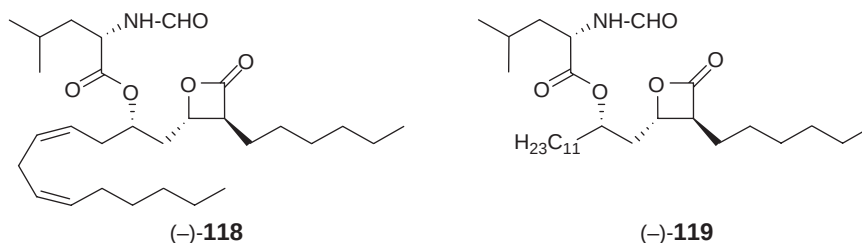


2.05.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

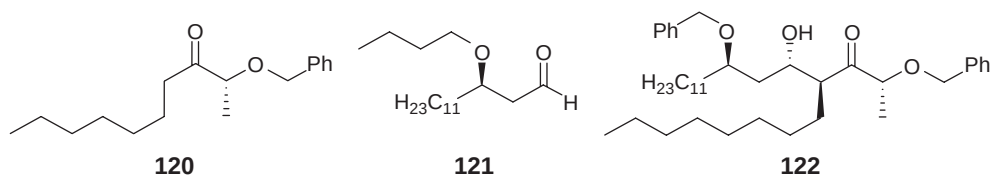
2.05.11.1 2-Oxetanone-Based Natural Products

2.05.11.1.1 Studies with lipstatin and analogues

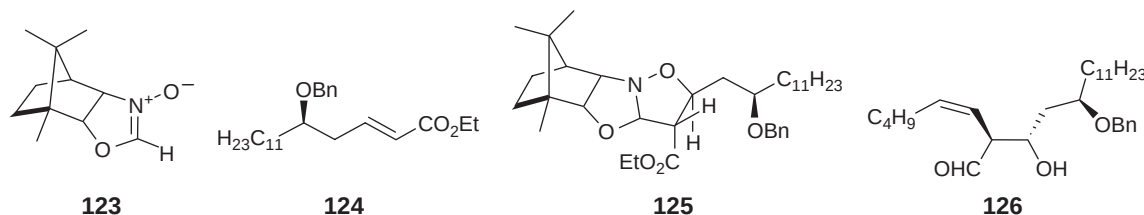
Lipstatin **118** and tetrahydrolipstatin **119** are well known to be potent inhibitors of pancreatic lipase and as such they have potential therapeutic properties as antiobesity drugs. Research in recent years has been focused on finding efficient stereoselective routes for the synthesis of (–)-tetrahydrolipstatin, (–)-**119**, which is now marketed as the antiobesity drug, Xenical®.



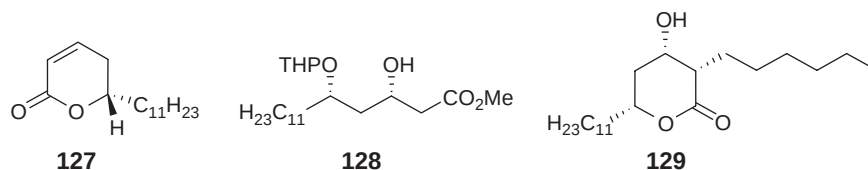
In most synthetic strategies, the β -lactone ring-forming step was carried out by treatment of a 3-hydroxycarboxylic acid with sulfonyl chloride and a base <1998J(P1)2679, 1999TL393, 1999OL753, 1999CC1743, 2000OL2405, 2004TL3873>. This standard method is discussed further in Section 2.05.9.2. There are four chiral centers in (–)-tetrahydrolipstatin ((–)-**119**) that must be established during a total synthesis. Silicon-containing compounds have been used to control the stereoselectivity of several key steps <1998J(P1)2679>. Thus, the alkylation of a β -silyl ester and the hydroboration of an allylsilane both proceeded with high stereoselectivity. A high degree of stereo-control (>98% d.s.) was also achieved using a boron-mediated *anti*-selective aldol coupling between an (*R*)-ketone **120** and aldehyde **121**, to give intermediate **122** which was converted into **119** by a further four-step sequence <1999TL393>. An *anti*-selective aldol reaction using the titanium enolate of an asymmetric ester was a key step in total synthesis by Ghosh and Fidanze <2000OL2405>. This reaction, along with a nitro-aldol reaction to add the C-11 side chain and diastereoselective reduction of a β -hydroxyketone, allowed three of the chiral centers in **119** to be established.



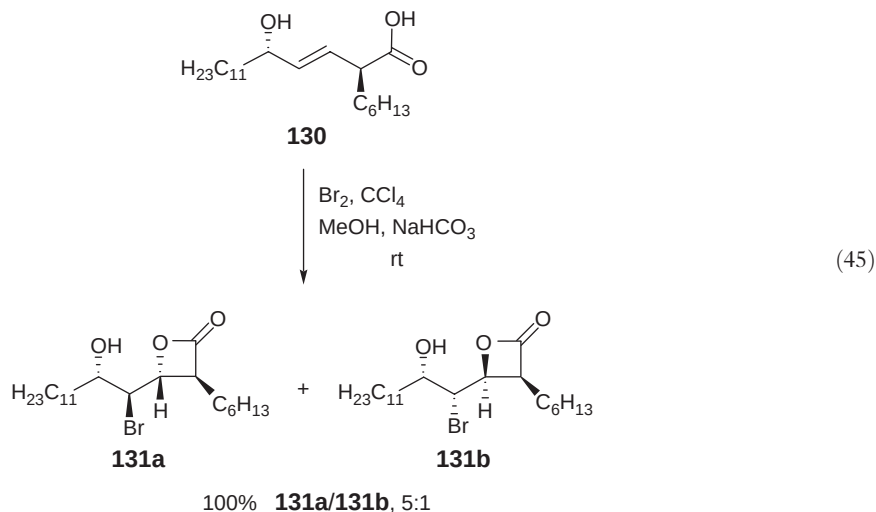
Several total syntheses of (–)-tetrahydrolipstatin ((–)-**119**) have involved the formation and subsequent opening of cyclic systems as key steps [<1999OL753, 1999CC1743, 2004TL3873>](#). An example of this is the [2+3] cycloaddition of a camphor-derived *N*-oxide **123** to the α,β -unsaturated ester **124**, to give compound **125**, which was subsequently converted into **119** by a nine-step sequence [<1999OL753>](#). These subsequent steps included ring opening by oxidation with *m*-chloroperbenzoic acid (MCPBA) and hydrolysis to give the aldehyde **126**, with three defined stereocenters.



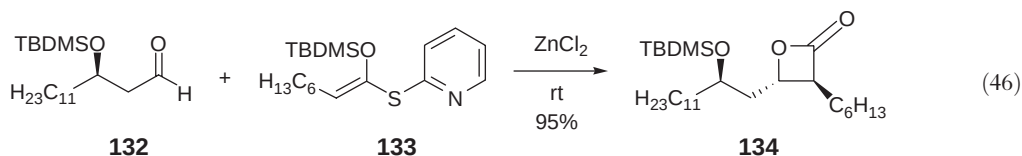
Another total synthesis of compound **119** included formation of a six-membered cyclic lactone **127** by olefin metathesis and the subsequent nine-step sequence included ring opening with triethylamine to give a β -hydroxy ester **128**, with two defined stereocenters [<1999CC1743>](#). An alternative lactone intermediate, (3*S*,4*S*,6*R*)-**129**, was formed with greater than 98% ee by asymmetric hydrogenation, using a chiral phosphine–ruthenium complex as the catalyst [<2004TL3873>](#).



While all of the examples discussed above utilize the standard sulfonyl chloride method for formation of the tetrahydrolipstatin β -lactone ring, a few alternative approaches to this cyclization reaction have been investigated [<2003TL2869, 2005CC1448>](#). A 3-vinyl-carboxylic acid **130** was converted to the corresponding β -lactone by an electrophile-mediated cyclization using bromine (Equation 45) [<2003TL2869>](#). Here it was shown that conditions could be optimized to favor formation of the desired *trans*-isomer **131a** (*trans*:*cis* = 5:1).

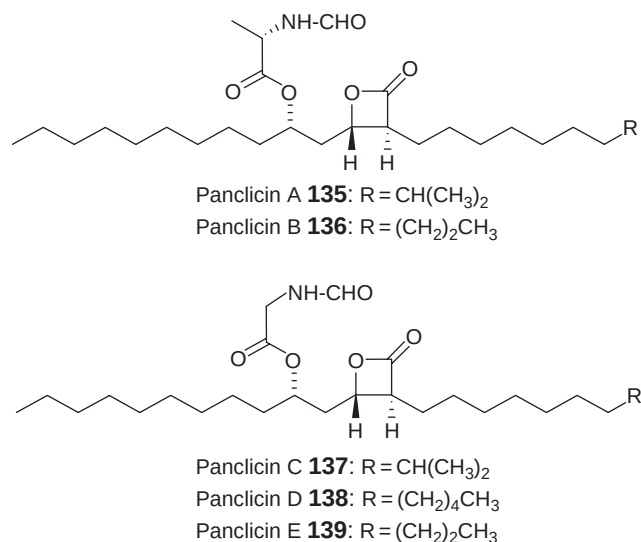


Diastereoselective β -lactone formation was also carried out by a tandem Mukaiyama aldol lactonization between an aldehyde **132** and a thiopyridyl ketene acetal **133** (Equation 46) <2005CCL1448>. This reaction gave the β -lactone **134** as a 10:1 (*trans:cis*) mixture of diastereoisomers and the major isomer was converted into (–)-tetrahydrolipstatin by silyl deprotection followed by a Mitsunobu coupling to form the ester.

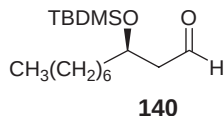


2.05.11.1.2 Other β -lactone natural products

While the synthesis of (–)-tetrahydrolipstatin still makes up a large volume of the literature, syntheses of various other β -lactone enzyme inhibitors have been explored in recent years. Panclicins A–E **135–139** are a group of lipase inhibitors that are twice as potent as (–)-tetrahydrolipstatin <1997T16471, 1998J(P1)1373>.

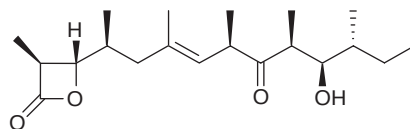


A diastereoselective Mukaiyama aldol lactonization between thiopyridylsilylketene acetals and aldehydes was used to form the β -lactone ring in the total synthesis of (–)-panclicin D <1997T16471>. Noyori asymmetric hydrogenation was a key step in a total synthesis of panclicins A–E and was used to establish the stereocenter in aldehyde **140**, which in turn directed the stereochemistry of subsequent reactions <1998J(P1)1373>. The β -lactone ring was then formed by a [2+2] cycloaddition reaction of **140** with alkyl(trimethylsilyl)ketenes and a Lewis acid catalyst.

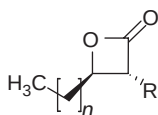


Another class of β -lactone enzyme inhibitors that have attracted attention recently is the ebelactones <2002OL2043, 2004OBC1051>. These compounds are known to be potent inhibitors of esterases, lipases, and aminopeptidases located on cellular membranes. In recent years, synthetic studies have focused on (–)-ebelactone A **141** as the target compound. A total synthesis was reported by Mandal, with key steps being hydroboration of an alkene, a Suzuki–Miyaura cross-coupling, silylcupration of an acetylene, and iodosilylation <2002OL2043>.

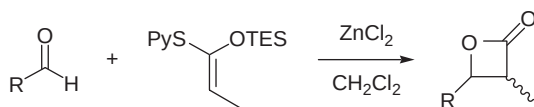
The β -lactone was formed by the cyclization of a 3-hydroxycarboxylic acid with sulfonyl chloride. An alternative synthesis attempted to control all stereochemical relationships in the molecule using the properties of silyl moieties attached to substrates and reagents <2004OBC1051>. Stereoselective reactions of this type included the use of silyl groups in enolate alkylations, hydroboration of allylsilanes, and an *anti* S_E2' reaction of an allenyl silane with an aldehyde and *syn*-silylcupration of an acetylene. The β -lactone was again formed by the standard sulfonyl chloride cyclization method.

**141**

A series of C-3-unsubstituted and C-3-methyl-substituted 2-oxetanones, **142**, were synthesized as potential inhibitors of yeast 2-hydroxymethyl-3-methylglutaryl-coenzyme A (HMG-CoA) synthase <1998BMC1255>. These β -lactone inhibitors could be used to reduce sterol levels in humans, as has been demonstrated with commercially available HMG-CoA synthase inhibitors such as lovastatin and fluvastatin. Various lactonization methods were considered for the preparation of these analogues. Racemic C-3,C-4-disubstituted β -lactones were prepared by an aldol lactonization from aldehydes. An alternative method, which gave good yields and high diastereoselectivities, was the single-pot tandem Mukaiyama aldol lactonization (TMAL) reaction between aldehydes and thiopyridyl-ketene acetals (Equation 47).

**142** $n = C_0$ to C_{16}

R = H or Me

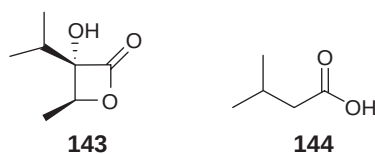


(47)

R = alkyl (*trans/cis* > 19/1)R = aryl (*trans/cis* < 1/19)

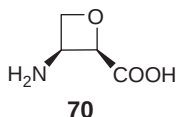
The highest yielding synthesis of C-4-monosubstituted β -lactones was a two-step process involving a [2+2] cycloaddition between aldehydes and ketene catalyzed by a novel chiral aluminium Lewis acid, followed by removal of the silyl group. This reaction showed good diastereoselectivities, but enantioselectivities were variable (28–84% ee). The potency of these compounds as HMG-CoA inhibitors was shown to be dependent on the chain length of the C-4 substituent, with a chain length of 10–11 carbons giving the optimal potency. This result was attributed to hydrophobic interactions within the synthase active site.

Viridifloric β -lactone, **143**, has been identified as one of the pheromone components of a complex mixture of volatiles released by the pheromone glands of the male *Idea leuconoe* butterfly during courtship <1996BMC341>. A racemic mixture of both diastereoisomers was synthesized in four steps from the dilithio salt of 3-methylbutyric acid **144**: alkylation with ethanal, dehydration of the secondary alcohol with phosphorus pentoxide, dihydroxylation of the C–C double bond with osmium tetroxide, and finally formation of the β -lactone by cyclization with sulfonyl chloride. By comparison with the sample isolated from *I. leuconoe*, the absolute configuration was established to be (2*S*,3*S*)-2-hydroxy-2-(1-methylethyl)-3-butanolide **143**.

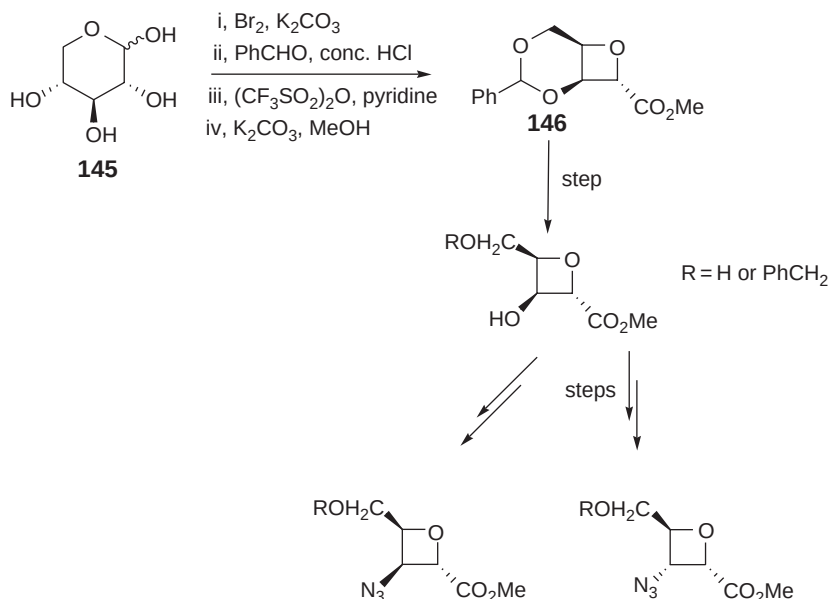


2.05.11.2 β -Peptides Containing Oxetane Residues

β -Peptide foldamers have shown potential therapeutic properties due to their ability to form organized secondary structures. To this end, a series of short-chain peptide oligomers have been synthesized from unnatural amino acids containing an oxetane ring <2001TL4247, 2001TL4251, 2004TA2667, 2005MI517, 2005MI303>. The only naturally occurring oxetane containing β -amino acid that has been reported is the antibiotic oxetin **70**.

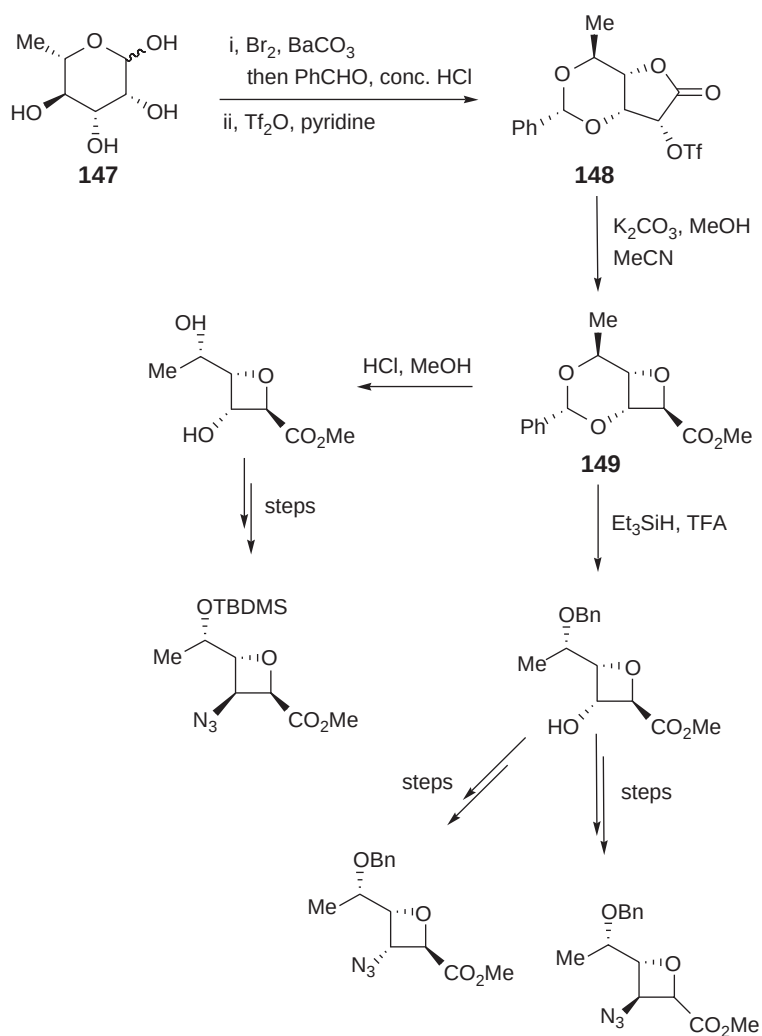


Analogues of **70** have been prepared by various methods including nucleophilic displacement of triflate esters attached directly to the oxetane ring (see Section 2.05.7.2) <2001TL4247>, from xylose, **145**, via the benzylidene-protected oxetane, **146** (Scheme 24) <2004TA2667>, or from L-rhamnose, **147**, via a 1,4-lactone-2-*O*-triflate, **148** (and key oxetane **149** (Scheme 25)) <2004TA2681>. The β -azidoester 'monomers' formed by these methods were converted to the β -amino acids and subsequently to β -peptides by reduction of the azide and ester hydrolysis.

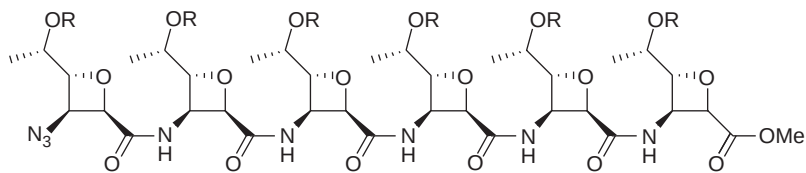
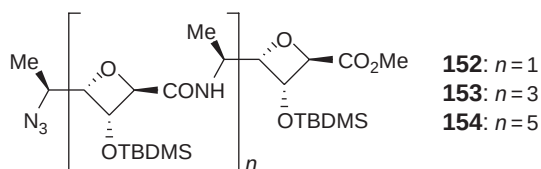


Scheme 24

Of the various β -peptide oligomers formed, hexamers **150** and **151** showed the greatest potential as foldamers, adopting a novel 10-helical conformation in organic solvents due to hydrogen-bonding interactions <2001TL4251>. Oligomers **152–154**, part of the L-rhamnonate series, also adopted an ordered conformation, but this was due to steric interactions of the bulky *tert*-butyldimethylsilyl (TBDMS) group rather than through hydrogen bonding <2005MI517>.



Scheme 25

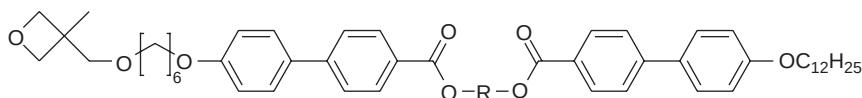
**150:** $\text{R} = \text{TBDMS}$ **151:** $\text{R} = \text{Bn}$ **152:** $n = 1$ **153:** $n = 3$ **154:** $n = 5$

2.05.12 Important Compounds and Applications

2.05.12.1 Polymers

2.05.12.1.1 Oxetane polymers

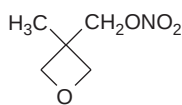
Oxetanes are very versatile monomers because a wide range of side groups can be attached. This provides ready access to the corresponding polymers with useful properties conferred by pendant functionalities. In recent years, this has been exploited for the synthesis of polymers with liquid crystalline side chains <1997PSA2843, 2001JMC1590, 2002MAC975, 2005MAC1731>. The liquid crystalline side chains that have been attached to oxetane monomers have a general structure containing one or two biphenyl mesogen units with alkyl spacers (e.g., **155** <2005MAC1731>). Despite the bulky side chains, polymerization of functionalized oxetane monomers proceeded in high yields and polymers displayed useful liquid crystalline properties that were not disturbed by the polyoxetane backbone.



155

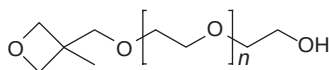
R = alkyl or oxymethylene spacer

Oxetanes with pendant nitrate esters can be converted to highly energetic polymeric materials. A carefully controlled polymerization of 3,3-(nitratomethyl)-methyl oxetane (NIMMO) **156** led to the formation of low molecular weight oligomers <1996PLM3461>. Furthermore, the use of a diol or triol core allowed for the synthesis of di- and tribranched oligomers. These nitrate oligomers have potential uses as plasticizers in propellant and explosives polymer formulations.

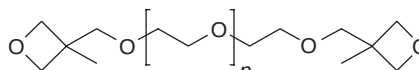


156

Silicon-containing pendant groups were used to confer useful properties on oxetane polymers, such as resistance to chemicals, ozone and ultraviolet (UV)-induced degradation, as well as antifouling properties <2004PSA1415>. Polymers of this nature have potential applications in coatings as marine paint additives. Poly(fluorinated) oxetanes were prepared for use as water-dispersible surfactants <2002L5933>. These surfactants were seen to adopt a novel 'comb-like' architecture and displayed unusually low surface tensions at low critical micelle concentrations. Oxetane monomers with pendant cyanoethoxy or triethylene oxy functional groups were used to synthesize polymers with sufficiently high ion conductivity to make them potentially useful as polymer electrolytes for lithium batteries <2005PIN1440>. Cross-linked polyoxetanes bearing PEG chains (PEG-400 or PEG-1500) have been used as novel polymer supports, known as SPOCC resins, in solid-phase organic synthesis <1999JA5459>. SPOCC resins were synthesized by cationic polymerization of the mono-oxetane-functionalized PEG chains **157** using dioxetane-functionalized PEG chains **158** as the cross-linker. These polymer supports were stable to strongly acidic conditions and displayed good swelling properties across a range of solvents. They have been used as polymer supports for peptide and glycopeptide synthesis, nucleophilic reactions, and enzymatic reactions in aqueous solvents.



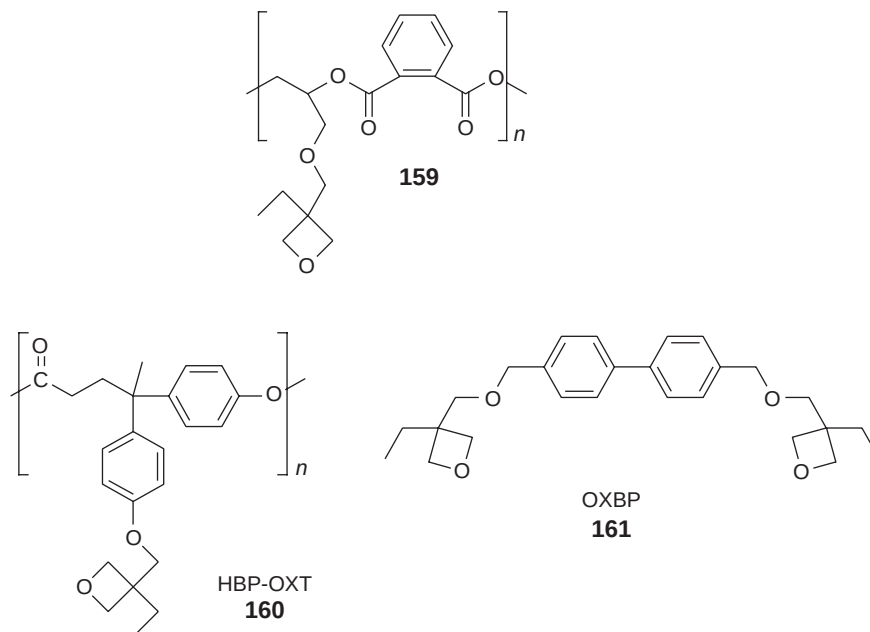
157



158

In addition to providing ready access to a polyether backbone, the readiness of oxetanes to polymerize under photoinitiated cationic conditions has led to their use as cross-linking agents and in UV-curable formulations. Monofunctional and oligofunctional oxetane acetals were UV-cured using triarylsulfonium hexafluorophosphate initiator <2001PSA613>. These compounds have potential uses as reactive diluents or binders. Polyesters with pendant oxetane groups **159** were synthesized by the copolymerization of 3-ethyl-3-(glycidylloxymethyl) oxetane with carboxylic anhydride. A photoacid generator could then be used to photo-cross-link the pendant hydroxyl groups

giving insoluble polymers. A hyperbranched polymer with pendant oxetane groups (HBP-OXT) **160** was used as an additive in the cationic photopolymerization of 4,4'-bis[(3-ethyl-3-oxetanyl)methoxymethyl]biphenyl (OXBP), **161** <2003PSA1952, 2005JAP293>. HBP-OXT **160** acted as a cross-linker, resulting in a polymer with a higher glass transition temperature.



2.05.12.1.2 2-Oxetanone polymers

Poly(*R*- β -hydroxybutyrate) is the most common of a class of naturally occurring polyesters known as polyhydroxyalkanoates (PHAs) that are produced by both bacterial and mammalian organisms. They have a wide range of cell functions, including the formation of metal ion transport channels in cell membranes and acting as an intracellular carbon and energy store. Poly(*R*- β -hydroxybutyrate) is fully biodegradable in aerobic conditions, giving water, carbon dioxide, and methane. Biodegradability, along with favorable melting properties, has led to increasing interest in the synthesis of poly(*R*- β -hydroxybutyrate), structural isomers, and other structurally related PHAs for use as packaging materials <1996PIN479, 1996MM3773, 1998MM3473, 1998MM6718, 2001BMM623, 2002PSA2184, 2002JA15239, 2004T7177>. Ring-opening polymerization can proceed by two mechanisms depending on the initiator used: the coordination-insertion mechanism or the anionic mechanism. While most studies focused on the synthesis of poly(β -hydroxybutyrate), alternative PHAs were synthesized from α -methyl- β -pentyl- β -propiolactone <2001BMM623>, β -valerolactone <2002JA15239>, and α -methyl- β -pentylpropiolactone <2004T7177>. The polyester formed from the latter monomer was used in the formulation of immiscible blends or block copolymers with the biodegradable aliphatic polyester polylactide <2004T7177>.

2.05.12.2 Biologically Active 2-Oxetanones

β -Lactones have been found in structures of many naturally occurring compounds. The synthesis of the viridifloric β -lactone pheromone components released by male *I. leuconoe* is discussed in Section 2.05.11.1 <1996BMC341>. A vittalactone was also found in a mixture of volatiles released by male striped cucumber beetles feeding on curcubis <2005JNP26>. Serine and threonine β -lactones have been described as a new class of hepatitis A virus 3C cysteine proteinase inhibitors and were mentioned in Section 2.05.3.1. Analogues of oxazolomycin, which exhibits activity against P-388 leukemia cells and has antiviral properties, notably 16-methyloxazolomycin, have been isolated <1997JAN1064>. Synthetic studies toward the spirolactone moiety of oxazolomycin have also been described <2000OL1987>.

2.05.12.3 Pharmaceutical Applications

The biological and pharmaceutical properties of oxetanes have been highlighted throughout the chapter when other aspects such as their synthesis is described. For example, as discussed in [Section 2.05.11](#), oxetanones form part of the structure of potent inhibitors of lipases and other enzymes. The naturally occurring amino acid oxetin is used as an antibiotic, and foldamers derived from analogues of oxetin have other potential therapeutic uses. The antiobesity drug tetrahydrolipstatin [119](#) was described in [Section 2.05.11](#) and the β -lactone F-244 (1223 A) has been reported with antibiotic properties [<1998BMC1255>](#).

2.05.13 Further Developments

Recent developments include the synthesis of oxetane building blocks as promising modules for attachment to molecular scaffolds and use in drug discovery applications [<2007AG\(E\)7736>](#). Notably, the oxetane motif was found to improve key drug physicochemical properties. Oxetanes have been described as intermediates in synthetic strategies to a range of compounds including: a 5-hydroxy-functionalized 2-trifluoromethyl-1-alkene [<2006S128>](#); asymmetric 1,2-dioxolane-3-acetic acids [<2006JOC2283>](#); the anti-tubular agent erogorgiaene [<2007TL2841>](#) and tetrahydropyran-based liquid crystals via a Lewis acid catalyzed ring opening of oxetanes [<2006EJO3326>](#). An interesting tetraoxo spiro oxetanone has been formed from an indanedione ketene in quantitative yield [<2007JOC502>](#). Other oxetanes recently prepared include an oxetane lactone via modification of the sesquiterpene dehydrocostuslactone [<2006T7747>](#), oxetane δ -amino acids using a chemoenzymatic strategy [<2006MI187>](#) and route to spiroannulated glyco-oxetanes [<2006TL3875>](#). Furthermore, a new enantioselective synthesis of (–)-[119](#), the active ingredient of Xenical® a novel antiobesity agent, has been described [<2007OPRD524>](#) suitable for large scale preparations.

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1998J(P1)3253
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1999JOC4152
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1999JOC7074
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Biographical Sketch



Helen Hailes completed her Ph.D. in chemistry in 1991, with Professor James Staunton (FRS), at St. John's College, University of Cambridge. Her project focused on a biomimetic synthesis of rocaglamide and investigations into tetronasin biosynthesis. She then carried out postdoctoral research for one year with Professor Staunton on biosynthetic studies with polyether antibiotics. This was followed by a short postdoctoral position with Professor Steven Ley (FRS), at Imperial College London, on combinatorial synthesis. A further postdoctoral position in 1993–94 was carried out with Dr. David Widdowson, at Imperial College London, on solid-phase organic synthesis. She joined University College London as a lecturer in 1994, becoming a senior lecturer in 2002, and a reader in 2005.

Research activity in her group is focused on the use of synthetic organic chemistry to probe and solve biological problems. Many of her projects involve the development of new synthetic strategies to construct molecules as tools to identify or perturb biological targets, which can lead to the identification of novel compounds with improved biological properties. In particular, research is carried out into: nonviral gene therapy and the design and synthesis of novel lipids for use in a ternary delivery system; PI3-kinase and PKB activators and inhibitors; a major programme with Biochemical Engineering and Biochemistry at UCL on the biocatalytic synthesis of aminodiols using transketolases and transaminases; the design and synthesis of novel cytosine-based hydrogen-bonding arrays; organic synthesis using SPOS or LPOS; and carbon–carbon bond forming reactions in aqueous media.



As an undergraduate, Jonathan Behrendt studied for a B.Sc. in Chemistry and Law from the University of Exeter, where he was awarded a 2.1 hon. degree in 2001. He went on to study for a Ph.D. in chemistry at University College London, with Dr. Helen Hailes. His Ph.D. research project focused on the use of polymeric supports for the synthesis of structurally defined oligomers and cyclic ethers. Having been awarded his Ph.D. in 2005, he is currently working on the synthesis and functionalization of polystyrene microspheres as cellular delivery vectors, in the research group of Dr. Andy Sutherland at Aston University.

2.06

Oxetanes and Oxetenes: Fused-ring Derivatives

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2.06.1 Introduction

This chapter reviews developments related to fused-ring and spiro oxetanes over the period 1995–2007. Monocyclic oxetanes are reviewed in Chapter 2.05. CHEC-II(1996) included reviews of monocyclic <1996CHECII(1B)721> and fused-ring oxetanes <1996CHEC-II(1B)755>; CHEC(1984) included a comprehensive review of oxetanes <1984CHEC(5)363>. Oxetanes and oxetanones are included in reviews of heterocycles <2002J(P1)2301, 2005PHC(17)64>, while a number of reviews describe oxetanones or related systems <2002CRV29, 2004H(64)605, 2002T7075>. Reviews on more specific topics are described within individual sections.

2.06.2 Theoretical Methods

Ab initio calculations have been used to predict conformations maximizing singlet–triplet state mixing in the diradical intermediates of Paterno–Büchi reactions <2001JA9279>, as well as the bonding in dioxaspiro[3.2.0]hexanones (spiro epoxy/ β -lactones; see Section 2.06.7.2), in which shortening of the C–O bonds was attributed to a double anomeric effect <2005JA16754>. For the analogous dioxaspiro[3.2.0]hexanes (spiro epoxy/oxetanes), calculations support the intermediacy of four-membered ring oxycarbenium ions during acid-promoted reactions (see Section 2.06.7.2) <2003JOC1480>. Molecular modeling has been used to predict the solvent accessibility for oxetane analogues of a commercial odorant <2004HCA1616>. Semi-empirical methods have been employed to compare the solvation of taxol (Section 2.06.12.3) with analogues lacking the oxetane D-ring <2000JOC1059>. A recent overview of taxol chemistry includes summaries of both molecular modeling and crystallographic studies of taxanes <2005RJO315>.

Molecular modeling and semi-empirical calculations have been employed in conjunction with experimental methods to study the conformations of oxetane-constrained sugar rings (see Section 2.06.12.1). For example, a series of 3'-O-4'-C-oxetane nucleoside analogues were studied by nuclear magnetic resonance (NMR), X-ray, and semi-empirical calculations <2002T3039>. In particular, the $^3J_{1,2}$ coupling constants revealed the modified nucleosides to almost exclusively populate the S-type, 2'-*endo*-conformer <1972JA8205>. PM3 calculations suggested that the presence of the oxetane adds as much as 10 kcal mol⁻¹ to the cost of populating the alternative C₃-*endo*- or C₄-*endo*-conformers. In general, the appendage of a fused oxetane is thought to greatly raise the barrier to pseudorotation of the furanose ring <2005JOC4918>, as exemplified by the results of molecular dynamics (MD) simulations on a 1'-C,2'-O-fused oxetane <2004JA11484>.

2.06.3 Experimental Structural Methods

NMR and crystallographic studies found that incorporation of a spiro-oxetane onto the skeleton of a sesquiterpene lactone significantly altered the molecular conformation; the downfield shift of protons on the oxetane ring was indicative of cyclization from the diol <2006T7747>. In oxetane-constrained nucleosides (see Section 2.06.12.1), ¹H NMR coupling constants ($^3J_{\text{H}}$) have proven diagnostic for characterizing the presence of a fused oxetane <2003OBC3738>, the *endo/exo*-relationship of adjacent furanose substituents to the oxetane fusion <2001JOC4878>, and the puckering angle of the ribofuranose <2005JOC4918>. The preferred solution structures are often similar to those in the crystal <2002T3039>. NMR studies have determined that oxetane-modified nucleosides exert only minimal impact on the conformations available to adjacent sugars in di- and trisaccharides <2002JOC4150>. Nuclear Overhauser enhancements (NOEs) have proved to be a powerful tool for elucidation of side-chain (*exo/endo*)-stereochemistry in fused oxetanes <2001CEJ4512>; differential NOE has been employed to differentiate α - and β -nucleoside anomers <2005OBC4362>.

NMR analysis of *seco*-D-ring taxane analogues <1999BML3041, 2000JNP726> supports the hypothesis that the oxetane serves to rigidify the overall molecular backbone (see Section 2.06.12.3). NOE and nuclear Overhauser effect spectroscopy (NOESY) experiments have been used to establish stereochemistry in taxanes, their synthetic precursors, and model structures <2005JOC3484, 2001S1013>. Fluorescence spectroscopy and rotational-echo double

resonance (REDOR) solid-phase NMR have been applied to elucidate the interactions of taxanes with the tubulin receptor <2000JNP726>. Solid-state NMR spectra of taxol have been reported <2006MRC581>.

Chemically induced dynamic nuclear polarization (CIDNP) has been used to discriminate radical and nonradical processes in cycloadditions of electron-rich alkenes and electron-poor carbonyl components <1998MI9>. Spectroscopic observation of the fragmentation of an oxetane radical anion revealed the generation of the most stable alkene radical <2003JOC10103, 2006PPS51>. Transient absorption spectroscopy has been employed to monitor the Paterno–Büchi cycloaddition of benzophenone and furan <2004JA2838>.

The oxetane components of both [3.2.0] and [4.2.0] fusions are nearly planar, as seen for the crystal structures of a Paterno–Büchi adduct <2001CEJ4512> and a taxane; the latter structure also revealed the oxetane to be involved in hydrogen bonding <2000JOC1059>. Co-crystals of imidazole or 2-propanol with baccatin III provide a means of separating this valuable intermediate from related taxanes <2000OL3269>. A crystal structure of the bicyclic oxetane derived from photocycloaddition of methyl benzoate and furan (see Section 2.06.9.1) identified the major product as having an *endo*-phenyl, correcting an earlier misassignment <1998JOC3847>. A crystal structure of a methylene oxetane revealed bond lengths and angles similar to β -lactones <1999JOC7074>. A crystal structure of a spiro epoxy/ β -lactone (1,5-dioxaspiro[3,2]hexanone) revealed shortened C–O linkages for both the oxirane and lactone units compared with monocyclic epoxides or β -lactones <2001OL1499>. Theoretical and synthetic studies related to these spiro compounds are described in Sections 2.06.2 and 2.07.7.2, respectively.

2.06.4 Thermodynamic Aspects

Theoretical investigations suggest that the reactivity of oxetanes can be largely attributed to strain <2003JOC2639>; substitution on the ring is thought to provide net stabilization <2002JOC2588>. However, ring opening of oxetanes is often surprisingly slow, a trait exploited in approaches to syntheses of oxetane-containing molecules <1996JOC9135>. As described in Section 2.06.10.1, epoxy alcohols undergo acid- or base-promoted isomerization to hydroxymethyl oxetanes. The synthetic chemistry of several β -lactone natural products (Section 2.06.12.4) suggests that fused [3.2.0]oxetanones are favored relative to the spiro[4.3.0]isomers.

A series of conformationally immobile inositols presenting varying arrays of ethers (spiro-linked tetrahydrofurans, oxetanes, oxiranes, or alkoxides) were investigated for solution- and gas-phase complexation of alkali ions. An assembly of three spirotetrahydrofurans was the most effective agent, with a K_a for Li^+ $> 10^{-7}$. An analogue replacing a single tetrahydrofuran with a spirooxetane displayed a 10-fold reduced K_a for Li^+ , while the assembly bearing three spirooxetanes was a much less effective complexing agent <2001JOC8629>.

2.06.5 Reactivity of Fully Conjugated Rings

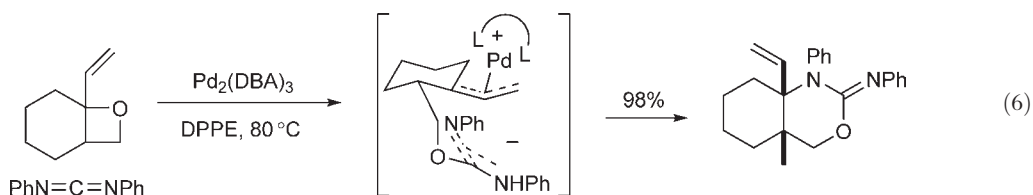
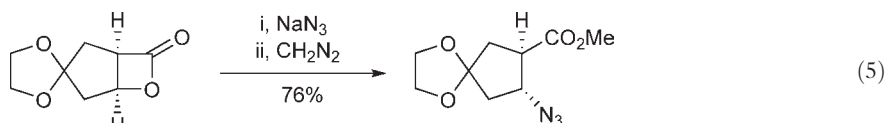
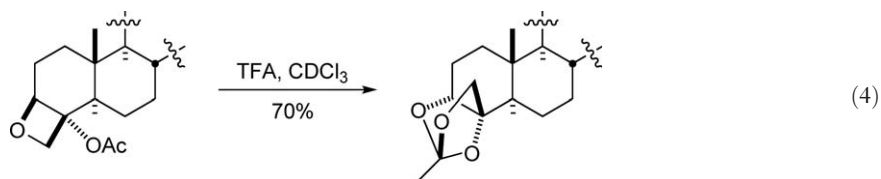
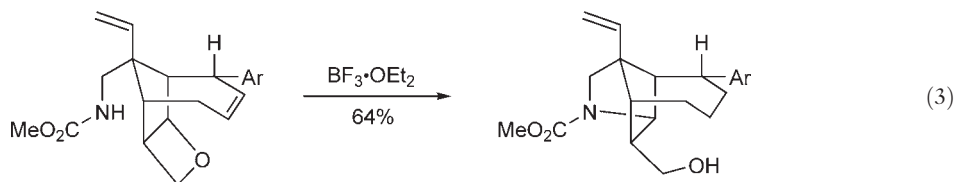
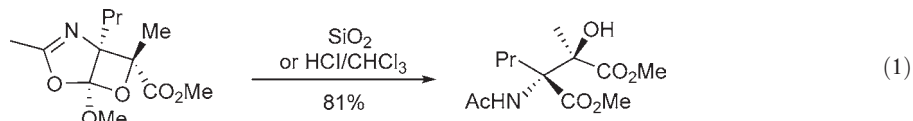
No examples of this class of compounds have been found in the literature in the period covered.

2.06.6 Reactivity of Nonconjugated Rings

2.06.6.1 Reaction with Nucleophiles

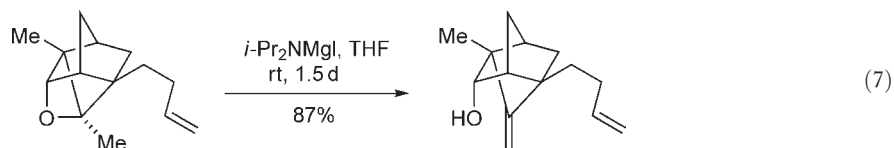
Opening of unactivated oxetanes is typically promoted by Brønsted or Lewis acids (Equations 1–6). Depending upon substrate and conditions, the reactions can display attributes typical of either $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ pathways. For example, an oxetane orthoester undergoes hydrolytic opening under nearly neutral conditions (Equation 1) to furnish a functionalized β -hydroxy amino acid <2004OBC1113>. However, opening of the taxane D-ring oxetane, although requiring a powerful Lewis acid (TMSI, Equation 2), cleanly furnishes the product of inversion from attack at the more substituted center <2000JNP726>. A stereospecific and regioselective Lewis acid-promoted opening of an oxetane by a neighboring carbamate is a central step in the synthesis of gelsemine (Equation 3) <2002JA9812>. Acid-catalyzed opening of a steroidal oxetane by a neighboring ester (Equation 4) proceeds through an intermediate dioxycarbenium ion, which undergoes intramolecular trapping by the liberated alcohol to furnish an orthoester. Interestingly, the analogous subunit of taxol (Section 2.06.12.3) is unreactive under identical conditions <2003HCA3613>. Acid-catalyzed attack of nitriles on the least substituted C–O of a steroidal oxetane furnishes 1,3-oxazines; the epimeric oxetane undergoes a skeletal rearrangement under the same conditions <1998CCC1613>. Bicyclic β -lactones react with azides and similar nucleophiles through $\text{S}_{\text{N}}2$ inversion at the alkyl C–O (Equation 5);

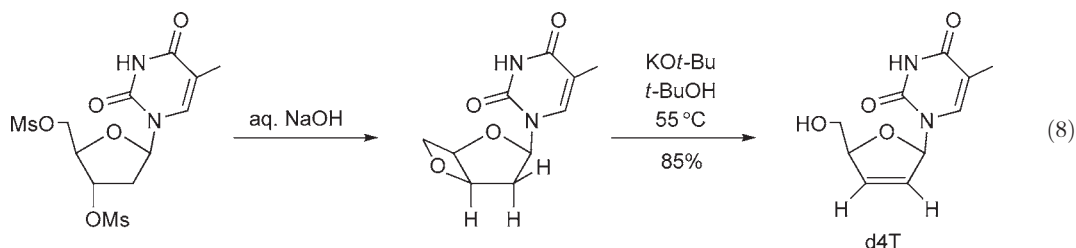
attack of amines or metal hydrides takes place at the acyl center [<2002T7075>](#). Pd-mediated insertion of heterocumulenes into bicyclic vinyl oxetanes ([Equation 6](#)) provides a highly regio- and stereoselective route to oxazinones (from isocyanates) or oxazineimines (from diimides) through backside attack on the intermediate π -allyl Pd-complex derived from vinyllogous opening of the oxetane [<1999JOC4152>](#).



2.06.6.2 Elimination

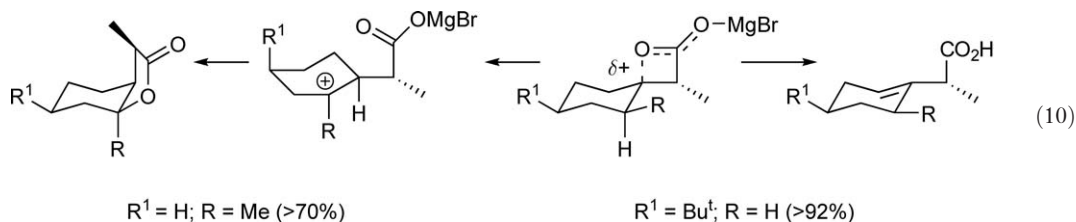
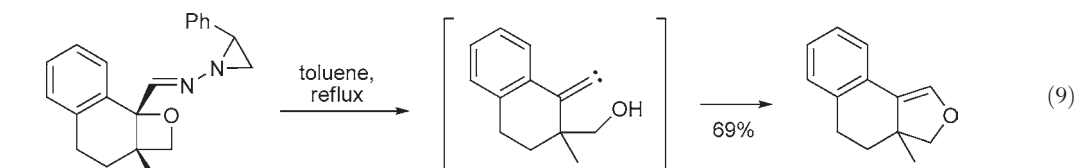
Oxetanes undergo elimination in the presence of strong base to form unsaturated alcohols ([Equation 7](#)) [<1997CC2381>](#); this transformation forms the key step in a synthesis of the antiviral d4T ([Equation 8](#)) [<2003TL1003>](#). Elimination of 2-methylene oxetanes generates homopropargyl alcohols [<1998JOC6782>](#). As described in [Section 2.06.6.3](#), oxetanones undergo both eliminations and rearrangements in the presence of Lewis acids. The taxane D-ring oxetane has been found to undergo E_1CB fragmentation (β -fragmentation) when the C–O bond is β to a ketone [<2001JOC3321>](#).





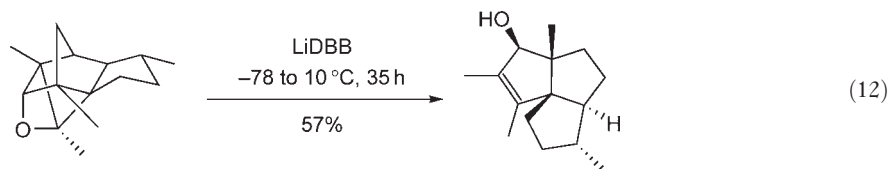
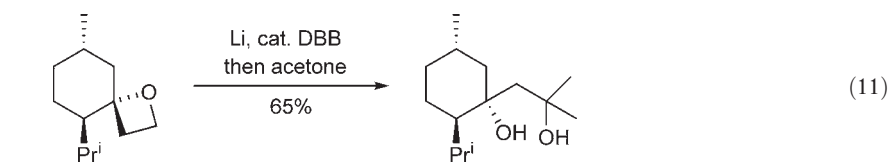
2.06.6.3 Ring Expansion

Thermolysis of an oxetanyl *N*-aziridinylium generates a dihydrofuran via intramolecular insertion of a vinylidene carbene into an alcohol (Equation 9) <2000S1622>. Reaction of β -lactones with Lewis acids can result in elimination to unsaturated acids or rearrangement to γ -lactones; the product distribution depends upon the stability of the derived cations and the ability to access conformers featuring an *anti*-periplanar relationship between the migrating bonds and the breaking C–O bond (Equation 10) <1995TL3679, 2001CC753>.



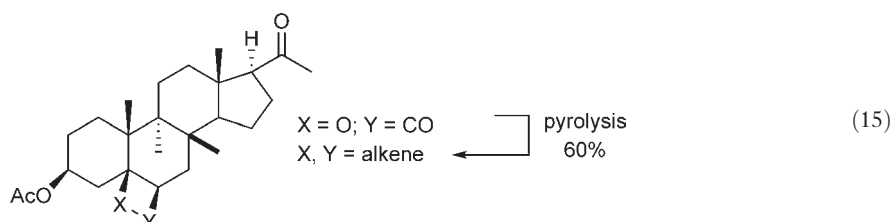
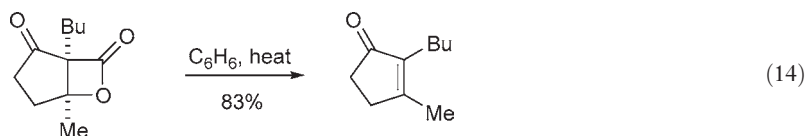
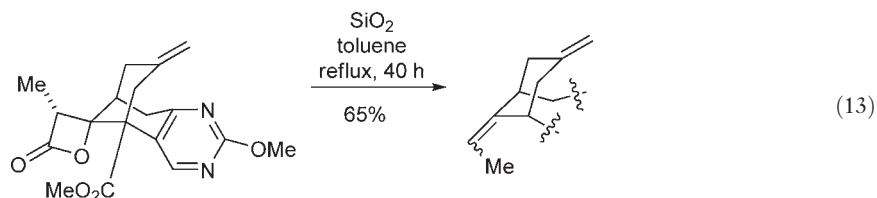
2.06.6.4 Reduction

Spirooxetanes undergo stereospecific reduction by lithium at $T \leq 0^\circ\text{C}$ in the presence of a catalytic amount of di-*tert*-butylbiphenyl (DBB); the resulting organolithium reagents can be trapped by electrophiles (Equation 11) <1997TA2633>. Under similar conditions, a polycyclic Paterno–Büchi product (see Section 2.06.9.2) undergoes fragmentation, providing an efficient entry to triquinanes (Equation 12) <2000OL2711>. As illustrated later in this chapter (Equation 25), Pd-mediated hydrogenolysis of benzylic oxetanes provides a useful route to functionalized alcohols <2000SL1699>. Reduction of β -lactones with metal hydrides generates products typical of acyl reduction <2002T7075>.



2.06.6.5 Cycloreversion

Thermal cycloreversion of β -lactones provides a useful approach to alkenes as illustrated for the conversion of a spirolactone to an exocyclic alkene (Equation 13) <1996J(P1)1287> and several cyclic alkenes (Equations 14 and 15) <2001JOC7818, 2000T3559>.



Oxetanes can undergo cycloreversion via radical cations or anions <2003H(60)1921>. Although theoretical studies suggest that cation radicals undergo initial C–C cleavage, <2000JA5510>, intramolecular trapping experiments point to an initial C–O scission <2002JA6532>. The tandem application of the Paterno–Büchi cycloaddition (Section 2.06.9.1) and electron-transfer cycloreversion has been proposed as an avenue for reversible alkene/oxetane meta-thesis <2006PPS51>. Methanolysis of oxetanes in the presence of Ce^{4+} , while attributed to cleavage of an intermediate oxetane radical cation, furnishes products indistinguishable from simple acid-catalyzed displacement <2003TL4585>.

Photomediated cycloreversion of oxetanes is key to enzymatic repair of 6-4 DNA cross-links derived through a Paterno–Büchi process (Figure 1) <2006PPS51>. Binding of the damaged section of DNA by photoproduct lyases is

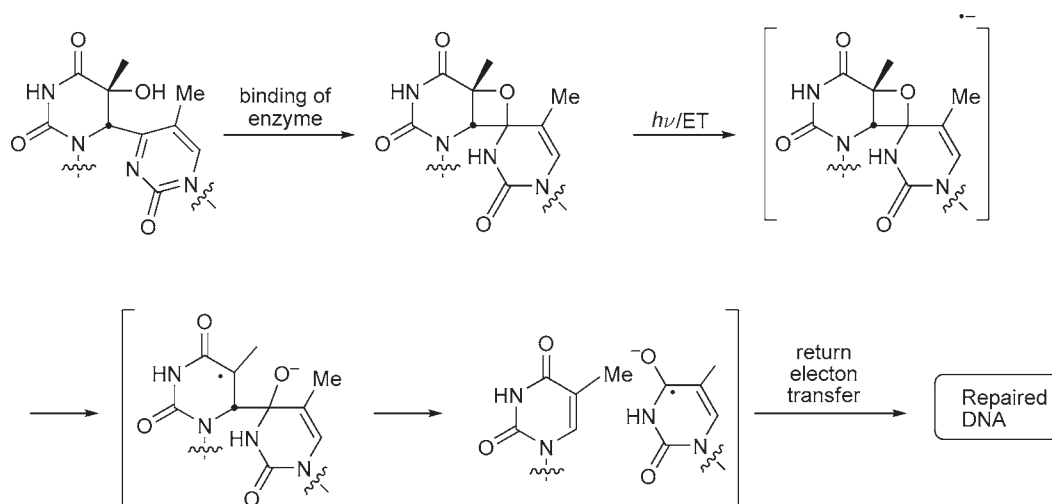


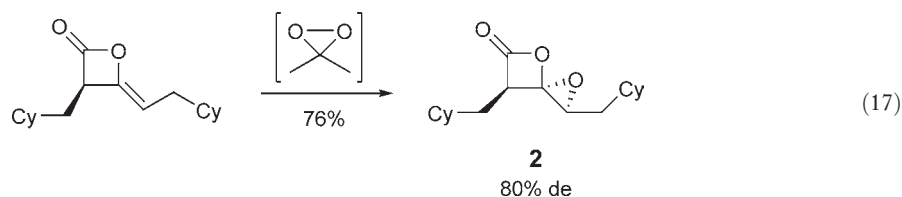
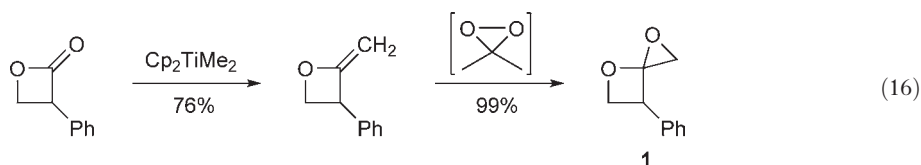
Figure 1

thought to induce (re)closure to the oxetane. Electron transfer within the enzyme/substrate complex generates a pyrimidone radical anion, which undergoes oxetane cleavage. Loss of a radical anion and return electron transfer generate the repaired DNA <2003CRV2203>. The proposed mechanism is supported by the rapid ($\leq 5 \times 10^7 \text{ s}^{-1}$) cycloreversion of thymine oxetanes observed upon flash photolysis <2000JA11219>. An enhancement in the efficiency of thymine oxetane cycloreversion has been observed within a supramolecular complex, a result believed to model the ability of the photolyase to suppress back electron transfer <2006OBC2575>.

2.06.7 Reactivity of Substituents Attached to Ring Carbon Atoms

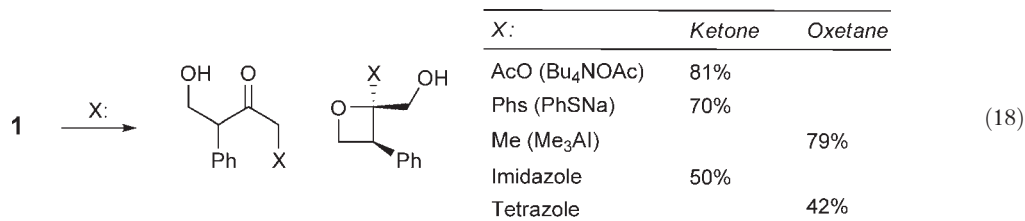
2.06.7.1 Exocyclic Alkenes

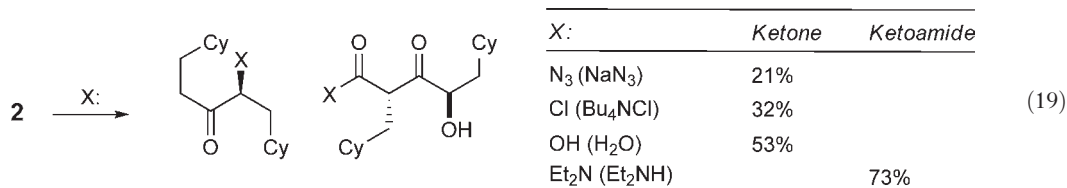
Methylene oxetanes are available through methylenation of β -lactones (Equation 16) or through reductive fragmentation of iodomethyl[2.2.0]dioxabicyclohexanes <2003OL399, 1999TL7051>. Methylene oxetanes undergo epoxidation to furnish dioxaspiro[3.2.0]hexanes (spiro epoxy/oxetanes), exemplified by compound **1** (Equation 16). A similar epoxidation of methylene oxetanones, available through ketene dimerization, furnished dioxaspiro[3.2.0]hexanones (spiro epoxy/ β -lactones), exemplified by product **2** (Equation 17) <2005JA16754, 2003OL399>. Sections 2.06.2 and 2.06.3 include discussions of bonding and crystal structures in these compounds. The corresponding spirocyclopropanes are available from reaction of the methylene oxetanes or methylene oxetanones with zinc carbenoids <2001NJC673>.



2.06.7.2 Exocyclic Epoxides and Cyclopropanes

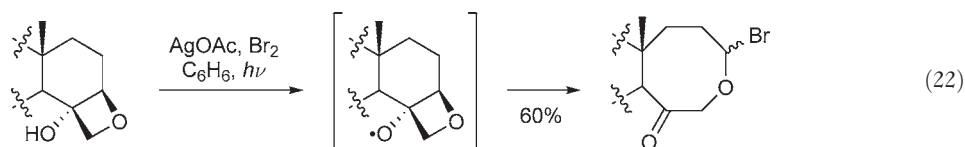
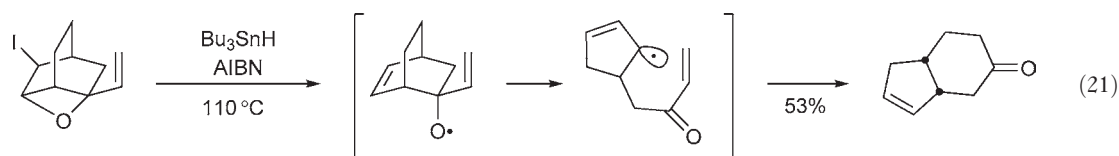
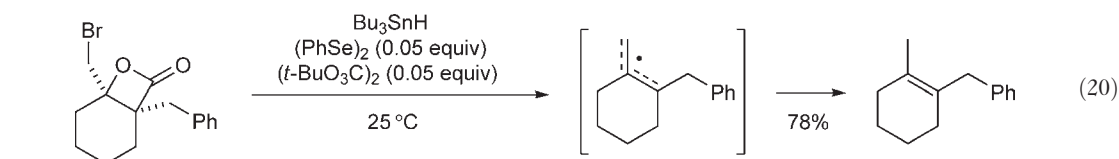
Under neutral or basic conditions, nucleophilic attack on spiro epoxy/oxetanes occurs at the less-substituted oxirane C–O bond to furnish substituted ketones (Equation 18). Reaction under acidic conditions furnishes oxetanes, apparently through the intermediacy of a four-membered oxycarbenium ion (see Section 2.06.2) <1999OL825, 2003JOC1480>. Spiro epoxy/ β -lactones react with azide, water, and chloride via attack at the less-substituted oxirane C–O bond to furnish, after decarboxylation, ketones (Equation 19). In contrast, attack by diethylamine occurs at the lactone acyl group to furnish a diastereomerically pure ketoamide <2005JA16754>. Spirocyclopropanes (oxaspirohexanes or oxaspirohexanones) react with $\text{BF}_3 \cdot \text{OEt}_2$ to furnish a mixture of products <2001NJC673, 2000J(P1)2109>. The spiro cyclopropyl β -lactones react with $\text{Cu}(\text{acac})_2$ to afford butenolides (acac = acetylacetonate) <2000J(P1)2109>.





2.06.7.3 Exocyclic Radicals

Generation of a radical adjacent to the alkyl C–O of a β -lactone results in rapid (10^6 – 10^7 s^{−1}) ring opening, followed by decarboxylation of the resulting carboxyl radical (Equation 20) <1998JA8298>. A similar reactivity is observed in the radical fragmentation of a bicyclic oxetane (Equation 21) <2002AGE4321>. A radical fragmentation has been postulated to underpin the conversion of the taxane D-ring to a methyl ether <1993JOC5028>. Fragmentation of the alkoxy radical of a 3-hydroxyoxetane has been used to generate ring-enlarged analogues of taxanes (Equation 22) <2006T8503>. The fragmentation of small-ring heterocycles has been reviewed recently <2003AGE5556>.



2.06.8 Reactivity of Substituents Attached to Ring Heteroatoms

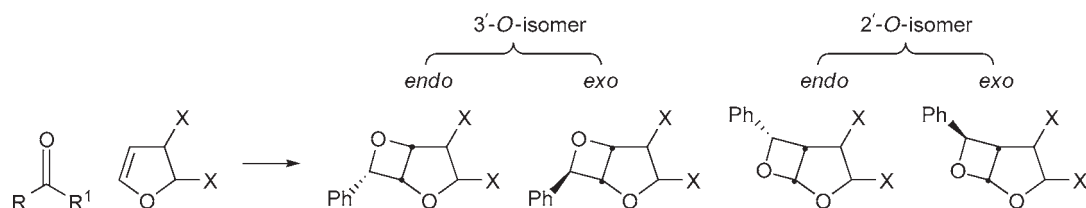
No examples of this class of compounds have been found in the literature in the period covered.

2.06.9 Ring Synthesis Classified by the Number of Ring Atoms

2.06.9.1 Intermolecular [2+2] Cycloaddition Reactions

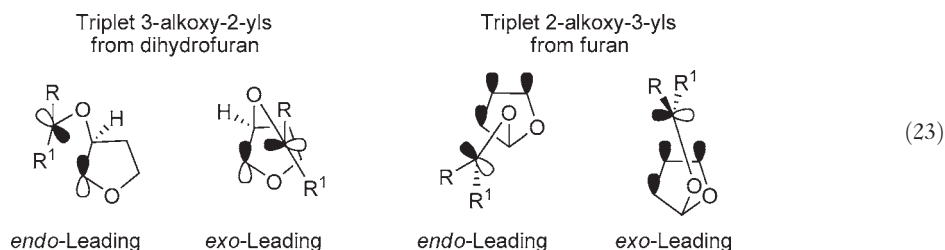
The Paterno–Büchi cycloaddition of carbonyls and alkenes is described in several general reviews <1995HOU(E21c)3133, B-2004MI59-1, B-2004MI62-1>. More specific reviews describe the development of the reaction <2005MI89>, applications to stereoselective synthesis <1998S683>, cycloadditions involving *N*-acyl enamines or furans <2000SL1699, 2003COR1443>, the formation and reactions of heteroatom-substituted oxetanes <1997LA1627>, and methods for the control of the absolute stereochemistry <2000CC251>.

A number of recent investigations have advanced the understanding of the factors controlling the regio- and stereoselectivity of the cycloaddition. These are summarized in Scheme 1 and Equation (23) for reactions of furan and dihydrofuran <2004ACR919, 1998JOC3847>.



	<i>R</i>	<i>R</i> ¹	Conditions	3'-O endo/exo	Major regioisomer	2'-O endo/exo
<i>X</i> = H (dihydrofuran)	Ph	H	0.01 M, C ₆ H ₆	88% <i>endo</i>	3'-O	
	Ph	H	0.01 M, CH ₃ CN	88% <i>endo</i>	3'-O	>85% <i>exo</i>
	Et	H	0.01 M, C ₆ H ₆	>80% <i>endo</i>	3'-O	
	Et	H	1 M, C ₆ H ₆	~50:50	3'-O	
<i>X</i> = alkene (furan)	Ph	H	0.01 M, C ₆ H ₆		2'-O	>99% <i>exo</i>
	Ph	H	0.01 M, CH ₃ CN		2'-O	>99% <i>exo</i>
	Ph	OMe	0.01 M, C ₆ H ₆		2'-O	>95% <i>endo</i>

Scheme 1



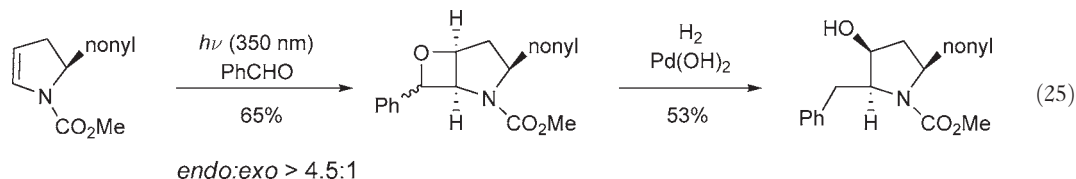
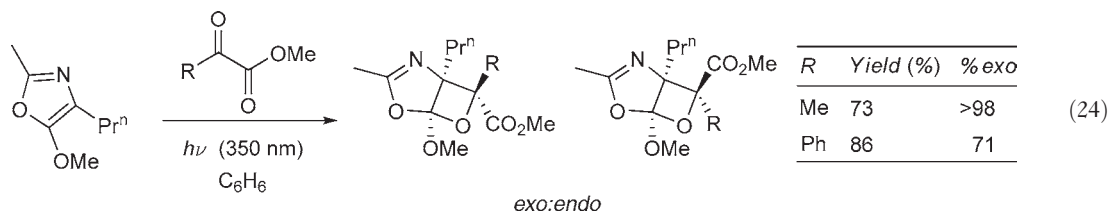
Regioselection is dictated by the relative stability of the intermediate diradicals (see Equation (23) for structures of typical diradicals). For example, reaction of the benzaldehyde excited-state triplet with dihydrofuran in nonpolar media (benzene) predominantly forms the 3-alkoxyoxetane via 3-alkoxy-2-yl diradicals. The same is observed with an aliphatic aldehyde, whether at low aldehyde concentrations (conditions favoring reaction via triplet excited state) or at high aldehyde concentrations (conditions favoring trapping of the initially formed singlet excited state). However, photolysis of benzaldehyde and dihydrofuran in a polar solvent (acetonitrile) proceeds with reduced regioselectivity due to a competing electron-transfer process. For furan, where the electron-transfer process is energetically disfavored, reaction in either benzene or acetonitrile furnishes the 2-alkoxyoxetane via the initial formation of a 2-alkoxy-3-yl diradical stabilized by allylic conjugation <B-2004MI59-1, 2003SL451>.

The factors governing diastereoselection are more complex. For reactions that involve addition of a triplet excited state of a carbonyl to an alkene, the stereoselectivity depends upon the relative stabilities of those triplet diradical adducts maximizing spin-orbit coupling. These conformers will be most likely to undergo intersystem crossing (ISC) to short-lived singlet diradicals, which collapse directly to oxetanes <B-2004MI59-1, 2003SL451>. For dihydrofuran, the conformations of the *endo*-leading and *exo*-leading diradicals are illustrated in Equation (23) <2001JA9279>. The greater stability of the *endo*-leading radical results in preferential formation of the corresponding singlet diradical, and therefore formation of the *endo*-oxetane. Conditions resulting in the direct formation of a singlet diradical intermediate, such as the photochemical reaction of aliphatic aldehydes and dihydrofuran at high concentration, avoid this conformational 'gating' and diastereoselection is altered <2004ACR919>. Similar factors control the ISC of 2-alkoxy-3-yl diradicals derived from additions to furan (Equation 23), except that the *exo*-leading triplet diradical is now stabilized by molecular orbital interactions and remains the predominant intermediate as long as *R*¹ is small.

In accordance with this prediction, cycloaddition of furan and benzaldehyde ($R^1 = H$) furnishes almost exclusively the *exo*-oxetane, whereas reaction with methyl benzoate ($R^1 = OMe$) furnishes mainly the *endo*-oxetane <1998JOC3847, B-2004MI62-1, 2004JA2838>.

Recent studies suggest the need to consider conformational reorganization of the intermediate triplet diradicals in flexible substrates. At -80°C , *cis*- and *trans*-cyclooctene react with the triplet excited state of benzophenone to stereoselectively afford the *cis*- and *trans*-oxetanes, respectively. At higher reaction temperatures, both geometric isomers selectively furnish the *trans*-oxetane. However, this selectivity is attenuated as the reaction temperature is increased further. The results suggest that, in addition to the factors described above, diastereoselection may also be influenced by the direction of approach (outside or inside) of the excited-state carbonyl and alkene, and by conformational interconversion of *cis*-leading and *trans*-leading diradicals through reorganization of the substrate backbone <2002JA3600>.

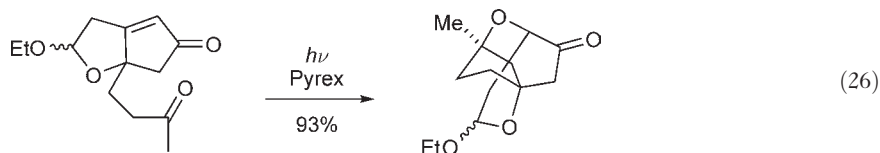
Two examples of the intermolecular Paterno–Büchi reaction are illustrated in Equations (24) and (25). As expected from the preceding discussion of selectivity in addition to conjugated alkene substrates, reaction of pyruvates or glyoxalates with methoxyoxazoles regioselectively affords reactive orthoesters (see Section 2.06.6.1) with moderate (phenylglyoxalate) to high (pyruvate) *exo*-selectivity (Equation 24). The difference in stereoselectivity is attributed to the relative energies of the triplet biradical conformers able to undergo ISC <2004OBC1113>. As expected, based upon the analysis described above, a chiral dihydropyrrole undergoes regioselective formation of the 3'-*O*-oxetane with moderate *endo*-selectivity (Equation 25). Chemoselective hydrogenation of the major product furnished an advanced intermediate in the synthesis of the alkaloid (+)-preussin <2001CEJ4512>. The same review describes the use of a hydrogen-bonding-induced preorganization to enhance diastereoselectivity in the reaction of a dihydropyrindone with a chiral benzylic aldehyde.

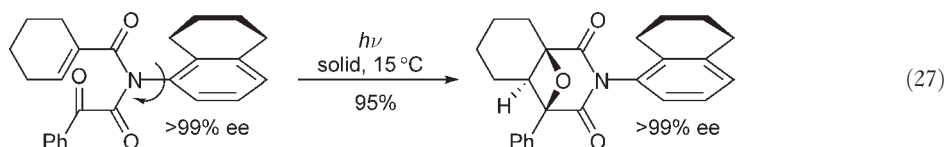


The Paterno–Büchi reaction has also been investigated in the solid state. Whereas irradiation of acetylcyclopentane in solution results in formation of dicyclopentane, photolysis within the crystal affords one major oxetane regioisomer through cycloaddition of a caged alkene/aldehyde pair derived from a Norrish-type fragmentation <2001OL3361>. Photolysis of powdered mixtures of 2-pyrone and benzophenone provides improved yields and regioselectivity compared with solution reactions <2004H(63)1541>.

2.06.9.2 Intramolecular Paterno–Büchi Cycloadditions

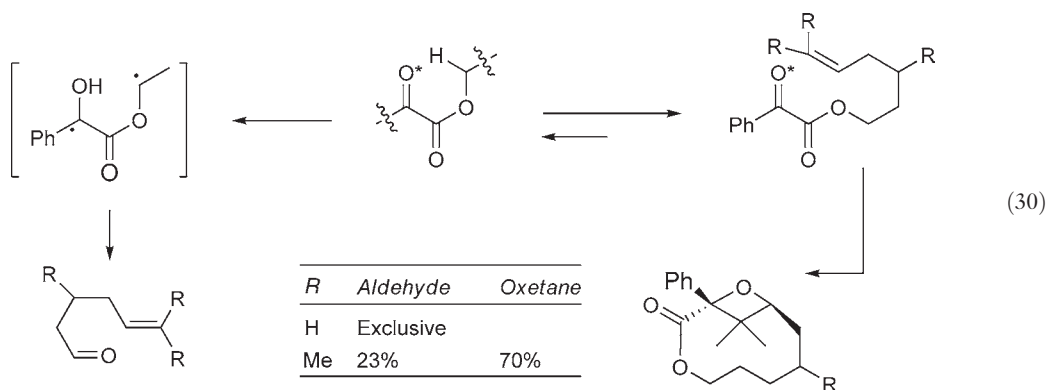
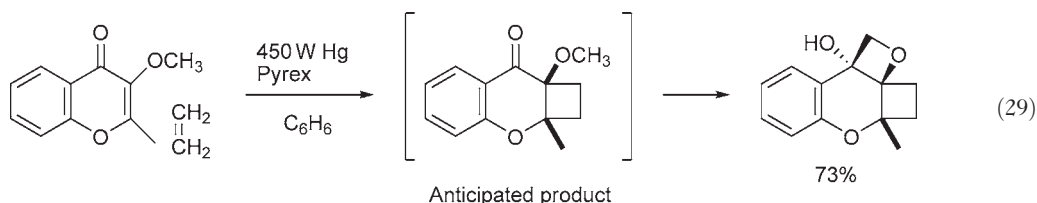
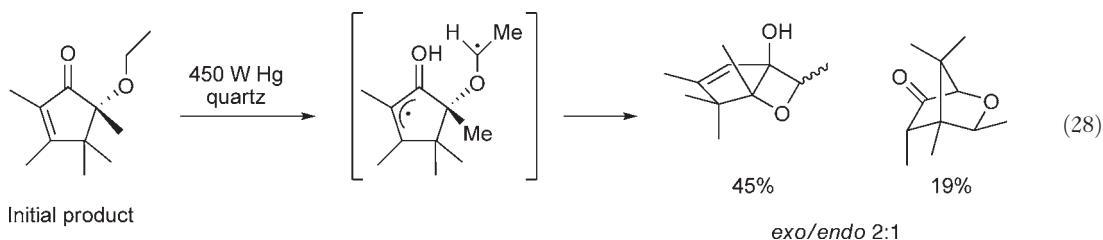
The intramolecular Paterno–Büchi reaction is capable of installing new oxetane units with significant regio- and stereoselectivity, as is evident in the construction of a tetracycle related to merrilactone (Equation (26); see also Section 2.06.12.2) <2005OL3969>. The chirality of an atropoisomer recrystallized from an interconverting ($t_{1/2} = 468$ s at -20°C) mixture of enantiomers was preserved by photocycloaddition (Equation 27); the atropoisomeric oxetane products do not interconvert unless heated <2003JOC942>.





2.06.9.3 Norrish II (Biradical) Cyclization

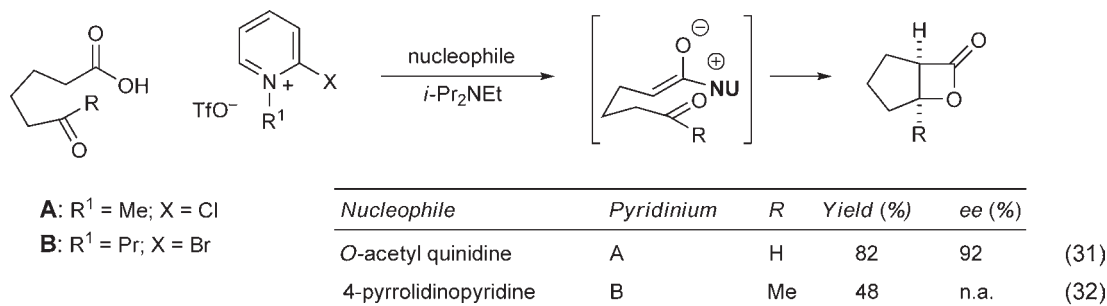
Intramolecular hydrogen abstraction from the triplet state of alkoxyketones can generate fused oxetanes; [Equations \(28\) and \(29\)](#) represent examples in which this process resulted in the isolation of oxetanes as unexpected secondary photoproducts [<1999JOC1626, 1996JOC4391>](#). The relative tendency of an excited-state carbonyl triplet to undergo Paterno–Büchi cycloaddition versus intramolecular hydrogen abstraction has been investigated for glyoxylates. The hydrogen abstraction required for Norrish cleavage is disfavored by the need to populate the *s-trans*-ester conformer, and becomes competitive only for electron-deficient alkenes. Paterno–Büchi cycloaddition dominates for alkenes with an electron density at least as great as a disubstituted alkene [<1997JOC564>](#). The intramolecular cycloaddition is also the dominant reaction ([Equation 30](#)) if an electron-rich alkene and a glyoxylate are joined by a chain of the appropriate length (for brevity, no difference is drawn between ground state and excited states in terms of conformational interconversion). The formation of a single major cycloadduct is attributed to the limited conformations of the intermediate triplet diradical able to interconvert to a short-lived singlet state [<1997JOC6820>](#).



2.06.9.4 Cycloadditions of Ketene Equivalents

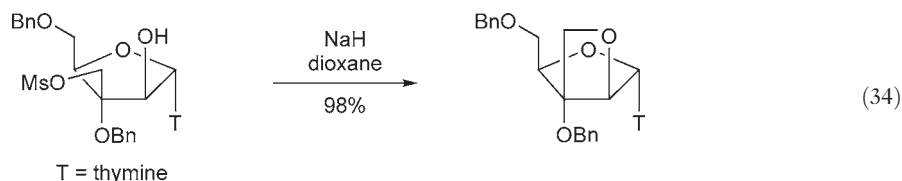
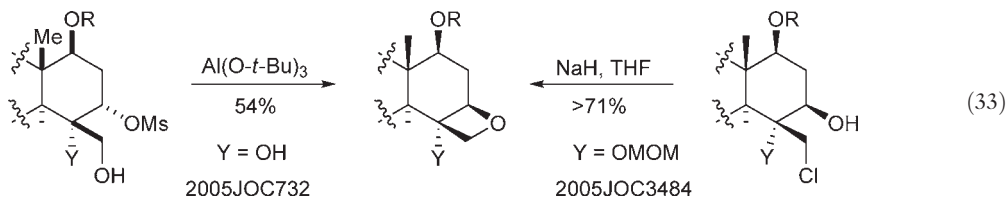
The nucleophile-catalyzed aldol lactonization (NCAL) reaction of carboxyl-derived zwitterions and unactivated aldehydes has been applied to the catalytic asymmetric synthesis of bicyclic β -lactones ([Equation 31](#))

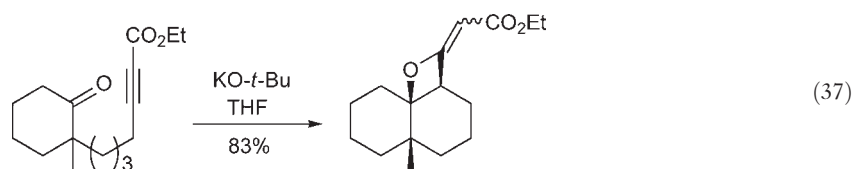
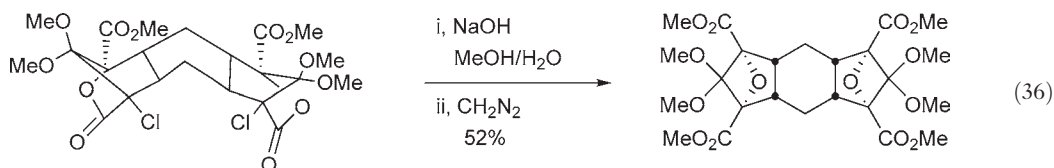
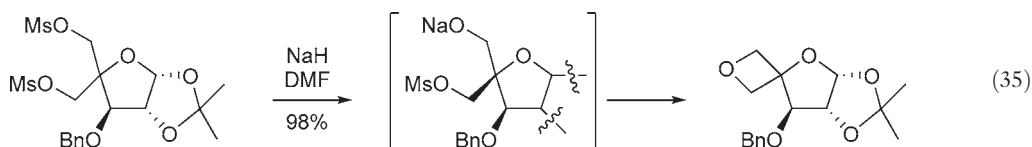
<2005JOC2835>. The use of a more nucleophilic catalyst allowed the racemic synthesis of ketone-derived β -lactones (Equation 32) <2006OL4363>. An NCAL-like process appears to be involved in the synthesis of a β -lactone from the Baylis–Hillman-type reaction of an unsaturated acyl pyridinium intermediate <2006OL1717>. Enolates of phenyl esters react with cyclohexanone to furnish spiro β -lactones, analogous to established reactions of thioesters <1995JOC758>. The β -lactone enolate derived from cycloaddition of an ynolate with a ketoester undergoes Dieckmann cyclization; the resulting bicyclic β -lactones are used as substrates for cycloreversion to cycloalkenone (see Section 2.06.6.5) <2001JOC7818>. Cyclization of a steroidal ketoacid to a β -lactone presumably involves the generation of an intermediate ketene <2000T3559>. A review of the methodology for β -lactone synthesis has been published <1999T6403>.



2.06.9.5 Intramolecular Nucleophilic Displacements

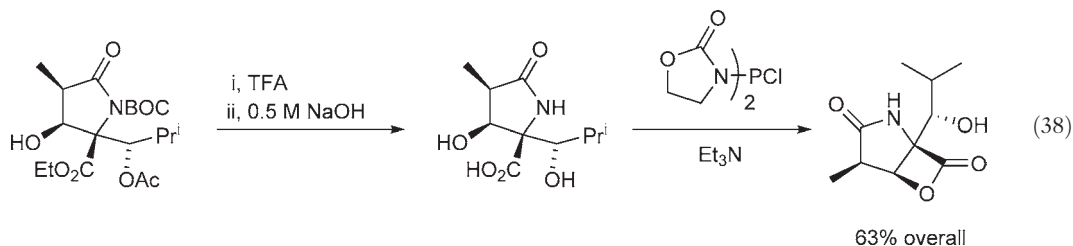
Intramolecular displacements are summarized in Equations (33)–(37). The intramolecular 4-*exo-tet*-displacement at primary or secondary centers is the method of choice for introduction of the D-ring oxetane in taxanes (Equation (33); also see Section 2.06.12.3) and for incorporation of oxetane constraints onto a sugar backbone (Equation (34); also see Section 2.06.12.1) <2005JOC732, 2005JOC3484, 2005JOC4918>. Leaving groups are nearly always halides or sulfonates, but displacement of a tertiary amine from a tetralkylammonium salt has been observed <1998EJO2185>. The 4-*exo*-pathway is rarely competitive with 5-*exo*- or 3-*exo*-cyclizations <2003OBC3738>, and reactions within polyols typically require masking of competing nucleophiles <2004TA2667>. Within the 4-*exo*-series, formation of a fused oxetane appears favored over formation of a spiro isomer <2000CCC395>. Formation of a spiro oxetane through base-promoted cyclization of a 1,3-bis-sulfonate, a reaction described as involving a cyclic sulfonate, appears more likely to involve fragmentation with loss of sulfene, CH₂=S=O, to liberate a reactive alkoxide (Equation 35) <2006TL3875>. The synthesis of a rigid polycycle offers a rare example of displacement at a tertiary center (Equation 36) <2005JOC7565>. The formation of methylene oxetanes during cyclizations of ketoalkynoates has been attributed to the conjugate addition of an alkoxide to an alkynoate (Equation 37) <2001OL2689>. Isomerization of 3,4-epoxy alcohols to oxetane alcohols is discussed in Section 2.06.10.1.





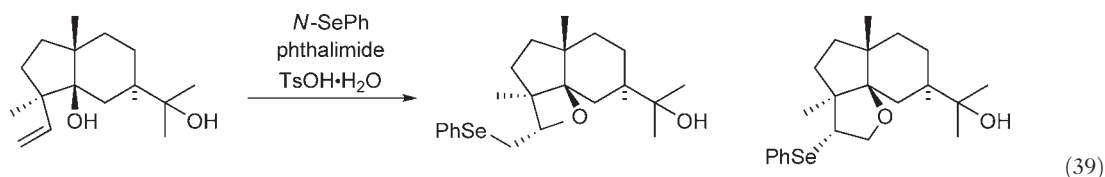
2.06.9.6 Dehydration of Hydroxy Acids

3-Hydroxyalkanoic acids are easily dehydrated to either spiro or fused β -lactones. Sulfonyl chlorides have been the traditional reagents employed for this transformation [\[1996S586, 2001CC753\]](#). However, as illustrated in [Equation \(38\)](#) for a cyclization used as part of a synthesis of lactacystin/omuralide (see also [Section 2.06.12.4](#)), bis(oxazolidinone) phosphinyl chloride (BOP-Cl) has proven an effective agent for application in sensitive structures; note also the selectivity for introduction of the fused (vs. spiro) lactone [\[2006JOC1220\]](#).

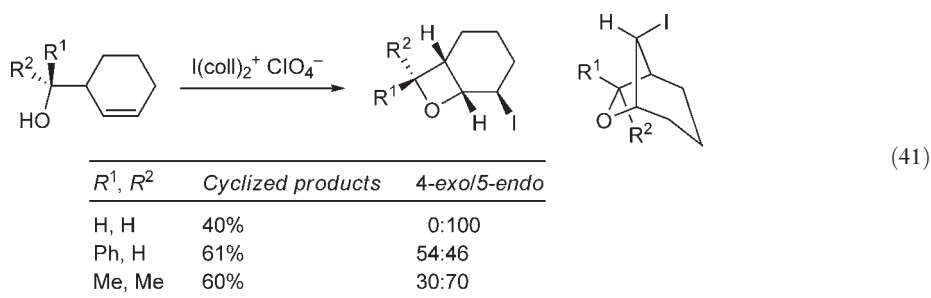
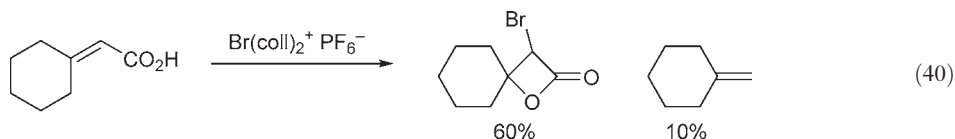


2.06.9.7 Electrophilic Cyclizations onto Alkenes

Electrophilic cyclizations of unsaturated alcohols or acids to form oxetanes or β -lactones have been achieved with reagents based upon positive halogen, selenium, sulfur, or mercury [\[1995HOU\(E21c\)4704, 2002EJO3099\]](#). The most common examples involve 4-*exo*-attack on onium-type intermediates ([Equation 39](#)), although 4-*endo*-reactions have been observed ([Equation 40](#)). Reactions are often, but not always, stereospecific. The selectivity for the formation of four-membered rings is enhanced by strain in the transition state for the competing 5-*endo*-cyclization, the presence of proximal substitution on the alkene [\[2003JOC4422\]](#), and substitution on the tether linking nucleophile and alkene [\[2003SC2167\]](#). The products can sometimes undergo equilibration ([Equation 39](#)) and maximum yields of four-membered ring products are favored by short reaction times, by use of stronger nucleophiles (carboxylates rather than carboxylic acids), or by use of highly electrophilic cationic complexes of bromine and iodine ([Equation 41](#)) [\[1988S862, 1999JOC81, 2001TL2477\]](#). Control of the absolute stereochemistry has been achieved through use of chiral auxiliaries [\[1999SL843\]](#).

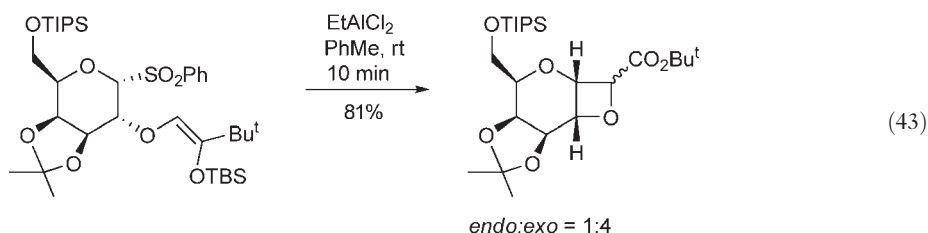
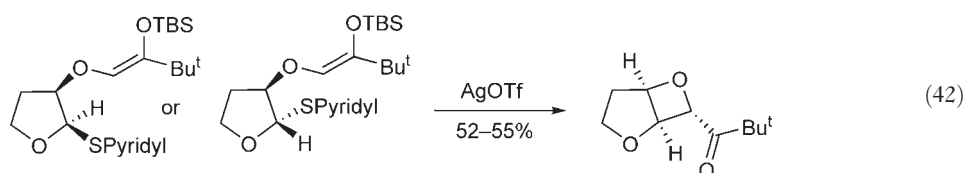


Reaction time (h)	Oxetane	Tetrahydrofuran
2	51%	22%
6.5	0%	75%



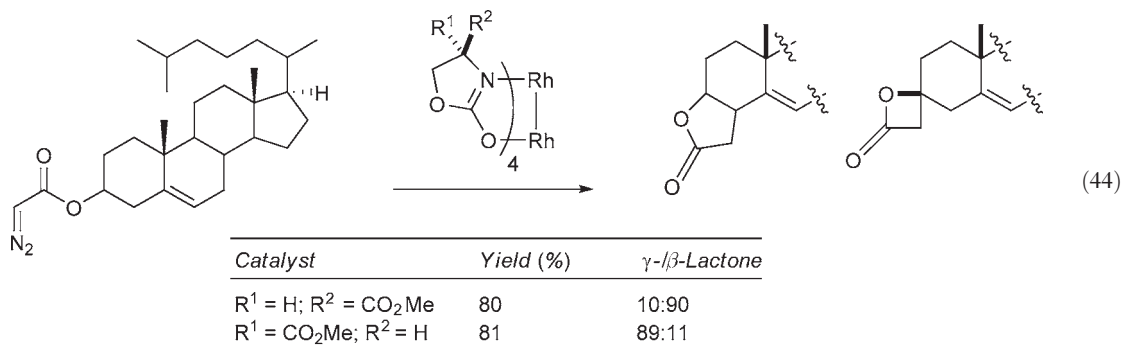
2.06.9.8 Cationic Cyclizations

Intramolecular Ag-promoted reactions of thiopyridyl acetals with ether-linked silyl enol ethers furnish *cis*-[3.2.0]oxetanes substituted with an *exo*-acyl group, an outcome consistent with the presence of an intermediate carbenium ion (Equation 42). Similar reactions are observed for tetrahydrofuran phenylsulfonyl acetals in the presence of excess SnCl_4 at -78°C . Cyclization of analogous phenylsulfonylacetals in the presence of Et_2AlCl proceed with initial selectivity for formation of *endo-cis*-[6,4]-fused oxetanes (Equation 43); increasing amounts of *exo*-product are observed at longer reaction times or upon equilibration with Lewis acids <1999T15025>. An analogous reaction in which the developing cation is stabilized by an exocyclic thioether provides good yields of the [5,4], but not the [6,4], fusion products <1997SL1001>.



2.06.9.9 Intramolecular C–H Insertion

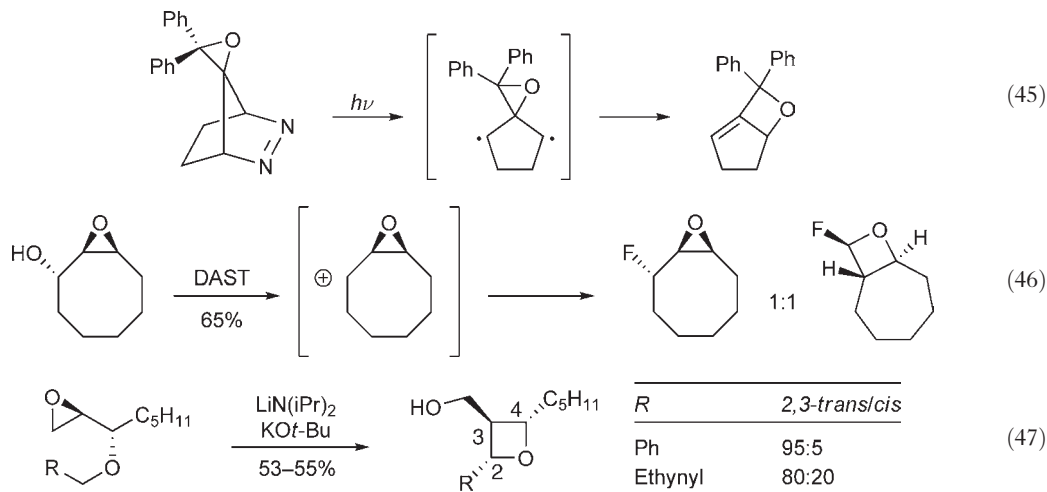
The decomposition of diazoacetate esters of chiral alcohols in the presence of chiral rhodium(II) carboxamidates can generate either spiro- β -lactones or fused γ -lactones, depending on the configurational match or mismatch between catalyst and substrate (Equation 44). The corresponding phenyldiazoacetates generate β -lactones regardless of the catalyst <2001JOC8112>.



2.06.10 Ring Synthesis by Transformation of Another Ring

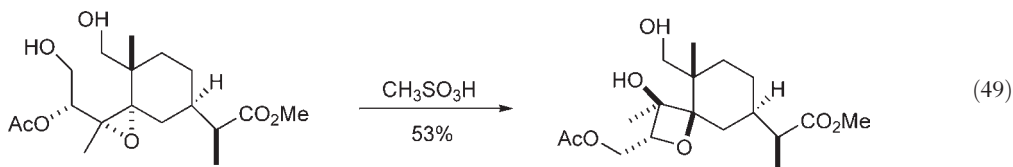
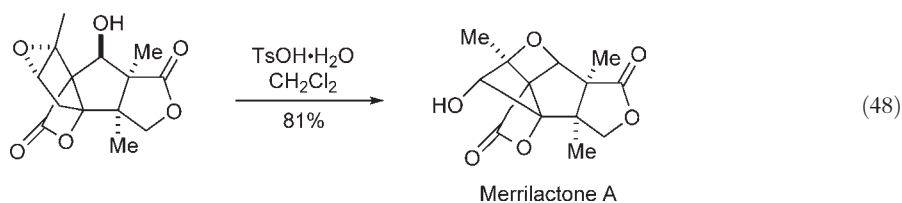
2.06.10.1 Rearrangements of Epoxides

Photochemical fragmentation of an azo-epoxide furnishes an oxetane via a 1,2-shift of a C–O bond in the intermediate diradical (Equation 45) <2002T7043>. Reaction of *trans*-2,3-epoxycyclooctanol with diethylaminosulfur trifluoride (DAST) furnishes both the expected epoxy fluoride as well as a 2-fluoro-oxetane derived from a Wagner–Meerwein shift (Equation 46); the *cis*-epoxycyclooctanol furnishes only a ring-expanded enol ether under the same conditions <2002OL451>. Deprotonation of benzyl or propargyl ethers of epoxy alcohols with a mixed alkyl lithium/metal alkoxide superbases results in intramolecular 4-*exo*-cyclization of the intermediate carbanion to afford hydroxyoxetanes (Equation 47) <2001JOC3201>.



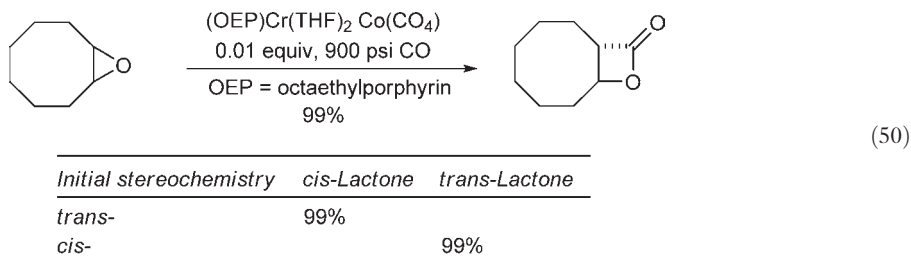
The stereospecific isomerization of 3,4-epoxyalcohols under acidic or basic conditions <2002T6199, 1998TL8259> has been the method of choice for the final step in syntheses of merrilactone (Equation 48) <2006AGE4843>. An analogous acid-promoted closure of benzyl ethers of epoxy alcohols has also been observed <2000H(52)171>. An unusual 4-*endo*-isomerization of a hydroxy epoxide apparently reflects the inability of a primary alcohol to cyclize via 4-*exo*- or 5-*endo*-modes; transesterification liberates the secondary alcohol, which undergoes a 4-*endo*-cyclization (Equation 49). An X-ray structure of the product has been reported <2003JOC4422>. Section

2.06.11.1 includes a comparison of epoxide isomerization relative to other methods for oxetane synthesis; additional information regarding merrilactone can be found in Section 2.06.12.2.



2.06.10.2 Carbonylation of Epoxides

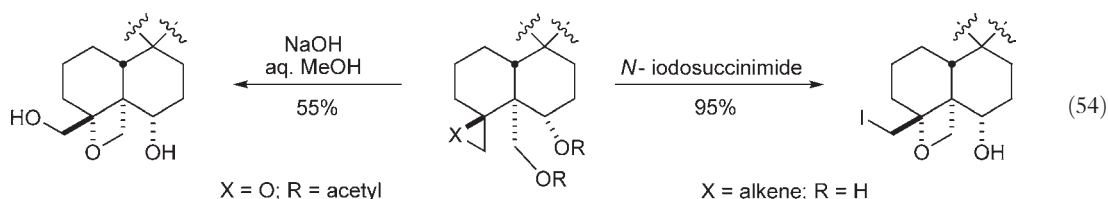
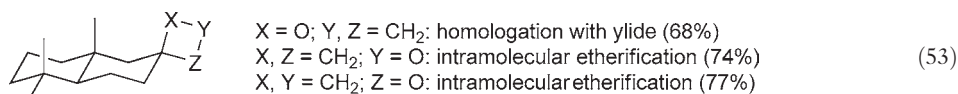
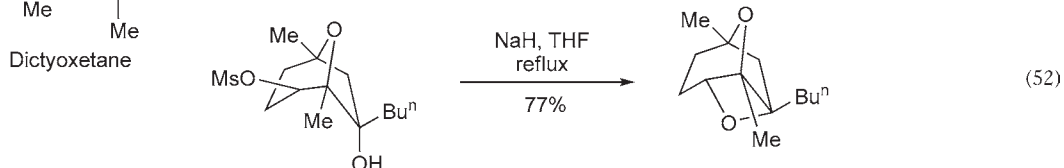
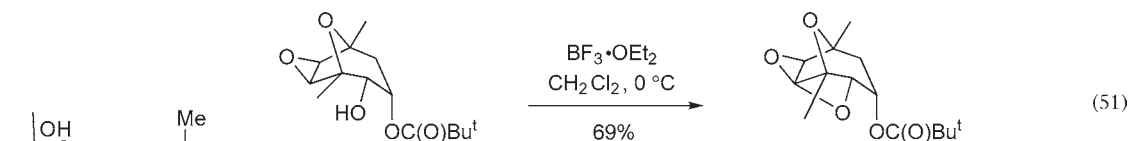
A catalyst combining a Lewis-acidic Cr(III) with a tetracarbonyl cobalt anion promotes the carbonylation of epoxides at pressures as low as 1 atm CO (Equation 50) <2006OL3709>. S_N2 ring opening by the Co(CO)₄ anion generates a 2-hydroxyethylcobalt intermediate which undergoes cyclocarbonylation <2005JA11426>. For substrates where direct cyclocarbonylation of the ring-opened intermediate is precluded by strain, a slower cationic pathway may operate. The carbonylation of propargyl alcohols in the presence of Pd⁺, CuCl₂ or CuBr₂, benzoquinone, and CO, furnishes 3-halomethylidene-2-oxo-1-oxaspiroalkanes through a *cis*-halopalladation, followed by carbonylation and cyclization <2005JOC2568>.



2.06.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

2.06.11.1 Oxetanes

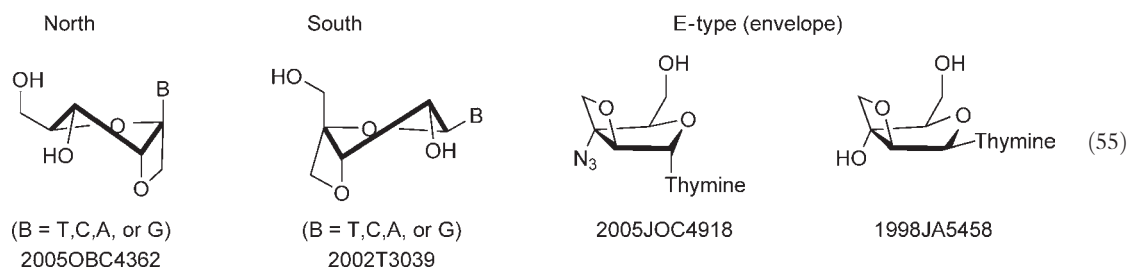
Equations (51)–(54) compare several methods for oxetane synthesis. The 2,7-dioxatricyclononane core of the natural product dictyoxetane <1985JOC3665> has been prepared through isomerization of an epoxy alcohol (Equation 51) and through an intramolecular S_N2 displacement (Equation 52) <2002T6199, 1996JOC9135>. An analogous S_N2' displacement was unsuccessful <1996JOC9135>. An X-ray study of this structural core has been reported <2002T6199>. The preparation of three isomeric spirooxetanes allows a comparison of one-carbon homologation of an epoxide with trimethylsulfoxonium ylide relative to intramolecular S_N2 displacements. (Equation 53). The yields for the two approaches were comparable <2004HCA1616>. Finally, the synthesis of neoclerodane diterpenoids provides the opportunity to compare isomerization of epoxy alcohols with iodoetherification (Equation 54) <2000T8007>.



2.06.12 Important Compounds and Applications

2.06.12.1 Conformationally Constrained Nucleosides

Bicyclic [3.2.0] nucleosides containing a fused oxetane are of interest for their ability to preferentially populate individual ribofuranose conformers (Equation 55). For example, α -linked 1'-C,2'-O-oxetanes favor N-type (C_3' -*endo*) twist conformers <2005OBC4362, 2004JA11484>. An isomeric α -2'-O,3'-C-linkage imparts a bias for E-type conformers <1998JA5458, 2005JOC4918>, while an α -3'-O,4'-C fusion imparts a preference for the S-type (2'-*endo*) twist conformer <2002T3039>. For a discussion of N/S formalism, the reader is directed to a key early reference <1972JA8205>. The oxetane linkages are invariably introduced through intramolecular displacements of halides or sulfonates (see Section 2.06.9.5). Spiro-linked oxetane sugars have also been prepared but conversion to nucleosides has been problematic <2006TL3875>. Sections 2.06.2 and 2.06.3 discuss spectroscopic and theoretical approaches related to oxetane-constrained nucleosides.



The modified nucleosides, which can be incorporated within oligonucleotides using standard phosphoramidite methodology <1998JA5458>, are of interest for incorporation into antisense oligonucleotides (AONs) designed to downregulate selected genes by formation of AON/RNA complexes <2002BMC841, 1999BBA167, 2000J(P1)3539>. The interactions between the oxetane AONs and DNA or RNA are dependent upon the structure and the extent of incorporation. Although incorporation of a 2'-O,3'-C-oxetane-modified thymine as 13 of 14 units of an

oligo-T-sequence resulted in enhanced duplex stability with both DNA and RNA <1998JA5458>, the modified nucleosides are more frequently incorporated at a limited number of sites. For example, while incorporation of a single oxetane-modified nucleoside into a 14-mer results in increased RNA affinity, a fully modified 10-mer has a decreased affinity relative to the unmodified sequence. The ability of the AON/RNA hybrids to recruit RNAase cleavage can be enhanced by use of 'gapmers', which are oligonucleotides in which the modified nucleosides are separated by some number of unmodified residues <2005OBC4362>.

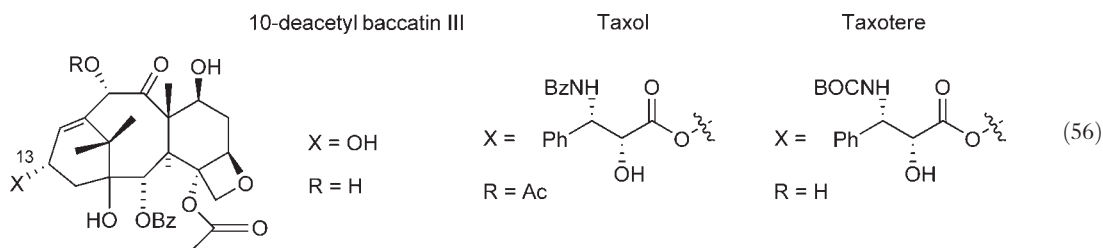
The constrained nucleosides are of interest as leads for small-molecule therapeutics. For example, the β -2'-O,3'-C-oxetane analogues of the antiviral 3'-azido-3'-deoxythymidine (AZT), which exist predominantly in the E-like conformation (see, for example, Equation 55), were investigated for inhibition of human immunodeficiency virus 1 (HIV-1). Neither the modified nucleosides nor their 5'-monophosphate analogues inhibit HIV-1, supporting a hypothesis that reverse transcriptase inhibitors must have conformational freedom <2001JOC4878, 2002J(P1)1655>.

2.06.12.2 Merrilactone

Merrilactone A, a pentacyclic oxetane able to stimulate neurite growth in cortical neurons, is of interest in relation to potential therapies for the neurodegeneration associated with Alzheimer's and Parkinson's diseases (Equation 48). Crystal structures have been reported for merrilactone A and C; the absolute stereochemistry of the former was established by differential NMR shifts in chiral ester derivatives <2001T4691>. The biological activity of merrilactone has inspired a number of synthetic approaches <2006AGE4843, 2006AGE953, 2006ACR539>, all of which introduce the oxetane through acid-promoted isomerization of a hydroxy epoxide (see Section 2.06.10.1 and Equation 48). The efficiency of this transformation, first demonstrated in the conversion of anisactone to merrilactone A, presumably reflects the enforced proximity of the reacting partners <2001T4691>.

2.06.12.3 Taxol

Taxol (paclitaxel) and its synthetic analogue taxotere (Equation 56) are the most prominent members of a class of anticancer agents that promote assembly of tubulin into microtubules <B-2005MI89, 2002MI53>. Taxol is available in very small quantities from the bark of the Pacific yew, *Taxus brevifolia*, and large-scale preparations of taxol or taxotere are based upon semisynthesis from 10-deacetyl baccatin III, readily available from the European yew, *Taxus baccata*. The D-ring oxetane, which is believed to act as a hydrogen-bond acceptor and a rigidifying structural element, is found in the majority of active analogues <2000JNP726, 2000JOC1059>. However, predictions based upon a model for the taxol receptor suggest that it should be possible to prepare active analogues lacking the oxetane.

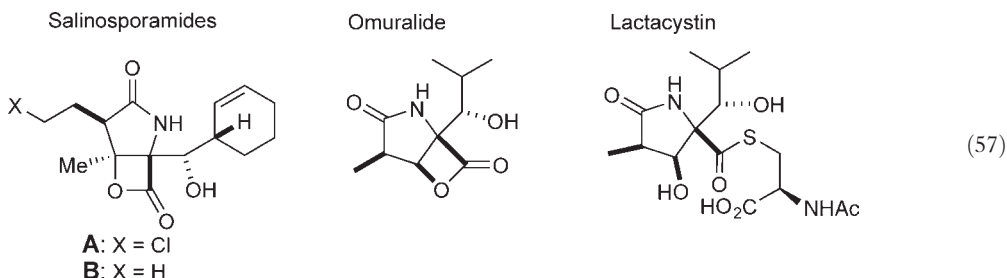


The structural complexity and biological activity of taxol and related taxanes have inspired a remarkable array of synthetic approaches; the interested reader is directed to some leading references <2005JOC732, 2005RJO315>. However, introduction of the D-ring oxetane is almost invariably achieved via intramolecular nucleophilic displacement, as illustrated in Section 2.06.9.5 (Equation 33).

2.06.12.4 Omuralide and Salinosporamide

Omuralide, also known as lactacystin β -lactone <1991JAN113>, and the salinosporamides <2003AGE355>, a family of marine natural products, feature β -lactones fused onto a γ -lactam (Equation 57) <2005JOC6196>. Lactacystin, a monocyclic lactam, is a prodrug which cyclizes to generate omuralide <2005JME3684, 2006OBC193>. X-Ray structures of salinosporamide A have been reported <2003AGE355, 2005JA8298>. Both omuralide and the salinosporamides inactivate the 20S proteasome through acylation of an active-site threonine <2003AGE355>. This hypothesis is substantiated by a recent crystal structure, which also suggests that the greater potency of

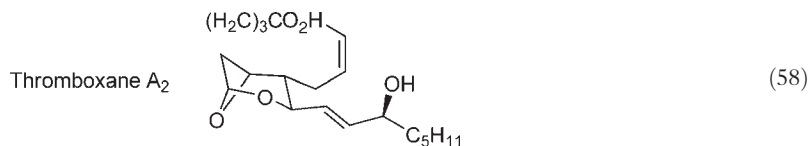
salinosporamide A may result from the presence of the chloroethyl side chain, which is suitably oriented to alkylate the tertiary alcohol resulting from opening of the β -lactone <2006JA5136>. Because of the integral role of the 20S proteasome in protein degradation and cell cycle progression, this family of molecules is of interest both as biochemical reagents and as potential therapeutics <2006JOC1220>. Structure–activity relationship (SAR) studies have revealed some tolerance for modifications and, in particular, omuralide/salinosporamide hybrids have proved to be moderately active <2001OL1395, 2005JA15386>.



While a full discussion of synthetic approaches toward this family is beyond the scope of this chapter, the fused β -lactone is invariably introduced via dehydration of a hydroxy acid (see Section 2.06.9.6 and Equation 38) <2006JOC1220>. Dehydration is most commonly achieved with BOP-Cl, although Ph_3PCl_2 has also been used <2005OL2699>. The fused β -lactone can be installed in the presence of the exocyclic alcohol, suggesting that the fused lactone may be more stable than the spiro isomer <2006JOC1220, 2006OBC2845>.

2.06.12.5 Thromboxanes

A review of synthetic approaches to thromboxanes (Equation 58) has been published <1998MI1>.



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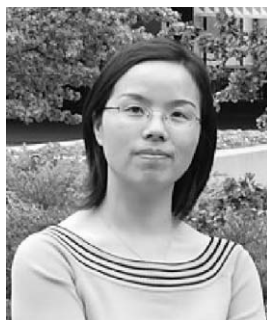
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Biographical Sketch



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2.07

Thietanes and Thietes: Monocyclic

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2.07.1 Introduction

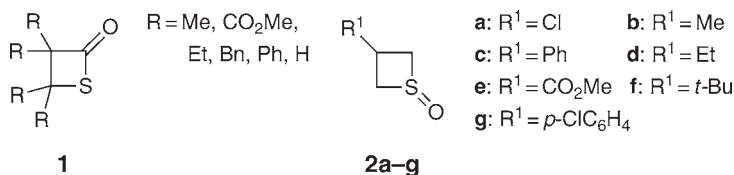
Monocyclic thietanes and thietes constitute an important group of so-called small-ring heterocycles and have been of interest for a long time. According to modern chemical vocabulary, these are fully saturated or unsaturated four-membered rings bearing one sulfur atom. The rapid development of this group of compounds began about 25 years ago. More profound studies on these compounds are due to important technological progress, which enabled chemists to detect and to investigate ephemeral or simply unstable species.

The previous editions (CHEC(1984) and CHEC-II(1996)) presented two excellent reviews authored and co-authored by Block <1984CHEC(7)403, 1996CHEC-II(1b)773> describing the advances in thietane chemistry from its beginning until 1995.

This chapter continues this work covering the literature of the last 10 years, that is, from 1996 until 2005. The preparation of this review was based on a literature search through SCOPUS and the Beilstein Database, which revealed 104 important papers published within this period. This chapter is organized in accordance with the general structure of CHEC-III, which includes a division into 12 sections including the same aspects as in CHEC-II(1996). For some aspects of thietane and thiete chemistry, such as their synthesis from six- and seven-membered rings, no new papers were published within the discussed period.

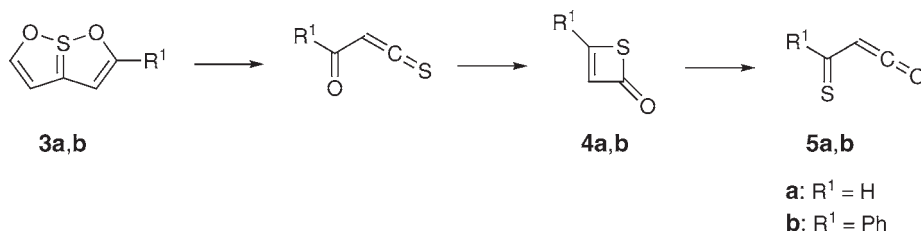
2.07.2 Theoretical Methods

The literature describing theoretical studies on monocyclic thietanes and thietes until 1995 has been fully covered in CHEC-II(1996). However, the described papers were confined to semi-empirical or molecular orbital(MO) calculations. During the last decade, computational abilities have increased dramatically, and several papers have appeared dealing with *ab initio* calculations of thietane structures. Extensive *ab initio* calculations have been carried out in order to establish the isotropic shielding constant σ and chemical shifts δ of 14 variously substituted thietanes **1** <2000MRC468>. These values have been computed using the HF/6-31++G** and geometries for this purpose have been optimized using the B3LYP/6-31++G**.



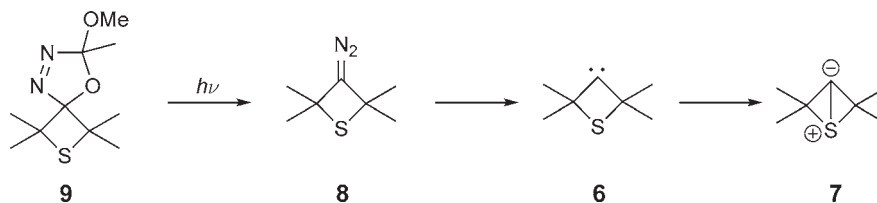
The *trans-cis*-isomerization of 3-chlorothietane-1-oxide **2a** has been studied using *ab initio* methods <2001JMT235>, where for the prediction of this system's thermodynamics, the Møller–Plesset perturbation theory has been used. The calculation predicted that in the gas phase the *cis*-isomer was predominantly present, reaching 85%, and that in solution of polar and nonpolar solvents the concentration of the *cis*-isomer decreased to 25%. Similar results have been found for 3-methylthietane-1-oxide **2b**. For both compounds, transition states have been found to have a quasi-planar structure. Activation energies for compounds **2a** and **2b** have been computed and they were 49 and 45 kcal mol⁻¹ in the gas phase as well as 37 and 33 kcal mol⁻¹ in solution, respectively. For the similar group of compounds **2a-g**, the *trans-cis*-isomerization has been studied in the frame of MO theory <2005JMT207>. These studies demonstrated that the size and the nature of the substituent has no influence on the isomerization and that in the gas phase the *cis*-isomer is predominant, but in CCl₄ solution the formation of the *trans*-isomer occurred to some extent. ¹H and ¹⁷O nuclear magnetic resonance (NMR) spectra of these compounds have been calculated and compared to experimental data. Studies on the flash vacuum

pyrolysis(FVP) of 1,6-dioxo-6a λ^4 -thiapentalenes **3a** and **3b** demonstrated the formation of thietenones **4a** and **4b** and subsequently thiocarbonylketenes **5a** and **5b** <2001J(P2)2047>. Using theoretical methods at the B3LYP/6-311+G**//B3LYP/6-31G*+ZPE level, the Pedersen group <2001J(P2)2047> performed the calculations of relative energies of, among others, both species **4** and **5**. For thietenone **4a**, the relative energy was calculated to be 5.3 kJ mol⁻¹ and it was demonstrated that its ring opening to form thioformylketene **5a** requires a small activation barrier of 3 kJ mol⁻¹. So, according to these authors, the formation of the thietane ring **4a** is improbable (Scheme 1) <2001J(P2)2047>.



Scheme 1

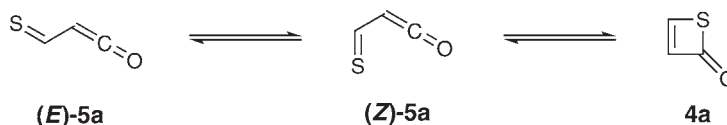
4-Phenylthietan-2-one **4b** is definitely more stable than the thiocarbonylketene **5b** by 1 kJ mol⁻¹, which was computed at the QCISD(T)/6-311+G(3df,2p) level <2001J(P2)2047>. Because ring opening of 4-phenylthietanone **4b** requires a small energy barrier (5 kJ mol⁻¹), the authors suggested that it was improbable that both forms **4b** and **5b** could coexist (Scheme 1). Two papers dealt with the thietane-HCl complexes <2001AGE935, 2002CPL123>. Alonso *et al.* applied the VSEPR model to understand results of rotational spectroscopy measurements <2001AGE935>, while the Polish authors <2002CPL123> reported their stability as well as axial and equatorial HCl arrangement in complexes calculated at the Møller-Plesset second-order perturbation theory (MP2) level using 6-311++G** and aug-cc-pVDZ basis sets. The shape of the potential functions was studied for ring-puckering motions as well as for HCl inversion. Thietane complexes turned out to have a higher barrier of ring puckering than the vibrational energy <2002CPL123>. The relative rates of attack of ammonia on a thietane molecule were calculated in the gas phase at the MP2(full)/6-31+G(d) level with respect to the model thiomethylethane <2003JOC2639>. The reactivity of the thietanes could be explained by relief of the strain energy in the transition state, which was calculated to be 19.6 kcal mol⁻¹. These results were compared to results of calculations of oxetanes, thiiranes, and oxiranes, which demonstrated that three-membered rings showed much greater reactivity than four-membered ones. Structures **6** and **7**, as well as their diazo precursor **8**, are, among others, transiently formed in the course of laser flash and steady-state photolysis of oxadiazoline derivative **9**. Theoretical approaches have been performed to examine the structures **6** and **7** by *ab initio* MO theory <2001PCA2106>. The geometries of structures **6-8** were optimized at the MP2/6-311+G** level and frequency calculations were made at the B3LYP/6-311+G** level. Relative energies of structures **6** and **7** were also reported (Scheme 2) <2001PCA2106>.



Scheme 2

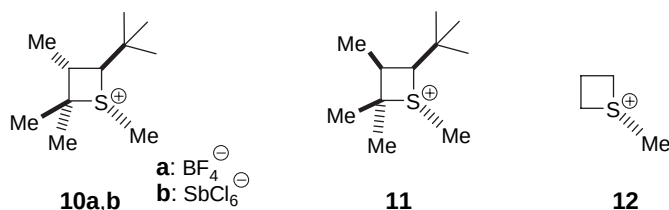
A theoretical study on the dimerization of thioformylketene **5a** has been performed at the B3LYP and G3MP2B3 level <2005OL5817>. Authors considered the [4+2] reaction pathway involving the formation of thietenone **4a** and calculated the participation of both (*E*)- and (*Z*)- conformations of thioformylketene. Obtained results have shown that thietenone **4a** is less stable than thioformylketene **5a** and that the barrier for ring closure is low

(about 6–7 kcal mol⁻¹). The authors demonstrated that there was an equilibrium between thioformylketene **5a** and thietenone **4a** (Scheme 3).



Scheme 3

The organometallic compound [CpRu(PPh₃)(SC₃H₆)₂](CF₃SO₃) as well as pure thietane have been the objects of theoretical calculations <2001ICA13>. A valence triple-zeta 6-311G(d,p)++ basis set has been used at the MP2 level. Calculations supported the hypothesis that for thietane ligands the energy related to ligand folding was rather small, so that crystal packing forces could compete with it. It was demonstrated <2001HCA860> that (*tert*-butyl)-substituted thiiranium ions undergo, in the absence of nucleophiles, a concerted and stereoselective anionotropic methyl rearrangement to the corresponding thietanium ions **10a** and **10b**. The authors stated that a nonconcerted mechanism would lead to the simultaneous formation of **10** and **11**. The geometry of cations **10** and **11** as well as that of the hypothetical cation **12** has been optimized by *ab initio* calculations at the RHF/6-31G* level of theory and compared to experimentally obtained data <2001HCA860>.



2.07.3 Experimental Structural Methods

Almost all papers describing the synthesis of thietes and thietanes give a variety of spectroscopic data for new obtained compounds including ¹H and ¹³C NMR, infrared (IR), and mass spectrometry (MS) spectra. Papers cited in the sections concerning the synthesis should therefore be consulted for routine spectroscopic information on thietane derivatives.

2.07.3.1 X-Ray Diffraction and Microwave Spectroscopy

Several bond lengths and angles for various monocyclic thietanes, thietes, and their derivatives as determined by X-ray crystallography, microwave spectroscopy, and electron diffraction were presented in CHEC(1984) and CHEC-II(1996).

The following structures appeared since 1995: (2',3',4',4')-1-(3-hydroxy-4-hydroxymethylthiacyclobutan-2-yl)thymine <1996TL7569>; *o*-acetoxy-*N*-(3,3,4,4-tetramethylthietan-2-ylidene)aniline <2000JP13039>; *o*-hydroxy-*N*-(3,3,4-trimethylthietan-2-ylidene)aniline <2000J(P1)3039>; *t*-4-(*tert*-butyl)-*r*-1,2,2,*c*-3-tetramethylthietanium tetrafluoroborate and hexachloroantimonate <2001HCA860>.

The X-ray structures of a number of thietane–metal complexes have also been published. These include W(CO)₅(SCH₂CH₂CH₂) <1996CB313> where the W(CO)₅ group is coordinated to the sulfur atom in the heterocycle. The tungsten–sulfur distance is 2.540(3) Å. The W–C bond length for the carbonyl ligand that is *trans* to the sulfur ligand is significantly shorter than that for the *cis*-ligands, as expected due to the weaker *trans*-effect of sulfur compared to CO. The thietane ligand is only slightly puckered; the C(6)–S–C(8)/C(6)–C(7)–C(8) dihedral angle is 11.2° <1996CB313>. The structure of (EtMe₄C₅)ReCl₄(SCH₂CH₂CH₂) was determined by an X-ray diffraction study <2000OM4925>. The molecular structure confirms that the intact thietane is weakly coordinated to Cp'ReCl₄

through a long Re–S bond 2.5892(14) Å ($C_p' = EtMe_4C_5$). Other selected bond distances (angstroms, Å) and angles (degrees, deg) for this compound are: Re–Cl(1) 2.3876(13); Re–Cl(2) 2.4061(14); Re–Cl(3) 2.4045(13); Re–Cl(4) 2.4167(13); S–Re–Cl(1) 72.80(5); S–Re–Cl(2) 77.42(5); S–Re–Cl(3) 73.83(5); S–Re–Cl(4) 73.01(5); Re–S(1)–C(12) 116.2(2); Re–S(1)–C(14) 114.4(2). The Re–Cl bond distances in this complex are all similar, with an average value of 2.404 Å. However, the chloride ligand that lies above the thietane (Cl(2)) is displaced upward relative to the other chlorides. The S–Re–Cl(2) angles are 77.42(5)°, while the other S–Re–Cl angles average 73.21° <2000OM4925>.

The molecular structure of $Re_2(CO)_9(SCH_2CMe_2CH_2)$ was determined by single crystal X-ray diffraction analysis <1997OM2612>. In this complex, the equatorially positioned ligands on the two metal atoms are arranged in a staggered rotational conformation similar to that found in $Re_2(CO)_{10}$. The thioether ligand is coordinated to one of the rhenium atoms in an equatorial site. Selected bond distances and angles are as follows: Re–Re = 3.042(1) Å, Re–S = 2.485(4) Å, S–C(1) = 1.82(2) Å, S–C(3) = 1.81(2) Å, C(1)–S–C(3) = 73.9(8)°. The 3,3-dimethylthietane ring appears to be planar within the experimental error. This contrasts with other structural studies of thietane ligands where a slight puckering has been observed <1997OM2612>.

The complex $[CpRu(PPh_3)(SCH_2CH_2CH_2)_2]CF_3SO_3$ has been obtained <2001ICA13>. The single crystal X-ray structure shows a disparity in the puckering of the two thietanes. One thietane ligand is near planar, with torsion angles of $\pm 1.5(5)^\circ$ for CSCC and $\pm 1.8(4)^\circ$ for CCCS; the second thietane ligand has torsion angles of $\pm 21.0(4)^\circ$ for CSCC and $\pm 25.0(3)^\circ$ for CCCS <2001ICA13>.

The reaction of $Mn_2(CO)_7(\mu-S_2)$ with thietane resulted in the formation of new complexes $Mn_2(CO)_6(\mu-SCH_2CH_2CH_2)(\mu-S_2)$ and $Mn_4(CO)_{14}(SCH_2CH_2CH_2)(\mu_3-S_2)(\mu_4-S_2)$ <2002IC5525>. The first compound consists of two manganese tricarbonyl groups held together by a bridging disulfide ligand and a bridging thietane ligand. The bridging sulfur atom of the thioether ligand donates two electrons to each metal atom. There is no metal–metal bond. Selected distances: nonbonding Mn–Mn 3.4338(7) Å; S–S in the disulfide ligand 2.0459(11) Å; Mn(1)–S, and Mn(2)–S to the bridging thietane 2.3153(9) Å and 2.3038(9) Å, respectively. The second obtained complex contains four manganese atoms with two bridging disulfide ligands; one is a triple bridge, and the other is a quadruple bridge. There are no metal–metal bonds in this compound. The thietane ligand is terminally coordinated to the manganese atom Mn(4) that lies outside the cluster. The Mn–S distance to the thietane ligand, 2.3387(15) Å, is similar to that found in other manganese complexes that have terminally coordinated thietane ligands <2002IC5525>.

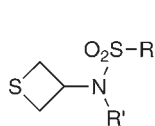
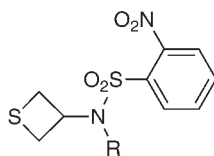
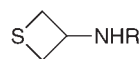
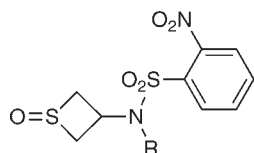
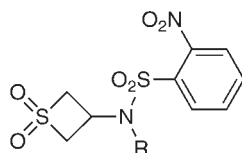
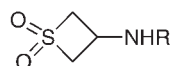
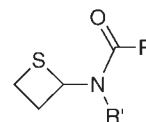
X-ray crystallography was used to determine the structure of 1-(4-diethylamino-2-*p*-bromophenylimino-2*H*-3-thietyl)-1-ethanone <2001SL361>. The striking features of the crystallographic data are that the N(2)–C(9) bond length of 1.311(6) Å is closer to $Csp^2=N$ (1.28 Å) than to the Csp^2-N bond (1.38 Å), and the C(8)–C(9) bond length of 1.411(7) Å is much larger than normal for C=C (1.32 Å). In addition, the dihedral angle C(14)–N(2)–C(9)–C(8) of $-3.0(9)^\circ$ and C(12)–N(2)–C(9)–C(8) of $176.3(6)^\circ$ clearly reveals that atoms C(14), C(12), N(2), C(9), and C(8) are almost coplanar. These data imply that the enamino N(2)–C(9)–C(8) bonds must be delocalized in a way that the major contributing form is that of a betaine <2001SL361>.

The rotational spectra of the thietane/HCl complex have been registered by Fourier transform microwave spectroscopy <2001AGE935, 2002CEJ4265>. It was found that the equivalence of the nonbonding pairs at sulfur is broken by complexation as a consequence of the appearance of axial and equatorial conformers in the thietane–HCl complex. Several aspects on the axial and equatorial structures have been discussed <2001AGE935, 2002CEJ4265>.

2.07.3.2 NMR Spectroscopy

2.07.3.2.1 Proton NMR spectroscopy

Detailed proton NMR spectroscopic data on a variety of fused and spiro thietane and thiete derivatives was tabulated in the corresponding sections of CHEC(1984) and CHEC-II(1996). Therefore, only limited, newer information is presented here. A series of *N*-(4-methoxyphenyl), *N*-(1-naphthyl), *N*-benzyl, and *N*-(4-nitrophenyl)-*N*-(thietan-3-yl)benzene- or methanesulfonamides **13** as well as the analogous *N*-aryl-*N*-(thietan-3-yl)-2-nitrobenzenesulfonamides **14**, 3-arylaminothietanes **15**, *N*-(4-aryl)-*N*-(1-oxothietan-3-yl)-2-nitrobenzenesulfonamides **16**, *N*-(1,1-dioxothietan-3-yl)-*N*-(aryl)-2-nitrobenzenesulfonamides **17**, 3-(4-arylamino)thietane 1,1-dioxides **18**, and *N*-(4-aryl)-*N*-(thietan-2-yl)benzamides **19** were identified on the basis of their ^1H NMR spectra <2005RJO1023>.

**13a:** R = Ph; R' = 4-MeOC₆H₄**13b:** R = Me; R' = 4-MeOC₆H₄**13c:** R = Me; R' = 1-naphthyl**13d:** R = Ph; R' = benzyl**13e:** R = Ph; R' = H**13f:** R = Ph; R' = 4-NO₂C₆H₄**14a:** R = Ph**14b:** R = 4-MeOC₆H₄**14c:** R = 2-*i*-PrC₆H₄**14d:** R = 4-ClC₆H₄**14e:** R = 1-naphthyl**14f:** R = 3-NO₂C₆H₄**14g:** R = 4-NO₂C₆H₄**15a:** R = Ph**15b:** R = 4-MeOC₆H₄**15c:** R = 2-*i*-PrC₆H₄**15d:** R = 4-ClC₆H₄**15e:** R = 1-naphthyl**15f:** R = 3-NO₂C₆H₄**16b:** R = 4-MeOC₆H₄**16d:** R = 4-ClC₆H₄**17b:** R = 4-MeOC₆H₄**17d:** R = 4-ClC₆H₄**18b:** R = 4-MeOC₆H₄**18d:** R = 4-ClC₆H₄**19a:** R = R' = Ph**19b:** R = Ph; R' = 4-MeOC₆H₄**19d:** R = Me; R' = 4-ClC₆H₄

In the ¹H NMR spectra of compounds **13–15**, protons in the aliphatic three-carbon fragment give rise to a complex AA'BB'X spin system which is characterized by similar ³J_{cis} and ³J_{trans} values. As a result, it is observed as a pseudo-simple spectrum consisting of triplets in the δ region 3.0–3.5 ppm with a pronounced 'roof' effect and a quintet at δ 4.5–6.0 ppm. In some cases, these signals are additionally split, in particular due to nonzero long-range *W* coupling constants (⁴J). The H-3 proton in 3-(arylaminothietanes) **15c** and **15f** appears as a sextet as a result of coupling with the NH proton. Introduction of a bulky substituent into the *ortho*-position of the aromatic ring (**14c**) or replacement of the benzene ring by a naphthalene system (**13c** and **14e**) hampers the free rotation about the C_{Ar}–N bond, thus giving rise to an additional chirality axis. Therefore, the aliphatic region of the ¹H NMR spectra of compounds **13c**, **14c**, and **14e** becomes more complicated (diastereotopic methylene protons appear as asymmetric multiplets). The NMR spectra of thietane 1-oxides **16** and thietane 1,1-dioxides **17** and **18** display analogous patterns differing in the position of the upfield signals. Structural variations affect most strongly the position of the H-3 signal in the ¹H NMR spectra. The chemical shifts of H-3 in sulfoxides **16** are 4.8 and 6.2 ppm (the difference in chemical shifts between two diastereoisomers exceeds 1 ppm), and are 5.2–5.4 ppm in the case of dioxides **17**. In going to 3-(arylamino)thietane 1,1-dioxides **18**, the H-3 signal shifts upfield to δ 4.0–4.2 ppm, and the shape of the signals from the thietane fragment also changes.

¹H NMR spectra of different β-propiothirolactones (mono- and disubstituted at the α- or β-positions) have been reported <2000MRC468>. These data clearly exhibit a downfield resonance trend for the α-protons. All of the ¹H chemical shifts at the α-position of the compounds studied are larger than 3.5 ppm, and the α-protons of unsubstituted β-propiothirolactone are deshielded by ca. 1 ppm compared to those of cyclobutanone. This effect was rationalized by two main factors. One is the less efficient overlap between the C=O π and s 3p orbitals, resulting in a stronger deshielding effect by the carbonyl group. The other effect involves a through-space interaction between the occupied orbital of the α-carbon and the vacant orbital of sulfur <2000MRC468>.

The ¹H NMR spectra of the two thietane-containing complexes M(CO)₅L (where M = W and Cr, respectively) showed in the case of M = W only two resonances: 3.80 (*t*, J_{H–H} = 7.7 Hz, 4H) and 3.03 (*q*, J_{H–H} = 7.7 Hz, 2H). This can be explained by the structure observed in the solid state and by assuming rapid inversions of configurations at the pyramidal sulfur atom. The second compound with M = Cr is spectroscopically similar to the first one and is thus believed to be structurally similar as well <1996CB313>.

2.07.3.2.2 Heteronuclear NMR spectroscopy

The ¹³C NMR chemical shifts have been determined for both the α- and β-carbons in a series of β-propiothirolactones <2000MRC468>. Mono- and disubstituted α-carbons show chemical shifts larger than 65 and 72 ppm, respectively.

Relatively smaller values of chemical shifts have been observed for β -carbons. For example, β,β -dimethyl- β -propiothirolactone has chemical shifts of 67.3 and 40.7 ppm for its α - and β -carbon, respectively. In the case of 4-(7-*tert*-butyldimethylsiloxyhept-3-enyl)thietan-2-one, the analogous signals have been observed at 62.5 or 60.6 and 37.6 ppm, whereas that corresponding to the C=O is at 190.9 ppm <2003T833>. Also, 4-(7-*tert*-butyldimethylsiloxyheptyl)thietan-2-one exhibits analogous signals at 63.89 or 61.61, and 38.53 ppm, and for the C=O at 189.58 ppm <2003PS1163>. The ^{13}C NMR spectrum of a ^{13}C O-enriched sample of $\text{W}(\text{CO})_5$ thietane complex in the CO region shows resonances at 201.0 ppm (s, $^2J_{^{183}\text{W}-^{13}\text{C}} = 157.2$ Hz, 1CO) and 197.5 ppm (s, $^2J_{^{183}\text{W}-^{13}\text{C}} = 128.7$ Hz, 4CO) <1996CB313>.

2.07.3.3 Mass Spectrometry

Gas chromatography–mass spectrometry (GC–MS) which was used to investigate individual variations in volatile components of male and female ferret urine confirmed that thietanes were one of the major compounds used by them for marking, for sex, and individual recognitions <2005CHS727>. The volatile constituents in the anal gland secretions of two sympatric *Mustela* species, the Siberian weasel (*M. sibirica*) and the steppe polecat (*M. eversmani*), were studied by GC–MS analysis. The following compounds were identified: 2,2-dimethylthietane, (*Z*)- or (*E*)-2,4-dimethylthietane, (*E*)-2,3-dimethylthietane, 2-ethylthietane, (*E*)-2-ethyl-3-methylthietane, (*Z*)-2-ethyl-3-methylthietane, 2-propylthietane <2002JE1287>. 4-Aryl-thiet-2-ones have been identified, using tandem mass spectrometry, as products of flash vacuum thermolysis (FVT) of 6-aryl-1,3-dioxine-4-thiones <2000JOC2706>. Its immediate extrusion of CO gave rise to an ion with an m/z 134. Ethyl (9*Z*, 12*Z*)-9,12-octadecadienoate was reacted with dimethyl disulfide and iodine in diethyl ether. 2-(8-Ethoxycarbonyl-1-methylthiooctan-1-yl)-4-(1-methylthiohexan-1-yl)thietane was formed as one of the four major products. The peak at 57.4 min resolved by capillary GC–MS was characterized as the thietane mentioned above <1996CPLP81>. Low- and high-resolution mass spectra of 4-(7-*tert*-butyldimethylsiloxyheptyl)thietan-2-one were used for its identification <2003PS1163>.

2.07.3.4 UV, Photoelectron, Pressure Tuning Spectroscopy, and Laser Flash Photolysis

Tunable synchrotron radiation with photofragment translational spectroscopy (PTS) for thietane at 193 nm gives direct evidence that the sulfur atom is formed solely in the excited state $\text{S}(^1\text{D})$ <2001MI127> and has also been used to probe the dissociation dynamics of thietane (C_3H_6 S) at 193 nm. It provides selective determination of the translational energy distribution of both excited (^1D) and ground-state (^3P) sulfur atoms, with momentum-matching to the C_3H_6 co-fragment. The obtained results again suggest that the sulfur atom is produced almost exclusively in its excited (^1D) state, with ground-state (^3P) production of less than 5% <2002CPL204>. The ability to produce a pure excited state of the S atom makes the 193 nm photodissociation of thietane a potentially important method for producing such atoms for spectroscopic or dynamic studies. The addition reaction of 1,3-dihydro-2*H*-imidazole-2-thione (IT) in its triplet state with different alkenes leading to thietanes has been studied by measuring absorption profiles for the decay of IT^+ (at 540 nm) <1999BCJ339>. The formation of sulfur ylides as intermediates in the reactions of arylchlorocarbenes or phenylcarbene with thietane under photolytic and thermal conditions has been demonstrated by laser flash photolytic (LFP) techniques. LFP at 355 nm of a solution of chlorophenyldiazirine in isooctane produces a transient absorption at 300 nm, due to the formation of the chlorophenyl carbene, whose decay rate constant is $3.8 \times 10^5 \text{ s}^{-1}$. In the presence of thietane, a new transient species, attributed to the *S*-ylide, grows in at 340 and 400 nm at a rate equal to that of the decay of the carbene measured at 300 nm <2001TL207>. Similarly, LFP (308 nm, 17 ns) of phenyldiazomethane in Freon-113 produces singlet phenylcarbene in rapid equilibrium with the ground triplet state, which has no significant absorption above 300 nm. LFP in the presence of thietane produces a new transient signal at 340 nm. The transient is assigned to the *S*-ylide, which has a lifetime longer than 10 μs <2003TL6519>.

2.07.3.5 IR Spectroscopy

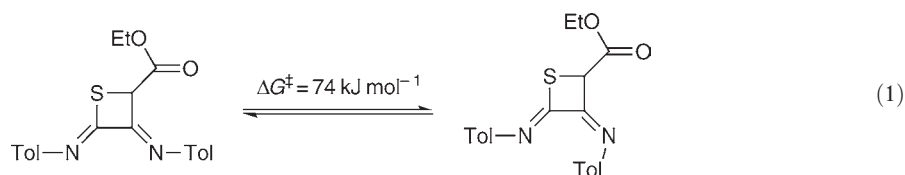
The IR spectra of several derivatives of thietane-3-yl-thiourea exhibit characteristic absorptions at 670–680, 720–730, and 1420–1445 cm^{-1} , which are typical for stretching vibrations of the four-membered thietane ring, as well as at 1500–1510 cm^{-1} characteristic of $\text{NHC}(\text{S})$ fragments, and at 3380 and 3430 cm^{-1} characteristic of the NH group. Also, an absorption band at ca. 3040 cm^{-1} was observed corresponding to the $\text{NH} \cdots \text{S}$ intramolecular hydrogen bond <2000ZOR589, 2001RJAC114>. IR spectrum of 4-(4-methoxyphenyl)thiet-2-one exhibits absorption bands at 1825,

1821, 1499, 1216, and 1174 cm^{-1} <2000JOC2706>. 3-Oxothietane-2-carboxylic acid ethyl ester exhibits carbonyl stretching bands at 1792 and 1694 cm^{-1} <2001CJC1259>. 4-(7-*tert*-Butyldimethylsiloxyhept-3-enyl)thietan-2-one exhibits absorption bands in the IR spectrum at 3053, 2980, 2925, 2853, 1747, 1655, 1419, 1265, 1096, 979, 886, 840, 753, and 702 cm^{-1} <2003T833>. The hydrogen bond acceptor (HBA) strength of thietane has been measured by IR spectrometry. For complexation with 4-fluorophenol in CCl_4 at 25°C , several thermodynamic parameters were determined and compared with other tetrahedral sulfur bases <2005CJC138>.

2.07.4 Thermodynamic Aspects

Axial and equatorial hydrogen-bonded conformers of HF/thietane complexes have been generated and characterized in the supersonic jet of a molecular beam Fourier transform microwave experiment. It has been shown that the ring-puckering large amplitude motion of thietane (TMS) is responsible for the observed axial and equatorial conformers. The axial conformer has been found to be the most stable one. The conformational preference has been explained in terms of a delicate balance between primary and secondary hydrogen bonds. The interconversion between both conformers takes place through the ring-puckering motion of the heterocycle. The μ -type R-branch spectra corresponding to the $^{12}\text{C}_3\text{H}_6\text{S}\cdots\text{HF}$, $^{13}\text{C}_\alpha^{12}\text{C}_2\text{H}_6^{32}\text{S}\cdots\text{HF}$, and $^{13}\text{C}_\beta^{12}\text{C}_2\text{H}_6^{32}\text{S}\cdots\text{HF}$ isotopomers have been detected in their natural abundances. Using He as carrier gas, the transitions of the equatorial conformer are approximately 7 times less intense than those corresponding to the axial conformer (ax:eq $\approx 7:1$). The relaxation from the equatorial to the axial form occurs in the supersonic expansion during the formation of the $\text{TMS}\cdots\text{HF}$, being the axial conformer and the most stable one. Despite the presence of secondary hydrogen bond interactions in both forms, the smaller value for the $r(\text{F}\cdots\text{H}_\beta)$ distance in the axial conformer would explain the relative stability ax:eq observed in $\text{TMS}\cdots\text{HF}$ complexes. On the basis of the observed relaxation, the barrier of the ring-puckering motion of TMS has been assumed to be maintained below $\approx 400\text{ cm}^{-1}$ after complexation, and the interconversion between conformers took place through the ring inversion of TMS <2002CEJ4265>.

2,3-Diiminothietane undergoes isomerization according to Equation (1). The free energy of activation of this process ($\Delta G^\ddagger = 74.0\text{ kJ mol}^{-1}$) lies in the range of typical activation barriers for (*E*)/(*Z*)-isomerization of imines <1999CC2439>.



Measurements of deviation of the standard adsorption entropy at graphitized carbon black have been carried out for thietane and other heterocyclic molecules. The theoretical standard entropy for the thietane molecule shows a greater deviation from the experimental value in comparison to others, which seems to indicate that for thietane a simple model of an adsorbed molecule with 2° of freedom is not accurate <1997ZP1333>.

2.07.5 Reactivity of Conjugated Rings

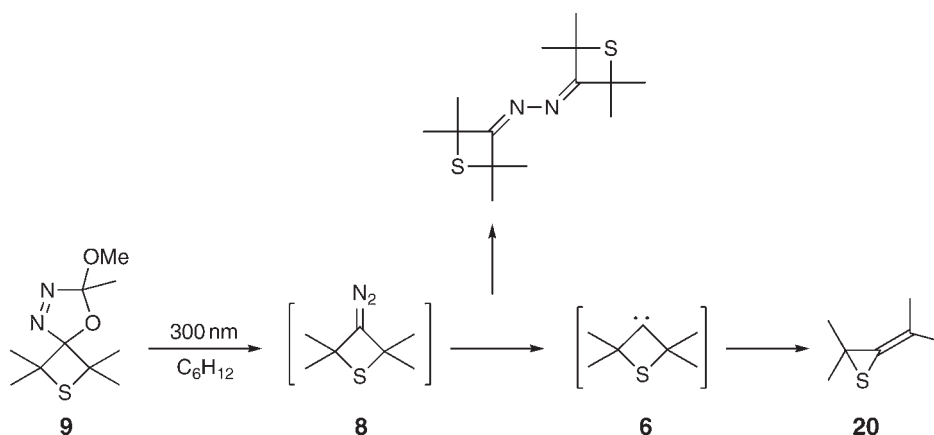
Since the publication of CHEC-II(1996), there have been no new reports on the reactivity of fully conjugated monocyclic thietanes and thietes.

2.07.6 Reactivity of Nonconjugated Rings

2.07.6.1 Unimolecular Thermal and Photochemical Reactions

2.07.6.1.1 Rearrangements

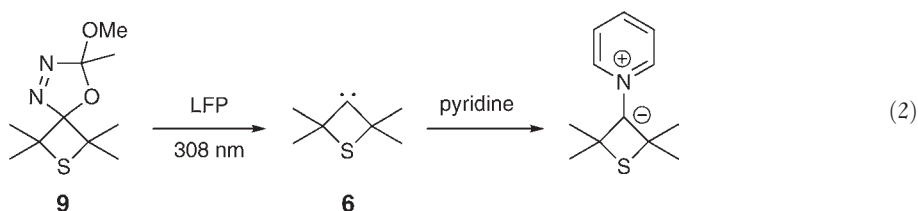
Steady-state photolysis (Ray-o-Net) of 7-methoxy-1,1,3,3,7-pentamethyl-8-oxa-2-thia-5,6-diazaspiro[3,4]oct-5-ene **9** in cyclohexane at 300 nm followed by GC-MS analysis of the resulting mixture showed the formation of 3-isopropylidene-2,2-dimethylthiirane **20** as a product of the rearrangement of 2,2,4,4-tetramethyl-3-thietan-1-ylidene **6** (Scheme 4). The second product observed from the photolysis of **9** had strong peaks in the mass spectrum at m/z



Scheme 4

284 and 142, which were attributed to the corresponding azine. The azine is most likely derived from the diazo intermediate **8**, which is initially formed by fragmentation of **9** <2001PCA2106>.

LFP (308 nm, XeCl) of compound **9** in 1,1,2-trifluorotrichloroethane (Freon 113) did not produce a detectable transient absorption. In the presence of pyridine, however, a transient species with $\lambda_{\max} = 350$ nm, attributed to corresponding ylide, was observed (Equation 2).



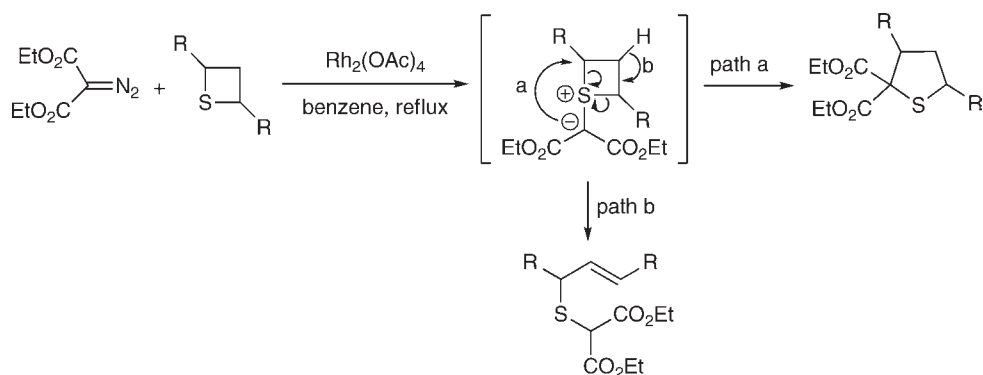
Irradiation (254 nm) of 3-alkyl-2,2-dimethyl-4-(*tert*-butyl)-2*H*-thietes leads to a photostationary equilibrium with corresponding enethiones in a 3:1 ratio <1997HCA510>.

2.07.6.2 Electrophilic Attack

2.07.6.2.1 At sulfur

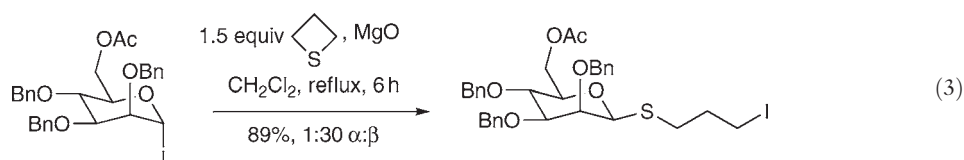
Oxidation of benzoic acid 2-benzoyloxymethylthietan-3-yl ester with MCPBA (*m*-chloroperbenzoic acid) in CH_2Cl_2 at 0 °C leads to a diastereomeric mixture of the corresponding sulfoxide <1996TL7569>. The analogous reaction has been reported for benzoic acid 3-benzoyloxymethylthietan-2-ylmethyl ester. This sulfoxide was used in the synthesis of the enantiomerically pure 3'-thio analog of oxetanocin A <1999TL7385>. Benzoic acid 3-benzoyloxymethylthietan-3-ylmethyl ester has been oxidized by $NaIO_4$ in MeOH to give the sulfoxide in good overall yield <1996TL7569>. *N*-(4-Methoxyphenyl)- and *N*-(4-chlorophenyl)-*N*-(thietan-3-yl)-2-nitrobenzenesulfonamides **14b** and **14d** were readily oxidized with hydrogen peroxide in glacial acetic acid under $WO_3 \cdot H_2O$ catalysis to the corresponding *S*-mono- or dioxide **16b** and **16d** or **17b** and **17d** depending on the reaction conditions <2005RJO1023>. An efficient and easy method for oxidation of trimethylene sulfide to thietane-1-oxide with nitric acid in the presence of supported P_2O_5 on silica gel under solvent-free conditions in high yield has been described <2005TL5503>. Freestanding ultrathin films of a porphyrin homopolymer synthesized by interfacial polymerization of a mercaptoporphyrin have been used to promote photooxidation of thietane to thietane-1-oxide by sensitizing singlet oxygen production <1997JA7726>. A facile Rh(II)-catalyzed reaction of diethyl diazomalonate with 2-mono or 2,4-disubstituted thietanes leading to highly substituted tetrahydrothiophenes has been described <2004TL5759>. Mechanistically, the reaction has been viewed as occurring by the initial formation of a sulfonium ylide followed by the Stevens rearrangement (path a). It was assumed that the open-chain compound arises via a fragmentation predicted by the β -elimination process (path b) (Scheme 5).

Photocatalytic oxidation of thietane, responsible for malodorous emissions from sewage and being present in industrial wastewater, using an annular plug flow reactor with TiO_2 in a supported form has been carried out. The

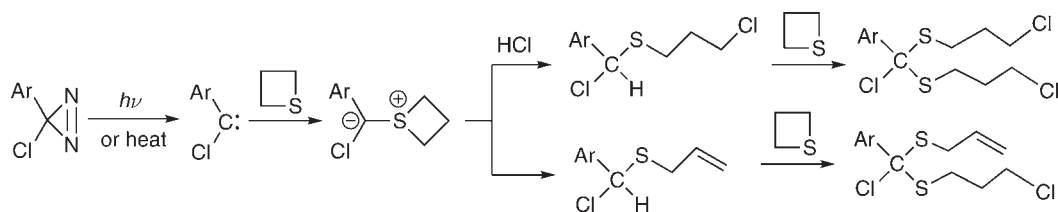


Scheme 5

formation of the products and by-products was monitored using a mass spectrometry online system [<1999EST2788>](#). Oxidation of thietane with 1-butyl-4-aza-1-azoniabicyclo[2.2.2]octane dichromate (BAAOD) to thietane-1-oxide in refluxing acetonitrile was carried out in 92% yield [<2003PS2441>](#). Tetrafluorodiboronperoxide, formed *in situ* from KO_2 and BF_3 in dry acetonitrile, proved to be a highly chemoselective and efficient reagent for the fast and effective oxidation of thietane to thietane-1-oxide. The reaction proceeds in an ice-water bath in excellent yield without any interference in the presence of ketone, alkene, ether, and hydroxyl functionalities. This method also offers a short reaction time, no overoxidation to sulfones, and no complex catalysts or toxic metallic compounds were used [<2005TL4205>](#). The reaction of trimethylene sulfide with mannosyl iodide provided predominantly the β -anomer after 6 h heating under reflux (Equation 3) [<2004OL973>](#).

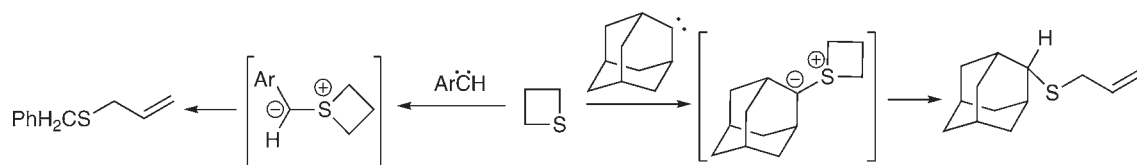


Reaction of arylchlorodiazirines with thietane gives a mixture of aryl(3-chloropropyl)thioacetal and aryl(2-propenyl)(3-chloropropyl)thioacetal in a good yield. The reaction goes through a sulfur ylide intermediate (Scheme 6) [<2001TL207>](#).



Scheme 6

Reaction of adamantylidene and phenylcarbene with thietane involves the formation of a sulfur ylide intermediate, followed by ring opening (Scheme 7) [<2003TL6519>](#).



Scheme 7

2.07.6.3 Nucleophilic Attack at Heterocyclic Carbon Atoms

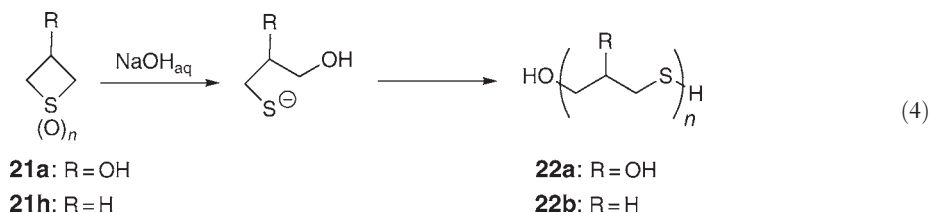
2.07.6.3.1 By oxygen

Treatment of 3-hydroxythietanes **21b–g** with aqueous sodium hydroxide led to retro-aldol ring cleavage to produce the carbonyl derivatives **23b–g** (Table 1) <1997J(P2)425>. It was proven that the rate of the reaction was determined by the nature of the substituent at the 3-position and by the oxidation state of sulfur. 3-Phenylthietane-3-ol **21b** underwent retro-aldol reaction to give sulfide ketone **23b**. Thietane-1-oxide-3-ol **21c–e** or thietane-1,1-dioxide-3-ol **21f** and **21g** derivatives underwent retro-aldol reaction to produce carbonyl sulfoxides **23c–e** and carbonyl sulfones **23f** and **23g** (Table 1) <1997J(P2)425>.

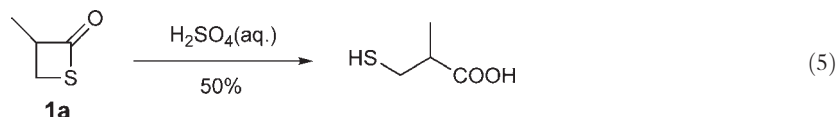
Table 1 Retro-aldol cleavage of thietan-3-ols **21b–g**

Entry	R^1	n	Yield (%)
b	Ph	0	ng
c	H	1 (<i>cis</i>)	ng
d	H	1 (<i>trans</i>)	ng
e	Ph	1	96
f	H	2	ng
g	Ph	2	100

Thietane-3-ol **21a** yielded the polymeric product poly(3-hydroxythietane) **22a**. The same results were obtained when thietane **21h** was treated with aqueous sodium hydroxide and the polymeric substance **22b** was obtained (Equation 4).

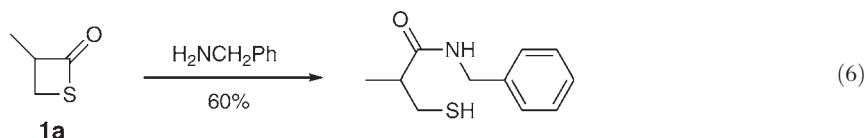


The ring-opening reaction of thietanone **1a** in sulfuric acid solution led to the formation of 3-mercapto-2-methylpropionic acid in 50% yield (Equation 5) <2000MRC468>.

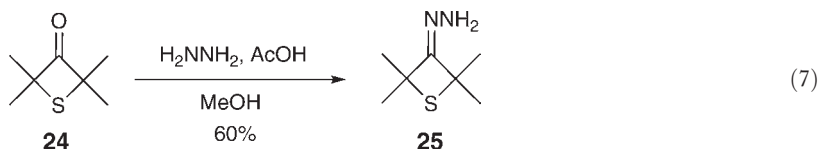


2.07.6.3.2 By nitrogen

The ring-opening reaction of 2-thietanone **1a** by the action of benzylamine led to the formation of *N*-benzyl-3-mercapto-2-methylpropionamide in 60% yield (Equation 6) <2000MRC468>.

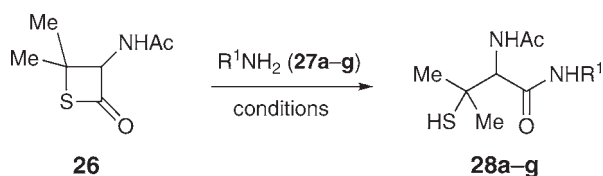


The reaction of 2,2,4,4-tetramethyl-3-thietanone **24** with hydrazine in the presence of acetic acid in methanol led to the formation of the corresponding hydrazone **25** in 91% yield (Equation 7) <2001PCA2106>.



The reaction of *N*-(2,2-dimethyl-4-oxo-thietan-3-yl)-acetamide **26** with complex heterocyclic amines **27a–d**, cyanoguanidine derivatives **27e–f**, or a sugar derivative, namely 1-amino-1-deoxy-D-fructopyranose **27g**, in various conditions resulted in cysteine amide derivatives **28a–g** in satisfactory yields (Table 2) <2000BML1347, 2001T7173, 2001T825, 2002BMC2303>.

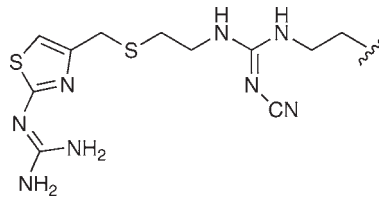
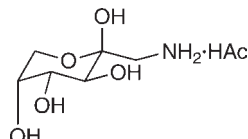
Table 2 The reaction of *N*-(2,2-dimethyl-4-oxo-thietan-3-yl)-acetamide **26** with amines **27a–g**



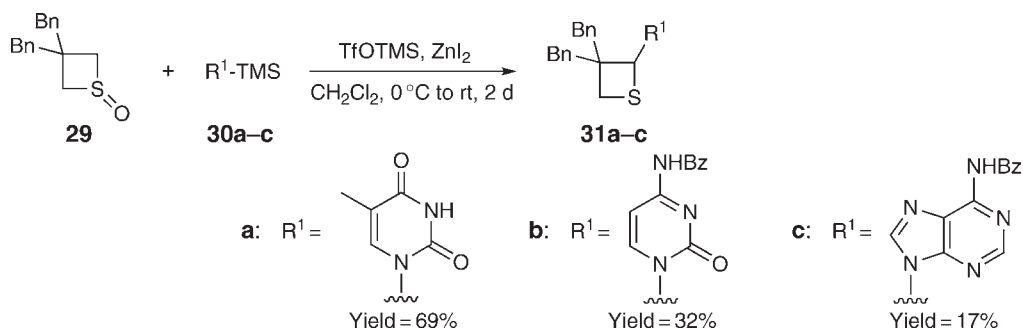
Entry	R ¹	Conditions	Yield (%)	References
a		CHCl ₃ , 5 h, 25 °C	61	2000BML1347, 2001T7173
b		DMF, 18 h, 25 °C	30	2000BML1347, 2001T7173
c		CHCl ₃ /1 M NaOH, 2 h, 25 °C	61	2000BML1347, 2001T7173
d		CH ₂ Cl ₂ , 5 h, 25 °C	85	2000BML1347, 2001T7173
e		MeOH, 11 h, rt	81	2000HCA287

(Continued)

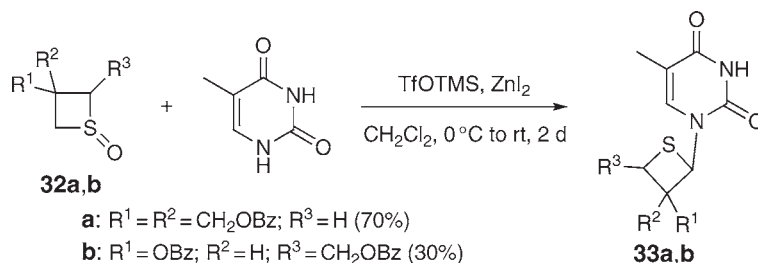
Table 2 (Continued)

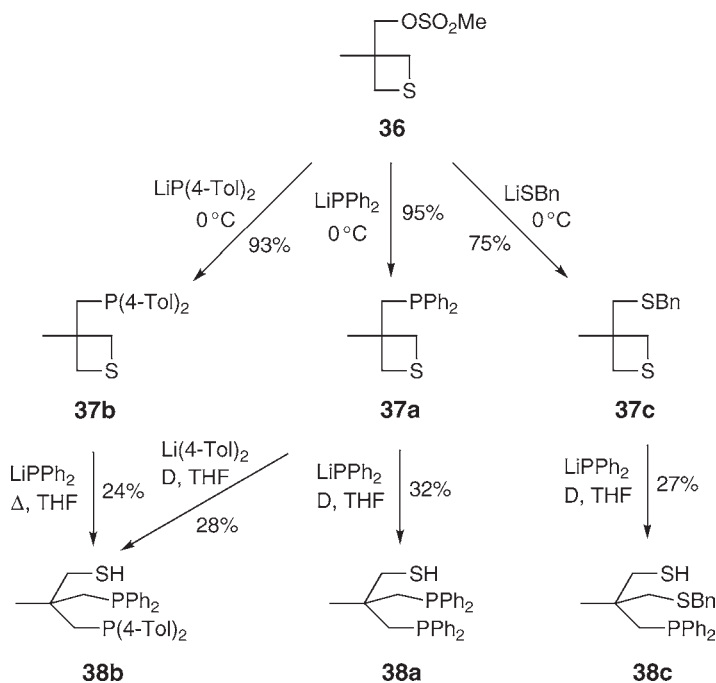
Entry	R ¹	Conditions	Yield (%)	References
f		MeOH, 2 h, rt	90	2000HCA287
g		Pyridine, Et ₃ N, 0 °C, 20 h	81	2001T825, 2002BMC2303

Several authors reported the use of thietane-1-oxides for the synthesis of modified nucleosides bearing a thietane moiety instead of the ribose one <1997SL1247, 1996TL7569>. This method is called the Pummerer reaction and since the isolation of oxetanocin A from *Bacillus megaterium*, the structural similarity of its thietane derivatives is of much interest. The reaction of 3,3-dibenzylthietane-1-oxide **29** with silylated nucleic bases (thymine **30a**, cytosine **30b**, and adenine **30c**) in dichloromethane in the presence of ZnI₂ yielded 3,3-dibenzylthietane-bearing nucleosides **31a–c** in moderate to good yields (Scheme 8) <1997SL1247>.

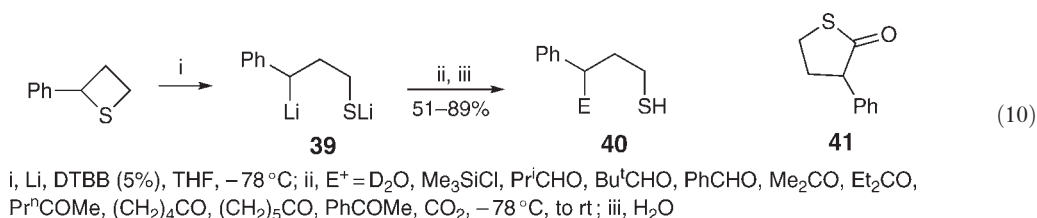
**Scheme 8**

The Pummerer reaction of 3,3-dibenzoyloxyethyl-thietane 1-oxide **32a** with thymine in the presence of trimethylsilyl triflate (TMSOTf), triethylamine, and ZnI₂ in dichloromethane allowed the synthesis of the thietane-derived thymidine **33a** in 70% yield <1996TL7569>. The treatment of thietane-1-oxide derivative **32b** under similar conditions but in toluene resulted in the modified nucleoside **33b** in 30% yield (Scheme 9) <1996TL7569>.

**Scheme 9**



Scheme 10

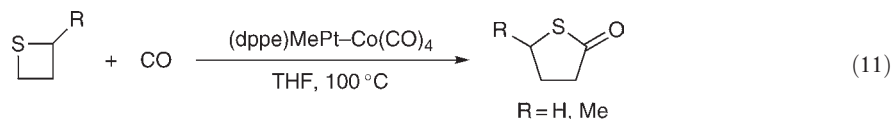


2.07.6.5 Reactions with Cyclic Transition States, Formally Involving a Second Species

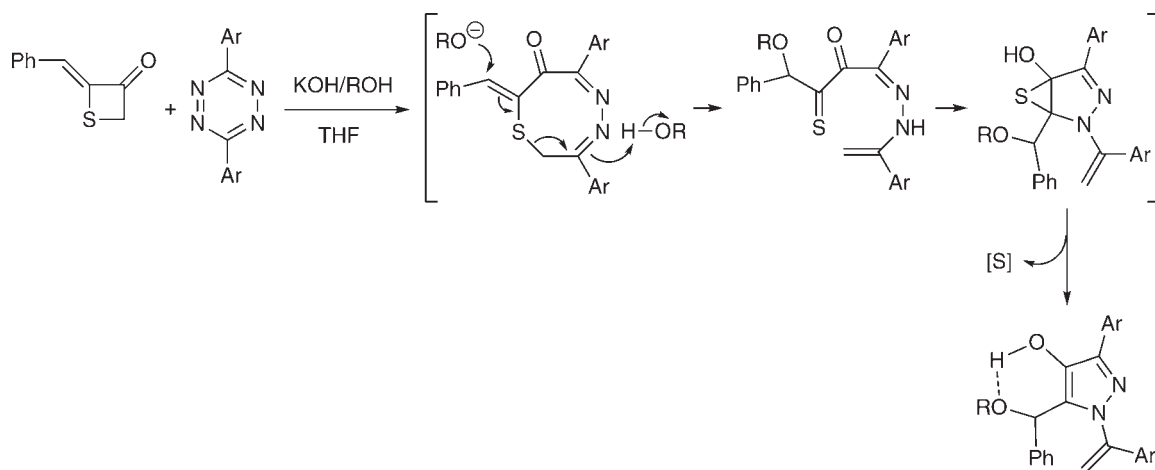
The reaction of thietanone with 1,2,4,5-tetrazines has been reported as a simple method for the synthesis of fully substituted pyrazol-4-ols [<2005JOC8468>](#). This process proceeds by a tandem condensation–fragmentation–cyclization–extrusion reaction. 2*H*-[1,4,5]Thiadiazocin-7-one was proposed as an intermediate in the mechanism of pyrazol-4-ols formation (Scheme 11). A Michael addition to the thiadiazocin-7-one initiates a cascade event leading to a ring-open thioketo/enamine structure. The nitrogen of this enamine attacks the thioketo group, which, probably via a three-membered thiirane ring intermediate, ultimately excludes sulfur and delivers the pyrazol-4-ol [<2005JOC8468>](#).

2.07.6.6 Reaction with Metals and Metal Complexes

Heterodinuclear organoplatinum–cobalt complexes having a 1,2-bis(diphenylphosphino)ethane ligand (dppe) MePt–Co(CO)_4 catalyze CO insertion into a C–S bond of thietanes in THF at 100°C under a 1.0 MPa atmosphere of CO (2 h) to give γ -thiobutyrolactones in quantitative yield (Equation 11) [<2003CC2046>](#).

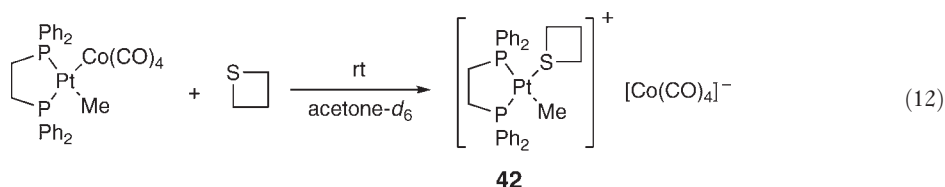


This carbonylation (Equation 11) can be achieved quantitatively, even at ambient temperature, if the reaction is performed during 1 day. When the ancillary methyl ligand in the heterodinuclear Pt–Co complex was displaced by



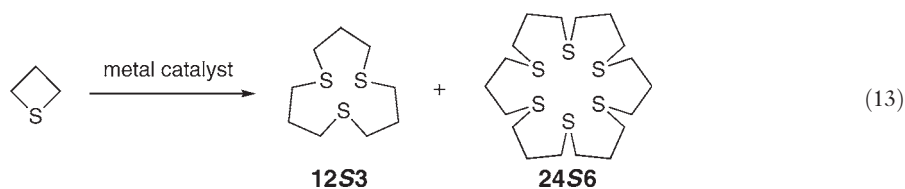
Scheme 11

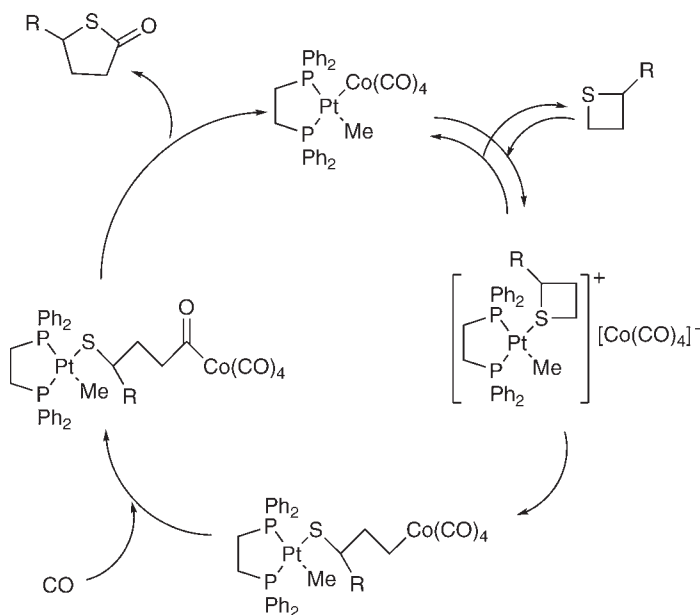
other organic ligands, a slight change in catalytic activity for this carbonylation was observed. The catalytic activities for neopentyl- and phenylplatinum(II) derivatives (dppe)RPt–Co(CO)₄ (R = CH₂CMe₃, Ph) decreased to give slightly lower yields than (dppe)MePt–Co(CO)₄ under the same conditions, whereas the acetylplatinum–cobalt complexes (dppe)(MeCO)Pt–Co(CO)₄ showed a comparable catalytic activity to (dppe)MePt–Co(CO)₄. When 2-methylthietane was used as a reactant in the reaction with (dppe)MePt–Co(CO)₄, γ -thiovalerolactone was exclusively formed in 89% yield. This result indicates that insertion of carbon monoxide took place at the less hindered C–S bond of 2-methylthietane, suggesting the involvement of an S_N2-type C–S bond cleavage reaction [\[2003CC2046\]](#). When (dppe)MePt–Co(CO)₄ was treated with thietane in acetone-*d*₆ at room temperature for 1 h, heterocyclic cleavage of the Pt–Co bond took place to give the cationic (thietane- κ S)platinum(II) complex with [Co(CO)₄][–] anion, [PtMe(thietane- κ S)(dppe)]⁺[Co(CO)₄][–] **42** (Equation 12).



Further treatment of complex **42** with 0.1 MPa of CO at room temperature afforded a mixture of (dppe)MePt–Co(CO)₄ (71%) and acetylplatinum complex (dppe)(MeCO)Pt–Co(CO)₄ (25%) with concomitant formation of γ -thiobutyrolactone in 91% yield after 2 days [\[2003CC2046\]](#). A plausible mechanism of this catalytic reaction has been proposed (Scheme 12).

Subsequently, it was discovered that the third-row transition metal complexes containing terminal coordinated thietane ligands are effective catalysts for the formation of thiacycrown ethers, which has been reviewed in detail [\[2000ACR171, 2000MI39\]](#). During the last decade, a number of papers appeared on the application of these methods to the oligomerization of different thietanes. The thietane-containing complexes M(CO)₅L (M = Cr and W, L = thietane) were obtained by the displacement of NCMe with thietane in the complex M(CO)₅(NCMe). The catalytic ring-opening cyclooligomerization of thietane by these complexes yielded a mixture of 12S3 and 24S6 products (Equation 13). The activity of the chromium complex was relatively low, whereas the vanadium compound exhibited significantly higher catalytic activity [\[1996CB313\]](#).



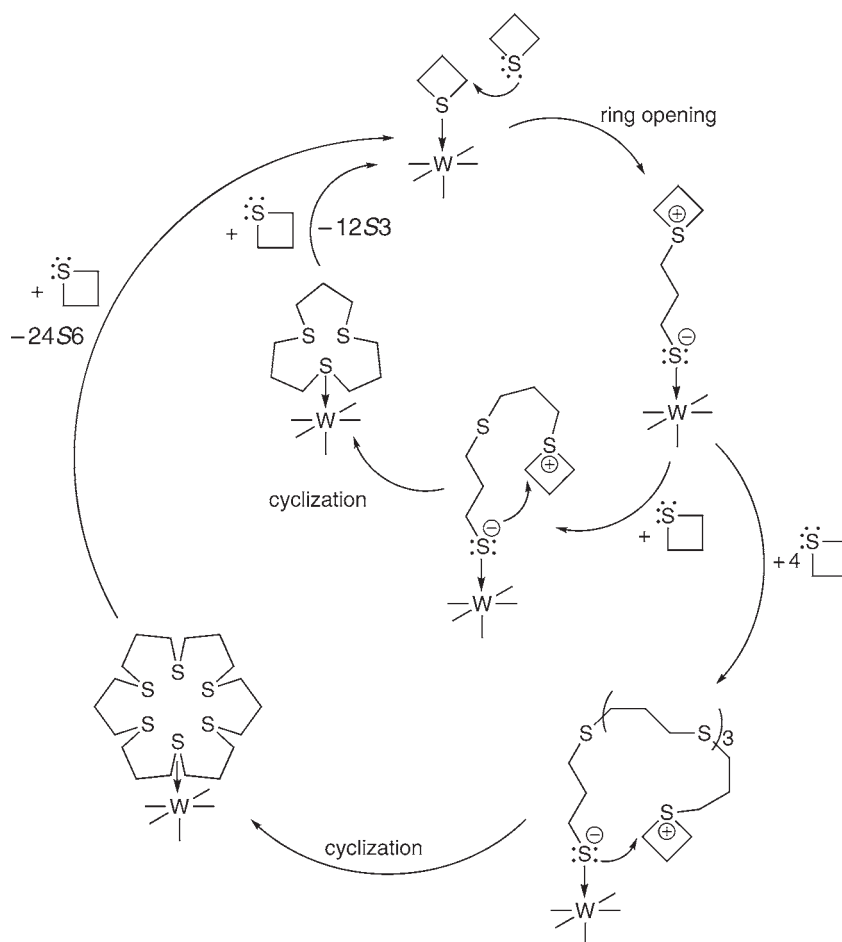


Scheme 12

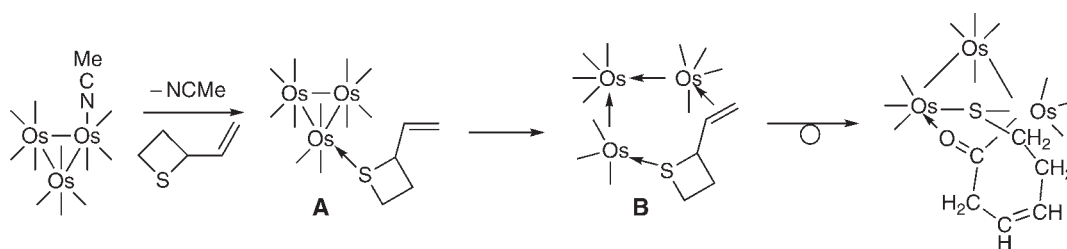
The mechanism for the catalytic cyclooligomerization is shown in [Scheme 13](#).

The new compounds $\text{Re}_2(\text{CO})_9(\text{SCH}_2\text{CHMeCH}_2)$ and $\text{W}(\text{CO})_5(\text{SCH}_2\text{CHMeCH}_2)$ have been prepared by the reactions of $\text{Re}_2(\text{CO})_9(\text{NCMe})$ and $\text{W}(\text{CO})_5(\text{NCMe})$ with 3-methylthietane. These compounds react with 3-methylthietane at reflux to yield substantial amounts of the polythioether macrocycle 3,7,11-trimethyl-1,5,9-trithiacyclododecane ($\text{Me}_3\text{12S}$), by metal-induced ring-opening cyclooligomerization of three molecules of 3-methylthietane, as two isomers (*cis,trans,trans*-3,7,11-trimethyl-1,5,9-trithiacyclododecane and *cis,cis,cis*-3,7,11-trimethyl-1,5,9-trithiacyclododecane) due to different orientations of the methyl substituents in the ring. A comparison of these catalysts shows that the rhenium catalyst exhibits a higher activity and higher selectivity for the formation of $\text{Me}_3\text{12S}$ than the tungsten complex [<1996OM2489>](#). Similarly, the reaction of $\text{Re}_2(\text{CO})_9(\text{NCMe})$ with 3,3-dimethylthietane yielded the complex $\text{Re}_2(\text{CO})_9(\text{SCH}_2\text{CMe}_2\text{CH}_2)$. This complex has been found to react with 3,3-dimethylthietane at 100°C to yield analogously the macrocycles 3,3,7,7,11,11-hexamethyl-1,5,9-trithiacyclododecane ($\text{Me}_6\text{12S}$), 3,3,7,7,11,11,15,15-octamethyl-1,5,9,13-tetrathiacyclohexadecane ($\text{Me}_8\text{16S4}$), and 3,3,7,7,11,11,15,15,19,19-decamethyl-1,5,9,13,17-pentathiacycloicosane ($\text{Me}_{10}\text{20S5}$). Therefore, a macrocyclization mechanism consisting of a metal-induced ring-opening cyclooligomerization of three, four, and five molecules has been proposed [<1997OM2612>](#). The chiral polythioether macrocycles, (*R,R,R*)-2,6,10-trimethyl-1,5,9-trithiacyclododecane, [(*R,R,R*)-12S3], and (*R,R,R*)-2,6,10,14-tetramethyl-1,5,9,13-tetrathiacyclohexadecane, [(*R,R,R*)- $\text{Me}_4\text{16S4}$], have been synthesized from (*R*)-2-methylthietane using the dirhenium carbonyl catalyst $\text{Re}_2(\text{CO})_9[(\text{R})\text{-2-SC(H)MeCH}_2\text{CH}_2]$. The mechanism of formation for these macrocycles has been discussed [<2000JOM115>](#). Thietane reacts with the high-valent metal complex $\text{Cp}'\text{ReCl}_4$ in a THF solution to form a simple adduct $\text{Cp}'\text{ReCl}_4(\text{SC}_3\text{H}_6)$, and no ring-opening reaction has been identified [<2000OM4925>](#). Dissolution of $[\text{CpRu}(\text{PPh}_3)(\text{SC}_3\text{H}_6)_2]\text{CF}_3\text{SO}_3$ in thietane/ CH_2Cl_2 yields the ruthenium bis(thietane) complex $[\text{CpRu}(\text{PPh}_3)(\text{SC}_3\text{H}_6)_2]\text{CF}_3\text{SO}_3$ [<2001ICA13>](#). The reaction of $\text{Os}_3(\text{CO})_{11}(\text{NCMe})$ with 2-vinylthietane at 25°C yielded two products: $\text{Os}_2(\text{CO})_6(\eta^4\text{-}\mu\text{-SCH}_2\text{CH}_2\text{CH}_2)$ (18% yield) and $\text{Os}_3(\text{CO})_{10}\eta^2\text{-}\mu\text{-O}=(\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}_2\text{S})$ (36% yield) [<2000JMT439>](#). The formation of $\text{Os}_3(\text{CO})_{10}\eta^2\text{-}\mu\text{-O}=(\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}_2\text{S})$ probably proceeds by displacement of the NCMe ligand in $\text{Os}_3(\text{CO})_{11}(\text{NCMe})$ by 2-vinylthietane with formation of an unobserved transient thietane intermediate complex such as **A**. A second intermediate such as **B** could be formed by opening one of the Os–Os bonds without loss of CO ([Scheme 14](#)) [<2000JST439>](#).

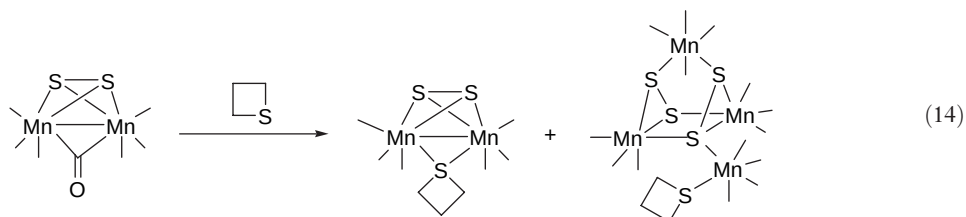
The reaction of $\text{Mn}_2(\text{CO})_7(\mu\text{-S}_2)$ with thietane yielded $\text{Mn}_2(\text{CO})_6(\mu\text{-S}_2)(\mu\text{-SCH}_2\text{CH}_2\text{CH}_2)$ and $\text{Mn}_4(\text{CO})_{14}(\text{SCH}_2\text{CH}_2\text{CH}_2)(\mu_3\text{-S}_2)(\mu_4\text{-S}_2)$ in 12% and 52% yields, respectively ([Equation 14](#)) [<2002IC5525>](#).



Scheme 13

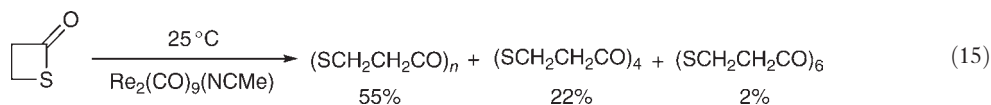


Scheme 14

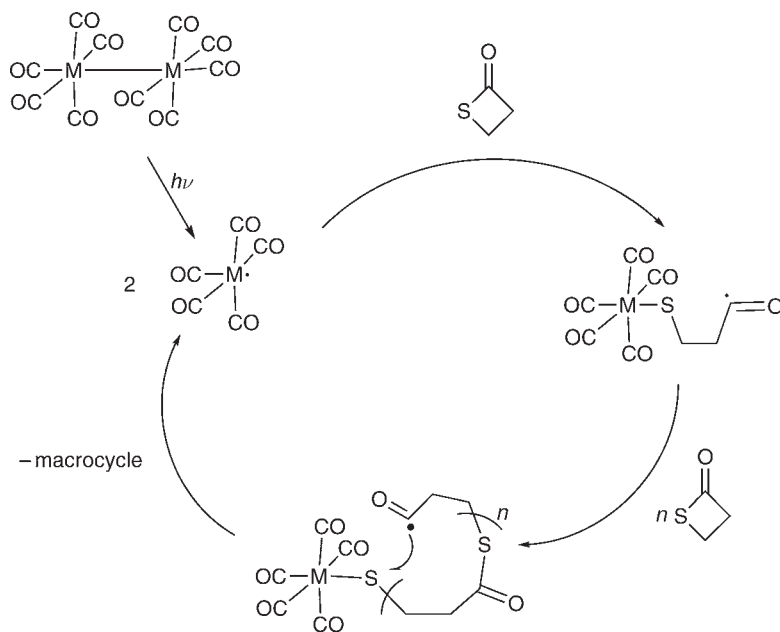


(14)

The thietane ligand in $\text{Mn}_4(\text{CO})_{14}(\text{SCH}_2\text{CH}_2\text{CH}_2)(\mu_3\text{-S}_2)(\mu_4\text{-S}_2)$ is terminally coordinated to the manganese atom (Mn-4) that lies outside the cluster. The Mn–S distance is similar to that found in other manganese complexes that have terminally coordinated thietane ligands. The mechanism of the formation of the tetramanganese compounds has been shown to proceed by a ligand-induced dimerization involving the formation of bridging disulfide ligands <2002IC5525>. It was found that $\text{Re}_2(\text{CO})_9(\text{NCMe})$ catalyzes polymerization of β -propiothiolactone under mild conditions leading to the polymer $(\text{SCH}_2\text{CH}_2\text{C=O})_n$ and a mixture of two cyclooligomers (Equation 15) <1996JA9442>.



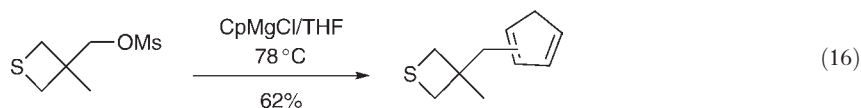
The analogous catalytic ring openings of β -propiothiolactone and 3,3-dimethyl β -propiothiolactone by $\text{Re}_2(\text{CO})_9(\text{NCMe})$, $\text{Mn}_2(\text{CO})_9(\text{NCMe})$, and $\text{Mn}_2(\text{CO})_{10}$ have been investigated <1997OM4479>. The reaction of $\text{Re}_2(\text{CO})_9(\text{NCMe})$ with β -propiothiolactone has been described above, whereas reaction with 3,3-dimethyl β -propiothiolactone resulted in the formation of the analogous tetra and hexamer but in lower yields (2% and 5%, respectively). Both manganese compounds exhibit activity similar to $\text{Re}_2(\text{CO})_9(\text{NCMe})$. $\text{Mn}_2(\text{CO})_{10}$ was completely inactive as a catalyst in the absence of light, whereas the other two showed a low residual but significant activity even in the absence of light. A radical mechanism for the oligomerization process has been proposed (Scheme 15) <1997OM4479>.



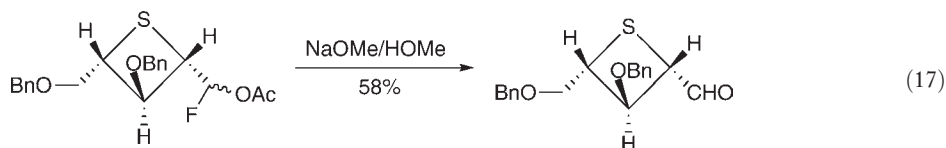
Scheme 15

2.07.7 Reactivity of Substituents Attached to Ring Carbon Atoms

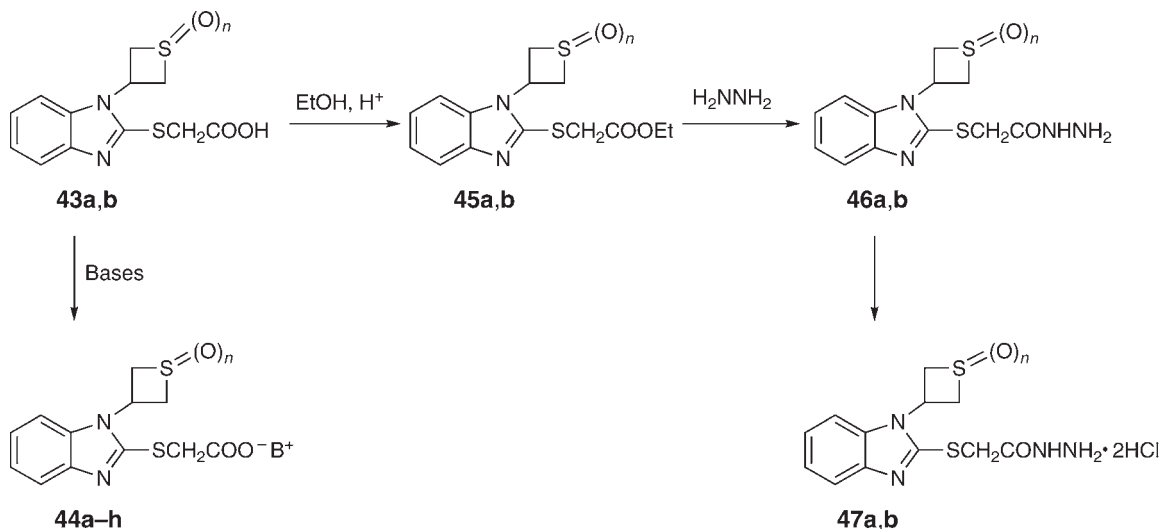
3-Cyclopentadienylmethyl-3-methyl thietane has been obtained by substitution of a mesyloxy group using cyclopentadienylmagnesium chloride as nucleophile (Equation 16) <1998JOM433>.



The protection of the hydroxyl group in 3-hydroxymethyl-3-methylthietane was carried out in 91% yield by reaction with mesyl chloride in the presence of triethylamine at 0 °C <1996CB97>. The substitution of the mesylate function in 3-methyl-3-(methylsulfonyloxymethyl)thietane **36** by treatment with LiPPh₂, LiP(4-Tol)₂, or LiSBn affords the corresponding functionalized thietane **37a–c** in good yields (Scheme 10) <1996CB97>. 3-Methyl-2-[(*Z*)-phenylmethylidene]-3-thietanol was acetylated with acetic anhydride in pyridine in the presence of 4-(dimethylamino)pyridine (DMAP) in 43% yield <2000EJO2391>. Treatment of 1-(3-benzyloxy-4-benzyloxy-methyl-thietan-2-yl)-1-fluoromethyl acetate with NaOMe in MeOH afforded the corresponding aldehyde in 58% yield (Equation 17) <1998TL5201>.



Reactions of 2-[1-(thietan-3-yl)-benzimidazolyl-2-thio]acetic acid **43a** and 2-[1-(1,1-dioxothietan-3-yl)-benzimidazolyl-2-thio]acetic acid **43b** with bases (amino alcohols or sodium hydroxide) led to the corresponding salts **44a–h**. By treatment of the ethyl esters **45a** and **45b**, obtained by the reaction of acids **43a** and **43b** with ethanol in the presence of sulfuric acid, with hydrazines, (benzimidazolyl-2-thio)acetic acid hydrazides **46a** and **46b** were synthesized and subsequently converted into the corresponding dihydrochlorides **47a** and **47b** (Scheme 16). Salts **44a–h** and **47a** and **47b** were tested as immunotropic compounds <2001PCJ11>.



$n=0$ (**43a**, **44a–d**, **45a**, **46a**, **47a**); $n=2$ (**43b**, **44e–h**, **45b**, **46b**, **47b**); B = Na (**44h**); B = H₃NCH₂CH₂OH (**44a**, **44e**); B = H₃NC(CH₂OH)₃ (**44c**, **44f**); B = H₃NCH₂CH₂CH₂CH₂OH (**44b**); B = HN(CH₃)₂CH₂CH₂CH₂OH (**44d**, **44g**)

Scheme 16

3-Aryloaminothietanes **15a–f** were obtained from *N*-aryl-*N*-(thietan-3-yl)-2-nitrobenzenesulfonamides **14a–f** by the removal of the sulfonyl protecting group <2005RJO1023>. It was found that the 2-nitrophenylsulfonyl group could be removed under very mild conditions by the action of thiolates (Table 3).

Similarly, deprotection of *S,S*-dioxides **17b** and **17d** with thiolates furnished the corresponding 3-arylaminothietanes *S,S*-dioxides **18b** and **18d** <2005RJO1023>. 3-Phenyl-, 3-(4-methoxyphenyl)-, and 3-(4-chlorophenyl)aminothietanes **15a**, **15b**, and **15d** were acylated to illustrate the possibility of using these compounds in combinatorial chemistry. The reaction readily occurs with benzoyl chloride or acetic anhydride in the presence of *N*-methylmorpholine or pyridine to afford the target *N*-acyl derivatives **19a**, **19b**, and **19d** in high yields and is not accompanied by polymerization or thietane ring opening by electrophilic acylating agents <2005RJO1023>.

Table 3 The action of thiolates on *N*-aryl-*N*-(thietan-3-yl)-2-nitrobenzenesulfonamides **14a–f**

Entry	Ar	RS [−]	Yield of 15 (%)
14a	Ph	PhSH + K ₂ CO ₃	80
14b	4-MeOC ₆ H ₄	PhSH + K ₂ CO ₃	86
14c	2- <i>i</i> -PrC ₆ H ₄	PhSH + K ₂ CO ₃	71
14d	4-ClC ₆ H ₄	PhSH + K ₂ CO ₃	60
14e	1-Naphthyl	PhSH + K ₂ CO ₃	80
14f	3-O ₂ NC ₆ H ₄	HSCH ₂ CO ₂ H + K ₂ CO ₃	85

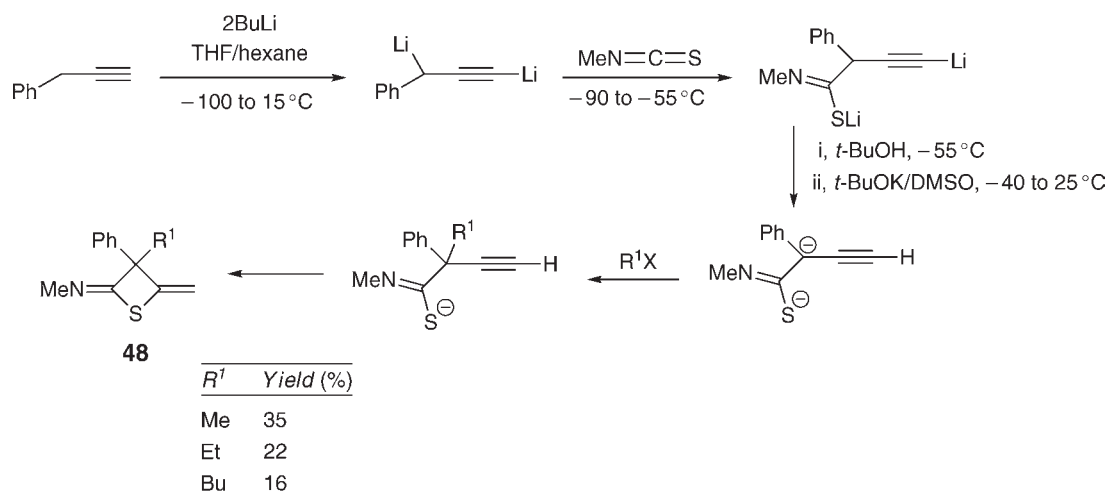
2.07.8 Reactivity of the Substituent Attached to the Ring Sulfur Atom

In CHEC-II(1996), Pummerer reactions were considered as reactions of a substituent attached to a ring sulfur atom because they are initiated by electrophilic attack at the sulfoxide oxygen. In this chapter, the Pummerer reaction has been discussed in Section 2.07.6.3.2.

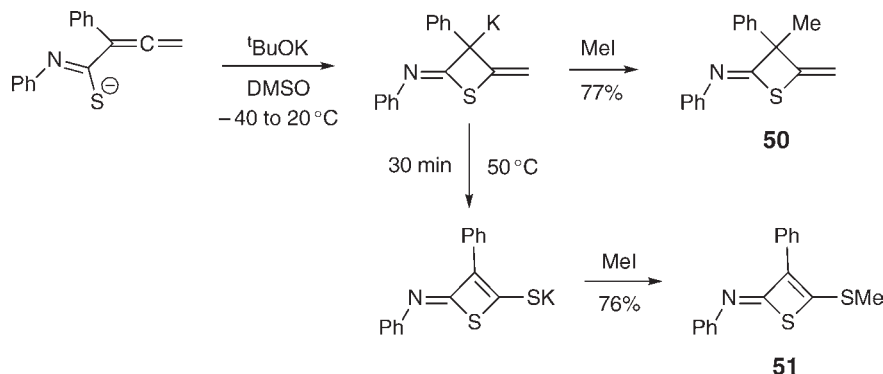
2.07.9 Ring Syntheses from Acyclic Compounds Classified by the Number of Ring Atoms Contributed by Each Component

2.07.9.1 Ring Syntheses from an Acyclic Precursor with the Same Number of Carbons

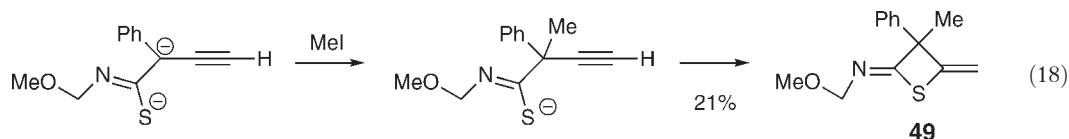
Brandsma, Tarasova, and co-workers <2001TL4687, 2003RJO1451> have reported the reaction of 1,3-dilithio-3-phenylpropyne with methyl isothiocyanate in THF–hexane at −90 to −55 °C, followed by the successive treatment of the intermediate product with a proton donor, a superbase, and an alkyl halide, yielding isomeric iminocyclobutenes and iminothietanes **48**. The ratio of the products depends on the nature of the proton donor, the base, the co-solvent, and the alkyl halide. The formation of the thietane derivatives proceeded in rather poor yields (Scheme 17).

**Scheme 17**

The same Dutch–Russian group has reported several varieties of this method, which allows the preparation of *N*-methoxymethyl thietanylidene amines **49** and **50** (Scheme 18; Equation 18) <2004RJO131> or 2,3-thietes **51** (Scheme 14) <2004RJO753>.

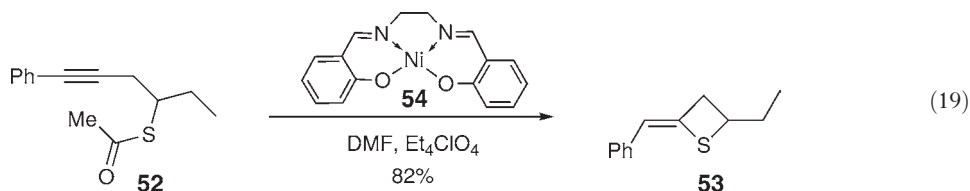


Scheme 18



The synthesis of the thietanes and thietes presented in Scheme 18 is, contrary to the previous ones, quite satisfactory and efficient with much better yields <2004RJO753>.

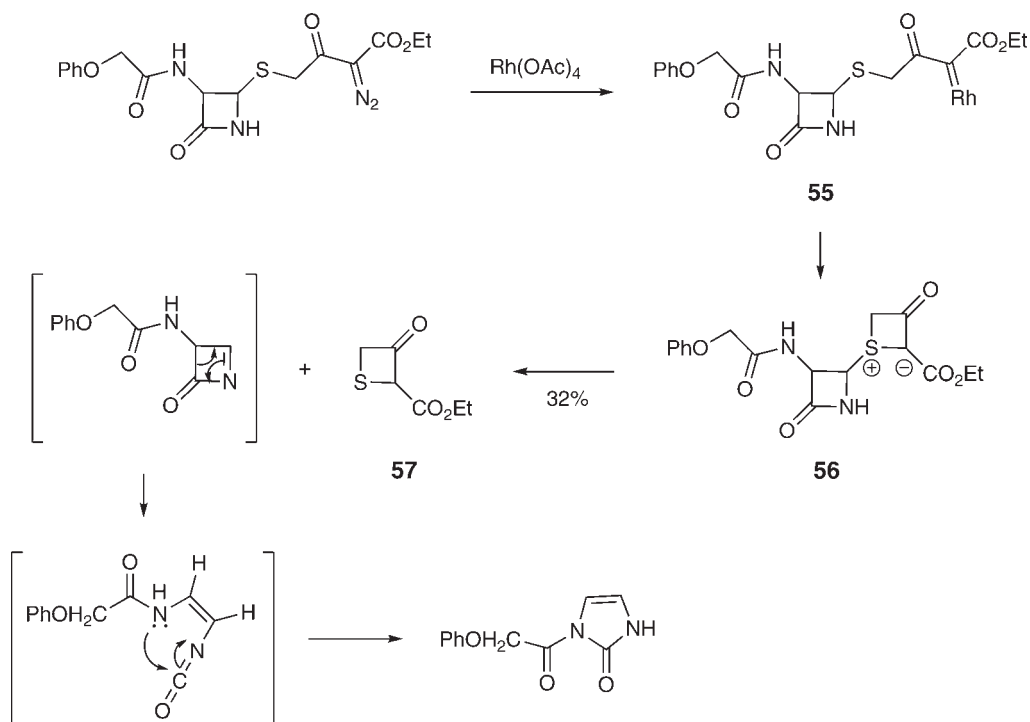
Ozaki and co-workers <1998TL8121> applied an electrochemical method for the synthesis of thietanes by the electroreduction of the acetylenic derivative of thioacetic acid **52**. The electrochemical reaction was carried out in dimethylformamide (DMF) using tetraethylammonium perchlorate as a supporting electrolyte at a graphite plate electrode in the presence of an *N,N'*-bis(salicylaldehyde)ethylenediamine (salen) nickel complex **54** (Equation 19). The desired 2-benzylidene-4-ethyl-thietane **53** was obtained in fair yield.



The intramolecular cyclization of the azetidine **55** has been described. This reaction resulted in the formation of the ylide **56** and was followed by fragmentation into the thietane **57** and an unstable azetinone, which after ring opening and recyclization led to *N*-phenoxyacetylimidazolone (Scheme 19) <2001CJC1259>.

Mitsunobu has described the cyclization of *S*-benzoxazolo-3-mercaptopropane-1-ol derivatives **58** promoted by potassium hydride <1997SL1247>. In the course of this reaction, the substituted thietanes **59** were obtained with satisfactory yields (Table 4).

An elegant and very efficient synthesis of thietanes has been reported <2002S1502>. The Michael addition of phosphorodithioate to α,β -unsaturated ketones led to the formation of 3-oxopropyl phosphorodithioate, which then underwent nucleophile-induced cyclization to form a series of variously substituted thietanes **60a–i** (Table 5) <2002S1502>.

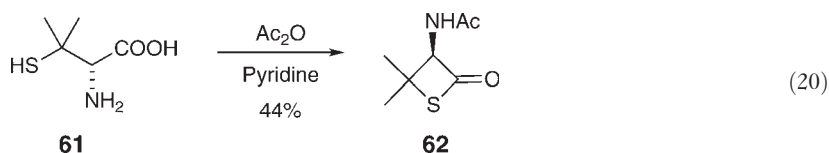


Scheme 19

Table 4 Cyclization of *S*-benzoxazolo-3-mercaptopropane-1-ol derivatives **58**

R^1	R^2	R^3	Yield of 59 (%)
H	H	Ph	44
Bn	Bn	H	60
Et	H	Ph	72
Me	H	Ph	52

From the point of view of biological applications, important work has been reported by two independent teams <1996BML2575, 2000BML1347, 2001T7173, 2004BML4995>. As part of a study of a variety of new nucleosides, β -mercaptovaline **61** was cyclized by the action of acetic anhydride in pyridine to obtain 3-aminothietan-2-one **62** (Equation 20).

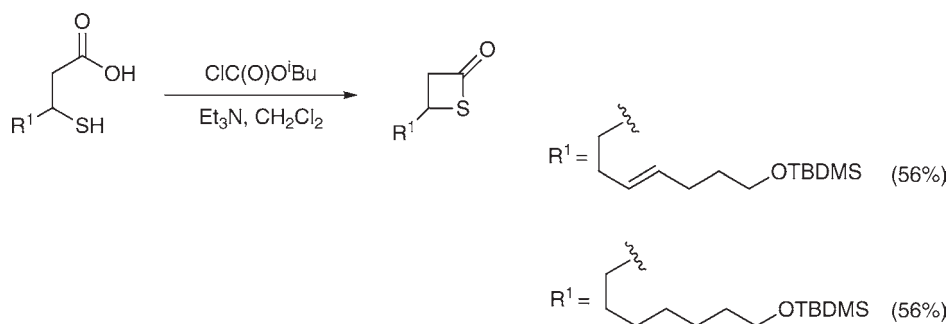


A synthesis of the functional core of the antibiotic leinamycin consisted of several steps, one of them being the preparation of an alkyl-substituted thietanone in moderate yield by cyclization of 2-mercapto propionic acid derivatives in isobutyl chloroformate and in the presence of triethylamine (Scheme 20) <2003T833, 2003PS1163>.

Table 5 The Michael addition of phosphorodithioate to α,β -unsaturated ketones

$$R^1-CH=CH-C(=O)R^2 \xrightarrow{HS-P(=S)(OEt)_2} (EtO)_2P(=S)-S-CH(R^1)-CH_2-C(=O)R^2 \xrightarrow{Nu^-} \text{Thietane } 60a-i$$

Entry	R^1	R^2	Nu	Yield of 60 (%)
60a	Ph	Ph	CN	84
60b	<i>p</i> -Cl-C ₆ H ₄	Ph	CN	87
60c	<i>p</i> -Cl-C ₆ H ₄	<i>p</i> -Cl-C ₆ H ₄	CN	92
60d	Ph	Ph	MeS	81
60e	<i>p</i> -Cl-C ₆ H ₄	Ph	MeS	83
60f	<i>p</i> -Cl-C ₆ H ₄	<i>p</i> -Cl-C ₆ H ₄	MeS	88
60g	Ph	Ph	EtS	77
60h	<i>p</i> -Cl-C ₆ H ₄	Ph	EtS	80
60i	<i>p</i> -Cl-C ₆ H ₄	<i>p</i> -Cl-C ₆ H ₄	EtS	85

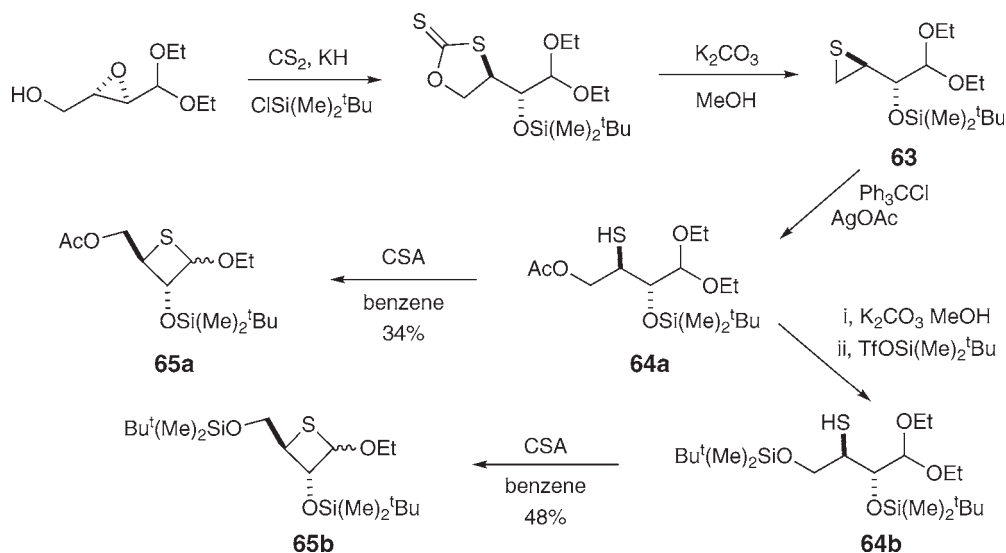
**Scheme 20**

Analogously to oxetanose, that is, a four-membered sugar, which was observed in oxetanocine and thromboxane A₂, an elegant synthesis of thietanose was reported [<1998H\(47\)439>](#). It was achieved by the ring opening of thiirane derivative **63** to form thioerythrose **64** followed by its cyclization to thietanose **65** using camphorsulfonic acid (CSA) ([Scheme 21](#)).

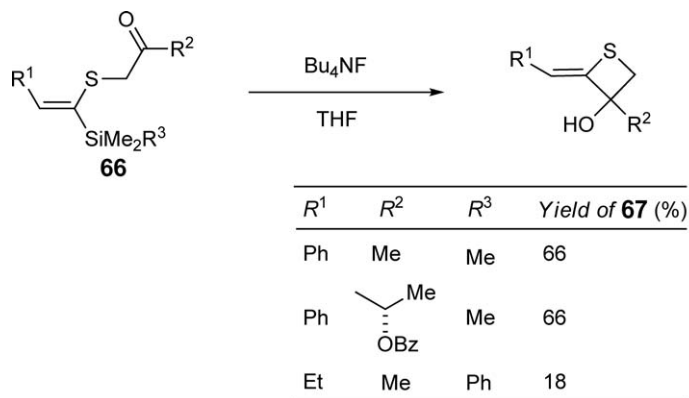
Bonini *et al.* [<1997J\(P1\)3211, 2000EJO2391>](#) synthesized a series of 2-benzylidene-3-hydroxythietanes **67** by ring closing of 1-(1-trimethylsilylpropenylsulfanyl)-propan-2-one derivatives **66** using fluoride. The reaction was carried out in THF, and tetrabutylammonium fluoride (TBAF) was used as the source of fluoride anions ([Scheme 22](#)).

The products of the FVT of 6-aryl-1,3-dioxine-4-thione **68** at 500 and 750 °C were characterized by Ar-matrix IR spectroscopy on a BaF₂ window at 14 K as well as by online tandem mass spectrometry ([Scheme 23](#)) [<2000JOC2706>](#). Loss of acetone from compound **68a** under mild conditions led to the identifiable benzoylthio-ketene **69a**. At higher temperatures **69a** rearranges to the thioacylketene **70a**, which undergoes electrocyclicization to thiet-2-one **71a**. The thiet-2-one decomposes by cycloreversion to give OCS and phenylacetylene **72a**. A second mode of decomposition is the cheletropic extrusion of CO to furnish phenylthioketene **73a**, formally by means of a Wolff rearrangement of the putative thiobenzoylcarbene ([Scheme 23](#)). The *p*-methoxyphenyl (anisyl) derivative **68b** reacted analogously, with the only exception that the thiet-2-one **71b** appeared already at 550 °C and reached its maximum intensity at 650 °C as the electron-rich anisyl substituent undergoes the 1,3-shift more readily, giving **70b** and further **71b**, as expected.

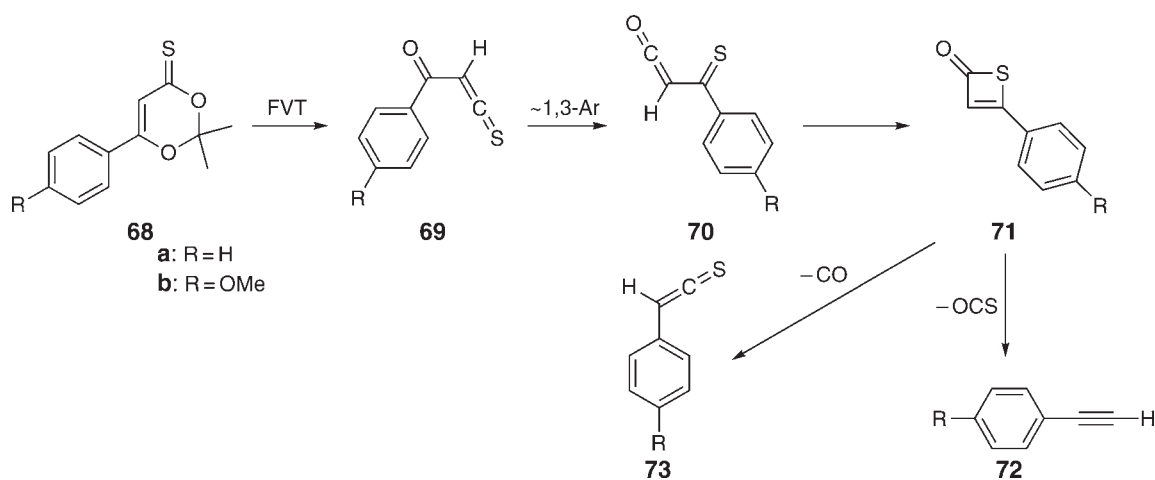
Kamigata and co-workers [<1997TL8529, 2000JOC1721>](#) described the cyclization of 1,3-diphenyl-1,3-bis(thio-benzyl)allene **74** in refluxing xylene. The reaction led to 2,3,5-triphenyl thiophene **75** as the predominant product and, among the side products, thiete **76** was detected ([Scheme 24](#)).



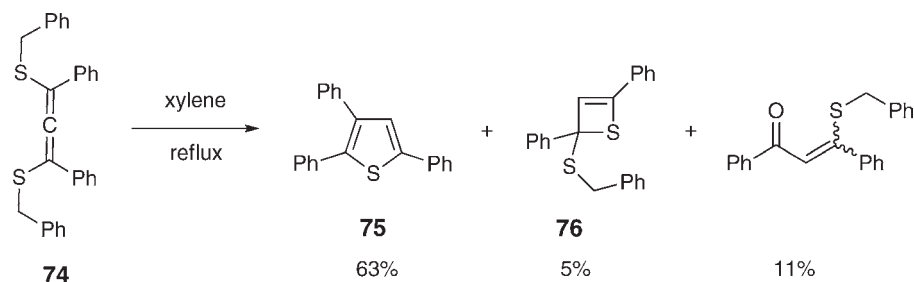
Scheme 21



Scheme 22



Scheme 23

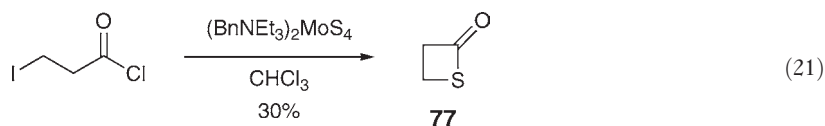


Scheme 24

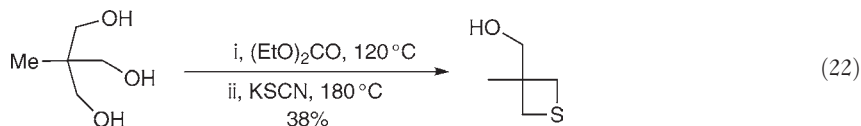
2.07.9.2 Ring Synthesis via Formation of Two Bonds

2.07.9.2.1 From [3+1] fragments

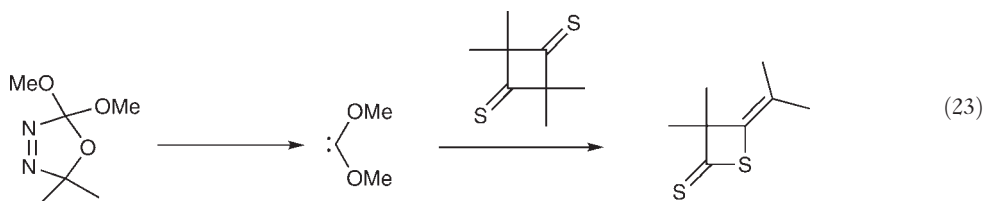
The reaction of 3-iodopropionyl chloride with benzyltriethylammonium tetrathiomolybdate gave β -thiolactone **77**, but in rather poor yield (Equation 21) <1997T11835>. According to the authors, the poor yield resulted from the fact that 2-thietanones easily react with various nucleophilic reagents that are present in the reaction mixture and which result in cleavage of the S–C=O bond.



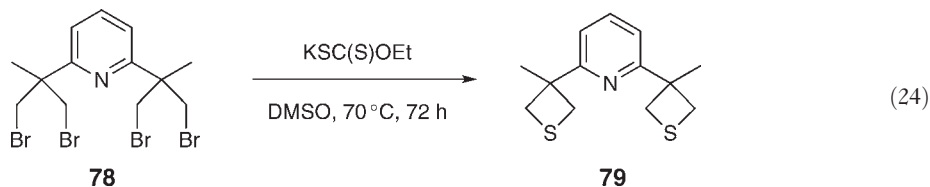
Treatment of 2,2-bis-hydroxymethyl-propan-1-ol with diethyl carbonate and then with potassium thiocyanate at 180 °C gave 3-hydroxymethyl-3-methylthietane in 38% yield (Equation 22) <1996CB97>.



An interesting but not synthetically useful reaction has been reported by Mlostoń and co-workers <2002CEJ2184>. The treatment of 2,2,4,4-tetramethylcyclobutan-1,3-dithione with dimethoxycarbene, generated by thermolysis of 2,2-dimethoxy-5,5-dimethyl-2,5-dihydro-[1,3,4]oxadiazole, led to the formation of 4-isopropylidene-3,3-dimethyl-thietane-2-thione in trace amounts (2% yield), together with other products (Equation 23).

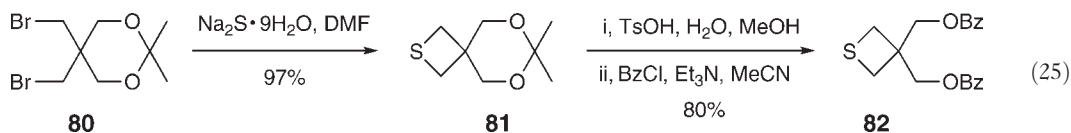


2,6-Bis-(2-bromo-(1-bromomethyl-1-methyl)ethyl)pyridine **78** is a precursor for tetrapodal ligands. Its reaction with an excess of potassium *O*-ethyl xanthogenate in DMSO at 70 °C (72 h) gave 2,6-bis-(3-methylthietan-3-yl)pyridine **79** (Equation 24) <2002ZN1256>. The yield of the product was not reported.

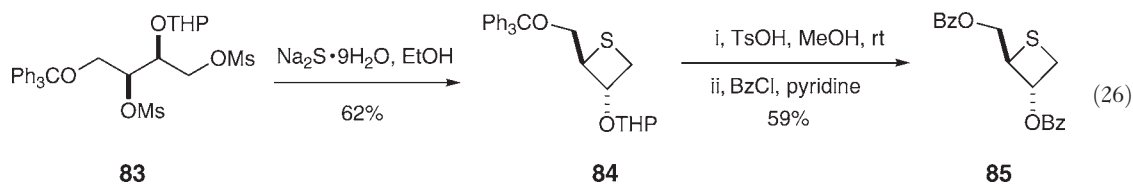


Workers targeting thietanyl nucleosides via the Pummerer reaction have reported a [3+1] synthesis of thietanose derivatives (i.e., thietane ring-based monosaccharides). Nishizono *et al.* performed the synthesis of

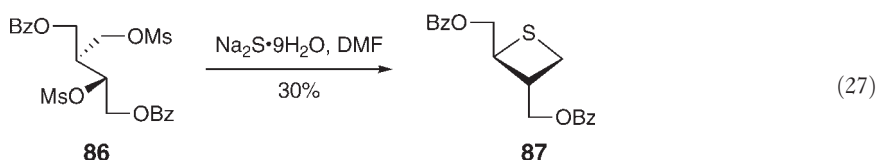
3,3-(dibenzoyloxymethyl)thietane **82** by the action of sodium sulfide on 5,5-bis-bromomethyl-2,2-dimethyl[1,3]dioxane **80** <1996TL7569>. This reaction first led to 7,7-dimethyl-6,8-dioxo-2-thia-spiro[3.5]nonane **81** in 97% yield and subsequent treatment of the latter with *p*-toluenesulfonic acid followed by acylation with benzoyl chloride allowed the synthesis of thietane **82** in 80% yield (Equation 25) <1996TL7569>.



The same authors described the synthesis of 2-deoxy thietanose **85** (Equation 27) <1996TL7569>. The reaction of a tetraol **83** derivative with sodium sulfide led to the bis-*O*-protected thietanose **84** in 62% yield; subsequent treatment of compound **84** with *p*-toluenesulfonic acid followed by acylation with benzoyl chloride provided di-*O,O*-benzoyl thietanose **85** in 59% yield (Equation 26) <1996TL7569>.

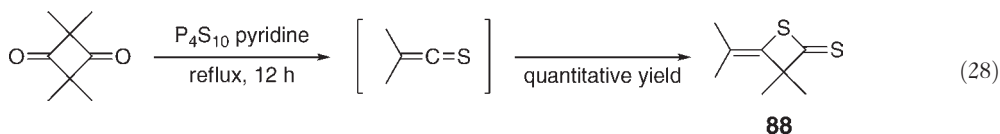


Ichikawa *et al.* synthesized bis-benzoyl-protected 2-deoxy thietanose **87** directly from tetraol derivative **86** in 30% yield (Equation 27) <1999NAS5, 1999TL7385>.

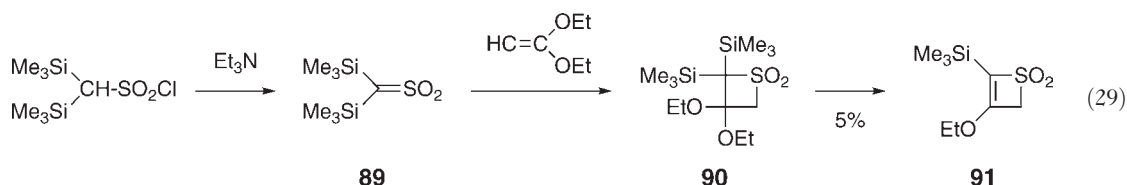


2.07.9.2.2 From [2+2] fragments

The reaction of 2,2,4,4-tetramethyl-1,3-cyclobutanedione with tetraphosphorus decasulfide (P_4S_{10}) led to ring cleavage and the formation of the intermediate dimethylthioketene, which underwent [2+2] cycloaddition after 12 h in refluxing pyridine to give 4-isopropylidene-3,3-dimethylthietane-2-thione **88** in nearly quantitative yield (Equation 28) <2004BCJ187>.



The treatment of bis(trimethylsilyl)methanesulfonyl chloride with triethylamine led to the formation of a sulfene **89**, which upon reaction with diethyl ketene acetal gave a thietane adduct **90**. The latter led to thiete 1,1-dioxide **91** in very poor yield (5%) after the loss of trimethylsilyl ethoxide (Equation 29) <2000CJC1642>.



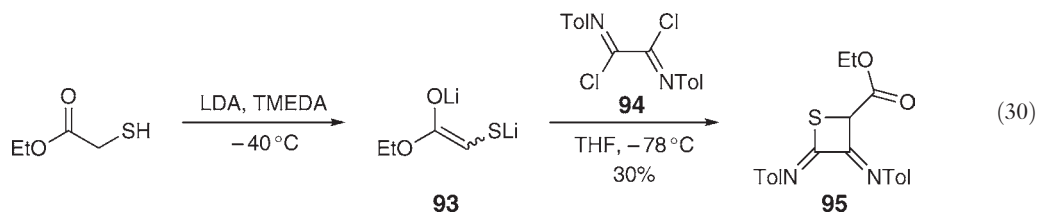
The [2+2] cycloaddition reactions of various 4-dialkylamino-3-buten-2-ones with substituted phenyl isothiocyanates in refluxing tetrahydrofuran gave access to a series of thietimines **92a-j** in poor to satisfactory yields (Table 6) <2001SL361>. As it may be concluded from Table 6, when diethylamine derivatives were replaced by dimethylamine

Table 6 [2+2] Cycloadditions of 4-dialkylamino-3-butyne-2-ones with phenyl isothiocyanates

Entry	R^1	R^2	Yield of 92 (%)
92a	Et	H	63
92b	Et	Cl	71
92c	Et	Br	80
92d	Et	NO ₂	46
92e	Et	OMe	44
92f	Me	H	19
92g	Me	Cl	25
92h	Me	Br	23
92i	Me	NO ₂	22
92j	Me	OMe	12

derivatives, the yields of the thietimines **92** decreased dramatically. The authors suggest that *N,N*-dimethyl ynamines underwent self-condensation since they are relatively less stable than *N,N*-diethyl ynamines <2001SL361>.

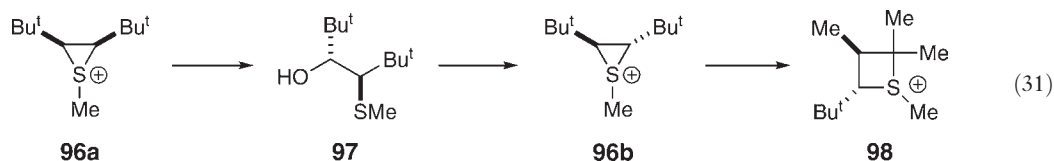
[2+2] Cycloaddition of bis(imidoyl chloride) **94** with the dianion of ethyl thioglycolate **93** allowed the synthesis of 2,3-diiminothietane **95** in 30% yield (Equation 30) <1999CC2439>. The thietane **95** was easily isolated by column chromatography.



2.07.10 Ring Synthesis by Transformation of Another Ring

2.07.10.1 Formation from Three-Membered Heterocycles

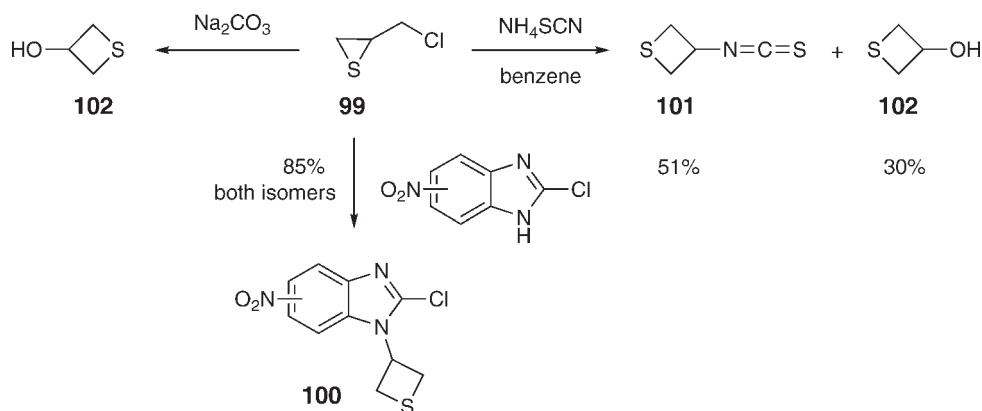
A number of papers describe the synthesis of thietane rings starting from thiirane rings. Lucchini *et al.* studied the different reactivities of *cis* and *trans* di-*tert*-butylthiiranium ions, **96a** and **96b**, with water <1997JOC7018>. It was demonstrated that the reaction of *cis* di-*tert*-butylthiiranium ion **96a** with water led first to the formation of an open-chain alcohol **97**, which, after ring closure, formed the *trans* di-*tert*-butylthiiranium ion **96b**. The *trans* di-*tert*-butylthiiranium ion **96b** then rearranged to the thietanium ion **98** (Equation 31).



The same team studied also *tert*-butyl-substituted thiiranium and thiirenium ions in reactions with disulfides, which led to the formation of thietanium and thietium ions, respectively. However, this paper only reported upon the kinetics of this

reaction <1999JA3944>. It was found that the $\Delta G^\ddagger_{298}$ values for the rearrangements from the *cis* and *trans* *t*-butyl groups of **96**·hexachloroantimonate into thietanium ion (two intramolecular S_N2 displacements) and for the rearrangement of 2,3-di-*tert*-butyl-1-methylthiirenium hexachloroantimonate to thietium ions (an intramolecular S_N2 -Vin displacement) were linearly correlated with the strength of the breaking of C–S bonds. This suggests that the two mechanisms were, in the absence of sterical hindrance, uniquely governed by the nucleofugality of the leaving group <2000JOC3367>.

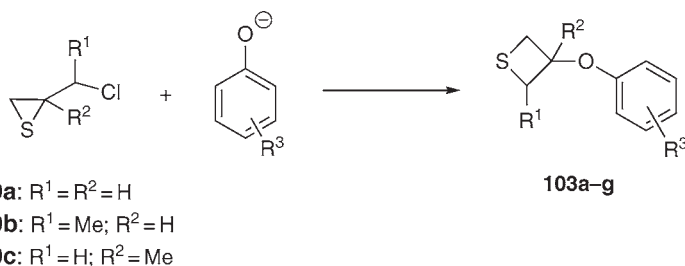
A series of papers have reported the application of 2-chloromethylthiirane **99** for the synthesis of a variety of thietanes. Reaction with a mixture of 5- and 6-nitro-2-chlorobenzimidazoles in aqueous sodium hydroxide leads to a mixture of 5- and 6-nitro-2-chloro-1-thietan-3-yl-1*H*-benzimidazoles **100** in 85% overall yield (Scheme 25) <2002RJO1507>. The reaction of thiirane **99** with ammonium isothiocyanate in benzene gave 3-isothiocyanato-thietane **101** and 4-hydroxythietane **102** in 51% and 30% yield, respectively (Scheme 25) <2000ZO589>. The same 4-hydroxythietane **102** was also obtained by the action of sodium carbonate on 2-chloromethylthiirane **99** (Scheme 25) <2001RJAC114>.



Scheme 25

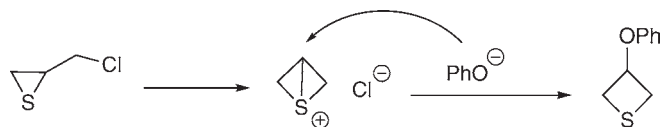
Treatment of 2-chloromethylthiirane **99a–c** derivatives with substituted phenoxides led to the formation of 3-phenoxythietanes **103a–g** in poor to satisfactory yields (Table 7) <2003RJO226>.

Table 7 Reactions of 2-chloromethylthiirane **99a–c** derivatives with phenoxides



Entry	R ¹	R ²	R ³	Yield of 103 (%)
103a	H	H	H	24
103b	H	Me	H	61
103c (<i>cis</i>)	Me (<i>S</i>)	H	H	44
103c (<i>trans</i>)	Me (<i>R</i>)	H	H	28
103d	H	H	<i>m</i> -CHO	61
103e	H	H	<i>p</i> -CHO	69
103f	H	H	<i>p</i> -COOH	68
103g	H	H	<i>p</i> -COOMe	93

A suggested mechanism for this reaction involves formation of the $1\lambda^4$ -thionia-bicyclo[1.1.0]butane ion, which as a result of attack by phenoxide anion at the 3-position forms the desired 3-phenoxythietane (**Scheme 26**) <2003RJO226>.



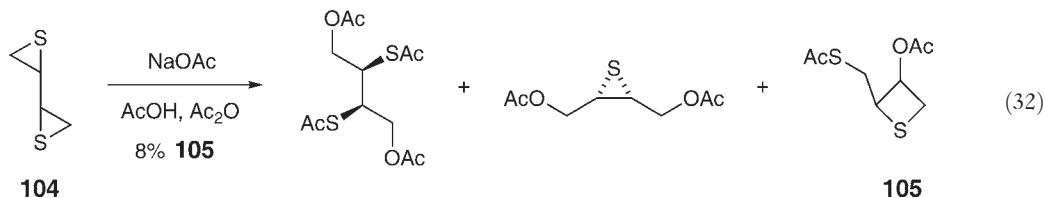
Scheme 26

The action of various *N*-substituted sulfonamides on 2-chloromethylthiirane **99a** led to the formation of *N*-thietan-3-yl sulfonamides **13a–f** and **14a–g** in poor to satisfactory yields (**Table 8**) <2005RJO1023>.

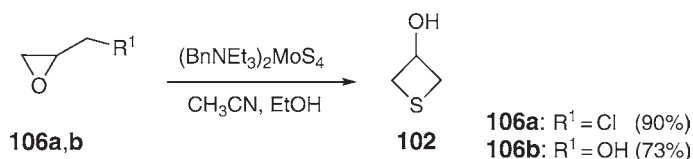
Table 8 The action of various *N*-substituted sulfonamides on 2-chloromethylthiirane **99a**

	99		13,14
Entry	<i>R</i> ¹	<i>R</i> ²	Yield of 13 and 14 (%)
13a	4-MeOC ₆ H ₄	Ph	62
13b	4-MeOC ₆ H ₄	Me	56
13c	1-Naphthyl	Me	25
13d	CH ₂ Ph	Ph	5
13e	H	Ph	25
13f	4-O ₂ NC ₆ H ₄	Ph	30
14a	Ph	2-O ₂ NC ₆ H ₄	35
14b	4-MeOC ₆ H ₄	2-O ₂ NC ₆ H ₄	41
14c	2- <i>i</i> -PrC ₆ H ₄	2-O ₂ NC ₆ H ₄	27
14d	4-ClC ₆ H ₄	2-O ₂ NC ₆ H ₄	31
14e	1-Naphthyl	2-O ₂ NC ₆ H ₄	44
14f	3-O ₂ NC ₆ H ₄	2-O ₂ NC ₆ H ₄	26
14g	4-O ₂ NC ₆ H ₄	2-O ₂ NC ₆ H ₄	1.3

The treatment of diepithiobutane **104** with sodium acetate in an acetic acid–acetic anhydride mixture at 120 °C gave the thietanose derivative **105** in only 8% yield (**Equation 32**) <1996JOC3611>.



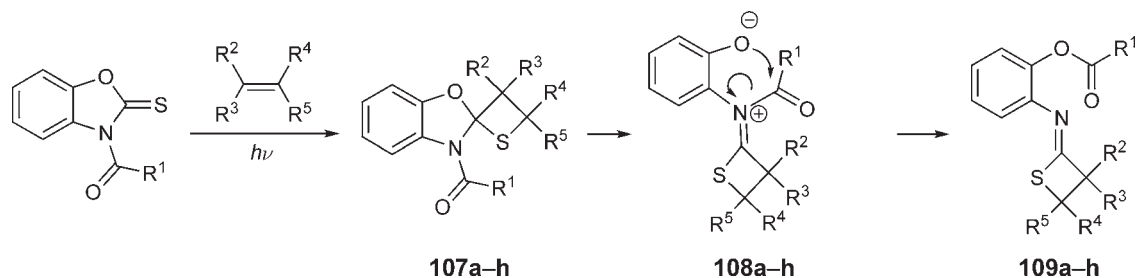
Oxiranes can also be converted into thietanes. When 2-chloromethyloxirane **106a** or 2-hydroxymethyloxirane **106b** were treated with benzyltriethylammonium tetrathiomolybdate 3-thietanol, thietane **102** was obtained in 90% and 73% yield, respectively (**Scheme 27**) <2002JOC9417>. However, the reaction with 2-hydroxymethyloxirane **106b** required activation with a DCC–CuCl pair (DCC = dicyclohexylcarbodiimide).



Scheme 27

2.07.10.2 Formation from Four-Membered Heterocycles

The photochemical reaction of *N*-acylbenzoxazole-2-thiones with alkenes gave substituted benzoxazoles and iminothietanes **109** <1998J(P1)1007, 2000J(P1)3039, 2003H(59)399>. This photoreaction was studied in detail and it was demonstrated that formation of spirothietanes **107** is the first step. Then, C–O bond cleavage of the spirothietane molecule occurs and the open-chain intermediate **108** undergoes intramolecular rearrangement to form iminothietane **109** in moderate to good yields (Table 9) <1998J(P1)1007, 2000J(P1)3039, 2003H(59)399>.

Table 9 The photochemical reaction of *N*-acylbenzoxazole-2-thiones with alkenes

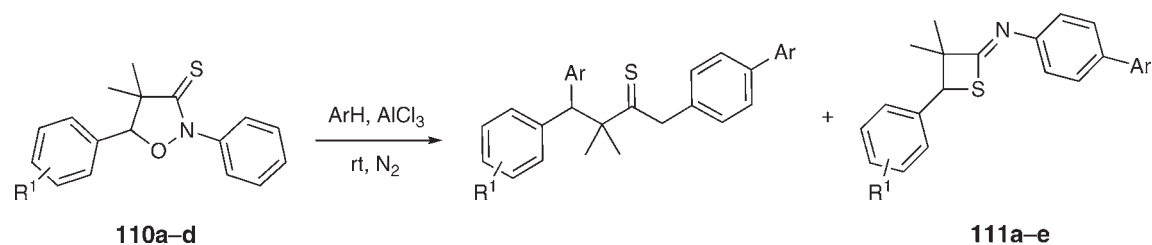
Entry	R ¹	R ²	R ³	R ⁴	R ⁵	Yield of 103 (%)	Reference
109a	Me	Me	Me	Me	Me	52	1998J(P1)1007
109b	Me	Me	Me	H	CH=CM ₂	31	1998J(P1)1007
109c	Me ₂ CH	Me	Me	Me	H	53	1998J(P1)1007
109d	Me ₂ CH	Me	Me	Me	Me	51	1998J(P1)1007
109e	Me ₂ CH	Me	Me	H	CH=CM ₂	48	2000J(P1)3039
109f	Me ₂ CH	Me	C(Me)=CH ₂	H	H	20	2000J(P1)3039
109g	PhCH ₂	Me	Me	Me	Me	11	2000J(P1)3039
109h	PhCH ₂ CH ₂	Me	Me	Me	Me	63	2000J(P1)3039

2.07.10.3 Formation from Five-Membered Heterocycles

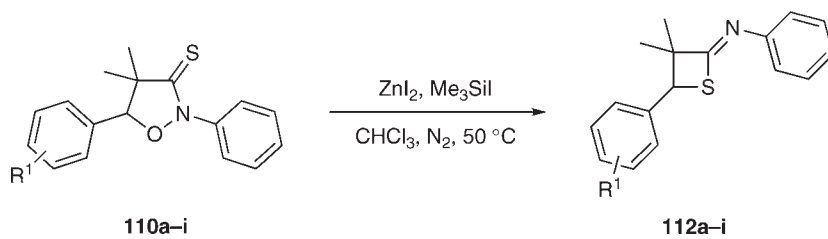
Reactions of 4,4-dimethyl-2,5-diphenylisooxazolidine-3-thiones **110a–d** with toluene or benzene in the presence of anhydrous aluminium chloride at room temperature led to the formation of 3,3-diaryl-*N*-(*p*-biphenyl)-2,2-dimethylpropanothioamides and 4-aryl-2-[(*p*-biphenylimino)]-3,3-dimethylthietanes **111a–e** in satisfactory yields (Table 10) <1996H(43)1211>.

The rearrangement reaction of isooxazolidine-3-thiones **110a–i** catalyzed by zinc iodide and trimethylsilyl iodide allowed the synthesis of 2-[(*p*-biphenylimino)]-3,3-dimethylthietanes **112a–i** in moderate to high yields after several days (Table 11) <1996H(43)1211>.

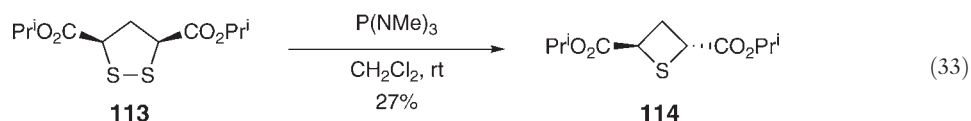
The reaction of *cis*-3,5-di(isopropoxycarbonyl)-1,2-dithiolane **113** in dichloromethane with hexamethylphosphorus triamide (HMPT), added over a period of 12 h at room temperature, led to the formation of *trans*-2,4-di(isopropoxycarbonyl)thietane **114** in 27% yield (Equation 33) <2000J(P1)1595>.

Table 10 Reactions of 4,4-dimethyl-2,5-diphenylisooxazolidine-3-thiones **110a–d** with arenes

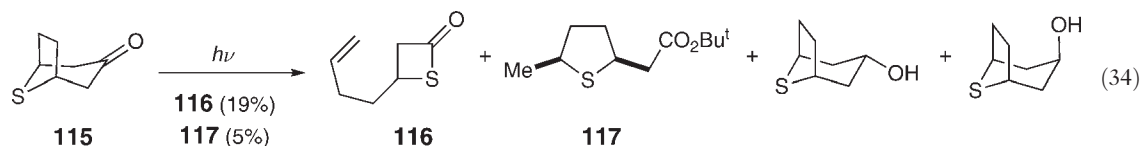
Substrate 110	Product 111	R^1	Ar	Yield of 111 (%)
a	a	H	Ph	45
a	b	H	4-MeC ₆ H ₄	28
b	c	2-Cl	Ph	26
c	d	3-Cl	Ph	27
d	e	4-Cl	Ph	19

Table 11 The rearrangement reaction of isooxazolidine-3-thiones **110a–i**

Entry	R^1	Yield of 112 (%)
112a	H	67
112b	2-Cl	61
112c	3-Cl	29
112d	4-Cl	66
112e	2-Br	51
112f	4-Br	53
112g	2-Me	74
112h	3-Me	75
112i	4-Me	83



Photolysis of 8-thia-bicyclo[3.2.1]octan-3-one **115** in *tert*-butyl alcohol resulted in the formation of 4-but-3-enylthietan-2-one **116** in 19% yield and a tetrahydrothiophene derivative **117** in 5% yield accompanied by traces (4% and 3%) of *exo*- and *endo*-8-thiabicyclo[3.2.1]octan-3-ol (Equation 34) <1996J(P1)2265>.



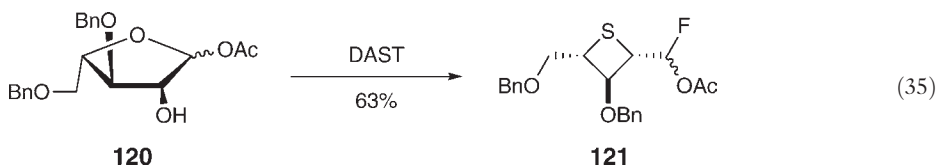
The photodecarbonylation reaction of thiophenones **118a–c** leading to the formation of alkyl-substituted thietes **119a–c** in high yields turned out to be a useful method for their synthesis (Table 12) <1997HCA510>.

Table 12 The photodecarbonylation reaction of thiophenones

118a–c **119a–c**

Entry	R^1	Yield of 115 (%)
119a	Me	80
119b	Me_2CHCH_2	44
119c	PhCH_2	35

Thiofuranose **120** was treated with diethylaminosulfur trifluoride (DAST) and underwent a ring contraction to give a thietanose derivative **121** in 63% yield (Equation 35) <1998TL5201>.

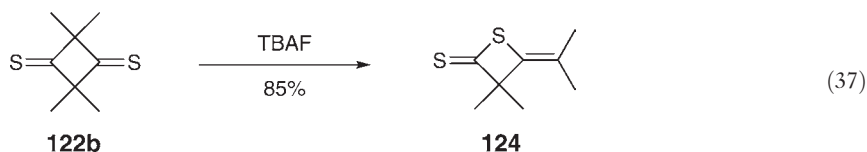


2.07.10.4 Formation from Carbocyclic Rings

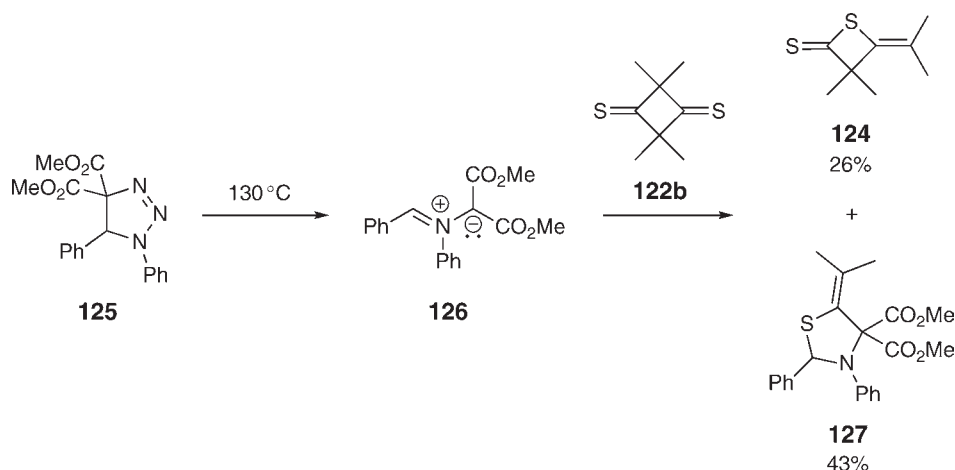
The treatment of 2,2,4,4-tetramethyl-3-thioxocyclobutanone **122a** with trimethyltrifluoromethyl silane and TBAF in THF led to the formation of (4-isopropylidene-3,3-dimethyl-2-trifluoromethyl-thietan-2-yloxy)trimethyl silane **123** in high yield (Equation 36) <2002HCA1644>.



The treatment of 2,2,4,4-tetramethyl-1,3-cyclobutanedithione **122b** with TBAF led to 4-isopropylidene-3,3-dimethyl-thietane-2-thione **124** in 85% yield (Equation 37) <2002HCA1644>.



Thermal reaction of 1,2,3-triazol derivative **125** at 130 °C led to an open-chain intermediate **126**, which with 2,2,4,4-tetramethyl-1,3-cyclobutanedithione **122b** gave the 1,3-thiazole derivative **127** and thietane **124** in 43% and 26% yield, respectively (Scheme 28) <2002HCA2644>.



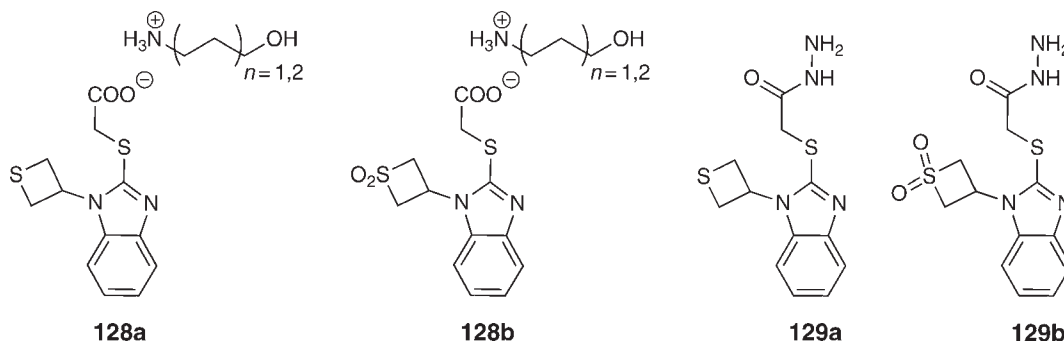
Scheme 28

2.07.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Although many effective methods for the synthesis of thietanes and thietes were reported, it is not easy to distinguish the general ones for the syntheses of particular classes of compounds. There are rather specific methods for synthesis of particular compounds. Many papers are reporting very efficient syntheses of thietanes and thietes by intramolecular cyclization of acyclic compounds and this methodology seems to be the most powerful and of the greatest scope. Syntheses performed by transformation of three-, four-, and five-membered rings are equally efficient and of general use. Intermolecular [2+2] cycloadditions are less popular than methods based on transformations of carbocyclic rings although they may be considered as efficient. However, these methodologies are more limited in scope than those mentioned above. [3+1] Cycloadditions are of the same value, but of special interest as this methodology was used for the preparation of thietanoses – thietane analogs of cyclic sugars.

2.07.12 Important Compounds and Applications

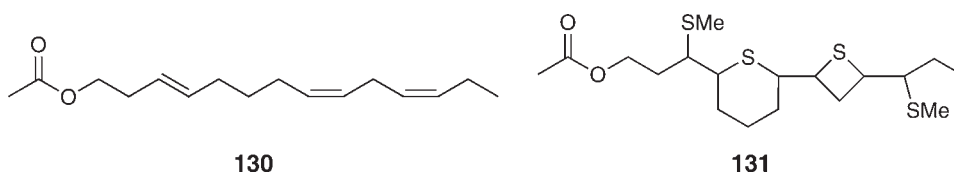
A series of benzimidazole-substituted thietanes **128a**, **128b** and **129a**, **129b** has been the subject of biological studies concerning their immunotropic value. Investigations demonstrated that these compounds are capable of producing both immunosuppressive and immunostimulating effects, so they may be promising as new immunotropic agents <2001PCJ11>.



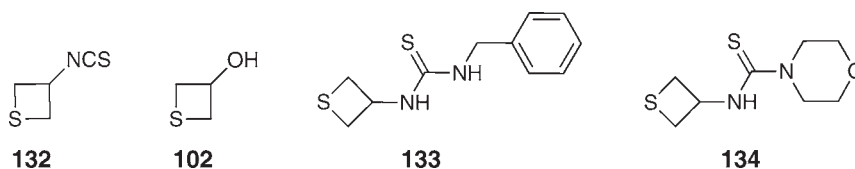
Thietanes, and especially 2-propylthietane, were tested as a rat repellent, as it is probably an odorant of carnivores' feces <2001JE1029, 1997JE2175>.

Thietanes are also useful as analytical tool for mass spectrometric determination of pheromone **130**. This type of pheromone may undergo derivatization with dimethyl disulfide to give the thietane derivative **131**, which undergoes

a distinct fragmentation during mass spectrometry enabling the determination of the exact pheromone structure <1996TL411>.



3-Substituted thietanes **102** and **132–134** are inhibitors of the cumene oxidation to cumyl hydroperoxide. These properties result from the termination of the radical oxidation chain process as well as from the catalysis of the hydroperoxide degradation <2001RJAC114>.



2.07.13 Further Developments

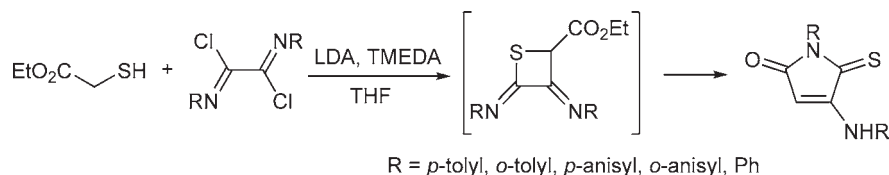
The attack of a nitrene on a thietane sulfur atom was described for the reaction of 2-substituted or 2,4-disubstituted thietanes with *N*-(*p*-tolylsulfonylimino)phenyliodinane. The reaction led to the formation of a series of substituted *N*-*p*-tolylsulfonyl-isothiazolines in fair yields and high regioselectivity <2006TL1109> (Table 13).

Table 13 Reaction of thietanes with *N*-(*p*-tolylsulfonylimino)phenyliodinane

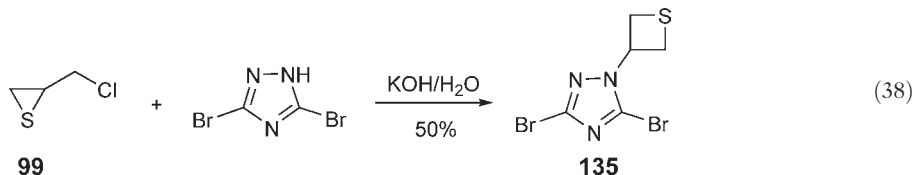
R^1	R^2	Yield (%)
<i>p</i> -Cl-C ₆ H ₄	H	67
Ph	H	63
<i>p</i> -F-C ₆ H ₄	H	60
<i>m</i> -Cl-C ₆ H ₄	H	56
<i>n</i> -C ₆ H ₁₃	H	54
<i>p</i> -Me-C ₆ H ₄	<i>p</i> -Cl-C ₆ H ₄	76
Ph	Ph	73
<i>p</i> -Cl-C ₆ H ₄	<i>p</i> -Cl-C ₆ H ₄	72
<i>m</i> -Cl-C ₆ H ₄	<i>m</i> -Cl-C ₆ H ₄	75

3,4-Diimino-thietane-2-carboxylic acid derivatives has been detected as an intermediate in synthesis of 4-amino-5-thioxo-1,5-dihydro-pyrrol-2-ones from ethyl mercaptoacetate and oxalodiimidoyl dichloride <2006JOC2332> (Scheme 29).

The synthesis of 3,5-dibromo-1-(thietan-3-yl)-1,2,4-triazole **135** was performed by the reaction of 2-chloromethylthiirane **99** with 3,5-dibromo-1,2,4-triazole yielding the product in 50% <2005RJO1847> (Equation 38).



Scheme 29



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Biographical Sketch



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Professor Jarosław Lewkowski was born in 1966 in Łódź (Poland). In 1990, he obtained his M.Sc. degree from the University of Łódź, Poland, studying the electrochemical oxidation of 5-hydroxymethylfurfural derivatives at the nickel oxide/hydroxide electrode. He then joined Professor Skowroński's group from the University of Łódź, Poland, cooperating simultaneously with Professor Descotes' team from the University of Lyon 1, France. In 1996, he obtained his Ph.D. degree from the University of Łódź, investigating the selective conversions of furfural, 5-hydroxymethylfurfural, and their derivatives.

He then joined Professor Vaultier's team from the University of Rennes 1 for his postdoctoral studies, where he worked on conversions of organophosphorus compounds in reactions with boron compounds.

After presenting his dissertation entitled 'Studies in the Field of Aminophosphonic and Aminophosphonous Derivatives of Furfural, Ferrocenecarbaldehyde and Terephthalic Aldehyde', he received his D.Sc. degree in 2005.

He is the author and co-author of over 40 papers (including book chapters). Now, he is an associated professor at the University of Łódź, Poland. His main areas of scientific interest are: the chemistry of furans, the chemistry of ferrocenes, as well as the chemistry of organophosphorus compounds. He is also interested in medicinal chemistry of anticancer drugs.

2.08

Thietanes and Thietes: Fused-ring Derivatives

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2.08.1 Introduction

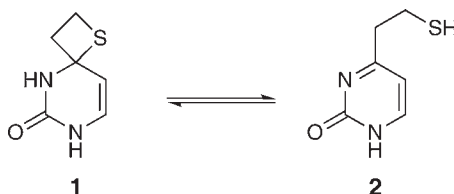
In CHEC(1984) and CHEC-II(1996) <1984CHEC(7)403, 1996CHEC-II(1b)803>, fused thietanes and thietes (including spiro-compounds) are described and these chapters cover all aspects of their chemistry and physicochemistry in the literature until 1995. In this chapter, we continue describing fused thietanes and thietes to cover the literature since 1996 until 2006.

Preparation of the chapter was based on a literature search through SCOPUS and the Beilstein Database, which identified 53 papers of value and which are discussed in this chapter. It is remarkable that so few papers appeared on fused thietanes and thietes during this period, and many of them are a continuation of previously published studies. To the best of our knowledge, only taxoids with fused thietane rings as well as mono- and disaccharides bearing fused thietane moieties constitute new classes of fused-ring thietanes and thietes.

The chapter is organized in 12 sections as in CHEC-II(1996). For some aspects of fused thietane and fused thiete chemistry, no new papers were published within the discussed period, so contents of subsections concerning these aspects are confined to a statement of this fact.

2.08.2 Theoretical Methods

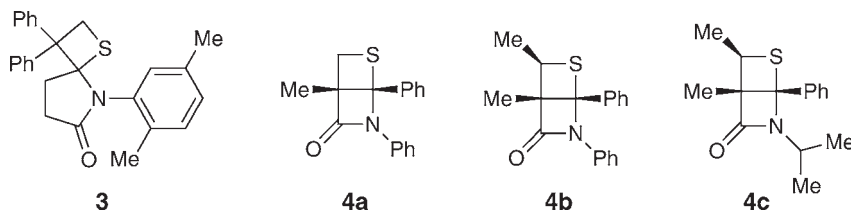
In CHEC-II(1996), Block and Wang discussed very extensively theoretical methods, which were applied to solve some problems of fused-thietane chemistry. They covered the literature until 1995. Since then, there has only been one paper describing the results of theoretical calculations concerning the equilibrium states of the thietane **1**. Liu and Taylor <1996JA3287> performed AM1 semi-empirical calculations on the equilibration of the thietane **1** and the thiol **2** and compared it to the analogous equilibrium between the oxetane and its ring-opened form. The authors demonstrated that the difference in the heat of formation between the forms **1** and **2** is relatively small ($\Delta H = -1.5 \text{ kcal mol}^{-1}$) in comparison to the oxetane and its ring-opened form ($\Delta H = -25.2 \text{ kcal mol}^{-1}$) <1996JA3287>. This phenomenon may be useful for characterizing mercapto bases and furthermore to map RNA tertiary structures.



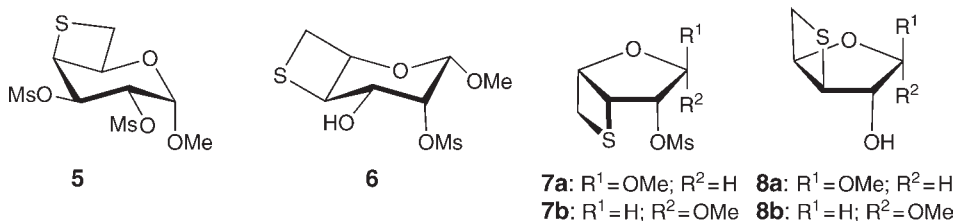
2.08.3 Experimental Structural Methods

2.08.3.1 X-Ray Diffraction

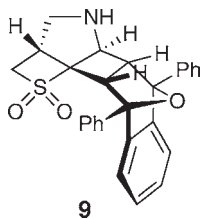
Several bond lengths and bond angles for various fused thietanes and thietes and their derivatives were determined by X-ray crystallography, microwave spectroscopy, and electron diffraction, and are presented in CHEC(1984) and CHEC-II(1996). Since 1995, the following structures have been published: 5-(2,5-dimethylphenyl)-3,3-diphenyl-1-thia-5-aza-spiro[3.4]octan-6-one **3** <2003CC2218>; (+)(1*S*,4*R*)-4-methyl-1,6-diphenyl-2-thia-6-azabicyclo[2.2.0]hexan-5-one **4a** <2001T6713>; 3,4-dimethyl-1,6-diphenyl-2-thia-6-azabicyclo[2.2.0]hexan-5-one **4b** <2001T6713>; 6-isopropyl-3,4-dimethyl-1-phenyl-2-thia-6-azabicyclo[2.2.0]hexan-5-one **4c** <2001T6713>.



Several structures of thietane-fused carbohydrates have been reported: methyl 2,3-di-*O*-mesyl-4,6-thioanhydro- α -D-galactopyranoside [(1*R*,3*S*,4*R*,5*R*,6*S*)-4,5-bis(methanesulfonyloxy)-3-methoxy-2-oxa-7-thiabicyclo[4.2.0]octane] **5** <2000CAR237>; methyl 2-*O*-mesyl-4,6-thioanhydro- α -D-gulopyranoside [(1*R*,3*S*,4*R*,5*S*,6*R*)-4-mesyloxy-3-methoxy-2-oxa-7-thiabicyclo[4.2.0]octan-5-ol] **6** <2000CAR237>. Both the α - and β -anomers of methyl 3,5-anhydro-2-*O*-mesyl-3-thio-L-xylofuranoside **7a** and **7b** and methyl 3,5-anhydro-3-thio-D-xylofuranoside **8a** and **8b** were also determined <2004CAR1787>. The β -anomer of the latter was oxidized to methyl 3,5-anhydro-3-thio- β -D-xylofuranoside *S*-dioxide. X-Ray structural analysis confirmed its structure, which shows a remarkably flat thietane ring with a folding angle of only 2°.



The *endo*-stereochemistry of highly strained multicyclic fused thietane *S*-dioxide **9** and the relative configuration of its seven contiguous stereogenic centers were ultimately revealed by X-ray crystallographic analysis <2004OL1313>.



2,6-Dithiaspiro[3.3]heptane and 2-thia-6-selenaspiro[3.3]heptane have been characterized by X-ray diffraction <2005IC77>. In the spirocyclic molecule 2,6-dithiaspiro[3.3]heptane, the central tetrahedral carbon atom angles range from 96.1° to 121.1°. The S–C distance average is 1.835 Å, the S···S separation range is 4.690 Å, and the C–S–C angle average is 76.65°. Corresponding values for 2-thia-6-selenaspiro[3.3]heptane averaged for the two mixed positions are 97.0–120.0°, 1.908 Å, 4.792 Å, and 74.12°, respectively. Additionally, a new coordination product, {[Cu(hfac)₂]₃·2(2-thia-6-selenaspiro[3.3]heptane)}, was analyzed by X-ray diffraction (hfac = hexafluoroacetylacetonate) <2005IC77>.

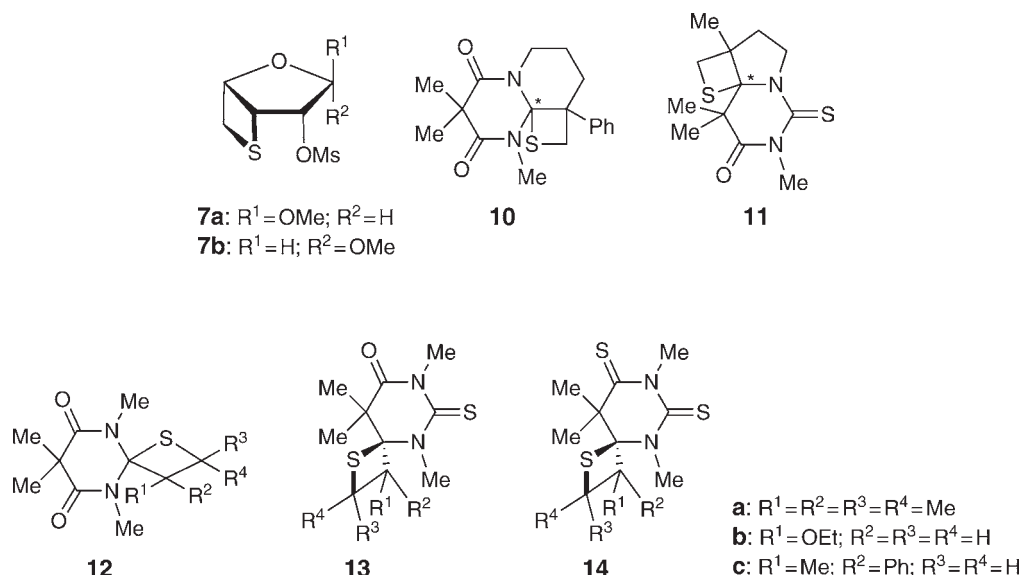
2.08.3.2 NMR Spectroscopy

2.08.3.2.1 Proton NMR spectroscopy

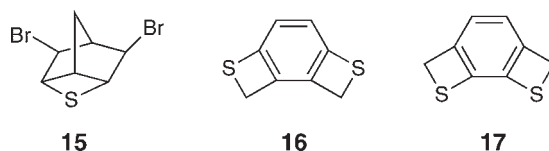
Detailed ¹H nuclear magnetic resonance (NMR) spectroscopic data on a variety of fused and spiro thietane and thiete derivatives were tabulated in sections of CHEC(1984) and CHEC-II(1996). Therefore, only limited, newer information is presented here. ¹H NMR spectra of methyl 2,3-di-*O*-mesyl-4,6-thioanhydro- α -D-galactopyranoside [(1*R*,3*S*,4*R*,5*R*,6*S*)-4,5-bis(methanesulfonyloxy)-3-methoxy-2-oxa-7-thiabicyclo[4.2.0]octane] **5** and methyl 2-*O*-mesyl-4,6-thioanhydro- α -D-gulopyranoside [(1*R*,3*S*,4*R*,5*S*,6*R*)-4-mesyloxy-3-methoxy-2-oxa-7-thiabicyclo[4.2.0]octan-5-ol] **6** have been reported <2000CAR237>, showing among other features, a proton–proton coupling ranging from 2.9 Hz (H(1)–H(2)) to 10.4 Hz (H(6)–H(6')) for the first one and 2.6 Hz (H(1)–H(2)) to 10.1 Hz (H(6)–H(6')) for the second. The chemical shifts have been assigned to all protons. The structure and configuration of **7a** and **7b**, the derivatives of 3,5-anhydro-3-thio- α -furanoside, were proved by analysis of their ¹H spectra <2004CAR1787>. In particular, the large proton–proton coupling constants $J_{4,5 \text{ } exo}$ 6.3/7.2 Hz as compared to $J_{4,5 \text{ } endo}$ 3.0/3.2 Hz, as well as the large coupling constants $J_{2,3}$ 8.0 Hz and $J_{3,4}$ 6.9 Hz, are in agreement with the approximately eclipsed arrangement of H-2, H-3, H-4, and H-5_{exo} in the *L-lyxo*-configuration.

The ¹H NMR and spectra of two tricyclic thietanes **10** and **11** have been reported <2003H(59)303>. In the ¹H NMR spectra of thietanes **10** and **11**, the signals due to methylene protons appeared at 2.96 and 3.71 ppm (each 1H, d, J = 9.7 Hz), and 2.71 and 3.06 ppm (each 1H, d, J = 9.0 Hz), respectively. The fact that a signal due to one of the methylene protons has been shifted downfield for **10** as compared to that of **11** has been explained by an

anisotropic effect of the benzene ring. ^1H NMR spectra of different derivatives of 5,7,7,9-tetramethyl-1-thia-5,9-diaza-spiro[3.5]nonane-6,8-dione **12**, 5,7,9,9-tetramethyl-6-thioxo-1-thia-5,7-diaza-spiro[3.5]nonan-8-one **13**, and 5,7,9,9-tetramethyl-1-thia-5,7-diaza-spiro[3.5]nonan-6,8-dithione **14** have been reported <1997CPB1>. On the basis of these spectra the structures of **12a-c**, **13a-c**, and **14a-c** have been confirmed. The conformations of thietane isomers **13b** and **14b** were assigned from the results of nuclear Overhauser effect (NOE) experiments.



The ^1H NMR spectrum of 2,6-dibromo-8-thiatricyclo[2.2.1.2^{3,5}]heptane **15** has been reported <1996RCB2393, 2000RJO794>. The chemical shifts in the ^1H NMR spectrum have been assigned to all protons of **15**. ^1H NMR spectra of angular benzobisthietes 4,9-dithia-tricyclo[6.2.0.0^{2,5}]deca-1(8),2(5),6-triene **16** and 3,10-dithia-tricyclo[6.2.0.0^{2,5}]deca-1,5,7-triene **17** were recorded <1998TL9639>. The chemical shifts for both isomers are similar. For example, the singlets at 4.16 and 4.27 ppm for **16** and **17**, respectively, correspond to four CH_2 protons.



The following complexes were studied using NMR spectroscopy: $[\text{W}(\text{CO})_5\text{L}^1]$, $[\{\text{W}(\text{CO})_5\}_2\text{L}^1]$, $[\text{W}(\text{CO})_5\text{L}^2]$, and $[\text{W}(\text{CO})_5\text{L}^3]$, where $\text{L}^1 = 2,6\text{-dithiaspiro}[3.3]\text{heptane}$ (2,6-DTSH), $\text{L}^2 = 2,6\text{-DTSH-2-oxide}$, and $\text{L}^3 = 2,6\text{-DTSH-2,2'-dioxide}$ <1999POL1345>. In solution, these complexes exhibit pyramidal inversion of the metal-coordinated sulfur atom(s). The rates and activation energies were evaluated by total NMR band shape analysis. The $\text{W}(\text{CO})_5$ complexes were studied in detail by variable-temperature ^1H NMR and their chemical shift and scalar coupling constant data. In all cases, the spectra showed gross changes on cooling the solutions as a result of slowing down of the pyramidal inversion of W-coordinated sulfur atoms. Inversions were rapid on the ^1H NMR timescale at room temperature but became slow by ca. -60 to -80°C . For example, in the case of $[\text{W}(\text{CO})_5(2,6\text{-DTSH})]$, the room temperature spectrum consists of two singlets due to the methylene protons of each four-membered ring. On cooling, the higher-frequency signal, due to the methylenes of the metal-bound sulfur ring, splits into an apparent AB quartet, whereas the lower-frequency signals, due to the methylenes of the other ring, split into two singlets. The splitting of signals on cooling was followed by band shape analysis and reliable rate data were obtained. The analogous studies were carried out for the other complexes mentioned above <1999POL1345>.

2.08.3.2.2 Heteronuclear NMR spectroscopy

The structures and configurations of anomers **7a** and **7b**, the derivatives of 3,5-anhydro-3-thio- α -furanoside, were proved by analysis of their ^{13}C NMR spectra <2004CAR1787>. The ^{13}C chemical shifts for C-3 (43.9 and 43.2 ppm) of **7a** and **7b** are characteristic of an annellated thietane, whereas the ^{13}C chemical shifts for C-2 (82.1 and 76.3 ppm,

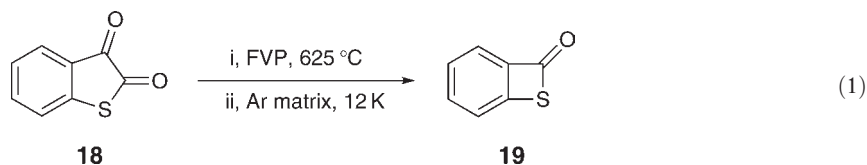
respectively) are in agreement with oxygen-substituted carbon centers. The ^{13}C NMR spectra of two tricyclic thietanes **10** and **11** have been reported <2003H(59)303>. The position of a thiocarbonyl group reacting with a carbon–carbon double bond moiety was confirmed by comparison of their ^{13}C NMR spectra. For compound **10**, the signal due to a quaternary carbon atom ($^{\circ}$) adjacent to two nitrogens and a sulfur atom appeared at 88.4 ppm, whereas the corresponding signal of **11** appeared upfield at 80.7 ppm in comparison with that of **10**. ^{13}C NMR spectra of different derivatives of 5,7,7,9-tetramethyl-1-thia-5,9-diaza-spiro[3.5]nonane-6,8-dione **12**, 5,7,9,9-tetramethyl-6-thioxo-1-thia-5,7-diaza-spiro[3.5]nonan-8-one **13**, and 5,7,9,9-tetramethyl-1-thia-5,7-diaza-spiro[3.5]nonan-6,8-dithione **14** have been reported <1997CPB1>. On the basis of these spectra, the structures of compounds **12a–c**, **13a–c**, and **14a–c** were confirmed. For **12a**, a signal due to a quaternary carbon atom adjacent to two nitrogen atoms and a sulfur atom appeared at 87.9 ppm, whereas the corresponding signals of **13a** and **14a** appeared at 79.8–80.0 ppm, at a higher field (by about 8 ppm) in comparison with that of **12a**. Similarly, the signals due to the quaternary carbon atoms of 4-thietanes **13b** and **13c** and **14b** and **14c** at 83.4–85.9 ppm showed a similar upfield shift of those at 92.6–92.7 ppm for 2-thietanes **12b** and **12c**. ^{13}C NMR spectra of angular benzobisthietes 4,9-dithia-tricyclo[6.2.0.0^{2,5}]deca-1(8),2(5),6-triene **16** and 3,10-dithia-tricyclo[6.2.0.0^{2,5}]deca-1,5,7-triene **17** have been recorded <1998TL9639>. The bisthiete **16** exhibits signals at 34.7 (CH_2), 121.5 (CH), 137.9, and 133.3 ppm, whereas bisthiete **17** exhibits the analogous signals at 37.8 (CH_2), 119.1 (CH), 139.8, and 133.1 ppm.

2.08.3.3 Mass Spectrometry

The mass spectral fragmentation patterns of a variety of fused and spiro thietanes and thietes were presented in CHEC(1984) and CHEC-II(1996). Only more recent data are included here. The mass spectrometry (MS) spectra of thietanes **10** and **11** show molecular ion peaks at m/z 330 and 270, respectively, corresponding to the molecular weights of thiobarbiturates used for their preparation by photolysis in acetonitrile <2003H(59)303>. The structures of different derivatives (substituted in the thietane ring by CH_3 , Ph, or OC_2H_5 groups) of 5,7,7,9-tetramethyl-1-thia-5,9-diaza-spiro[3.5]nonane-6,8-dione **12**, 5,7,9,9-tetramethyl-6-thioxo-1-thia-5,7-diaza-spiro[3.5]nonan-8-one **13**, and 5,7,9,9-tetramethyl-1-thia-5,7-diaza-spiro[3.5]nonan-6,8-dithione **14** were determined on the basis of their mass spectra <1997CPB1>. Their mass spectra showed molecular ion peaks (M^+) consistent with alkanes and thiobarbiturates used for their preparation and present as impurities.

2.08.3.4 IR Spectroscopy

Since the publication of Block's review on fused-ring thietanes and thietes in CHEC-II(1996), only one paper has been published dealing with some infrared (IR) studies on fused-ring thietanes. Jørgensen *et al.* <1997J(P2)173> reported the flash vacuum pyrolysis (FVP) reaction of benzothiophene-2,3-dione **18**. Flash vacuum thermolysis of **18** at 625 °C caused the formation of benzothietanone **19**, which has been isolated in an argon matrix at 12 K (Equation 1). The IR spectrum of the benzothietanone **19** has been recorded showing bands at 1857, 1826, 1806, 1436, 1418, 1269, 1045, and 813 cm^{-1} . The authors <1997J(P2)173> compared this spectrum with the IR spectrum of the starting benzothiophenedione **18** and the IR data confirmed the structure of the benzothietanone **19**.



2.08.4 Thermodynamic Aspects

Since the publication of the CHEC-II(1996), there have been no new important reports on thermodynamic aspects of fused and spiro thietanes and thietes.

2.08.5 Reactivity of Fully Conjugated Rings

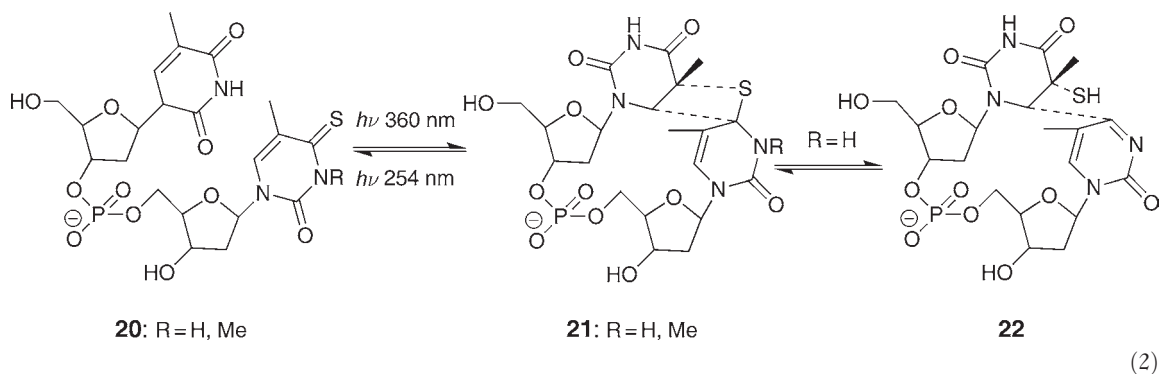
Since the publication of the CHEC-II(1996), there have been no new reports on the reactivity of fully conjugated fused and spiro thietanes and thietes.

2.08.6 Reactivity of Nonconjugated Rings

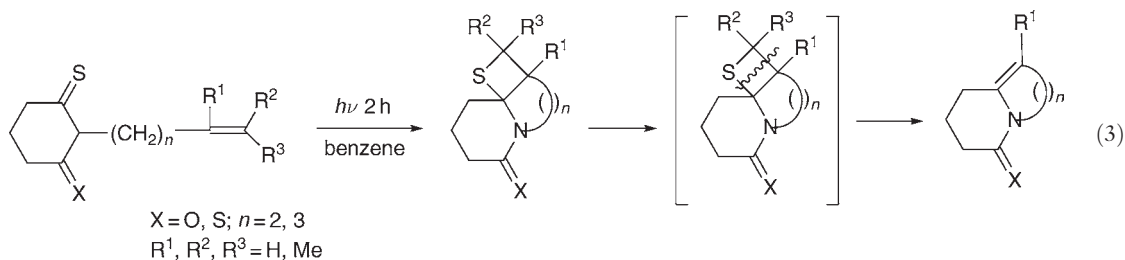
2.08.6.1 Unimolecular Thermal and Photochemical Reactions

2.08.6.1.1 Fragmentations and eliminations

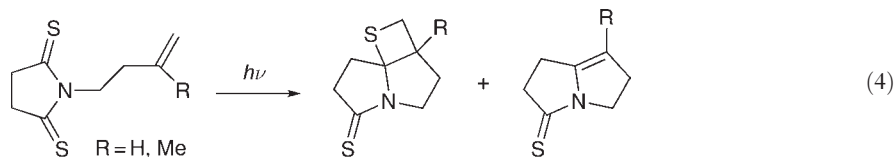
Retro [2+2] ring opening of 2*H*-benzo[*b*]thiete under thermal or photochemical conditions leading to an *ortho*-thiobenzoquinone methide was reported in CHEC-II(1996). Since then, three isomeric naphthothietes – 2*H*-naphtho[1,2-*b*]thiete, 1*H*-2-naphtho[2,1-*b*]thiete, and 2*H*-1-naphtho[2,3-*b*]thiete – provide have been described by Meier <1996S327, 1998JHC1505>. Irradiation of thymidyl(3'-5')-thiothymidine **20** leads to two main products **21** and **22** (Equation 2) <1996CHEC-II(1b)803>. It was reported that short-wavelength irradiation (254 nm) of a neutral solution containing an interconverting mixture of thietane **21** and its open form **22** quantitatively restored **20** (Equation 2) <1996CC2203, 1996JA3287, 1998JPH109>.



The photolysis of *N*-(3- or 4-alkenyl)mono- or di-thioglutarimides seems to proceed in several steps involving initial intramolecular thietane formation between thiocarbonyl and *N*-substituted alkene. Photochemical cleavage of both C–S and C–C bonds of a thietane resulted in the formation of the corresponding indolizines or quinolizines (Equation 3) <2000H(53)2781>.

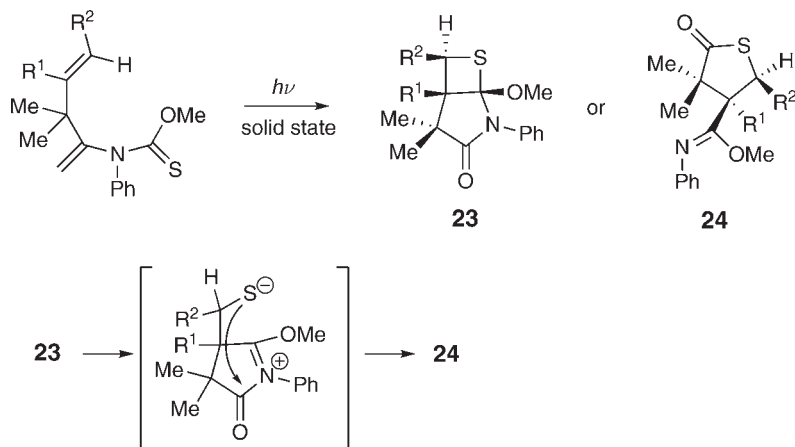


Similarly, the formation of the fission products of the thietane ring was observed as by-products upon irradiation of *N*-(3-alkenyl)-pyrrolidine-2,5-dithione (Equation 4) <2001OL1781, 2004JOC33>.



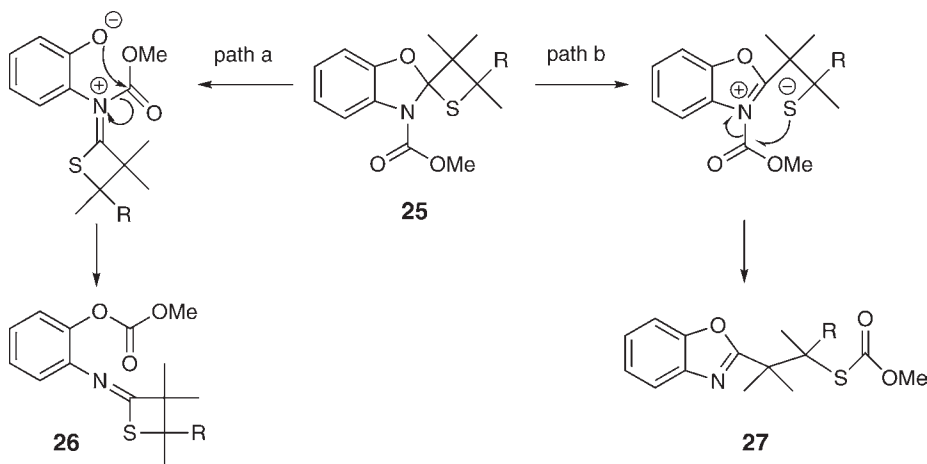
2.08.6.1.2 Rearrangements

The solid-state photoreaction of *O*-methyl *N*-(β,γ -unsaturated carbonyl)-*N*-phenylthiocarbamate resulted in intramolecular [2+2]-thietane **23** formation, followed by rearrangement to γ -thiolactone **24** (Scheme 1) <1998CC2315>.



Scheme 1

Stable spirocyclic aminothietanes **25** ($R = \text{Me}$ or H), obtained by photocycloaddition *N*-alkoxy- and *N*-aryloxycarbonylbenzoxazole-2-thiones with alkenes upon reflux in toluene, were transformed into iminothietanes **26** (path a) and/or 2-substituted benzoxazole **27** (path b) (Scheme 2) <1999J(P1)1151, 2002HCA2383>.



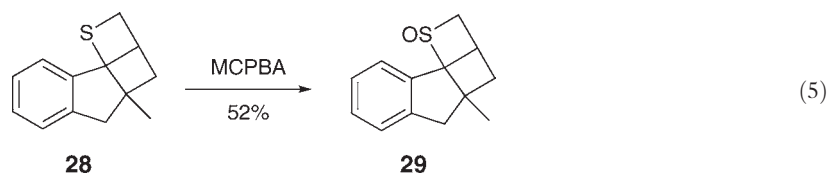
Scheme 2

Analogue rearrangement products, from indoline-2-thiones or *N*-acylbenzoxazole-2-thiones and alkenes, were also described. However, in these cases, the initially formed spirocyclic aminothietanes were unstable and could not be isolated <1997HCA388, 1998J(P1)1007, 2000J(P1)3039, 2003H(59)399>.

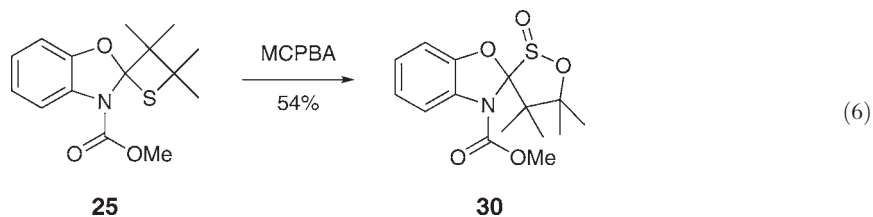
2.08.6.2 Electrophilic Attack

2.08.6.2.1 At sulfur

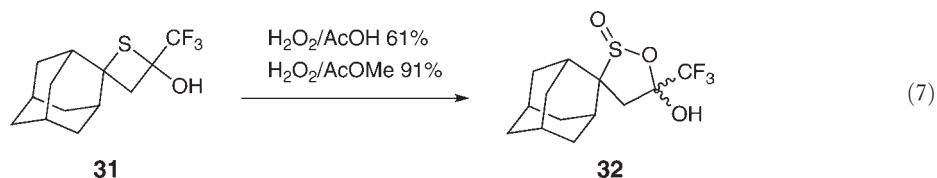
A multifused thietane **28** was oxidized with an equimolar amount of *m*-chloroperbenzoic acid (MCPBA) to the sulfoxide **29** in 52% yield (Equation 5) <1996LA117>.



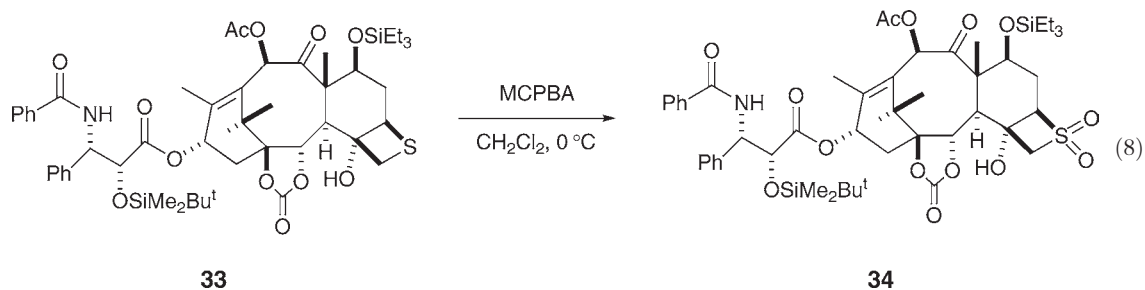
Methyl 3,5-anhydro-3-thio- β -D-xylofuranoside was oxidized with hydrogen peroxide to a mixture of the *endo*-sulfoxide, the *exo*-sulfoxide and the sulfone. Only the methyl 3,5-anhydro-3-thio- β -D-xylofuranoside *S,S*-dioxide could be isolated from the mixture by column chromatography in the pure crystalline form in 34% yield [\[CAR1787\]](#). Treatment of spirocyclic thietane **25** (R=Me) with 2 equiv of *m*-chloroperbenzoic acid (MCPBA) yielded the sultine **30** in 54% yield (Equation 6) [\[J991151, HCA2383\]](#).



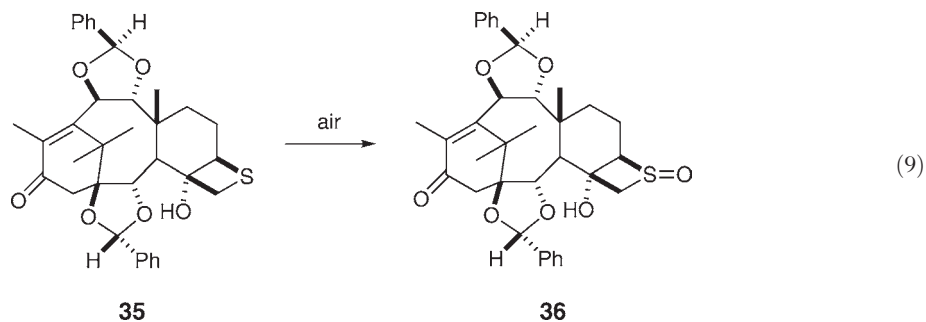
The oxidation of 4'-(trifluoromethyl)spiro[adamantine-2,2'-thietan]-4'-ol **31** by hydrogen peroxide afforded sulfone **32** (Equation 7) [<1996JOC1986>](#).



The paclitaxel (Taxol) analogue **33** in which the D-ring is modified by sulfur has been oxidized with MCPBA to the *S,S*-dioxide **34** in 61% yield (Equation 8) [<1999JOC2694>](#).

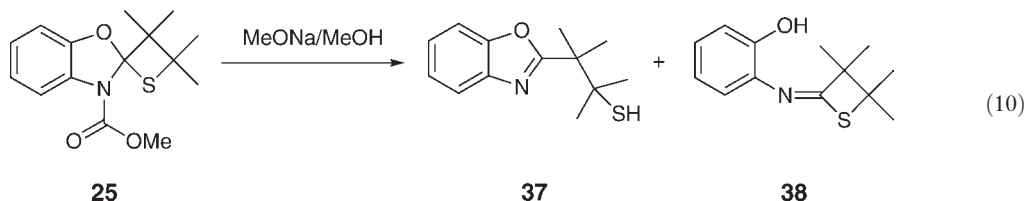


Compound **35** in methanol solution is spontaneously oxidized by air to the sulfoxide **36** (Equation 9) [<2000TL4891>](#).



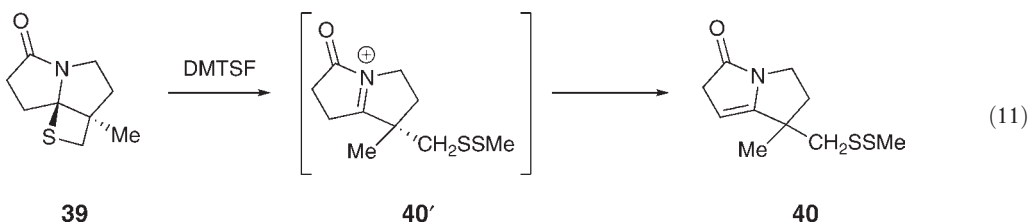
2.08.6.3 Nucleophilic Attack at Heterocyclic Carbon Atoms

The spirocyclic aminothietane **25** was treated with MeONa in MeOH to yield 2-substituted benzoxazole **37** and iminothietane **38** in 23% yield each (Equation 10) <2002HCA2383>.



2.08.6.4 Nucleophilic Attack at the Sulfur Atom

The ring-opening reaction on 4-methyl-2-thia-7-aza-tricyclo[5.3.0.0^{1,4}]decan-8-one **39** was carried out by treatment with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) <2001OL1781, 2004JOC33>. Methylthiolation of the thietane sulfur produces a transient alkylthiosulfonium salt which easily dissociates to the *N*-acyliminium ion **40'**. Once formed, **40'** readily undergoes loss of a proton to give the product **40** (Equation 11).



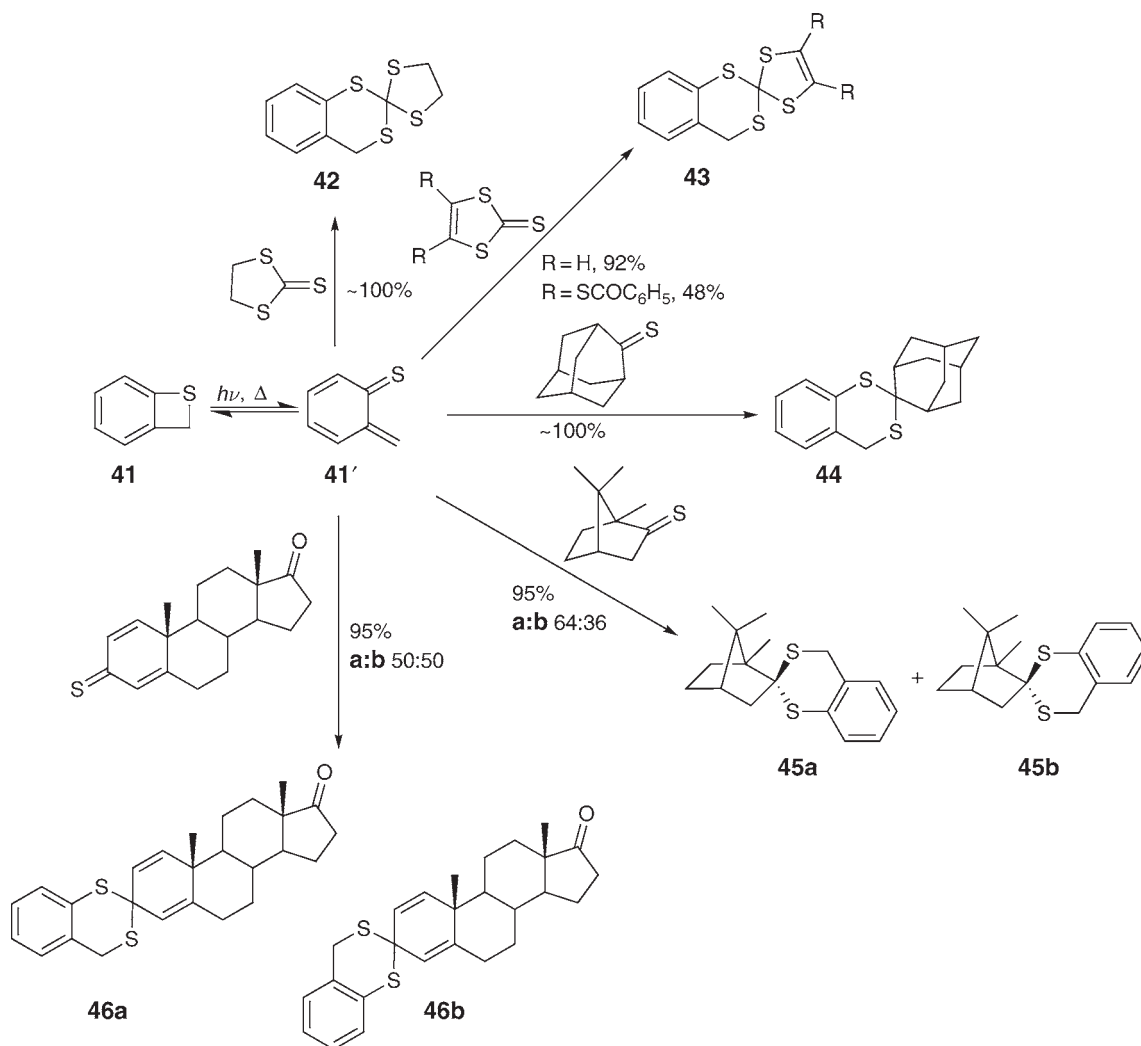
2.08.6.5 Reactions with Cyclic Transition States, Formally Involving a Second Species

2*H*-Benzo[*b*]thiete **41** reacts in the *ortho*-quinoid isomer **41'** with cyclic trithiocarbonates such as 1,3-dithiolane-2-thione, (ethylene trithiocarbonate), 1,3-dithiole-2-thiones, and adamantanethione <1997LA1603>. In boiling toluene, 1,3 dithiolane and dithiole derivatives formed the spiro compound **42** and **43** in good yield. The related 1,3-dithiole-2-thiones reacted chemoselectively at the C=S double bond. The use of adamantanethione yielded the polycyclic adduct **44** in a smooth and quantitative reaction (Scheme 3).

By considering the symmetry plane in dienophiles that contain a C=S double bond, the attack of **41'** could occur with equal probability from both sides. On the other hand (1*R*)-(-)-thiocamphor and the cross-conjugated 3-thioxosteroid have diastereotopic π -faces, but the reaction was stereoselective only in case of formation of isomers **45**. Attack preferentially occurred on the *endo*-side. The lack of diastereoselectivity in the formation of isomers **46** is probably due to the long distance between the reactive center and the 18-Me group <1997LA1603>. A variety of dienophiles and heterodienophiles reacting with **41'** were investigated. Thus, heterodiene **41'**, generated *in situ* from 2-oxo-4*H*-3,1-benzoxathiin in boiling xylene, reacts with dimethyl fumarate to afford the *trans*-dimethyl 2*H*-3,4-dihydro-1-benzothiopyran-2,3-dicarboxylate with ester groups in pseudo-equatorial positions (Scheme 4) <1996S327>. The reactions of 2*H*-benzo[*b*]thiete **41** with conjugated dienes in boiling toluene provided benzo-condensed six-membered ring systems with sulfur atoms and possibly further heteroatoms (Scheme 4) <1996JHC1727>. However, diphenylisobenzofuran reacted differently in comparison to other dienes, and it gave the oxygen-bridged dibenzothiocin (Scheme 4) <1996JHC1727>.

The reactivity of the benzo analogue of compound **41**, that is, 2*H*-naphtho[1,2-*b*]thiete **47**, has also been studied. Cycloaddition reactions with dienophiles or heterodienophiles performed in boiling toluene yielded naphtho-condensed sulfur heterocycles (Scheme 5) <1998JHC1505>.

Three isomers – 2*H*-naphtho[1,2-*b*]thiete **47**, 1*H*-2-naphtho[2,1-*b*]thiete **48**, and 2*H*-1-naphtho[2,3-*b*]thiete **49** – obtained *in situ* from 3-oxo-4*H*-3,1-naphtho[1,2-*d*]oxathiin, 3-oxo-1*H*-4,2-naphtho[2,1-*d*]oxathiin, and 2-oxo-4*H*-3,1-naphtho[2,3-*d*]oxathiin, respectively, were subjected to reaction with dimethyl or diethyl fumarate. Refluxing a solution of the corresponding precursors in toluene (for **49** in diethyl fumarate at 200 °C) in the presence of



Scheme 3

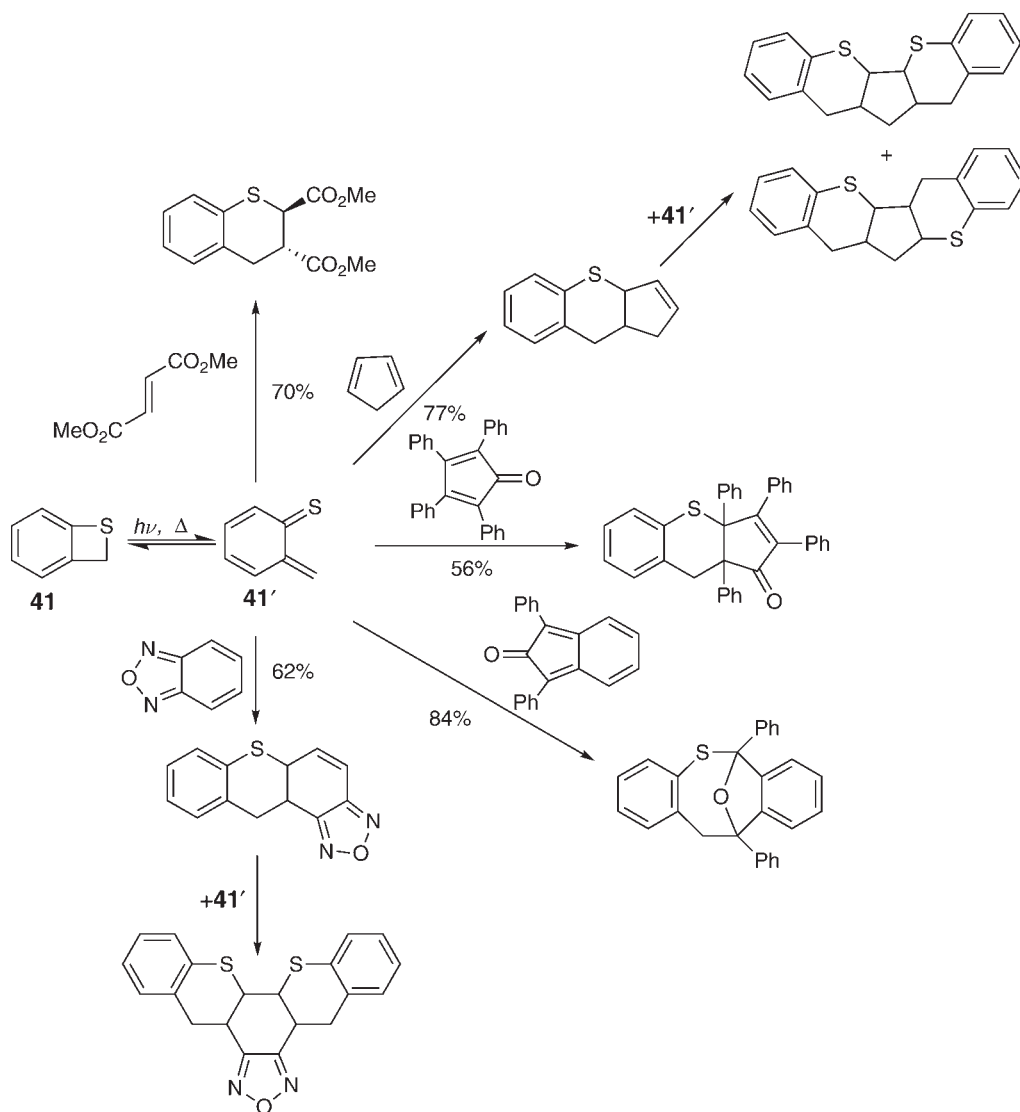
1 equiv of fumarate diester affords the corresponding *trans*-dimethyl 2*H*-3,4-dihydronaphtho[1,2-*b*]thiopyran-2,3-dicarboxylate, *trans*-dimethyl 1*H*-2,3-dihydronaphtho[2,1-*b*]thiopyran-2,3-dicarboxylate, and *trans*-diethyl 2*H*-3,4-dihydronaphtho[2,3-*b*]thiopyran-2,3-dicarboxylate, respectively (Scheme 6) <1996S327>.

The ability of the benzobisthietes **50** and **51** to form ring enlargement products by Diels–Alder reactions was investigated with dimethyl fumarate. In competition to oligomerization processes of **50** and **51** the bis-adducts **52** and **53** were formed in boiling toluene. The consecutive $[8\pi+2\pi]$ cycloaddition reactions of the opened thiete rings furnish stereoselectively thiopyran rings with *trans*-standing ester groups (Scheme 7) <1998TL9639>.

The reactions of benzobisthiete **50** and its isomer **54** with 1,4-dihydro-1,4-epoxynaphthalene derivatives were applied to the synthesis of linear or bent ribbons (Scheme 8) <1998TL9639, 1997LA1173>.

2.08.6.6 Reaction with Metals and Metal Complexes

2-Thia-6-selenaspiro[3,3]heptane with Cu(hfac)₂ provided a new coordination product, [Cu(hfac)₂]₃2SeSC₅H₈. This complex statistically mixes positions of the donor sulfur and selenium atoms to give an average axial Cu⋯S/Se contact at 2.892 Å <2005IC77>. The following complexes were synthesized: [W(CO)₅L¹], [{W(CO)₅]₂L¹],

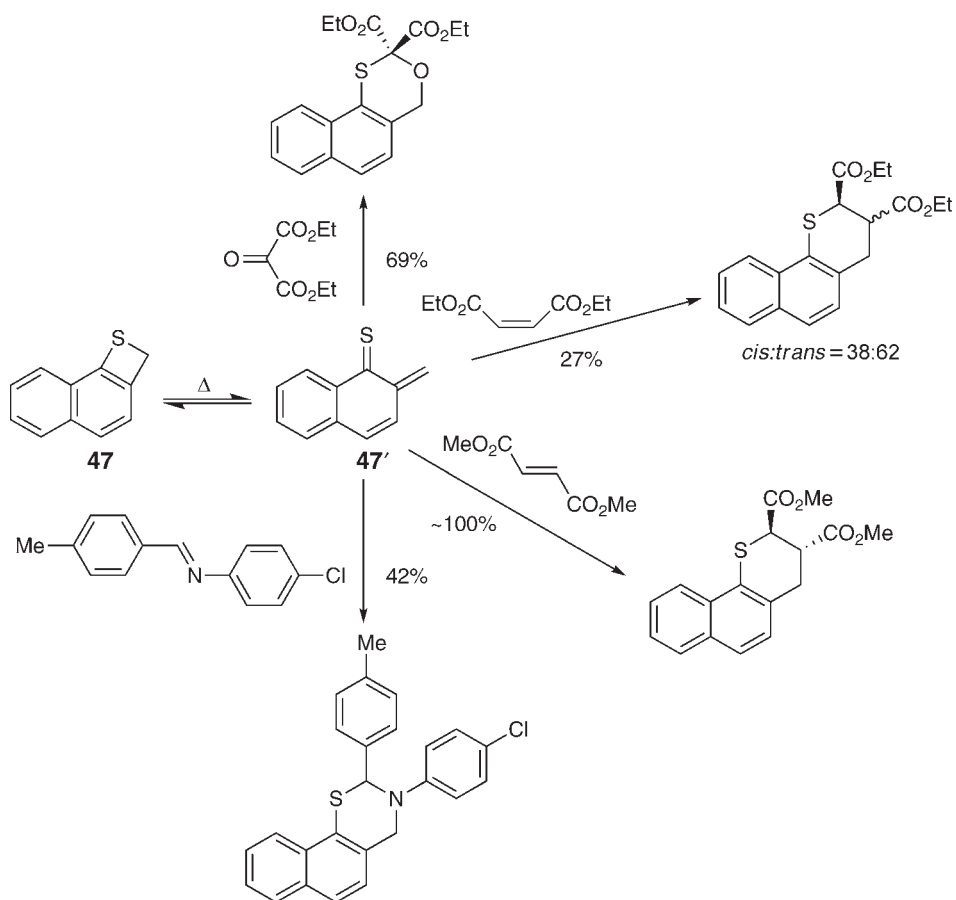


Scheme 4

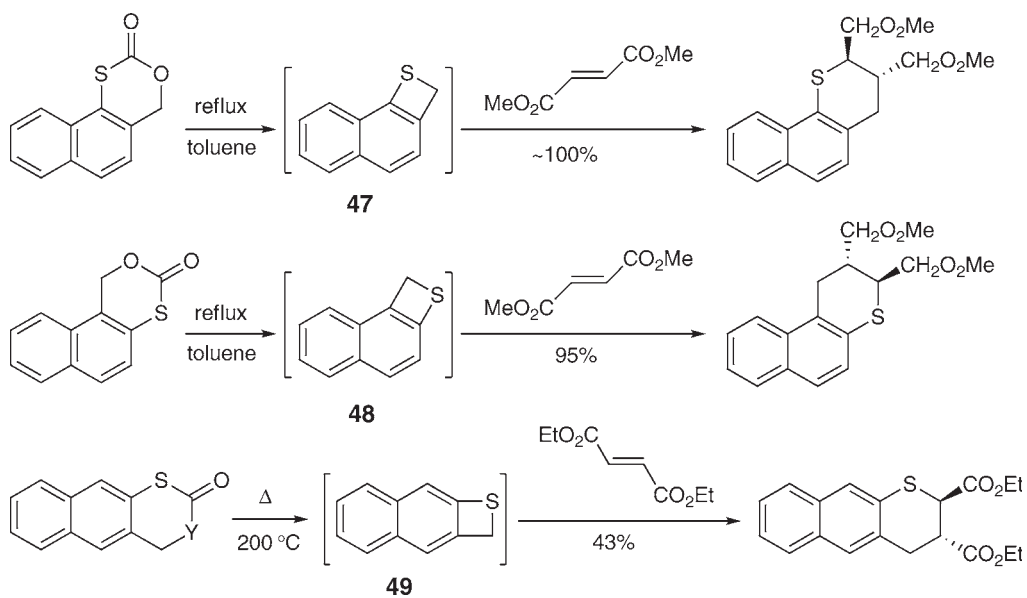
$[\text{W}(\text{CO})_5\text{L}^2]$, $[\text{W}(\text{CO})_5\text{L}^3]$, $[\{\text{PdCl}_2(\text{PPh}_3)_2\}\text{L}^1]$, $[\text{PdCl}_2(\text{PPh}_3)\text{L}^2]$, and $[\text{PdCl}_2(\text{PPh}_3)\text{L}^3]$, where $\text{L}^1 = 2,6\text{-DTSH}$, $\text{L}^2 = 2,6\text{-DTSH-2-oxide}$, and $\text{L}^3 = 2,6\text{-DTSH-2,2'-dioxide}$ <1999POL1345>. In solution, these complexes exhibit pyramidal inversion of the metal-coordinated sulfur atom.

2.08.7 Reactivity of Substituents Attached to Ring Carbon Atoms

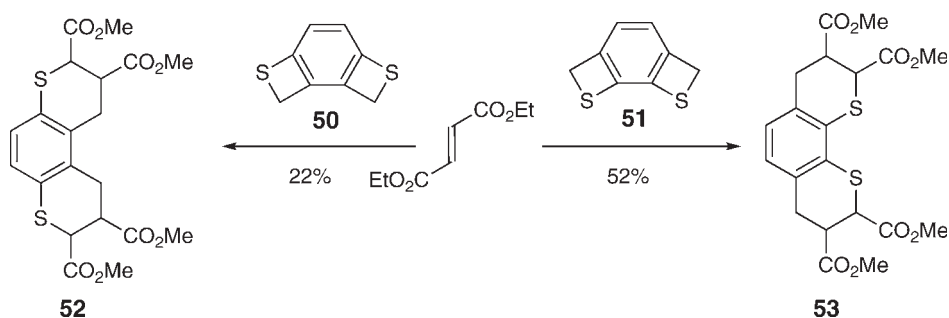
The reactivity of substituents attached to ring carbon atoms is of much interest, mainly when it concerns complex fused-ring thietanes linked to naturally occurring compounds. The representative example of such a case is conversion of the thymine–thietane derivative **55** to its flavin derivative **56** in the presence of 1-hydroxybenzotriazole (HOBt) and 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (Equation 12) <2005OBC1937>.



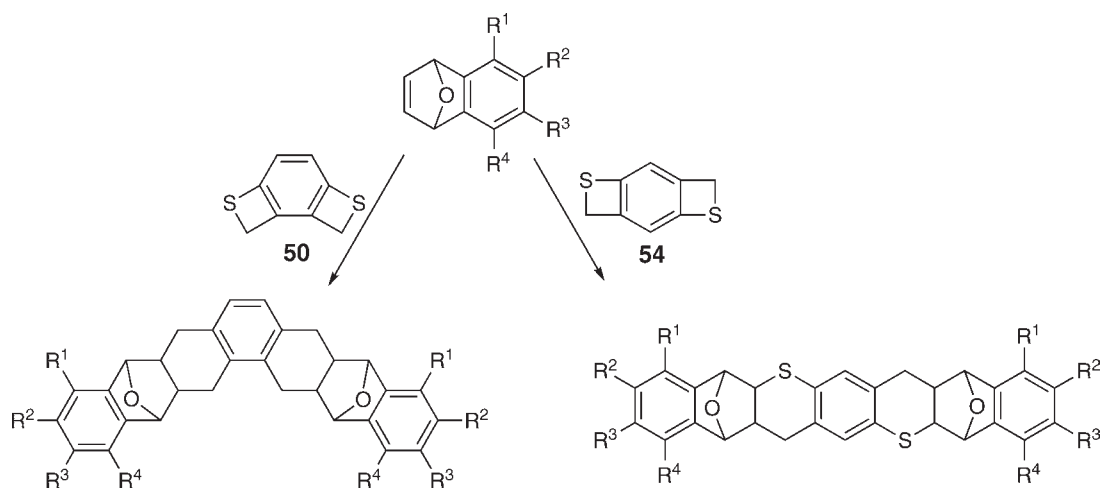
Scheme 5



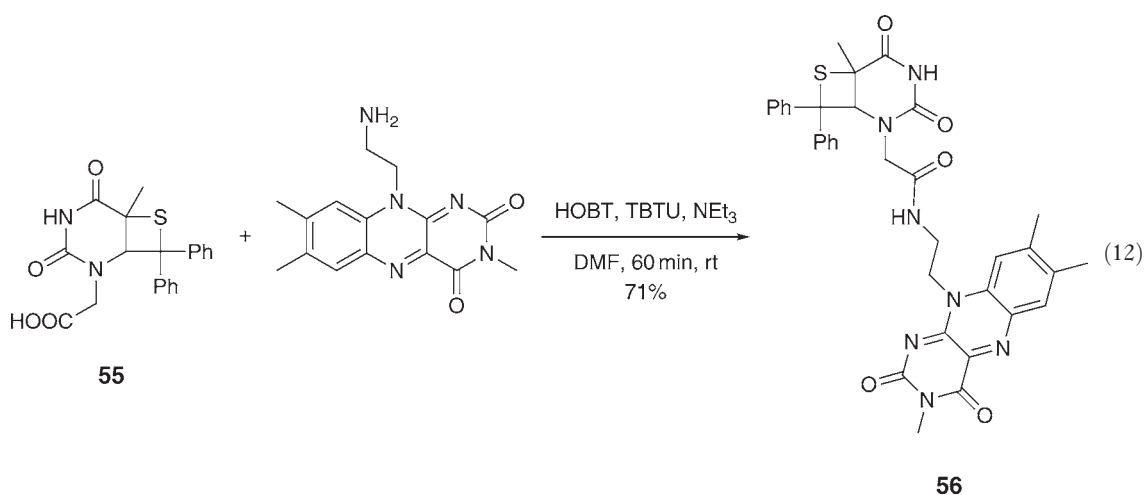
Scheme 6



Scheme 7

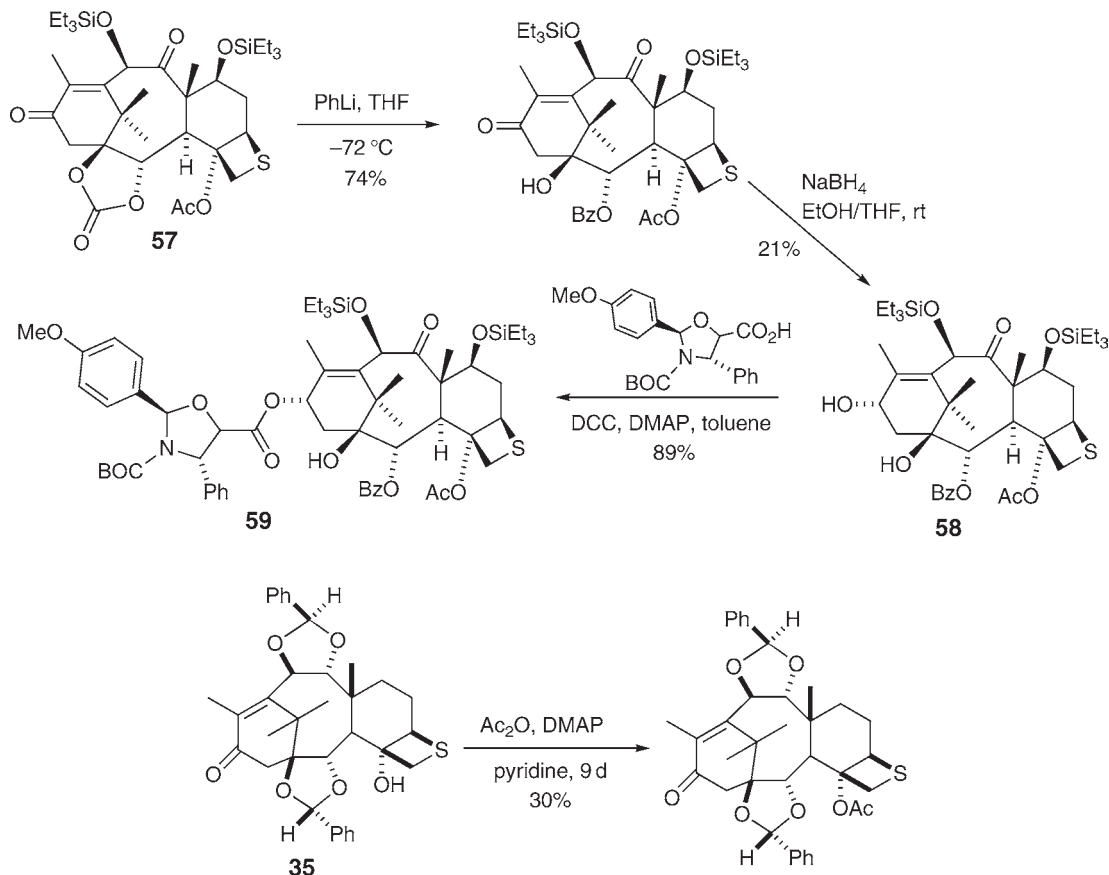


Scheme 8



Interesting conversions of thietane taxol derivatives have also been studied and discussed [\[1999JOC2694, 2001JOC5058, 2000TL4891\]](#) and may be considered as transformations of the thietane ring substituents. The protected derivative **57** has undergone benzylation and subsequently has been reduced to give compound **58**,

which has then been condensed with the 2-(4-methoxyphenyl)-1,3-oxazolidine derivative of *N*-BOC-phenylisoserine to afford the sophisticated taxoid compound **59** (Scheme 9) <2001JOC5058>. A hydroxyl group attached to a thietane ring in taxoid compound **35** has been acetylated with an Ac₂O–DMAP acylating system in pyridine in 30% yield (DMAP = 4-dimethylaminopyridine; Scheme 9) <2000TL4891>.



Scheme 9

In order to confirm the structure of the tricyclic thietane **60**, it underwent several reactions <2004OL1313>, which were performed on the substituent of the ring carbon atom. The thietane **60** underwent hydrogenation on palladium-on-charcoal to give the fully saturated compound **61**. The presence of a double bond in compound **60** was also confirmed by [4+2] Diels–Alder cycloaddition of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate as well as of diphenylisobenzofuran, which led to the formation of cycloadducts **62** and **63**, respectively (Scheme 10) <2004OL1313>.

2.08.8 Reactivity of Substituent Attached to Ring Heteroatoms

Since the publication of the CHEC-II(1996), there have been no new reports on the reactivity of substituent attached to fused thietane and thiete rings.

2.08.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

2.08.9.1 Ring Syntheses from Acyclic Precursors of Same Number of Carbons

Padwa *et al.* <2004JOC33, 2001OL1781> established a method for the synthesis of complex fused-ring thietanes by the intramolecular [2+2] photochemical cyclization of thiosuccinimide and dithiosuccinimide derivatives. In the



(13)

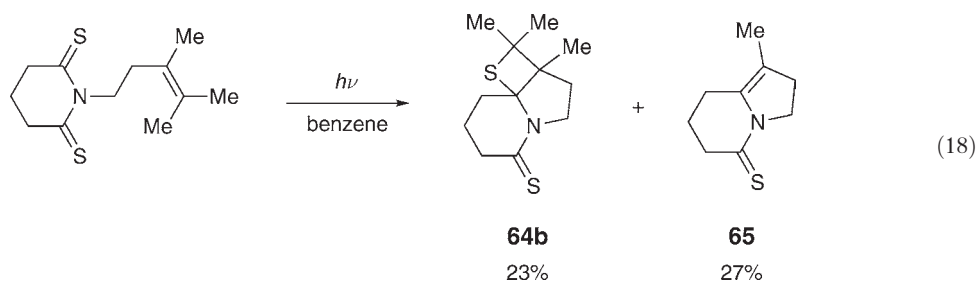
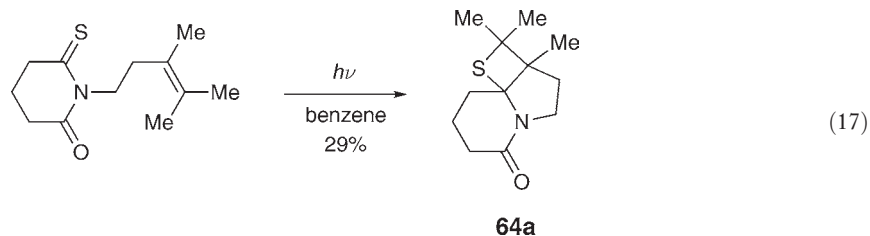
(14)

(15)

R = H 43% 19%
 R = Me 72% 10%

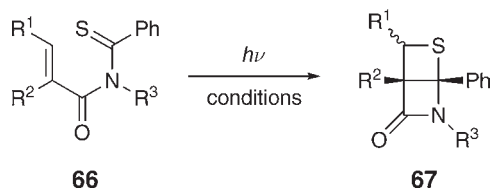
(16)

A similar synthesis of tricyclic fused-ring thietanes by photochemical cyclization of N-substituted mono- and dithioglutarimides has been reported (Equations 17 and 18) <2000H(53)2781>. The carbonyl compound **64a** and thiocarbonyl derivatives **65** were obtained in moderate yields. An analogous route was used for thiosuccinimides, where the use of a dithioglutarimide derivative resulted in the formation of a bicyclic side product **65**.



Photochemical cyclization of the but-2-enoic acid thioacetyl amide **66** derivatives to the bicyclic thietane **67** has been reported (Table 1) <2001T6713>. The reactions were carried out either in solution or in solid state. The yields of the reactions performed in the solid state were higher.

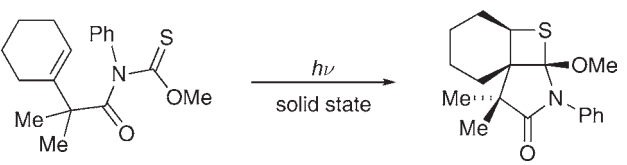
Table 1 Synthesis of 1-phenyl-2-thia-6-aza-bicyclo[2.2.0]hexane derivatives



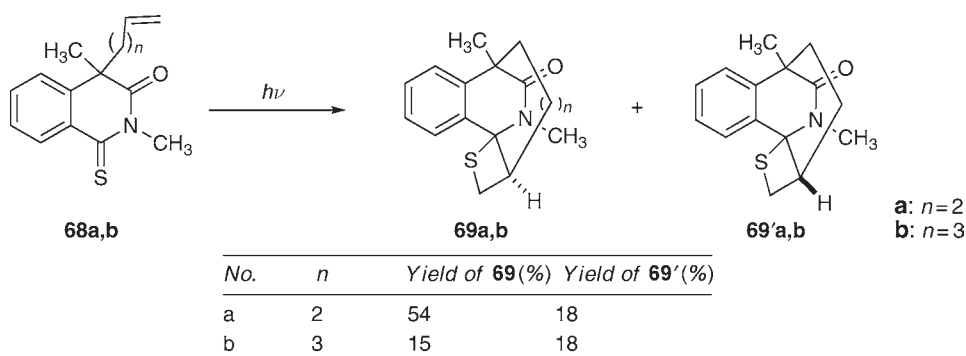
R^1	R^2	R^3	Conditions	Yield (%)
H	Me	Ph	Benzene, 15 °C	77
H	Me	Ph	Solid, 0 °C	75
H	Me	<i>i</i> -Pr	Benzene, 15 °C	73
H	Me	<i>i</i> -Pr	Solid, 0 °C	93
Me	Me	Ph	Benzene, 15 °C	80
Me	Me	Ph	Solid, 0 °C	92
Me	Me	<i>i</i> -Pr	Benzene, 15 °C	80
Me	Me	<i>i</i> -Pr	Solid, 0 °C	95

It has been reported <1998CC2315> that a similar [2+2] intramolecular cyclization of (2-cyclohex-1-enyl-2-methyl-propionyl)phenyl-thiocarbamic acid *O*-methyl ester leads to the formation of tricyclic thietane in 85% yield (Table 2).

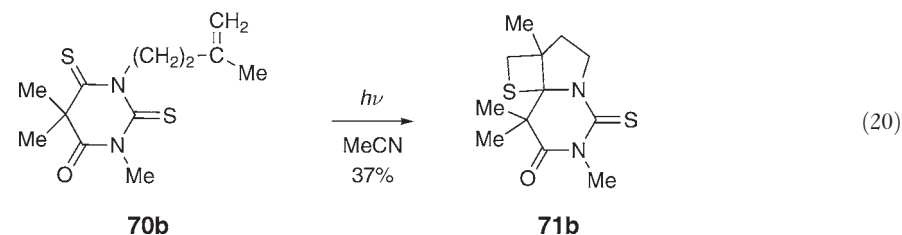
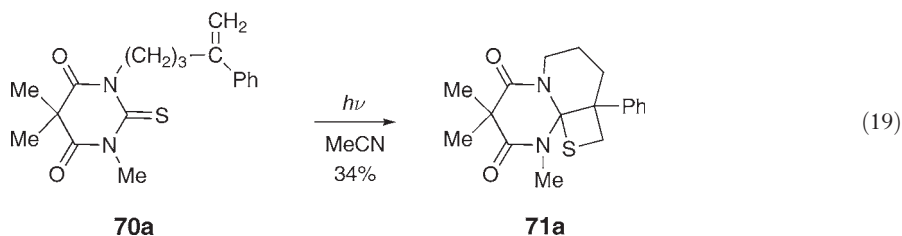
Takechi has reported that the photochemical cyclization of 4-alkenyl-2,4-dimethyl-1-thioxo-1,4-dihydro-2*H*-isoquinolin-3-one derivatives **68a** and **68b** leads to the formation of the tricyclic thietanes **69a** and **69b** and **69'a** and **69'b** in moderate yields (Scheme 11) <2005JHC201>.

Table 2 Photochemical synthesis of 4-thia-3-aza-cyclopenta[1,4]-cyclobutan-2-one derivative


Conditions	Yield (%)
Benzene, +20 °C	83
Solid state, 0 °C	81
Solid state, -78 °C	85

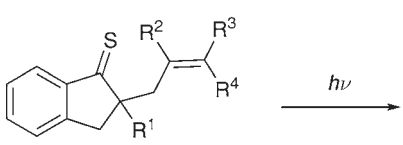
**Scheme 11**

A similar intramolecular [2+2] cycloaddition was performed on thiobarbiturates **70a** and **70b** <1996H(42)117, 2003H(59)303>, leading to the formation of tricyclic thietanes **71a** and **71b** (Equations 19 and 20).

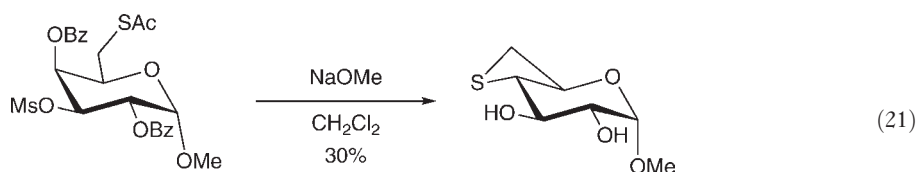


Nishio *et al.* performed similar photochemical intramolecular [2+2] cycloadditions of 2-allylindan-1-thione derivatives <1996LA117>. The reaction provides access to tetracyclic thietanes in mostly satisfactory yields (Table 3).

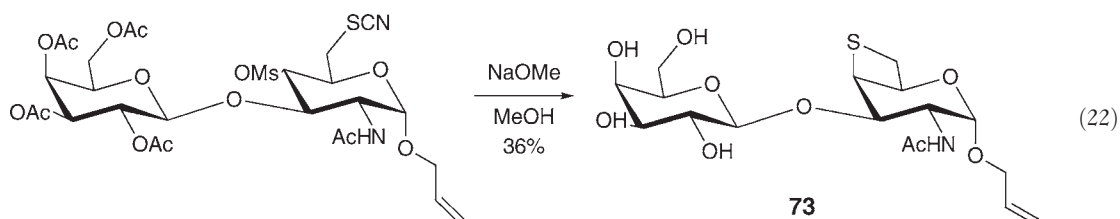
Several articles within the discussed period were devoted to the synthesis of carbohydrates (mono- and disaccharides) with a fused thietane ring. Cubero *et al.* <1996CAR145> synthesized a galactose thietane derivative **72** using sodium methoxide as a condensing agent (Equation 21).

Table 3 Photochemical [2+2] cyclization of 2-allyl-indan-1-thione derivatives


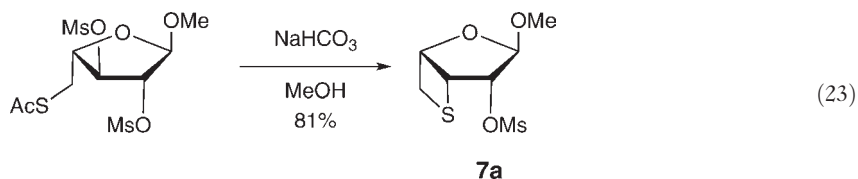
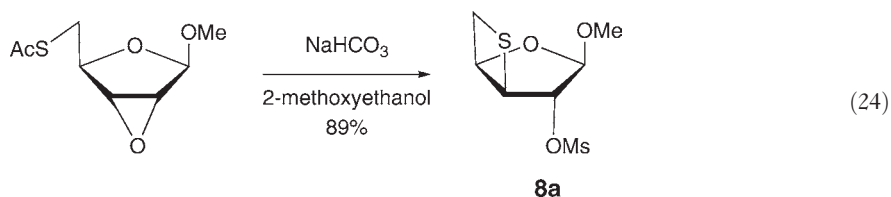
R^1	R^2	R^3	R^4	Yield (%)
Me	H	H	H	69
$\text{CH}_2=\text{CHCH}_2$	H	H	H	65
Me	H	Me	Me	20

**72**

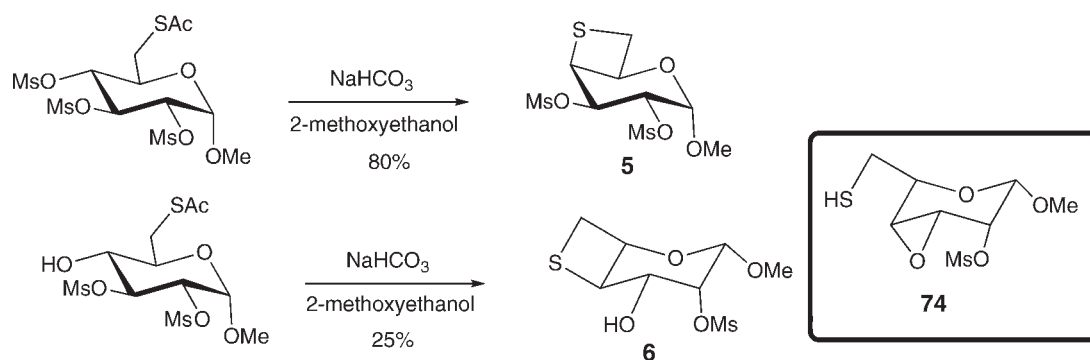
This reaction was also applied to disaccharides, allowing synthesis of the thietano-3-*O*-galactopyranosyl derivative **73** (Equation 22) <2000BML1369, 2002M531>. The cyclization was accomplished by reaction of the thiocyno group with the mesyloxy moiety in the presence of sodium methoxide.

**73**

Schulze *et al.* <2004CAR1787> proposed an analogous cyclization with arabinose and ribose derivatives in order to obtain the corresponding fused-ring systems **7a** and **8a** (Equations 23 and 24). Reactions were carried out in the presence of sodium bicarbonate or sodium acetate.

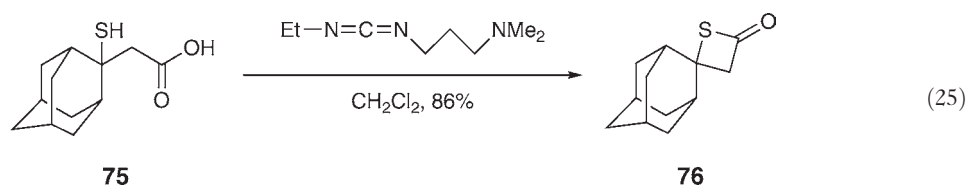
**7a****8a**

S-Acetylmethyl glucose derivatives were converted to the corresponding fused thietanes **5** and **6** by the action of sodium bicarbonate in 2-methoxyethanol (Scheme 12) <2000CAR237>. When a mesyloxy group was in the 4-position of a pyranose ring, the yield was much higher than in the case of a 3-mesyloxy group, due to the fact that the formation of product **6** goes via the intermediate oxirane **74** (Scheme 12) <2000CAR237>.

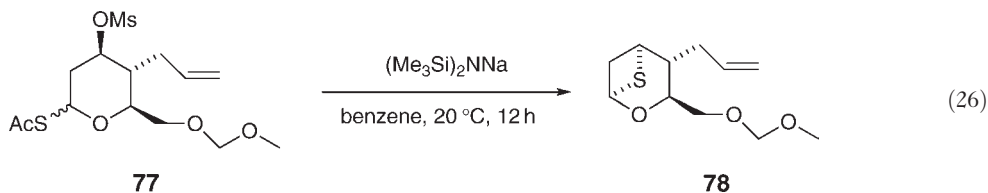


Scheme 12

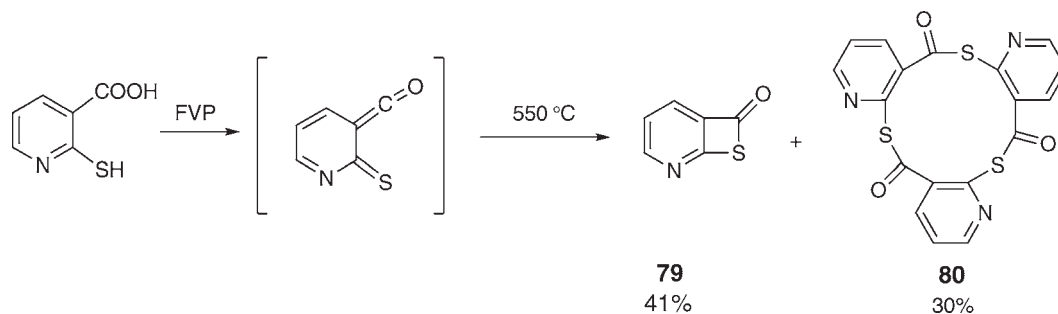
The spiro fused-ring thietane **76** has been prepared in high yield by the intramolecular cyclization of (2-mercaptoadamantan-2-yl)-acetic acid **75** using a carbodiimide as a condensing agent (Equation 25) <2004JME2276>.



An interesting condensation leading to bicyclic 4-allyl-3-methoxymethoxymethyl-2-oxa-6-thiabicyclo[3.1.1]heptane **78** by the action of sodium bis-(trimethylsilyl)amide on pyran derivative **77** has been reported (Equation 26) <2003RJO834>.



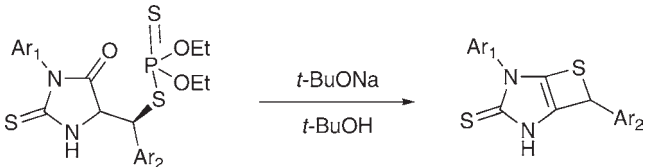
The synthesis of a fused pyridothietone **79** by the FVP of 2-mercapto nicotinic acid was described (Scheme 13) <2002TL5285>. However, the selectivity of this reaction was shown to be poor, since the formation of trimer **80** was observed as a side product.



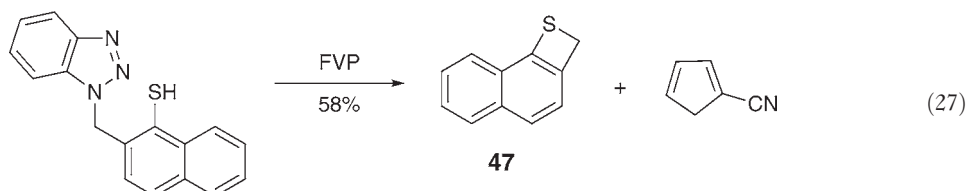
Scheme 13

Synthesis of a range of fused thietes **82** was achieved by utilizing the reaction of *tert*-butoxide with the thiophosphoryl-imidazole derivatives **81** (Table 4) <2003S340>.

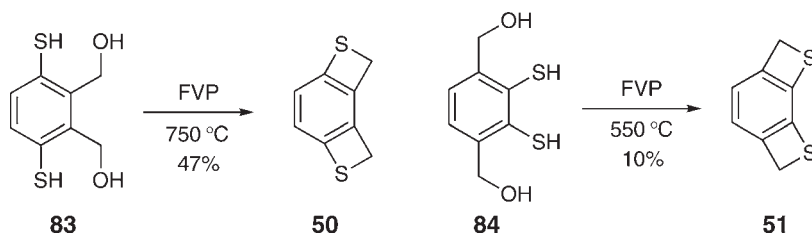
Meier and co-workers synthesized thieta[*a*]naphthalene **47** in 58% yield by FVP of a benzotriazole-substituted naphthalene <1998JHC1505>, together with cyanocyclopentadiene as a side product (Equation 27).

Table 4 Synthesis of 6-thia-2,4-diaza-bicyclo[3.2.0]hept-1(5)-ene-3-thione **82**


Ar_1	Ar_2	Yield of 82 (%)
Ph	Ph	78
4-MeOC ₆ H ₄	Ph	76
Ph	4-MeOC ₆ H ₄	83
4-MeOC ₆ H ₄	4-ClC ₆ H ₄	80
Ph	4-MeOC ₆ H ₄	72
4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	70



Also, Meier and Rumpf synthesized angular benzobisthietes **50** and **51** in moderate yields, by the dehydration of bis(hydroxymethyl)dimercaptobenzenes **83** and **84** (Scheme 14), which may be versatile reagents for synthesis of polycyclic sulfur-containing compounds <1998TL9639>.

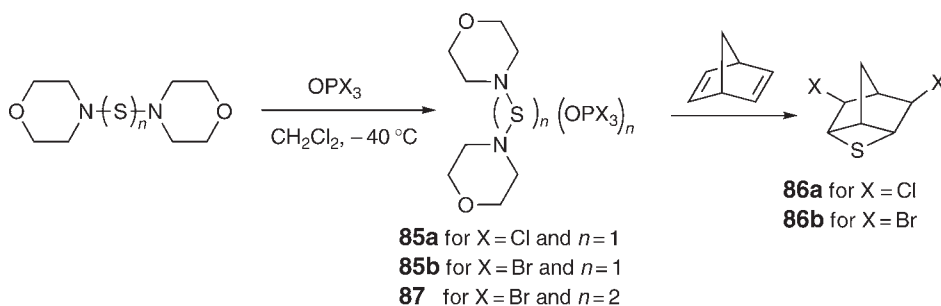
**Scheme 14**

2.08.9.2 Ring Synthesis via Formation of Two Bonds

2.08.9.2.1 From [3+1] fragments

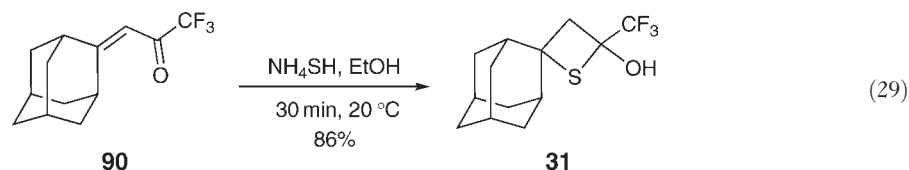
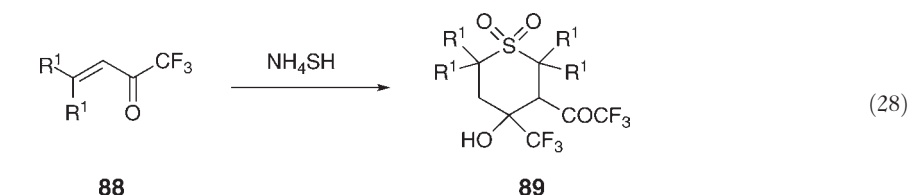
Zyk *et al.* <2000RJO794> reported the synthesis of fused-ring thietanes by the reaction of the bis-morpholine sulfide-phosphoryl trihalide complex **85** with norbornadiene. The formation of 4-thiatricyclo[3.2.1.0^{3,6}]octane **86** was demonstrated and yields varied slightly depending on the phosphoryl trihalide used. When phosphoryl trichloride was used, the yield was 69%; in the case of phosphoryl tribromide, it was 72%. The complex **84** was obtained by the reaction of the bis-morpholine sulfide with phosphoryl trihalide in dichloromethane at -40°C (Scheme 15). The same authors <1996RCB2393> performed a similar reaction of norbornadiene with bis-morpholine disulfide-phosphoryl tribromide complex **87**, which led to the formation of the same thietane **86** in 63% yield (Scheme 15). These reactions have also been described by Robin and Rousseau in a review <2002EJO3099>.

Sanin *et al.* described the reaction of α,β -unsaturated fluorinated ketones **88** with ammonium sulfide in ethanol, which led to the formation of thiopyran-*S,S*-dioxide derivatives **89** (Equation 28) <1996JOC1986>. However, one of the studied ketones (3-adamantan-2-ylidene-1,1,1-trifluoro-propan-2-one **90**) demonstrated an unusual behavior in the course of this reaction, which led to the formation of the fused-ring thietane **31** in 86% yield (Equation 29) <1996JOC1986>.



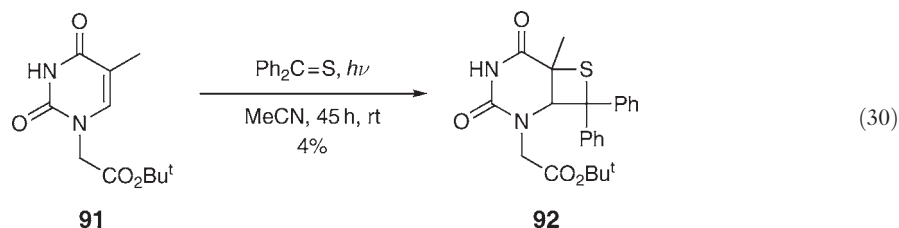
n	X	Yield (%)
1	Cl	69
1	Br	72
2	Br	63

Scheme 15



2.08.9.2.2 From [2+2] fragments

The reaction of thioketones with any compound with an activated double C=C bond leads to the formation of a thietane. Friedel *et al.* <2005OBC1937> performed the photoreaction of 1-substituted thymine **91** with thiobenzophenone, achieving the bicyclic thietane **92**, but in a very poor yield (4%) (Equation 30).



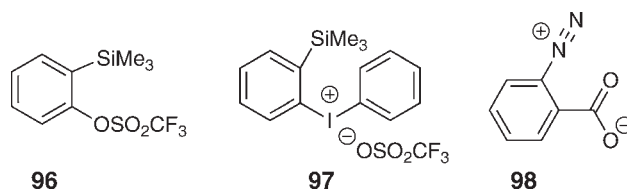
Sakamoto *et al.* <2003CC2218> reported a detailed study of the photochemical reaction of *N*-phenyl-substituted thiosuccinimides **93** with 1,1-diphenylethene in benzene. The reaction led to the spirothietanes **94** as the predominant product with minor amounts of 5-benzhydrylidene-1-phenylpyrrolidin-2-one derivatives **95** (Table 5). Due to the fact that diastereoselectivity of this reaction is very high (100% de), the authors discussed the stereochemical aspects of this reaction <2003CC2218>.

Okuma *et al.* <1998CL79, 2000BCJ155, 1999J(P1)2997, 2005H(65)1553> published a series of papers describing reactions of various thioketones with benzyne generated from 2-trimethylsilylphenyl trifluoromethanesulfonate **96**, phenyl[2-(trimethylsilyl)-phenyl]iodonium trifluoromethanesulfonate **97**, or benzenediazonium-2-carboxylate **98**, which led to the formation of benzothietes. Compounds **96–98** are good precursors of benzyne, but not in the

Table 5 The [2+2] cyclization of *N*-phenyl thiosuccinimides with olefins

<i>R</i> ¹	<i>R</i> ²	Yield of 94 (%)	Yield of 95 (%)
Me	H	65	18
Cl	H	85	12
OMe	H	71	15
Me	Me	89	6

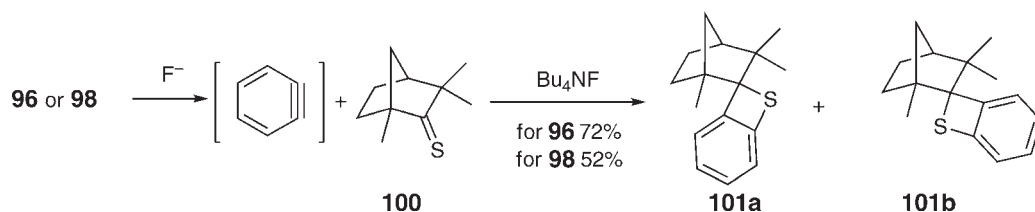
same degree. According to some authors, benzyne formation depends on the thioketone used. The competitive formation of thiopyran derivatives was also reported by Okuma *et al.* <1999J(P1)2997>. The reaction of benzyne with thiopivaloylphenones <1998CL79, 2000BCJ155> gave a series of benzothietes **99a–d**. When compound **96** was used as the benzyne precursor, yields were much lower than the yields in the case of the precursor **97** (Table 6).

**Table 6** The [2+2] cyclization of thioketones with benzyne

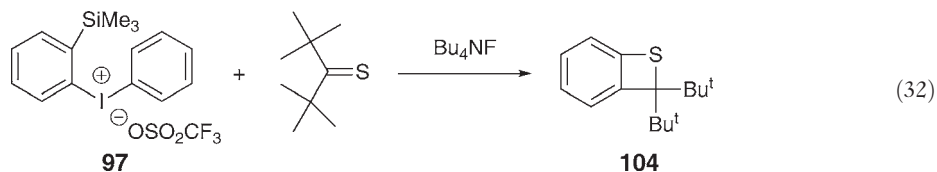
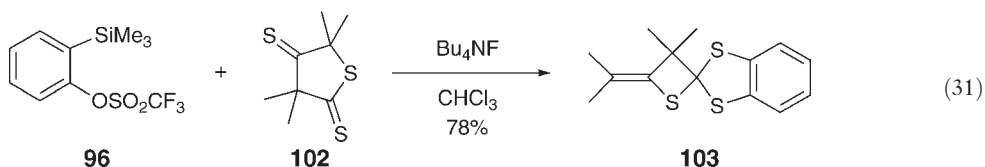
Precursor	<i>R</i> ¹	Solvent	Yield of 99 (%)
96	MeO	MeCN	24
96	MeO	CH ₂ Cl ₂	12
97	MeO	MeCN	58
97	MeO	CH ₂ Cl ₂	49
97	Me	CH ₂ Cl ₂	51
97	H	CH ₂ Cl ₂	44
97	PhO	CH ₂ Cl ₂	48

A similar comparative study was performed in case of thiofenchone **100** <2000BCJ155>, which underwent the reaction with two benzyne precursors **96** and **98**. This time the benzyne precursor **96** turned out to be more efficient, as the reaction resulted in two isomeric benzothietes **101a** and **101b** in 72% yield, while the use of compound **98** decreased the yield to 52% (Scheme 16).

Some other examples reported by Okuma show the scope of this reaction and the generated benzyne led to thietane **103** and benzothiete **104** in high yields with 3,5,5-tetramethyl-thiophene-2,4-dithione **102** or with 3-di-*tert*-butyl thioketone (Equations 31 and 32) <2005H(65)1553, 1999J(P1)2997>.

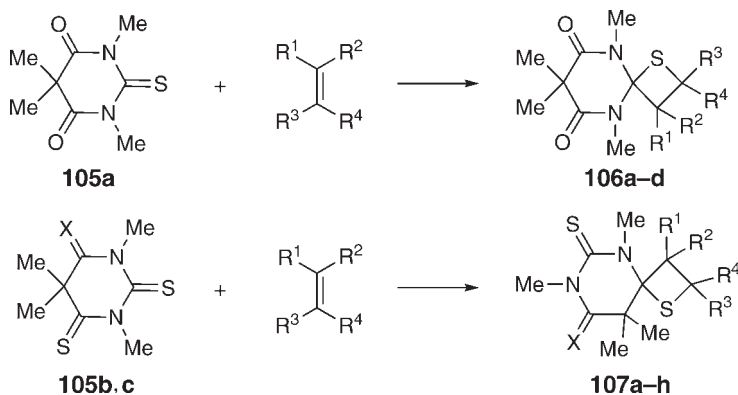


Scheme 16



Takechi and Machida reported the [2+2] photochemical reaction of thiobarbiturates with alkenes [<1997CPB1>](#). They pointed out the differences in reactions of mono- **105a**, di- **105b**, and trithiobarbiturates **105c**, leading to different spirothietanes **106** and **107** in fair yields (Table 7). The authors presented a detailed discussion of the stereochemistry of this reaction [<1997CPB1>](#).

Table 7 The photochemical [2+2] reaction of thiobarbiturates with olefins

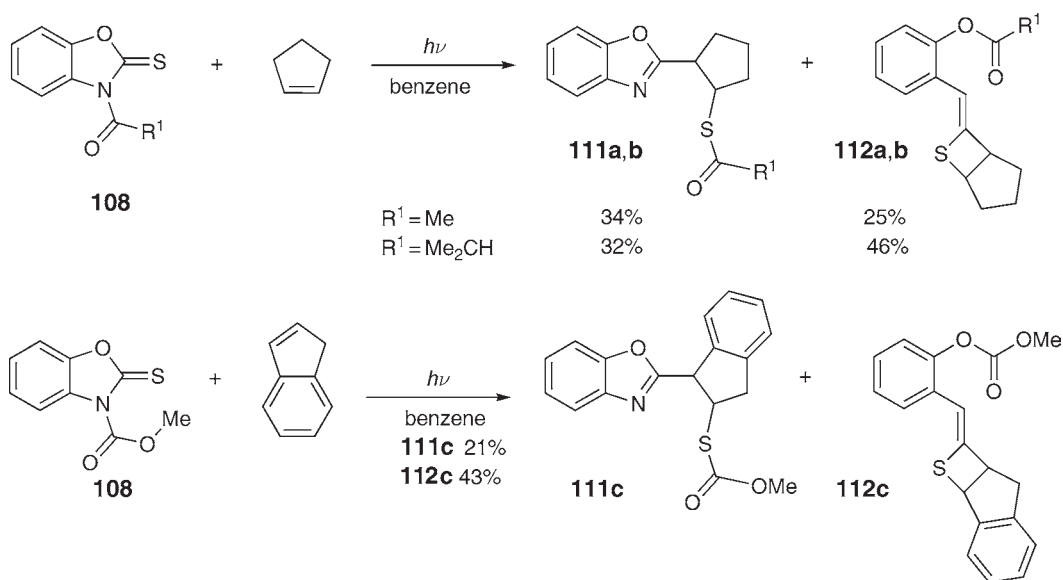


No.	X	R ¹	R ²	R ³	R ⁴	Yield of 106 (%)	Yield of 107 (%)
106a		Me	Me	Me	Me	51	
106b		OEt	H	H	H	17	
106c		Me	Ph	H	H	7	
106d		CN	H	H	H		
107a	O	Me	Me	Me	Me		91
107b	O	OEt	H	H	H		46
107c	O	Me	Ph	H	H		77
107d	O	CN	H	H	H		
107e	S	Me	Me	Me	Me		51
107f	S	OEt	H	H	H		33
107g	S	Me	Ph	H	H		19
107h	S	CN	H	H	H		

Nishio *et al.* <2002HCA2383> performed a photochemical [2+2] cyclization reaction between *N*-alkoxycarbonylbenzo-1,3-oxazol-2-thione **108** and a noncyclic alkene **109**. The reaction led to the formation of spiro-thietanes **110**, in most cases in high yields (Table 8). They also reported <2003HCA3255> that when in a similar reaction a cycloalkene was used, the reaction led to the formation of compounds **111** and iminothietanes **112**. Cyclopentene and indene were used as model cycloalkenes (Scheme 17).

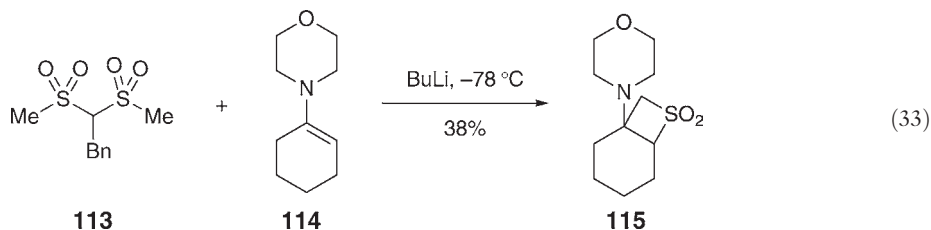
Table 8 The photochemical [2+2] cyclization of benzooxazoles with alkenes

Product no.	R^1	R^2	R^3	R^4	R^5	Yield of 110 (%)
110a	Me	Me	Me	Me	Me	50
110b	Me	Me	Me	Me	H	75
110c	Me	Me	CN	H	H	98
110d	Me	Me	Me	H	Me ₂ C=CH	50
110e	Et	Me	Me	Me	Me	73
110f	Et	Me	CN	H	H	96
110g	Bn	Me	Me	Me	Me	43
110h	Ph	Me	Me	Me	Me	68
110i	Ph	Me	Me	Me	H	28
110j	Ph	Me	CN	H	H	67
110k	Ph	Me	Me	H	Me ₂ C=CH	16
110l	CH=CH ₂	Me	CN	H	H	67
110m	CH ₂ CH=CH ₂	Me	Me	Me	Me	24
110n	CH ₂ CH=CH ₂	Me	CN	H	H	82
110o	(CH ₂) ₂ CH=CH ₂	Me	CN	H	H	61



Scheme 17

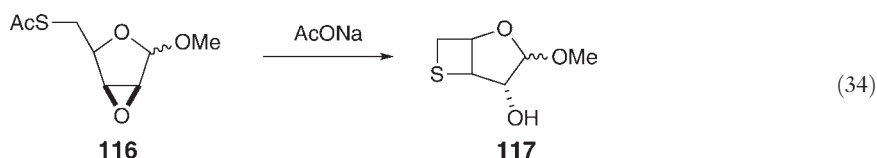
An interesting transformation has been reported by Burlingham and Widlanski [<2001JA2937>](#), who synthesized fused-ring thietane-1,1-dioxide **115**, in 38% yield, by the reaction of *N*-benzyl dimethyldisulfonimide **113** with the morpholine derivative **114** in the presence of butyllithium (Equation 33).



2.08.10 Ring Synthesis by Transformation of Another Ring

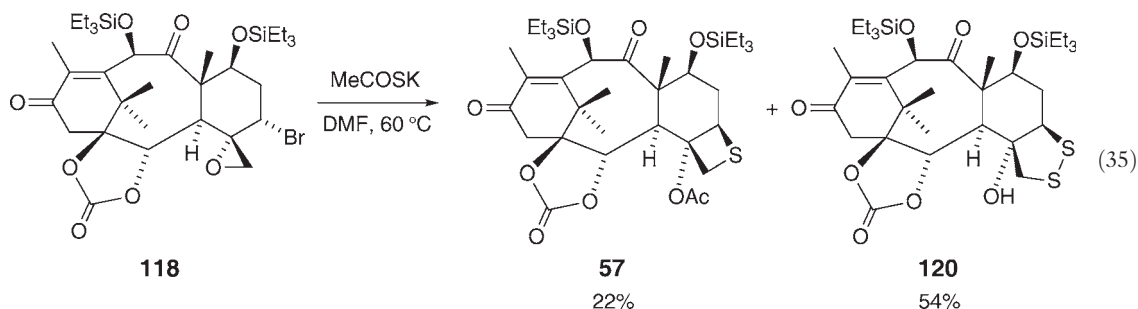
2.08.10.1 Formation from Three-Membered Heterocycles

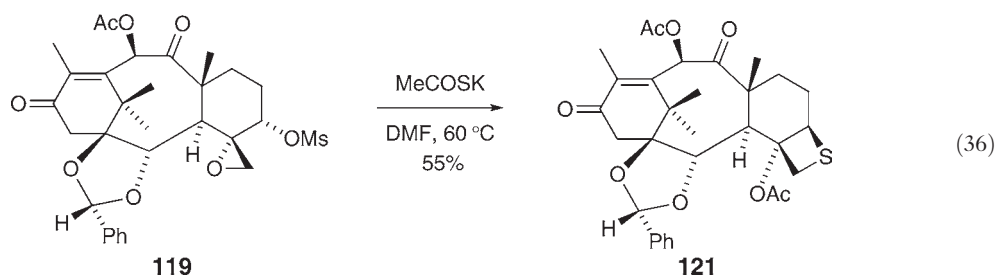
For the period 1995–2006, the formation of fused-ring thietanes from three-membered rings is exclusively confined to the transformation of oxiranes fused to complex ring systems. It was reported [<1997PS389>](#) that the 5-*S*-acetyl-2,3-epoxide derived from D-xylose **116** was easily converted to 2-oxa-6-thia-bicyclo[3.2.0]heptane **117** by the action of sodium acetate (Equation 34).



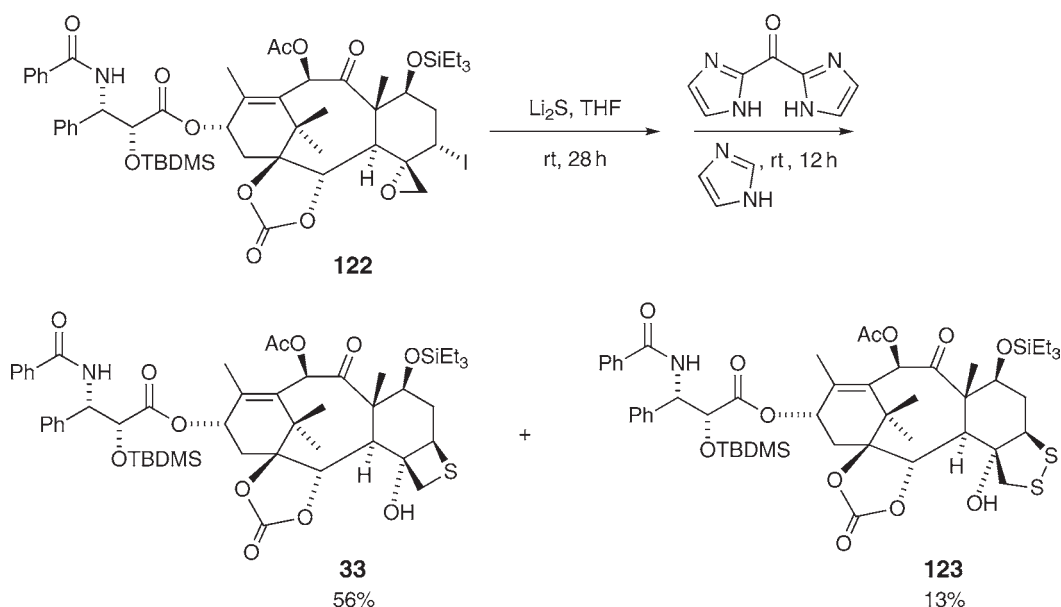
Further studies were performed several years later, and the results suggested that in the course of the Mitsunobu reaction of *O*-mesylated 6-*S*-acetyl hexose derivatives, the formation of a thietane ring fused to the furanose or the pyranose ring occurred through an oxirane intermediate [<2004CAR1787, 2000CAR237>](#). This topic has already been discussed in Section 2.08.9.1 and presented in Scheme 12 and Equations (23) and (24).

Oxirane taxol derivatives have also been found to be convenient starting materials for the synthesis of taxols fused with a thietane ring. The oxirane-derived taxine B derivatives **118** and **119** have undergone reaction with potassium thioacetate in dimethylformamide (DMF) at 60 °C [<2000TL4891, 2001JOC5058>](#), leading to the formation of thietane-derived taxine B derivatives **57** and **121**. In the case of the bromine derivative **118**, the thietane-taxol **57** was not the exclusive product and the 1,2-dithiolane derivative **120** occurred as the major product (Equations 35 and 36).



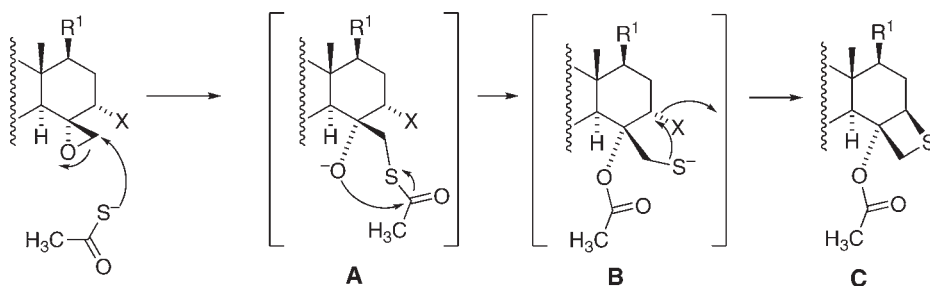


Gunatilaka *et al.* <1999JOC2694> reported the synthesis of the thietane-derived 5,20-thiapaclitaxel derivative **33** by the action of lithium sulfide on the oxirane-derived paclitaxel derivative **122**. This reaction led to the thietane derivative **33** in 56% yield and to minor amounts (13%) of 1,2-dithiolane-derived taxol **123** (Scheme 18).



Scheme 18

Mercklé *et al.* <2001JOC5058> proposed a mechanism for the formation of taxol-thietanes **57** and **33** from spiro taxol-oxiranes **118** and **122**. According to these authors, the reaction starts with the attack of the sulfur atom from a thioacetate anion on an oxirane carbon atom to form the intermediate **A**. Then, an acetyl group migrates from sulfur to oxygen to form the intermediate **B**, and the X group leaves with simultaneous formation of a fused thietane product **C** (Scheme 19).

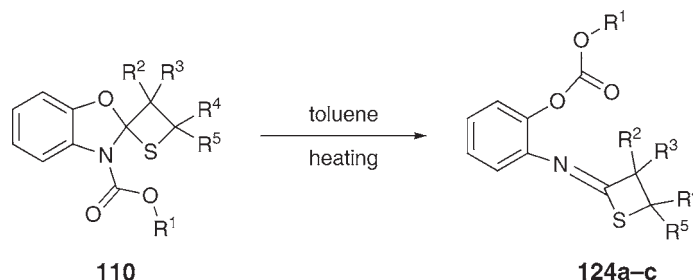


Scheme 19

2.08.10.2 Formation from Four-Membered Heterocycles

Nishio *et al.* <2002HCA2383> reported the reaction of spirocyclic aminothietanes **110**, which after heating in refluxing toluene were easily converted to iminothietanes **124a–c** in good yields. According to the authors, this reaction proceeded by thermally induced cleavage of a C–O bond of the oxazole ring and further migration of an alkoxycarbonyl group from nitrogen to oxygen (Table 9). This mechanism has been depicted in Section 2.08.6.1.2.

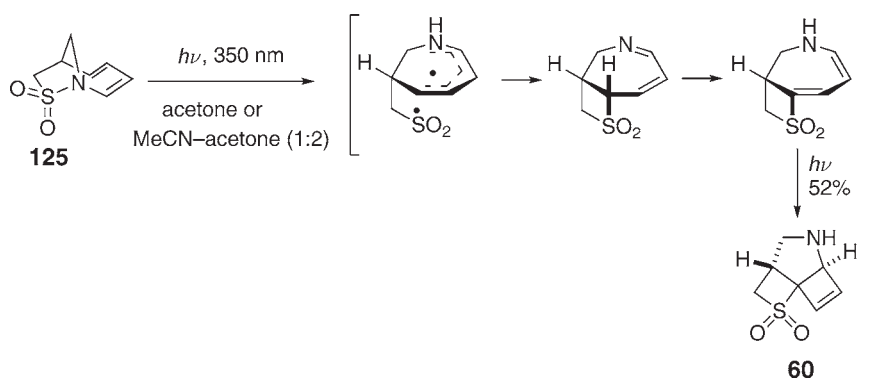
Table 9 Thermal conversion of spirocyclic aminothietanes **110** to iminothietanes **124a–c**



Product no.	R^1	R^2	R^3	R^4	R^5	Yield (%)
124a	Me	Me	Me	Me	Me	Quantitative
124b	Ph	Me	Me	Me	Me	90
124c	$\text{CH}_2\text{CH}=\text{CH}_2$	Me	Me	Me	Me	Quantitative

2.08.10.3 Formation from Five-Membered Heterocycles

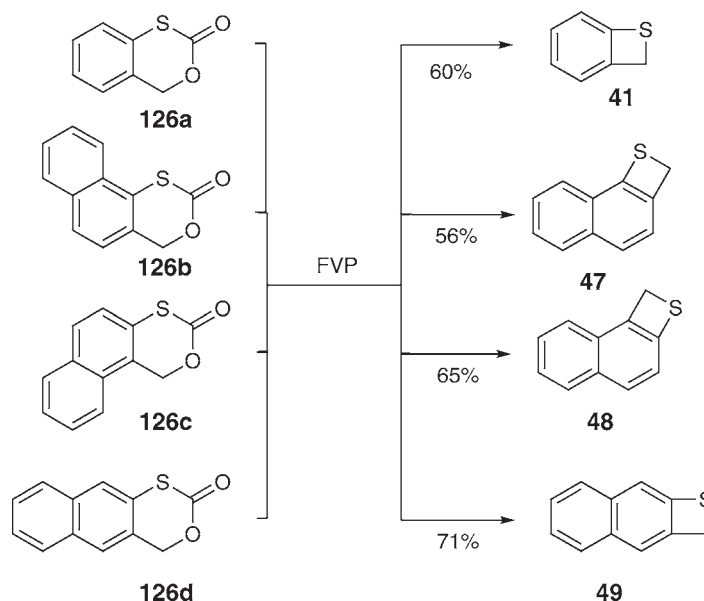
The irradiation of 8-thia-1-aza-bicyclo[4.2.1]nona-2,4-diene 8,8-dioxide **125** with 350 nm ultraviolet (UV) light in pure acetone resulted in the formation of 2-thia-6-aza-tricyclo[5.2.0.0^{1,4}]non-8-ene 2,2-dioxide **60** in 52% yield <2004OL1313>. However, photopolymerization occurred as a side reaction, but this can be prevented by the use of acetone with acetonitrile (2:1) as a solvent, although the yield diminished significantly to 28%. The authors proposed a mechanism for this reaction (Scheme 20) <2004OL1313>.



Scheme 20

2.08.10.4 Formation from Six-Membered Heterocycles

FVP of benzooxathiinone **126a** and naphthooxathiinones **126b–d** at 550 °C and 100 Pa through a quartz tube led to the formation of a benzothiete **41** and three isomeric naphthothietes **47–49** in satisfactory yields (Scheme 21) <1996S327>.



Scheme 21

2.08.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Among the available methods to synthesize fused-ring thietes and bi- or tricyclic thietanes (but not spiro-compounds), the most efficient method seems to be the synthesis from acyclic precursors with the same number of carbons. Photocyclization reactions lead to thietes and thietanes in satisfactory to high yields. Mono- and disaccharides bearing fused thietane moieties have been synthesized using this method.

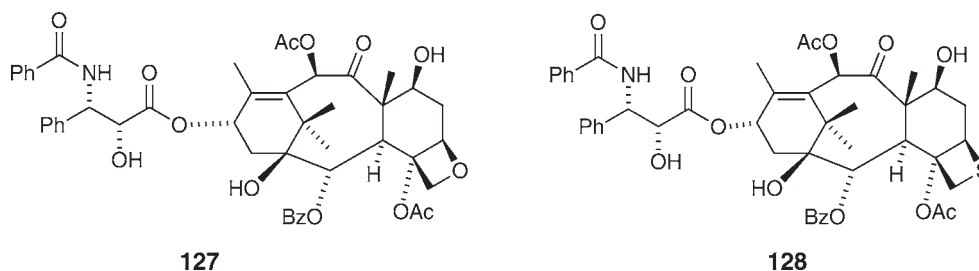
For spiro-thietane derivatives, the [2+2] two-fragment cyclization turns out to be the most valuable method. Using this methodology, various spiro-thietanes of complex structure have been synthesized in rather high yields.

The transformation of three-membered oxiranes was successfully applied to the synthesis of thietane-containing taxoids, which were obtained in fair yield.

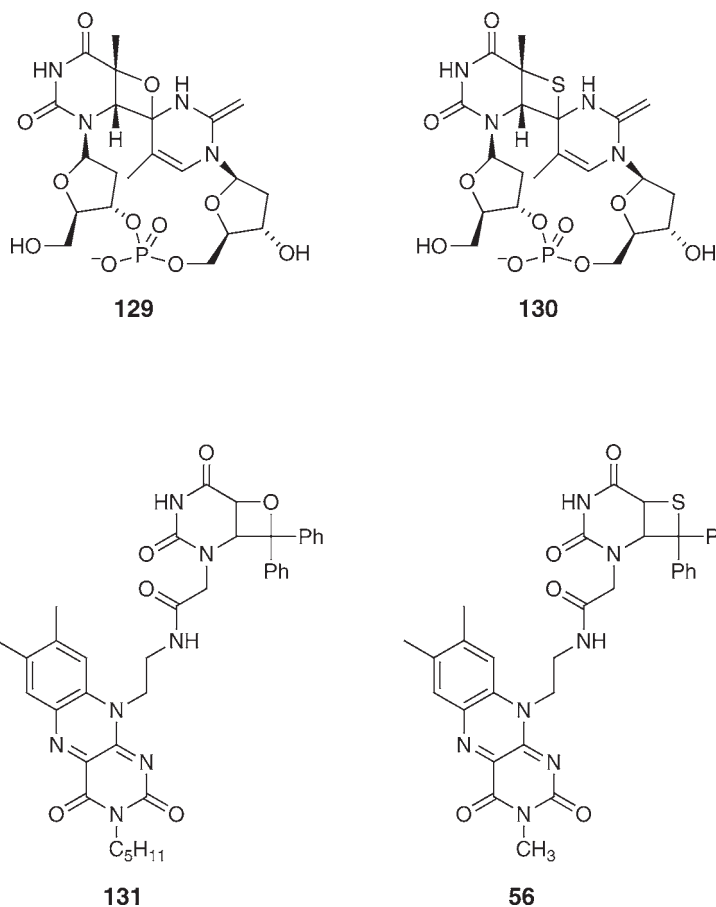
There are few examples of the [3+1] two-fragment cyclization reactions and of transformations from four-membered rings to seven-membered ones. These methods are rather limited in scope, because they are only for the synthesis of particular compounds, for example, 2,8-dihalo-4-thia-tricyclo[3.2.1.0^{3,6}]octanes.

2.08.12 Important Compounds and Applications

The anticancer drug paclitaxel **127** is a clinically used anticancer drug. Intensive studies on its chemistry and structure–activity relationships have established that, among others, the oxetane ring is essential for biological activity. Replacement of the oxygen atom with a sulfur atom would maintain the neutrality of the ring and variations of both steric and electronic effects could be predicted [<1999JOC2694, 2001JOC5058, 2000TL4891>](#). So taxol-thietane **128** has potential applications in various fields of medicine.



The axiomatic fact is that UV irradiation of cells leads to severe damage, as it has a mutagenic action. The lesion caused by this is repaired in organisms by the enzyme photolyase <2005OBC1937>. It is known that photolyases contain a reduced and deprotonated flavin <2005OBC1937>. The key step of the repair mechanism is the electron-transfer-induced cleavage of the oxetane ring in intermediate **129**, which can be mimicked by the thietane analogues **130** <2005OBC1937>. In their biochemical study on the repair mechanism, these authors compared the oxetane model compound **131** with the thietane one **56** <2005OBC1937>.



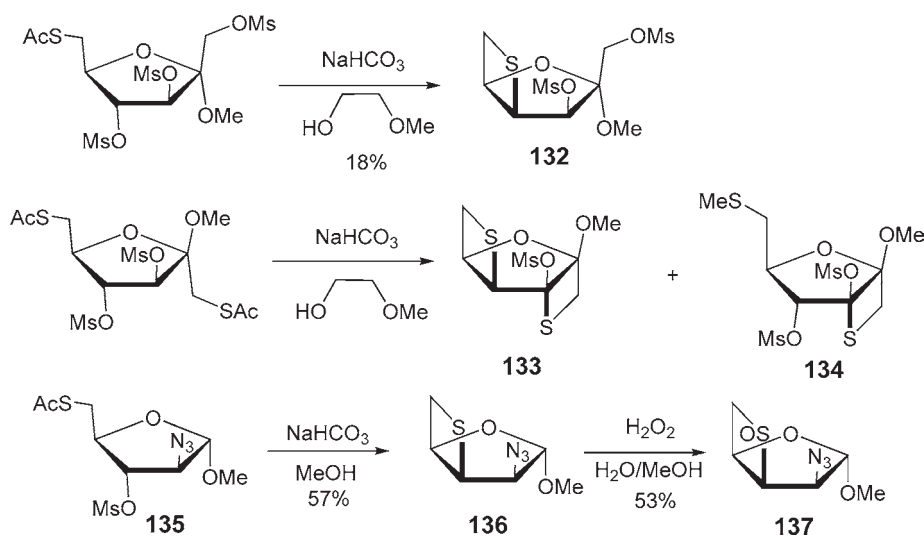
2.08.13 Further Developments

The treatment of methyl 6-*S*-acetyl-1,3,4-tri-*O*-mesyl-6-thio- α -D-fructofuranoside with 2-methoxyethanol in the presence of aqueous sodium bicarbonate gave bicyclic thietane **132** derivative belonging to a tagatose series in 18% yield <2005PS1755> (Scheme 21).

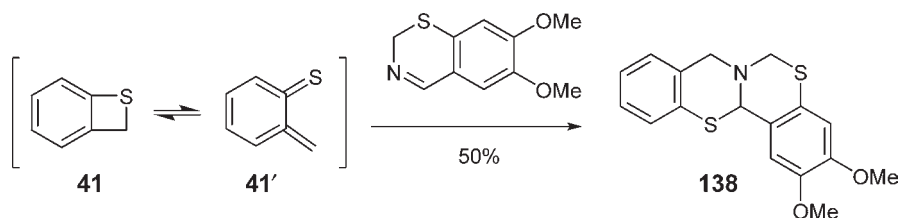
The similar reaction of di-*S*-acetyl derivative of fructofuranose gave the tricyclic bis-thietane **133** belonging to a sorbose series and the bicyclic thietane **134** of a psicose series in 60% and 11% yield respectively <2005PS1755> (Scheme 21).

The reaction of *S*-acetyl azidoarabinofuranoside derivative **135** with sodium bicarbonate in methanol gave bicyclic thietane derived azidolixofuranoside **136**, which was subsequently oxidized with hydrogen peroxide to a sulfoxide derivative **137** <2006PS1249> (Scheme 22).

The reaction of benzothiete **41** with 6,7-dimethoxy-2*H*-benzo[*e*][1,3]thiazine, which led to the formation of benzothiazino[4,3-*b*]-6,7-dimethoxy-2*H*-benzo[*e*][1,3]thiazine **138** revealed that benzothiete had the character of a heterodiene **41'**. The tetracyclic compound was obtained in 50% yield <2006M231> (Scheme 23).



Scheme 22



Scheme 23

References

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Biographical Sketch



Professor Jarosław Lewkowski was born in 1966 in Łódź (Poland). In 1990, he obtained his M.Sc. degree from the University of Łódź, Poland, studying the electrochemical oxidation of 5-hydroxymethylfurfural derivatives at the nickel oxide/hydroxide electrode. He then joined Professor Skowroński's group from the University of Łódź, Poland, cooperating simultaneously with Professor Descotes' team from the University of Lyon 1, France. In 1996, he obtained his Ph.D. degree from the University of Łódź, investigating the selective conversions of furfural, 5-hydroxymethylfurfural, and their derivatives.

He then joined Professor Vaultier's team from the University of Rennes 1 for his postdoctoral studies, where he worked on conversions of organophosphorus compounds in reactions with boron compounds.

After presenting his dissertation entitled "Studies in the Field of Aminophosphonic and Aminophosphonous Derivatives of Furfural, Ferrocenecarbaldehyde and Terephthalic Aldehyde," he received his D.Sc. degree in 2005.

He is the author and co-author of over 40 papers (including book chapters). Now, he is an associated professor at the University of Łódź, Poland. His main areas of scientific interest are the chemistry of furans, the chemistry of ferrocenes, as well as the chemistry of organophosphorus compounds. He is also interested in medicinal chemistry of anticancer drugs.



Professor Stanisław Lesniak was born in 1952 in Gorlice in Poland. He obtained his M.Sc. degree in chemistry from the University of Łódź (Poland) in 1976, studying the reactivity of aziridines. He received a Ph.D. in chemistry from the same university in 1983 for study of stereoselective reduction of aziridinyl ketones. He presented his habilitation thesis at the University of Łódź in 1996. Professor Lesniak lectured at the University of Łódź from 1977 and six months at the University Claude-Bernard Lyon 1 in 1987/1988. He was a research fellow in the Department of Chemistry at the University Claude-Bernard Lyon 1 in a group of Prof. Andre Laurent in 1984–85, 1987–88, and 1991–92. At the same university, he was employed as a CNRS research worker in 2001–2002 in the group of Prof. P. Goekjian. The focus of his studies has been the synthesis and reactivity of small molecules, radical reactions, and reactions under flash vacuum thermolysis conditions.



Professor Wojciech Janusz Kinart was born on 17 May 1953 in Łódź in Poland. He obtained an M.Sc. Honors degree in chemistry from the University of Łódź on 3 August 1977. He was awarded a Ph.D. in chemistry from the same university on the 17 April 1980. He presented his habilitation thesis at the University of Łódź on 17 January 1996. Professor Kinart lectured at the University of Łódź from 1977, at the University of Maiduguri, Nigeria, from 1982 up to 1986, at the Polytechnic of Radom, Poland, from 1998 up to 2000, and at the Polytechnic of Warsaw, Poland, from 2000 up to 2003. He was a research fellow in the Department of Chemistry at University College London in 1988–89 and 1993, and in the Department of Chemistry at Duke University, Durham, USA, from 1990 up to 1991. He is an author of 102 articles in the field of chemistry. He received the award of Minister of Education in Poland in 1995 for his achievements in the research. His science interests include tin organic chemistry, different aspects of organic synthesis, and physical chemistry.

2.09

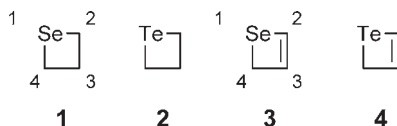
Four-membered Rings with One Selenium or Tellurium Atom

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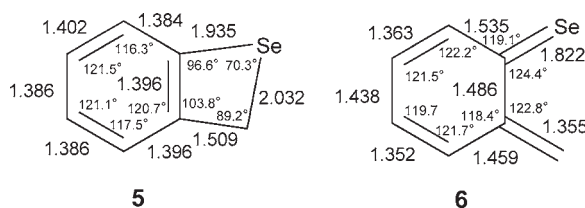
2.09.1 Introduction

This subject was covered previously in CHEC-II(1996) <1996CHEC-II(1)823>. This chapter is intended to update this previous version and to highlight major new preparations, reactions and concepts. We have provided at the beginning of each main section a short paragraph explaining the major advances since the publication of the earlier chapters and some deficiencies in CHEC-II(1996) that we have now attempted to address. Four-membered cyclic compounds with one selenium or tellurium atom are named selenetane **1**, tellurethane **2**, selenete **3**, and tellurete **4**. The literature regarding those compounds is quite limited. A few examples of compounds **1** and **3**, that is, three-substituted derivatives and tungsten-pentacarbonyl- or rhenium-complexes, in particular, have been described since the publication of CHEC-II(1996) <1996CHEC-II(1)823>. Compounds **3** and **4**, the unsaturated analogs of **1** and **2**, have not been described since the publication of CHEC(1984) and CHEC-II(1996). No discussions on tellurethane **2** and tellurete **4** were found in the literature in the period 1995–2005. In this chapter, we describe crystal structures, nuclear magnetic resonance (NMR), and syntheses of the derivatives of **1** and **3** which have been mentioned.



2.09.2 Theoretical Methods

The stabilities of benzoselenete **5** and the *o*-quinoid form **6** were calculated and compared. With the geometry optimization of the 6-31G basis set, the benzoselenete **5** is calculated to be 58.41 kJ mol⁻¹ (13.96 kcal mol⁻¹) more stable than the *o*-quinoid form **6** in the ground-state S0. Bond lengths (C=Se) of the calculated value are quite similar to the observed X-ray crystallographic data <2001JA7166, 2001HCA1578>.

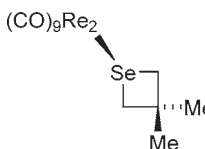
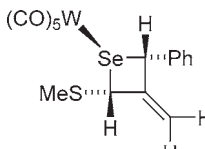


2.09.3 Experimental Structural Methods

2.09.3.1 X-Ray Diffraction

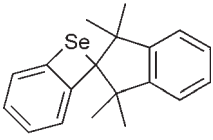
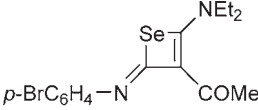
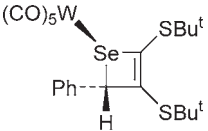
Crystal structures of selenetane derivatives were not described in CHEC(1984) and CHEC-II(1996) (1984CHEC-I, 1996CHEC-II). For the first time in 1995, selenetane derivatives were characterized by X-ray diffraction <1995CB1149, 1995CC2461> and since then six selenetane derivatives were determined by X-ray diffraction. The bond angles, bond lengths, and torsion angles are shown in Table 1. The selenete ring of the reported compounds is almost planar, while the torsion angle of the selenetane ring is about 23°. In most cases, due to the larger radius of Se, the C4-X-C2 angle in the selenetane ring is smaller than that in the thietanes (*cis* 79.3°, *trans* 76.6°) <1975BCJ2339, 1981BCJ3701>. Also, the structures of complexes with some metal atoms were obtained: the selenetane ring can be coordinated to tungsten <1995CB1149, 1995CC2461> or to a rhenium atom <1997CC525, 1997OM3895> via the selenium atom.

Table 1 X-ray diffraction of selenetane derivatives

Compound	Bond angle (°)		Bond length (Å)		Torsion angle (°)	CCDC No.	Reference
	C4-Se1-C2		Se1-C2	C2-C3			
 7	72.0(1)		1.978(3) ^a (Se-C)	1.536(4) ^a (C-C)	-18.74(19) 24.65(18)	215350	2004IC5558
 8	72.2(9)		1.93(2) 1.91(2)	1.51(3) 1.54(3)	ND ^b	SI ^c	1997OM3895
 9	70.9(3)		2.032(7) 2.041(6)	1.484(11) 1.512(8)	-23.6(5)	CSD-401939	1995CB1149

(Continued)

Table 1 (Continued)

Compound	Bond angle (°)	Bond length (Å)		Torsion angle (°)	CCDC No.	Reference
	C4–Se1–C2	Se1–C2 C4–Se1	C2–C3 C3–C4	Se1–C2–C3–C4		
 10	70.4(6)	1.92(1) 2.00(1)	1.49(2) 1.39(2)	ND ^b	SI ^c	2001JA7166
 11	83.5(1)	2.014(2) 1.921(2)	1.416(3) 1.447(3)	–3.44(16)	251943	2004H(62)521
 12	68.9(2)	1.953(5) 2.061(5)	1.516(7) 1.330(8)	–5.4(5)	ND ^b	1995CC2461

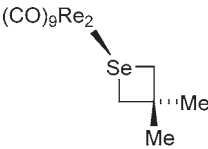
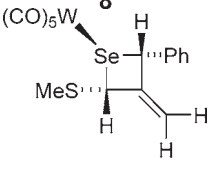
^aAveraged.^bNo information available.^cSee supporting information of the literature.

2.09.3.2 NMR Spectroscopy

2.09.3.2.1 ¹H NMR spectroscopy

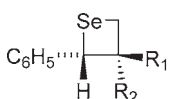
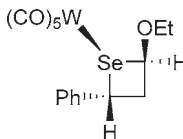
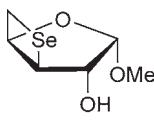
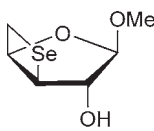
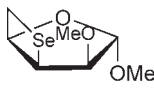
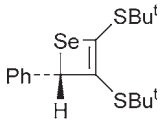
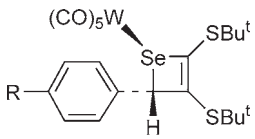
In ¹H NMR spectra of selenetane derivatives, the H-2, H-3, and H-4 signals of the saturated selenetanes **7–8**, **14–17** are observed in the range of 2.8–3.7 ppm, while those of the unsaturated selenetes **12** and **18** are in the range of 5.5 ppm (Table 2).

Table 2 ¹H NMR data for selenetane derivatives

Compound	H-2 (ppm)	H-3 (ppm)	H-4 (ppm)	Reference
 7	3.14		3.14	2004IC5558
 8	3.20		3.58	1997OM3895
 9	5.66 (C(C ₆ H ₅)H)		5.85 (C(SCH ₃)H)	1995CB1149

(Continued)

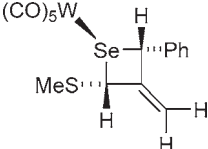
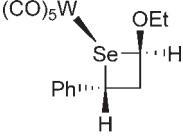
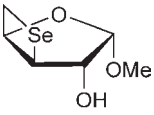
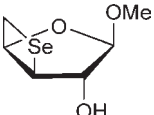
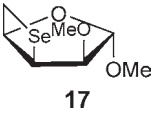
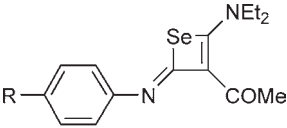
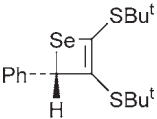
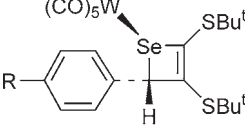
Table 2 (Continued)

Compound	H-2 (ppm)	H-3 (ppm)	H-4 (ppm)	Reference
 $R^1 = \text{H or Me}$ $R^2 = \text{H, Me, or Et}$ 13	4.41 ± 0.95 $(\text{C}(\text{C}_6\text{H}_5)\text{H})$	3.56 ± 0.12	2.81 ± 0.24 (CH_2)	1995CB1149
 14	5.57 $(\text{C}(\text{OEt})\text{H})$	3.55 3.99	4.65 $(\text{C}(\text{C}_6\text{H}_5)\text{H})$ 2.93	1996CB1169
 15	3.68 $(\text{H}3)$	5.40 $(\text{H}4)$	$(\text{H}5a)$ 3.43 $(\text{H}5b)$	2000CAR107
 16	3.71 $(\text{H}3)$	5.59 $(\text{H}4)$	3.16 $(\text{H}5a)$ 3.39 $(\text{H}5b)$	2000CAR107
 17	4.21 $(\text{H}3)$	5.40 $(\text{H}4)$	2.89 $(\text{H}5a)$ 3.45 $(\text{H}5b)$	2004CAR1787
 18	5.52			1995CC2461
 $R = \text{OMe, H or CF}_3$ 12	5.55 ± 0.025			1995CC2461

2.09.3.2.2 ^{13}C NMR spectroscopy

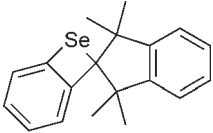
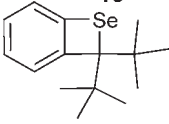
In ^{13}C NMR spectra of selenetane derivatives, the C-2, C-3, and C-4 signals of the saturated selenetanes **7**, **14–17** are observed in the range of 18–84 ppm, while those of the unsaturated selenetes **11**, **12**, and **18–20** are in the range of 50–89 ppm (single bond) and 128–150 ppm (double bonds) (Table 3).

Table 3 ^{13}C NMR data for selenetane derivatives

Compound	C-2 (ppm)	C-3 (ppm)	C-4 (ppm)	Reference
 7	28.7	54.4	28.7	2004IC5558
 9	58.0		62.2	1995CB1149
 14	40.9 [C(H)OEt]	44.9	83.1 [C(H)Ph]	1996CB1169
 15	34.62 (H3)	81.42 (H4)	18.43 (H5)	2000CAR107
 16	35.97 (H3)	83.99 (H4)	21.66 (H5)	2000CAR107
 17	33.59 (H3)	82.18 (H4)	18.07 (H5)	2004CAR1787
 11 R = H, Br or Cl	148.6 ± 0.7	140.3 ± 0.3	112.5 ± 0.05	2004H(62)521
 18	136.8	143.5	50.8	1995CC2461
 12 R = OMe, H or CF ₃	144.2 ± 0.85	142.4 ± 0.25	63.5 ± 1.5	1995CC2461

(Continued)

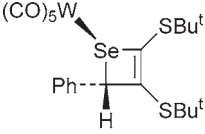
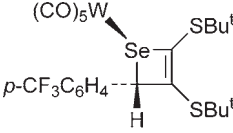
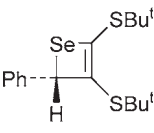
Table 3 (Continued)

Compound	C-2 (ppm)	C-3 (ppm)	C-4 (ppm)	Reference
	128.3	149.8	83.0	2001JA7166
19 	130.3	149.2	88.5	2001JA7166
20				

2.09.3.2.3 ^{77}Se NMR spectroscopy

Only for three selenete complexes **12a**, **12b**, and **18** have ^{77}Se NMR data been reported <1995CC2461>. The chemical shifts of ^{77}Se NMR spectra in the selenetes are compiled in **Table 4**.

Table 4 ^{77}Se NMR data for selenetes

Compound	^{77}Se chemical shifts		Reference
	Solvent	ppm	
 12a	CDCl_3	745	1995CC2461
 12b	CDCl_3	762	1995CC2461
 18	CDCl_3	833	1995CC2461

2.09.3.3 Mass Spectrometry

No discussions on mass spectrometry related to four-membered cyclic compounds with one selenium or tellurium atom were found in the literature in the period 1995–2005.

2.09.3.4 Infrared Spectroscopy

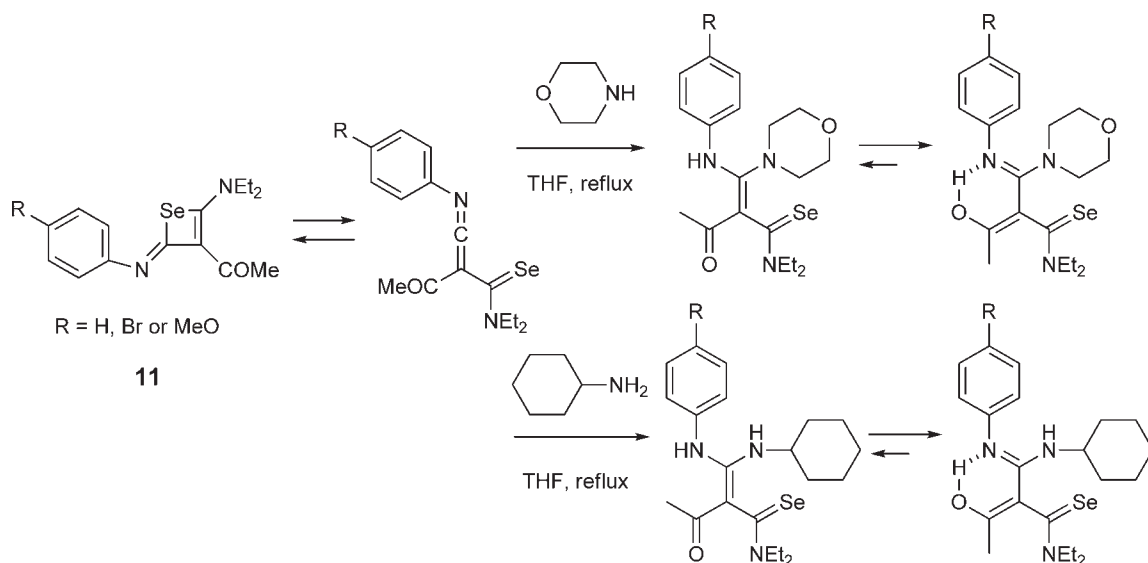
No discussions on infrared spectroscopy related to four-membered cyclic compounds with one selenium or tellurium atom were found in the literature for the period 1995–2005.

2.09.4 Thermodynamic Aspects

No discussions on thermodynamic aspects related to four-membered cyclic compounds with one selenium or tellurium atom were found in the literature for the period 1995–2005.

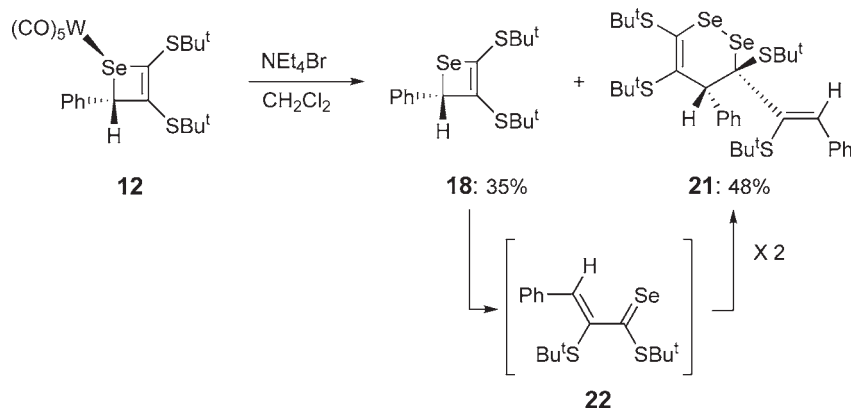
2.09.5 Reactivity of Fully Conjugated Rings

2-Iminoselenete **11** has been reacted with morpholine or cyclohexylamine to afford 2-diaminomethylene-3-oxobutane selenoamides. The products exist in an enolized form (Scheme 1) <2004H(62)521>.



Scheme 1

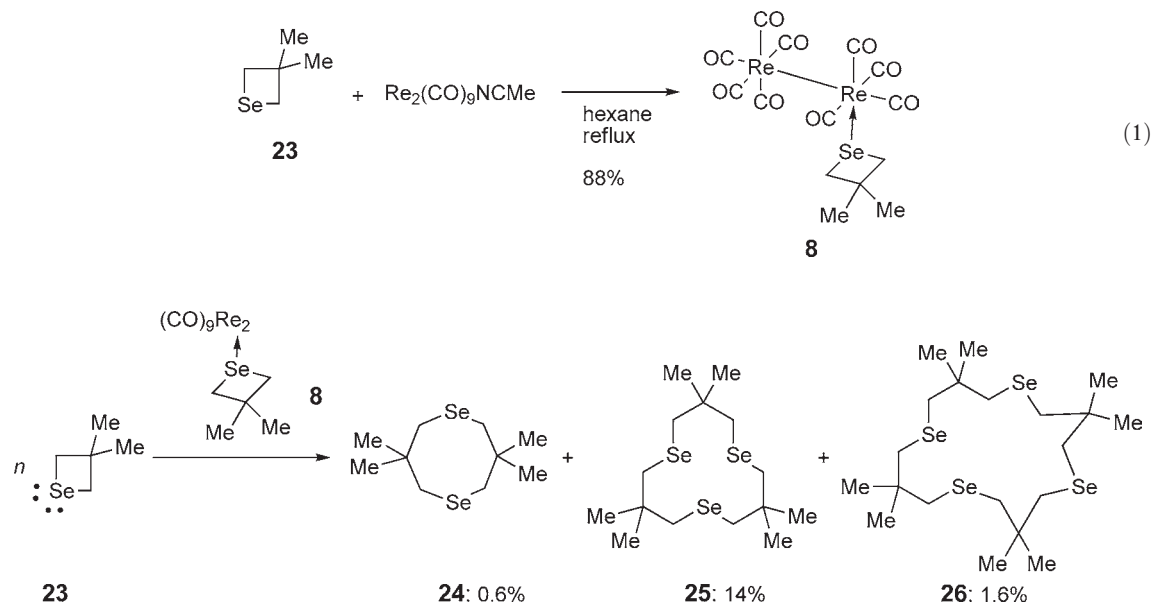
The decomplexation of the selenete ligand of **12** has been achieved with NEt_4Br to give a mixture of selenete **18** and 3,4-dihydro-1,2-diselenine **21**. The structure of compound **21** was confirmed by an X-ray diffraction. Formation of diselenine **21** proceeds by ring opening of selenete **18** to form the α,β -unsaturated thioselenocarboxylic ester **22** which then serves both as a 4π selenadiene ($\text{C}=\text{C}-\text{C}=\text{Se}$) and as a 2π dienophile ($\text{Se}=\text{C}$) in a 'head-to-head' Diels–Alder reaction to form **21**. Ring opening and cycloaddition are highly regio- and stereoselective (Scheme 2) <1995CC2461>.



Scheme 2

2.09.6 Reactivity of Nonconjugated Rings

Complex $\text{Re}_2(\text{CO})_9$ -3,3-dimethylselenetane **8** has been obtained by reaction of $\text{Re}_2(\text{CO})_9\text{NCMe}$ with 3,3-dimethylselenetane **23** in hexane under reflux conditions in 88% yield (Equation 1). 3,3-Dimethylselenetane **23** has also been cyclo-oligomerized catalytically by the complex $\text{Re}_2(\text{CO})_9$ -3,3-dimethylselenetane **8**. It serves as a catalyst for the ring-opening macrocyclization of the 3,3-dimethylselenetane **23** to afford 3,3,7,7-tetramethyl-1,5-diselenacyclooctane **24**, 3,3,7,7,11,11-hexamethyl-1,5,9-triselenacyclododecane **25** and 3,3,7,7,11,11,15,15-octamethyl-1,5,9,13-tetraselenacyclohexadecane **26** (Scheme 3). All three macrocycles have been characterized by X-ray diffraction. The mechanism involves a series of ring-opening additions of **23** to the 3,3-dimethylselenetane ligand in **8**. The catalytic cycle is completed by exchange of the macrocycle with another 3,3-dimethylselenetane molecule (Scheme 4) <1997CC525, 1997OM3895>.



Scheme 3

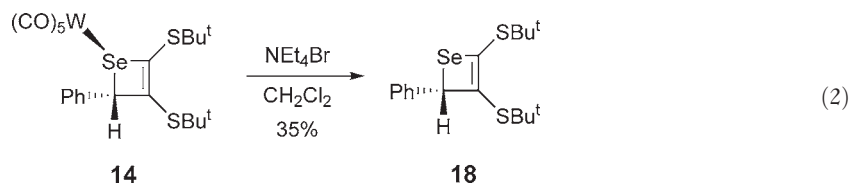
Acylation of the C-4 hydroxy group of **27** has been carried out using LHMDs/methyl chloroformate. However, the isolation of the 4-acyl analog **28** was difficult and, instead, a mixture of **28** and the ring-opened derivative **29** was tentatively identified. The presumed compound **28** was unstable and was converted to **29** either on attempted purification or on standing in a CDCl_3 solution (Scheme 5) <1999JOC2694>.

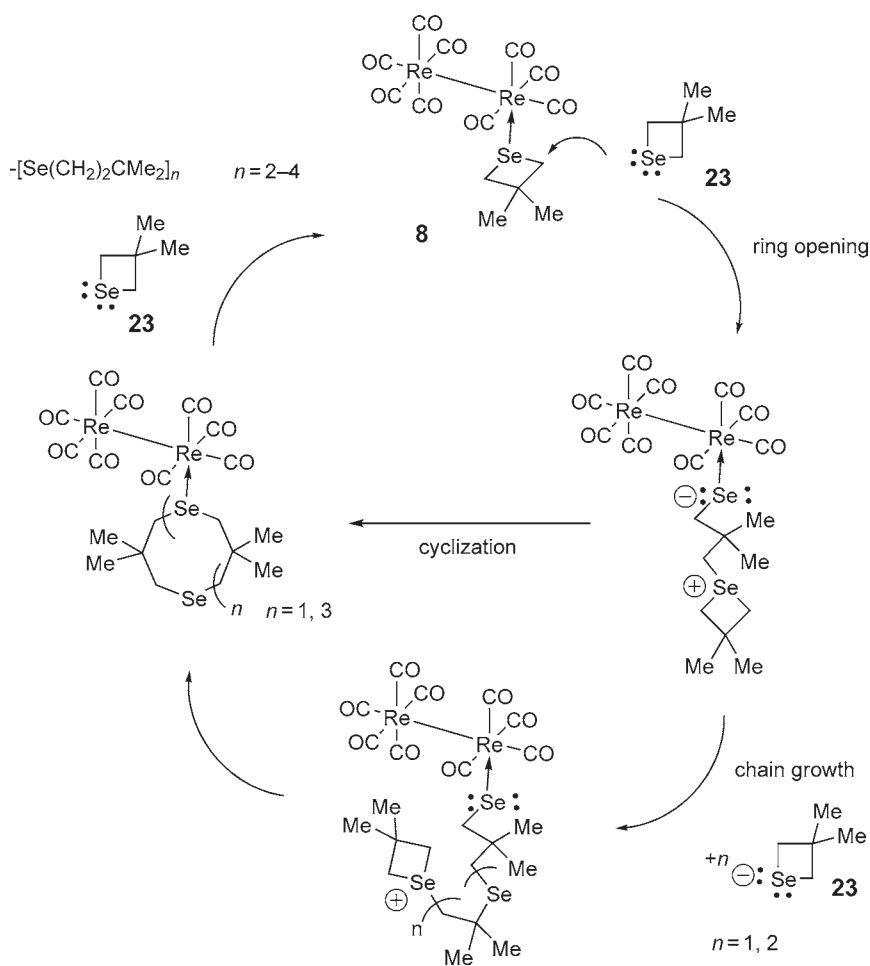
2.09.7 Reactivity of Substituents Attached to Ring Carbon Atoms

No discussions on these reactions related to four-membered cyclic compounds with one selenium or tellurium atom were found in the literature for the period 1995–2005.

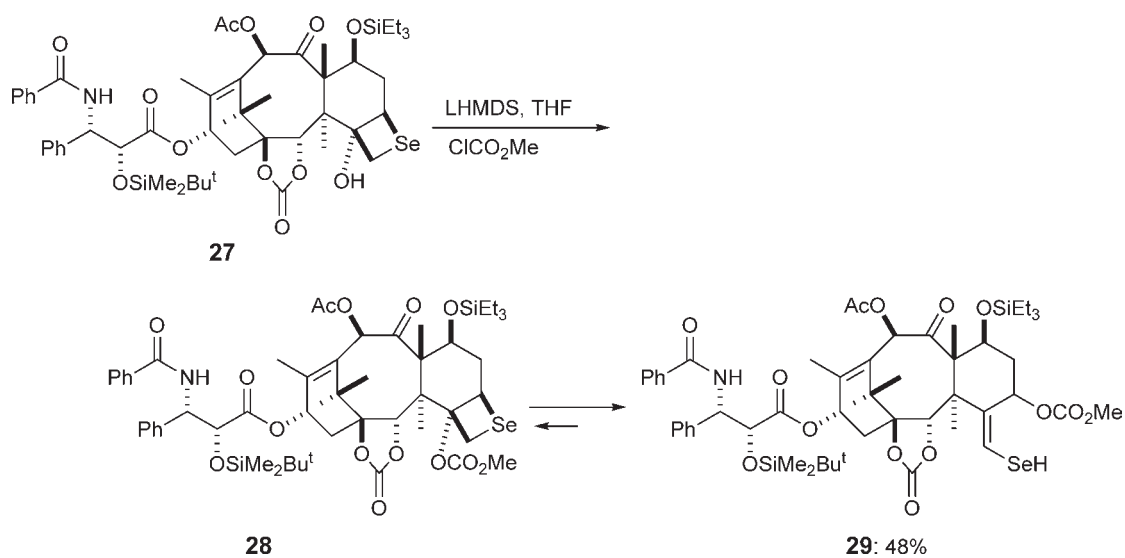
2.09.8 Reactivity of Substituents Attached to Ring Heteroatoms

Pentacarbonyltungsten-coordinated selenete **14** has been treated with NEt_4Br to lead to decomplexation of the selenete to give selenete **18** (Equation 2) <1995CC2461>.





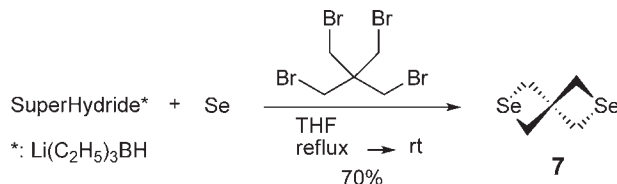
Scheme 4



Scheme 5

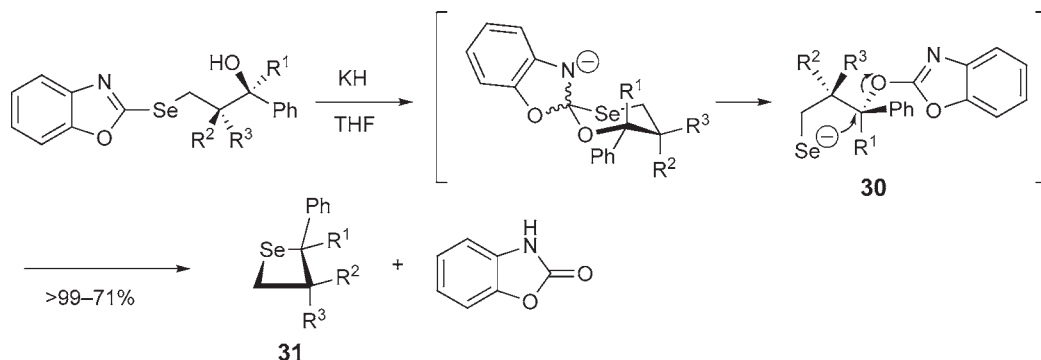
2.09.9 Ring Synthesis from Acyclic Compounds

The preparations of the parent selenetane (SeC_3H_6 **1**) and telluretane (TeC_3H_6 **2**) have been described in CHEC-II(1996) <1996CHEC-II(1)823>. They have been prepared by the reaction of disodium chalcogenide with 1,3-dibromopropane. Using a similar reaction, spiroseletane **7** has been obtained. Treatment of a heterogeneous milky white suspension, prepared from superhydride ($\text{Li}(\text{C}_2\text{H}_5)_3\text{BH}$) and selenium powder, and 1,3-dibromo-2,2-bis(bromomethyl)propane affords spiroseletane, 2,6-diselenaspiro[3.3]heptane, $\text{Se}_2\text{C}_5\text{H}_8$ **7** in 70% yield (Scheme 6) <2004IC5558>.



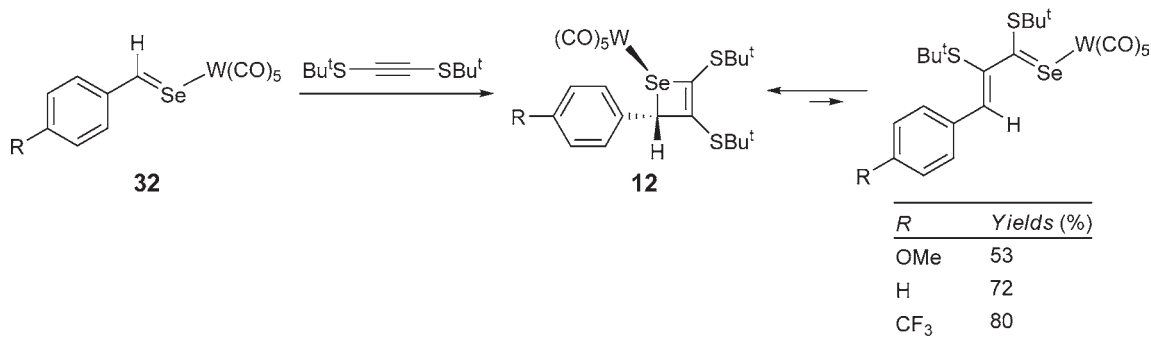
Scheme 6

Reactions of 2-(3-hydroxy-3-phenylpropylseleno)benzoxazole with KH in tetrahydrofuran (THF) give selenetane **31**. In the cases of *tert*-alcohols ($\text{R}^1 = \text{C}_2\text{H}_5$ or CH_2Ph), complex mixtures of products and no expected selenetane **31** are obtained because of steric hindrance at the reaction site. The formation of a selenetane is explained by a spiro intermediate which is converted into a selenolate anion. Intramolecular displacement of **30** gives the selenetane **31** (Scheme 7) <1998H633>.



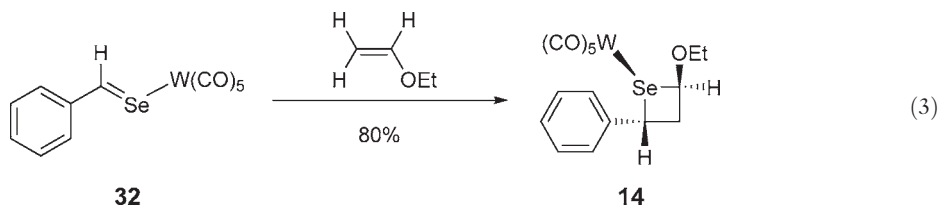
Scheme 7

Pentacarbonyltungsten-coordinated selenobenzaldehydes, $(\text{CO})_5\text{W}[\text{Se}=\text{CH}(p\text{-RC}_6\text{H}_4)]$ ($\text{R} = \text{OMe}$, H , CF_3) **32**, react with $\text{Bu}^t\text{SC}\equiv\text{CSBu}^t$ (2.5 equiv) by addition of the $\text{C}\equiv\text{C}$ to the $\text{Se}=\text{C}$ bond to give 2*H*-selenete complexes **12** (Scheme 8) <1995CC2461>.

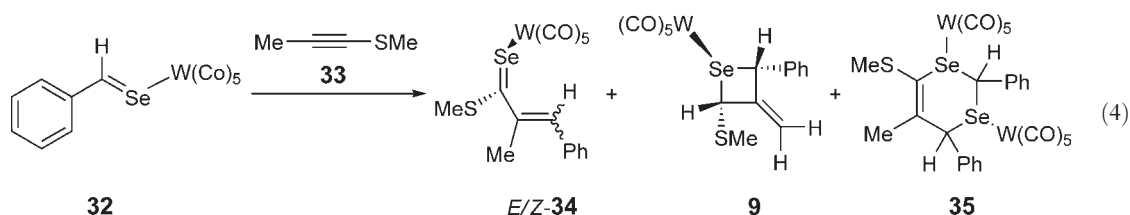


Scheme 8

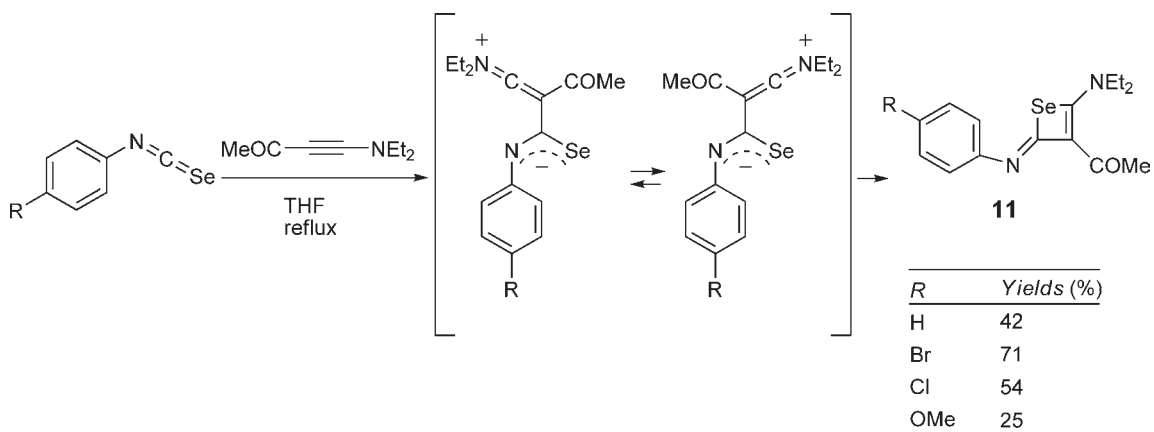
Pentacarbonyl(selenobenzaldehyde)tungsten, $(\text{CO})_5\text{W}[\text{Se}=\text{CH}(\text{C}_6\text{H}_5)]$ **32**, reacts with ethyl vinyl ether by [2+2] cycloaddition of the $\text{C}=\text{C}$ to the $\text{Se}=\text{C}$ bond to give selenetane **14** (Equation 3) <1996CB1169>.



Reaction of pentacarbonyltungsten-coordinated selenobenzaldehyde, $[(\text{CO})_5\text{W}(\text{Se}=\text{CHPh})]$ **32**, with eightfold excess of 1-methylthio-1-propyne ($\text{MeC}\equiv\text{CSMe}$) **33** gives three complexes: the thioselonocarboxylic ester complex as a mixture of the (*E*)- and (*Z*)- ($\text{C}=\text{C}$) isomers **34**, a selenetane complex **9**, and a dihydrodiselenine complex **35**. The product distribution depended on the ratio **32:33** and on the solvent (Equation 4) <1995CB1149>.

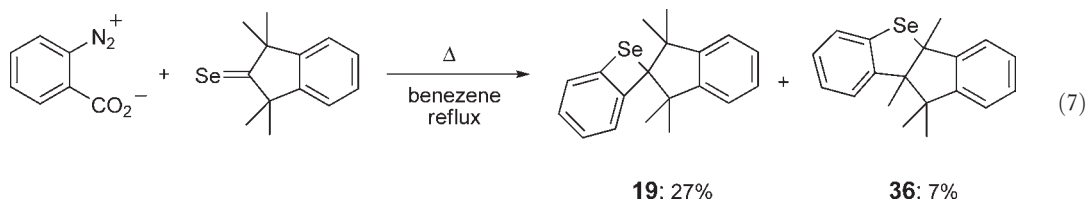
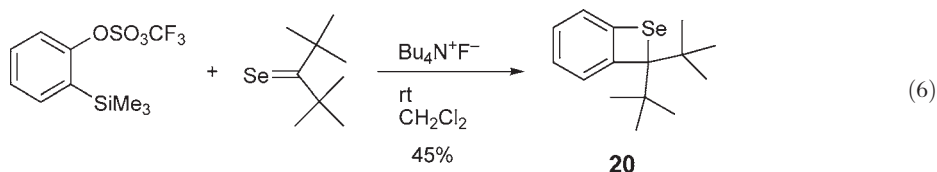
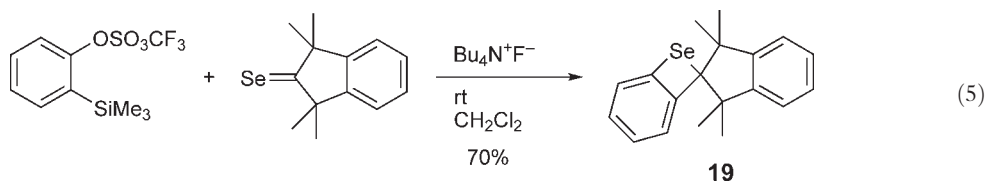


Aryl isoselenocyanates $4\text{-RC}_6\text{H}_4\text{NCSe}$ ($\text{R} = \text{H}, \text{Br}, \text{Cl}, \text{MeO}$) (prepared by selenation and dehydration of *N*-arylformamides) undergo regioselective cycloaddition reactions with 4-diethylamino-3-butyne-2-one in refluxing THF yielding *N*-arylselenetimines **11** (Scheme 9) <2004H(62)521>.

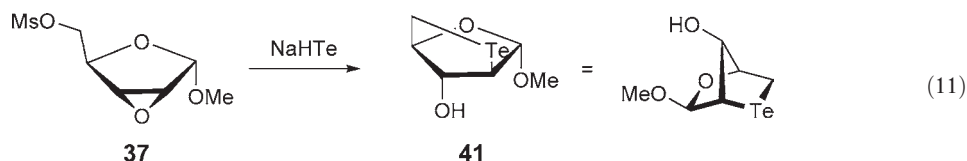
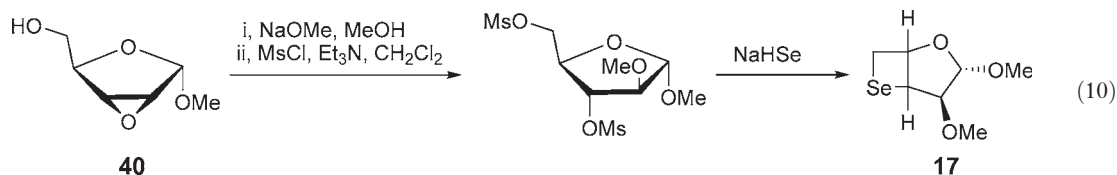
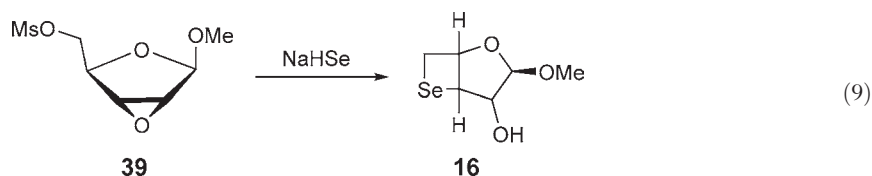
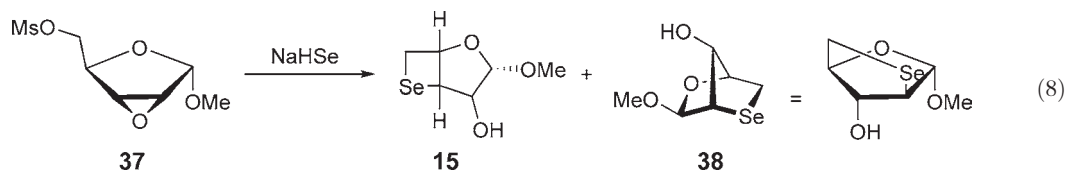


Scheme 9

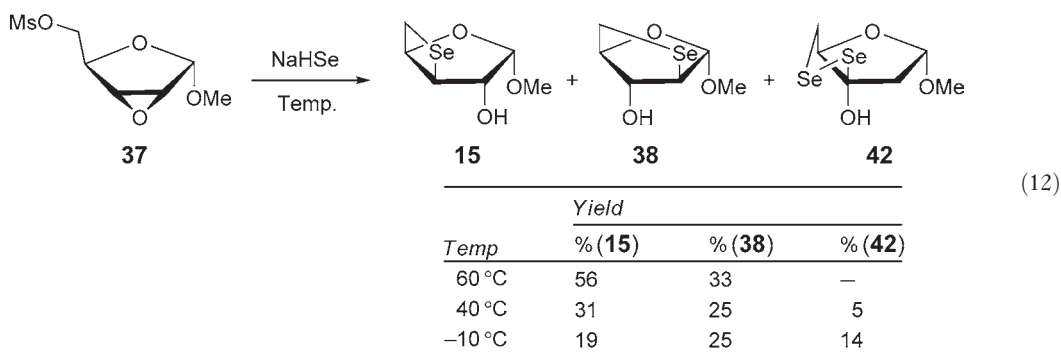
Reaction of 1,1,3,3-tetramethylindane-2-selenone with *o*-trimethylsilylphenyl trifluoromethanesulfonate in the presence of tetrabutylammonium fluoride affords benzoselenete **19** in 70% yield (Equation 5). Another sterically crowded selenone, di-*tert*-butyl selenoketone, gives the corresponding benzoselenete **20** in 45% yield (Equation 6). When 1,1,3,3-tetramethylindane-2-selenone is treated with benzenediazonium-2-carboxylate in refluxing benzene, compound **19** is obtained (27%) along with the rearranged product **36** in 7% yield (Equation 7) <2001JA7166>.



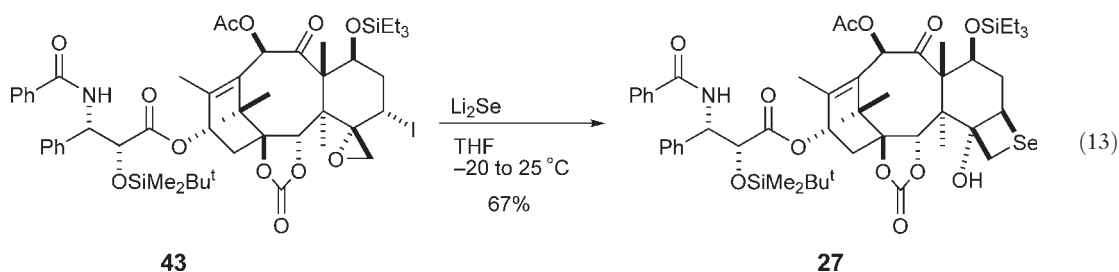
Methyl 2,3-anhydro-5-*O*-mesyl- α -D-*ribo*-furanosides **37** are treated with sodium hydrogen selenide to give selenabicycloheptanes. Reaction of furanoside **37** affords both selenetane **15** and selenolane **38** (Equation 8). Reaction of β -furanoside **39** gave only selenetane **16**. Selenolane **38**, a bicyclo[2.2.1]heptane derivative, is not formed from **39** (Equation 9). Selenetane **17** is obtained from methyl 2,3-anhydro- α -D-*ribo*-furanoside **40** via the dimethylate (Equation 10). On the other hand, the analogous reaction of furanoside **37** with sodium hydrogen telluride gives the elusive tellurabicyclo[2.2.1]heptane **41** (Equation 11) <1999PS429, 2004CAR1787>.



Reaction of **37** with sodium hydrogen selenide affords selenetane **15**, selenolane **38**, and diselenide **42** (Equation 12). The ratio of the products was dependent on the reaction temperature <2000CAR107>.



Treatment of a THF solution of the 5 α -iodo-20-epoxy derivative **43** with Li₂Se afforded the 5,20-seleno derivative **27** in 67% yield (Equation 13) <1999JOC2694>.



2.09.10 Ring Synthesis by Transformation of Another Ring

No discussions on this reaction related to four-membered cyclic compounds with one selenium or tellurium atom were found in the literature for the period 1995–2005.

2.09.11 Synthesis of Particular Classes of Compounds

The selenetanes that have been described in the literature have been constructed via three types of reactions. Selenetane derivatives are generally prepared via the [2+2] two-component syntheses (Schemes 8 and 9; Equations 3–7). The [1+3] two-component syntheses via the reaction of a selenium nucleophile with a three-carbon unit have been carried out (Scheme 6, and Equations 8–10, 12, and 13). One-component syntheses via rearrangement-cyclization have also been performed (Scheme 7).

2.09.12 Important Compounds and Applications

No discussions on this issue related to four-membered cyclic compounds with one selenium or tellurium atom were found in the literature for the period 1995–2005.

2.09.13 Further Developments

Recently, generation of selenetane and telluretane has been reported. 2,6-Diselenaspiro[3.3]heptane and 2-thia-6-selenaspiro[3.3]heptane have been prepared and were fully characterized by spectroscopic methods and by X-ray diffraction <2005IC77>. Formation of telluretane by the reaction of tellurium with 1-bromo-3-chloropropane in the system hydrazine hydrate-alkali has been confirmed <2006RJGC1970>.

The prediction of the homolytic bond dissociation enthalpy (BDE) and adiabatic ionization potential (IP) of 4-hydroxy-2,2,3,5,6-pentamethylbenzoselenete and benzotelluretes has been calculated <2006OBC846>.

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Biographical Sketch



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2.10

Four-membered Rings with One Phosphorus, Arsenic, Antimony, or Bismuth Atom

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The University of Tokyo, Tokyo, Japan

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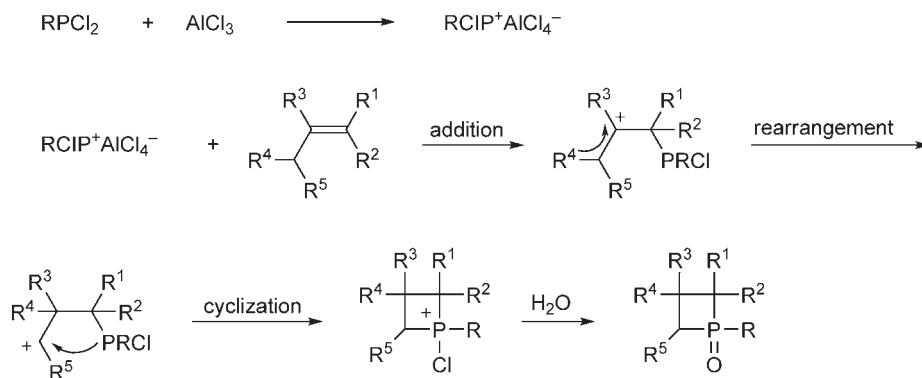
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2.10.1 Introduction

2.10.1.1 Historical Perspective

Four-membered rings containing one phosphorus, arsenic, antimony, or bismuth atom are pnictogenetanes (Pn = P, As, Sb, or Bi). Although a systematic study has only been carried out using the reaction of dichlorophosphines with highly substituted alkenes in the presence of aluminium trichloride ([Scheme 1](#)), some new approaches to this class of

compounds have been developed. Brief reviews on four-membered rings with one phosphorus atom appeared <1979COC(4)871, 2002CRV201>. Since several interesting compounds including the above compounds have also been summarized in CHEC(1984) <1984CHEC(7)449> and CHEC-II(1996) <1996CHEC-II(1B)883>, covering the literature up to about 1982 and 1994, respectively, in this chapter more recent work published until 2006 has been collected. Since the first report on four-membered rings containing one arsenic atom <1977JCD704>, a few new compounds of this class have been synthesized, and the first four-membered ring compound containing one antimony atom has been reported <1996HAC383>, but four-membered rings with one bismuth atom are still unknown, according to our knowledge. Theoretical calculations on four-membered ring compounds with one group 15 element (except for bismuth) have been reported and the heavier analogues present an open field of research.



Scheme 1

2.10.1.2 Nomenclature

Four-membered rings containing one phosphorus, arsenic, antimony, or bismuth atom can be classified mainly under three categories:

1. *Phosphetane, arsetane, stibetane, or bismetane*. Saturated four-membered rings containing one phosphorus atom are named as phosphetane. Arsetane, stibetane, and bismetane are arsenic, antimony, and bismuth analogues of phosphetane, respectively.

These compounds can also be named as phospho-, arsa-, stiba-, or bismacyclobutane derivative.

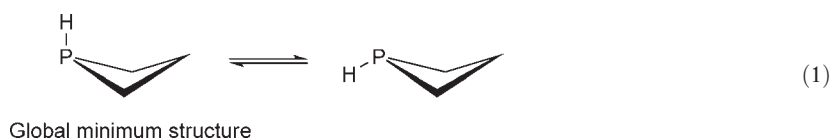
2. *Phosphetene, arsetene, stibetene, or bismetene*. Four-membered rings with one phosphorus, arsenic, antimony, or bismuth atom and one double bond in the ring are called phosphetene, arsetene, stibetene, or bismetene. These compounds can be named as phosphacyclobutene derivative, etc. The two isomers based on the position of the double bond can be named as Δ^1 -phosphetene and Δ^2 -phosphetene, for example.

3. *Phosphete, arsete, stibete, or bismete*. Four-membered rings with one phosphorus and two double bonds are named as phosphetes. Arsetes, stibetes, and bismetes are used for four-membered rings with one arsenic, antimony, or bismuth atom with two double bonds. These compounds are also named as phospho-, arsa-, stiba-, or bismacyclobutadienes.

2.10.2 Theoretical Methods

2.10.2.1 Theoretical Studies

Theoretical studies on parent trivalent phosphetanes have already been reported in the 1980s and the optimized structure of phosphetane has been revealed. Another theoretical study <1997HAC451>, aimed at understanding the ^{31}P NMR properties of phosphorus-containing heterocycles, has optimized the geometry of the parent phosphetane at a higher level of theory (MP2/6-31G(d)) and the energies were calculated at the MP2/6-311G(d,p) level. This study revealed that the pseudoaxial P-H form is more stabilized than the equatorial form by $1.32 \text{ kcal mol}^{-1}$ (Equation 1). It also indicates that the highest occupied molecular orbital–lowest unoccupied molecular orbital (HOMO–LUMO) gap in phosphetane is smaller than this in phosphirane, phospholane, and phosphinanes. From a more straightforward analysis of the molecular orbitals (at STO-3G), the characteristics of the phosphetane lone pair are found to be a nonbonding $\text{sp}^{2.12}$ orbital.



A relatively recent theoretical study concerning radical or cationic species of phosphetane has been reported <1996JPC585>. Geometry optimization of the C_3P radical (at MP2/6-31G(d) level) found four isomers, one linear isomer, three four-membered ring structures, and a three-membered ring structure. From the comparison of the relative energies at different levels of theory, the linear structure is much more stable than other ring isomers (Figure 1; Table 1). From the calculation of a cationic species of C_3P^+ , a linear triplet state is also found to be the most stabilized form and the four four-membered ring isomers and two three-membered ring isomers have a local minima (Figure 2; Table 2).

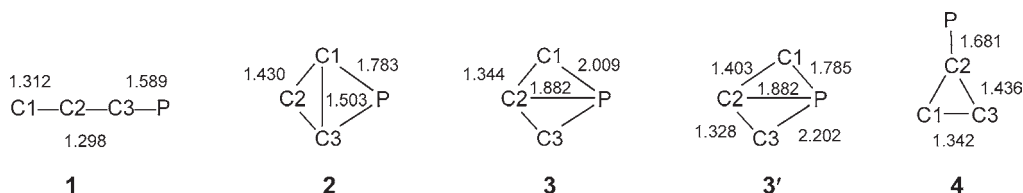


Figure 1 MP2/6-31G(d) optimized geometries for the different C_3P radicals. Distances are given in angstroms.

Table 1 Relative energies^a (kcal mol⁻¹) for the C_3P radicals at different levels of theory

	1	2	3	3'	4
HF/6-31G(d)	0.0	24.3	37.9		38.1
MP2/6-31G(d)	0.0	5.9	33.3	32.3	19.7
HF/MC-311G(d)	0.0	24.4	38.0	39.5	39.4
MP4/MC-311G(d)	0.0	13.3	35.6	33.3	23.7
PMP4/MC-311G(d)	0.0	17.0	39.5	35.5	26.9
PMP4 + $\Delta ZPVE^b$	0.0	15.4	36.9	33.1	24.4

^aThe results with MC-311G(d) basis set were obtained employing the MP2/6-31G(d) optimized geometries.

^bZero-point vibrational energy differences were obtained scaling the MP2/6-31G(d) vibrational frequencies.

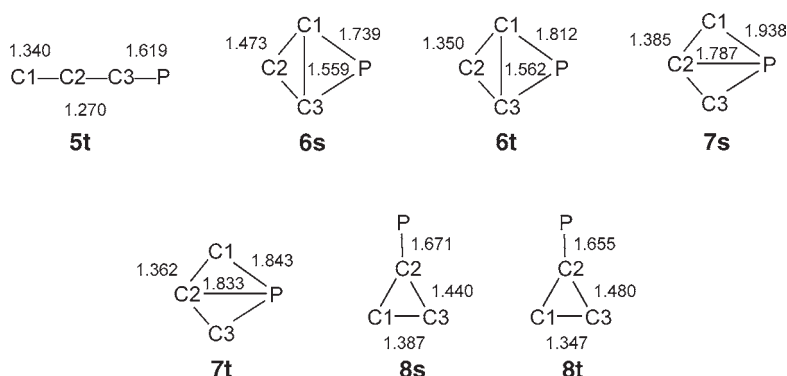


Figure 2 MP2/6-31(d) optimized geometries for the singlet and triplet states of C_3P^+ . Distances are given in angstroms.

A multiconfiguration self-consistent field (MCSCF) level calculation on phosphacyclobutadiene (phosphete) compared to cyclobutadiene, aza-, 1,3-diaza-, and 1,3-diphosphacyclobutadiene has been reported <1993AGE617>. Density functional calculations about a trivalent phosphete and arsete and pentavalent dihydro- and difluorophosphetes and arsetes have been performed <2001HCA1578>. Species **9** and **10** have a planar structure with two unequal C–P(As) bonds, while pentavalent phosphetes and arsetes **11–14** have approximately C_2 symmetries and the four-membered rings are planar. In contrast to structures **9** and **10**, the two C–P(As) bonds in **11–14** are equal (Figure 3).

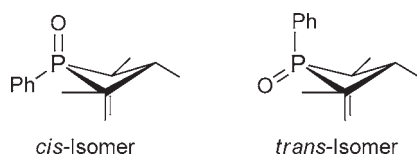
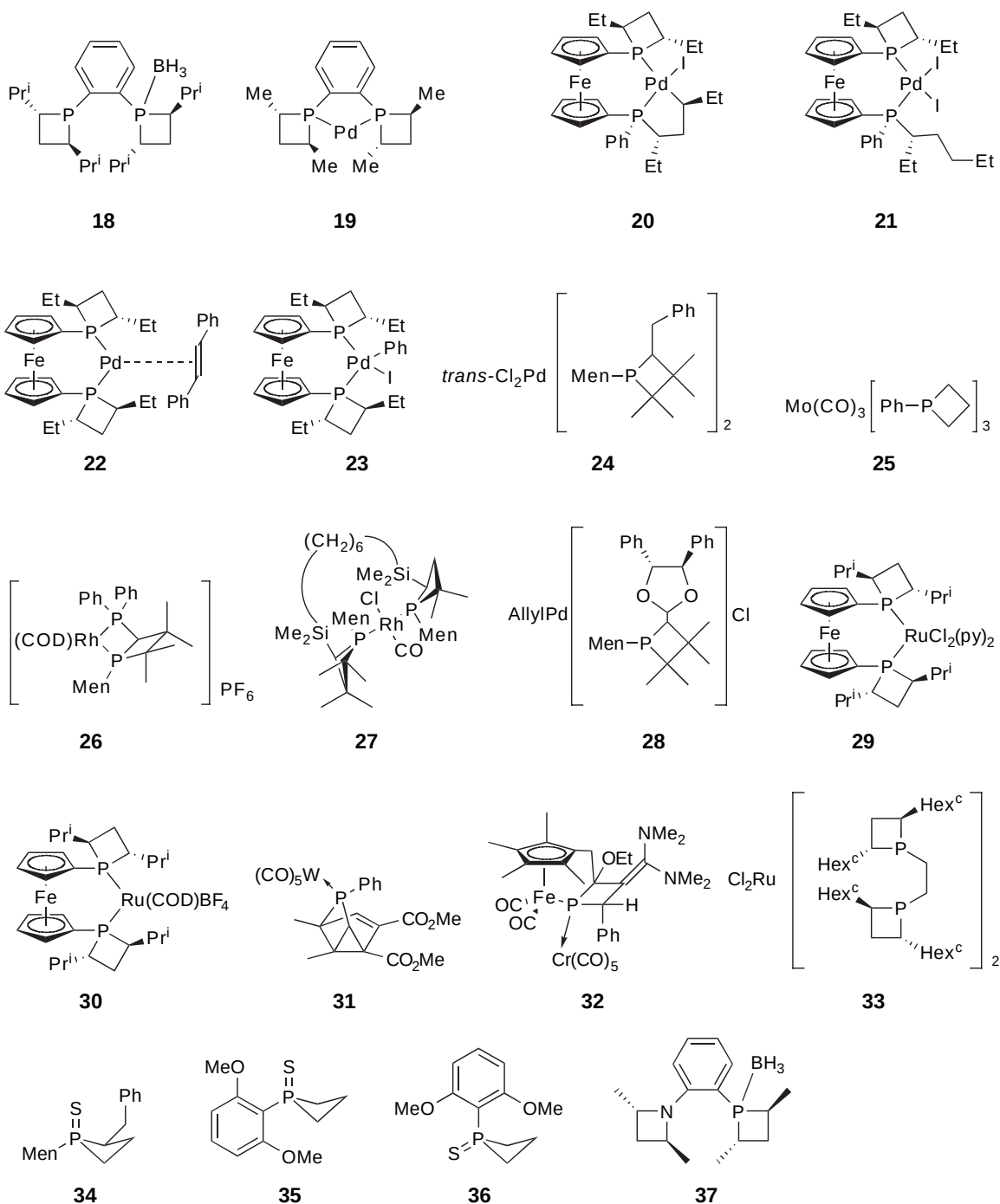
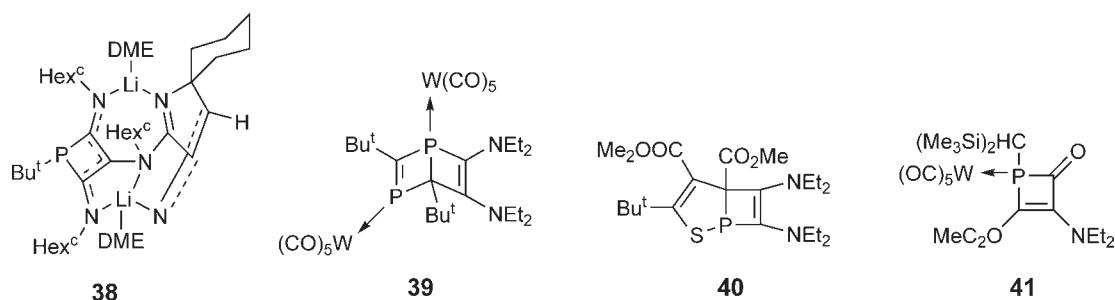
**Figure 5** Solid-state geometries for phosphetane oxides.**Figure 6**

Table 3 Selected bond lengths (Å) and bond angles (deg) in phosphetane derivatives

	<i>Bond length</i>		<i>Bond angle</i>		<i>Reference</i>
	<i>P–C(2)</i>	<i>P–C(4)</i>	<i>C(2)–P–C(4)</i>	<i>C(2)–C(3)–C(4)</i>	
18 P(III) P–BH ₃	1.863(3)	1.887(3)	76.9(1)		2000T95
	1.851(2)	1.849(3)	80.1(1)		
19	1.841(3)	1.859(4)	79.5(2)		2004OM2228
20	1.871(4)	1.876(4)	77.21(18)	98.0(3)	
21	1.864(7)	1.875(7)	78.3(4)	100.2(7)	2005OM2730
23	1.869(6)	1.887(6)	77.4(3)	100.5(7)	
	1.862(6)	1.872(6)	78.1(4)	100.0(6)	
22	1.874(2)	1.877(2)	77.26(9)	97.88(15)	
	1.869(2)	1.867(2)	77.24(10)	97.45(17)	1994OM3956
24	1.85(1)	1.86(1)	76.2(6)		
25	1.851(5)	1.857(5)	77.1(2)	100.4(5)	1996OM1301
26	1.873(8)	1.898(7)	78.3(3)	97.9(5)	1995OM4983
27	1.889(3)	1.882(3)	77.6(1)		1996JOM(522)223
28	1.840(4)	1.886(4)	76.7(2)		1997JOM(529)465
29	1.892(3)	1.887(3)	76.3(1)		2003EJI2583
	1.908(3)	1.884(3)	77.3(2)		
30	1.877(4)	1.884(4)	78.1(2)		1997OM4145
	1.885(3)	1.869(4)	77.9(2)		
31	1.936(5)	1.806(4)	77.6(2)	99.0(3)	1998CEJ469
32	1.933(4)	1.921(4)	76.7(2)	102.8(3)	
33	1.867(3)	1.852(3)	77.8(1)		2001JOM(624)162
34	1.841(2)	1.848(2)	79.1(1)		1997T4363
35	1.821(3)	1.813(3)	78.67(12)		1999JOM(585)167
36	1.832(3)	1.832(3)	76.7(2)		2001S2095
37	1.855(2)	1.849(2)	78.33(7)	97.5(1)	

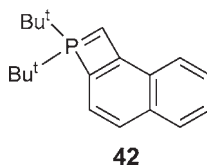
Several X-ray crystallographic analyses for phosphetenes have been reported (Figure 7; Table 4). In contrast to phosphetanes, the four-membered rings in phosphetenes have a nearly planar structure. Single bonds for P–C(sp²) are shorter than those of P–C(sp³).

**Figure 7**

In the naphthalene-annulated tetracoordinated phosphete (phosphacyclobutadiene) **42**, all the ring atoms lie in the same plane (maximum deviation: 0.042 Å). As observed in the nonconjugated derivatives, the value of the inner ring angle at the phosphorus atom is small (78.9(3)°), and that of the opposite angle is large (106.7(6)°). The four-membered ring is almost a symmetrical rhombus: the two P–C bond lengths (1.772(8) and 1.773(6) Å) are in the range of those reported for semi-stabilized phosphorus ylides. Furthermore, the two C–C bond lengths lie halfway between those of single and double bonds (Figure 8) <1996CEJ68>.

Table 4 Selected bond lengths (Å) and bond angles (deg) in phosphetene derivatives

	Bond length		Bond angle		Reference
	P–C(2)	P–C(4)	C(2)–P–C(4)	C(2)–C(3)–C(4)	
38	1.888(4)	1.898(4)	71.6(2)		2005OM842
39	1.830(9)	1.874(8)	75.7(4)	103.8(8)	2002JOM(643)409
40	1.802(3)	1.910(3)	74.02(12)	100.7(2)	2003EJO512
41	1.834(4)	1.880(4)	72.0(2)	97.2(3)	1999EJI1567

**Figure 8**

The X-ray crystallographic analysis of a phosphete Rh-complex has been reported <1999OM4838>. The four-membered ring in the phosphete has a planar structure and the two P–C bond lengths are almost equal (1.806(6) and 1.789(7) Å), indicating the delocalization of π -electrons in the phosphete ring.

An arsetene iron complex <1995OM1434> and free arsetene <2005OM842> were analyzed by X-ray crystallographic analyses to reveal that they had structures similar to those of the corresponding phosphorus analogues, although the As–C bond lengths are elongated compared to the P–C bond length and the C–As–C bond angles are smaller than the C–P–C bond angles by about 5°.

X-Ray crystallographic analysis of antimony containing four-membered ring compounds is still unknown to the best of our knowledge.

2.10.3.2 NMR Studies

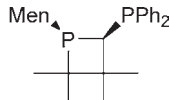
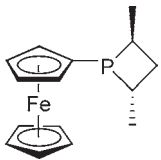
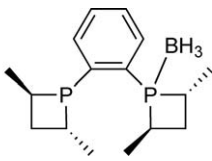
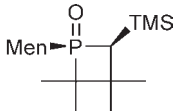
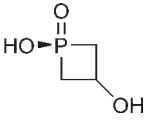
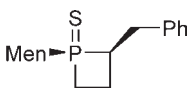
Nuclear magnetic resonance (NMR) data for five nuclei (^{31}P , ^{13}C , ^1H , ^{19}F , and ^{17}O) have been used to elucidate the structural properties of phosphetanes. Detailed discussions concerning these aspects are summarized in CHEC-II(1996) <1996CHEC-II(1B)883>. Hence, only additional ^{31}P NMR data reported in this decade are mentioned in this section and these are given in Table 5. Usually, ^{31}P NMR of the phosphorus atom in the phosphetane ring shows a large lower field shift, compared to the corresponding acyclic compounds. For example, 1-phenylphosphetane shows its ^{31}P NMR chemical shift at 13.9 ppm, while that for diethylphenylphosphine is at –15.5 ppm. To clarify such lower field shifts in ^{31}P NMR, MP2/6-311G(d,p) level gauge-independent atomic orbital (GIAO) calculations were performed <1997HAC451>. The chemical shielding can rationalize the degree of coupling between phosphorus lone pair orbital and the LUMO orbital. In the case of phosphetanes, the HOMO–LUMO gap is smaller than those of phosphiranes, phospholanes, and phosphinanes. The phosphorus atom in the phosphetane ring has an sp^2 hybrid orbital for the lone pair. From these features, the coupling is more effective in the phosphetanes and leads to the deshielding effect, which causes the lower field shift in the ^{31}P NMR. On the other hand, in phosphiranes, the coupling is relatively ineffective because of the lower p character of the lone pair orbital and the larger HOMO–LUMO gap, resulting in a large upfield shift in the ^{31}P NMR.

2.10.4 Thermodynamic Aspects

2.10.4.1 Aromaticity

Several phosphete-containing transition metal complexes have been structurally determined. In their crystallographic structures, phosphete rings indicated their delocalized structures. Therefore, the aromaticity and antiaromaticity of these classes of compounds attract special attention, and encourages comparison to the highly antiaromatic cyclobutadienes.

Table 5 ^{31}P NMR data for selected phosphetane derivatives

Compound	δ_{P} (ppm)	Reference
43 	24.4 −18.6 [$J_{\text{PP}} = 87 \text{ Hz}$] (C_6D_6)	1995OM4983
44 	18.4 (C_6D_6)	2001S2095
45 	13.9 (C_6D_6)	1996OM1301
46 	49.1 16.9 [$J_{\text{PP}} = 36 \text{ Hz}$] (CDCl_3)	1997TL2947
47 	68.0 (C_6D_6)	1996JOM(522)223
48 	40.0 (D_2O)	1995JOC6076
34 	77.3 (THF)	1997T4363

Nucleus-independent chemical shift (NICS) values, which were proposed by Schleyer, are widely discussed in view of the aromaticity of the compounds. The NICS values of λ^3 - and λ^5 -phosphetes and arsetes were calculated at the GIAO-SCF/6-31+G(d)//B3LYP/6-311+G(d,p) level and they are summarized in [Table 6 <2001HCA1578>](#). For λ^3 -phosphete **9** and arsete **10**, the NICS values are very close to the cyclobutadiene values, which indicates that the incorporation of a λ^3 -P or an As-group does not change the antiaromaticity of cyclobutadiene. In contrast to the λ^3 -phosphete and arsete, the $\text{NICS}_o(0)$ values of λ^5 -phosphetes **11** and **12** and arsetes **13** and **14** are much less than that of cyclobutadiene and these compounds have small negative $\text{NICS}_\pi(0)$ values (−3.1 to −8.2 ppm). Hence, the incorporation of λ^5 -P(As) X_2 units weakens the antiaromaticity of the cyclobutadiene significantly. This difference can be attributed to the contributions of pseudo- π -electrons from two P–X (or As–X) bonds to the 4π -electron rings.

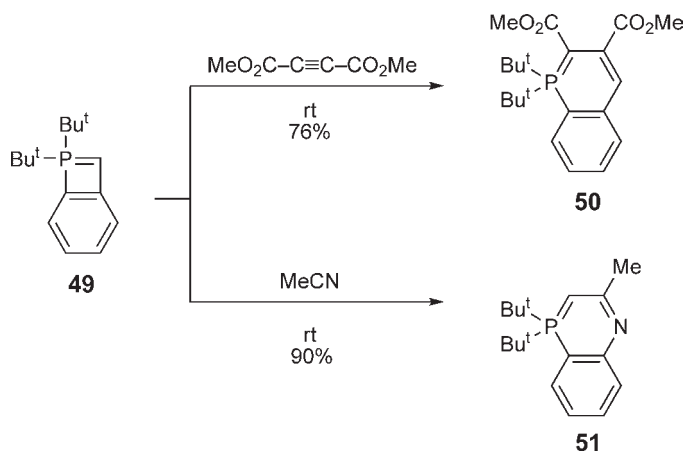
2.10.5 Reactivity of Fully Conjugated Rings

Benzene- and naphthalene-annulated tetracoordinated phosphetes have been synthesized and their reactivities toward insertion reactions were investigated. As expected, benzophosphete **49** is very reactive because it contains a phosphorus ylide moiety. Insertion of dimethyl acetylenedicarboxylate and acetonitrile occurred at room

Table 6 NICS_{tot}, NICS_π, and NICS_σ at point 1 Å above and at the ring center

	NICS _{tot} (1)/(0)	NICS _π (1)/(0)	NICS _σ (1)/(0)
	12.7/20.9	14.1/−0.2	1.7/23.2
 9	13.1/22.2	13.7/0.2	1.6/23.0
 10	13.4/22.9	12.8/0.3	1.9/22.4
 11 : X = H	1.6/0.8	3.4/−8.2	0.0/11.9
 12 : X = F	4.8/−0.4	7.8/−5.3	−1.9/5.6
 13 : X = H	2.3/1.5	3.6/−6.5	0.0/10.1
 14 : X = F	4.8/0.4	7.9/−3.1	−1.9/1.9

temperature, giving rise to the bicyclic[4.4.0]decanes **50** in 76% and **51** in 90% isolated yields, respectively. Surprisingly, the mode of insertion is different for each substrate (Scheme 2). Dimethyl acetylenedicarboxylate inserts into the P=CH bond as expected, while acetonitrile inserts into a formal carbon–carbon bond and not into a phosphorus–carbon bond as expected <1996CEJ68>.

**Scheme 2**

2.10.6 Reactivity of Nonconjugated Rings

The preparation of poly(propylphosphine) by ring opening of a phosphetane is a desirable method for the phosphorus-containing polymer, but it seems to be difficult because the ring strain of the phosphetane does not diminish the stability of phosphetane very much. Hence, such ring-opening polymerization is only observed in the C-unsubstituted trivalent phosphetane. Furthermore, diluting the phosphetane substantially reduced the rate of polymerization <1996OM1301>. Analogous ring-opening reactions were also observed in ferriphosphetane **52** (Figure 9) <2002OM1998>. By sulfurization or complexation with borane, the stability of the phosphetane against ring-opening polymerization is much improved <1997T4363, 1997TL2947>.

Ring-opening reactions of phosphetanes (phosphetanium salts) are known to be promoted by nucleophiles. The reaction profile has been analyzed by theoretical calculations (HF/6-31+G(d)) <2001JOC915> and compared with those of a phosphirane and an acyclic phosphine as shown (Equations 2–4). The activation energy (E_a) for the reaction of a four-membered ring is twice as high as that for a three-membered ring, whereas exothermicities (ΔE_0) of both reactions are almost identical.

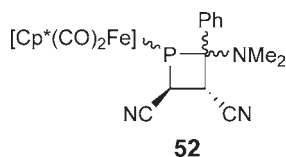
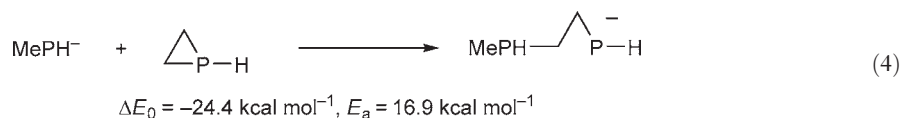
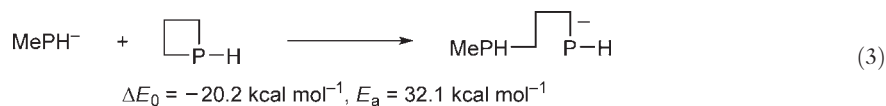
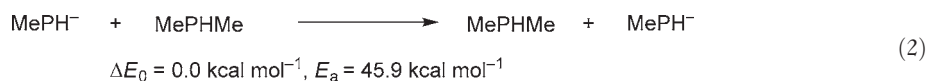
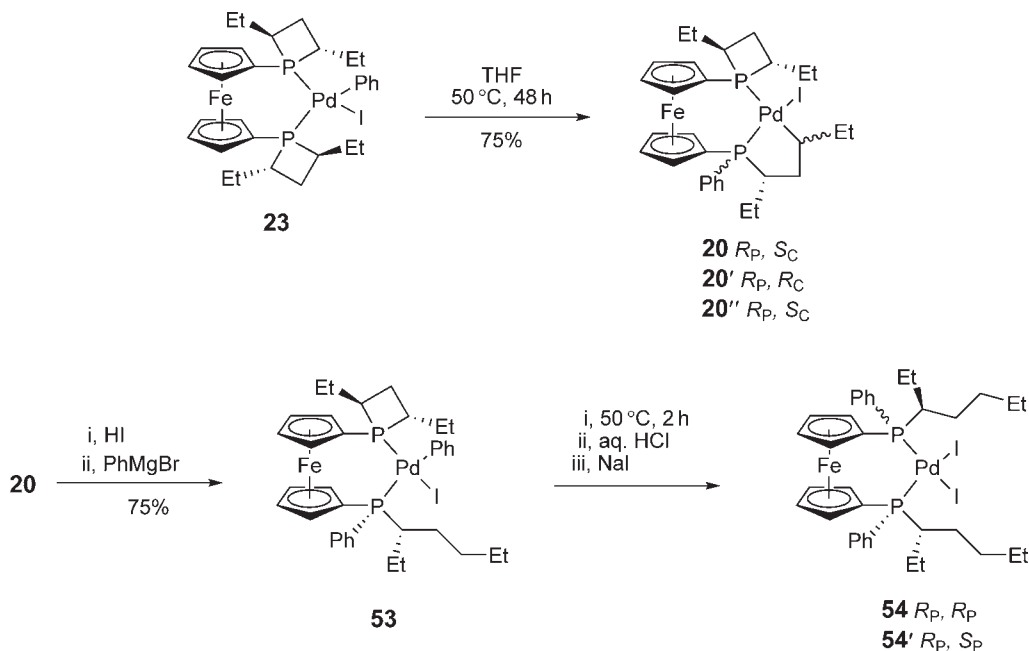


Figure 9



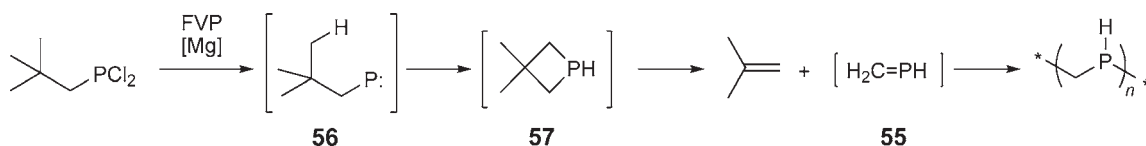
Such a ring-opening reaction is also encouraged in a palladium complex. Heating a tetrahydrofuran (THF) solution of **23** to 50 °C for 48 h resulted in a slow decomposition to afford three palladacycles **20**, **20'**, and **20''**, (Scheme 3) <2004OM2228>. The cleavage of the second phosphetane ring proceeded from **53**, which was obtained from **20** by reaction with aqueous HI and subsequent treatment with PhMgBr. The double ring-opened products **54** and **54'** contain unusual examples of chiral bidentate phosphine ligands with both P- and C-stereocenters.



Scheme 3

Flash vacuum pyrolysis of dichloroneopentylphosphine in the presence of magnesium gave a phosphathene polymer. The formation of a phosphathene polymer from phosphalkene **55** had been noted elsewhere

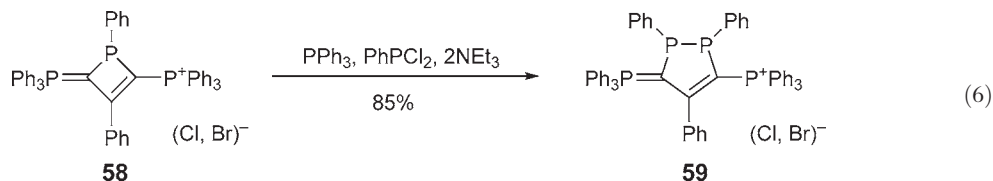
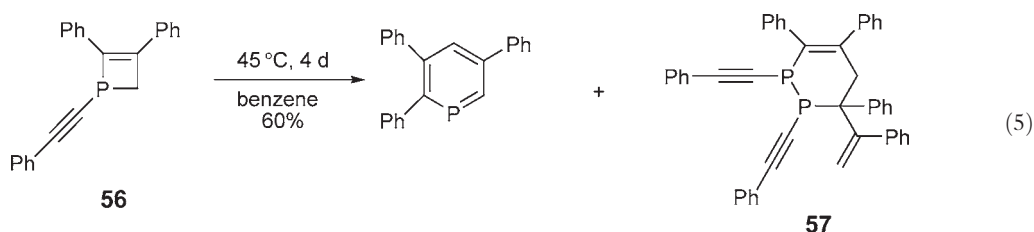
<1987TL5811> but it had not been fully characterized. These products probably result from the formation of neopentylphosphinidene **56** which can undergo an intramolecular insertion to give the phosphetane **57** that fragments into isobutene and **55** (Scheme 4) <1997TL8417>.



Scheme 4

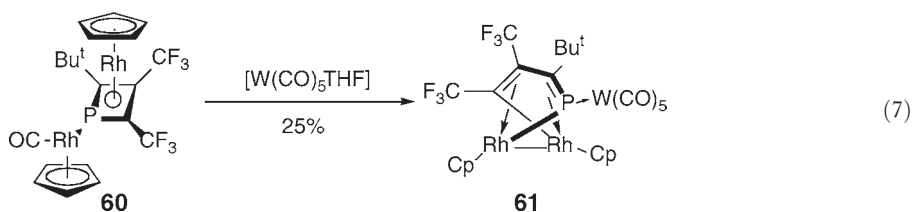
The photochemical reaction of phosphetane sulfide **35** gave some ring-cleaved product like phosphinidene sulfide and methylene(thio)phosphorane as well as the ring-expanded product. However, characterization of the final products was not complete <1999JOM(585)167>.

Ring-opening reaction accompanied by ring expansion also occurred in the phosphetene bearing an alkynyl group on the phosphorus atom <1996HAC397, 1998JOM(567)151> to give a phosphinine. Upon mild heating of **56** for several days in benzene, **56** was indeed transformed into the corresponding phosphinine with a trace amount of the [4+2] dimer **57** (Equation 5). The mechanism probably involves the electrocyclicization of an intermediate phosphadiene. The formation of an intermediate phosphadiene was ascertained by the characterization of the [4+2] dimer **57**. The similar ring-opening-expansion reaction is also observed in the phosphetenylphosphonium halide **58** attached to a phosphorus ylide moiety in *exo*-fashion. Compound **58** is converted to diphospholylphosphonium halide **59** by reaction with dichlorophenylphosphine and triphenylphosphine in the presence of Et₃N (Equation 6) <1996CEJ221>.



Tungsten-coordinated phosphetenes reacted with double- or triple-bond compounds, like *N*-phenylmaleimide, dimethyl acetylenedicarboxylate, and benzaldehyde, to give formal [4+2] cycloaddition products <1988TL3077>. Several years later, non-metal-coordinated phosphetenes were found to be reactive toward multiple bond compounds after prolonged heating (at 150 °C for several weeks) <1998HAC9>.

In phosphite rhodium complex **60**, the phosphite coordinates to the rhodium center in two fashions; the phosphorus lone pair coordinates to the rhodium center in an η¹-form, and the phosphacyclobutadiene moiety coordinates to the other rhodium center in an η⁴-fashion. From its reactivity, η¹-coordination seems to be labile, suggesting the possibility of metal exchange. Stirring a solution of **60** with [W(CO)₅THF] led to the 'flyover' complex **61** (Equation 7). The structure of **61** was confirmed by X-ray crystallographic analysis and it revealed that the phosphite ring is cleaved and that P=C and C=C bonds coordinate to the rhodium metals in η²-mode <1999OM4838>.



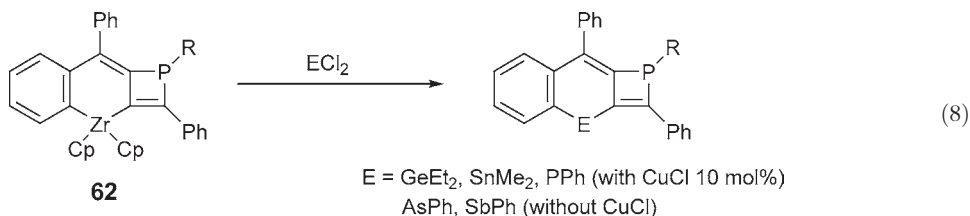
2.10.7 Reactivity of Substituents Attached to Ring Carbon Atoms

As described in Section 2.10.8.2, phosphetanes are widely used as chirality-inducing ligands in asymmetric catalytic reactions. To improve their enantioselectivities, further modifications of the substituents attached to the ring carbon atoms has been energetically investigated. Introduction of substituents onto the ring carbon atoms is easily achieved via the direct lithiation of the α -carbon to the phosphorus atom in phosphetane oxides. In the case of the introduction of a benzyl group, the desired products are obtained in >75% yields with high diastereoselectivities <1993T10291>, probably due to steric constraints in the hindered four-membered ring. In addition to a benzyl group, allyl, formyl, and silyl groups can be introduced onto α -carbon atoms in moderate to high yields using allyl halides, DMF, or silyl chlorides as electrophiles <1997JOM(529)465, 1994OM3956, 1996JOM(522)223>. Similarly, these deprotonation–alkylation protocols can be utilized for phosphetane sulfides <1997T4363>.

The substituents on the ring carbon atoms show the usual reactivities. For example, a formyl group is converted to an acetal group <1997JOM(529)465, 1994OM3956>. Such transformations on the ring carbon atom furnish the improvement of the enantioselectivity in the asymmetric catalytic reactions like Rh-catalyzed hydrogenations. As other examples, a formyl group is converted to a hydroxymethyl group, an allyl group to hydroxyethyl, and hydroxypropyl groups are converted by reaction with O_3 and 9-borabicyclo[3.3.1]nonane (9-BBN), respectively. These hydroxyalkyl groups are further converted to phosphalkyl groups using the usual experimental conditions <1998S1539>.

Deprotonation of the α -carbon can be further applied in the synthesis of diphosphetenyl ligands, which showed high enantioselectivities in asymmetric catalytic reactions <2004TA2213>. Diphosphetenyl dioxides are obtained by copper chloride(II)-mediated oxidation of organolithium compounds, which are generated from the corresponding benzophosphetenes in moderate yields.

Interesting reactivities of air-stable phosphetene fused zirconacycles **62** have been reported <2004T1317>. The Cp_2Zr moiety was exchanged with higher group 14 and 15 elements. Attempted exchanges with Et_2GeCl_2 and Me_2SnCl_2 failed even under prolonged reaction times or at high temperature. However, expected derivatives were obtained when the reaction was conducted in the presence of 10 mol% of CuCl. In the case of the reaction with $PhAsCl_2$ and $PhSbCl_2$, it is not necessary to use CuCl (Equation 8). In addition to the exchange reactions, such zirconacyclic complexes afford the *exo*-alkyldienephosphetene by treatment with 2 equiv of HCl. Hence, zirconacyclic complexes appear to be useful reagents, *via* reactions involving selective Zr–C bond cleavage or Zr–group 14–15 element exchanges, allowing the formation of a variety of new polyunsaturated mono- or tricyclic systems.



2.10.8 Reactivity of Substituents to Ring Heteroatoms

2.10.8.1 Coordination Chemistry

Comparatively little is known about phosphetane coordination compounds, which first appeared in 1984 <1984NJC453>, and are now accessible through two distinct synthetic pathways. The first is direct coordination of phosphetanes to the desired metal center. The second is a built-up method from its components within a metal

coordination sphere <1993IC5720, 1998CEJ469, 1997PS545>. The performance of this second method is often excellent, as demonstrated by the synthesis of the iron-coordinated phosphetane complex, which is achieved in high yield (84%) as much as its phospholane and phosphorinane analogues <1995OM1434>. Low oxidation state, strongly binding metal centers such as $[\text{W}(\text{CO})_5]$ <1999AGE215>, and $[\text{CpFe}(\text{PR}_3)_2]^+$ fragments are used. This method is very useful, especially when the desired complex incorporates a phosphetane that is either very labile or not available by the usual preparations of free phosphetanes.

In most cases, complexes can be prepared by the simple addition of a phosphetane ligand to the desired metal center. For example, reactions of 1-phenylphosphetane with $\text{Mo}(\text{CO})_4(\text{NBD})$ and $\text{Mo}(\text{CO})_3(\text{mesitylene})$ provided *cis*-**63** and *fac*-**25** (Figure 10) in 58% and 81% isolated yields, respectively (NBD = 2,5-norbornadiene) <1996OM1301>.

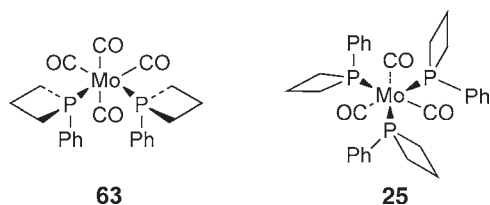


Figure 10

The coordination chemistry of optically pure, chiral phosphetanes has been studied with special attention to the preparation and characterization of complexes since they are suitable for asymmetric catalytic reactions. The optically active *P*-menthylphosphetanes showed similar reactivities with usual trivalent phosphines to afford stable palladium(II) and ruthenium complexes, under usual reaction conditions. Similarly, the Pd-allyl complex **28** <1997JOM(529)465> has been prepared from $[(\text{allyl})\text{PdCl}]_2$ and was characterized by X-ray crystallography. Reaction of the *P(R),C(S)*-2-benzyl-3,3,4,4-tetramethyl-1-menthylphosphetane **64** with $\text{Ru}_3(\text{CO})_{12}/\text{HCO}_2\text{H}$ proceeds normally to give the formate bridged dimer **65** (Figure 11) <1998S1539>.

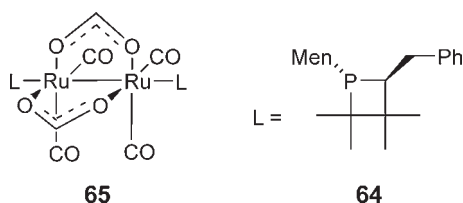


Figure 11

The sterical hindrance between the two *cis*-ligated phosphetanes could be responsible for the lability of these complexes. This assumption is supported by the easy formation of stable bis(phosphetane)rhodium complexes, such as **66**, from less-hindered phosphetanes <2000H(52)905, 2001S2095>, as well as by the observed stability of the *trans*-complex **67** obtained from phosphetane **64** and $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ by halide bridge cleavage and CO displacement (Figure 12) <1998S1539>.

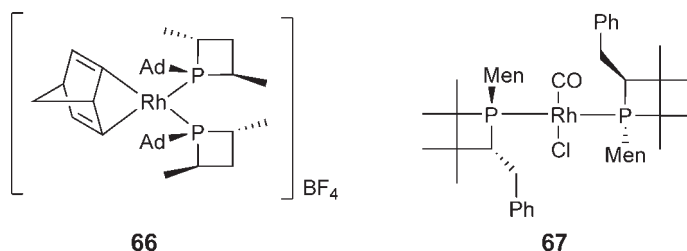
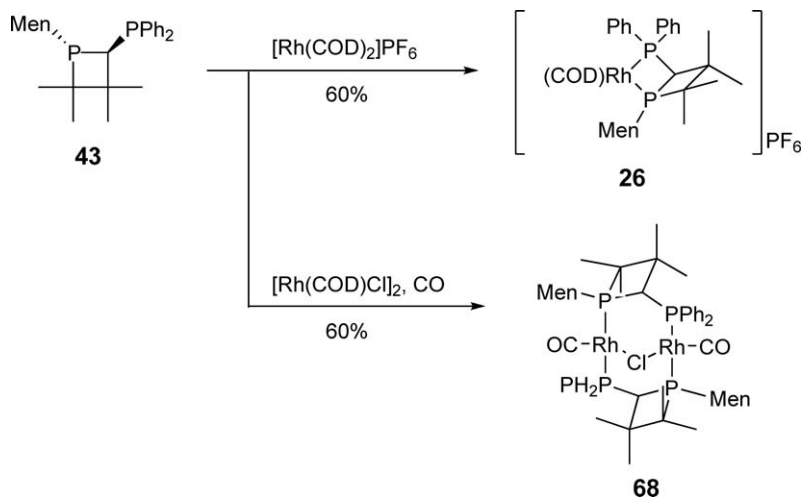


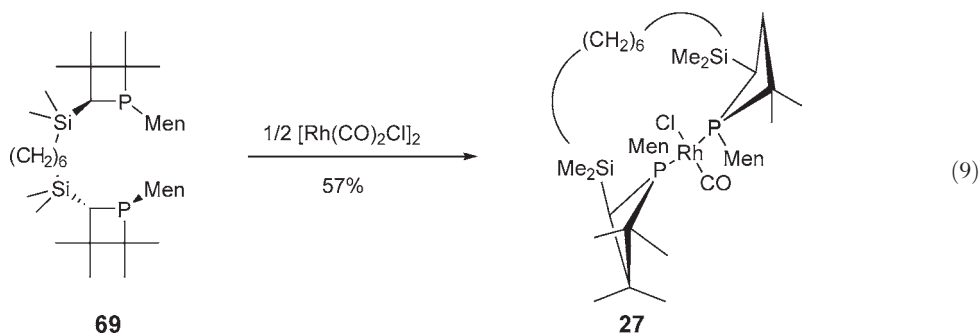
Figure 12

Because of the relatively poor coordinating properties displayed by the *P*-menthyl-substituted monodentate ligands toward some catalytically useful metals like rhodium and iridium, development of the coordination chemistry of chelating phosphetanes was required. Early studies established that the bidentate ligand *P*(*S*),*C*(*S*)-**43** binds well to rhodium centers. It gives the chelating complex **26** with $[\text{Rh}(\text{COD})_2]\text{PF}_6$ and the bimetallic compound **68** when reacted with $[\text{Rh}(\text{COD})\text{Cl}]_2$ under an atmosphere of CO (COD = cyclooctadiene; [Scheme 5](#) [<1995OM4983>](#)).



Scheme 5

The bisphosphetane **69**, in which two coordination centers are bound by a long alkyl chain, was also found to coordinate readily to the $[\text{RhClCO}]$ fragment to afford **27** (Equation 9) [<1996JOM\(522\)223>](#).



More recently, the analogues of the DuPHOS and BPE series of ligands, 1,2-bis(phosphetanyl)benzene **70** and bis(phosphetanyl)ethane **71**, have been found to be useful for the synthesis and isolation of a variety of potential catalyst precursors (Figure 13). Full details of the synthesis of the $\text{Ru}(p\text{-cymene})\text{Cl}(\textbf{70})\text{BF}_4$, $\text{PdCl}_2(\textbf{70})$, and $\text{RuCl}_2(\textbf{71})_2$ complexes have appeared [<2000T95, 2001JOM\(624\)162>](#).

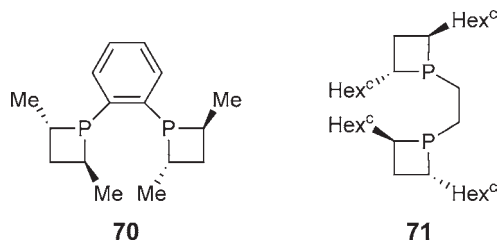
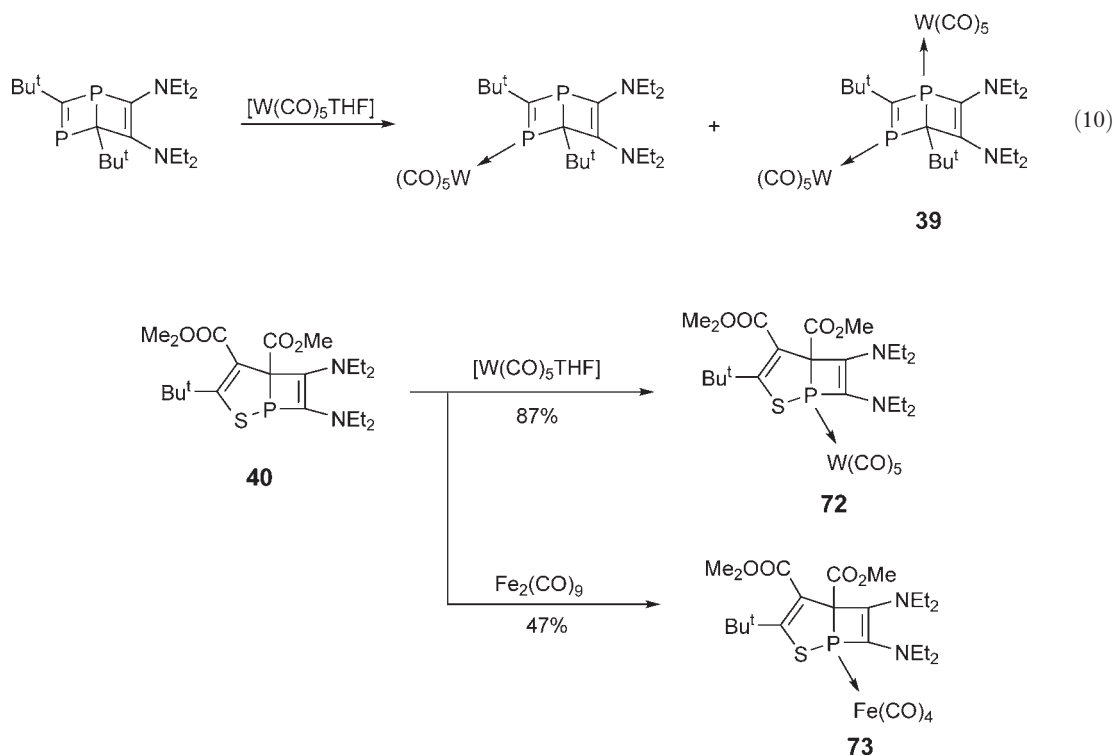


Figure 13

Clearly, the coordination chemistry of monodentate phosphetanes differs slightly from that of classical trialkylphosphine ligands. Hindered phosphetane derivatives may have labile bonding to the metals and are expected to play an important role in processes where ligand dissociation is important. The stability of complexes containing chiral chelating phosphetane ligands is showing considerable promise as asymmetric catalysts.

Several transition metal complexes with unsaturated four-membered rings containing phosphorus have been reported. For phosphetene-coordinated transition metal complexes, there are two synthetic pathways similar to those for phosphetane coordination compounds. The first is simple coordination of a phosphetene to the desired metal center, and the second is phosphetene ring construction using the components within a metal coordination sphere. In both cases, the tungsten complexes **39**, **72**, and **41** have been reported <2002JOM(643)409, 2003EJO512, 1999EJI1567>. Complex **39**, a 1,3-diphospha-Dewar-benzene tungsten complex, is obtained as the minor product in the reaction of 1,3-diphospha-Dewar-benzene with 2 equiv of $[\text{W}(\text{CO})_5\text{THF}]$, and the major product is the mono-tungsten complex, in which the sp^2 phosphorus coordinates to tungsten (Equation 10). From these results, it can be concluded that the sp^2 phosphorus in 1,3-diphospha-Dewar-benzene is a stronger Lewis base than the sp^3 phosphorus, probably because of the difference in steric congestion around the phosphorus atom. In **39**, **72**, and **41**, the $^1J_{\text{PW}}$ values (235.4 Hz for **39**, 255.1 Hz for **72**, and 241.2 Hz for **41**) are quite normal for $^1J_{\text{PW}}$ coupling constants. The iron analogue **73** was also obtained by the reaction of phosphetene **40** with nonacarbonyldiiron(0) in good yield (Scheme 6) <2003EJO512>.



Scheme 6

A phosphete can coordinate to a rhodium center in two fashions: one is σ -complexation by the phosphorus lone pair <1999OM4838> and the other is by η^4 -interaction using π -electrons in phosphacyclobutadiene. These two interactions were characterized by ^{31}P NMR and the structure was confirmed by X-ray crystallographic analysis. The ^{31}P NMR spectrum of complex **60** consists of a double quartet centered around 23.5 ppm. The two large coupling constants of 251 and 42.9 Hz can be assigned respectively to the σ - and π -type one-bond interactions with the rhodium centers. The former value is typical for a one-bond interaction between a sp^2 -hybridized phosphorus and rhodium. Similarly, the latter value is comparable with $^1J_{\text{PRh}}$ coupling also observed in other systems. The resolution of the double doublet into individual quartets is due to the coupling with the CF_3 group on the phosphacyclobutadiene ring. From the solid-state structure, the phosphacyclobutadiene ring was found to be planar with delocalized

carbon–phosphorus and carbon–carbon bonds (C–P: 1.806(6), 1.789(7) Å; C–C: 1.459(9), 1.456(8) Å). The carbon–phosphorus and carbon–carbon bond lengths are slightly longer than the expected values for the corresponding double bonds (C=P: 1.67 Å; C=C: 1.30–1.34 Å), but shorter than the corresponding single bonds (C–P: 1.85 Å; C–C: 1.52 Å). The observation that each bond length is closer to the single bond rather than the double bond is indicative of the increase in single-bond character due to a decrease of π -electron density by coordination to the rhodium center.

Only one example for the transition metal complex **75** coordinated to an arsetane is known now <1995OM1434>. This compound was synthesized in a similar manner as the phosphorus analogue **74**. The structure of **75** was confirmed by X-ray crystallographic analysis revealing a pseudooctahedral coordination environment around iron. The Fe–As bond is similar to that in $[(\eta^5\text{-C}_5\text{H}_5)(\text{CO})_2\text{Fe}(\text{AsPh}_3)]\text{BF}_4$ (Figure 14).

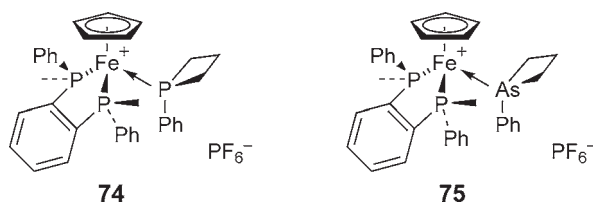


Figure 14

2.10.8.2 Catalytic Applications of Phosphetanes

Chiral cyclic phosphines have useful properties as ligands in transition metal asymmetric catalytic systems. The most impressive example is the five-membered ring phosphorus (phospholane)-based chiral ligand DuPHOS <2000ACR363>.

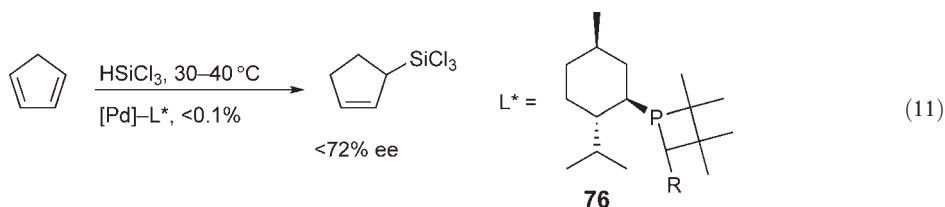
The four-membered analogues, phosphetanes, are also attractive for application as chiral ligands in asymmetric catalytic systems, especially because phosphetanes have a rigid structure, restrict the conformational flexibility, and can enhance the efficiency of the chiral transfer in the catalytic process. Hence, many efforts in the development of catalytic chemistry using chiral phosphetane have been performed <1998CCR755>.

Two classes of phosphetane-based chiral ligands have been developed: one consists of monodentate phosphetanes with a chiral substituent, such as a menthyl group, on the four-membered ring. The other consists of C_2 -symmetric bidentate phosphetanes.

2.10.8.2.1 Monodentate phosphetanes

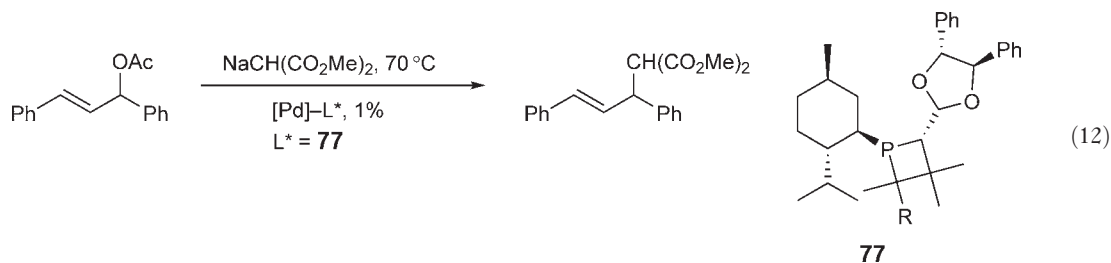
P-Menthylphosphetane **76**, in which the chiral menthyl group was introduced on the phosphorus atom, is a highly hindered, chiral, and electron-rich monodentate ligand. It is expected to provide good activity in asymmetric catalytic applications and has been reported for specific applications in organometallic catalysis <2000CPB315>.

The monodentate phosphetane **76** is used as a ligand for Pd-catalyzed hydrosilylation of alkenes like cyclopentadiene and styrene (Equation 11) <1994OM3956, 1994TL5861>.



When phosphetane was used in a 1:1 molar ratio with palladium, it showed high catalytic activity. This result supports the mechanism of the hydrosilylation reaction in which a mono(phosphine)–Pd complex must be the catalytically active species. The second phosphetane ligand has inhibitory results. In the hydrosilylation of styrene using phosphetanes, the ee is low (<20%); however, the ee values were improved up to 65% by introducing a sterically bulky group at the 2-position. These values are competitive with those given by the most effective phosphines known at present <1997JOM(529)465>.

P-Menthylphosphetanes **77**, in which an optical active dioxolane group is introduced at the α -position, have also provided asymmetric catalytic activity in the palladium-catalyzed allylic nucleophilic substitution of 1,3-diphenylpropenyl acetate with the sodium salt of dimethyl malonate (Equation 12).



The electron-rich nature of these phosphines gives only moderate activation of the allylpalladium complexes toward nucleophiles, as understood from the low reaction rates. Nevertheless, the ee values observed were up to 82%, indicating that phosphetane ligands act as good enantioselective ligands. The other phosphetane acetal ligands with an additional one-carbon spacer between the dioxolane moiety and the four-membered ring were also tested in the reaction. However, an increased distance between the phosphorus atom and the dioxolane group lowers the ee's. Moreover, a phosphetane-to-palladium ratio (1:1 vs 2:1) does not affect the ee's (ee changes from 82% to 91%). These results indicate that the phosphetane acetal ligand may coordinate to palladium in a bidentate fashion, but a detailed rationalization of these data is not obvious at present.

A few experiments have been performed to evaluate the potential of the *P*-menthyl-substituted class of phosphetanes **76** in rhodium-mediated alkene-hydrogenation reactions <1998S1539>. Within this series, monodentate ligands show low catalytic activity and poor enantioselectivity when employed in the hydrogenation of model dehydroamino acid derivatives. This observation is clearly consistent with the observed lability of their rhodium complexes, due to steric hindrance.

The other phosphetane ligands with a biphenyl group on the phosphorus atom instead of a menthyl group were used in atropselective Suzuki couplings <2003JOC4897>. Whereas the dimethyl-substituted ligand **78a** furnished a nearly racemic product (6% ee), there was a 10% increase in the enantioselectivity together with a better yield using the dicyclohexyl analogue **78b**. The alkyl groups on the phosphetane ring seem to have a crucial influence on the reactivity and the enantioselectivity. On the other hand, 1-phenylphosphetane **79** (R = cyclohexyl) gave a very low conversion and no enantioselectivity, which shows the positive influence of the biphenyl moiety on the ligand activity (Figure 15).

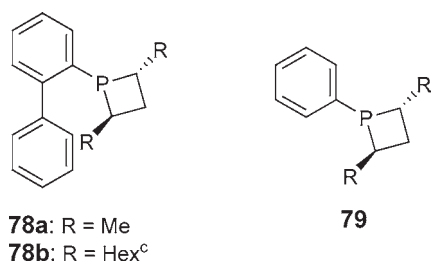


Figure 15

The less-hindered phenyl-substituted monodentate phosphetanes **79**, however, give stable rhodium complexes and moderate to high enantioselectivities (up to 86% ee) in rhodium-catalyzed hydrogenation of functionalized alkenes <2001S2095>.

2.10.8.2.2 Bidentate C_2 -symmetric phosphetanes

The C_2 -symmetric, bidentate phosphetanes **71**, **80**, **81**, and **82** are especially suited for use in ruthenium- and rhodium-catalyzed hydrogenations of prochiral substrates (Figure 16). These ligands are easily available from optically pure anti-1,3-diols, and their catalytic properties can be modulated and optimized by variation of the alkyl substituents on the phosphetane rings.

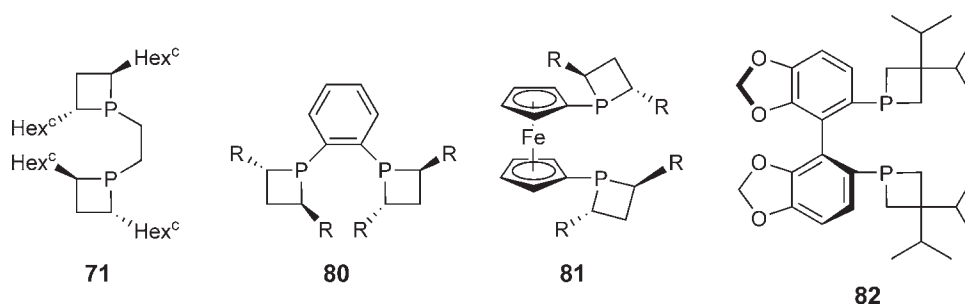
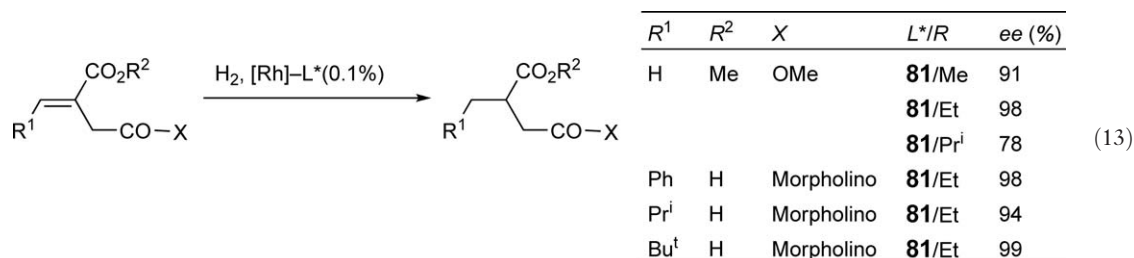


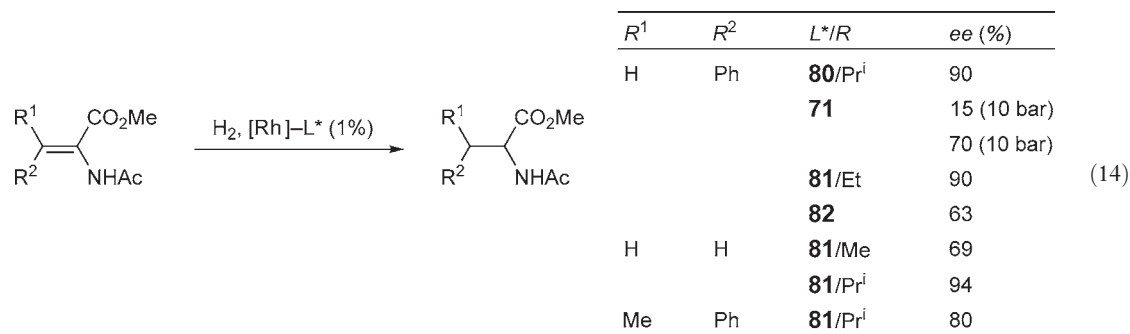
Figure 16

All the ferrocenylphosphetanes **81**, as well as the bis(phosphetanyl)benzenes **80** and the bis(phosphetanyl)ethane **71** bearing hindered substituents, are air-stable compounds in the solid state and are slowly oxidized in solution. They have been tested in rhodium-catalyzed alkene hydrogenations. The bis(phosphetanyl)ferrocenes **81** show high efficiency and enantioselectivity, with unprecedentedly high enantioselectivities attained in hydrogenations of itaconate derivatives (up to 99% ee; Equation (13)) <1999SL1975, 2000AGE1981>.



An important point of these ligands may be the combination of the flexible ferrocene backbone (to increase the catalytic activity) with the rigid phosphetane moiety (to control stereochemistry). In this respect, it is noteworthy that simple monodentate phosphetanes such as **79** perform better than the corresponding phospholanes in various rhodium-catalyzed hydrogenations, as a result of their restricted flexibility.

In preliminary studies, some of the bis-phosphetanes **71**, **80**, **81**, and **82** have been tested in the hydrogenation of model dehydroamino acid derivatives. Selected results are given in Equation (14) <1999SL1975, 1999TL8365, 2004TA2169>.



The rhodium complexes of **71** and **80** show high catalytic activities but only moderate enantioselectivities (up to 90% ee) compared to the very high optical yields of analogous phospholane-based DuPHOS and BPE ligands.

However, unusual effects of H_2 pressure on the enantioselectivity, with increased ee's at higher H_2 pressures, are observed in these reactions. These experimental data contributed to point out the unusual behavior of electron-rich phosphines and the corresponding mechanistic implications. The most recent literature suggests that hydrogenations mediated by electron-rich diphosphines (DuPHOS, BPE, BisP*, etc.) follow a 'hydride mechanism' <2000JA7183>, while most of the usual chiral ligands (2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP), Chiraphos, 2,2-bis(diphenylphosphanyl)-1,1'-binaphthyl (BINAP), etc.) follow a kinetically controlled 'alkene mechanism'. Phosphetanes seem to have an intermediate behavior at low hydrogen pressure, but they resemble electron-rich ligands at higher hydrogen pressures.

These effects presumably result from the slightly lowered electron-donor capacity of the phosphetane ligands relative to phospholanes.

Recently, the novel diphosphetanyl ligand **83** showed good catalytic activity with high enantioselectivities (Equation 15) <2004SI1353>. The reaction proceeded with a S/C ratio of 10 000/1 at 3 atm of H_2 and even with a S/C ratio of 50 000/1 at 6 atm H_2 to furnish an almost quantitative yield in >99% enantioselectivity (Table 7).

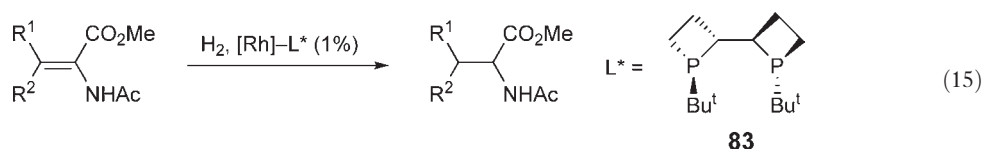


Table 7 Asymmetric hydrogenation of methyl α -acetylaminoacrylate catalyzed by **83**

R^1	R^2	S/C^a	H_2 (atm)	Time (h)	ee (%)
H	Ph	100	1	1	>99
H	Ph	10 000	3	27	>99
H	Ph	50 000	6	43	>99
H	Ar ^b	100	1	1	>99
H	H	100	1	1	>99
Me	Me	100	6	5	15
	-(CH ₂) ₄ -	100	6	5	1

^aS/C = substrate to catalyst ratio.

^bAr = 3-MeO-4-AcOC₆H₃.

Bis(phosphetanyl)ferrocene **81** is applicable in rhodium-catalyzed hydrogenation of an unprotected β -enamine to afford a β -amino acid (Equation 16). The ee in this reaction is moderate (88.0%), but it is interesting since it does not require an N-protecting group like an acyl group in this reaction. Although no detailed mechanistic study has been performed, the reaction is considered to proceed via the imine tautomer as shown in Figure 17.

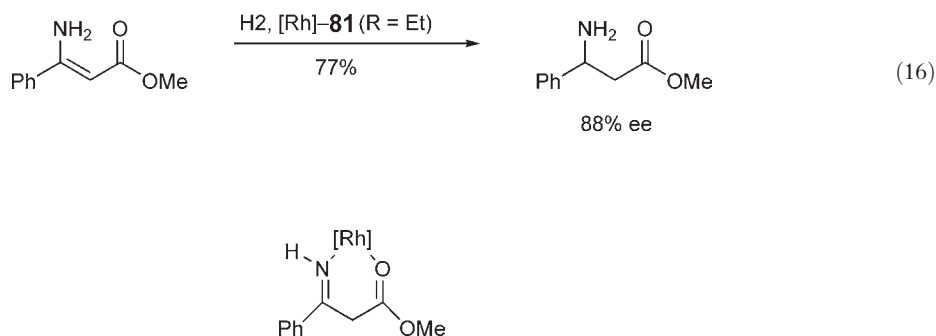
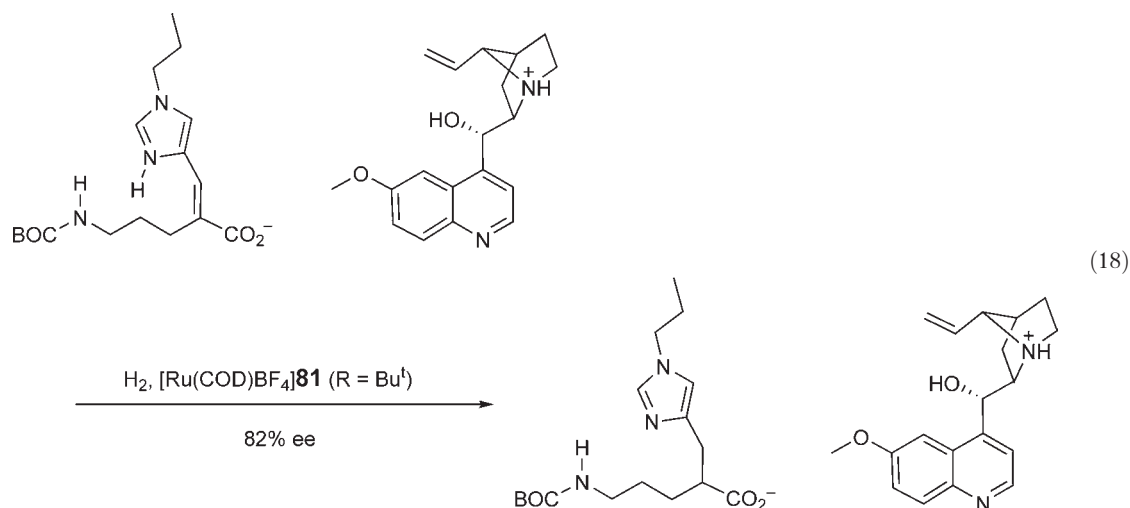
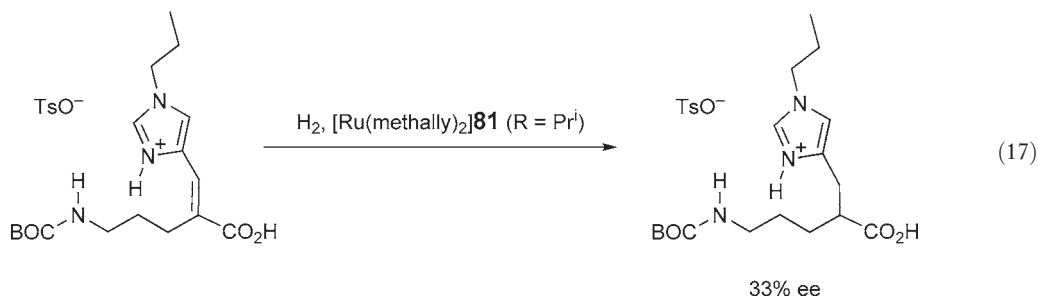
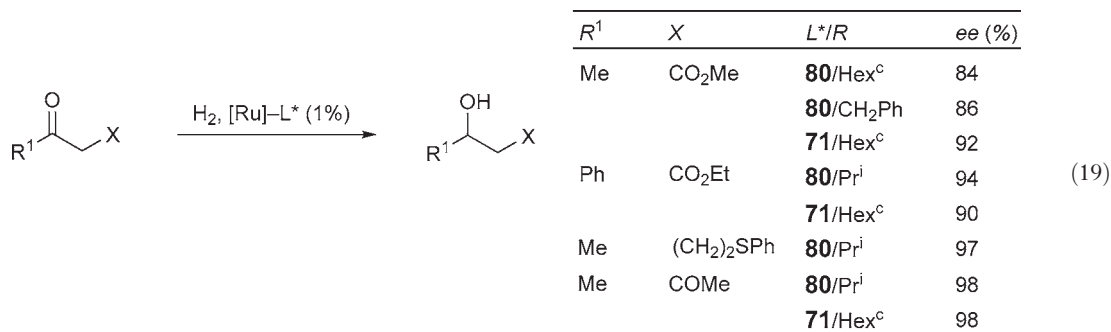


Figure 17

Recently, such catalytic hydrogenation systems were also applied to the synthesis of imidazole-substituted δ -amino acids [<2005OL1931>](#). The *t*-butoxycarbonyl (BOC)-protected acrylic acid was converted to a δ -amino acid using a ruthenium catalytic system. However, the ee in the reaction using **81** ($R = \text{Pr}^i$) is low (33%) compared to other chiral diphosphine ligands ($[(R)\text{-Tol-BINAPRu}(\text{C}_6\text{H}_6)\text{Cl}]\text{Cl}$: 77%) ([Equation 17](#)). When this system used a free amino acid, the ee (56%) was slightly improved. Instead of free acids, the quinidine salt gave better ee's. In the case of $[\text{Ru}(\text{COD})\text{BF}_4]$ **81**, the reaction gave an ee of 82% ([Equation 18](#)).



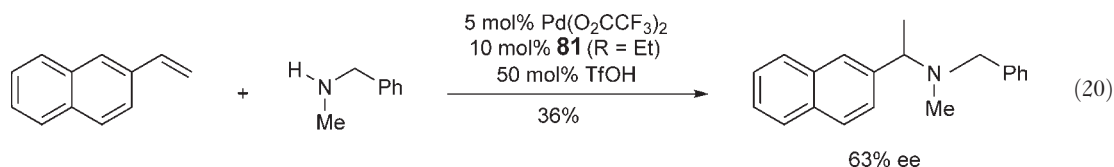
The bis(phosphetanyl)benzenes **80** and bis(phosphetanyl)ethane **71** also show a significant potential in ruthenium-promoted hydrogenations of functionalized carbonyl derivatives ([Equation 19](#)) [<1999CEJ1160, 2000T95, 2001JOM\(624\)162>](#). With ligands **80**, the catalytic activity is moderate, so rather severe reaction conditions must be employed (80 bar, 80 °C).



The enantioselectivity was controlled by the nature of the substituents on the phosphorus atom: hindered groups, such as Pr^i , CH_2Ph , or cyclohexyl, usually give the best selectivity. Moreover, sterically hindered ligands display increased air stability and are thus preferred for practical reasons.

High ee's are obtained in the hydrogenations of β -keto esters, γ -keto sulfides, and, particularly, β -diketones. The last reaction affords *anti*-1,3-diols in high de's and good optical purity (>95% ee for the crude hydrogenation product, increased to 100% after crystallization). The same diols can be used as starting materials for the synthesis of the phosphetane ligands in a crossed, self-breeding cycle. Analogous catalytic properties, with slightly increased activity, have been noticed for the bis(phosphetanyl)ethane–ruthenium complexes <2001JOM(624)162>.

The bidentate chiral phosphetane ligands are used not only in hydrogenations but also in transition metal-catalyzed coupling reactions. In Ni(0)-catalyzed allylic aminations, ligand **81** gave only low ee's (<10% ee) <2004OL2661>. However, in the Pd-catalyzed hydroamination to vinylarenes, ligand **81** gave a moderate result with 36% yield and 63% ee (Equation 20). Despite moderate yield and selectivity, these data demonstrate the feasibility of enantioselective addition of alkylamines <2003JA14286>.



Although C–P cross-coupling of an aryl halide with a phosphine or a phosphine borane is a well-known reaction, the stereochemical aspects have been studied only recently. Ligand **81** provides a good contribution in asymmetric P–C cross-coupling (Equation 21). A preliminary study with aryl iodides and phosphines $\text{Ph}[2-(\text{Ph})\text{C}_6\text{H}_4]\text{PH}$ gave the corresponding phosphines with a significant ee of 71%. Lithium halides were found to influence the reaction considerably; the optimal rate as well as the enantioselectivity were obtained using LiBr as an additive. The scope of the catalytic system was investigated and is summarized in Table 8. For dihydrooxazole, up to 90% ee was achieved <2004CC530>. For P–C coupling between phosphine boranes and *m*-iodoanisole, only lower ee's were obtained (12%). The decrease in ee is probably due to the lack of steric hindrance in the substrates <2005CC2393>.

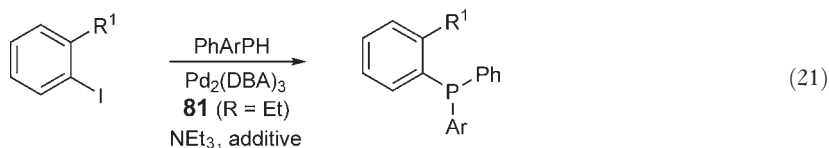


Table 8 Pd-catalyzed C–P cross-coupling according to Equation (21)

R^1	Ar	Additive	Yield (%)	ee (%)
COO-Bu^t	2-(Ph) C_6H_4		63	71
COO-Bu^t	2-(Ph) C_6H_4	LiF	76	66
COO-Bu^t	2-(Ph) C_6H_4	LiCl	66	86
COO-Bu^t	2-(Ph) C_6H_4	LiBr	76	90
COO-Bu^t	2-(Ph) C_6H_4	LiI	58	87
COO-Bu^t	2-(Ph) C_6H_4	Bu_4NBr	76	25
COO-Bu^t	2-MeOC $_6\text{H}_4$	LiBr	79	40
COO-Bu^t	2-CF $_3\text{C}_6\text{H}_4$	LiBr	39	93
COOMe	2-(Ph) C_6H_4	LiBr	69	85
CHO	2-(Ph) C_6H_4	LiBr	71	63
3,4-Dihydrooxazol-2-yl	2-(Ph) C_6H_4		45	90
3,4-Dihydrooxazol-2-yl	2-(Ph) C_6H_4	LiBr	58	68

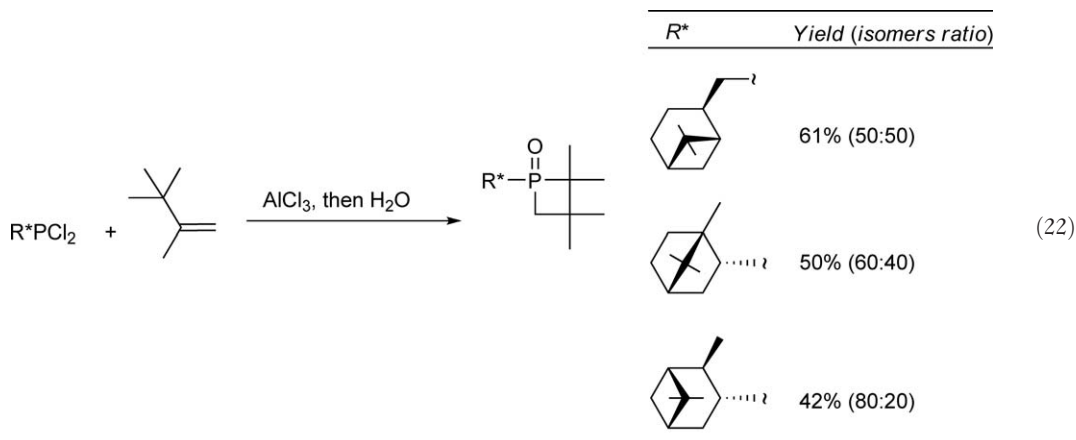
The few catalytic studies described above emphasize that bidentate chiral phosphetanes are interesting agents for both fundamental studies and more applied uses. Further catalytic developments are expected. Furthermore, the easily available monodentate phosphetanes, bearing either chiral or chirotopic phosphorus centers, are also promising ligands for specific applications in enantioselective catalysis.

2.10.9 Ring Syntheses from Acyclic Compounds

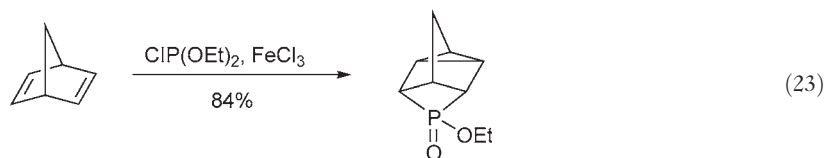
Three fairly general synthetic routes are available for the construction of phosphetane rings from acyclic compounds. The first route is the McBride synthesis, which was developed in the early 1960s and involves the apparent electrophilic addition of a phosphonium cation to suitable alkenes <1962JOC606>. The second route is the electrophilic alkylation–cyclization of phosphorus derivatives <1968JA518>. This method was also established in the 1960s, although the combination of disfavored entropic effect and the ring strain means that four-membered rings are usually more difficult to synthesize by cyclization than other homologues. The third route is an intra- or intermolecular [2+2] cycloaddition reaction between phosphalkenes and activated alkenes or alkynes. Although each of these three methods are well established and well described in preceding reviews <2002CRV201, 1998CCR755> including CHEC(1984) <1984CHEC(7)449> and CHEC-II(1996) <1996CHEC-II(1B)883>, several new reactions classified as this methodology have been reported. Hence, in this section, these new reactions are summarized.

2.10.9.1 McBride Synthesis

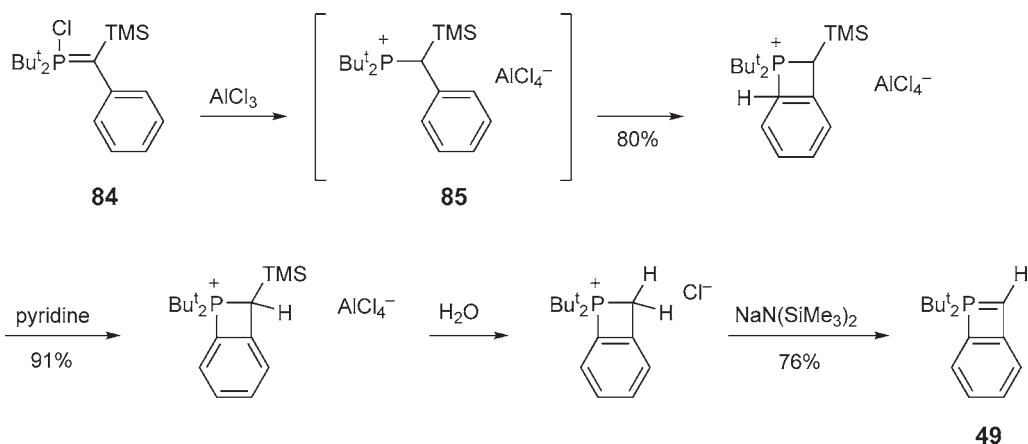
The McBride synthesis has been applied to the preparation of chiral phosphetane oxides by the reaction of optically active dichlorophosphines with 2,3,3-trimethyl-1-butene. Thus, myrtanyl-, bornyl-, and isopinocampenyldichlorophosphines afforded the corresponding phosphetane oxides having chirality localized on both the phosphorus substituent and the phosphorus center. In all cases, epimeric mixtures are obtained (Equation 22) <1997JOC297>.



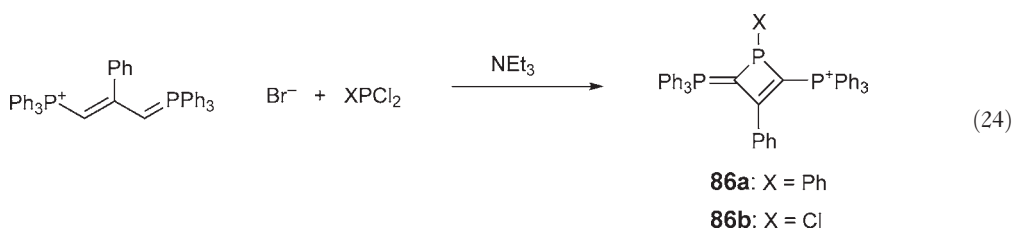
In addition to the conventional McBride synthesis using simple alkenes, a few other unsaturated substrates serve as starting materials for the construction of phosphetane rings. For example, the reaction of norbornadiene with chlorophosphines ($\text{ClP}(\text{OEt})_2$), instead of dichlorophosphines, afforded tetracyclic phosphetane oxides (Equation 23) <1996JHC979>.



Modified McBride syntheses are also useful in the synthesis of four-membered ring compounds. Treatment of the P-halogenated ylide **84** with freshly sublimed AlCl_3 afforded a transient methylene phosphonium salt **85**, which possesses a highly electrophilic phosphorus center. An intramolecular electrophilic cyclization leads to the corresponding dihydrophosphonium salt, which is finally converted to benzophosphetenes **49** in good yields (Scheme 7) <1996CEJ68>. 2-Phenyl-1,3-bis(triphenylphosphonio)propenide bromide reacted with phenyldichlorophosphine or phosphorus trichloride to give phosphetene **86** (Equation 24) <1996CEJ221>.

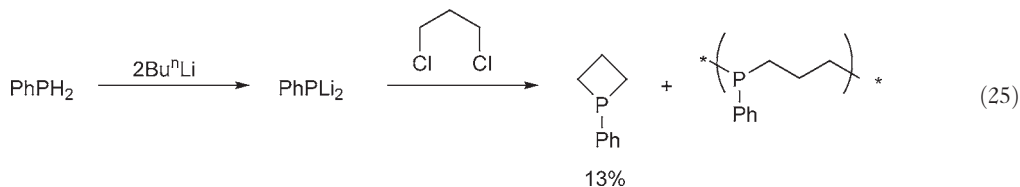


Scheme 7

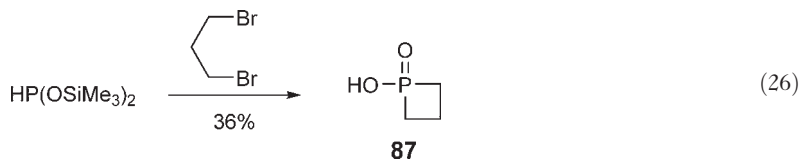


2.10.9.2 Alkylation–Cyclization

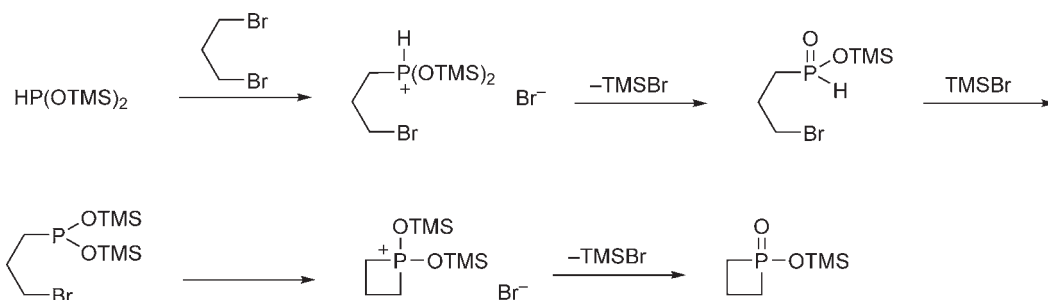
The direct synthesis of a phosphetane ring by the alkylation–cyclization method using dilithium phosphide and 1,3-dihalopropane resulted in a low yield (13%), because of thermally favored chain-forming side reactions and the instability of the final product in the reaction mixture (Equation 25) <1996OM1301>.



The coordination to borane or the sulfurization of phosphetanes prior to the workup has been shown to improve the yields of C-unsubstituted aryl- and alkylphosphetane derivatives (Equation 26) <1997T4363, 1999JOM(585)167, 2004S1353>. This method is also improved using iron-facilitated phosphide instead of simple phosphides <1995OM1434>. This reaction is believed to proceed by a stepwise mechanism involving the (3-bromopropyl)-(phenyl)phosphine complex. The desired phosphetane complex was isolated in high yield. The main features in this reaction are as follows: (1) coordinated primary or secondary phosphines are known to be easily deprotonated <1989OM2360>; and (2) the stability of the final phosphetane is increased by complexation at phosphorus. The same strategy can be employed for the synthesis of the 1-phenylarsetane complex 75.



A further approach to phosphetane rings is available in a single step by double Arbuzov reaction of bis(trimethylsiloxy)phosphine with dibromopropane <1995JOC6076>. Bis(trimethylsiloxy)phosphine is generated *in situ* from hexamethyldisilazane and ammonium phosphite. The proposed mechanism for this reaction is shown in Scheme 8.

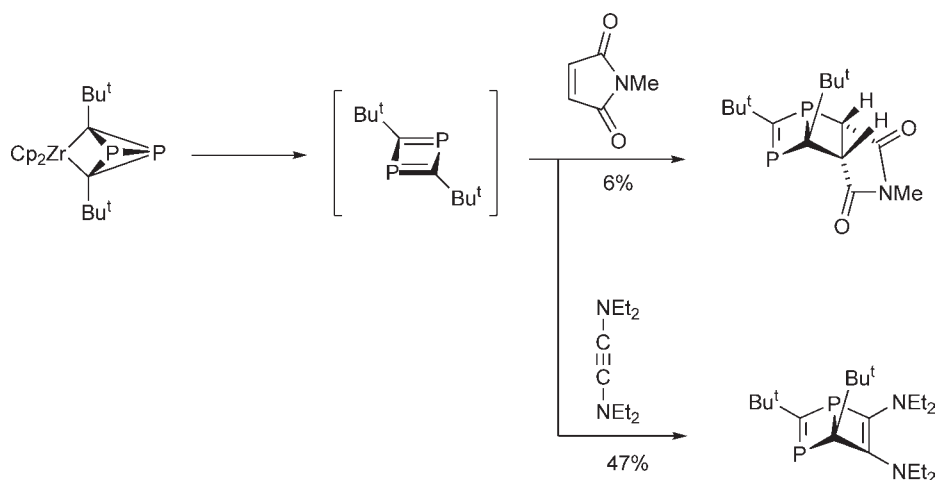


Scheme 8

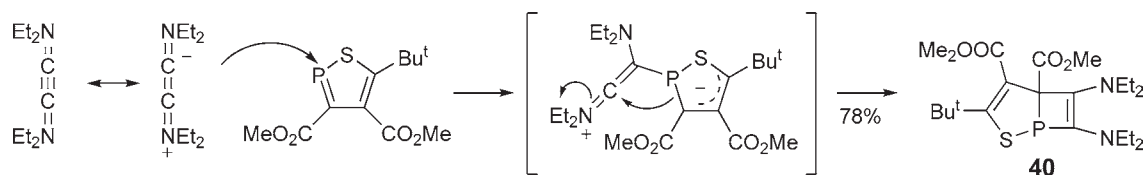
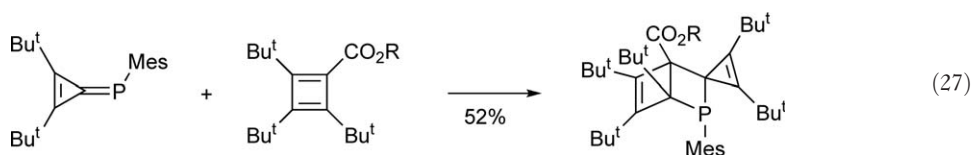
2.10.9.3 Cycloaddition

[2+2] Cycloaddition reactions between phosphalkenes or -alkynes and activated alkenes or alkynes are also an available synthetic route to the four-membered rings. These reactions afforded not only phosphorus-containing rings, such as phosphetanes, phosphetenes, and phosphetes, but also arsine-containing rings.

Phosphalkenes, $P=C$ compounds with a trivalent phosphorus atom, can react with various $C=C$ compounds, like maleimide (Scheme 9) <2002JOM(643)409>, cyclobutadienes (Equation 27) <1994T759>, and $C\equiv C$ compounds, like ynamines (Scheme 10) <2003EJO512>, to afford the corresponding phosphetanes and phosphetenes.

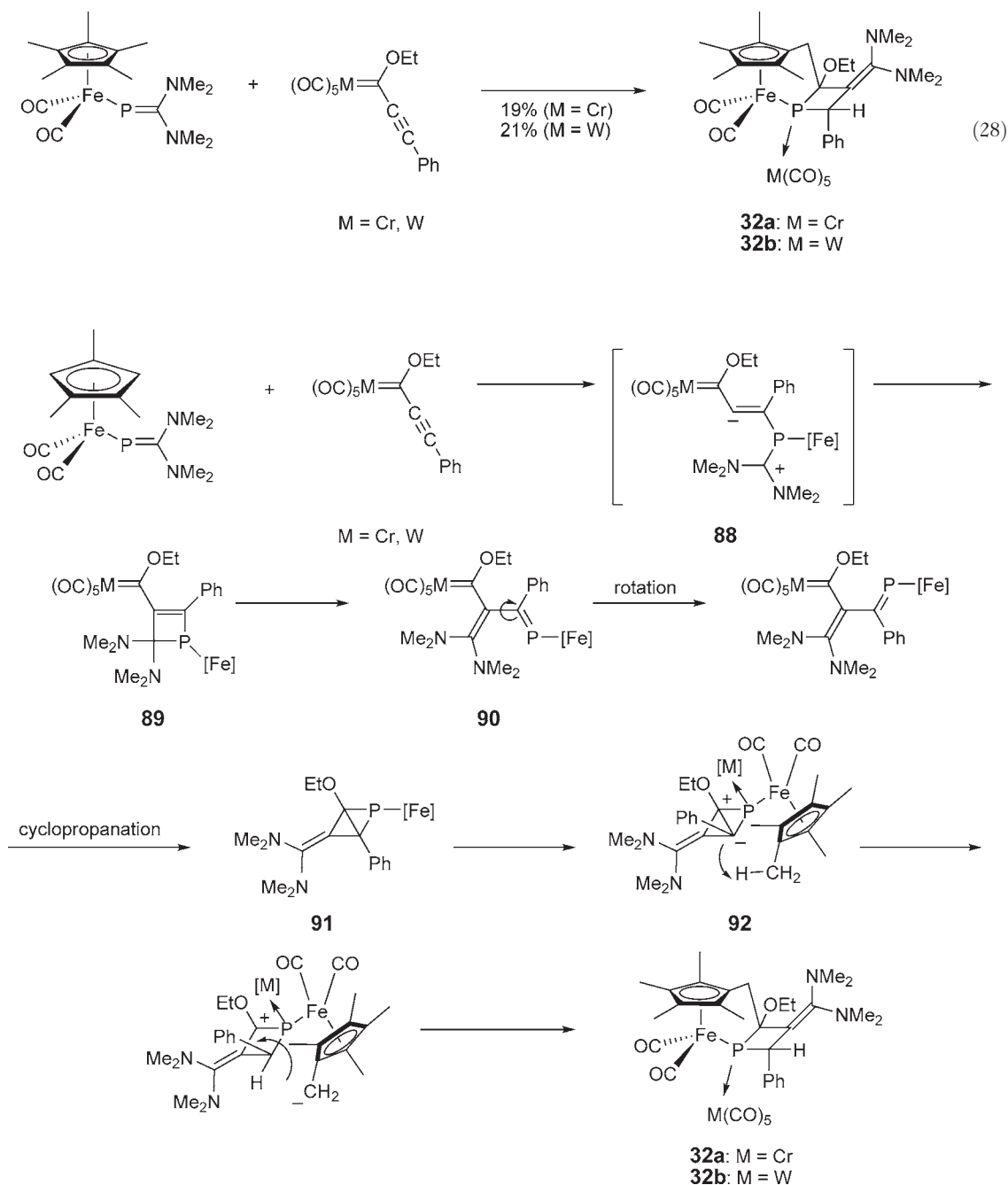


Scheme 9



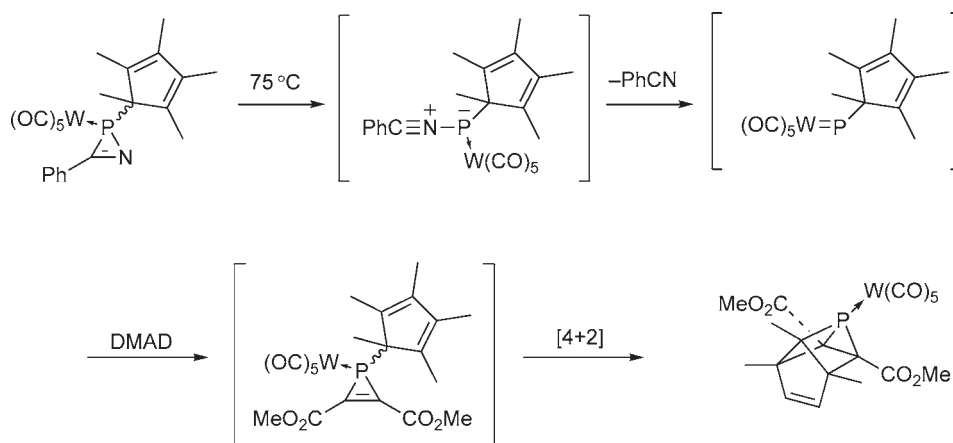
Scheme 10

In a similar way, *P*-metallophosphaalkenes show the same reactivity against electron-deficient alkenes to give *P*-metallophosphetanes <2002OM1998>, and this methodology is applicable to the synthesis of *As*-metalloarsetanes using *As*-metalloarsaalkenes instead of phosphaaalkenes. These *P*-metallophosphaalkenes can also react with Fischer-type carbene complexes and subsequent rearrangement gives phosphetane complexes **32** (Equation 28) <1998CEJ469>. In this reaction mechanism (Scheme 11), the nucleophilic phosphorus atom attacks at the β -carbon atom of the $C\equiv C$ bond to give adduct **88**. Formation of a transient phosphetene **89** and subsequent cycloreversion affords phosphabutadiene **90**. Rotation about the C–C single bond and intramolecular cyclopropanation leads to bicycphosphabutane **91**, which can open to the highly reactive zwitterions **92**. Proton transfer from the ring methyl group to the phosphetane carbanion and combination of the carbocationic and anionic centers eventually gives phosphetane complexes **32**.

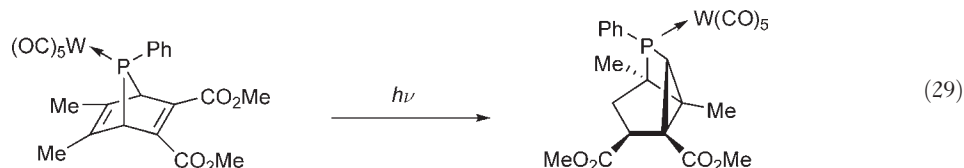


Scheme 11

Scheme 12 and **Equation (29)** show two examples of polycyclic phosphetanes that are obtained by intramolecular cyclizations. These reactions involve a [4+2] cycloaddition of cyclopentadienylphosphirene <1999AGE215, 1999EJI1567> and photoinduced rearrangement of a 7-phosphanorbornadiene <1997OM4145>, respectively.

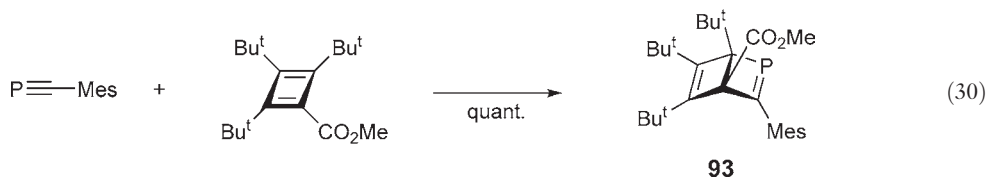


Scheme 12



Phosphorus ylides, $\text{P}=\text{C}$ compounds with a pentavalent phosphorus atom, can give phosphetanes as well as phosphalkenes. By the reaction of a stabilized phosphorus ylide with activated alkenes, the phosphetane ring is formed via a zwitterionic betaine <1997HAC157>.

In contrast to cycloaddition reactions of phosphalkenes, cycloaddition reactions between phosphalkynes and other unsaturated systems are comparatively rare. Indeed, there are only a limited number of reports for monophosphacyclobutadiene complexes, which are obtained from the corresponding phosphalkyne. Relatively recently, the reaction of phosphalkynes with highly electron deficient alkynes was reported <1999OM4838>. Treatment of a $\text{CF}_3\text{C}\equiv\text{CCF}_3$ -coordinated dimeric rhodium complex with phosphalkynes in hexane at -20°C followed by warming to room temperature afforded the red air- and moisture-stable phosphete complexes **60** in ca. 50% isolated yields. When phosphalkynes are allowed to react with a kinetically stabilized cyclobutadiene, 2-Dewar-phosphinines, for example **93** (Equation 30), are obtained <1998S1305>.

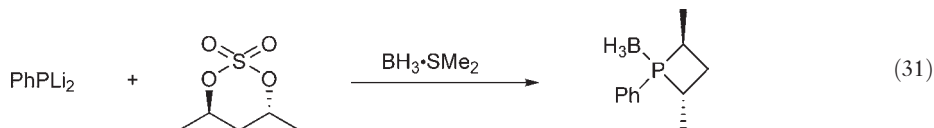


In summary, the construction of phosphetane or arsetane rings is usually carried out by McBride synthesis or alkylation–cyclization methods. These methods are quite useful, with a good selectivity in most cases. [2+2] Cycloaddition reactions are also available, but this method is limited to particular cases. In addition to these methods, other useful methods based on the transformation from another ring system have been developed. These methodologies are described in [Section 2.10.10](#).

2.10.10 Ring Syntheses by Transformation of Another Ring

2.10.10.1 Ring-Opening Reactions

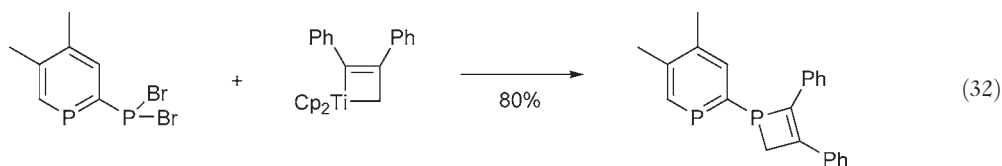
Transformation of cyclic sulfates into phosphetane rings is one of the most powerful strategies for the construction of phosphetane rings. The reaction of dilithium phosphide with cyclic sulfates gives the desired phosphetanes, which can usually be isolated as borane complexes in moderate yield. An important aspect of this method is a stereospecific substitution with achiral phosphines to give *C*-chiral phosphetanes. This approach is illustrated in Equation (31) <1997TL2947, 2001S2095, 2003JOC4897, 2003JOC5020>. The cyclic sulfate starting material is derived from optically pure 1,3-diols, which are easily available from a large-scale synthesis by enantioselective Ru-catalyzed hydrogenation of β -diketones.



This method can be applied to the syntheses of the C_2 -symmetric bisphosphetanes, such as **80** <1997TL2947, 1999CEJ1160, 2000T95>, **71** <1999SL1975, 2000AGE1981>, **81** <2001JOM(624)162>, and **82** <2004TA2169> (Figure 16). These bisphosphetanes were widely used as chirality-inducing ligands in various asymmetric catalytic systems, as described in the previous section.

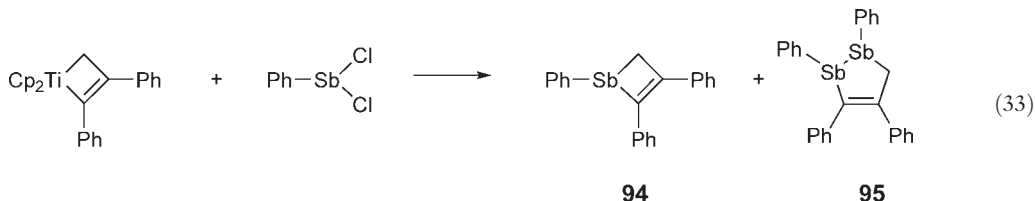
In most cases, the resulting phosphetanes are isolated as borane complexes, which are formed *in situ* just after the reaction; however, the borane can be easily removed by reaction with 1,4-diazabicyclo[2.2.2]octane (DABCO).

Metallacycles involving early transition metals such as Ti and Zr undergo main group element–metal exchange reactions and this reaction is a useful synthetic tool for the construction of phosphorus-containing heterocycles. Indeed, since the first example of this reaction was reported by two independent groups in 1989 and 1990 <1989JA9129, 1990AGE75>, several reactions have been developed (Equation 32) <1996OM1597>.

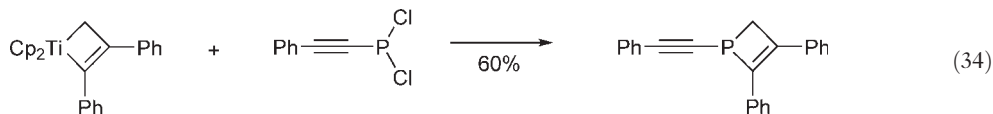


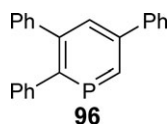
In the first report in 1990, bis(cyclopentadienyl)titanacyclobutene reacted rapidly and cleanly with group 15 aryl dichlorides (PhPCl_2 , PhAsCl_2) to give the corresponding phosphetene and arsetene with elimination of titanocene dichloride. In the following report in 1992, this methodology was expanded to unsaturated compounds. Bis(cyclopentadienyl)titanacyclobutene gave the corresponding phosphetane in a similar way <1992OM2944>. In this reaction, the product consists of a 1:1 mixture of *cis*- and *trans*-isomers due to the puckered structure of the phosphetane ring.

Several years later, this methodology was further expanded to the construction of antimony-containing heterocycles. When dichlorophenylstibine was allowed to react with titanacyclobutene instead of dichlorophosphines, the desired stibetene **94** was obtained as a mixture with distibacyclopentene **95** (Equation 33) <1996HAC383>.

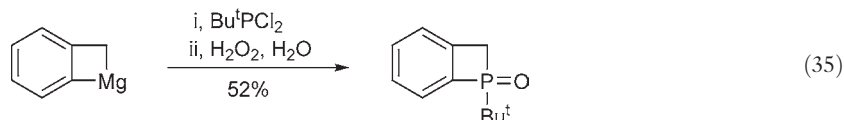


Not only aryl dichlorophosphine but also alkynyl dichlorophosphine is available in this reaction. Interestingly, the resulting alkynylphosphetene **56** was transformed into the corresponding phosphines **96** by mild heating for several days (Equation (34); Figure 18) <1996HAC397, 1998JOM(567)151>.



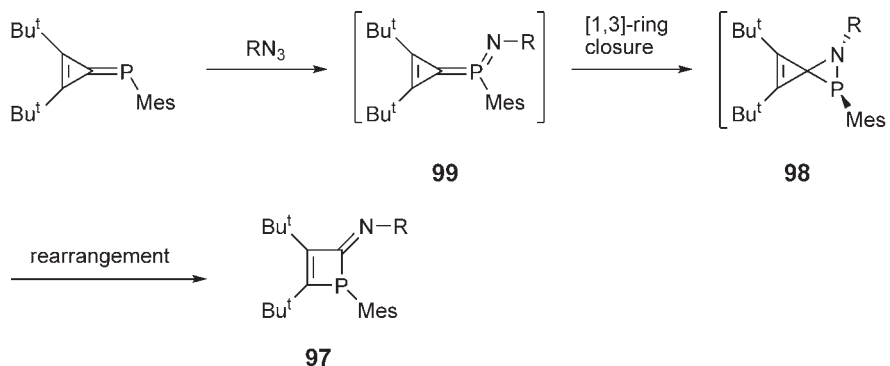
**Figure 18**

The construction of the phosphetene ring by transformation from another metallacycle was recently reported. The reaction of *tert*-butyldichlorophosphine with 1,2-dihydro-1-magnesacyclobutabenzene and subsequent treatment with hydrogen peroxide gave the desired benzophosphetene oxide (Equation 35) <2004TA2213>. This organomagnesium reagent was obtained by treatment of 2-bromobenzyl chloride with a large excess of magnesium.

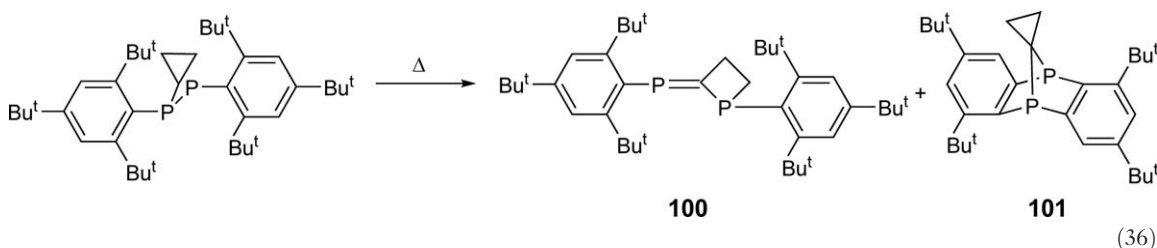


2.10.10.2 Ring-Expansion Reactions

Some phosphetene rings are constructed by ring-expansion reaction from three-membered ring systems. The reaction of phosphatriafulvene with azides provided the iminophosphetene **97** <1994TL1527>. This reaction proceeded via rearrangement of spiro compound **98**, which was formed by a [1,3]-ring-closure reaction of iminomethylenephosphorane **99** (Scheme 13).

**Scheme 13**

Similar phosphetane ring formation by thermal rearrangement of spirodiphosphirane has been reported <1994IC596>. In this reaction, the phosphetane **100** with an exocyclic phosphalkene moiety was obtained as a major product (70%) with 1,4-diphosphanorbornadiene **101** as a minor product (30%) (Equation 36).

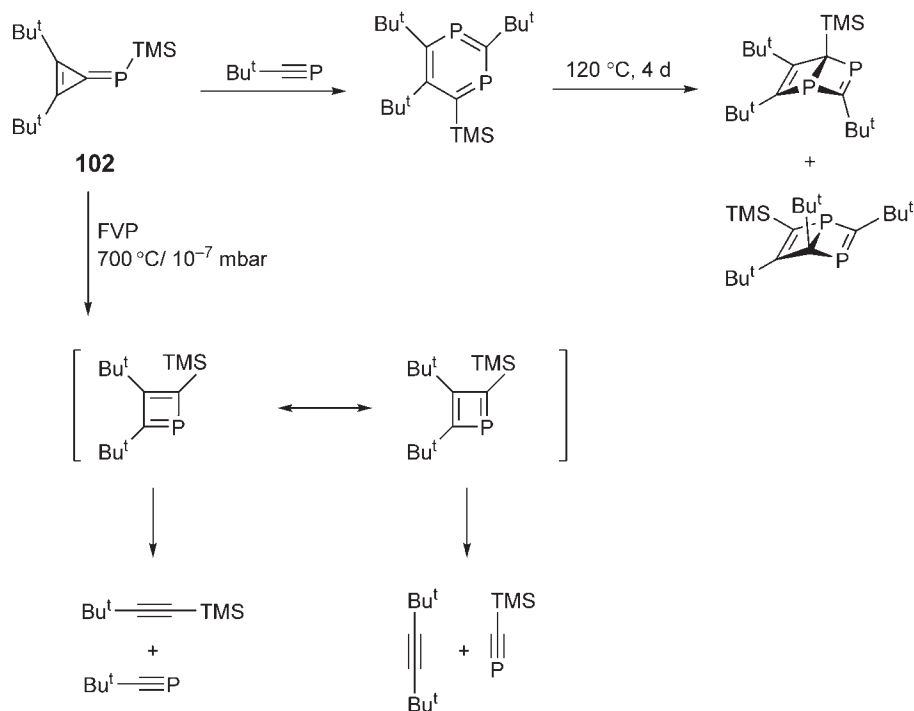


Although the interesting transformations classified in this section have been reported, each reaction proceeds only from specific starting materials and hence they have little synthetic utilities at present.

2.10.10.3 Reactive Intermediates

Although phosphorus-containing four-membered rings have been found in some reactions as intermediate, they are only a transient species in most cases.

The thermolysis of phosphatriafulvene **102** gave a set of phosphalkynes. In this reaction, two phosphetes are considered to be generated by the rearrangement of **102** as an equilibrium mixture of valence isomers. A [2+2] retrocycloaddition then leads to the phosphalkynes <2001S463>. Contrary to this argument, Dewar-1,3-diphosphenines are formed upon thermolysis of **102** in the presence of a phosphalkyne via a 1,3-diphosphenine (Scheme 14).

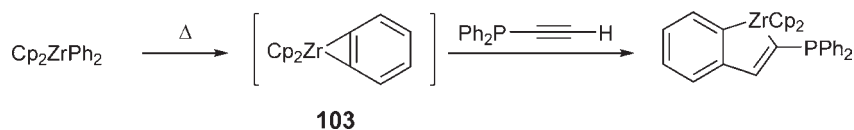


Scheme 14

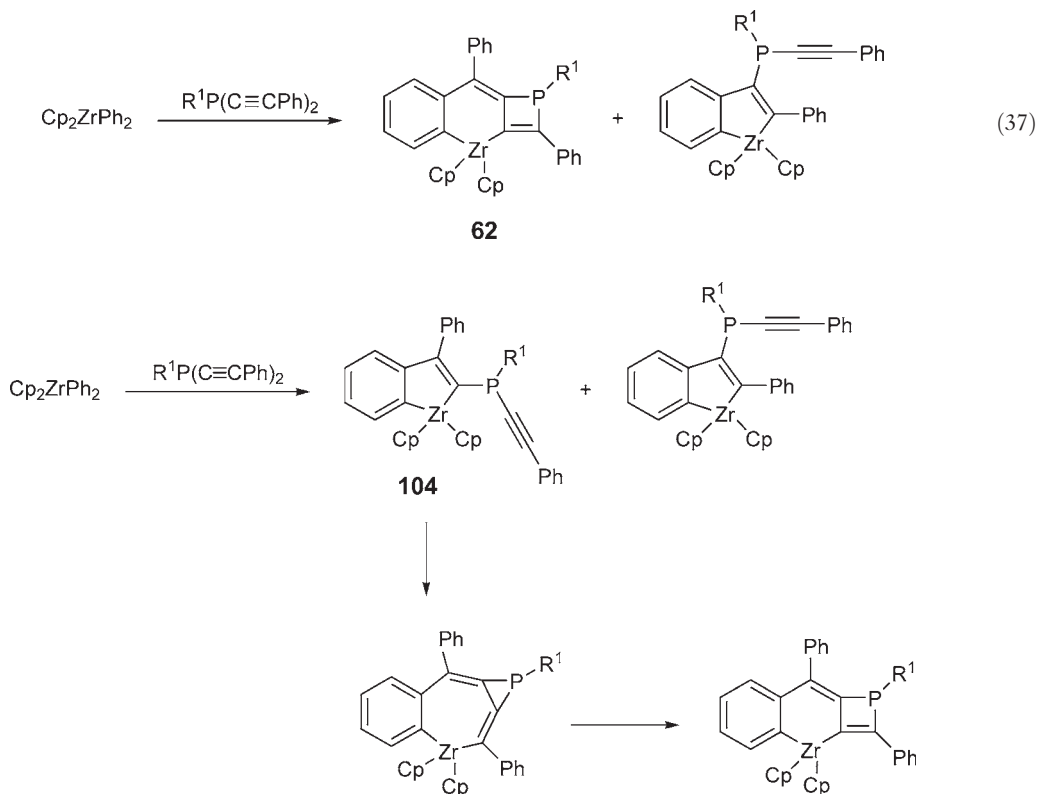
In the flash vacuum pyrolysis of dichloroneopentylphosphine, a phosphaethane polymer was obtained. The formation of a polymer from phosphalkene **55** has been noted but was not characterized. These products probably result from phosphetane intermediate **57** (Scheme 4) <1997TL8417>.

2.10.11 Synthesis of Particular Classes of Compounds

The reaction of $(\eta^5\text{-C}_5\text{H}_4\text{R})_2\text{ZrPh}_2$ with alkynylphosphines produced 2-phosphino-1-zirconaindene arising from the regiospecific insertion of the $\text{C}\equiv\text{C}$ bond into the zirconium–carbon bond of the *in situ*-generated zirconocene benzyne complex **103** (Scheme 15) <1997CC279>. A similar reaction with bis(alkynyl)phosphine afforded zirconahexadiene-fused phosphacyclobutene **62** in high yield (Equation 37). Compound **62** is fully characterized and its structure was confirmed by X-ray crystallographic analysis <2004T1317, 1997AGE987>. The proposed mechanism is shown in Scheme 16. As shown in Scheme 15, the alkynyl group of 2-(alkynyl)phosphino-1-zirconaindene **104** inserts into a Zr–C bond, providing the corresponding zirconacycloheptatriene with a phosphacyclopropane side ring. 1,2-Migration of the phosphanyl group leads to zirconacycle **62**. The regioisomer of **101** could not be further transformed and was isolated.

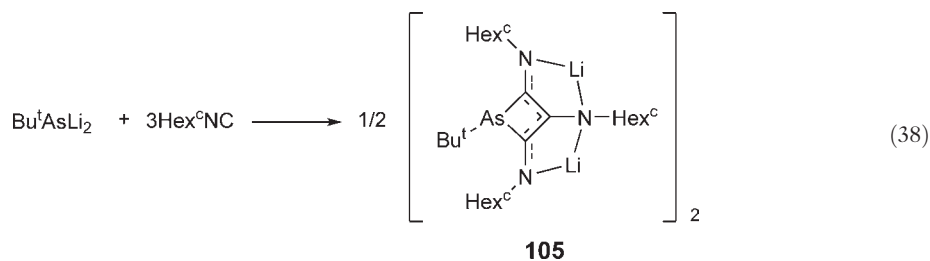


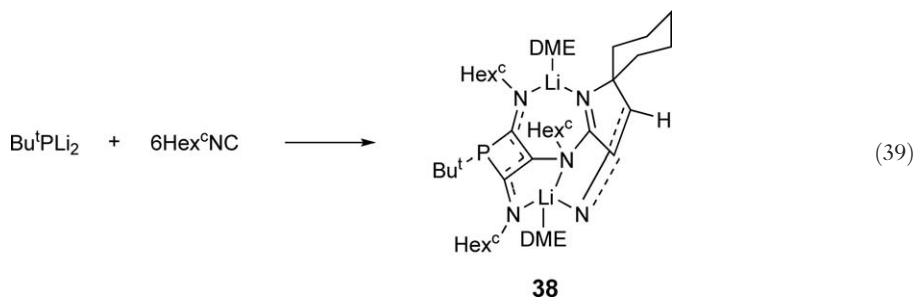
Scheme 15



Scheme 16

Interesting arsetes or phosphetes are formed by the reaction of the corresponding dilithium pnictogenide with α -hexylisonitrile via the oligomerization of isonitrile. The reaction of Bu^tAsLi_2 with 3 equiv of α -hexylisonitrile gives the dimer **105** (Equation 38). The monomer unit in **105** may be described as a vicinal dilithiated amine. The two negative charges are stabilized in different ways. One charge is delocalized through an allylic moiety in the arsetene ring. The other charge is mainly localized on a nitrogen atom. The arsetene ring was constructed by nucleophilic attack of arsenediide on two isonitrile molecules followed by two C–C bond formations in head-to-head reactions <2005OM842>. The reaction of the corresponding Bu^tPLi_2 with α -hexylisonitrile afforded a more complicated product **38** (Equation 39). The reaction obviously starts with the formation of the same structural motif as found in **105**. However, this intermediate can react with three additional isonitriles.





2.10.12 Important Compounds and Applications

As described in the previous sections, the phosphetane rings are usually puckered and the chirality can be easily enhanced by the introduction of substituents onto the carbon atoms. Substitution with chiral alkyl groups such as the menthyl group can also provide chiral phosphetanes. Furthermore, interconnection of phosphetanes with appropriate spacers, like a benzene ring, an alkane, or a ferrocene, leads to C_2 -symmetric bis(phosphetane) ligands. These chiral monodentate and bidentate ligands work well as chirality-inducing ligands in various asymmetric catalytic reactions, as in rhodium-catalyzed hydrogenations, and palladium-catalyzed cross-coupling reactions. Details of these applications are described in [Section 2.10.8.2](#).

2.10.13 Further Developments

The most interesting features of phosphetanes are their moderate strain and conformational rigidity. Considering from the reactivities of phosphetanes, they can be used as the precursors for phosphorus-containing polymers formed by ring-opening polymerization, as well as for phosphalkenes and phosphinidenes in the future. Furthermore, functionalization of phosphetane rings prior to retrocycloaddition to give phosphalkenes or phosphinidenes should also be involved in the applications of phosphetanes. The conformational rigidity of phosphetanes provides the utility in the asymmetric catalytic reactions and rapid advances in this area will be expected. The success of phosphetanes in asymmetric reactions will encourage the exploitation of arsetanes in this field.

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Biographical Sketch



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2.11

Four-membered Rings with One Silicon, Germanium, Tin, or Lead Atom

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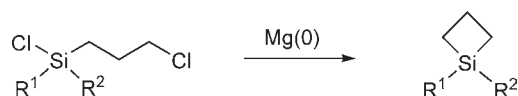
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2.11.1 Introduction

Previously published information on this class of heterocyclic compounds can be found in CHEC-II(1996) <1996CHEC-II(1B)867>. Other pertinent reviews are cited in the appropriate sections. This chapter primarily deals with the chemistry of silacyclobutanes (SCBs, siletanes), which are the most stable and thoroughly studied of the cyclobutane heterocycles that contain one group IV heteroatom. Germacyclobutanes have received attention as well; relevant germacyclobutane chemistry is discussed alongside the SCB chemistry where appropriate. The simple 1,1-dimethylstannacyclobutane is too unstable to be isolated <1983JA3336>, and no 'plombacyclobutanes' (four-membered rings with one lead atom) are known.

SCBs and germacyclobutanes are generally prepared by cyclization of 3-halopropylsilyl (or -germyl) halides under Barbier-type conditions, although other methods are discussed in the synthesis section of this chapter. Several SCBs are commercially available, including 1,1-dichloro-, 1,1-dimethyl-, and 1-chloro-1-methylSCB. The readily available chloro derivatives provide a convenient entry into a range of SCBs through the substitution reactions that are typical of chlorosilanes.



The structural characteristics of 1,1-dialkylsilacyclobutanes have been studied both computationally and experimentally. The internal C–Si–C bond angle (ca. 80°) deviates significantly from the ideal tetrahedral bond angle of 109.5°. The propensity of SCBs to form pentavalent ‘ate’ complexes is generally linked to this distorted bond angle, which itself is a function of the constrained four-membered ring. The relative ease by which SCBs form hypervalent species by accepting additional ligands provides the foundation for many applications in organic chemistry.

SCBs have become increasingly important in recent years. With respect to routine storage and handling, SCBs are convenient and easy to use, much like conventional organosilane reagents. However, the ring strain inherent to four-membered rings can be exploited in various ring-opening reactions. Furthermore, this ring strain is attenuated upon coordination with Lewis bases, thus imparting a degree of Lewis acidity to SCBs and germacyclobutanes. This chapter covers the literature between 1995 and 2006, during which time the utility of SCBs in organic synthesis has increased dramatically.

2.11.2 Theoretical Methods

Different SCBs have been optimized using various basis sets at different levels of theory (such as Hartree–Fock, Møller–Plesset, and density functional methods).

Structural parameters for SCBs obtained from different methods of quantum chemistry in comparison with the results from electron diffraction experiment have been reported (Table 1 <2006JST(800)146>).

Table 1 Barrier to the ring puckering (V_0), the ring-puckering angle (φ_e), and the main geometric parameters of SCB as calculated by different *ab initio* calculations

Method	V_0 (kcal mol ⁻¹)	φ_e (deg)	$r(\text{Si}-\text{C})$ (Å)	$r(\text{C}-\text{C})$ (Å)	$\angle\text{CSiC}$ (deg)
HF/6-31G**	0.77	26.9	1.896	1.561	78.8
HF/6-311G**	0.89	27.8	1.892	1.562	78.8
HF/6-311++G**	0.88	27.8	1.892	1.562	78.8
HF/6-311++G(df, pd)	0.97	28.6	1.890	1.561	79.0
MP2/6-31G**	1.85	33.1	1.896	1.556	78.0
MP2/6-311G**	2.18	34.2	1.893	1.562	78.2
MP2/6-311++G**	2.18	34.2	1.893	1.562	78.2
MP2/6-311+G(df, pd)	2.25	35.0	1.887	1.558	78.4
B3LYP/6-31G**	0.69	27.2	1.905	1.566	78.7
B3LYP/6-311G**	0.72	27.3	1.902	1.566	78.7
B3LYP/6-311++G**	0.70	27.3	1.902	1.566	78.8
B3LYP/6-311++G(df, pd)	0.79	27.9	1.899	1.564	78.8
B3LYP/cc-pVTZ	0.73	27.6	1.899	1.564	78.8
<i>Experiment</i>					
IR	1.26(1)	35.9(20)			
GED	0.82(60)	33.5(18)	1.885(1)	1.571(3)	77.2(9)

Geometric parameters of SCB <2006JST(800)146>, 1,1-dichlorosilacyclobutane <2001JST(559)7>, 1,1-difluorosilacyclobutane <2001JST(559)7>, 1,1-dimethylsilacyclobutane (DMSB) <2001JST(559)7>, 1,1-diethynylsilacyclobutane <2002JST(610)159>, 1,1-dicyanosilacyclobutane <2002JST(610)159>, 1,3-disilacyclobutane <1988ACA352>, and 1,1,3,3-tetramethyl-1,3-disilacyclobutane <1999JST(485)135> have been calculated employing *ab initio* methods.

For monosubstituted SCBs, such as 1-chlorosilacyclobutane <2001JST(559)7, 1996JSP321>, 1-fluorosilacyclobutane <2006JST(800)106, 2001JST(559)7>, 1-bromosilacyclobutane <2000SAA2563>, and 1-methylsilacyclobutane <1999JST(477)31>, structural parameters for both equatorial and axial conformers have been calculated.

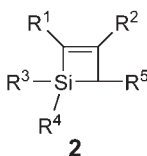
Restricted Hartree-Fock *ab initio* calculations have been performed on various isomers of silacyclobutenes <1988JPC3037> and silacyclobutadiene <1987OM1977>.

2.11.3 Experimental Methods

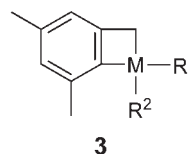
2.11.3.1 Electron and X-Ray Diffraction

The structures of the simplest members of SCBs (SCB and 4-silaspiro[3.3]heptane) were determined by electron diffraction and microwave spectroscopy. Naphthyl-substituted SCBs have been investigated by X-ray diffraction. These results were systematized <B-1989MI1>. Since the publication of these results, further investigations have been made. The molecular structures of 1,1-difluorosilacyclobutane, SCB, DMSB, 1,1-dichlorosilacyclobutane, 1,1-diethynylsilacyclobutane, 1,3-disilacyclobutane **1a**, 1,1,3,3-tetramethyl-1,3-disilacyclobutane **1b**, among monosubstituted 1-fluorosilacyclobutane and 1-chlorosilacyclobutane, have been studied by gas-phase electron diffraction with refinement of experimental data by means of *ab initio* calculations (Table 2). The molecule exists in a puckered conformation. During the structural refinement, it was assumed that all of the structural parameters except the puckering angle for both the equatorial and axial conformers are equal.

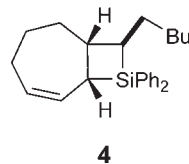
X-Ray techniques have been used to examine the molecular structure of some silacyclobutenes **2** <1984OM1930, 1988JA1315, 1989JA7615, 1991AGE1151, 1992OM3088>, benzosilacyclobutenes <1989JOM(379)217>, benzostannacyclobutenes **3** <1991JOM(415)343>, and fused SCB **4** <1994AG93>. The geometric parameters of metallacyclobutenes with the corresponding literature references are presented in Table 2.



- a:** $R^1 = R^3 = R^4 = \text{TMS}$; $R^2 = \text{Ph}$; $R^5, R^6 = \text{Ph}(\text{TMS})\text{C}=\text{CH}_2$
b: $R^1 = \text{Bu}^t$; $R^2 = [\text{Pt}(\text{PEt}_3)_2(\text{H}_2\text{O})]\text{SbF}_6$; $R^3 = R^4 = \text{Ph}$; $R^5, R^6 = \text{Bu}^t\text{CH}=\text{CH}_2$
c: $R^1 = R^2 = R^6 = \text{Bu}^t$; $R^3 = \text{OMe}$; $R^4 = \text{Mes}$; $R^5 = \text{TMS}$
d: $R^1 = \text{H}$; $R^2 = R^4 = \text{TMS}$; $R^3 = \text{Mes}$; $R^5 = \text{TMS-O}$; $R^6 = \text{Ad}$
e: $R^1 = \text{H}$; $R^2 = \text{Ph}$; $R^3 = \text{Mes}$; $R^4 = \text{TMS}$; $R^5 = \text{TMS-O}$; $R^6 = \text{Ad}$
f: $R^1 = \text{Me}$; $R^2 = \text{Ph}$; $R^3 = R^4 = \text{TMS}$; $R^5 = \text{TMS-O}$; $R^6 = \text{Bu}^t$
g: $R^1 = \text{TMS}$; $R^2 = \text{Ph}$; $R^3 = R^4 = \text{Cl}$; $R^5 = \text{H}$; $R^6 = \text{CH}_2\text{Bu}^t$
 Mes = 2,4,6-Me₃C₆H₂; Ad = 1-adamantyl



- a:** $M = \text{Si}$; $R^1 = \text{Mes}$; $R^2 = \text{NHSiBu}^t_3$
b: $M = \text{Sn}$; $R^1 = 2,4,6\text{-Bu}^t_3\text{-C}_6\text{H}_2$;
 $R^2 = \text{CH}_2\text{CMe}_2\text{C}_6\text{H}_3\text{Bu}^t_{2-3,5}$



2.11.3.2 NMR Spectroscopy

Proton, ¹³C, and ³¹P NMR spectra for different 1,1-disubstituted SCBs have been studied (Table 3) <1980JOM(190)9, 1983OMR412>. The influence on the ring carbon chemical shifts of substituents on the silicon atom is larger for SCBs than for silacyclopentanes and acyclic silanes. The δ C-2 and C-3 signals of SCBs are within the ranges 9.5–27.7 and 11.7–22.7 ppm, respectively.

The upfield shift of the $\delta(^{29}\text{Si})$ signal increases with the positive charge on the silicon atom <1980JOM(190)9>. The introduction of one or two methyl groups in the β -position of the SCB ring causes the silicon signals to shift upfield, and the $\delta(^{29}\text{Si})$ values for 1,1,3-trimethyl-1-silacyclobutane and 1,1,3,3-tetramethyl-1-silacyclobutane are 5.7 and 2.1 ppm, respectively <1980IZV1950>.

Chemical shifts and coupling constants for ¹³C, ¹⁵N (at natural abundance), and ²⁹Si are reported for 1,1-bis(alkylamino)-1-silacyclobutenes <1989SAA1101>. The ²⁹Si nuclear shielding of 1,1-bis(isopropylamino)-1-silacyclobutane

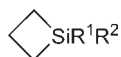
Table 2 Geometric parameters of SCBs  SiR¹R², silacyclobutenes **2**, and benzometallacyclobutenes **3**

Structure		<i>r</i> (Å)				Angles (deg)				Reference
<i>R</i> ¹	<i>R</i> ²	<i>M</i> – <i>C</i> (2)	<i>M</i> – <i>C</i> (4)	<i>C</i> (2)– <i>C</i> (3)	<i>C</i> (3)– <i>C</i> (4)	∠ <i>M</i>	∠ <i>C</i> -2	∠ <i>C</i> -3	∠ <i>C</i> -4	
H	H	1.885(2)		1.571(3)		77.2(9)	87.9(12)	97.0(15)		2006JST(800)146 B-1989MI1
–CH ₂ CH ₂ CH ₂ –		1.898(2)		1.579(3)		76.6				
Me	Me	1.885(2)		1.563(4)		79.2(11)	86.8	99.9		1999JST(477)71
F	F	1.836(3)		1.574(8)		82.7(6)	86.8(8)	100.6(8)		1988ACA352
Cl	Cl	1.860(3)		1.557(4)		81.1(10)	85.7(12)	102.0(15)		1998JST(445)207
HC≡C	HC≡C	1.874(2)		1.563(6)		79.2(6)	86.8	99.6		2002JST(610)159
F	H	1.855(1)		1.586		80.8(6)	85.3	98.6(19)		2001JST(559)7
Cl	H	1.864(2)		1.591(5)		80.7(14)	85.0	98.7(22)		2001JST(559)7
	1a	1.888(2)				90.6(3)	86.8(3)			1988ACA352
	1b	1.910(5)				92.2(4)				1999JST(485)135
Np ^a	Np ^a	1.894(4)	1.527(6)			81.3(2)	85.3(5)	107.9(3)		B-1989MI1
Np ^a	Si(CH ₂) ₃	1.877(3)	1.881(2)	1.475(5)	1.507(8)	78.8(1)	87.8(3)	106.2(4)	86.7(2)	B-1989MI1
	Np ^a									
Np ^a	OSi(CH ₂) ₃	1.863(2)	1.863(2)	1.537(3)	1.562(4)	79.5(1)	86.8(2)	100.5(2)	86.1(2)	B-1989MI1
	Np ^a									
2a		1.906(8)	1.915(8)	1.367(11)	1.500(11)	74.0(4)	91.9(5)	106.6(7)	87.5(5)	1984OM1930, 1988JA1315, 1989JA7615, 1991AGE1151, 1992OM3088
2b		1.86(1)	1.88(1)	1.40(1)	1.51(1)	75.3(4)	92.8(6)	103.1(7)	88.7(5)	1984OM1930, 1988JA1315, 1989JA7615, 1991AGE1151, 1992OM3088
2c		1.837(3)	1.928(3)	1.367(4)	1.599(4)	78.6(3)	91.7(2)	106.9(2)	81.8(2)	1984OM1930, 1988JA1315, 1989JA7615, 1991AGE1151, 1992OM3088

2d		1.972(7)			71.4(3)	97.7(5)	103.8(5)	86.6(4)	1984OM1930, 1988JA1315, 1989JA7615, 1991AGE1151, 1992OM3088
2e		1.991(13)			73.8(6)	96.3(4)	106.0(11)	83.9(8)	1984OM1930, 1988JA1315, 1989JA7615, 1991AGE1151, 1992OM3088
2f^b		1.981(18)			74.4(8)	95.5(14)	103.9(15)	82.8(10)	1984OM1930, 1988JA1315, 1989JA7615, 1991AGE1151, 1992OM3088
2g	1.828(1)	1.864(1)	1.354(1)	1.554(1)	80.7(1)	87.8(1)	110.4(1)		1984OM1930, 1988JA1315, 1989JA7615, 1991AGE1151, 1992OM3088
3a	1.885(1)	1.938(1)			77.3(5)	89.9(8)	107.3(10)	85.4(7)	1989JOM(379)217, 1991JOM(415)343
3b	2.185(5)	2.204(6)	1.417(9)	1.558(8)	67.5(2)	93.5(4)	110.0(6)	89.0(4)	1989JOM(379)217, 1991JOM(415)343
4	1.884(1)	1.880(1)	1.564(1)	1.589(1)	79.45(5)	86.44(7)	99.46(9)	85.88(7)	1994AG93

^a1-Naphthyl.

^bFor two independent molecules.

Table 3 NMR spectroscopic data (^1H , ^{13}C , ^{29}Si) for SCBs

R^1	R^2	$\delta^1\text{H}$ (ppm)				$\delta^{29}\text{Si}$ (ppm)
		$H-2, H-4$	$H-3$	Me	$C-2, C-4$ ($J(^{29}\text{Si}-^{13}\text{C})(\text{Hz})$)	
H	H	1.1	2.3		$\delta^{13}\text{C}$ (ppm)	22.7
H	Me	1.03	2.15	0.300	C-3	20.3
Me	Me	1.06	2.15	0.258	14.8(42)	18.1
Me	Cl	1.4	2.0	0.619	20.9(45)	15.9
Cl	Cl	1.95	1.95		27.7(52)	14.0
Me	EtO	0.9–2.0		0.238	18.6	13.5
Me	$\text{C}_7\text{H}_{15}\text{O}$			0.23	18.5	14.2
Me	PhO	1.1–2.0		0.358	19.4(47)	14.3
Me	AcO	1.2–2.0		0.383	18.3	15.0
Me	$\text{OSi}(\text{CH}_2)_3$	1.1	1.78	0.225	20.6(48)	13.7
	Me					
EtO	EtO	1.4	1.4		20.8(55)	11.7
Me	Et_2N	0.9–1.9		0.288	19.5(45)	14.5
Me	$\text{NHSi}(\text{CH}_2)_3$	1.0	1.8	0.125	20.4(45)	14.5
	Me					
Me	Ph	1.3	2.3	0.513	14.4(43)	18.3
Ph	Ph	1.5	2.3		14.0(44)	18.4
Ph	Cl				20.4	16.3
$\text{c-C}_6\text{H}_{11}$	$\text{c-C}_6\text{H}_{11}$	0.9	2.0		8.8(41)	18.8
$\text{CH}_2=\text{CHCH}_2$	$\text{CH}_2=\text{CHCH}_2$	1.03	2.07		12.2	18.2
$-\text{CH}_2\text{CH}_2\text{CH}_2-$		1.25	2.2		18.3(37)	18.2

($\delta(^{29}\text{Si}) = -10.2$ ppm) and 1,1-bis(*t*-butylamino)-1-silacyclobutane ($\delta(^{29}\text{Si}) = -14.9$ ppm) is increased compared to 1,1-dimethyl-1-silacyclobutane, and the value of $^1J(^{29}\text{Si}-^{15}\text{N})$ for the former compound is smaller (17.2 Hz) than for acyclic bis(alkylamino)silanes.

2.11.3.3 IR, Raman and Microwave Spectroscopy, Conformational Analysis

The study of IR spectra of SCBs indicates that many of the peaks are found in all spectra and can be considered as characteristic of the ring species <1965IZV1547, 1967JA1144, 1977JOM(139)11, 1980JOM(197)13>. There are six ring vibrations expected for a four-membered ring, one of which, ring puckering, has a frequency below 200 cm^{-1} . Three of the SCB ring modes occur between 850 and 950 cm^{-1} . Two absorption bands near 1120 and 1180 cm^{-1} result from vibrations involving methylene groups of the ring <1967JA1144>. IR spectra of SCB, DMSB, 1-methyl-1-chlorosilacyclobutane, and 1,1-dichlorosilacyclobutane in inert gas matrices at 10 K have been previously reported <1980IZV837>. For 1-silacyclobutane-1- d_1 , in the Si–H stretching region, in addition to the fundamental Si–H band at 2148.3 cm^{-1} , a second weaker band at 2151.3 cm^{-1} is observed. These two bands arise from the Si–H stretching for the molecule in two different conformations <1982JPC4335>.

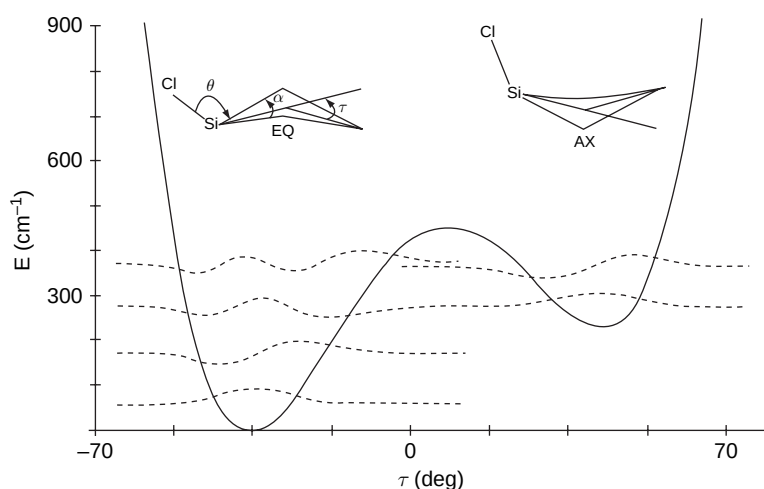
Since the previous review in CHEC-II(1996), IR spectra (in gaseous and solid phase) and Raman spectra for 1-bromosilacyclobutane <2000SAA2563>, 1-fluorosilacyclobutane <2006JST(800)106>, and 1-methylsilacyclobutane <1999JST(477)31> with complete vibrational assignment have been reported. Conformational analysis of these structures has been accomplished based on variable-temperature Fourier transform infrared (FTIR) spectra. Calculated enthalpy differences and the percentage of the axial conformer (minor) present in the fluid phase at ambient temperature as well as the estimated Si–H bond distance are summarized in Table 4.

Microwave studies have been accomplished on 1-fluorosilacyclobutane <1995JST(174)223> and 1-chlorosilacyclobutane <1996JSP321>.

Table 4 Enthalpy differences between equatorial and axial conformers (ΔH), Si–H bond distances ($r(\text{Si-H})$), and the percentage of the axial conformer based on IR data

R^1	R^2	ΔH (kJ mol^{-1})	$r(\text{Si-H})$ ($\text{\AA}$)		Axial (%)	Reference
			Equatorial	Axial		
H	F	$3.37 \pm 0.32 \text{ kJ mol}^{-1}$ ($282 \pm 27 \text{ cm}^{-1}$)	1.484	1.485	21 ± 2	2006JST(800)106
H	Br	$2.18 \pm 0.22 \text{ kJ mol}^{-1}$ ($182 \pm 18 \text{ cm}^{-1}$)	1.483	1.483	~ 22	2000SAA2563
H	Me	$1.46 \pm 0.32 \text{ kJ mol}^{-1}$ ($122 \pm 26 \text{ cm}^{-1}$)	1.490	1.490		1999JST(477)31

Conformational analysis of 1-chlorosilacyclobutane employing microwave spectroscopy data has shown that the equatorial conformer is more stable than the axial one by $185(40) \text{ cm}^{-1}$. The potential energy function of the ring-puckering motion has been determined for that molecule (Figure 1).

**Figure 1** Ring-puckering potential energy and wave functions of the first six vibrational states of 1-chlorosilacyclobutane <1996JSP321>.

2.11.3.4 UV Spectroscopy

Ultraviolet (UV) spectroscopy has been used for the investigation of charge-transfer complexes (CTCs) of silacyclobutanes with tetracyanoethylene <1975IZV1998, 1977IZV1038, 1979ZOB950>. The increase in the electron-donor ability of alkyl substituents in 1-methyl-1-alkyl-1-silacyclobutanes leads to a bathochromic shift of the CTC band. The first ionization potentials for these compounds were determined from ν_{CTC} values <1977IZV1038>. The comparison of the CTC UV spectra for 1-methyl-1-(*p*-x-phenyl)silacyclobutanes and trimethyl(*p*-x-phenyl)silanes ($X = \text{H, Me, Cl, CH}_2\text{TMS, OMe, NMe}_2$) indicates that both silyl substituents act as electron acceptors with respect to the π -electron system of benzene; this effect is larger for the 1-methyl-1-silacyclobutane group. The calculated σ^+ constants of the TMS and $\text{MeSi}(\text{CH}_2)_3$ groups are -0.22 and -0.20 , respectively <1975IZV1998>.

2.11.3.5 EPR Spectroscopy

Silacyclobut-1-yl, 1-methylsilacyclobut-1-yl, and 3-methylsilacyclobut-1-yl radicals were prepared by γ -irradiation of the corresponding silanes in adamantane matrices at 77 K. Electron paramagnetic resonance (EPR) studies show that the radicals have a nonplanar ring <1988JOM(341)273>. The reduction of phenylsilacyclobutanes with potassium gave anion radicals, and their EPR spectra were recorded at -75°C (Table 5) <1983ZOB1315>.

Table 5 Hyperfine splitting constants of SCB anion radicals

R^1	R^2	Hyperfine structure	Hyperfine splitting constants, G		
			a_1	a_2	a_3
Me	Ph	$2 \times 3 \times 3$	7.7	3.3	1.0
Ph	Ph	$2 \times 3 \times 3$	7.6	3.5	1.0
Bu ^t	Ph	$2 \times 3 \times 3$	8.3	3.0	1.1
Me	<i>p</i> -MeC ₆ H ₄	$4 \times 3 \times 3$	9.0	3.4	1.8

2.11.3.6 Mass Spectrometry

The electron-impact fragmentation of SCB <1967JA1144, 1976JCD558>, 1,1-dialkylsilacyclobutanes <1966ZOB96, 1972OMS309, 1979ZOB1307, 1985JOM(284)5>, 1-alkyl-1-aryl-1-silacyclobutanes <1984ZOB1125>, and SCBs with functional substituents on the silicon atom <1976JCD558, 1984JOM(277)311> or the methyl group in the 2- or 3-position of the ring <1979ZOB1307, 1981OMS242, 1984JOM(277)311> has been investigated. With rare exceptions, SCBs show intense molecular ion peaks. The main feature of the fragmentation process for the molecular ion of SCBs is the elimination of ethylene from the heterocycle. The loss of ethylene from these compounds also occurs when they are pyrolyzed in the gas phase. The mass spectrum of 1,1-dimethyl-1-germacyclobutane with respect to the silicon compound is enriched by light fragment ions, and exhibits lower intensities for odd-electron ions. The elimination of C₃H₆ from the molecular ion is more characteristic for germacyclobutane than for SCB <1972OMS309>.

2.11.4 Thermodynamic Aspects

The boiling point (82.75 °C) and the heat of evaporation (7.887 kcal mol⁻¹ (33.02 kJ mol⁻¹) at 298 K) of DMSB have been determined from the results of saturated vapor pressure (P) temperature (t) dependence. The coefficients in the Antoine equation,

$$\log P = 7.29978 - 1473.282/(t + 250.640)$$

were obtained from the experimental data <1974ZFK2890>.

Enthalpies of combustion for 1-methyl-, 1,1-dimethyl-, 1,1,2- and 1,1,3-trimethyl-, and 1-methyl-1-vinylsilacyclobutanes were determined in a precision isothermal calorimeter. The heats of formation of these compounds in both the liquid and gas phases were calculated at 298.15 K. The calculated energies of monosilacyclobutane ring strain vary within the range 23.8–25.0 kcal mol⁻¹ (107–112 kJ mol⁻¹), increasing with the introduction of substituents to the silicon atom and to the carbon atoms in the ring (Table 6) <1991JOM(401)245, 1991MI197>. The theoretical heat of formation at 298 K for DMSB is –23.8 kcal mol⁻¹ (–99.5 kJ mol⁻¹) <1989JPC1584>.

Table 6 Enthalpies of combustion, formation, and calculated energies of ring strain for SCBs (kcal mol⁻¹ (kJ mol⁻¹)) <1991JOM(401)245>

Compound	$-\Delta H^\circ_{\text{comb.,liq.}}$	$-\Delta H^\circ_f$	$\Delta H^\circ_{\text{ev.}}$	E_{cycle}
 SiMeH	930.2 ± 1.8 (3894.6 ± 7.6)	11.5 ± 1.8 (48.0 ± 7.5)	6.0 ± 1.8 (25.1 ± 7.6)	25.8 (108)
 SiMe ₂	1076.9 ± 2.1 (4508.8 ± 8.6)	28.2 ± 2.0 (118.1 ± 8.5)	7.9 ± 2.1 (33.1 ± 8.6)	26.0 (109)
 SiMe ₂	1231.3 ± 1.9 (5155.3 ± 8.0)	34.9 ± 2.0 (146.0 ± 8.5)	8.6 ± 2.0 (36.0 ± 8.4)	26.0 (109)
 SiMe ₂	1230.7 ± 1.9 (5152.8 ± 8.0)	35.5 ± 2.0 (148.5 ± 8.5)	8.5 ± 2.0 (35.5 ± 8.5)	26.8 (112)
 Si	1188.1 ± 1.9 (4974.4 ± 8.0)	9.8 ± 2.0 (41.1 ± 8.5)	7.9 ± 2.0 (33.1 ± 8.5)	26.0 (109)

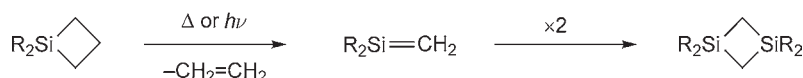
2.11.5 Reactivity of Fully Conjugated Rings

No work on fully conjugated ring systems has been published in the covered period.

2.11.6 Reactivity of Nonconjugated Rings

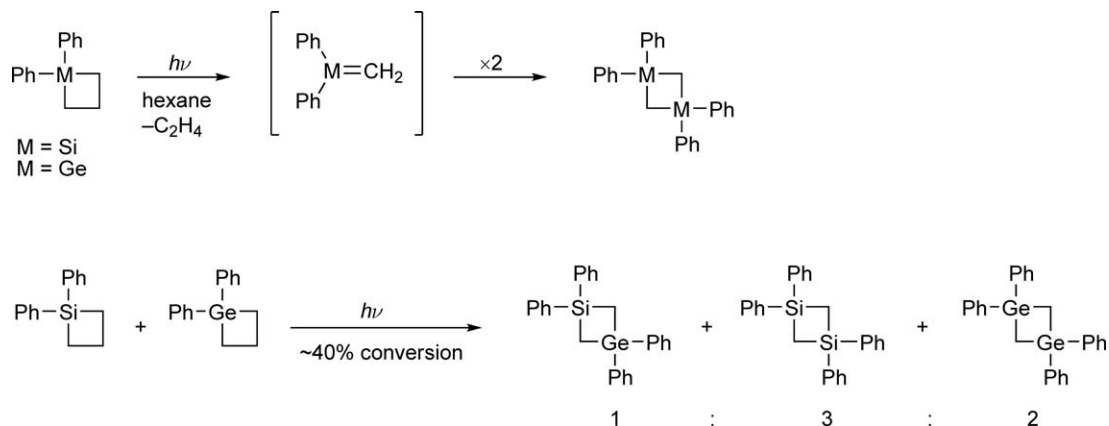
2.11.6.1 Pyrolysis and Photolysis Reactions

A detailed discussion on the pyrolysis and photolysis of SCBs and pyrolysis of germacyclobutanes can be found in the CHEC-II(1996) <1996CHEC-II(1B)867>. Pyrolysis of SCBs at 500–700 °C yields silenes *en route* to 1,3-disilacyclobutanes, ethylene being the predominant component of the gaseous reaction products (Scheme 1). Gas-phase and laser-pulsed photolysis proceed in the same way.



Scheme 1

Co-pyrolysis of two different SCBs produces a mixture of three possible 1,3-disilacyclobutanes. Photochemical silene formation proceeds with useful efficiencies from SCBs that bear alkyl, vinyl, ethynyl, silyl, and phenyl substituents at silicon <1999CJC1136>. In contrast, alkoxy substitution either directly at silicon or on the aromatic rings of phenylated derivatives stabilizes the SCB moiety with respect to photo-cycloreversion <1997CJC1393, 1998JA9504>. The photochemistry of 1,3-dimetallacyclobutanes has also been studied, including their relative propensities to undergo [2+2] cycloreversion to regenerate the free metallaene <1999OM5643>. The 1,3-dimetallacyclobutanes can be prepared by direct photolysis of monometallacyclobutanes (Scheme 2); the corresponding silenes formed under photolysis conditions undergo head-to-tail [2+2] cycloaddition to yield 1,3-dimetallacyclobutanes. 1,1,3,3-Tetraphenyl-1-germa-3-silacyclobutane was prepared by photolysis of 1:1 mixture of the two metalla-cyclobutanes (Scheme 2).



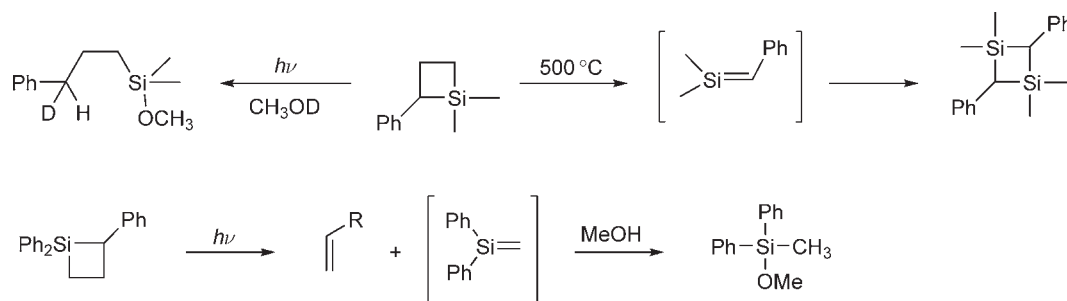
Scheme 2

1,1,3,3-Tetraphenyl-1,3-disilacyclobutane undergoes inefficient cycloreversion to the silene upon direct photolysis in solution. Quantum yields for the photocycloreversion are 4–5 times higher for 1-sila-3-germacyclobutane than for the 1,3-disilacyclobutane, whereas the quantum yields for photocycloreversion of 1,3-digermacyclobutane are about 15 times higher than for the analogous 1,3-disilacyclobutane <1999OM5643>. This variation in photochemistry is quite remarkable, considering that the monometallacyclobutanes under the cycloreversion process with equal quantum efficiencies under similar conditions.

The photochemical cycloreversion of SCBs is known to be initiated from the lowest (σ, σ^*) excited singlet state by cleavage of one of the ring Si–C(2) bonds to form a biradicaloid intermediate. This excited-state intermediate cleaves to silene and alkene, recloses to starting material, or undergoes an intramolecular disproportionation if an alkyl substituent is present at C-2 <1999CJC1136, 1989OM1112>.

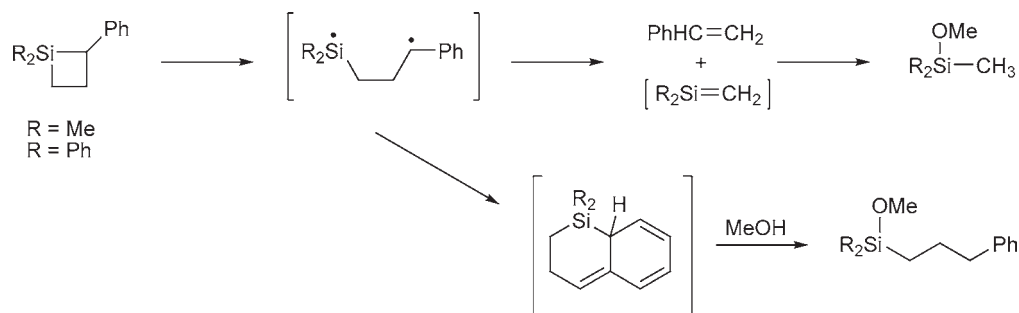
In contrast, the mechanism of the thermal cleavage of SCBs is shown to proceed by a stepwise mechanism involving initial C(2)–C(3) bond cleavage <1999CJC1136, 1975JA1957, 1989OM168, 1997JA11966, 1974JOC3543>.

Pyrolysis of 1,1-dimethyl-2-phenyl-1-silacyclobutane cleaves regioselectively through the Si–C(4) bond to give dimethylsilylphenylmethylene, which dimerizes to afford *cis/trans*-1,1,3,3-tetramethyl-2,4-diphenyl-1,3-disilacyclobutane. Photolysis of the same species cleaves regioselectively through Si–C(2) bond (as shown in **Scheme 3**) <1974JOC3543>. The ring-opening regioselectivity in the photolysis of 1,1,2-triphenylsilacyclobutane proceeds similarly (**Scheme 3**) <1993JA5332, 2000CJC1459>, as do photolysis reactions of 2-alkyl-substituted SCBs <1989OM1112>.



Scheme 3

Parallel with cycloreversion, [1,3]-silyl migration proceeds to give a bicyclic isotoluene analogue that undergoes rapid desilylation in methanol solution to give ring-opened products (**Scheme 4**) <2000CJC1459>. Previously, formation of these species was believed to occur by trapping of the 1,4-biradical/zwitterion formed upon Si–C bond cleavage of SCB.

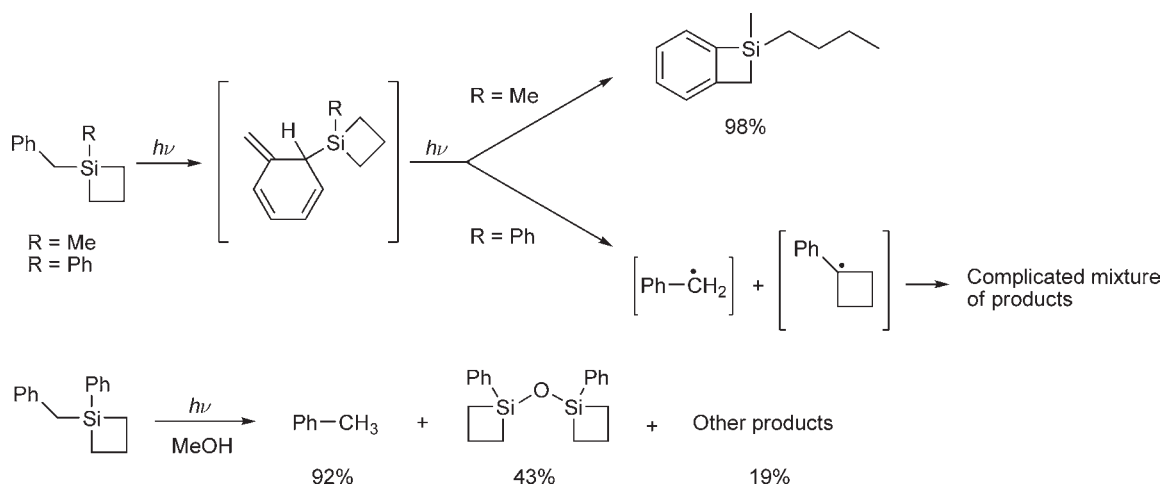


Scheme 4

Photolysis of 1-benzyl-1-methylsilacyclobutane and 1-benzyl-1-phenylsilacyclobutane also leads to formation of isotoluene derivatives as the major primary products (**Scheme 5**). The primary photolysis in both cases is dominated by reactivity specific to the benzyl chromophore rather than the SCB moiety, unlike the case with other SCBs. Silene formation competes significantly in the case of 1-benzyl-1-phenylsilacyclobutane, when the role of the primary chromophore is shared between the benzyl group and the SCB ring via a second phenyl group attached to silicon.

Photolysis of 1-benzyl-1-methylsilacyclobutane, which proceeds via rearrangement to an isotoluene intermediate followed by ring opening, produces 1-propyl-1-methyl-2,3-benzosilacyclobutene in quantitative yield <2000CJC1459>.

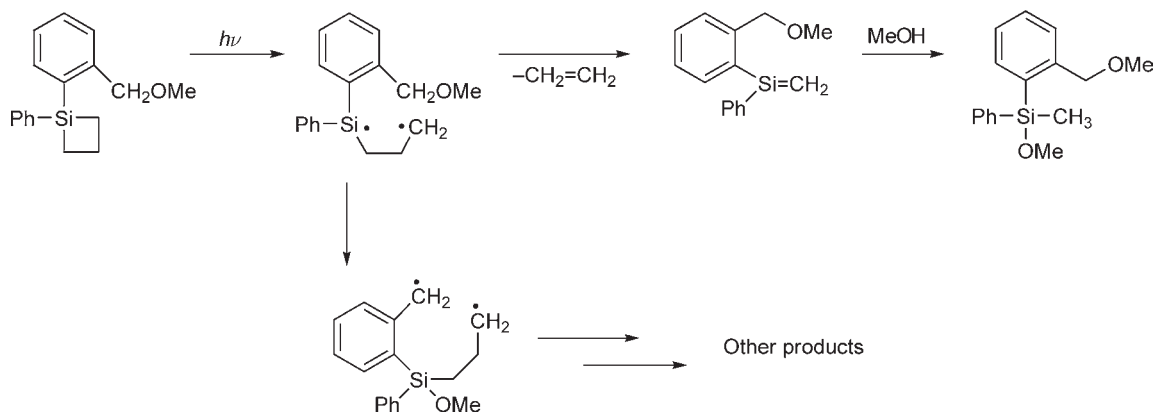
Photochemistry of the isotoluene derivative of 1-benzyl-1-phenylsilacyclobutane is initiated by preferential cleavage of the weaker of the exocyclic silacyclobutyl Si–C bonds, yielding benzyl- and phenylsilacyclobutyl radicals.



Scheme 5

This fact is supported by steady photolysis of 1-benzyl-1-phenylsilacyclobutane in deoxygenated methanol solution, which leads to the formation of two main products, toluene and disiloxane. In the absence of methanol, photolysis of this species produces a complicated mixture of products (Scheme 5).

When other free radical processes are available, the mixture of products becomes more complicated. For instance, *o*-(methoxymethyl)phenylsilacyclobutane, when irradiated, is proposed to undergo a competing loss of ethylene to yield silene and migration of the methoxy group from the benzylic carbon to silicon, leading to the mixture of products (Scheme 6) <2003JA8096>.



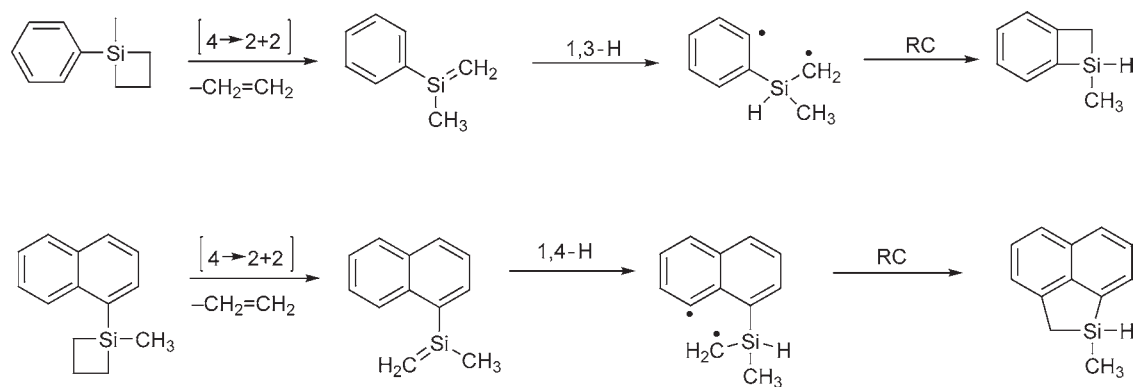
Scheme 6

Thermally induced rearrangements of SCB are known as well. 1-Methyl-1-phenylsilacyclobutane undergoes a [4→2+2] thermo-cyclodecomposition to give silene, which undergoes a sigmatropic 1,3-hydrogen shift through the resulting 1,4-diradical. Ring closing gives 3,4-benzo-1-methyl-1-hydro-1-silacyclobutene (Scheme 7) <1995JOM(492)C4>.

1-Methyl-1-naphthyl-1-silacyclobutane undergoes a similar transformation via a thermolytic [4→2+2] cyclodecomposition and 1,4-hydrogen shift to yield 1-methyl-1-hydro-1-silaacenaphthene (Scheme 7).

Surprisingly, 2-methylene-1-silacyclobutane at high temperatures does not undergo cycloreversion to produce silene and allene, but it undergoes rearrangement to 2- and 3-silacyclopentenes via the intermediacy of a carbene formed by a 1,2-silyl shift (Scheme 8) <1985JA731>.

When deuterium-labeled 2-methylene-1-silacyclobutane was investigated, scrambling of deuterium between the allylic methylene and the terminal vinyl was observed. This fact has been explained by ring opening to the 1,4-diradical at temperatures below those required for the rearrangement to the carbene <1995JA11695>.



Scheme 7



Scheme 8

Laser-induced decomposition of SCBs has been reported as an efficient route for the gas-phase deposition of thin films of Si-C-H and Si-C materials <1993JCF411, 1994JOM(466)29, 1990JOM(391)275>.

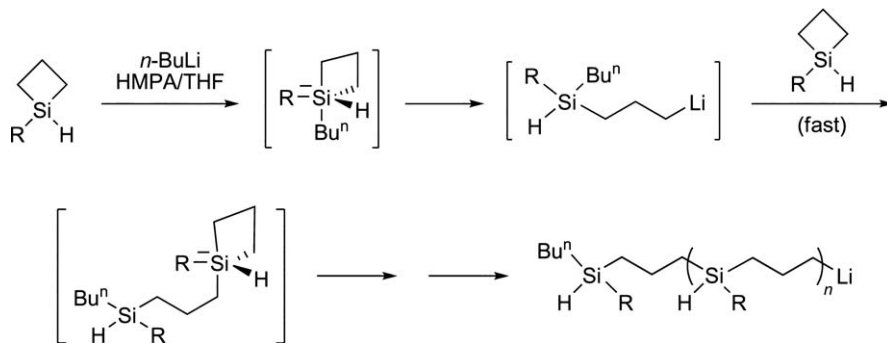
2.11.6.2 Ring-Opening Reactions

One of the primary advantages to the use of SCB reagents is the ease by which they undergo ring-opening processes. These strain-release events can trigger many important processes in organic synthesis.

2.11.6.2.1 Ring-opening reactions leading to polymerization

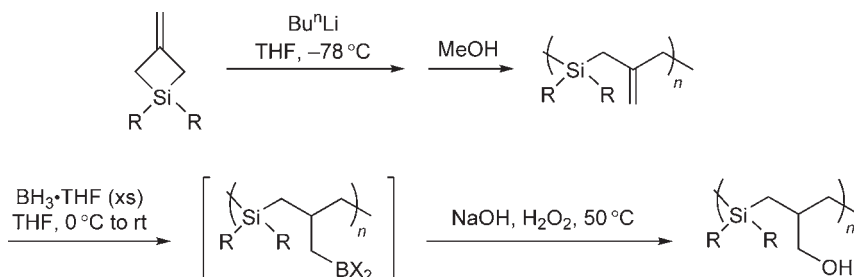
Ring-opening polymerization is one of the most important applications of SCBs in organic chemistry. Polymerization of SCBs, which gives rise to carbosilane polymers, has been carried out thermally, by transition metal catalysis, or, most commonly, by anionic initiation. Thermal polymerization is rare, however, and is not covered in this chapter. For leading references into thermal polymerization of SCBs, refer to <1996CHEC-II(1B)867> and <1995COMC-II(2)50>.

The strain-release Lewis acidity of SCBs makes them ideal monomers for anionic polymerization. For example, *n*-butyllithium reacts with SCBs by attack on the central silicon atom to generate a pentavalent silicate complex (Scheme 9). Although this initiation process is reversible in principle, the intermediate silicate breaks down with selective cleavage of a strained endocyclic bond to produce a new, silylpropyl carbanion. Chain propagation occurs as the silylpropyllithium species reacts with another molecule of the SCB monomer. Similarly, initiation may be achieved with oxyanion salts of group I metals, with potassium being the preferred counterion <1967DOK1068, 1964JA2687, 1965DOK268>.



Scheme 9

Anionic ring-opening polymerization of Si-disubstituted and monosubstituted SCBs (bearing alkyl, vinyl, or phenyl groups) thus provides the corresponding poly(carbosilanes) <1992MM1639, 1992PB281>. In the case of 1,1-dimethyl-1-silacyclobutene, polymerization proceeds with retention of alkene stereochemistry and yields predominantly poly(1,1-dimethyl-1-sila-*cis*-but-2-ene) <1992PB17>. Polymerization of 3-methylenesilacyclobutanes gives polymers with methylene groups attached, which can be further functionalized (**Scheme 10**) <1997MM2524>.

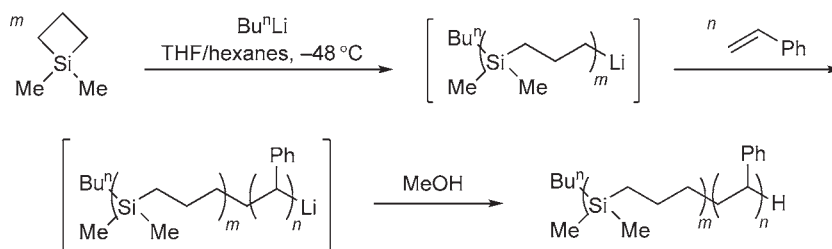


Scheme 10

Butyllithium-induced polymerization of dialkylsilacyclobutanes, typically conducted in THF–hexane mixed solvent systems, displays characteristics consistent with a living polymerization process. The living nature of polymerization – the ability to reinitiate polymerization upon addition of a fresh supply of monomer – was investigated by addition of a second portion of monomer, followed by end-capping the resulting polymer with an electrophile <1997PSA3207, 1995MM7029>. The end-capping efficiency, when poly(1,1-dimethylsilacyclobutane) was treated with chlorodimethylphenylsilane, was 0.9 <1997PSA3207>. The living nature of SCB polymerization means that the synthesis of polysilabutanes can be incorporated into block copolymers. Living polymerization can also translate into higher molecular weight polymers and narrower polydispersity (M_w/M_n).

2.11.6.2.1(i) Application for the synthesis of block copolymers

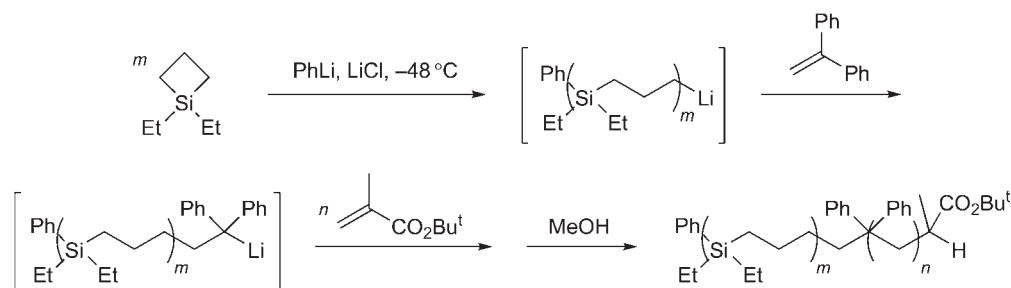
Anionic polymerization is widely used to prepare polymers with narrow molecular weight distribution. Addition of styrene to the living poly(1,1-dialkylsilabutane)s provided a poly(1,1-dialkylsilyl- β -styrene) block copolymer (**Scheme 11**) in 99% yield with $M_w/M_n = 1.19$ <1997PSA3207, 1995MM7029>.



Scheme 11

Amphiphilic block copolymers of SCB and methacrylic acid (and methacrylic acid derivatives) with narrow molecular weight distribution can be synthesized by sequential addition of 1,1-diphenylethylene and methacrylate or its derivatives to living poly(silacyclobutane) in the presence of lithium chloride (**Scheme 12**) <2001PSA86, 1998PSA2699, 1999MM6088>.

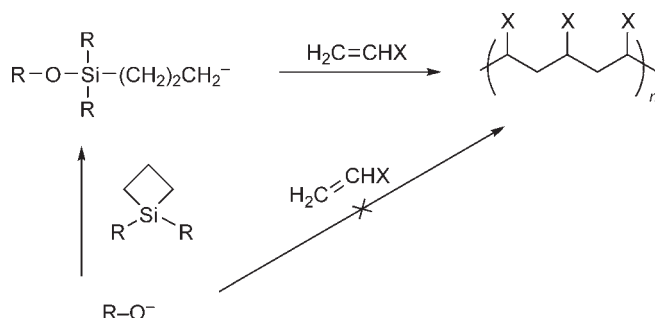
It is important to end-cap the living carbosilane polymer with 1,1-diphenylethylene to decrease the reactivity of the living center in order to obtain the block copolymer successfully. The diphenylethylene thus provides a milder carbanion for initiation of the methacrylate monomer. With this modification, efficiency of the end-capping by an electrophile (quenching) has reached 0.95 <2001PSA86, 1998PSA2699>.



Scheme 12

2.11.6.2.1(ii) Concept of ‘anionic pump’

SCBs play an important role in the formation of other block copolymers. For example, the relatively less nucleophilic poly(ethylene oxide) oxyanion cannot initiate the polymerization of styrene, which needs a more nucleophilic alkyl lithium initiator. To enable the synthesis of multi-block copolymers from various combinations of monomers by anionic mechanisms, it is important to modify the reactivity of the growing anionic chain end of each polymer so as to attack the co-monomer. There have only been a few reports on the polymerization of styrene initiated by an oxyanion (see <2001MM4384> and references cited). Thus, there exists a need for a transitional species that is capable of converting oxyanions into carbanions. In 2000, Kawakami and co-workers came up with the concept of the ‘carbanion pump’, in which the ring-strain energy of the SCB is harnessed to convert an oxyanion into a carbanion (<Scheme 13> <2000MI527>).

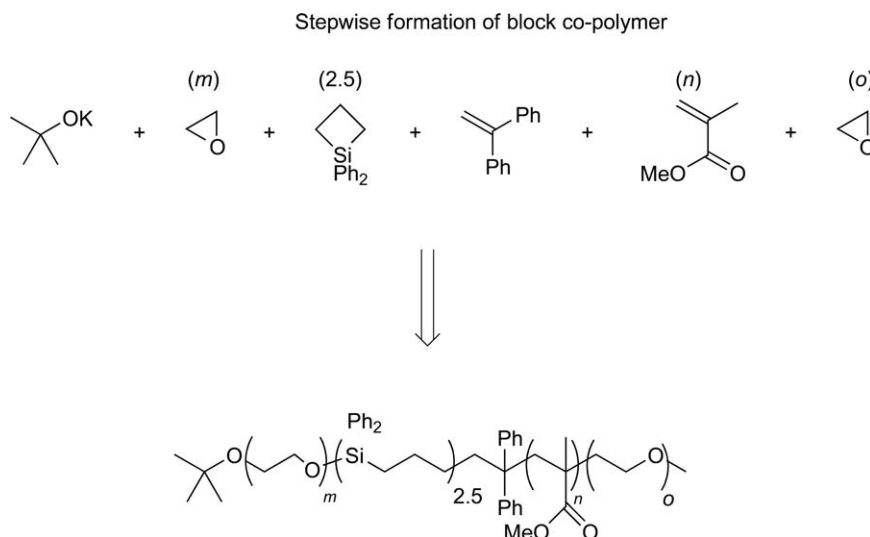


Scheme 13

Similarly, Teyssi  and co-workers <1998MM2724> used disilacyclopentane derivatives to ‘upgrade’ an oxyanion into a silyl anion, which initiated polymerization of styrene or methyl methacrylate with an efficiency of 35%. The efficiency of dimethylsilacyclobutane as a ‘carbanion pump’ was even lower (11%) <2000MI527>, but this situation was significantly improved by including 1,1-diphenylethylene to end-cap the initially formed carbanion <2001MM4384>. Apparently, the reactivity of the resulting diphenylpentyl anion toward dimethylsilacyclobutane is low, which helps to suppress side processes such as unwanted polymerization of the SCB.

Further studies were directed to examine different SCBs and the effect of different counterions. Potassium counterions provide improved efficiency as compared to lithium or sodium counterions. The most efficient system in terms of formation of carbanions was achieved with diphenylsilacyclobutane in combination with potassium *tert*-butoxide and diphenylethylene <2004MI856>. Di-block copolymers from ethylene oxide and methyl methacrylate (or styrene) were synthesized by this method with 85% efficiency (<Scheme 14> <2004MI856>).

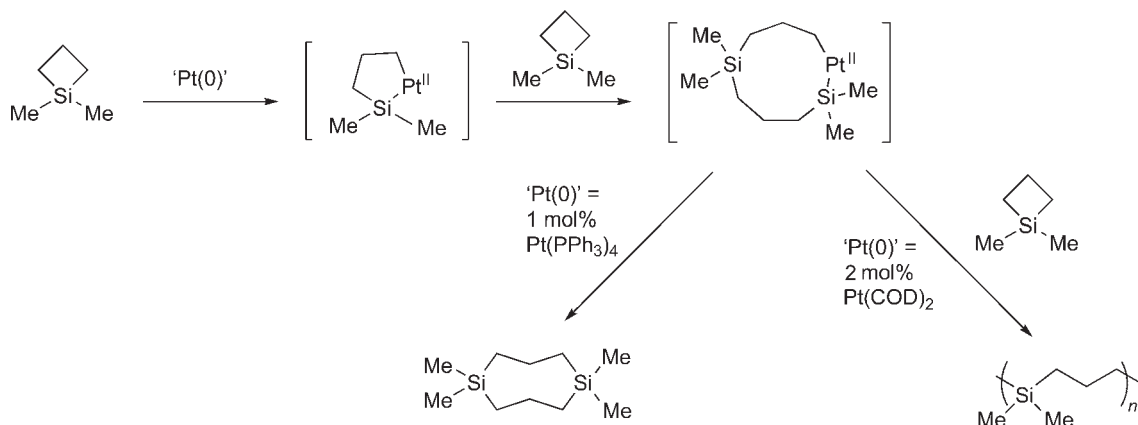
The ‘carbanion pump’ method has been successfully applied for the preparation of different block copolymers including poly(ethylene oxide)–block–polystyrene, poly(ethylene oxide)–block–polystyrene–block–poly(ethylene oxide), poly(ethylene oxide)–block–poly(methyl methacrylate), poly(ethylene oxide)–block–poly(methylmethacrylate)–block–poly(ethylene oxide) (shown in <Scheme 14>), and poly(ferrocenyldimethylsilane)–block–(methyl methacrylate) <2004MI856, 2004MM1720, 2006MI(928)292>.



Scheme 14

2.11.6.2.1(iii) Transition metal-catalyzed polymerization

Polymerization of DMSB occurs with up to quantitative yield in the presence of catalytic platinum(0) complexes, whereas dimerization is the predominant process in the presence of phosphine–platinum(0) complexes ([Scheme 15](#)) <1995JA8873, 1965JOC2618, 1966JC1137, 1972JOM(44)291>. Dimerization and polymerization apparently have the same intermediate, 2,2-dimethyl-1-platina-2-silacyclopentane, which can be isolated in moderate yield (45%) <1995JA8873>.



Scheme 15

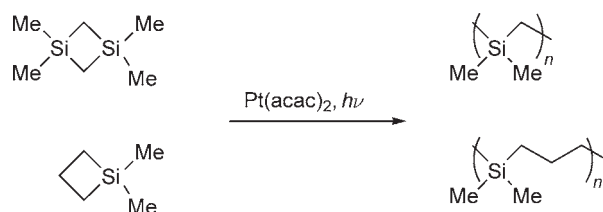
In the case of 1,1-diphenyl-1-silacyclobutane, the corresponding platinum insertion product (2,2-diphenyl-1-platina-2-silacyclopentane) can be isolated in 84% yield.

Irradiation of 1,1,3,3-tetramethyl-1,3-disilacyclobutane or 1,1-dimethylsilacyclobutane in the presence of Pt(acac)₂ induces the same type of polymerization (acac = acetylacetonate; [Scheme 16](#)) <1999MM6003, 1999CM3687>.

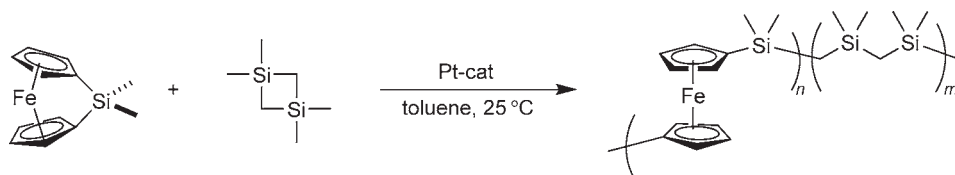
This discovery was employed for the photoinitiated cross-linking of poly(methacrylate) by ring-opening polymerization of a tethered SCB moiety <1999CM3687>.

Pt-catalyzed copolymerization of ferrocenylsilane and SCB, disilacyclobutane, or cyclic silane monomers can be accomplished to provide random copolymers ([Scheme 17](#)) <1996MAR319, 1995MM401>.

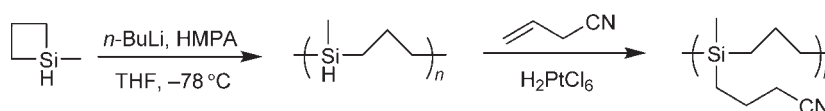
As Weber has shown, polymers bearing reactive Si–H bonds can be formed by ring-opening polymerization of 1-silacyclobutane <1992PB281>. These polymers can be further converted into Si-functionally-substituted polycarbosilanes by Pt-catalyzed hydrosilylation reaction of Si–H functionality with alkenes ([Scheme 18](#)) <1993MM563>.



Scheme 16

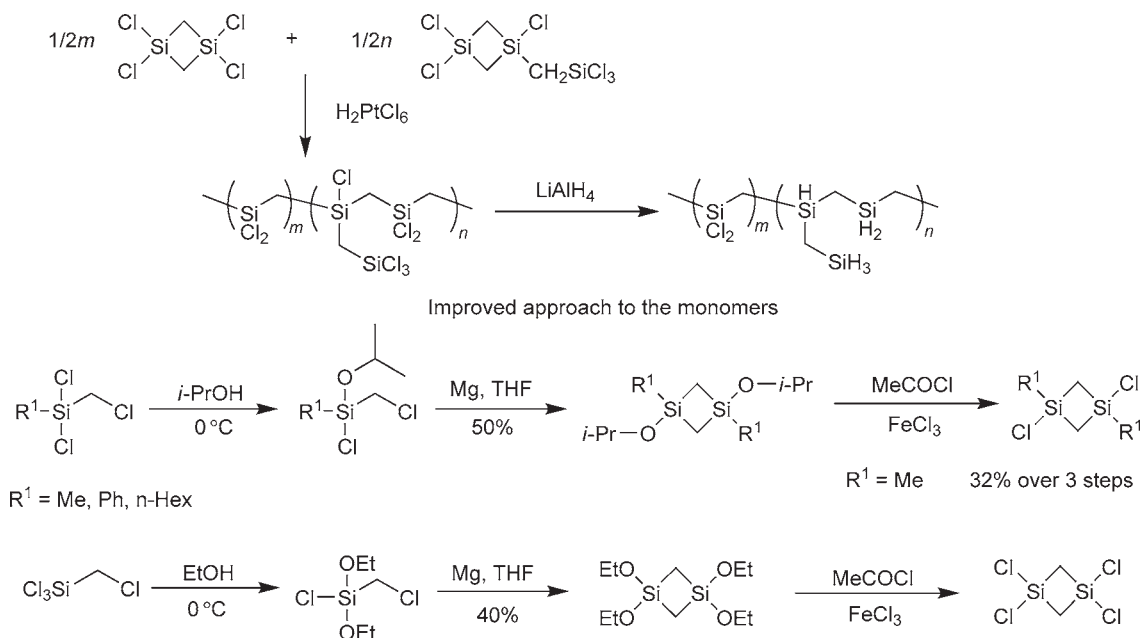


Scheme 17



Scheme 18

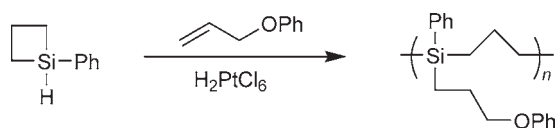
Different reactive functionalities on Si such as Si-Cl, Si-OR, and Si-H can be used to append side chains to the polymer backbone. Interrante and co-workers reported on the synthesis of functionalized poly(silylenemethylenes) and the corresponding monomers. The method they developed involves Pt-catalyzed polymerization of 1,3-dichloro-1,3-dimethyl-1,3-disilacyclobutane or 1,1,3,3-tetrachloro-1,3-disilacyclobutane [<1996MM5788, 1994JA12085>](#), then Si-Cl can be converted into Si-OR [<1996JOM\(521\)1>](#), Si-F [<1996JOM\(521\)1, 1997JA12020>](#), or reduced with LiAlH_4 to Si-H [<1996MM5788, 1994JA12085>](#) (Scheme 19). Tetraethoxydisilacyclobutane can be polymerized with H_2PtCl_6 at 100°C as well to provide directly poly[(diethoxysilylene)methylene], a moisture-sensitive solid [<1995MM5160>](#).



Scheme 19

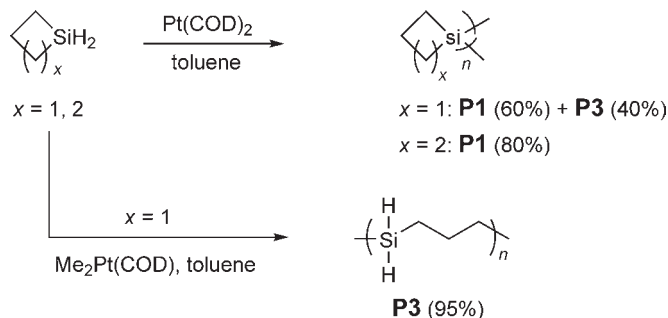
Before Interrante's studies, synthesis of poly(silylenemethylenes) was limited by the availability of the monomer. It was found that ethoxy substituents on silicon lead to improved yields for the formation of four-membered rings <1996JOM(521)1> (Scheme 19), then ethoxy functionality can be converted into chloride. Therefore disilacyclobutane monomers became easier to approach.

As been shown by Weber, simultaneous hydrosilylation–polymerization can be accomplished with a Pt-catalyst <1995BSF551>, as shown in Scheme 20.



Scheme 20

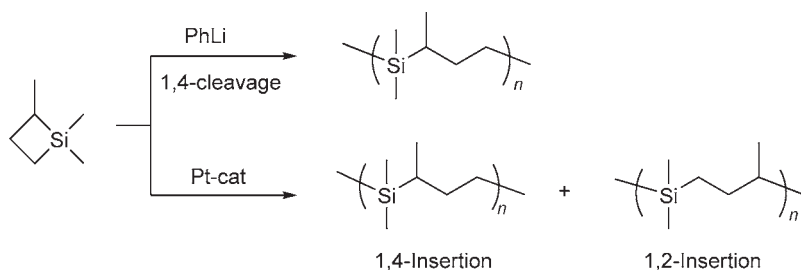
Tanaka has shown that conditions for dehydrocoupling of silanes, which employ Pt(COD)₂ in case of SCB, lead mostly to formation of polymers via ring opening (COD = cyclooctadiene; Scheme 21) <1997CL785>. In contrast, larger ring homologues gave polysilacyclic polymers via dehydrocoupling.



Scheme 21

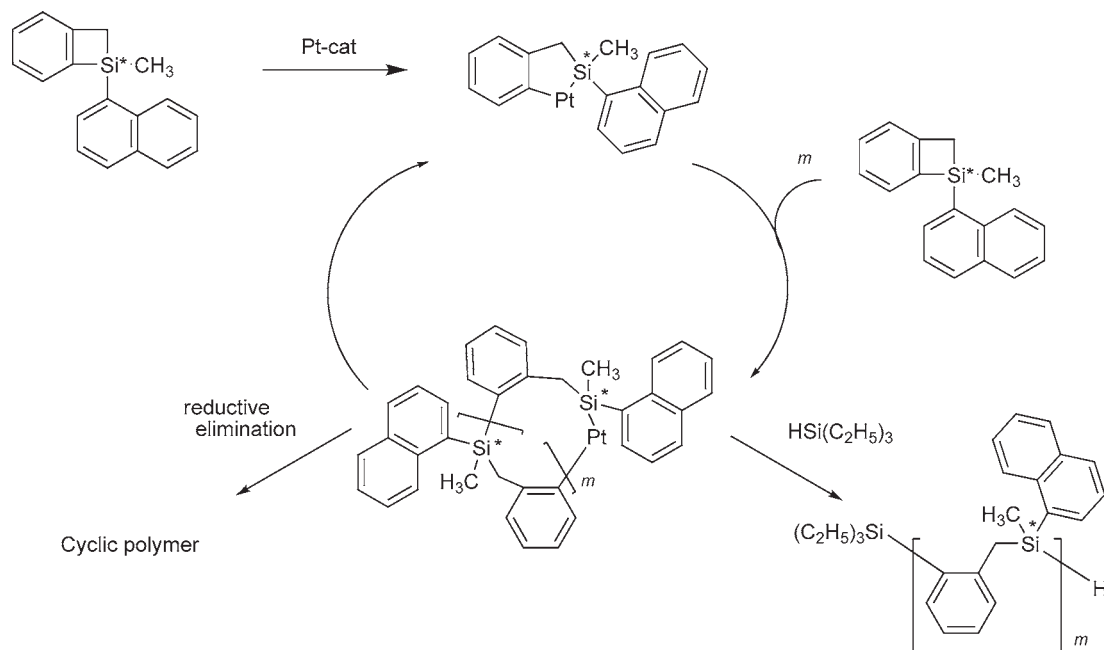
2.11.6.2.1(iv) Regioselectivity of ring opening in polymerization

Since data on the polymerization of DMSB do not reveal anything about the ring opening, a methyl group was introduced at the 2-position of the ring to probe the regioselectivity in the ring opening. Polymerization of 1,1,2-trimethylsilacyclobutane was carried out with PhLi and Pt-complexes <1999MI138> (Scheme 22). The 1,4-bond of the monomer was selectively cleaved in the anionic polymerization by phenyllithium. In case of the Pt-catalyzed polymerization, the propagation reaction proceeded via a Pt-complex insertion in either the 1,2- or the 1,4-bond of the SCB (Scheme 22).



Scheme 22

Stereoregular polymerization with a Pt-catalyst has been achieved for 1-methyl-1-(1-naphthyl)-2,3-benzosilacyclobut-2-ene (**Scheme 23**) <2003MI1619>. When this type of polymerization was attempted on optically pure (+)-1-methyl-1-(1-naphthyl)-2,3-benzosilacyclobut-2-ene, an optically active polymer was formed. The proposed mechanism is shown in **Scheme 23**.



Scheme 23

Oxidative addition of the Si–aryl carbon bond in the silacyclobutene ring to Pt gives the optically active intermediate Pt-complex. Further coordination of (+)-1-methyl-1-(1-naphthyl)-2,3-benzosilacyclobut-2-ene to the complex and σ -bond metathesis will provide the cyclic dimer Pt-complex. Reductive elimination from the intermediate platinum complex gives cyclic polymers and oligomers. Preference of σ -bond metathesis over reductive elimination gives polymers of higher molecular weight. The presence of Et_3SiH in the system results in the formation of linear products via σ -bond metathesis.

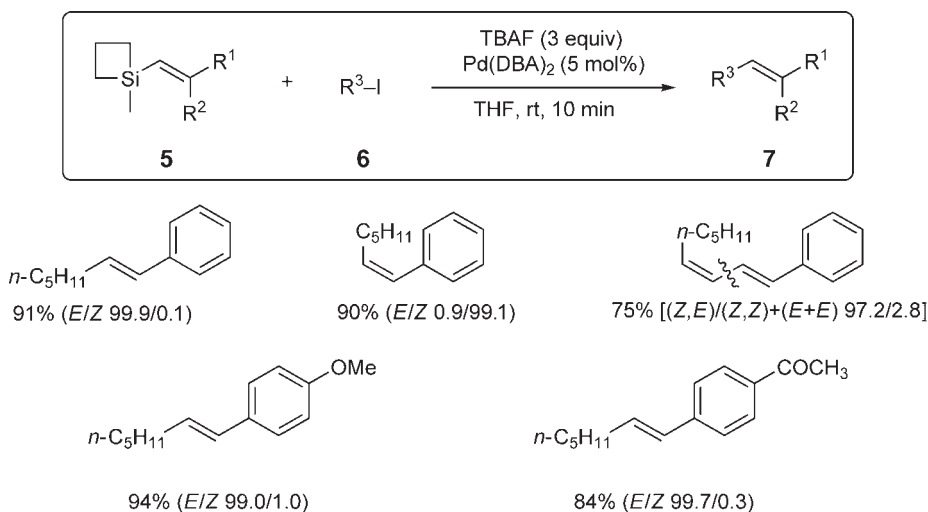
2.11.6.2.2 Ring-opening reactions leading to activated silanes for other reactions

Certain organosilane reactions require an activated silicon species in order to proceed under synthetically useful conditions. For example, Hiyama couplings <1988JOC918, 1989JOC270, 2002JOM58> of vinyl- and arylsilanes with electrophiles require a heteroatom activating group on the silicon in addition to the palladium catalyst. Similarly, the Tamao oxidation <1983OM1694, 1990OS96> of carbon–silicon bonds relies on electronegative heteroatom substituents to promote formation of the active silicate intermediate *en route* to the alcohol product.

Ring opening of SCBs can provide labile, heteroatom-activated silane species *in situ* as reactive intermediates for such transformations. Aqueous fluoride is frequently employed toward this end.

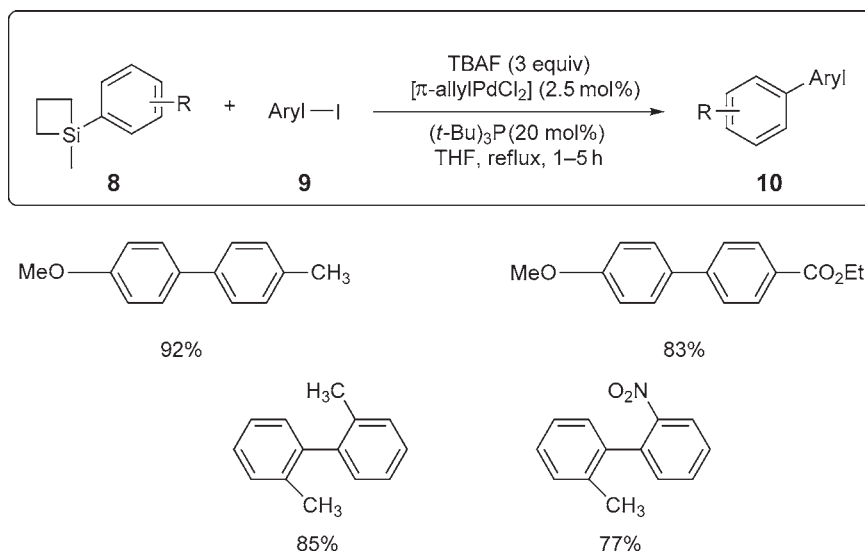
Denmark's group showed that alkenylsilacyclobutanes **5** can undergo facile palladium-catalyzed Hiyama-type cross-coupling with aryl and vinyl iodides **6** to give the alkenes **7** (**Scheme 24**) <2002ALD835, 2003ACA75, 2000S999, 1999JA5821>.

The reaction proceeds rapidly (10 min at ambient temperature) in the presence of 3 equiv of tetrabutylammonium fluoride (TBAF) and 5 mol% of $\text{Pd}(\text{DBA})_2$ in tetrahydrofuran (THF) <2002ALD835, 2000S999, 1999JA5821>. In cases when the reaction times were longer, triphenylarsine was utilized as a ligand. Reactions showed excellent stereospecificity with respect to alkene geometry for coupling with aryl halides and alkenyl iodides as well.



Scheme 24

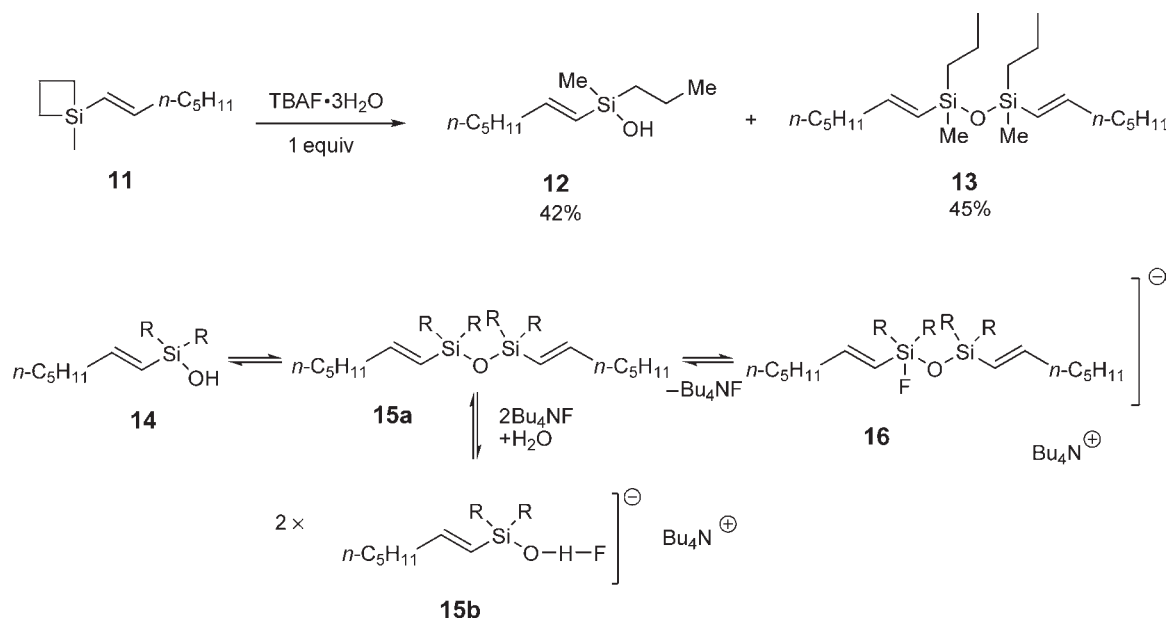
Halo(aryl)silacyclobutanes were employed to achieve biaryl coupling (Scheme 25) <1999OL1495>.



Scheme 25

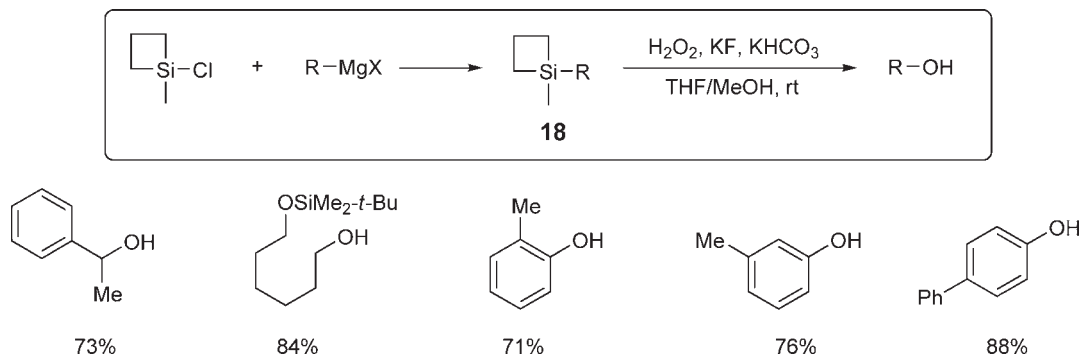
The enhanced reactivity of alkenylsiletanes toward palladium-catalyzed cross-coupling was first explained by strain-release Lewis acidity of the silicon center, which promoted formation of a pentacoordinate fluorosilicate that was the active species for transmetalation. However, further mechanistic elucidation by spectroscopic and kinetic analysis showed that siletanes undergo fast ring opening under the reaction conditions to form alkenyl(propyl)-(methyl)silanols and disiloxane (**12** and **13**) <2004JA4865>. As shown in Scheme 26, the species formed *in situ* exists in equilibrium with silanol **16**, a low-energy resting state along the reaction pathway. Silicate **16** was postulated to be the active species that undergoes transmetalation with palladium. Thus, the SCB serves as a stable precursor to the active transmetallating reagent.

These couplings usually proceed slowly at room temperature; therefore, they were conducted in THF at reflux. Addition of tri-(*tert*-butyl)phosphine was needed to suppress competing homocoupling of the aryl iodide.



Scheme 26

Another useful transformation of SCBs that involves active ring-opened species was reported by Dudley's group [<2003OL4571, 2005TL3283, 2006JOC420>](#). Alkyl- and arylsilylcyclobutanes can be oxidized under the mild oxidative conditions recommended by Tamao for the oxidation of heteroatom-activated silanes: aqueous hydrogen peroxide and potassium fluoride as a fluoride source at room temperature. This procedure was used to form a number of aliphatic alcohols and phenols ([Scheme 27](#) [<2003OL4571>](#)).



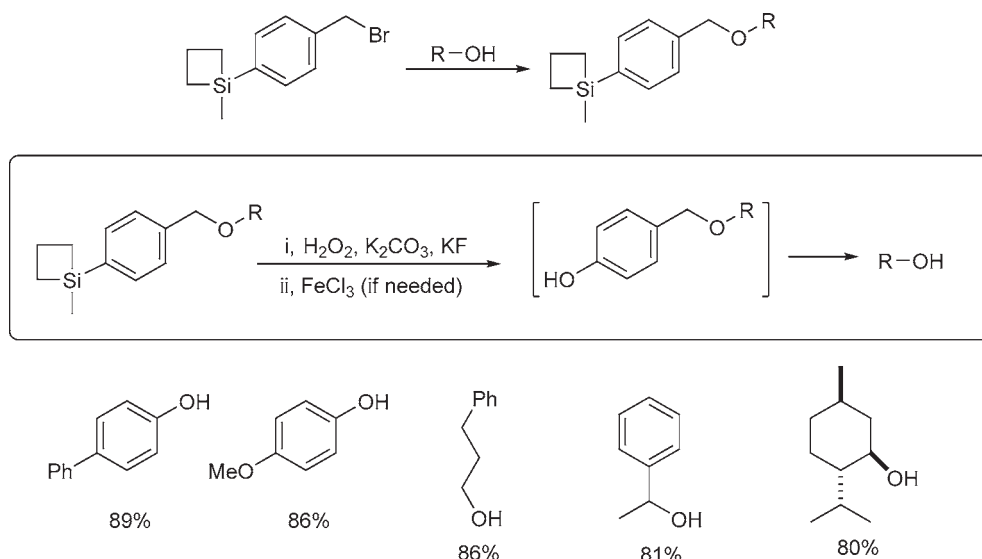
Scheme 27

By analogy to Denmark's proposed mechanism, SCB oxidation is believed to proceed via initial (and rapid) fluoride-promoted ring opening of the SCB, which generates *in situ* a heteroatom-activated organosilane for subsequent oxidation.

Because ring opening is much faster than the typical Tamao oxidation (minutes vs. hours), SCB oxidations occur under the typical Tamao conditions and within a similar duration. However, SCBs are stable to standard purification and handling, and SCBs can be carried through a wide range of organic reaction protocols, including acidic hydrolysis of silyl ethers [<2005TL3283>](#).

The fact that oxidation of carbon–silicon bond is possible in the presence of a silyl ether increases the attractiveness of siletanes as masked hydroxyl groups.

Siletane oxidation can be used as a trigger to promote cleavage of *p*-siletanylbenzyl (PSB) ethers [<2005TL3283>](#). Mild oxidation of the arylsiletane yields the *p*-hydroxybenzyl ether, which can be easily hydrolyzed to release the alcohol. This methodology appears to be most efficient for the protection and deprotection of phenols and primary alcohols ([Scheme 28](#)).

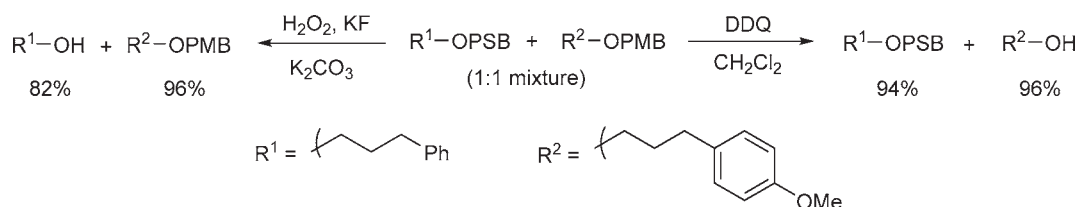


Scheme 28

Though direct reaction of secondary alcohols with PSB bromide appeared to be inefficient, PSB-protected secondary alcohols can still be approached via a two-step procedure [<2005TL3283>](#) or via regioselective reduction of *p*-silylbenzylidene acetals with diisobutylaluminum (DIBAL-H) [<2006JOC420>](#).

Easy removal under mild oxidative conditions makes the PSB group compatible with a wide range of functional groups. Another important advantage of this protecting group is its orthogonality with *p*-methoxybenzyl (PMB) protecting groups.

As shown in [Scheme 29](#), the PSB group can be removed selectively in the presence of the PMB ether by peroxide oxidation, while the PMB group can be cleaved without affecting the PSB ether using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).



Scheme 29

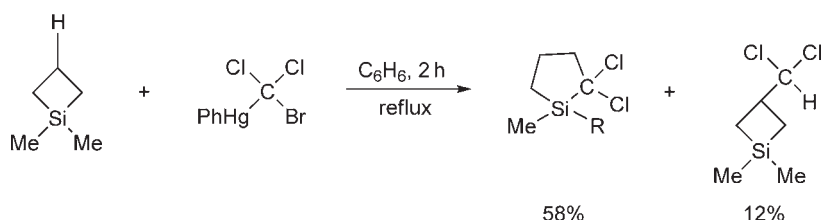
2.11.6.3 Ring-Expansion Reactions

2.11.6.3.1 Uncatalyzed (nucleophile-induced) ring expansions of SCBs using nucleophilic or carbenoid reagents

2.11.6.3.1(i) Ring expansions with electrophilic carbenes

Examples of carbene insertions into the carbon-silicon bond of SCBs have been known since 1967, when Seyferth studied the behavior of SCBs exposed to dichlorocarbene, which was generated by thermolytic activation of phenyl(bromodichloromethyl)mercury [<1967JA1538>](#). The reaction produces a mixture of products arising from Si-C and C-H bond insertions, with the major products being the ring-expanded silacyclopentanes that result from Si-C bond insertions ([Scheme 30](#)).

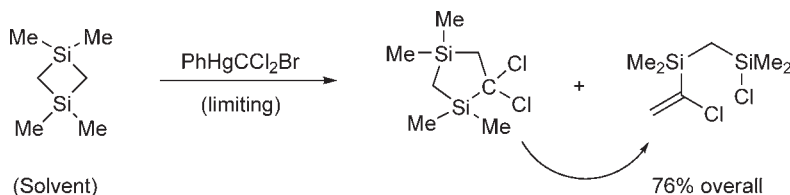
Seyferth's results were the first reported cases of carbene insertions into Si-C bonds. In the case of silacyclopentanes or silacyclohexanes, carbene insertions occur exclusively into C-H bonds, with no observed insertion into the endocyclic



Scheme 30

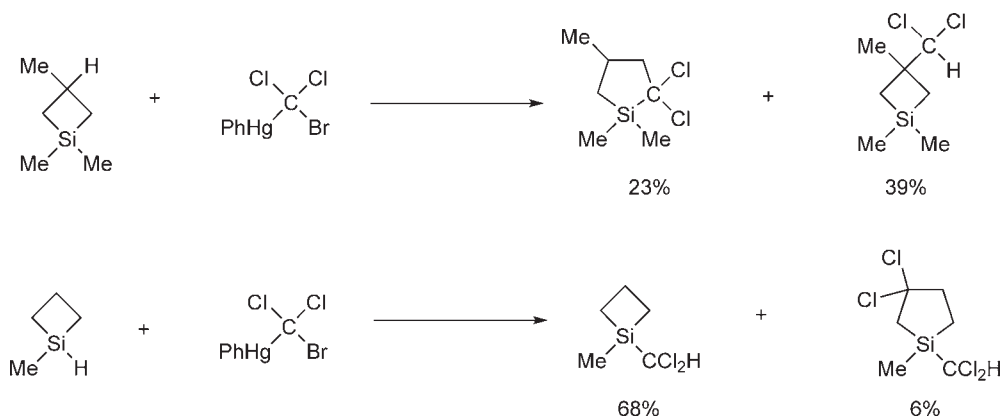
Si–C bonds. Therefore, the ring strain of sila- and 1,3-disilacyclobutanes must enhance the reactivity of the Si–C bond so as to favor Si–C bond insertion. In terms of atomic orbitals, the ‘ring strain’ of an SCB is a result of an increase in the p character of the endocyclic Si–C bonds and the high degree of s character in the exocyclic Si–C and Si–H bonds relative to the analogous silacyclopentane. Greater p character in the endocyclic Si–C bonds leads to poorer orbital overlap and weaker Si–C bonds [\[1971JA3709\]](#). This difference can be observed in the IR stretching frequencies: $\nu(\text{Si–H})$ for 1-methyl-1-silacyclobutane is 2130 cm^{-1} , whereas the analogous frequency for triethylsilane is observed at 2097 cm^{-1} .

1,1,3,3-Tetramethyl-1,3-disilacyclobutane is less reactive toward the phenyl(bromodichloromethyl)mercury-derived dichlorocarbene than the monosilyl version. Nonetheless, when the disilacyclobutane is used in excess, carbene insertion does occur. The initial disilacyclopentane product is subject to a facile ring opening via extrusion of the vicinal silicon and chloride species to afford the chlorovinylidisilyl chloride in 76% estimated yield ([Scheme 31](#)) [\[1971JA3709\]](#).



Scheme 31

The reaction of several other SCBs with dichlorocarbenes generated from phenyl(bromodichloromethyl)mercury was examined. In the case of 1,1,3-trimethyl-1-silacyclobutane bearing a tertiary C–H bond, which is more reactive toward carbene insertions, the C–H insertion was favored over Si–C bond insertion. The competing C–H and Si–C insertion products were obtained in 39% and 23% yields, respectively ([Scheme 32](#)) [\[1967JA1538, 1971JA3709\]](#). Also of interest was 1-methyl-1-silacyclobutane, since the Si–H bond is highly reactive as a carbene trap. Insertion into the Si–H bond proved to be more facile; the product distribution comprised 68% of the Si–H insertion product and 6% of material in which insertion had occurred into both the Si–H and Si–C bonds ([Scheme 32](#)) [\[1971JA3709, 1973JOM\(50\)39\]](#).



Scheme 32

2.11.6.3.1(ii) Ring expansions with nucleophilic reagents

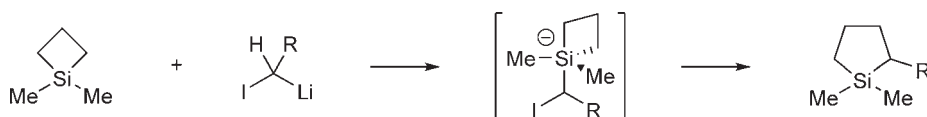
Oshima's group has worked extensively on ring-expansion reactions of SCBs promoted by various nucleophiles and nucleophilic carbenoid reagents. Intramolecular and intermolecular insertions of lithium carbenoids have been investigated; treatment of 1,1-dimethyl-1-silacyclobutane with lithium carbenoids provided silacyclopentanes smoothly with good yields (Table 7) <1990TL6055, 1993T8487>.

Table 7 Ring-expansion reactions of 1,1-dimethyl-1-silacyclobutane with lithium carbenoids

Entry	R	R ¹	R ²	X	Yield (%)
1	Me	H	I	I	83
2	Me	H	Br	Br	57
3	Me	H	Cl	Cl	49
4	Me	Bu ⁿ	I	I	59
5	Me	H	Ph	Br	61
6	Me	H	Me ₃ Si	I	56
7	Ph	H	I	I	72
8	Ph	H	Br	Br	74
9	Ph	H	Cl	Cl	72
10	Bu ⁿ	H	I	I	85
11	Bu ⁿ	H	Br	Br	79
12	Bu ⁿ C≡C	H	I	I	88

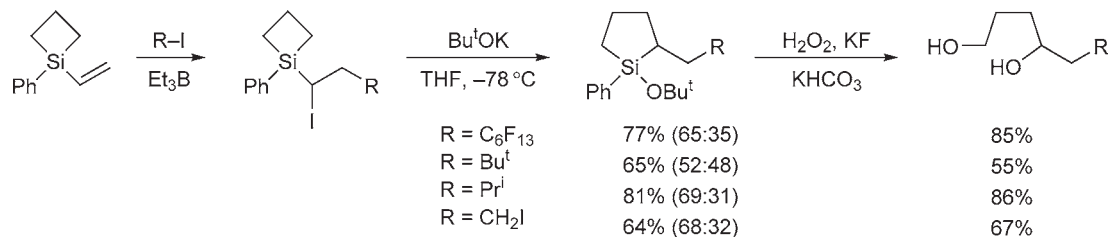
Substitution on silicon did not appear to affect the reaction pathway. These reactions are proposed to proceed via a pentacoordinate silicate intermediate.

Based on the presumed mechanism (Scheme 33), it was expected that 1-(1-iodoalkyl)-1-silacyclobutanes should also undergo ring expansions under the action of a nucleophile. Although methylolithium and other carbanionic nucleophiles provided ring-expansion products in only low yields, potassium *tert*-butoxide-induced ring-enlargement reactions of these species afforded silacyclopentanes in good yields <1991TL6383>.



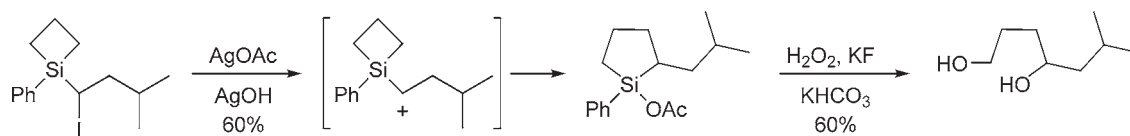
Scheme 33

Ring expansion in conjunction with Tamao-type oxidation of carbon–silicon bonds provides access to 1,4-diols. The 1-(1-iodoalkyl)-1-silacyclobutanes are available from 1-chlorosilacyclobutanes (addition of vinyl, Scheme 34) <1991TL6383>. The utility of silacyclopentanes formed by the ring expansion of SCB for the synthesis of diols has been reported <1992TL7031, 1995BCJ625>.



Scheme 34

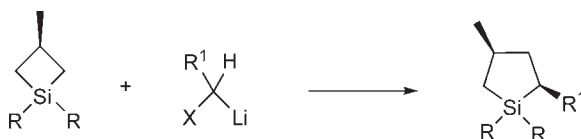
Another way to activate 1-(1-iodoalkyl)-1-silacyclobutanes toward ring expansion is to use silver acetate in acetic acid. In this case, the reaction is believed to proceed via formation of a carbocation α to the silicon. The acetate counterion acts as a nucleophile, attacking the activated SCB with C–Si bond migration (**Scheme 35**) <1991TL6383>. Silver tetrafluoroborate in dichloromethane induces ring enlargement as well, but shows much lower efficiency (30% yield upon treatment with MeLi) <1994BCJ1694>.



Scheme 35

The stereoselectivity of ring-expansion reactions of substituted SCBs has been explored. SCBs having a methyl substituent at the 3-position generally formed the corresponding silacyclopentanes upon treatment with lithium carbenoids with stereoselectivity favoring the *cis*-diastereomer (up to 93:7 ratio, **Table 8**) <1993T8487, 1998J(P1)2209>. One notable exception is the triphenyl system (entry 6, **Table 8**).

Table 8 Stereoselectivity in ring-expansion reactions of substituted SCBs



Entry	R	R ¹	X	Yield (%)	d.r.
1	Me	I	I	80	90:10
2	Me	Br	Br	58	89:11
3	Me	Ph	Br	40	90:10
4	Ph	I	I	97	93:7
5	Ph	Br	Br	88	93:7
6	Ph	Ph	Br	58	33:67

Similar ring-expansion reactions were observed for SCBs and oxiranyl anions bearing the silyl group <1994BCJ1694, 1990TL6059>.

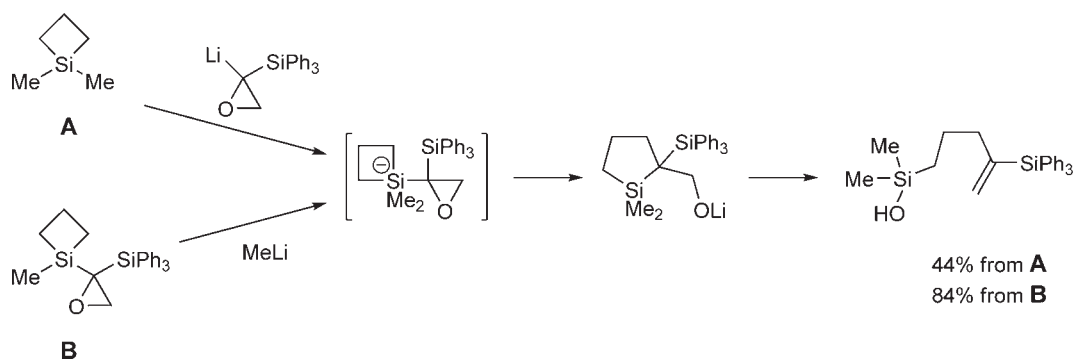
Reaction of DMSB with triphenylsilyl-substituted oxiranyllithium leads to the formation of an olefinic silanol via sequential (1) coordination to the silicon, (2) Si–C bond migration, and (3) Peterson-type Si–O elimination to furnish the alkene. A pentacoordinate siliconate intermediate is presumably involved in this transformation. Therefore, it was reasonable to expect that addition of a nucleophile (methylolithium or lithium *iso*-propoxide) to an oxiranyl-substituted SCB, which could generate a similar intermediate, would induce the C–Si bond migration to form the same silacyclopentane. Indeed, this alternative order of addition sequence provides the corresponding silanol with better efficiency (84% yield vs. 44%, **Scheme 36**).

The series of reactions leading to the 5-silyl-1-pentene – epoxidation, ring expansion, and Peterson elimination – are all stereospecific. Therefore, epoxides with different geometry can be transformed into the corresponding (*E*)- or (*Z*)-olefinic silanols <1994BCJ1694, 1991TL4545>. Subsequent Tamao oxidation affords stereodefined pentenols.

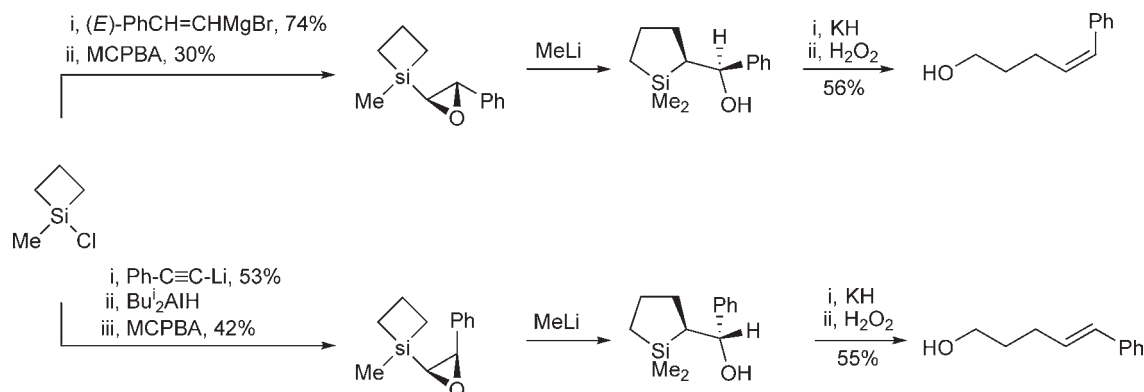
The divergent epoxide stereoisomers are available via epoxidation of the (*E*)- or (*Z*)-vinylsilanes, which in turn are prepared by (1) addition of an (*E*)-vinyl Grignard reagent to the chlorosilacyclobutane, or (2) partial hydrogenation of an alkynylsilacyclobutane, respectively (**Scheme 37**).

One can also take advantage of the complementary methods for effecting the Peterson elimination to prepare either the (*E*)- or (*Z*)-olefinic silanols from a single oxiranylsilacyclobutane via ring expansion followed by a *syn*- or *anti*-elimination (**Scheme 38**) <1994BCJ1694, 1991TL4545>.

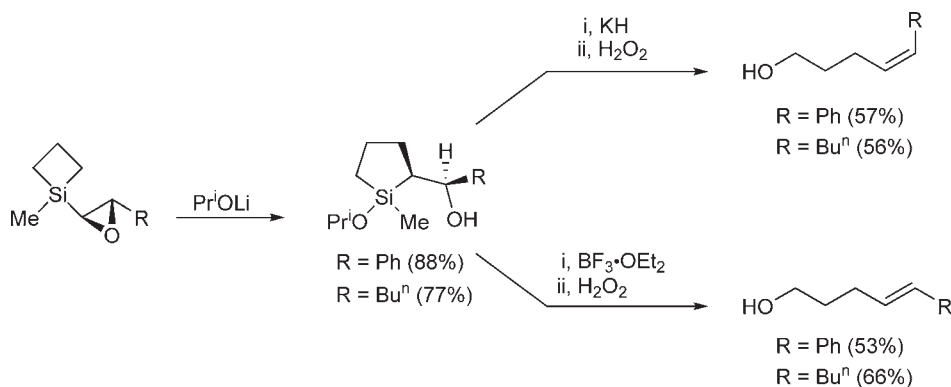
A review on the ring enlargement of SCBs leading to the formation of five- or six-membered heterocycles has been published <1998J(P1)2209>.



Scheme 36



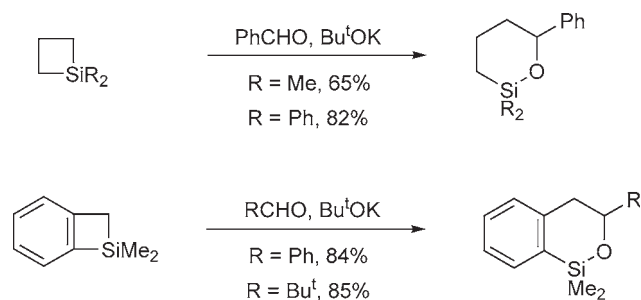
Scheme 37



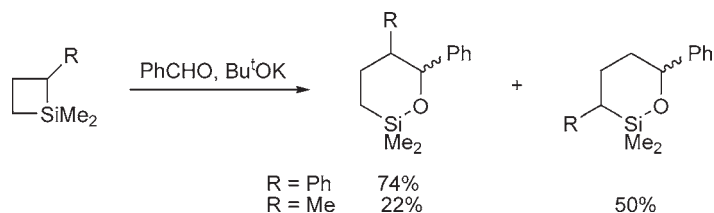
Scheme 38

In the presence of catalytic amounts of potassium *t*-butoxide, different SCBs undergo reaction with aldehydes to yield six-membered cyclic silyl ethers (Scheme 39) <1990TL6059>. Aldehyde insertion into the benzosilacyclobutene was regioselective.

Other unsymmetrically substituted SCBs were examined. In the case of 1,1-dimethyl-2-phenyl-1-silacyclobutane, aldehyde insertion occurred with essentially complete regioselectivity for migration of the benzylic carbon (Scheme 40). On the other hand, 1,1,2-trimethyl-1-silacyclobutane displayed opposite (though not complete) regioselectivity, with insertion taking place on the less-substituted side. The phenyl-substituted SCB also appeared to be more reactive. These data are consistent with the migrating group being the one that is best able to support a developing negative charge.

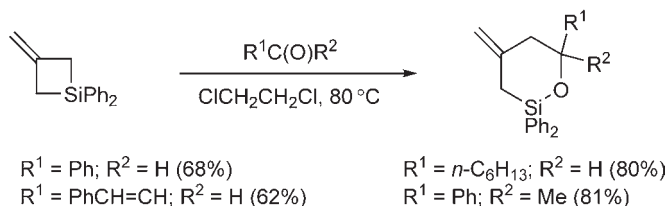


Scheme 39



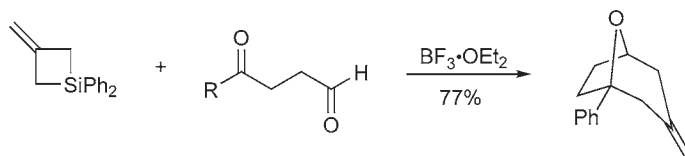
Scheme 40

3-Methylene-1,1-diphenyl-1-silacyclobutane, which incorporates an allylsilane moiety, reacts with ketones and aldehydes to afford insertion products even in the absence of catalytic potassium *tert*-butoxide (Scheme 41). The methylene unit may enhance the Lewis acidity of the SCB <1995TL8067>.



Scheme 41

The resulting 5-methylene-2-oxa-1-silacyclohexanes are insufficiently Lewis acidic to react with a second equivalent of the carbonyl compound. However, the incipient allylsilane does react with dimethyl acetals in decent yields in the presence of external Lewis acids including $\text{BF}_3 \cdot \text{Et}_2\text{O}$ or AlCl_3 . Based on these results, double allylation of dicarbonyl compounds with 3-methylene-1,1-diphenyl-1-silacyclobutane was examined, leading to the formation of 3-methylene-oxabicyclo[3.2.1]octanes. This transformation proceeded in one pot and in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (Scheme 42).



Scheme 42

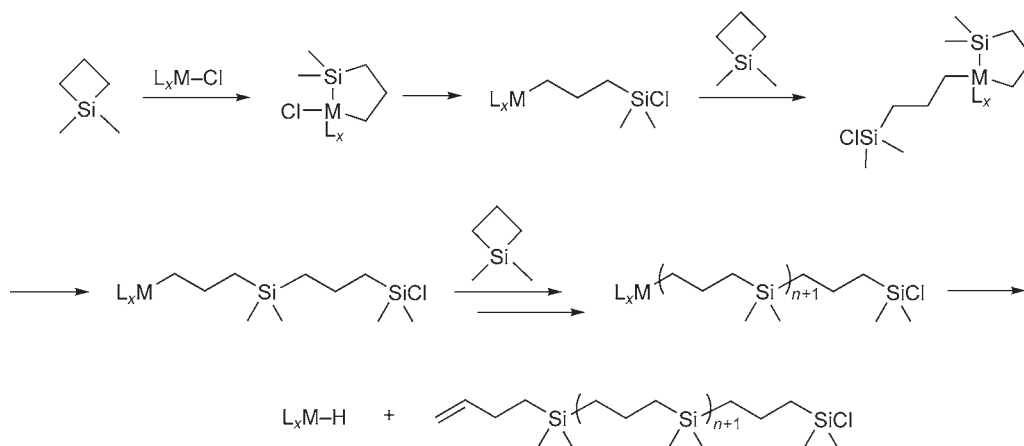
2.11.6.3.2 Transition metal-catalyzed ring expansions

SCBs and disilacyclobutanes are known to undergo ring-opening polymerization catalyzed by transition metal complexes including those of platinum, palladium, and rhodium <1965JOC2618>. Lappert and co-workers suggested that

an initial insertion of the metal catalyst into the strained Si–C endocyclic bond leads to a ring-expanded metallasilacycle, although no direct evidence was available at the time [<1972JOM\(44\)291>](#).

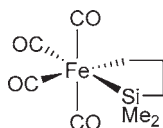
According to the proposed mechanism, polymerization involves several steps (**Scheme 43**):

- oxidative addition of the transition metal complex to the SCB (ring expansion);
- halogen or alkyl transfer from the metal to silicon (reductive elimination) leading to ring-opening; and
- polymer growth by insertion of the alkyl metal species into an additional molar equivalent of the SCB monomer.



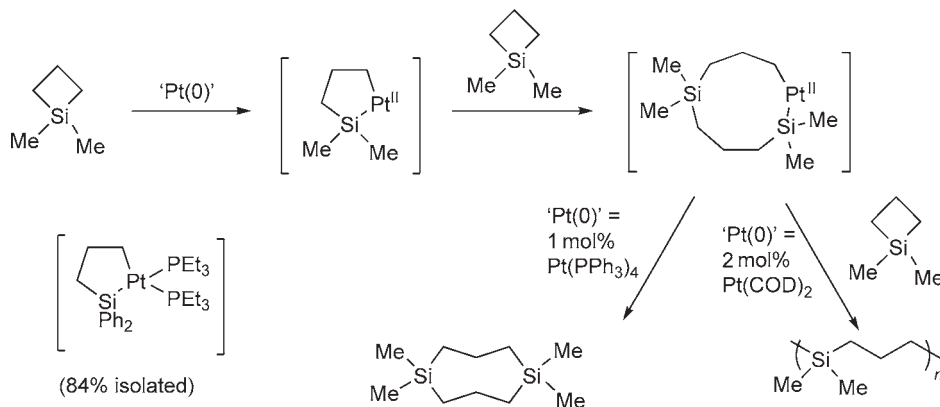
Scheme 43

The first insertion of a transition metal complex, such as pentacarbonyliron, into SCBs was described by Lappert's group and they isolated 2,2-dimethyl-1,1,1,1-ferra-2-silacyclopentane (**Scheme 44**) [<1972CC445>](#).



Scheme 44

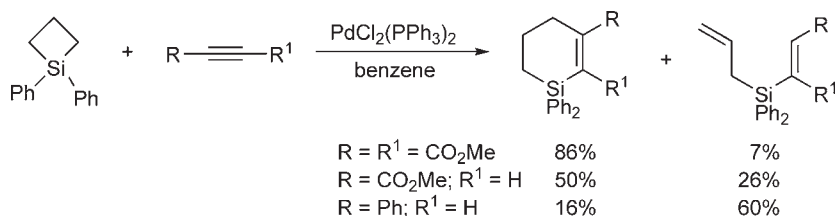
In 1995, Tanaka and co-workers isolated 2,2-diphenyl-1-platina-2-silacyclopentane (**Scheme 45**) and showed that such a complex is a viable intermediate for both dimerization and polymerization of SCBs [<1995JA8873>](#). The reactivity of 1,1-disubstituted SCBs toward oxidative addition of transition metals increases in the series of methyl < phenyl < chloro.



Scheme 45

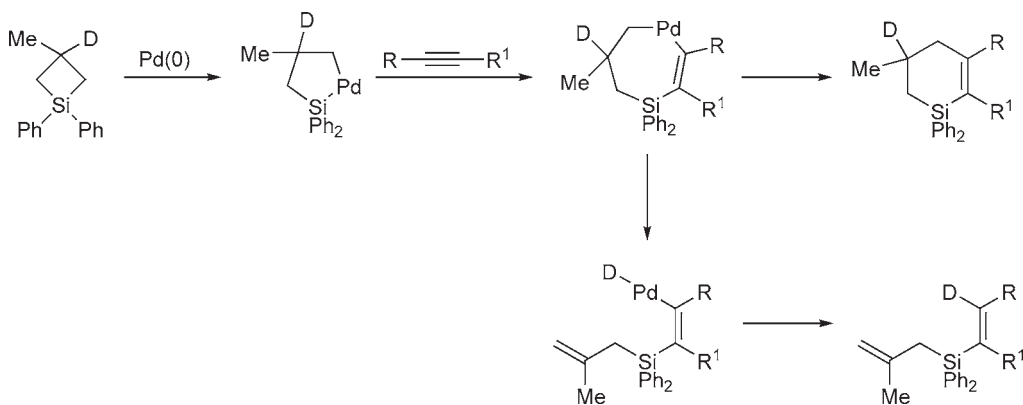
As shown in [Scheme 45](#), DMSB can undergo polymerization or dimerization in the presence of similar platinum catalysts in good to excellent yields. The course of the reaction is apparently linked to the presence or absence of phosphine ligands: platinum complexes that include added phosphines lead to dimerization, whereas polymerization usually occurred under 'ligandless' conditions. Divinyltetramethyldisiloxane also serves as a ligand for the platinum-catalyzed dimerization of SCBs and disilacyclobutanes as reported by Chu and Frye [<1993JOM\(446\)183>](#).

One of the first transition metal-catalyzed ring-expansion reactions of SCBs with the formation of new C–C bonds involved the insertion of acetylenes catalyzed by Pd-complexes to furnish silacyclohexenes ([Scheme 46](#)) [<1975CL891, 1991BCJ1461>](#). In addition to the acetylene-insertion products (silacyclohexenes), ring-opened allylvinylsilane products that also incorporate the acetylene moieties were observed. The ratio of the two types of the products depends heavily on the nature of acetylenic compounds.



Scheme 46

The acetylene-insertion reaction presumably occurs by the following mechanistic sequence: (1) insertion of Pd(0) into the SCB, (2) regioselective *syn*-silylpalladation of the acetylenic compounds to provide seven-membered 1-pallada-4-silacyclic intermediate, and (3) reductive elimination of Pd(0) to afford silacyclohexene. Alternatively, β -hydride elimination would open the palladacycle, generating a vinylpalladium hydride species that would undergo reductive elimination to yield the ring-opened allylvinylsilane. Isotopic labeling studies provided evidence in support of this mechanistic hypothesis ([Scheme 47](#)).

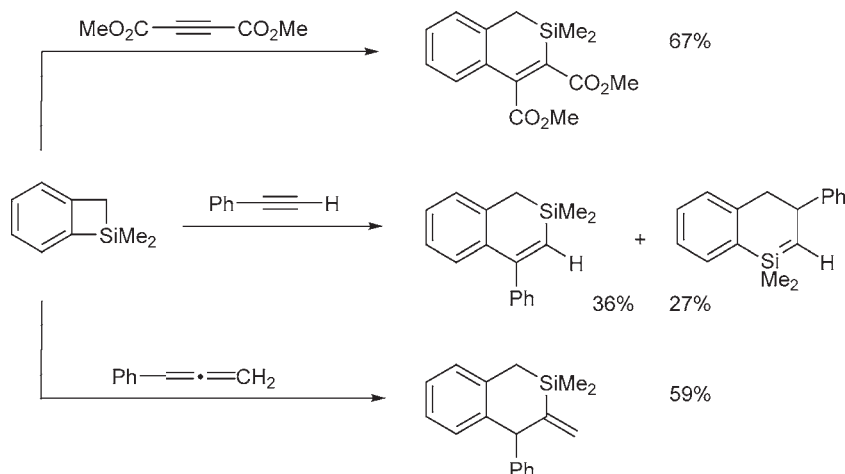


Scheme 47

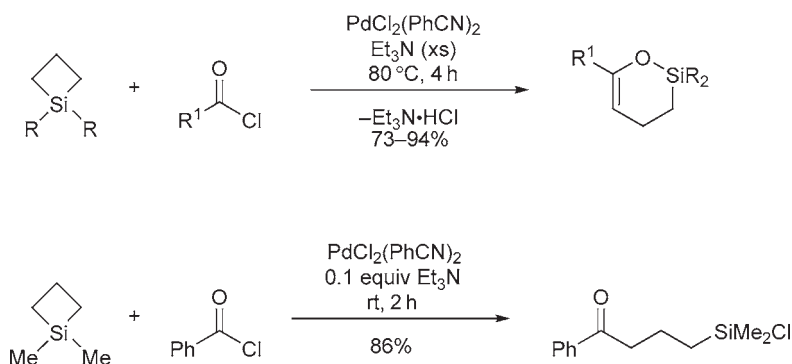
Under similar conditions, silabenzocyclobutane provided the corresponding dihydrosilanaphthalenes. Phenylallene also inserted into the silabenzocyclobutane in the presence of PdCl₂(PPh₃)₂ to give the ring-expanded *exo*-methylene product in which the internal alkene of phenylallene reacted ([Scheme 48](#)).

Tanaka and co-workers [<1996OM1524>](#) observed the insertion of acid chlorides into SCBs in the presence of palladium or platinum catalysts. When an excess of amine was employed, SCBs undergo ring-expansion reactions to afford cyclic silyl enol ethers in good to excellent yields ([Scheme 49](#)).

When only 0.1 equiv of triethylamine was used, 3-(chlorosilyl)propyl ketone was formed as the major product in 86% estimated yield (based on NMR analysis). According to the authors' mechanistic hypothesis, oxidative insertion of the transition metal catalyst occurs into the acid chloride, which is followed by ring insertion of the acylpalladium



Scheme 48

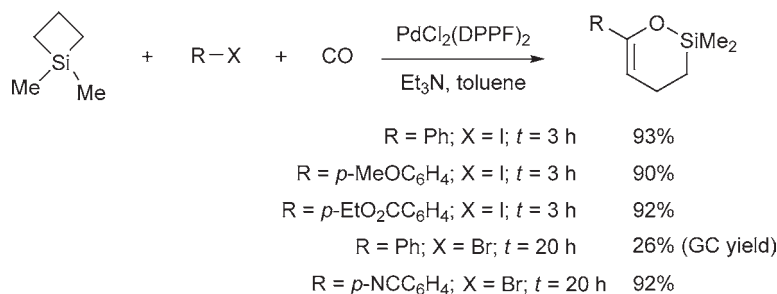


Scheme 49

(or platinum) species into the SCB ring. Amine-assisted cyclization then yields the observed silyl enol ethers. In the absence of excess amine, reductive elimination of the catalyst affords an acyclic chlorosilane. Although palladium can undergo oxidative addition to SCBs, addition to acid chlorides proceeds faster.

Insertion of acyl chlorides into appropriately substituted SCBs, followed by Tamao-type oxidation, has been used to prepare γ -lactols [<1998JOC422>](#).

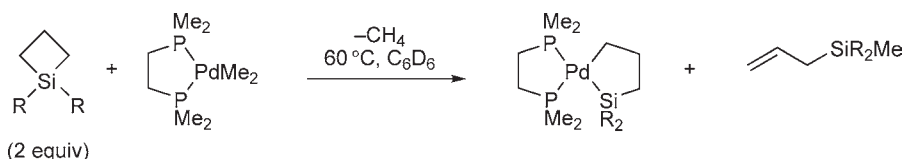
Palladium-catalyzed three-component coupling of dimethylsilacyclobutane, carbon monoxide, and aromatic iodides also yields cyclic silyl enol ethers via a ring/expansion/-insertion process [<1996CC1207>](#). Electron-rich and electron-deficient aromatic iodides are suitable substrates, giving rise to the corresponding cyclic silyl enol ethers in excellent yields ([Scheme 50](#)).



Scheme 50

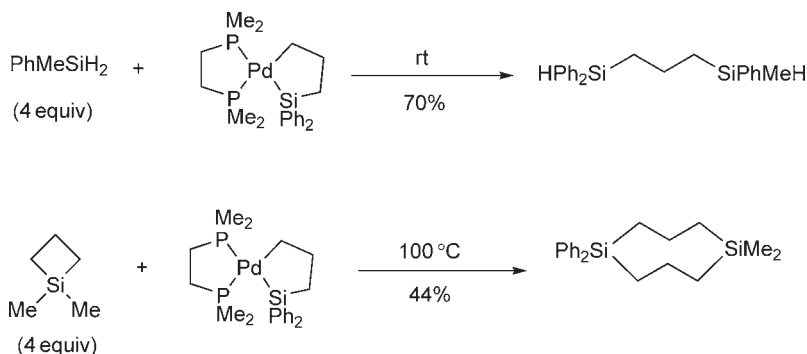
The mechanism of this three-component coupling reaction is probably analogous to the aforementioned insertion of acyl chlorides (above). One can imagine assembling an intermediate acylpalladium species either by oxidative addition to an acyl chloride or, in this case, by oxidative addition to the aromatic iodide followed by migratory insertion into carbon monoxide. Once formed, the acylpalladium intermediate can insert into the SCB to furnish a γ -(chlorosilyl)propyl ketone, which cyclizes in the presence of the amine to afford cyclic enol ethers.

Both ring-expansion reactions proceed via a putative pallada(sila)cyclopentane intermediate. In the course of the mechanistic elucidation studies, Tanaka succeeded in preparing a 1-pallada-2-silacyclopentane complex with quantitative conversion (**Scheme 51**) <1997OM3246>. Formation of the complex is reversible, and the starting SCB can be released by addition of an acetylene, which acts as a ligand for palladium and displaces the SCB.



Scheme 51

The formed 5-palladasilacyclopentane complex was examined as a model for the already known Pd-catalyzed ring-opening reaction of SCBs with hydrosilanes and dimerization of SCBs. Indeed it provided the expected products, suggesting that the 5-pallada-silacyclopentane complex represents an active intermediate in these reactions (**Scheme 52**).



Scheme 52

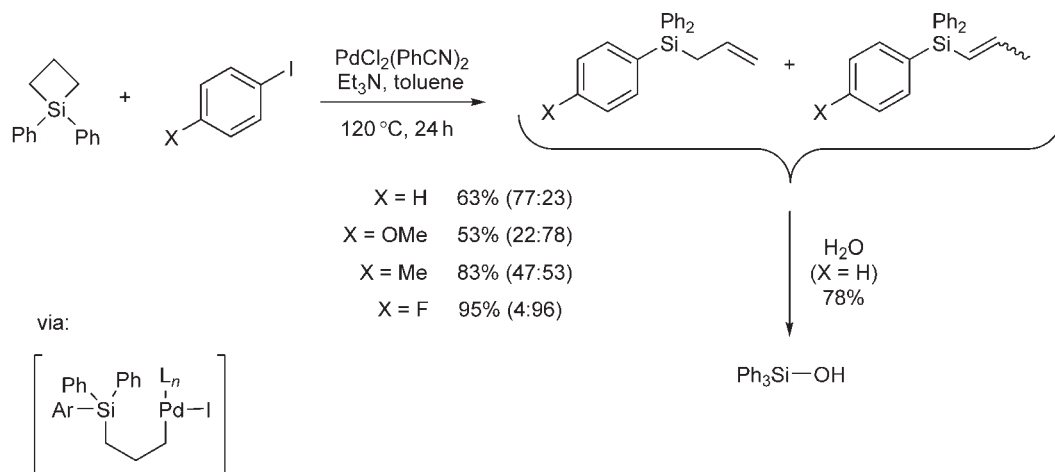
Following work on the palladium-catalyzed ring expansions of SCB substrates, Tanaka extended the list of substrates to aryl iodides in the absence of carbon monoxide. Rather than obtaining 3-(iodosilyl)propylarenes, however, Tanaka observed an unexpected regioselectivity that provided 1- and 2-propenyl(triaryl)silanes, in good yields (**Scheme 53**) <2001AOM667>. This outcome can be explained by phenyl group migration from palladium to silicon (rather than a halide migration) *en route* to the ring-opened species.

The resulting mixture of allyl- and vinylsilanes can be hydrolyzed to afford triarylsilanol (**Scheme 53**).

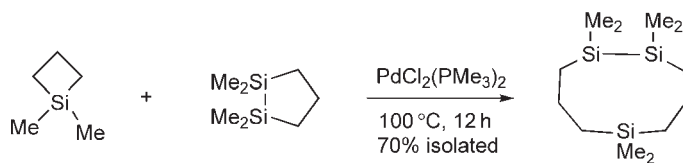
SCBs will also undergo palladium-catalyzed cross-metathesis reactions with disilanes (**Scheme 54**) <1996CC1865>.

Nickel-catalyzed transformations of SCBs have been studied by Oshima and co-workers <2006OL483>. Nickel-catalyzed ring opening of SCBs with aldehydes affords the corresponding alkoxyallylsilanes (**Scheme 55**). This transformation represents a hydrosilane-free reductive silylation of aldehydes. A wide range of aldehydes (aliphatic, aromatic, electron-rich, and electron-deficient) can be converted to alkoxyallylsilanes.

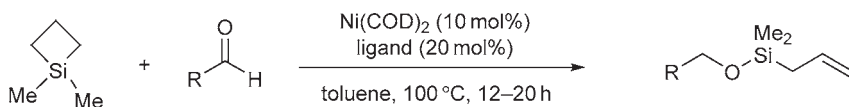
In contrast, under identical conditions, benzosilacyclobutene reacted with aldehydes in a highly regioselective ring expansion to give oxasilacyclohexenes (50–75% yields) (**Scheme 55**).



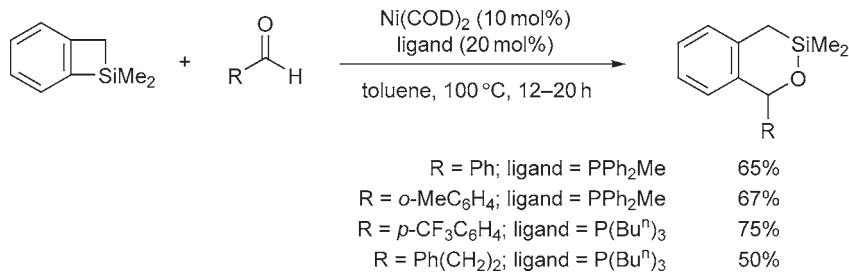
Scheme 53



Scheme 54



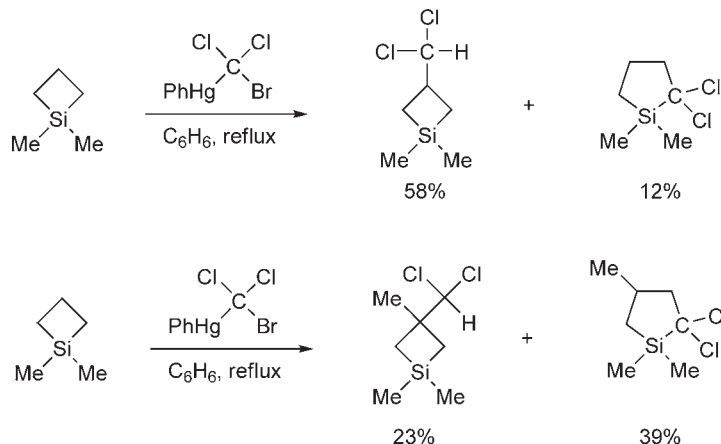
$\text{R} = \text{Ph}$; ligand = PPh_2Me	88%
$\text{R} = o\text{-MeC}_6\text{H}_4$; ligand = PPh_2Me	85%
$\text{R} = p\text{-MeOC}_6\text{H}_4$; ligand = PPh_2Me	47%
$\text{R} = p\text{-MeOC}_6\text{H}_4$; ligand = $\text{P}(\text{Bu}^n)_3$	53%
$\text{R} = p\text{-MeO}_2\text{CC}_6\text{H}_4$; ligand = $\text{P}(\text{Bu}^n)_3$	53%
$\text{R} = c\text{-C}_6\text{H}_{11}$; ligand = $\text{P}(\text{Bu}^n)_3$	59%



Scheme 55

2.11.7 Reactions of Substituents Attached to the Ring Carbon Atoms

It was mentioned in Section 2.11.6.3.1 that the reaction of siletanes with thermolytically generated carbenes produces mixtures of products arising from competing Si–C and C–H bond insertions (Scheme 56) <1967JA1538, 1971JA3709>.



Scheme 56

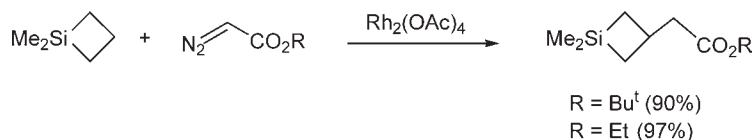
For siletanes with tertiary carbons, insertion into a C–H is favored over a Si–C insertion <1967JA1538>.

When carbenes are generated from haloforms with potassium hydroxide, exclusive insertion of carbene into a β -C–H bond has been reported <1980JOM(198)29> (Scheme 57).



Scheme 57

Regioselective introduction of an ester functionality into the β -position of SCBs can be accomplished by means of an $\text{Rh}_2(\text{OAc})_4$ -catalyzed C–H insertion reactions of α -diazo esters <1998JOC422, 1979ZOB2776> (Scheme 58). The reaction proceeds cleanly to give the products in excellent yields.



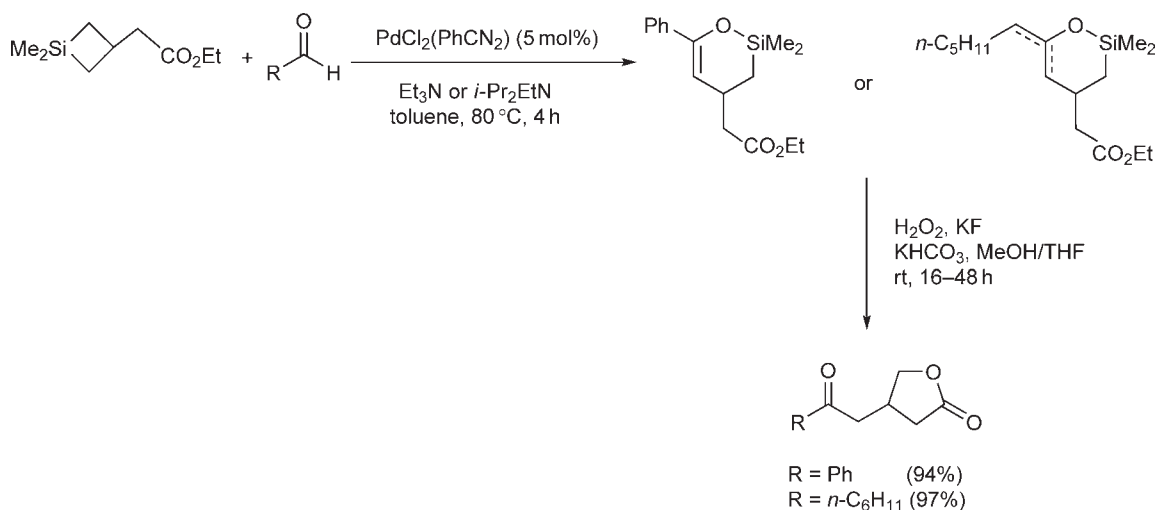
Scheme 58

The formed 3-[(alkoxycarbonyl)methyl]-1,1-dimethyl-1-silacyclobutanes undergo a palladium-catalyzed ring-opening coupling reaction with acid chlorides to give quantitative yields of cyclic silyl enol ethers (see Section 2.11.6.3.2). Under Tamao oxidation conditions, the produced silyl enol ethers furnish the corresponding γ -lactones bearing a ketone functionality at the C-3 position in good to excellent overall yields (Scheme 59) <1998JOC422>.

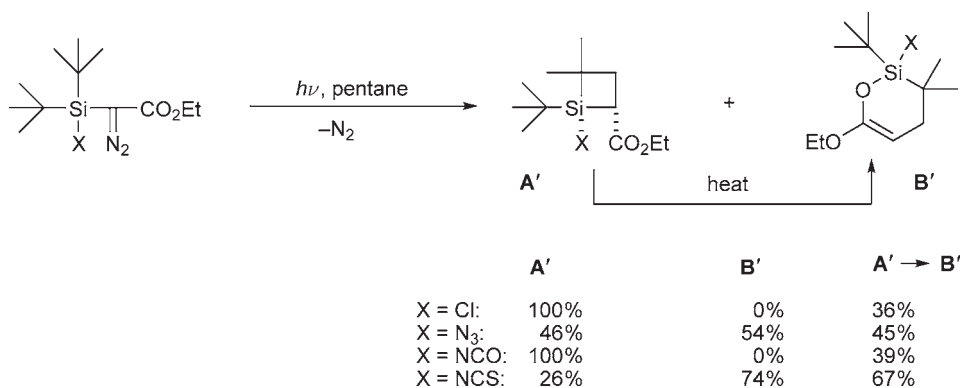
SCBs with an ester functionality at the α -position can undergo an uncatalyzed thermal rearrangement to give *O*-silyl ketene acetals in moderate yields. This ring expansion of silacyclobutane-2-carboxylate by a 1,3(C $\rightarrow$ O) silyl shift proceeds largely due to the relief of ring strain from the four-membered ring (Scheme 60) <2000CC437>.

2-Alkoxycarbonyl-1-silacyclobutanes, the starting materials for thermal rearrangements, can be accessed via a novel intramolecular 1,4-insertion of a carbene into the C–H bond of an Si-*t*-Bu group.

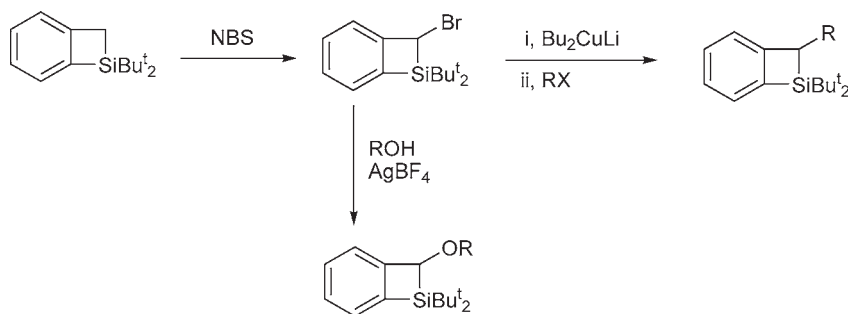
An alternative way to functionalize the SCB would be through bromination. Bromination of 1,1-di(*t*-butyl)-2,3-benzo-1-silacyclobutane with *N*-bromosuccinimide (NBS) gives the 4-bromo derivative (Scheme 61). Metallation



Scheme 59



Scheme 60

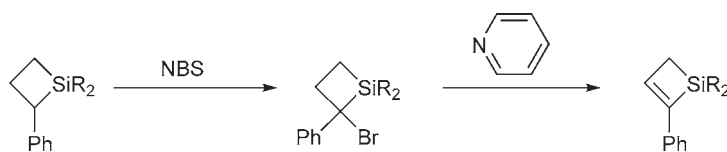


Scheme 61

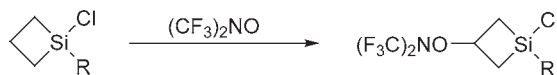
with Bu_2CuLi , followed by alkylation or acylation, generated the corresponding 4-alkyl or acyl compounds. The replacement of the bromine atom with an alkoxy group was achieved by treatment with an alcohol in the presence of AgBF_4 <1985CL617, <1996CHEC-II(1B)867>.

Bromination of 2-phenylsilacyclobutanes followed by dehydrohalogenation provides access to 1,1-disubstituted-2-phenyl-1-silacyclobut-2-enes (Scheme 62) <1975TL2153, 1996CHEC-II(1B)867>.

The attack of SCBs by the oxyl $(\text{CF}_3)_2\text{NO}$ leads to 3-substituted products; 2,3-disubstituted compounds were obtained as minor products (Scheme 63) <1994JFC(67)129, 1996CHEC-II(1B)867>.



Scheme 62

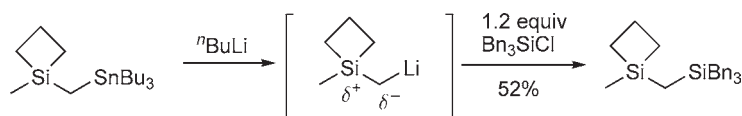


Scheme 63

2.11.8 Reactivity of Substituents Attached to the Ring Silicon

This section deals with reactions in which the SCB ring remains intact – most commonly, substitution reactions at silicon. Nonetheless, the strained four-membered ring plays a key role in the reactivity profile of SCB substitution reactions. 1-Halosilacyclobutanes are common substrates for the installation of different substituents on silicon such as alkyls or aryls (by reaction with Grignard reagents), as well as alkoxides, amines, or even hydrogen (by reduction with alkylaluminum hydrides). These reactions' parallel reactivity is seen in other halosilanes and have been substantially covered in CHEC-II(1996) <1996CHEC-II(1B)867>. Displacement of a hydrogen substituent on the silicon of SCBs through hydrosilylation of alkenes or by substitution with halogens, amines, or alkoxides is covered in the same review <1996CHEC-II(1B)867>. With any of these reactions, ring opening <1995BSF551> of the SCB competes and in many cases cannot be avoided. Under dehydrocoupling polymerization conditions, ring-opening polymerization predominates <1997CL785>. For more information, refer to Section 2.11.6.2.1.

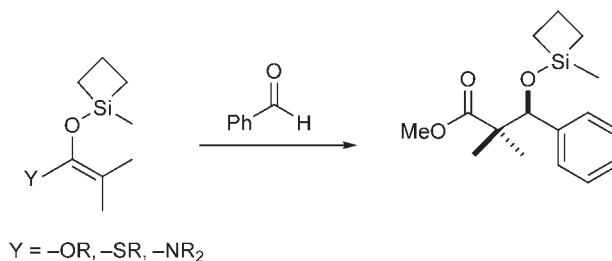
Aside from substitution reactions on silicon, interesting reactivity on SCB-substituted methylstannane has been described <2005CCC3047>. Upon treatment of the mixed SCB/stannane substrate with *n*-BuLi, transmetalation predominates over ring-opening and ambiphilic SCB-methylolithium can be generated (product formed after quenching with electrophile was isolated in 50–60% yield, Scheme 64).



Scheme 64

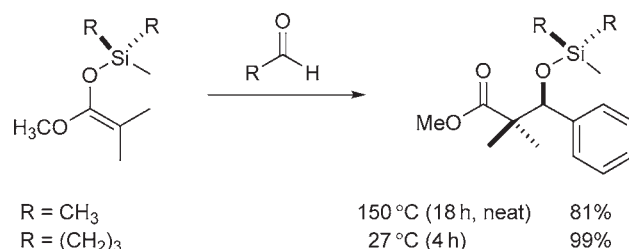
Disilacyclobutanes with alkoxy substituents, which can be approached directly from Cl(EtO)₂SiCH₂Cl (diethoxy-substituted chlorocarbosilanes), can be converted into the corresponding chlorides (with MeCOCl and FeCl₃) <1996JOM(521)1> or fluorides (with BF₃·Et₂O) <1997JA12020>.

O-(Silacyclobutyl)ketene acetals derived from esters, thioesters, and amides undergo facile aldol addition with a variety of aldehydes without catalyst at ambient or low temperatures (Scheme 65) <1992JA7922, 1993JOC988, 1994JA7026>. Such reactivity stands in contrast to traditional silyl enol ethers, suggesting that the SCB ring strain plays a role in promoting transfer of the enolate substructure.



Scheme 65

For example, methylsilacyclobutyl *O,O*-ketene acetal ($Y = \text{OMe}$) reacted completely and cleanly with benzaldehyde in benzene solution within 4 h at 27 °C to afford the corresponding aldol adduct quantitatively (Scheme 66) <1992JA7922>. In contrast, the analogous *O*-trimethylsilyl ketene acetal reacts with benzaldehyde only at 150 °C without solvent, and the reaction requires 18 h for completion. The dramatically enhanced reactivity has been attributed to the effect of the strained SCB ring. Prior to this report, *N,O*-ketene acetals were the only trialkylsilyl enol ethers known to undergo uncatalyzed aldol addition with aromatic aldehydes <1992JA7922, 1990JA9672> without heating or use of any activating agents like the fluoride ion.



Scheme 66

The enhanced reactivity of SCB-derived enol ethers is attributed to the combination of ring strain and the potential for silicon to expand its coordination number from penta- to hexacoordinate compounds. Specifically, for SCBs, the reaction with nucleophiles allows for relief of the strain energy via rehybridization of the geometry at silicon from tetrahedral to trigonal bipyramidal (tbp) upon formation of a pentacoordinate species.

Although no complexation between aldehydes and a variety of SCBs was spectroscopically detectable, the proposed mechanism for allylation of aldehydes using allylsilacyclobutanes involves a closed transition state (in analogy to allylboration of aldehydes) with intramolecular silicon group transfer via a pentacoordinate trigonal bipyramidal silicate <1994JA7026>. A double-label crossover experiment provided evidence in support of the intramolecular silicon group transfer <1994JA7026, 1992JA7922>.

Denmark <1993JOC988, 1994JA7026> and Myers <1992JA7922> led independent studies on the uncatalyzed aldol addition reactions of silacyclobutyl ketene acetals with a variety of aliphatic and aromatic aldehydes. Ester-derived silacyclobutyl *O,O*-ketene acetals are highlighted in Table 9. Interestingly, the silyl enol ether with an (*E*)-configuration furnishes the *syn*-aldol products with high diastereoselectivity; in some cases, the stereoselectivity of the aldol product exceeded the purity of the starting silyl enol ethers. In contrast, the (*Z*)-isomer reacted sluggishly with opposite, albeit weak, *anti*-selectivity (Table 9). Kinetic studies showed that the reaction rate for the (*E*)-isomer is significantly higher than it is for the (*Z*)-isomer <1994JA7026>.

Table 9 Uncatalyzed aldol addition reactions of silacyclobutyl ketene acetals to aliphatic and aromatic aldehydes

<i>E/Z</i>	<i>R</i>	$t_{1/2}$ (h)	Yield (%)	<i>syn/anti</i>
95:5	Ph	2.2	94	95:5
89:11	Cinnamyl	6.7	95	93:7
89:11	<i>n</i> -Pentyl	17.0	91	93:7
89:11	Cyclohexyl	38.3	85	>99:1
0:100	Ph	28.3	80	42:58

O-Silacyclobutyl *S,O*-ketene acetals (derived from thioesters) reacted more slowly with aldehydes than did their ester counterparts (Table 10) <1994JA7026, 1993JOC988>. The higher reactivity of the (1-phenyl)silacyclobutyl derivatives enabled the uncatalyzed aldols to proceed at a reasonable rate, affording the corresponding products after

50 h at room temperature. In these series, the *syn*-product formed stereoselectively from the (*Z*)-ketene acetal; the (*E*)-ketene acetal also yielded predominantly the *syn*-products, albeit with reduced selectivity (Table 10).

Table 10 Reaction of *O*-silacyclobutyl *S,O*-ketene acetals (derived from thioesters) with aldehydes

<i>E/Z</i>	<i>R</i>	<i>Solvent</i>	<i>t</i> (h)	<i>Conv.</i> (%)	<i>syn/anti</i>
4:96	Ph	CDCl ₃	50.5	84	98:2
4:96	Cinnamyl	CDCl ₃	51	91	70:30
4:96	<i>n</i> -Pentyl	CDCl ₃	50.5	42	90:10
4:96	Cyclohexyl	CDCl ₃	50	0	
4:96	Ph	Neat			99:1
100:0	Ph	Neat			85:15

O-Silacyclobutyl *N,O*-ketene acetals (derived from amides) demonstrated high reactivity toward aldehydes <1994JA7026, 1993JOC988, 1992JA7922>. Mixtures of *syn*- and *anti*-aldol products were obtained, with a slight preference for the *anti*-diastereoisomers in most cases (Table 11).

Table 11 Reaction of *O*-silacyclobutyl *N,O*-ketene acetals with aldehydes

<i>R</i>	<i>Solvent</i>	<i>t</i> _{1/2} (h)	<i>syn/anti</i>
Ph	CDCl ₃	0.67	9:91
Cinnamyl	C ₆ D ₆	3.6	31:69
<i>n</i> -Pentyl	C ₆ D ₆	4.6	40:60
Cyclohexyl	C ₆ D ₆	12.8	50:50

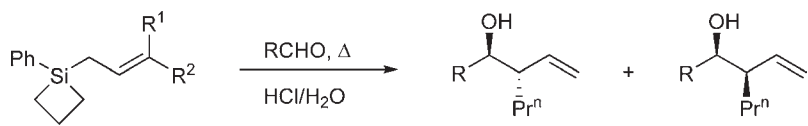
The unusual *syn*-diastereoselectivity of (*E*)-silyl ketene acetals for ester- and amide-derived species stands in contrast to the normal *anti*-selectivity of geometry-independent Lewis acid-promoted aldol additions, which are believed to involve open transition states. The preponderance of *syn*-diastereomer products is also at odds with the Zimmerman–Traxler predictive model that presumes a closed transition state with a chair-like geometry. Thus, on the basis of the stereochemical outcome and computational studies, it has been suggested that these reactions proceed via a closed boat transition state with pentacoordinate silicon. Indeed, computational modeling revealed that the boat conformation is slightly preferred over the chair <1994JA7026>. The fundamental difference between the boat and chair systems of strained SCBs and those of group I, II, and III metal enolates (e.g., lithium enolates) is that the group IV silicon enolates contain a pentacoordinate silicate center, rather than the traditional four-coordinate metal center. Thus, in the group IV systems, unfavorable eclipsing interactions in conventional boat transition states are apparently less important than other steric interactions.

Aldol reactions of both (*E*)- and (*Z*)-ketene acetals are highly susceptible to KOBu^t catalysis. In the presence of 5 mol% of KOBu^t, aldol reactions proceeded to completion within minutes at –78 °C <1994JA7026>. A double-label crossover experiment, devised to probe the nature of the silicon group transfer in the alkoxide-catalyzed aldol reaction, suggested that free metal enolates are the true reactive species adding to the aldehydes.

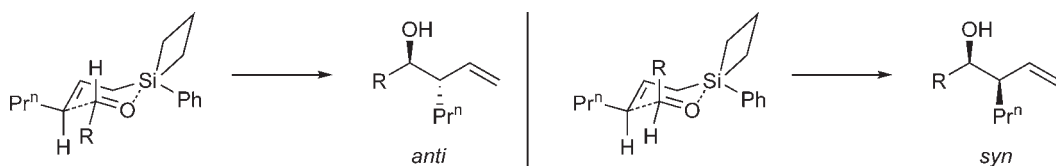
Asymmetric aldol additions have been examined. Chirally modified *S,O*-(alkoxysilacyclobutyl) ketene acetals react with aromatic aldehydes to afford the corresponding β -hydroxy thioesters in high enantiomeric excesses (91–94% ee) <1994JOC5136>.

Allylsilacyclobutanes react with carbonyl compounds in an uncatalyzed, stereoselective allyl-transfer process. A reaction mechanism involving a closed transition state with coordination of the aldehyde to silicon, similar to that advanced for the aldol reactions, has been proposed <1994JOC7152>. (*E*)-1-(2-Hexenyl)-1-phenylsilacyclobutane provided *anti*-homom-allylic alcohols with high regio- and stereoselectivity upon treatment with various aldehydes at 130°C for 24–48 h. In contrast, (*Z*)-1-(2-hexenyl)-1-phenylsilacyclobutane gave rise to the *syn*-allylation products selectively (Table 12). The stereoselectivity of these reactions suggests that a closed, chair-like transition state is in effect for these transformations. *Ab initio* calculations support the presumed role of a pentacoordinate silicon transition state <1996JA1750>.

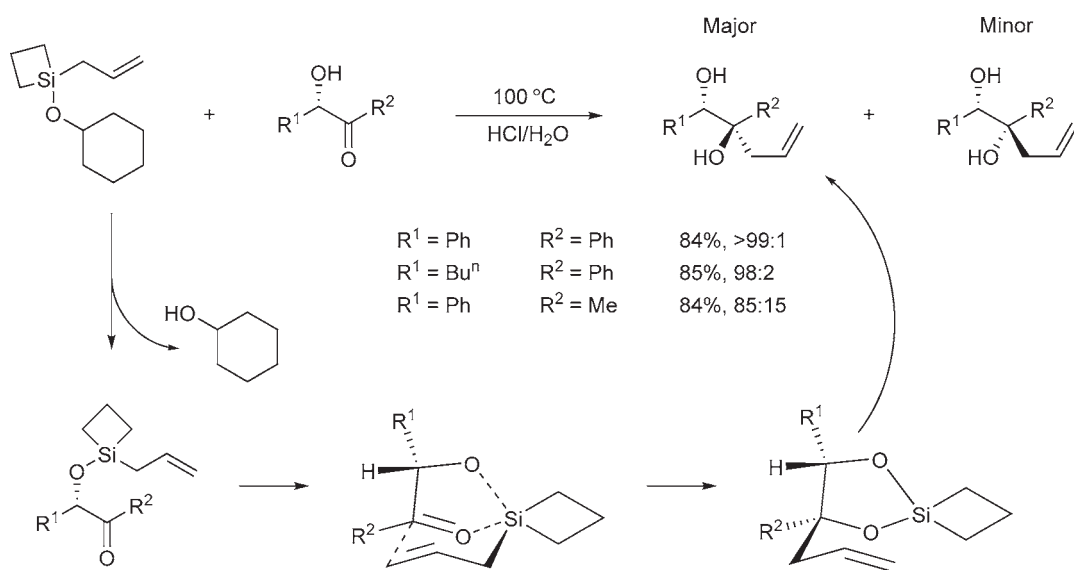
Table 12 Reaction 1-(2-hexenyl)-1-phenylsilacyclobutanes with aldehydes



R^1	R^2	R	Yield (%)	<i>anti/syn</i>
H	Pr ⁿ	Ph	68	95:5
H	Pr ⁿ	Hex ⁿ	59	90:10
Pr ⁿ	H	Ph	66	5:95
Pr ⁿ	H	Hex ⁿ	60	20:80



The reaction of 1-allyl-1-(cyclohexyloxy)silacyclobutane with α -hydroxy carbonyl compounds proceeded at a lower reaction temperature. The alkoxy group on silicon enhances the Lewis acidity of the allylsilacyclobutane and presents the possibility for ligand exchange to precede the allylation event, which then occurs intramolecularly (Scheme 67).

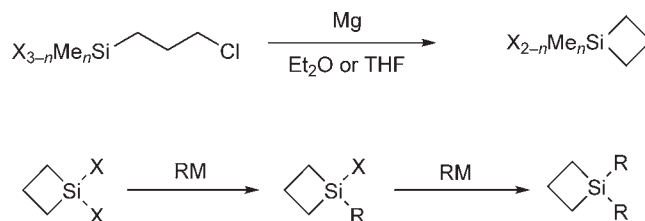


Scheme 67

2.11.9 Ring Syntheses from Acyclic as well as Cyclic Compounds

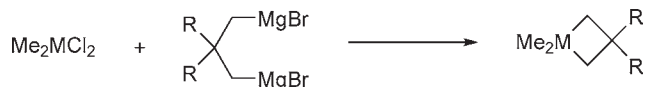
Previous reviews covered different ways to generate SCB <1996CHEC-II(1B)867>, germacyclobutane, and stannacyclobutane derivatives as well as their benzannulated analogues. One of the most commonly used approaches to prepare SCBs and germacyclobutanes is by cyclization of halopropyl-halosubstituted silanes and germanes with magnesium <1967JA1144, 1970JOM(25)367, 1972JOM(43)121, 1980JOM(188)25>.

1,1-Dihalosilacyclobutanes and 1-alkyl-1-chlorosilacyclobutanes can be further derivatized by substitution of the halide with different nucleophiles (Scheme 68) <1996CHEC-II(1B)867>.



Scheme 68

Another convenient method for the synthesis of metallacyclobutanes is the reaction of di-Grignard reagents with Me_2MCl_2 ($\text{M} = \text{Si}, \text{Ge}, \text{Sn}$) (Scheme 69) <1983JA3336, 1984JOM(277)319, 1987JOM(321)291>.



Scheme 69

2.11.10 Synthesis of Particular Classes of Compounds

No valuable information on specific classes has been published in the covered period.

2.11.11 Important Compounds and Applications

O-(Silacyclobutyl)ketene acetals derived from esters, thioesters, and amides represent a useful tool in the synthesis of aldol adducts <1992JA7922, 1993JOC988, 1994JA7026>. Another synthetically useful reaction is stereospecific allylation of carbonyl compounds employing allylsilacyclobutanes <1994JOC7152>. SCB-derived protecting groups for alcohols have been reported, based on oxidation of the SCB <2003OL4571, 2005TL3283, 2006JOC420>.

SCBs play an important role in the synthesis of polymers. They are used as monomers under ring-opening conditions <1992MM1639, 1992PB281, 1997MM2524, 1997PSA3207, 2001PSA86>. SCB species can serve as an 'anionic pump' in synthesis of block copolymers <2001MM4384, 2000MI527>.

Laser-induced decomposition of SCBs has been reported as an efficient route for the gas-phase deposition of thin films of Si-C-H and Si-C materials <1993JCF411, 1994JOM(466)29, 1990JOM(391)275>.

2.11.12 Further Developments

Further developments can be found in a recent article <2007JA6094>.

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Biographical Sketch



Gregory B. Dudley was born in Chicago, IL, in 1974 and raised in Miami, FL. He received a B.A. degree in chemistry (1995) from Florida State University (FSU) and a Ph.D. in organic chemistry (2000) under the supervision of Prof. Rick L. Danheiser at the Massachusetts Institute of Technology (MIT). His thesis work included the total synthesis of ascochlorin using Danheiser's benzannulation strategy. He then joined the lab of Prof. Samuel J. Danishefsky at the Sloan-Kettering Institute for Cancer Research, where his work culminated in the total synthesis of guanacastepene A. In 2002, he returned to FSU as an assistant professor of chemistry and biochemistry. His current research interests are in the area of synthetic organic chemistry, including fragmentation and ring-opening reactions and methodology directed toward the total synthesis of natural products.



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2.12

Four-membered Rings with One Boron or Other Atom

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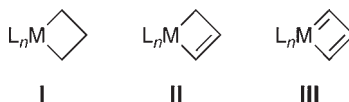
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2.12.1 Introduction

In contrast to the vast majority of heterocycles, four-membered rings containing boron or one of the transition metals have been known only since the mid-1950s, beginning with the synthesis of a platinacyclobutane complex by oxidative insertion into cyclopropane <1955JCS2045>. Although the development of such heterocyclobutane chemistry has continued unabated through the subsequent decades <1996CHEC-II(1b)887>, this class of reactive strained ring compounds remains unusual among organic heterocycles: no examples have been found in nature and none are considered probable pharmacophores. Nonetheless, metallacyclobutanes function as transient intermediates in important catalytic processes (i.e., the olefin metathesis) and an extensive range of relevant structures have been prepared as synthetic constructs for fundamental evaluation and exploratory purposes <1994CRV2241>.

In this chapter, recent developments in the chemistry of metallacyclobutane **I**, metallacyclobutene **II**, and metallacyclobutadiene **III** synthesis and reactivity chemistry are reviewed, with the inclusion of sufficient historical thread to connect to previous reviews in this area, including the coverage in CHEC-II(1996) <1996CHEC-II(1b)887>. Although significant applications to organic synthesis (aside from the olefin metathesis reaction) have yet to be reported, the current literature clearly anticipates the emergence of new methodology for organic synthesis. The potential exploitation of this highly reactive structural class in stoichiometric and catalytic organic synthesis constitutes the primary focus of this chapter.



2.12.2 Theoretical Methods

The use of computational methods to explain and predict experimental observations of metallacyclobutane, metallacyclobutene, and metallacyclobutadiene complexes has grown dramatically with the expansion of theoretical methodology. Organometallic compounds have greater numbers of electrons and have more energetically relevant orbitals than purely organic compounds, requiring greater computational resources to carry out meaningful theoretical studies. On this basis, density functional theory (DFT) is now most frequently used for structural and mechanistic investigations of organometallic complexes. The substitution of computationally less demanding model ancillary ligands for actual ligands (e.g., chloride for cyclopentadienyl and PH_3 for any phosphine) remains common, however, despite the inevitable introduction of substantial error to calculated structural and electronic parameters. Fortunately, this compromise is increasingly unnecessary, as sufficient computational resources have become more generally accessible.

Theoretical studies published since 1993 reporting computationally optimized structures for four-membered boracycles and metallacycles are listed in Table 1. Many of these investigations, however, maintain a specific focus on molecular transformations (i.e., reaction mechanisms) and no longer explicitly consider the details of metallacyclobutane structure. The most significant theoretical investigations of boracyclobutene derivatives were conducted sufficiently long ago to have been reviewed in CHEC-II(1996) <1996CHEC-II(1b)887> and are not discussed further.

A relatively large number of recent investigations have focused on the optimized structure and reactivity of tungstacyclobutadiene complexes, pertinent to issues of aromaticity and the alkyne metathesis reaction. The results from these studies are summarized in Table 2 <1993OM1289, 1994OM2878, 2004JOM1050, 2005JOM4939>. DFT-based computations for tungstacyclobutadienes such as $\text{Cl}_3\text{W}(\eta^2\text{-C}_3\text{H}_3)$ **1** predict a planar, symmetric ring structure and a delocalized π -system. This is consistent with experimental observations. In contrast, MP2-level calculations

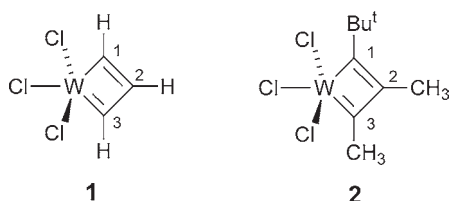
Table 1 Computational investigations of four-membered ring metallacycles since 1993

<i>Metallacyclobutanes</i>					
Ti	1996JA9772 1999JA5396 1999JOM179 1999OM2081 2003JOM75	Ru	1998JA7174 2000JA8204 2002AGE4484 2002CEJ3962 2002JA8965 2003OM93 2003OM940 2004JA3496 2004JA14332 2004OL3313 2004OM76 2004OM2027 2005AGE5974	Pd	1989OM1991 1993OM3019 1997JA12779 1997JOM185 1998JMT205 1999IC370 2000IC1113 2001JA6157 2001OM2751 2002OM2248 2004ICA1444 2004JMT191
Zr	1999OM2081 2002JOM268				
Hf	1999OM2081				
Nb	2001OM1334				
Cr	2000CJC265			Pt	1989OM1991 1999IC370 2004JOC8018 2004JMT191
Mo	1993OM325 1997JA8043 1998OM5901 2001JMO215 2002JMO371 2003ICA241 2003OM3649 2004JMO91 2005OM3200	Os	2005CEJ4700	Cu	2001JA7616 2004CEJ758 2004JMT193 2006JCD545
		Co	2004OL949		
		Rh	2001OM5606	B	1995AGE657 1995JMT235
Re	2003OM3671 2005JA14015	Ir	2001OM5606	Al	1995JMT235
		Ni	1995OM1834 1996JOC3490		
<i>Metallacyclobutenes</i>					
Ti	1997AG(E)606 1998JA6952 1999JOM179 2003JOM75	Mo	2001JA6662 2004OM3189	Ni	2000JOM164
		Ru	2005JA7444	Pd	2001OM1462
Cr	2003JOC4674	Os	2004JA11699	Pt	1999OM837 2000JOM164
<i>Metallacyclobutadienes</i>					
Ti	1999JPC1627	W	1993OM1289 1993OM5005 1994OM2878 2004JOM1050 2005JOM4939	Re	1994OM2878
Mo	1993OM1289			Rh	1994OM2878
				Ir	1994OM2878

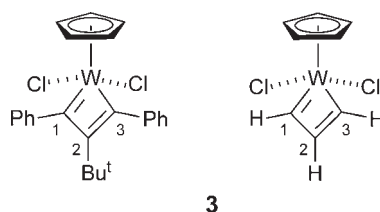
instead predict localized single and double carbon–carbon bonds in the C_3R_3 moiety of **2**, seriously underestimating the amount of electronic delocalization.

Perhaps surprisingly, the corresponding $CpCl_2W(\eta^2-C_3R_3)$ complexes **3** are distorted, with alternating single and double bonds (see Section 2.12.3). According to computations (Table 3), this arises from steric interactions between the cyclopentadienyl ligand and the ring substituents, which forces the rearrangement to a four-legged piano stool structure, interrupting the strong metal/ π -system interactions necessary for aromaticity. Electronic factors, however, strongly favor a symmetric structure, as established for the corresponding unsubstituted system.

The structures of 2-methylenetitanacyclobutene complexes **4**, which have also received considerable experimental attention, have been thoroughly studied by *ab initio* methods. Selected bond angles and lengths from experimentally determined and calculated structures are summarized in Table 4. The replacement of ancillary cyclopentadienyl ligands with chloride introduces minor deviations in the calculated C(1)–Ti–C(3) angles, but there is generally good agreement between calculated and experimental bond lengths and angles. The titanium–carbon lengths consistently

Table 2 Comparative computational results for selected tungstacyclobutadiene complexes^a

	1		2				
<i>Bond/angle^b</i>	<i>HF</i>	<i>B3LYP/B2</i>	<i>MP2/B1</i>	<i>MP2/B2</i>	<i>B3LYP/B1</i>	<i>B3LYP/B2</i>	<i>Experimental</i>
W–C(1)	1.89	1.902	1.991	1.916	1.924	1.915	1.816
W–C(3)	1.869	1.902	1.842	1.848	1.885	1.873	1.864
C(1)–C(2)	1.46	1.438	1.391	1.405	1.452	1.431	1.455
C(2)–C(3)	1.46	1.438	1.744	1.525	1.487	1.491	1.478
C(1)–W–C(3)	82.0	82					85.4
W–C(1)–C(2)	80.6	79	77.7	76.9	79.4	78.8	78.2
C(1)–C(2)–C(3)	116.8	120	118.3	121.2	117.8	119.0	118.9
C(2)–C(3)–W	80.9	79	74.6	76.5	79.3	78.8	77.6
References ^c	1	2	3	3	3	3	4

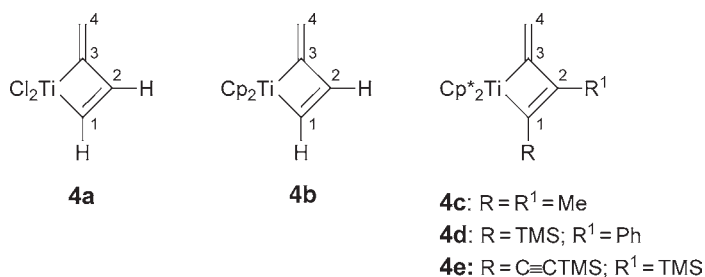
^aB1: LANL2DZ(W, Cl)/D95(C, H); B2: LANL2DZ(W, Cl)/6-13G**.^bBond lengths in Å. Bond angles in deg.^cReferences: 1, 1994OM2878; 2, 2004JOM1050; 3, 2005JOM4939; 4, 1982JA6808, 1984JOM201.**Table 3** Calculated structures for tungstacyclobutadiene complexes

<i>Bond/angle^a</i>	<i>Experimental</i>	<i>HF</i>
W–C(1)	1.943	2.03
W–C(3)	2.132	2.13
C(1)–C(2)	1.485	1.43
C(2)–C(3)	1.372	1.40
C(1)–W–C(3)	65.16	62.5
W–C(1)–C(2)	84.93	
C(1)–C(2)–C(3)	100.70	98.9
C(2)–C(3)–W	80.58	
References ^b	1	2

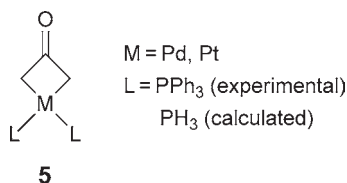
^aBond lengths in Å. Bond angles in deg.^bReferences: 1, 1983OM1046, 1985JOM403; 2, 1994OM2878.

calculate 0.1 Å shorter than experimentally determined values, but the carbon–carbon bond lengths are reasonably invariant. Both calculations and crystallographic data uniformly reveal a planar titanacyclobutene ring.

Selected structural data for 3-metallacyclobutanone complexes of palladium and platinum **5**, obtained from both experimental and computational determinations, are provided in **Table 5**. The *ab initio* structures calculated at the self-consistent field (SCF) and Hartree–Fock (HF) levels show good agreement with experimental values for the bond lengths of the metallacycle, but these computations deliver somewhat longer Pd–P bonds and smaller P–Pd–P

Table 4 Crystallographic and computationally determined structural parameters for α -methylene-titanacyclobutene complexes

	<i>HF</i>	<i>DFT</i>	<i>Experimental</i>		
<i>Bond/angle</i> ^a	4a	4b	4c	4d	4e
Ti–C(1)	1.987	2.069	2.109	2.173	2.111
Ti···C(2)	2.341	2.448	2.500	2.507	
Ti–C(3)	1.992	2.091	2.104	2.102	2.110
C(1)–C(2)	1.375	1.351	1.365	1.352	1.367
C(2)–C(3)	1.516	1.481	1.434	1.502	1.495
C(3)–C(4)	1.351	1.338	1.377	1.322	1.342
Ti–C(1)–C(2)	86.6	88.8	89.4	87.4	91.4
C(1)–C(2)–C(3)	115.0	115.9	114.8	116.7	112.1
C(2)–C(3)–Ti	82.5	84.7	87.8	86.5	88.0
C(3)–Ti–C(1)	75.8	70.6	68.0	69.3	68.5
Reference ^b	1	2	3	3	4

^aBond lengths in Å. Bond angles in deg.^bReferences: 1, 1999JOM179; 2, 2003JOM75; 3, 1996OM1176; 4, 1996OM4731.**Table 5** Crystallographic and computationally derived structural parameters for 3-metallacyclobutanone complexes of Pd and Pt

	<i>Pd</i>					<i>Pt</i>		
<i>Bond/angle</i> ^a	<i>Experimental</i>	<i>SCF</i>	<i>HF</i>	<i>MP2</i>	<i>DFT</i>	<i>Experimental</i>	<i>MP2</i>	<i>DFT</i>
M–P	2.3385	2.57	2.503	2.325	2.374	2.294	2.293	2.335
M–C(1)	2.135	2.11	2.114	2.131	2.147	2.132	2.110	2.133
M–C(2)	2.40	2.49	2.501			2.422		
C(1)–C(2)	1.47	1.49	1.485	1.484	1.483	1.484	1.500	1.502
C(2)–O	1.24	1.22	1.223	1.227	1.223	1.257	1.221	1.214
P–M–P	105.1	98.0	101.0	109.0	107.0	103.6	105.4	103.1
C(1)–M–C(3)	65.3			66.4	66.4	68.4	67.2	67.0
C(1)–C(2)–C(3)	105	101.9		103.5	104.9	107.7	102.2	103.2
θ^b	56.9	50.5	46.6	52.3	48.3	51.0	47.4	39.3
Reference ^c	1	2	3	4	4	2	4	4

^aBond lengths in Å. Bond angles in deg.^bFold angle defined by the dihedral angle between planes defined by C(1)–M–C(3) and C(1)–C(2)–C(3).^cReferences: 1, 1995OM2538; 2, 1989OM1991; 3, 1996IC231; 4, 2004JMT191.

bond angles and ring puckering. In contrast, the structures optimized at the MP2 level show overall agreement with experimental values for both palladium and platinum complexes. For comparison, [Table 5](#) also includes optimized structures obtained by DFT methods. The agreement between the experimental geometry and DFT-computed values is quite good, except that the calculated deviation from planarity of the ring is significantly smaller than that obtained experimentally. For both MP2 and DFT calculations, the fold angle predicted for the palladium complex is larger than that for platinum, as is discussed more thoroughly in the following sections.

2.12.3 Experimental Structural Methods

General crystallographic and spectroscopic features of a range of four-membered ring metallacycles have been discussed previously in CHEC-II(1996) <1996CHEC-II(1b)887>.

Although the structures of metallacyclobutadienes determined by X-ray diffraction analysis have also been reported previously, the inclusion of a brief discussion is pertinent to both theoretical and reactivity aspects covered in this chapter. The ring structure of tungstacyclobutadienes $X_3W(\eta^2-C_3R_3)$ (**1**, **2**; $X = Cl$, alkoxide, aryloxy) is planar and nearly symmetric; when $X = Cl$, the structure of the ring is quite symmetric (see [Section 2.12.2](#)) <1982JA6808, 1984JOM201, 1984OM1554, 1984OM1563, 1985JOM27>. In the ^{13}C nuclear magnetic resonance (NMR) spectra of these complexes, the resonances for both α -carbons appear downfield around 260 ppm with a $^1J_{CW}$ coupling constant of ca. 120 Hz, suggesting that both share substantial carbene character, while β -carbon resonances are seen in the normal olefinic region (ca. 120–150 ppm). These data provide evidence for π -electron delocalization (Figure 1).

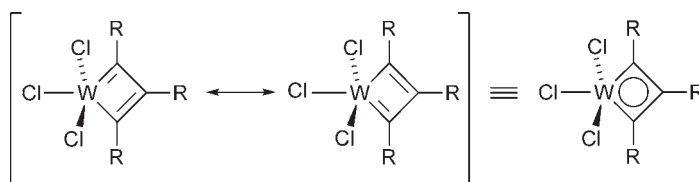
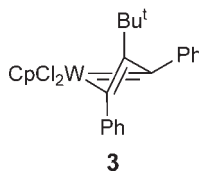
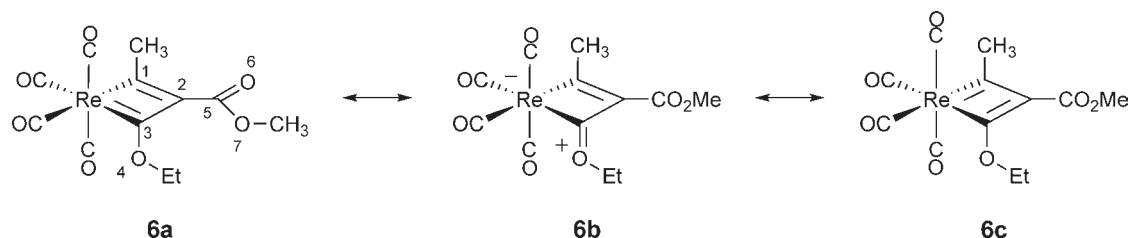


Figure 1 Electron delocalization in tungstacyclobutadiene complexes.

In contrast, the structure of $CpCl_2W(\eta^2-C_3R_3)$ **3** is quite different from that of $X_3W(\eta^2-C_3R_3)$ <1983OM1046, 1985JOM403>. The ring is nonplanar, with clearly alternating single ($W-C$: 2.132 Å, $C-C$: 1.485 Å) and double bonds ($W=C$: 1.943 Å, $C=C$: 1.372 Å), suggesting that this complex adopts a structure intermediate between a planar metallacyclobutadiene and an alkyne/carbyne complex. Delocalization of π -electron density is thus not anticipated for this structure.

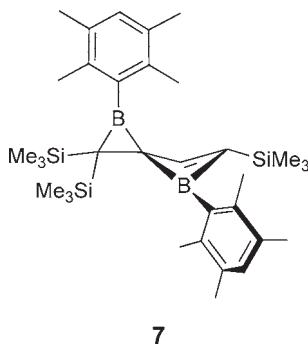


The crystal structure of a Fischer-type metallacyclobutadiene complex of rhenium **6** has also been reported <1993JA9986, 1990JOMC1>. The bond lengths between Re and the α -carbons (2.18 and 2.13 Å) are very similar, but the two $C-C$ bond lengths are considerably different ($C(1)-C(2)$: 1.36 Å, $C(2)-C(3)$: 1.45 Å). In addition, the $C(3)-O(4)$ bond distance (1.30 Å) is much longer than $C(5)-O(6)$ (1.19 Å) but shorter than $C(5)-O(7)$ (1.34 Å). Therefore, the structure of rhenacyclobutadiene **6** is expected to be best represented by significant contributions from the resonance structures **6a** and **6b** and a smaller contribution from structure **6c**.



In the main group series, spiro-diboracyclobutene compounds **7** exhibit a number of interesting structural and spectroscopic properties. Selected bond distances and angles obtained from X-ray crystallography are tabulated in Table 6 <1994AGE1487>. Of particular note is the fold angle of 30° across the boracyclobutene B–C diagonal and the short distance between the two centers (1.87 Å). *Ab initio* calculations predict a fold angle of only about 13° <1984AGE370>. NMR spectroscopic data for a range of these spirocycles are collected in Table 7, supporting the assertion of strong 1,3-bonding interactions between boron and the diagonal carbon. The boron center is shielded compared with typical trialkylboranes ($\delta(^{11}\text{B}) \sim 80$ ppm), while the adjacent vinyl carbon (C-3) is deshielded. This is best represented by including a contribution from the dipolar resonance structure (V, Table 7). The ^{13}C NMR data were collected at low temperature (–40 to –30 °C) to minimize ^{11}B quadrupolar line broadening, which was evident in both olefinic carbon resonances at room temperature.

Table 6 Selected structural parameters for boracyclobutene **7**



Bond	Bond length (Å)	Bond angle	Angle (deg)
B(1)–C(2)	1.620	B(1)–C(2)–C(3)	73.2
B(1)–C(3)	1.869		
B(1)–C(4)	1.534	B(1)–C(2)–B(6)	141.7
C(2)–C(3)	1.511	B(6)–C(5)–C(2)	59.1
C(3)–C(4)	1.377	C(5)–C(2)–B(1)	139.5
		B(6)–C(2)–C(3)	126.4
C(2)–C(5)	1.607	C(5)–C(2)–C(3)	128.2
B(6)–C(2)	1.519		
B(6)–C(5)	1.544	Fold angle	30

Although rife with exceptions caused by specific electronic and steric influences, some trends are evident in metallacyclobutane ^1H and ^{13}C NMR spectroscopy. In coordinatively saturated, formally 18-electron, complexes of low oxidation state late transition metals, the α -carbon and α -hydrogen resonances are more magnetically shielded (upfield) than those at the β -position. Square planar metallacyclobutanes of nickel(II), palladium(II), and platinum(II) show a similar trend, which might be anticipated by the relative electron richness of the metal centers. In contrast, metallacyclobutane complexes of early transition metals in high oxidation states (typically d^0 - and d^2 -metals) show an opposite trend: β -hydrogen resonances appear at very high magnetic field (typically around 0 ppm). The chemical shifts of the β -carbon resonances (typically 0–20 ppm) appear at higher field than in similarly substituted organic molecules, but not as far upfield as might be expected from the chemical shifts of the β -hydrogen resonances. These

Table 7 ^{11}B and ^{13}C NMR parameters for boracyclobutene **7**

IV **V**

R	R^1	R^2	$\delta(^{11}\text{B}^1)$	$\delta(^{11}\text{B}^6)$	$\delta(^{13}\text{C}^3)$	$\delta(^{13}\text{C}^4)$	$\delta(^{13}\text{C}^2)$	$\delta(^{13}\text{C}^5)$	Reference
Dur	Me	Me			155.8	164.5	51.2	24.6	1995AGE657
Dur	Et	Et			162.7	166.2	47.9	24.8	1995AGE1340
Dur	SnMe_3	$3,5\text{-(Bu}^t)_2\text{-C}_6\text{H}_3$			167.8	179.6	55.7	28.7	1994AGE2064
Dur	H	TMS	32	69	154.3	176.1	53.1	24.7	1994AGE1487
Bu^t	H	TMS	45	80	153.3	185.7	53.6	29.4	1994AGE2306
Bu^t	Me	Me	34.5	83	143.2	185.5	53.6	27.7	1984AGE369
Bu^t	H	Bu^t	40	81	135.1	195.0	56.5	27.9	1984AGE369
Bu^t	Ph	Ph			137.1–144.8	180.1	56.2	27.0	1983AGE877

Dur = 2,3,5,6-tetramethylphenyl.

**Figure 2** Canonical representations of metallacyclobutane distortion.

aspects indicate that the β -carbon and β -hydrogen atoms are, perhaps surprisingly, shielded by the metal center. In addition, the α -hydrogen and α -carbon resonances of early metal complexes show an unusually broad range of chemical shifts (1–7 ppm for ^1H NMR and 40–150 ppm for ^{13}C NMR). In d^0 -metallacyclobutanes, Schrock and co-workers have suggested that the difference in the chemical shifts for α - and β -carbon correlates with the distance between the metal center and the β -carbon, with a larger difference reflecting a shorter distance [<1990OM2535>](#). Complexes in this class can have very short transannular distances of ca. 2.3–2.4 Å. This criterion can be used in a predictive sense for d^0 -metallacyclobutane structures without resorting to X-ray diffraction analysis. It was also suggested that the characteristically low-field α -hydrogen and α -carbon resonances may reflect an intermediate structure between classical olefin-coordinated alkylidene and metallacyclobutane canonicals (e.g., **VI–VIII**, [Figure 2](#)), particularly given that such complexes can often be prepared by [2+2] olefin/alkylidene cycloaddition and can function as active metathesis catalysts. The relationship between structure and NMR characteristics, however, has neither been investigated thoroughly nor, in general, clearly rationalized.

Recent theoretical and experimental investigations suggest an alternative structural rationale for short distances between the metal center and the β -carbon: significant agostic interactions between a coordinatively unsaturated, electron deficient, metal center and the proximal $\text{C}_\alpha\text{--C}_\beta$ σ -bonds (e.g., **IX–XI**, [Figure 3](#)) [<2004OM76, 2005JCD2982, 2005JA16426>](#). Such agostic interactions may play an important role in activating carbon–carbon single bonds toward metathesis reactions, similar to the recognized importance of C–H agostic interactions in promoting C–H activation reactions. Significant agostic C–C donor interactions in unsaturated metallacyclobutane complexes is strongly supported by $^1J_{\text{CC}}$ coupling constant measurements obtained by ^{13}C INADEQUATE spectroscopy. Molybdacyclobutane **8** and tungstacyclobutane **9**, both 18-electron complexes, show normal $^1J_{\text{CC}}$ coupling constants of ca. 30 Hz, contrasting the

smaller $^1J_{\text{CC}}$ coupling constants of ca. 20 Hz observed in titanacyclobutane **10** and zirconacyclobutane **11**, which are coordinatively unsaturated 16-electron complexes. Consistent with previous rationalizations, this difference in $^1J_{\text{CC}}$ coupling is related to the distance between the metal and the β -carbon [\[2005JA16426\]](#). Such interactions may well be equally related to the unusual upfield β -carbon ^{13}C -NMR resonances observed for d^0 -metallacyclobutane complexes.

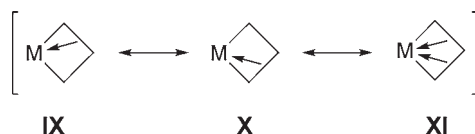
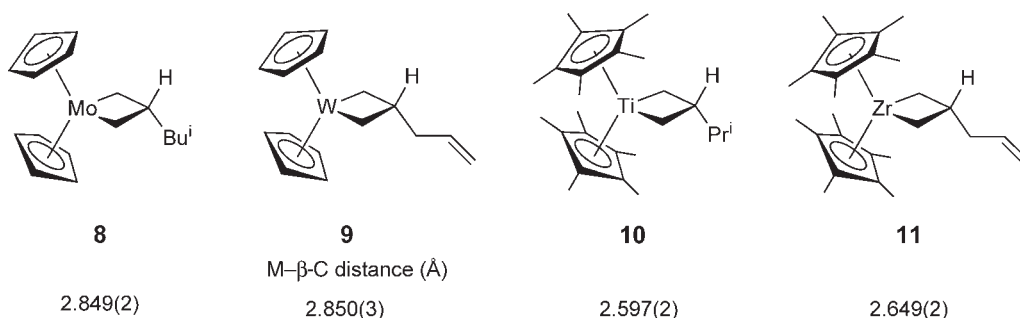


Figure 3 C–C agostic interactions in the metallacyclobutane core.



Spectroscopic and X-ray crystallographic analysis reveal that β -oxometallacyclobutane complexes, also termed oxatrimethylenemethane (OTMM) complexes, have an unusually puckered ring structure. The fold angle (defined as the dihedral deviation from a planar ring structure) for palladium and platinum OTMM complexes is between 48.0° and 56.9° (Pd: [\[1995OM2538\]](#); Pt: [\[1989OM1991\]](#)), while iridium [\[1986CC427\]](#) and ruthenium [\[1990JA5670, 1991OM3344\]](#) complexes display somewhat smaller angles of 41° and 45.6° , respectively. These fold angles are much larger than those observed in both organic cyclobutanones (0 – 10°) and simple metallacyclobutanones (0 – 30° , depending on substitution). This structural feature is explained by a significant contribution from an η^3 -coordination mode (e.g., **XIII**, [Figure 4](#)), which is supported by both spectroscopic and crystallographic data, viz., upfield shifts in the ^{13}C NMR resonance of the carbonyl carbon (ca. 175 ppm), lower C–O stretching frequencies (ca. 1600 cm^{-1}) in the infrared spectra, and slightly elongated C–O bond lengths in the crystal structures. In addition, NMR coupling constants are also useful indicators of structural information. The reported $^1J_{\text{CH}}$ coupling constants for the metallacycle α -position (ca. 150 Hz) in platina- and auracyclobutanones are significantly larger than typical coupling constants for $\text{C}(\text{sp}^3)\text{--H}$ bonds (ca. 125 Hz) [\[1997JOM243\]](#). In platinum phosphine complexes, $^1J_{\text{PtP}}$ coupling constants reflect the extent of trans-influence and can therefore provide important structural information. The $^1J_{\text{PtP}}$ coupling constants observed in platinacyclobutanone complexes (ca. 3000 Hz) [\[1984JCD1993, 1985JCD549, 1988JCD427, 1995OM2538\]](#) are intermediate between those observed for η^3 -allyl complexes (ca. 4000 Hz for unsubstituted allyl platinum complexes, 3500–4000 Hz for 2-alkoxyallyl platinum complexes) and platinacyclobutane complexes (≤ 2000 Hz) [\[1993OM3019\]](#). These data clearly support a contribution from the η^3 -allyl-like coordination mode in metallacyclobutanone complexes.

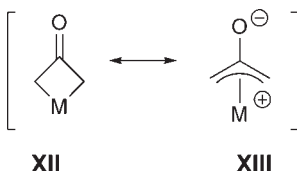


Figure 4 Oxatrimethylenemethane canonical structures.

2.12.4 Thermodynamic Aspects

Aromaticity is an electronic condition that typically pertains to planar, cyclic molecules that, most importantly, exhibit π -electron delocalization. A range of technical criteria have been developed to establish and measure the degree of aromaticity for a compound, including the Bird aromaticity index, homodesmotic reaction aromatic stabilization energy (HASE), nucleus-independent chemical shift (NICS), and absolute hardness. The core of metallocyclobutadiene complexes, while formally analogous to antiaromatic cyclobutadiene, could in principle evidence either aromaticity or antiaromaticity. Tungstacyclobutadienes, $X_3W(\eta^2-C_3R_3)$ **3**, have received considerable attention and all investigations concur that some degree of aromaticity is present in this complex. Unfortunately, the extent of aromatic character is difficult to quantify. Although the tungstacyclobutadiene core is typically planar (see [Figure 1, Section 2.12.3](#)), the number of π -electrons contributed by the metal and organic fragments is variously assigned as two or four, depending upon the technique used in the determination. One set of calculations, however, suggests that the metallocyclobutadiene moiety is both a 4π -electron system and, nonetheless, aromatic [<1993OM5005, 2004JOM1050, 2005JOM4939>](#).

In metallocyclobutane and metallocyclobutene complexes, aromatic character is not an issue, but the strain associated with the four-membered borane ring can have interesting thermodynamic consequences. Boracyclobutene **7**, for example, exhibits fluxionality, as observed by variable-temperature NMR measurements. The ^{13}C NMR resonances for the geminal trimethylsilyl groups appear sharp below $-30^\circ C$, but broaden as the temperature is raised, until coalescence is attained (reportedly at two different temperatures for the two trimethylsilyl (TMS) groups, one at $20^\circ C$ and the other at $30^\circ C$). To accommodate this observation, boracyclobutene ring opening is proposed ([Figure 5](#)), leading to a transient zwitterionic isomer, in which the anion is stabilized by delocalization onto the open valent boron atoms and the cation enjoys hyperconjugative donor interactions with the adjacent C–Si and C–B bonds. The energy barrier for this exchange was calculated to be 14 kcal mol^{-1} [<1994AGE1487>](#).

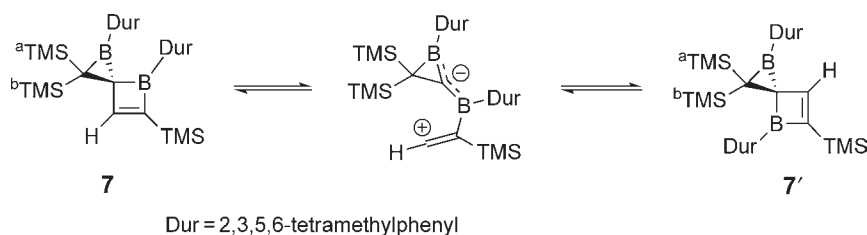
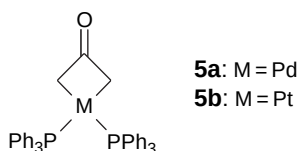


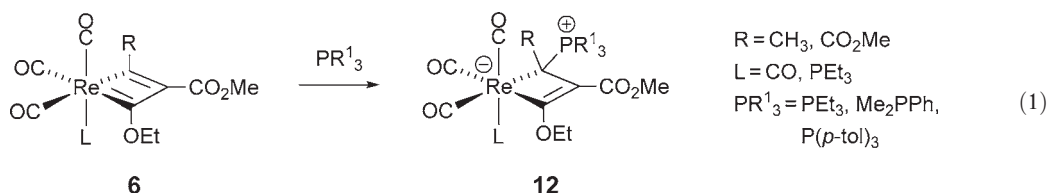
Figure 5 Structural fluxionality in bicyclic boracyclobutenes.

The relatively high activation barrier for the conformational inversion of pallada- and platinaacyclobutanone complexes (9.6 – $12.2 \text{ kcal mol}^{-1}$ and 8.4 – $9.2 \text{ kcal mol}^{-1}$, respectively), compared with that observed in simple metallocyclobutanes, can be rationalized by proposing significant $d \rightarrow \pi^*$ orbital interactions between the metal center and the distal carbonyl carbon, as discussed in a theoretical study of a model OTMM complex of palladium [<1989OM1991>](#). Kurosawa and co-workers have reported the pH of aqueous acetone solutions of complexes **5a** (pH = 9.7) and **5b** (pH = 8.6), which reveals that both complexes are markedly more basic than standard organic carbonyl compounds [<1993CC1039>](#). These data suggest a greater contribution of the η^3 -bonding mode in the palladium structure than in the corresponding platinum complex, presumably attributable to better orbital overlap for palladium.

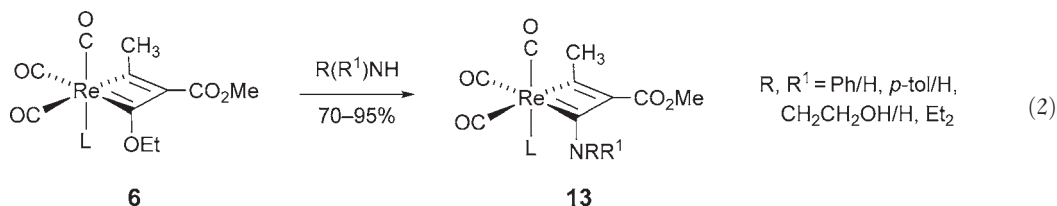


2.12.5 Reactivity of Fully Conjugated Metallacyclobutadiene Complexes

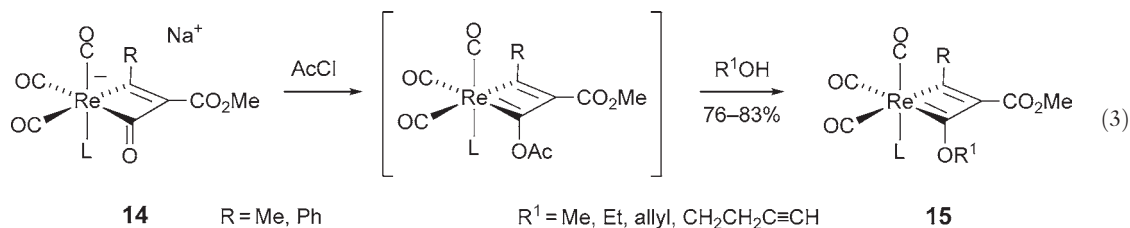
Most of the effort in metallacyclobutadiene reactivity reported since 1993 is focused on rhenacyclobutadiene complexes incorporating Fischer-type carbene functionality and strongly electron-withdrawing substituents on both the metal center and the β -position of the ring. The electrophilic rhenacyclobutadiene complexes **6** thus undergo conjugate addition of phosphine nucleophiles to form zwitterionic rhenacyclobutene complexes **12** (Equation 1) <1993JA9986, 2004JOM2000>.



In contrast, the addition of amines results in nucleophilic addition/elimination at the opposite α -position, resulting in substitution of the α -oxygen substituent, a reaction consistent with the Fischer carbene character embedded into this architecture (Equation 2) <2004JOM2000>. This regioselectivity difference almost certainly arises from the reversible nature of addition reactions using such weakly nucleophilic reagents.

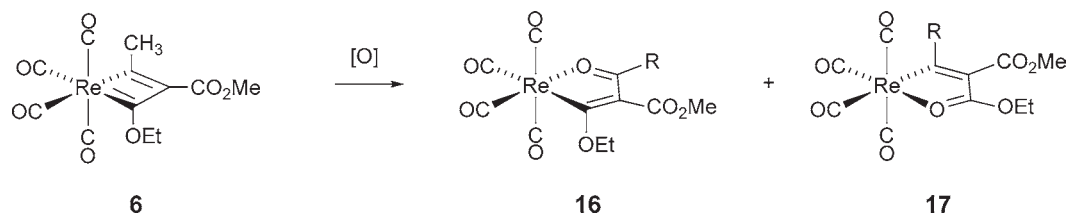


Similarly, α -acetoxyrhenacyclobutadiene complexes, generated *in situ* by the reaction of acetyl chloride with rhenacyclobutanone **14**, undergo substitution upon reaction with alcohols (Equation 3), giving α -alkoxyrhenacyclobutadiene complexes **15** <2004JOM2000>.



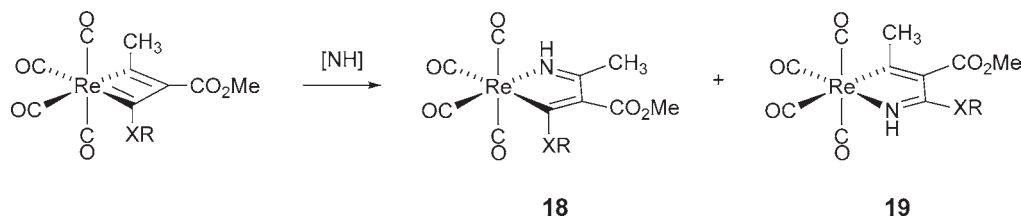
The oxidation of rhenacyclobutadiene complexes using ceric ammonium nitrate (CAN), EtNO_2 , dimethyl sulfoxide (DMSO), or Me_3NO results in a regioselective insertion of oxygen to afford chelated acyl-substituted vinyl complexes **16/17** (Equation 4) <1993JA9986, 2004JOM2000>. Hydrazines are also effective oxidants, yielding the analogous nitrogen-containing chelates **18/19** (Equation 5) <1994ICA199, 2004JOM2000>. In both cases, the ratio of regiochemical isomers is dependent on both the oxidant and the reaction conditions,

although the origin of the observed selectivity remains obscure. This reactivity pattern is again consistent with Fischer-type carbene character.



<i>R</i>	[O]	Reaction conditions	16/17
CH ₃	(NH ₄)[Ce(NO ₃) ₆] (xs)	acetone, rt	3/1
CH ₃	(NH ₄)[Ce(NO ₃) ₆] (1 equiv)	acetone, rt	7/1
CH ₃	(NH ₄)[Ce(NO ₃) ₆] (1 equiv)	acetone, reflux	4/1
CH ₃	EtNO ₂ /Et ₃ N	THF	16 only
CH ₃	DMSO	rt	3/1
CO ₂ Me	(NH ₄)[Ce(NO ₃) ₆] (xs)	acetone, rt	3/1
H	(NH ₄)[Ce(NO ₃) ₆] (xs)	acetone, rt	17 only

xs = excess reagent.

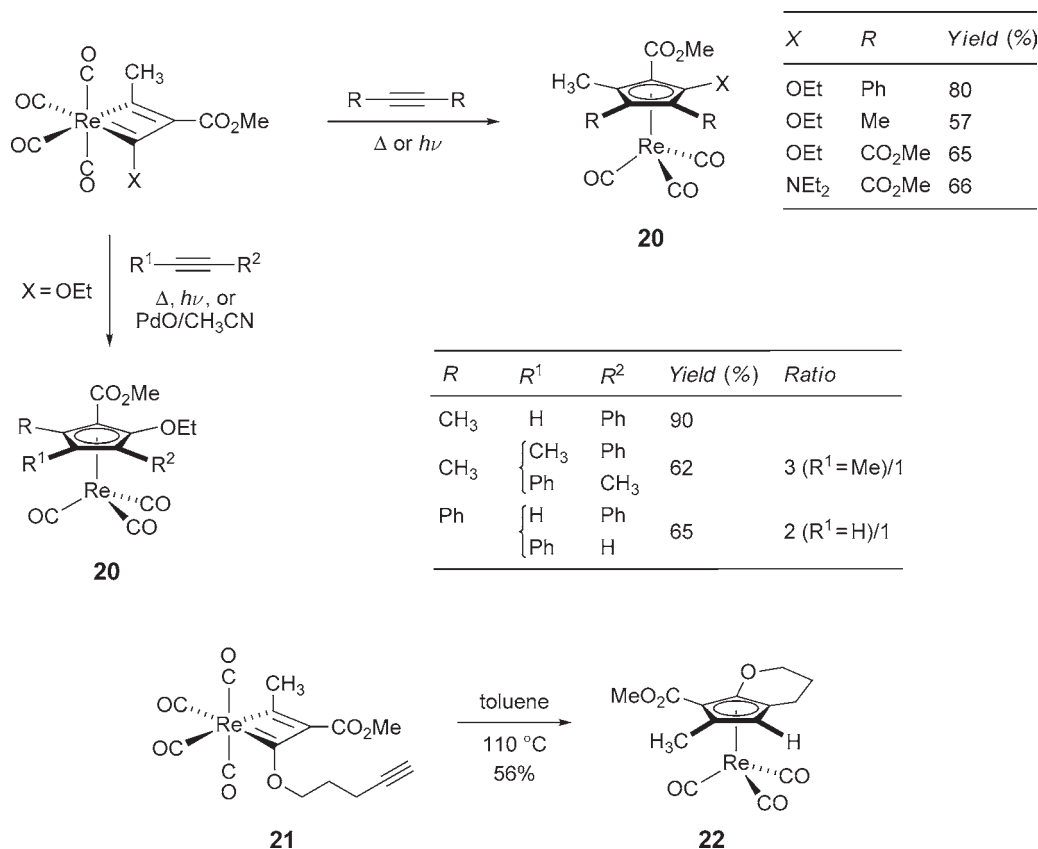


<i>XR</i>	[NH]	Reaction conditions	Product	Yield (%)
NEt ₂	H ₂ NNH ₂ ·H ₂ O	THF, 0 °C → rt, 24 h	18	84
OEt	H ₂ NNH ₂ ·H ₂ O	THF, 0 °C → rt, 12 h	19 ^a	26
OEt	H ₂ NNH[(2,4-NO ₂)C ₆ H ₃]	THF, rt, 2 d	18	90

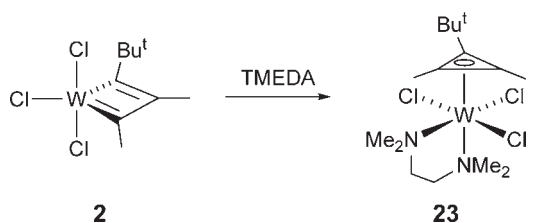
^aAn unquantified trace of **18** was also detected.

The most interesting transformation of the rhenacyclobutadiene ring is the conversion to a highly substituted cyclopentadienyl ligand upon treatment with a range of alkynes (**Scheme 1**). This reaction pathway, a net [3+2] cycloaddition process, is general for a range of electronically activated alkynes, both symmetrical and unsymmetrical. In the latter cases, two regiochemical isomers of the product are obtained. This reaction pattern is consistent with the established reactivity of Schrock-type alkylidene complexes and can be accomplished either thermally or photochemically. The intramolecular [3+2] cycloaddition reaction (e.g., **21** → **22**) has also been demonstrated <2004JOM2013>.

Coordinatively unsaturated tungstacyclobutadiene complex **2** isomerizes to η^3 -cyclopropenyl (metallatetrahedrane) complex **23** upon association of neutral ligands (e.g., **Equation 6**). Recent theoretical studies suggest that the η^2 -C₃R₃ (metallacyclobutadiene) fragment coordinates to the metal as an eight-electron donor through two σ -bonds and two π -bonds, whereas the η^3 -C₃R₃ (η^3 -cyclopropenyl) ligand coordinates to the metal as only a four-electron donor <1994OM2878>. The C₃R₃ moiety thus modulates the electron density provided to the metal through a shift of coordination mode, responding to changes in the metal coordination sphere – adopting the η^2 -coordination mode in response to an unsaturated, electron-deficient metal center but shifting to η^3 -coordination in response to a coordinatively saturated metal.



Scheme 1



(6)

2.12.6 Reactivity of Nonconjugated Four-Membered Metallacycles

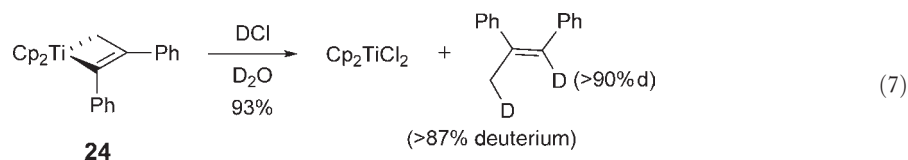
Fundamental investigations of synthesis and reactivity continue to be the focus in both organic and inorganic laboratories, revealing reactivity patterns and delineating general principles to bring such reactive intermediates into the realm of stoichiometric and catalytic organic synthesis. Outside of the olefin metathesis, however, few obviously important organic transformations have as yet been developed. Nonetheless, a range of unusual and potentially useful reaction classes has been demonstrated, supporting an expanded context for further development.

2.12.6.1 Reactivity of Boracyclobutenes and Metallacyclobutenes

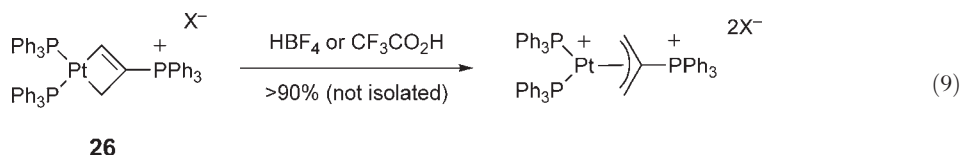
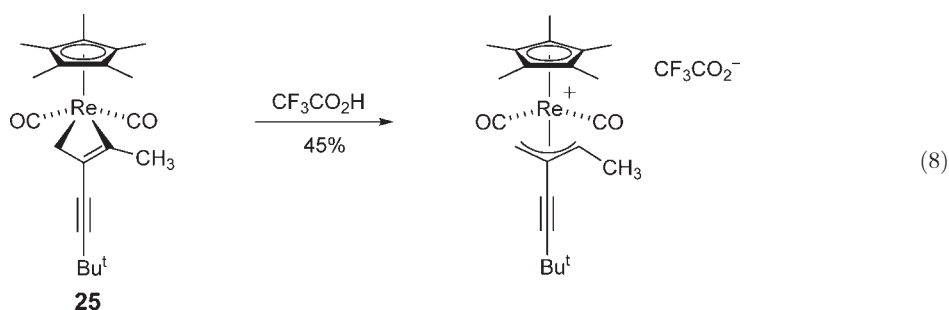
Progress in the development of boracyclobutene and metallacyclobutene chemistry continues to be inhibited by the dearth of general preparative methodology (Sections 2.12.9 and 2.12.10). A great deal of exploratory work has been done, however, exploiting the strain of the four-membered ring and the inherently high reactivity of the carbon–heteroatom bonds. In the transition metal series, the ring strain is inherently modest (ca. 5 kcal mol^{-1}), a consequence of the long metal–carbon bonds and more readily accommodated acute C–M–C bond angles.

2.12.6.1.1 Protonation

Although the transition metal–carbon bond is to some extent ionic in nature, the degree of ionic character depends dramatically on the metal, oxidation state, ancillary ligands, and coordination mode of the organic fragment. Protonolysis of hydrocarbyl ligands with strong acid generally results in cleaving the organic substituent from the metal. Metallacyclobutene protonolysis is consistent with this trend <1996CHEC-II(1b)887>, although complete liberation of the metallacyclic fragment requires 2 equiv of acid. Thus, protonation of titanacyclobutene **24** results in demetallation, providing methylstilbene and the metal dihalide, as illustrated for the corresponding deuterolysis reaction (Equation 7) <1997OM951>.



By controlling the stoichiometry of the reaction, selective conversion of metallacyclobutenes to the corresponding π -allyl complexes can be accomplished, illustrated for both rhenacyclobutene **25** (Equation 8) <1998JA722> and platinacyclobutene **26** (Equation 9) <1998OM2953>.



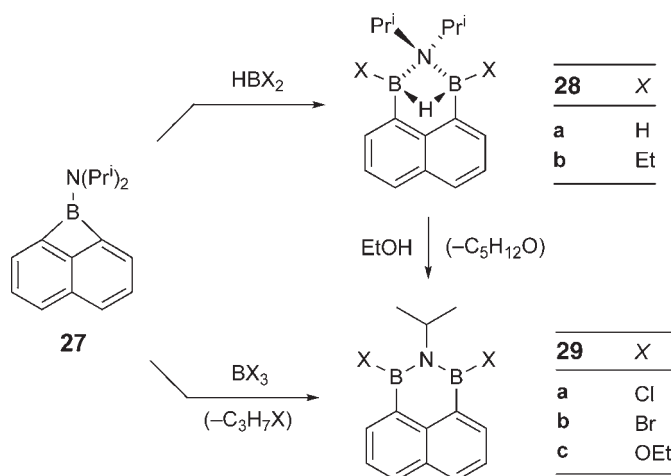
2.12.6.1.2 Transmetalation

The boracyclobutene embedded in [1,8]naphthaborate **27** reacts with a range of boron electrophiles with cleavage of the boron–carbon bond (Scheme 2). Borane, diethylborane, trihaloborane, and triethylborate all react similarly, returning azadiboracyclic products **28** and **29** <1994AGE1247>. Borane **28a** is converted into naphtho[1,8-*cd*][1,2,6]azadiborinin **29c** upon reaction with ethanol.

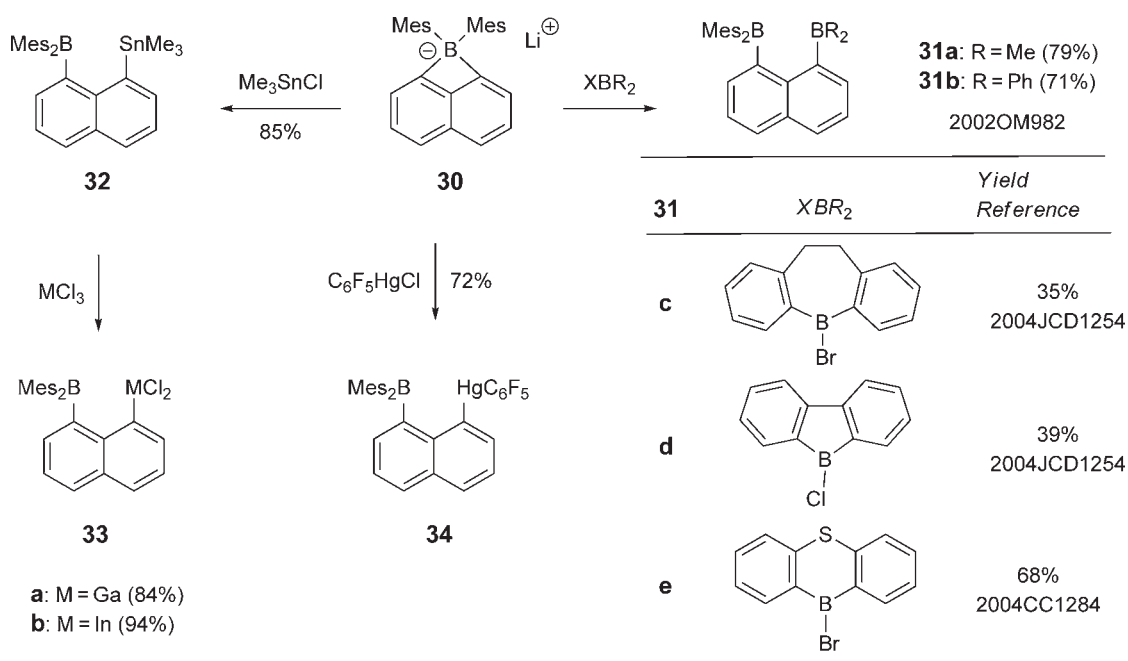
The reaction of anionic [1,8]naphthaborate **30** with dialkyl- or diarylhaloborane electrophiles leads to the formation of 1,8-diborylnaphthalenes **31** (Scheme 3); sulfur-bridged **31e** proved to be a very selective calorimetric fluoride sensor, functioning by coordination of fluoride to both boron centers <2004CC1284>.

Borate **30** also undergoes ring opening upon treatment with chlorotrimethylstannane, generating arylstannane **32** in high yield, which was subsequently converted into gallium and indium chloride derivatives **32** and **33**, respectively, the first group 13 heteronuclear bifunctional Lewis acids (Scheme 3) <2002CEJ3802>. This series could not be accessed directly starting from the borate complex. The boracyclobutene is also reactive towards mercuric salts, providing the heterobimetallic Lewis acid **34**; this compound was shown to be an effective phosphorescent sensor for fluoride ions <2005JA9680>.

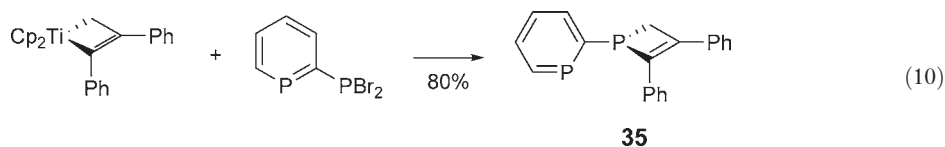
Titanacyclobutenes also undergo a transmetalation of sorts, reacting with dihalophosphine to form phosphacyclobutenes, a conversion first demonstrated by Doxide and Shen <1989JA9129, 1996HAC383, 1998HAC21>. More recently, difunctional phosphite **35** was prepared similarly (Equation 10) <1996OM1597>.



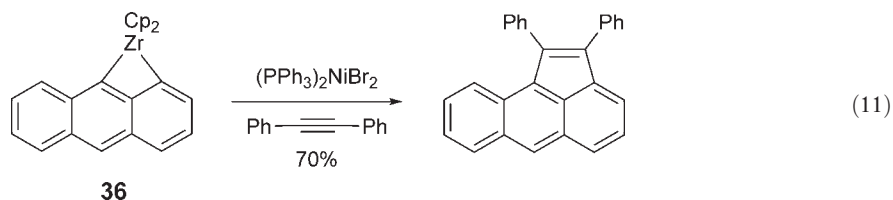
Scheme 2



Scheme 3



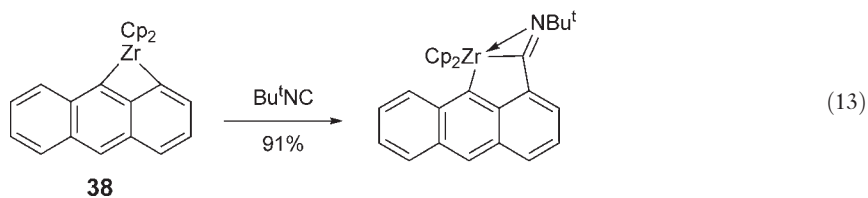
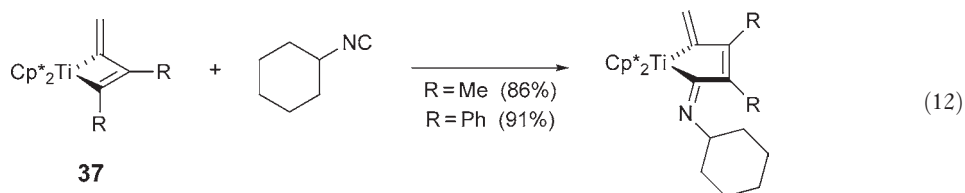
Transmetallation from an early to a late transition metal is kinetically accessible and, most often, thermodynamically favorable. Treatment of 1,9-anthracendiyl zirconocene **36** with bis(triphenylphosphine)nickel(II)bromide in the presence of diphenylacetylene gives 1,2-diphenylaceanthrylene in good yield (Equation 11), suggesting that the transmetallation of zirconium to nickel proceeds efficiently [\[2000JA9880\]](#).



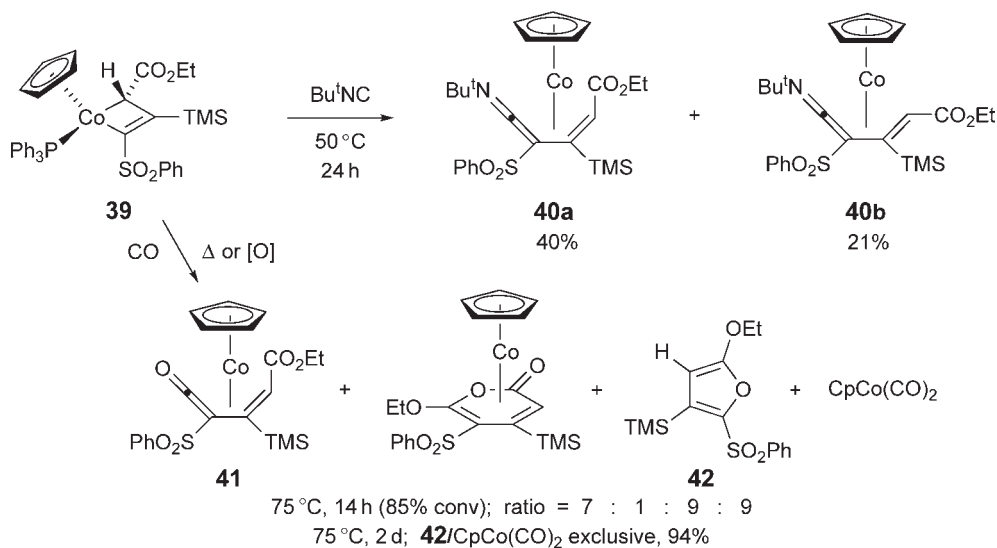
2.12.6.1.3 Insertion reactions

The development of significant synthetic applications of four-membered ring metallacycles depends critically on the discovery of downstream conversions to elaborated organic products.

Cyclohexylisocyanide inserts selectively into the endocyclic vinyltitanium bond of α -methylene-titanacyclobutene complexes **37**, although the reaction fails for many other isocyanides (Equation 12) <1996OM1176>. No insertion occurs upon treatment with nitriles or ketones, in contrast to the established reactivity of typical titanacyclobutenes <1996CHEC-II(1b)887>. The reaction of *tert*-butylisocyanide with 1,9-anthracenediyl-zirconocene complex **38** proceeds exclusively by insertion into the terminal ring zirconium–carbon bond, presumably due to steric considerations (Equation 13) <2000JA9880>.



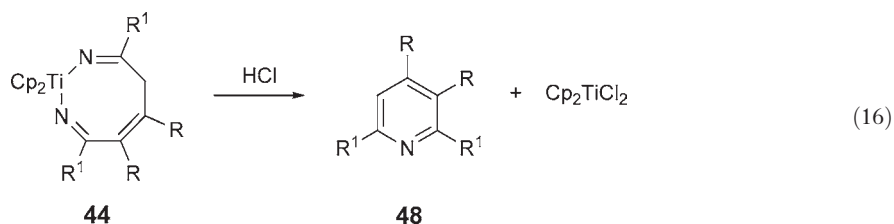
Among later transition metals, the reaction of cobaltacyclobutene **39** <1993JA1586> with *tert*-butylisocyanide yields two isomers of the η^4 -vinylketimine complex **40** (Scheme 4) <1993JA9846>. The reaction with carbon monoxide,



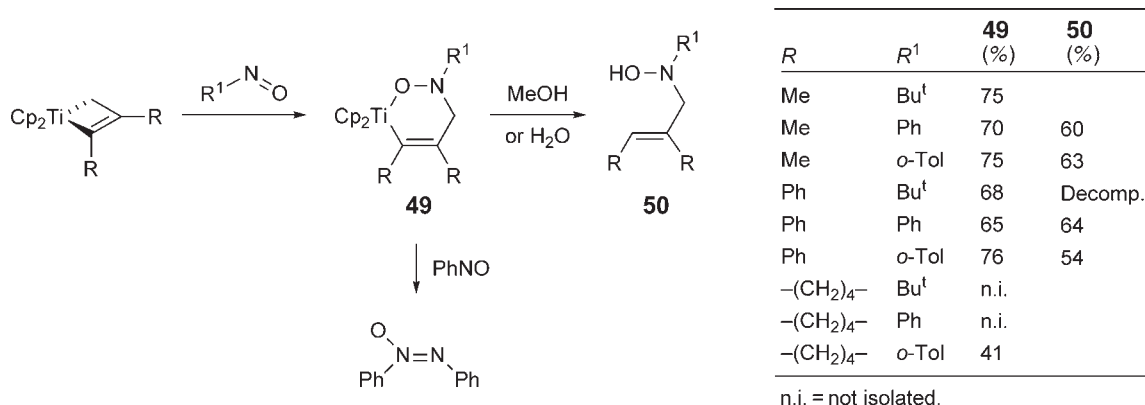
Scheme 4

In contrast to the insertion of isonitriles, nitrile insertion is limited to the early transition metals. The reactions of titanacyclobutene complexes with nitriles proceeds either by single or double insertion (Equation 14). The insertion of sterically large nitriles occurs preferentially into the Ti–C(sp³) bond, leading to the isolation of 1-aza-2-titana-3,1(6)-cyclohexadiene complexes **43**. Less bulky nitriles undergo double insertions, providing 1,3-diaza-2-titana-3,5,8-cyclooctatriene complexes **44** <1990OM3012, 1992SL13>. Importantly, the complex obtained from single insertion is not an intermediate in the formation of the product from double insertion, even under forcing conditions. Some insight into this unusual observation can be obtained from the reaction of 2,3-dimethyltitanacyclobutene **45**. Treatment with excess isopropylnitrile gives the expected product **46** from a formal double insertion. In the presence of 1 equiv of nitrile and excess trimethylphosphine, however, (butadienylimido)titanium complex **47** is isolated, trapping the intermediate from selective insertion to the vinylic Ti–C(sp²) bond (Equation 15) <1995T4321>. This strongly suggests that the mechanism for double nitrile ‘insertion’ is considerably more complicated than anticipated (Scheme 5). Finally, in a rare demonstration of synthetic organic potential, the intermediates obtained from double nitrile insertion are converted to highly substituted pyridines **48** upon treatment with HCl (Equation 16).



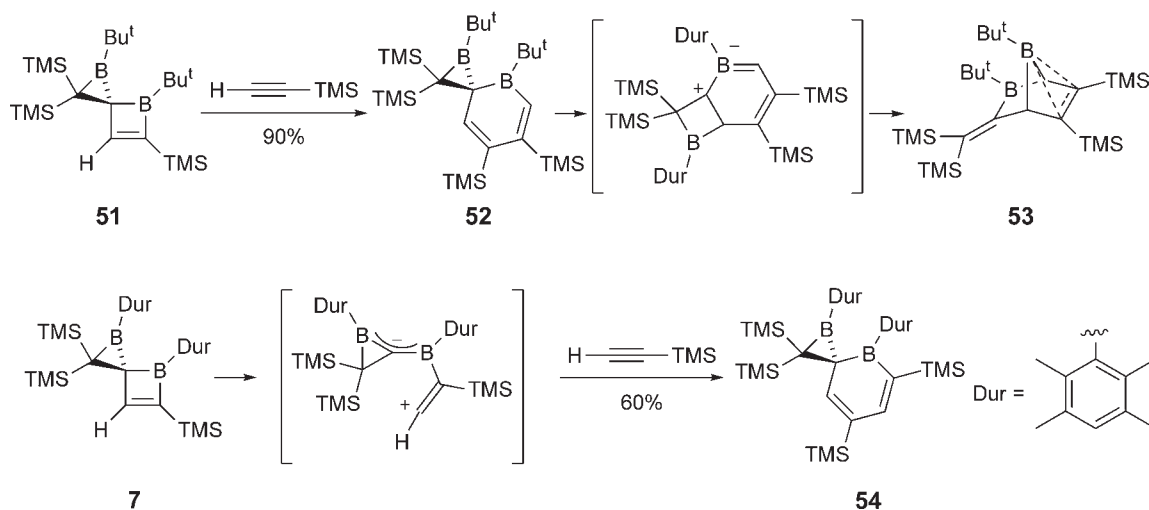


Organic nitroso compounds insert exclusively on the Ti-C(sp³) side of titanacyclobutene complexes (Scheme 6) <1994ICA305>. The 2-oxa-3-azatitanacyclohexene intermediate **49** can be hydrolyzed to the allylic hydroxylamine **50** or converted to azoxybenzene in the presence of excess nitrosobenzene, in an unusual reaction of indeterminant mechanism.



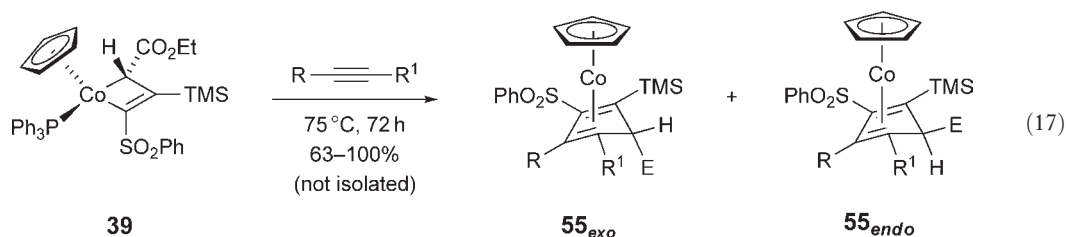
Scheme 6

The presence of a transition metal is not necessarily required for hydrocarbon insertion. Alkyne incorporation has been reported for boracyclobutenes, as well as metallacyclobutene complexes of the transition elements. Boracyclobutene **51**, a reactive intermediate prepared *in situ* (Section 2.12.9.2.1), inserts an additional equivalent of trimethylsilylacetylene into the B-C(sp²) bond to yield boracyclohexadiene **52** (Scheme 7). This isomerizes to the interesting bridged compound **53**, an analogue of a nonclassical carbocation <1994AGE2306>. The related boracyclobutene **7** inserts the alkyne to yield a persistent boracyclohexadiene **54**, but this product clearly arises from insertion into the boracyclobutene carbon-carbon bond rather than a boron-carbon bond <1994AGE1487>.

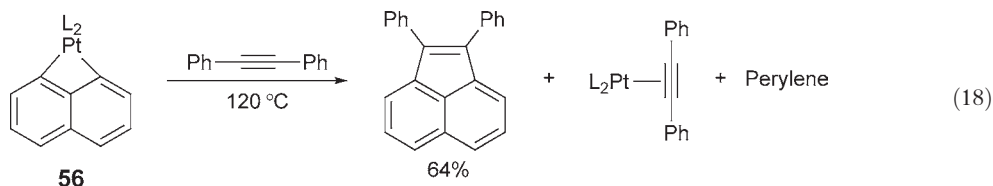


Scheme 7

Cobaltacyclobutene **39** reacts with alkynes in a net insertion/reductive elimination process to yield stereoisomeric cobalt- η^4 -cyclopentadiene complexes **55** (Equation 17) <1995JA8029>.

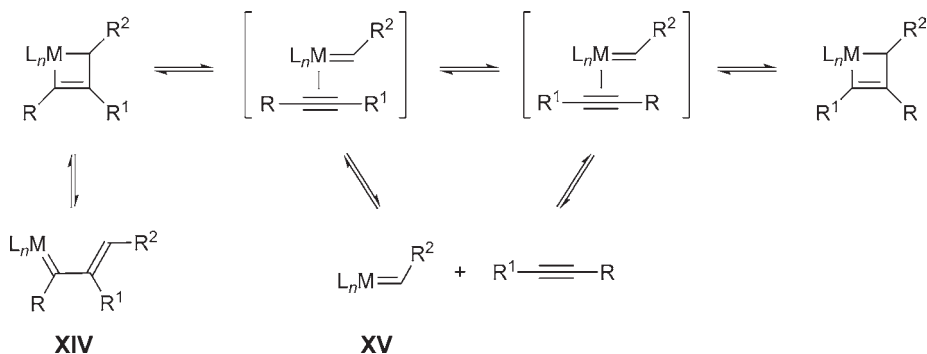


Bis(triethylphosphine)platinum[1,8]naphthalene **56** undergoes diphenylacetylene insertion and reductive elimination to yield 1,2-diphenylacenaphthalene (Equation 18) <2005JA13494>. As noted in Equation (11), an analogous zirconacyclobutene complex inserts alkyne only upon prior transmetallation to nickel.

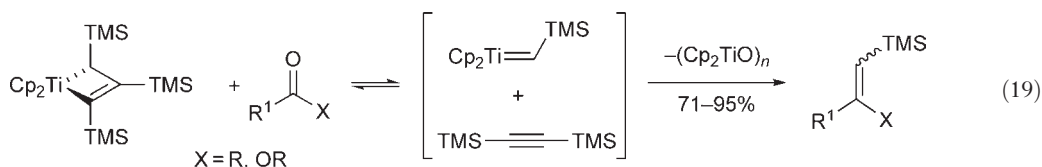


2.12.6.1.4 Cycloreversion reactions

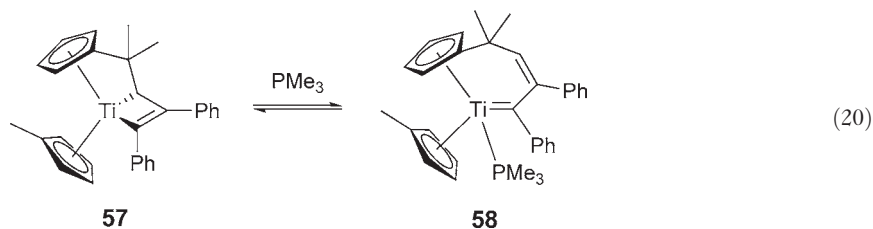
Metallacyclobutene complexes are known to undergo cycloreversion reactions to generate vinylalkylidene complex **XIV** or to liberate alkyne and give alkylidene complex **XV**, as shown in Scheme 8 <1996CHEC-II(1b)887>. This can lead to isomerization for unsymmetrically substituted systems or, in the presence of a second alkyne, generate a new metallacyclobutene complex by exchange <1996OM1176>. Alkylidene complexes from cycloreversion may be used *in situ* as Tebbe-type methylenation reagents for carbonyl compounds (Equation 19) <1996CHEC-II(1b)887, 1995TL3619>. The synthesis of allenes has been accomplished similarly, starting from titanium alkenylidene complexes <1997JOC782>.



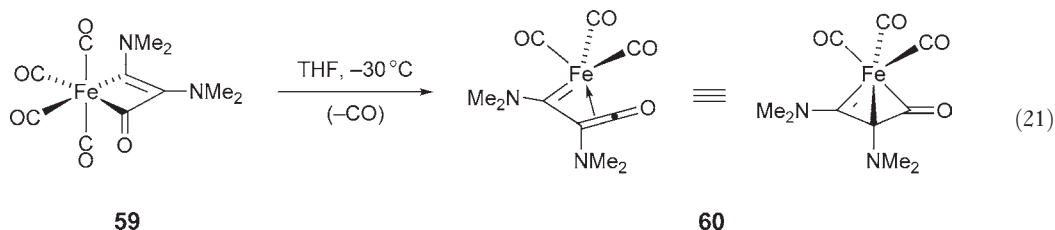
Scheme 8



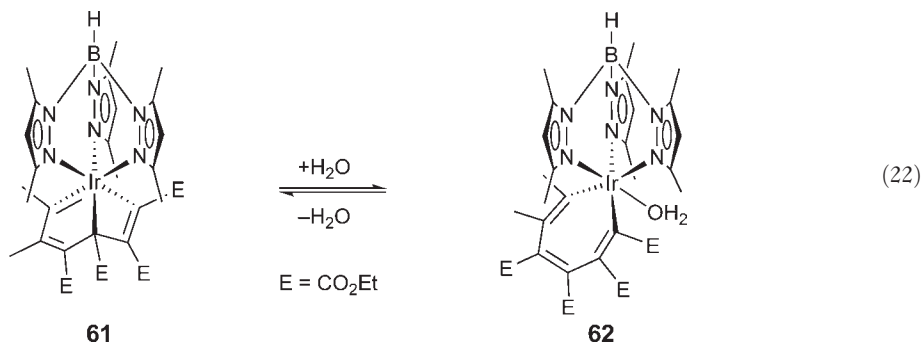
Cycloreversion to the vinylalkylidene is rarely observed directly, despite being a commonly proposed step in carbene or alkylidene/alkyne reaction cascades. Bridged titanacyclobutene complex **57**, however, clearly resists the formation of a strained internal alkylidene from alkyne extrusion, equilibrating instead with vinylalkylidene complex **58**, stabilized by the addition of trimethylphosphine (Equation 20) <2003ICA27>. This system provides a very rare simultaneous observation of interconverting metallacyclobutene and vinylalkylidene isomers.



In the late transition metals, functionalized metallacyclobutene complexes are presumed to undergo equilibrium cycloreversion to vinylcarbene intermediates of the Fischer type – the conversion is implicated in a number of vinylcarbene/alkyne cycloaddition processes related to the Dötz reaction <1998BCJ1525, 1989AGE908, 1991NJC769>. Although neither metallacyclobutene nor vinylcarbene intermediates are observed in such reactive systems, the ferracyclobutenone complex **59** converts at low temperature into η^3 -vinylcarbene complex **60** (Equation 21) <2002AGE2393>. In contrast to metallacyclobutadiene reactivity, this transformation is triggered by initial dissociation of a neutral ligand. The net conversion of metal alkylidene to η^1 - or η^3 -vinylalkylidene has been reported for the reaction of tantalum alkylidene complex $\text{CpCl}_2\text{Ta}=\text{CHCMe}_3$ with diphenylacetylene <1979JA3210> and for the reaction of Grubbs' second-generation metathesis catalyst $\text{IMes}(\text{Cy}_3\text{P})\text{Cl}_2\text{Ru}=\text{CHPh}$ with internal alkynes <2001OM3845>, both of which almost certainly proceed via a coordinatively unsaturated metallacyclobutene intermediate.



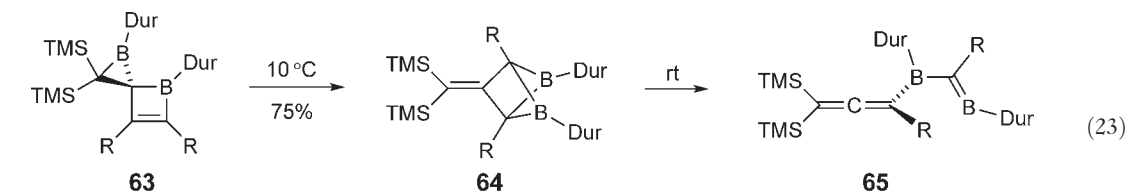
Bicyclic iridacyclobutene-containing complex **61** transforms into an iridacycloheptatriene **62** complex upon coordination of a water molecule (Equation 22), a reaction that can be interpreted as a cycloreversion, but is more readily visualized as a valence tautomerization of the five-membered iridacyclic alkylidene fragment <2004JA1610>.



2.12.6.1.5 Structural isomerization and rearrangement

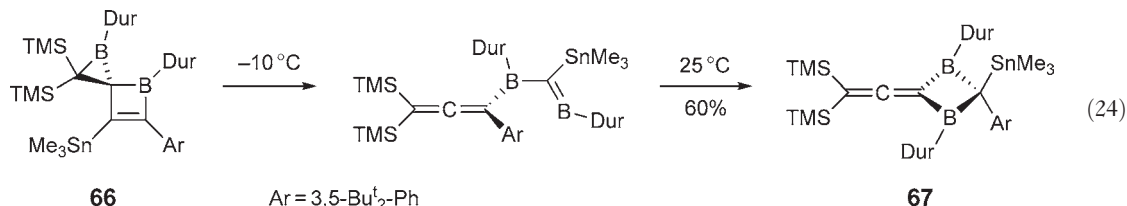
The highly strained spirobicyclic boracyclobutene **63** isomerizes at 10 °C to an isolable diborabicyclo[1,1,1]pentane **64**, which undergoes a further cycloreversion reaction at room temperature, ultimately providing the structurally fascinating diboryl allene **65** (Equation 23) <1995AGE657, 1995AGE1340>. Stannylated boracyclobutene **66** reacts

similarly, but proceeds further at room temperature to allenyl-1,3-diboracyclobutane **67** via an extensive rearrangement of undetermined mechanism (Equation 24). The diboryllallene moiety exhibits a very low barrier to rotation about the allene double bond carbon <1994AGE2064>.



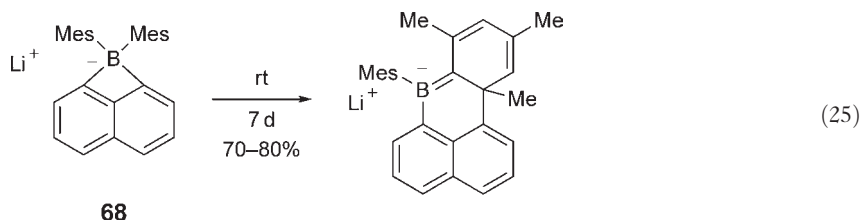
Dur = 2,3,5,6-tetramethylphenyl

R = Me, Et, Prⁿ



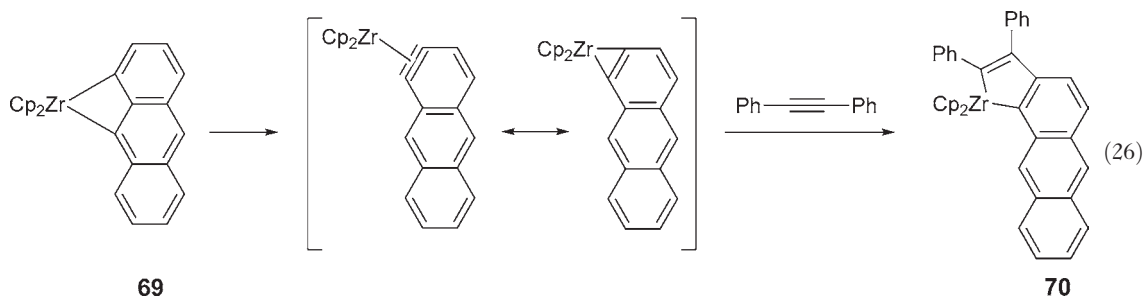
Ar = 3,5-Bu^t₂-Ph

Over 7 days at room temperature, the anionic dimesityl-1,8-naphthalenediylborate **68** undergoes ring expansion to the tetracyclic borataalkene, via an apparent 1,3-aryl shift (Equation 25) <2004JCD1254>.



2.12.6.1.6 β -Hydrogen elimination

Zirconocene 1,9-anthracenediyl complex **69** presumably undergoes rearrangement to an isomeric benzyne complex prior to the insertion of external alkyne (Equation 26). The isomerization can be understood as a β -hydrogen elimination/reductive elimination process, resulting in a formal reduction to Zr(II), followed by a typical alkyne/alkyne oxidative cyclization to the observed zirconacyclopentadiene product **70**. The coordinated benzyne intermediate can be observed spectroscopically as a trimethylphosphine adduct <2000JA9880>.



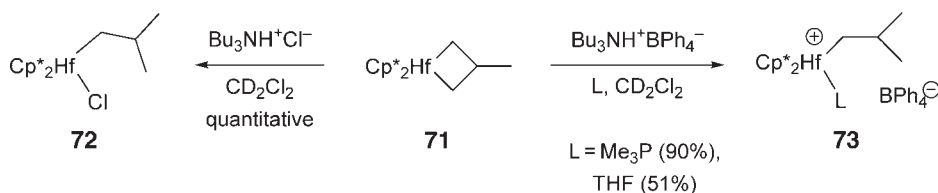
2.12.6.2 Reactivity of Boracyclobutanes and Metallacyclobutanes

Olefin metathesis provides the principal synthetic context for metallacyclobutane reactivity; this catalytic reaction proceeds by the transient, and reversible, formation of a metallacyclobutane intermediate from a metal alkylidene and an alkene. The olefin metathesis reaction has been exhaustively reviewed and is not directly discussed here

<1995ACR446, 2003AGE1900, 2004T7117, 2005NJC42, B-2003MI1>. Nonetheless, the [2+2] cycloaddition/cycloreversion reaction characteristic of the olefin metathesis remains pertinent to much of metallacyclobutane reactivity; relevant recent investigations comprise Section 2.12.6.2.4. A range of other reactivity patterns have also been determined for metallacyclobutane complexes, some complementary to metallacyclobutene reactivity, some unique to saturated ring systems.

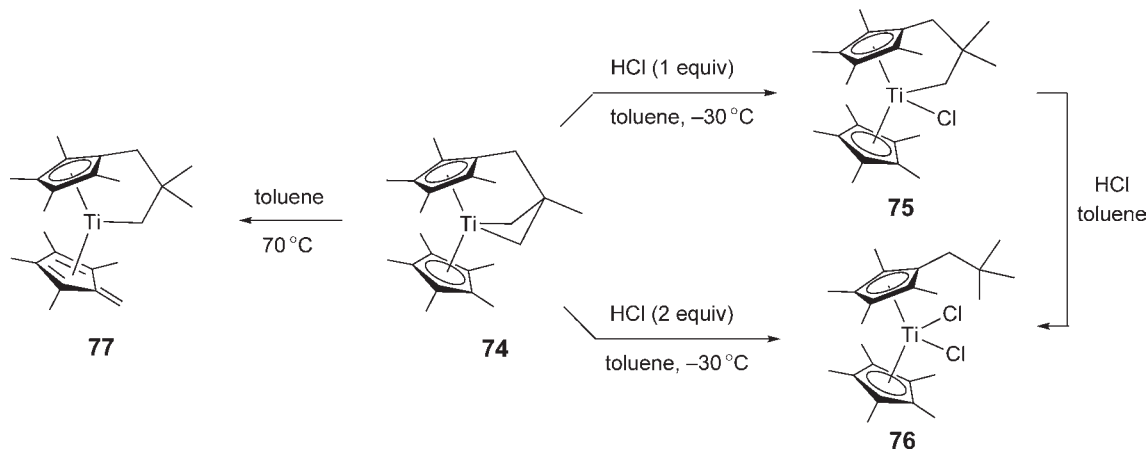
2.12.6.2.1 Reactions with acidic compounds

The reactions of protic electrophiles with metallacyclobutane complexes are generally analogous to the protonolysis reactions of metallacyclobutene complexes. The reaction of hafnacyclobutane complex **71** with 1 equiv of $[\text{Bu}_3\text{NH}]\text{Cl}$, for example, selectively cleaves one metal–carbon bond to give chlorohafnium alkyl complex **72**; with a noncoordinating counterion and a donor ligand, the reaction proceeds to the cationic hafnium alkyl complex **73** (Scheme 9) <1994OM1424>.



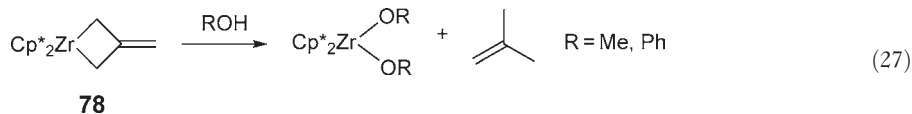
Scheme 9

Similarly, tethered titanacyclobutane complex **74** also undergoes protonolysis with 1 and 2 equiv of HCl in toluene to give alkyltitanium chloride **75** and titanocene dichloride **76**, respectively, in excellent yield (Scheme 10). Titanacyclobutane complex **74** can undergo also intramolecular proton transfer from one of the ligand methyl groups, presumably via a σ -bond metathesis, to give the η^6 -tetramethylfulvene alkyl complex **77** <1995OM5481>.



Scheme 10

Less acidic proton sources are also reactive, particularly toward the more polarized metal–carbon bonds of the early transition elements. Zirconacyclobutane complex **78** is protonated by methanol or phenol to form the dialkoxyzirconocene complex concomitant with the release of isobutene (Equation 27) <1994AGE2465>.

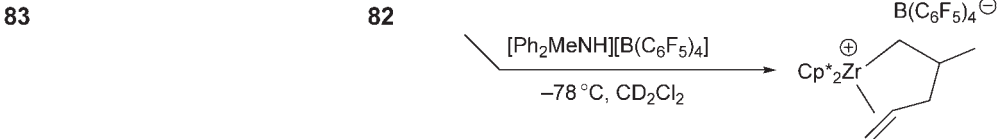


intermediate, which is more reactive toward protonation [<1994JOM179>](#).

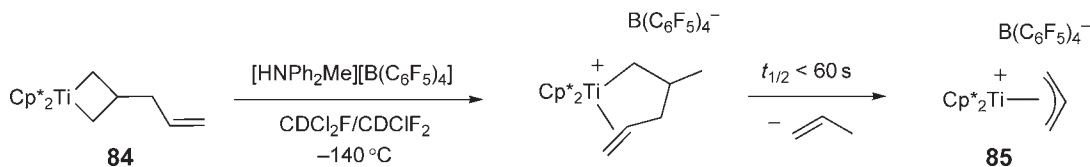


Scheme 11

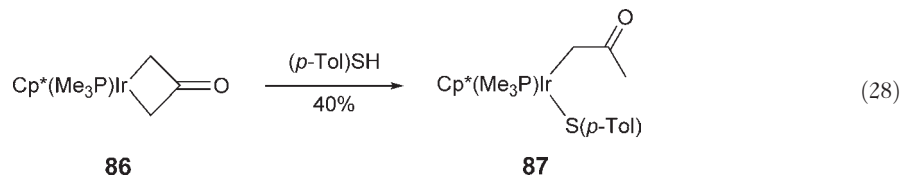
scenarios for both metallocene and Ziegler–Natta polymerization catalysts <2003ICC1287>.



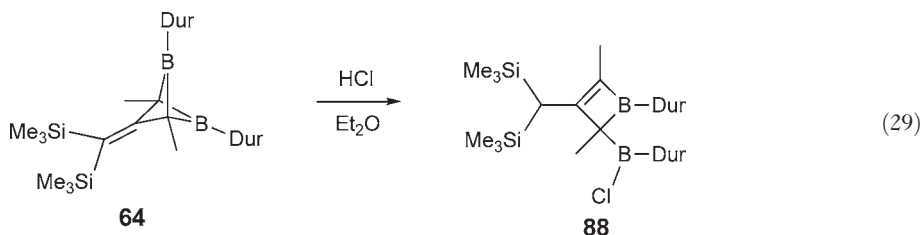
Scheme 12



Similar, albeit slower, reactions prevail in the later transition metals. The carbonyl oxygen of 3-metallacyclobutane complexes is the typical site for protonation rather than the less polarized metal–carbon bond (Section 2.12.7). The reaction of iridacyclobutanone complex **86** with *p*-toluenethiol, however, returns the carbon-bound iridium enolate complex **87** by eventual protonation of one Ir–C bond (Equation 28) <1995JOM143>.



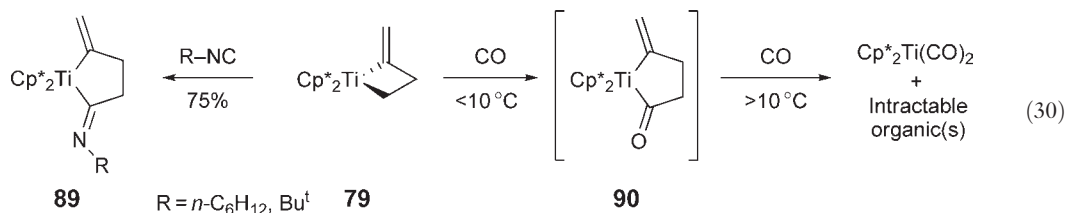
Finally, returning to the main group series, the diborapropellane **64** (R = Me) reacts with hydrochloric acid to give boracyclobutene **88** (Equation 29), presumably by initial protonation of the alkene to generate the β -silyl-stabilized carbocation <1999AGE2936>.



2.12.6.2.2 Insertion reactions

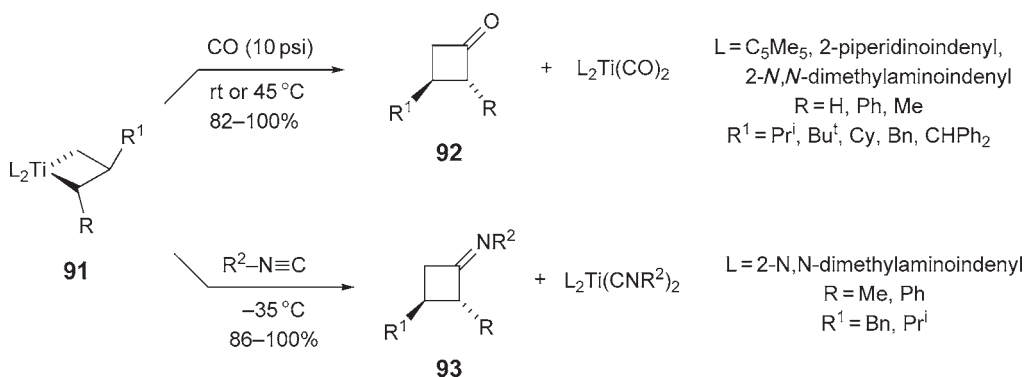
Migratory insertion of unsaturated small molecules into the metal–carbon bond(s) of metallacyclobutane complexes is reasonably general for polar reactants and reactive first-row transition elements, as well as for the other early transition metals. At least conceptually, this provides a pathway for the introduction of external organic components, with transformation of the metallacyclobutane into a range of functionalized organic products. Although some progress can be reported in the development of synthetic organic methodology, this area remains seriously underdeveloped. There is, however, enormous potential for further advancement.

Among fundamental reaction processes, the regioselective incorporation of carbon monoxide and isonitriles into the $\text{C}(\text{sp}^3)\text{--Ti}$ bond of α -methylenetitanacyclobutane complexes **79** has been reported, although the initial carbonylation product **90** decomposes unproductively above 10 °C (Equation 30) <1993JOM181>.

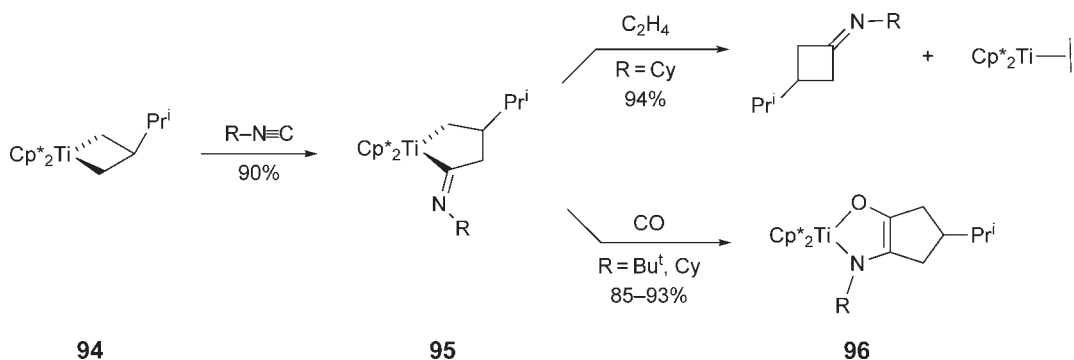


More interesting synthetically is isonitrile incorporation and carbonylation of a range of substituted titanacyclobutanes **91** formed by radical alkylation of allyltitanium(III) precursors (Section 2.12.9.3.4). In this way, an unusual but efficient [3+1] strategy for the construction of stereochemically pure cyclobutanones and cyclobutanimes has been realized (Scheme 13). Alkyl-substituted titanacyclobutanes undergo carbonylation and reductive cyclization at or above room temperature under low CO pressure to yield *trans*-disubstituted cyclobutanones **92** in excellent yield <2001JA8872>. The titanium is recovered as the bis(carbonyl)titanium(II) complex, which can be reused in the synthetic sequence. Alternatively, isonitrile insertion provides the analogous organic iminocyclobutanes **93** and the corresponding bis(isonitrile)titanium(II) complexes in excellent yield <2002OM1011>.

The use of the permethyltitanocene template **94** (Scheme 14) allows for the isolation of the intermediate iminoacyl complex **95**, which was not observed in reactions using the substituted bis(indenyl)titanocene.



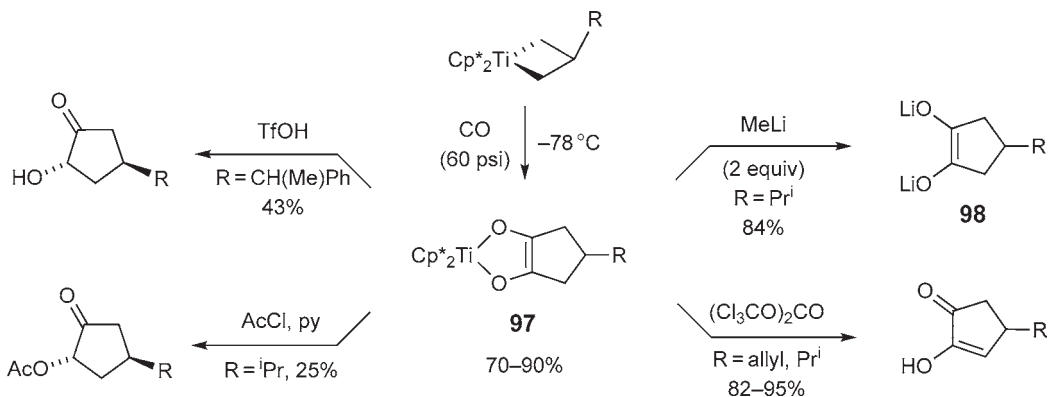
Scheme 13



Scheme 14

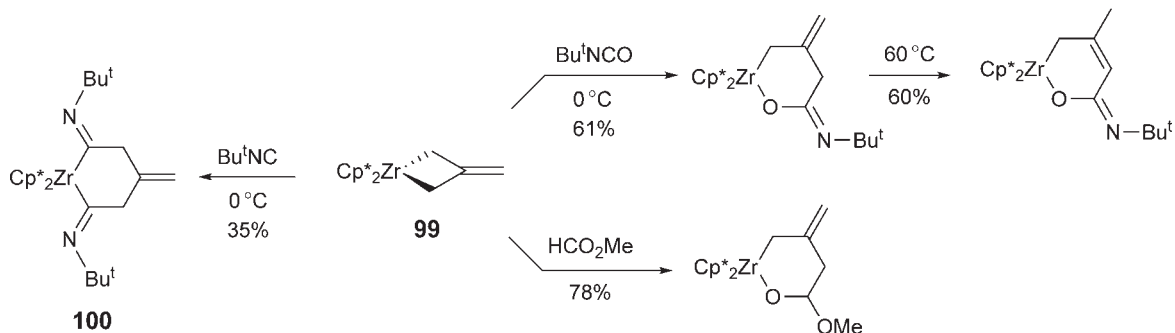
Reductive cyclization to release the cyclobutanimine is induced by the addition of a coordinating π -acidic ligand, whereas exposure to carbon monoxide promotes a second insertion to yield titanium cyclopentenamidate complexes **96** <2002OM1011>.

Under higher CO pressure and lower temperature, the permethyltitanocene complexes undergo the double carbonylation/reductive coupling process known as the Bercaw reaction (Scheme 15) <2001SL1046>. The resulting titanium cyclopentenenediolate complexes **97** can be further converted to a range of organic cyclopentane derivatives or transmetalated to give lithium enediolates **98**, opening a considerable range of further synthetic transformations. The double carbonylation can also be applied to zirconacyclobutane complexes <1993JA2083>. In the late metals, rhodacyclobutanes also undergo carbon monoxide and isonitrile insertion; with the latter, both single- and double-insertion products could be obtained <1998OM4484>.



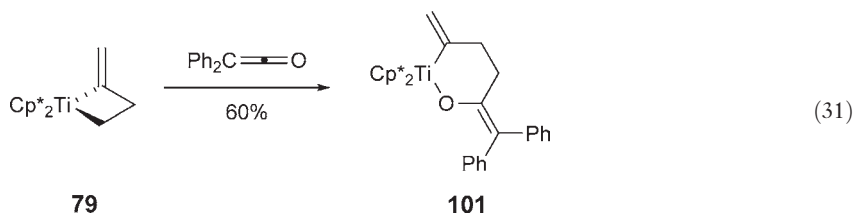
Scheme 15

β -Methylenezirconacyclobutane complex **99** undergoes double isonitrile insertion, but not reductive carbon–carbon bond formation, yielding the bis(iminoacyl) complex **100** (Scheme 16) <1994AGE2465>. Single insertion is observed using *tert*-butylisocyanate or methyl formate.

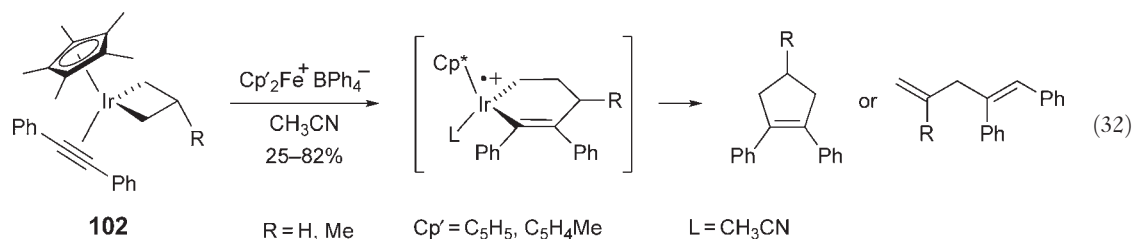


Scheme 16

Other metallacyclobutane derivatives demonstrate similar two-atom carbonyl insertion reactions, as previously reviewed in CHEC-II(1996) <1996CHEC-II(1b)887>. The insertion of diphenylketene occurs exclusively into the $\text{C}(\text{sp}^3)\text{--Ti}$ bond of α -methyleneitanacyclobutane complex **79** to give oxatitanacyclohexane **101** (Equation 31) <1993JOM181>. In contrast, no reaction was observed using carbon dioxide or arylisocyanate at room temperature (see Section 2.12.6.2.4).



Metallacyclobutanes of the late transition metals strongly resist the insertion of unsaturated hydrocarbons. Migratory insertion of a coordinated alkyne into iridacyclobutane complexes **102**, however, can be induced by one-electron oxidation (Equation 32) <1994JA11570>. The product distribution, remarkably, is controlled by the potential of the oxidant, with $(\text{C}_5\text{H}_5)_2\text{Fe}^+\text{BPh}_4^-$ promoting the high yield formation of cyclopentene products from insertion/reductive elimination. In contrast, the use of $(\text{C}_5\text{H}_4\text{Me})_2\text{Fe}^+\text{BPh}_4^-$ leads to the formation of the acyclic diene (in much lower yield) from a post-insertion β -hydride elimination. Thus, the oxidant not only lowers the barrier to migratory insertion, but also controls the subsequent reaction pathway by modulating the rate of back-reduction of the intermediate iridacyclohexene radical cation.



2.12.6.2.3 Cyclopropanation

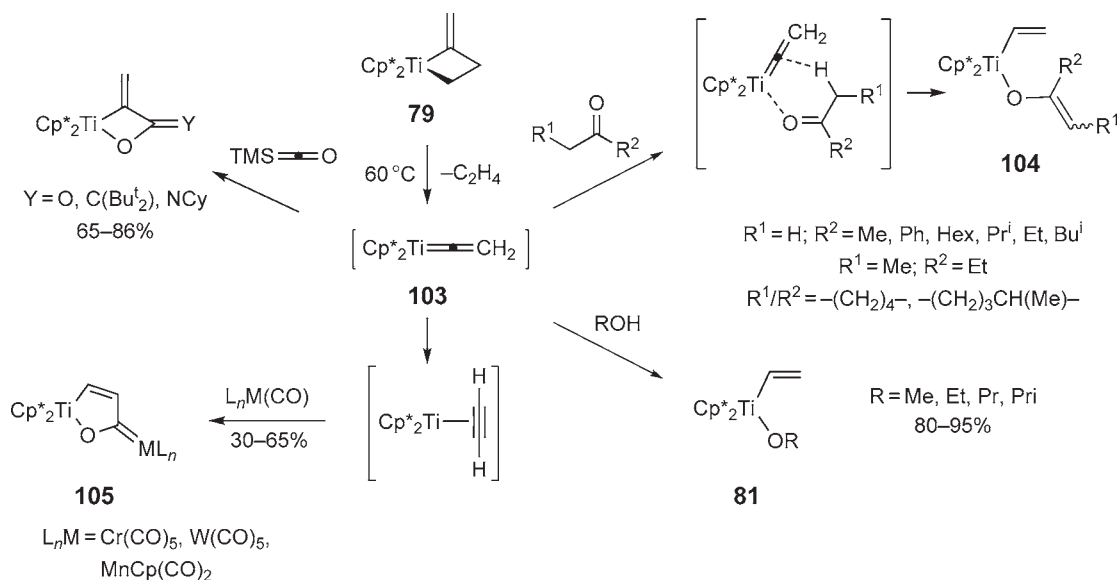
Reductive elimination of metallacyclobutanes results in the formation of cyclopropanes; recent examples are compiled in Table 8. Cyclopropane formation is observed throughout the transition series, typically induced by thermolysis or oxidation, depending on the metal.

Table 8 Reductive formation of cyclopropanes from metallacyclobutane complexes

$\text{L}_n\text{M} \begin{array}{c} \diagup \diagdown \\ \diagdown \diagup \end{array} \xrightarrow{\text{reagent or additive}} \begin{array}{c} \diagup \diagdown \\ \diagdown \diagup \end{array} \text{R}$					
<i>Metallacyclobutane</i>	<i>Reagent/additive</i>	<i>Conditions</i>	<i>Organic product</i>	<i>Yield</i>	<i>Reference</i>
	None	C ₆ D ₆ , 22 °C		Quantitative	2004JA10554
	CO	CH ₂ Cl ₂ , rt		Unspecified	1995AGE100
	AgOTf	CDCl ₃ , 2 h, -78 °C → rt		Quantitative	1993JA2083
	Et—≡—Et	80 °C, 5 d		Unspecified	2002JOM288

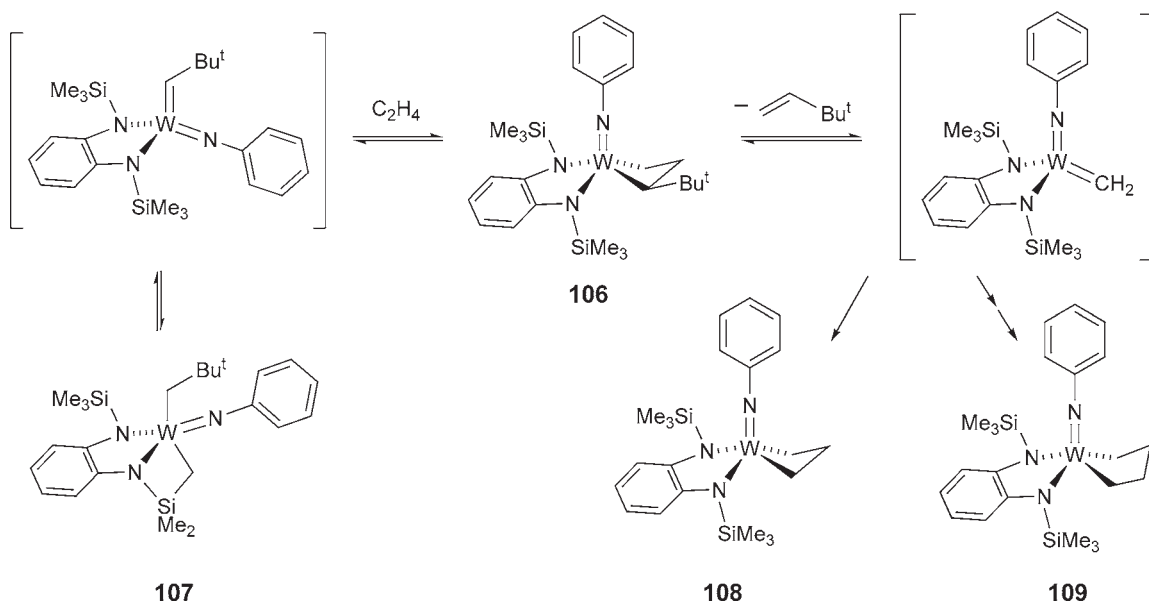
2.12.6.2.4 Cycloreversion

Equilibrium cycloreversion of metallacyclobutane complexes to alkylidene intermediates is similar to that of metallacyclobutene complexes (Section 2.12.6.1.3). Metallacyclobutane complexes thus provide convenient progenitors of reactive alkylidene intermediates. The α -methylene-titanacyclobutane complex **79** decomposes into the vinylidene intermediate **103** (Scheme 17), which manifests nucleophilic character at the α -carbon, consistent with

**Scheme 17**

other early metal alkylidenes and in contrast to the electrophilic character exhibited by most late transition metal vinylidene ligands. Confirming the experimental observations, a theoretical investigation of α -methylenetitanacyclobutane and α -methylenetitanacyclobutene stability found that cycloreversion is the dominant reactivity pattern for such systems <2003JOM75>. The vinylidene intermediate thus generated reacts with ketones to yield titanium enolate complexes **104** via protonation at the vinylidene carbon <1994JOM155>. Similar reactivity is obtained from reactions with alcohols, although the product vinyl alkoxides **81** were only characterized spectroscopically <1994JOM179>. Nucleophilic [2+2] cycloaddition reactions are observed from the addition of carbon dioxide, ketenes, and isocyanates. The vinylidene intermediates also react with group 6 and 7 metal carbonyl complexes, unexpectedly resulting in the formation of binuclear Fischer carbene complexes **105**. The reaction has been rationalized in terms of a vinylidene-to-ethyne isomerization, followed by a two-component oxidative coupling with a coordinated carbonyl, which can be considered in its metallaketene canonical <1993AGE264>.

Metallacyclobutane cycloreversion is fundamental to the mechanism of the olefin metathesis reaction and has been the subject of considerable investigation, particularly with respect to the design of robust catalysts with improved resistance to deactivation. Substituted tungstacyclobutane complex **106**, for example, reveals different decomposition pathways for each of the two cycloreversion modes (Scheme 18) <1998OM2628>. Equilibrium extrusion of ethylene leads to cyclometallation of a proximal trimethylsilyl substituent to give the interesting azatungstacyclobutane complex **107**, while loss of *tert*-butylethylene leads ultimately to tungstacyclobutane and tungstacyclopentane complexes **108** and **109**, which presumably arise from the formation and subsequent reaction of ethylene with, respectively, the expected alkylidene intermediate and with an elusive W(IV) reaction product.

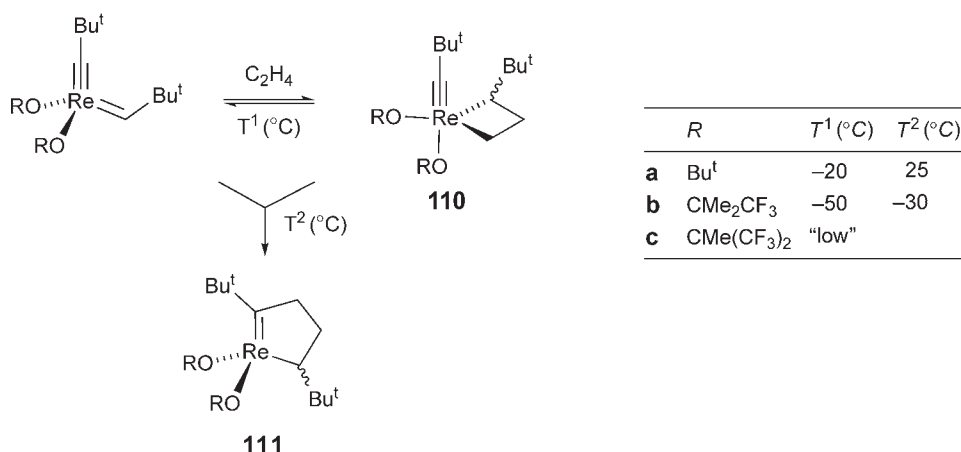


Scheme 18

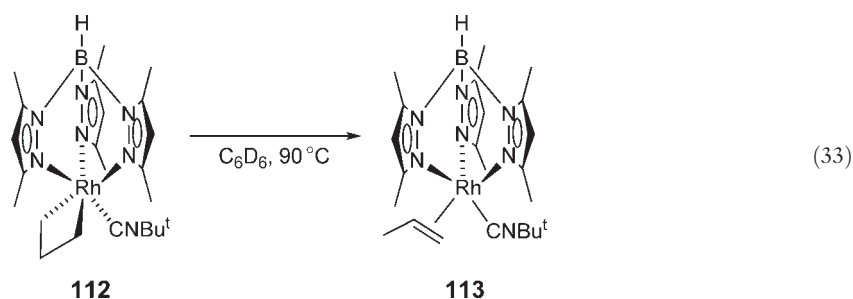
Rhenacyclobutane complexes **110** can be synthesized by the [2+2] cycloaddition of ethylene with rhenium alkylidene complexes at low temperatures (Scheme 19) <1993JA2980>. However, even at low temperature, the alkylidene and rhenacyclobutane complexes combine to yield the rhenacyclic alkylidene **111** by an indeterminate mechanism. At room temperature, the most electron-deficient rhenacyclobutane **110c** extrudes ethylene and reverts to the corresponding alkylidene complex.

2.12.6.2.5 β -Hydrogen elimination

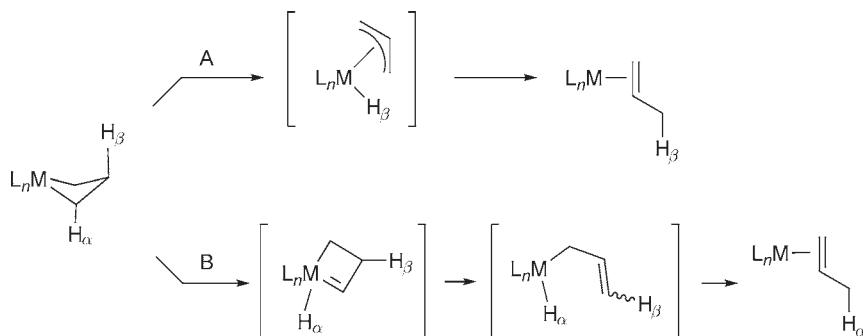
Metallacyclobutane complexes can undergo net reductive rearrangement to form alkene complexes or undergo decomposition with the liberation of free alkene. The rhodacyclobutane complex **112**, for example, rearranges thermally to give propene complex **113** (Equation 33) <1998OM4484>.



Scheme 19



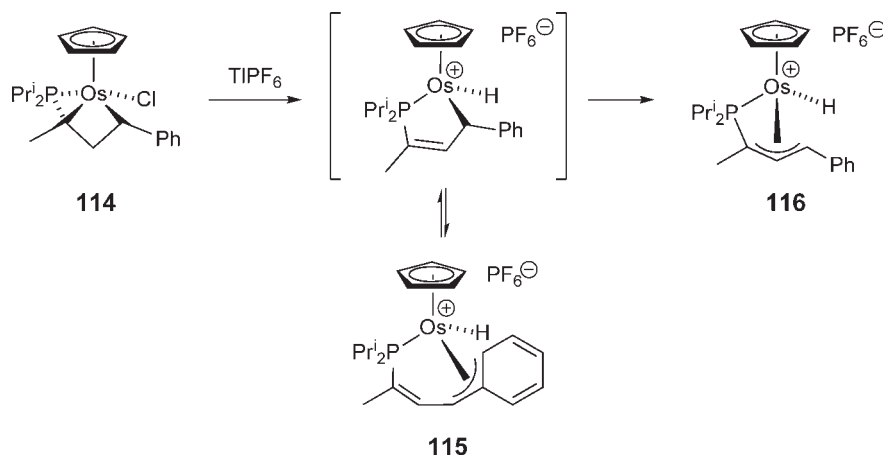
The mechanism of this general rearrangement has long been controversial, although most rationales invoke an initial β -hydride elimination. The β -hydrogen elimination, however, is a concerted reaction requiring a nearly coplanar arrangement of atoms in the cyclic four-centered transition state. This is clearly a problem for the constrained (but conformationally nonrigid) metallacyclobutane ring. Nonetheless, circumstantial evidence suggests that this process does not suffer a prohibitively high activation barrier, at least in some systems. The β -elimination pathway also provides the conceptually most simple pathway, proceeding via the allyl hydride intermediate to the alkene complex by reductive elimination (Scheme 20, path A). For platinacyclobutane isomerization, however, an alternative mechanism involving initial α -hydrogen elimination was established through a series of deuterium labeling experiments <1982CC412, 1986OM1312>. In this pathway, the hydrido alkylidene intermediate is converted to the alkene via subsequent 1,2-hydride migration (Scheme 20, path B). That said, allyl hydride intermediates suggestive of the β -hydride elimination mechanism have occasionally, if rarely, been observed.



Scheme 20

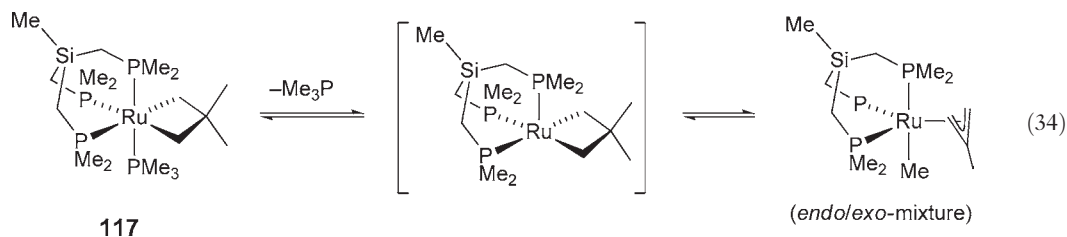
Regardless of the mechanism, recent reports confirm the generality of the metallacyclobutane isomerization <1995OM1278, 2004OM1997, 2004JA14332>. In addition, it has been reported that during the preparation of the Negishi reagent, Cp_2ZrBu_2 decomposes to the intermediate 2-methylzirconacyclobutane complex, which undergoes β -hydrogen elimination to form the zirconocene allyl hydride complex <1997OM1452>. A theoretical study of the decomposition of ruthenacyclobutane intermediates generated from the Grubbs' second-generation metathesis catalyst <2004JA14332> and the investigation of kinetic isotope effects in the decomposition of an osmacyclobutane complex <1992ICA57> both suggest that the straightforward β -hydrogen elimination is a reasonable reaction pathway.

Allyl hydride complexes of osmium are isolated from treatment of phosphine-substituted osmacyclobutane complex **114** with a thallium salt (Scheme 21). The reaction initially provides a mixture of an unstable η^3 -benzyl hydride complex **115** and the η^3 -allyl hydride complex **116**; the η^3 -benzyl intermediate ultimately isomerizes to the latter complex, a very rare instance of isolable allylic hydride products generated from a starting metallacyclobutane <2004OM4858>.



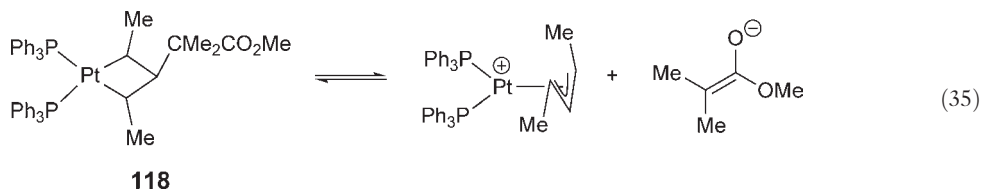
Scheme 21

A mechanistically similar, yet considerably less common, β -methyl elimination occurs in the rearrangement of 3,3-dimethylruthenacyclobutane complex **117** (Equation 34) <1995JA3625, 1997JA11244>. The reaction proceeds via reversible initial phosphine dissociation.



Platinacyclobutane complex **118** undergoes equilibrium heterolytic scission of the exocyclic carbon–carbon bond to form a cationic allyl complex and the organic enolate ion (Equation 35) <1993OM3019>. Similar dissociative ionization was previously reported for rearrangements of iridium and rhodium metallacyclobutane complexes formed by nucleophilic alkylation <1990JA6420>. This carbon–carbon bond activation is generally associated with reversible central carbon alkylation of π -allyl complexes (Section 2.12.9.3.3), but the homolytic equivalent has recently been

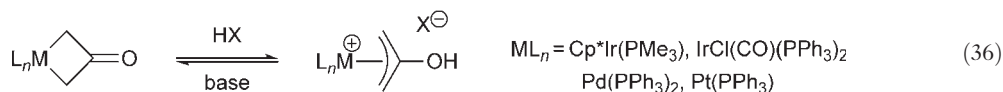
noted in the dealkylation of β -substituted titanacyclobutane complexes bearing a radical stabilizing β -substituent, reversibly generating the corresponding titanium(III) allyl complex <2001JA8872>.



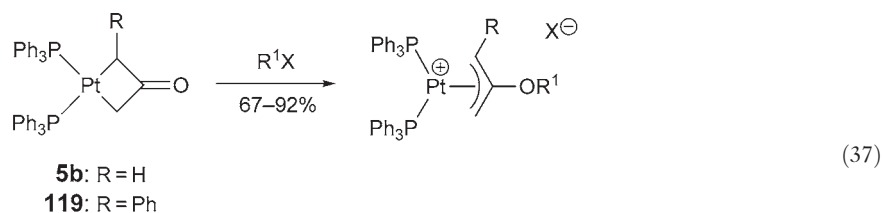
2.12.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Given that the investigation of four-membered ring boracycles and metallacycles remains relatively immature, it is unsurprising that the exploration of peripheral substituent reactivity remains in its infancy. The intrinsic challenges to this endeavor are significant. All small ring metallacycles incorporate two reactive metal–carbon bonds, some highly so – chemoselectivity issues, in particular, loom ominously. As a consequence, it is reasonable that research in this area has thus far focused exclusively on the late transition metals, where the relatively nonpolar metal–carbon bonds allow some latitude in the range of methodology compatible with selective reaction at peripheral sites.

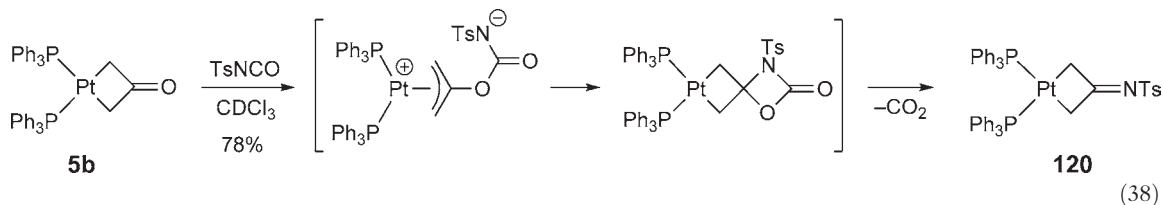
The reactions of protic acids and other electrophiles at remote Lewis basic functionality have been investigated as a pathway to both transformations and interconversions of carbonyl-substituted metallacycles. Irida-, pallada-, and platinacyclobutanones react reversibly with protic acid to yield η^3 -2-hydroxyallyl complexes (Equation 36), modulating between metallacyclobutane and hydroxyallyl structures (and further discussed in Section 2.12.9.3.5) <1993CC1039, 1995JOM143, 1997OM1159>.



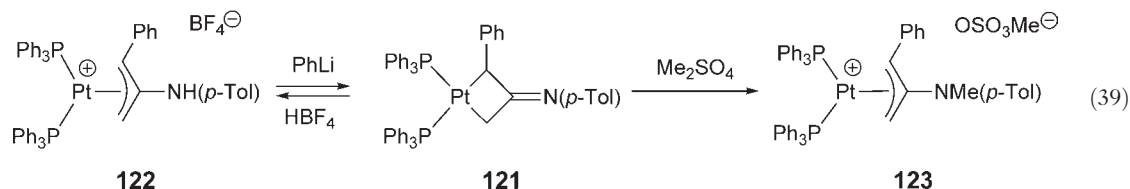
Metallacyclobutanone complexes also undergo electrophilic alkylation on the carbonyl oxygen. 2-Alkoxy-, acyloxy-, and silyoxyallyl platinum complexes are obtained in high yield from the reactions of platinacyclobutanone complexes **5b** and **119** with a range of standard electrophiles (Equation 37) <1994ICA1, 1997OM822>. Platinacyclobutanone complex **5b** also reacts with isocyanate to form the azatrimethylenemethane (ATMM) complex **120** by electrophilic addition followed by nucleophilic exchange and irreversible release of carbon dioxide (Equation 38) <1994JA4125>.



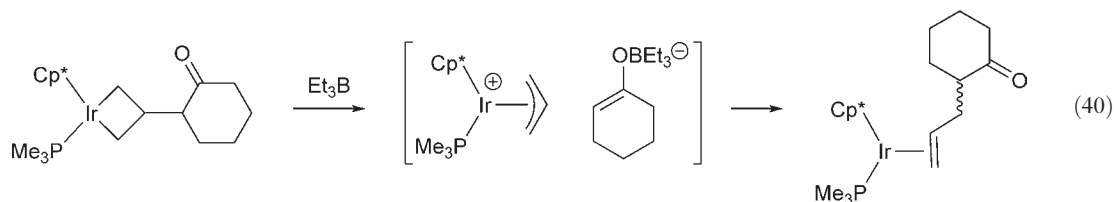
R = H, R¹X = TMSOTf, Ph₃C⁺BF₄[−], EtI, iPrI, CH₂=CHCH₂Br, MeC(O)Br, PhC(O)Br
R = Ph, R¹X = Et₃O⁺PF₆[−] (yield: quantitative)



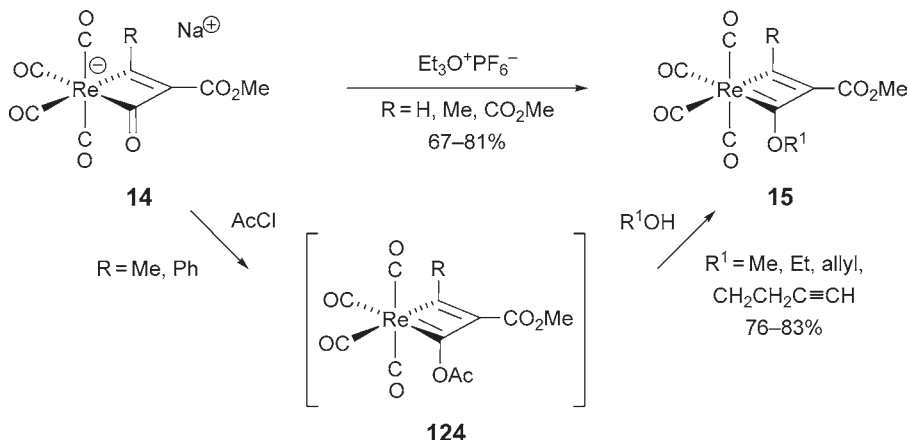
ATMM complex **121** reacts analogously, protonating and alkylating at nitrogen to form β -aminoallyl complexes **122** and **123**, respectively <1994ICA1>. The aminoallyl complex **122** can be deprotonated, regenerating the ATMM complex (Equation 39).



Lewis acids can be used to induce the rearrangement of iridacyclobutane complexes formed by central carbon alkylation of cationic π -allyl precursors with organic enolates (Section 2.12.9.3.3). The reaction, which presumably proceeds by Lewis acid coordination to the remote carbonyl functionality and release of the boron enolate, cleanly provides the thermodynamically more stable terminal carbon adducts (Equation 40) <1990JA6420>.

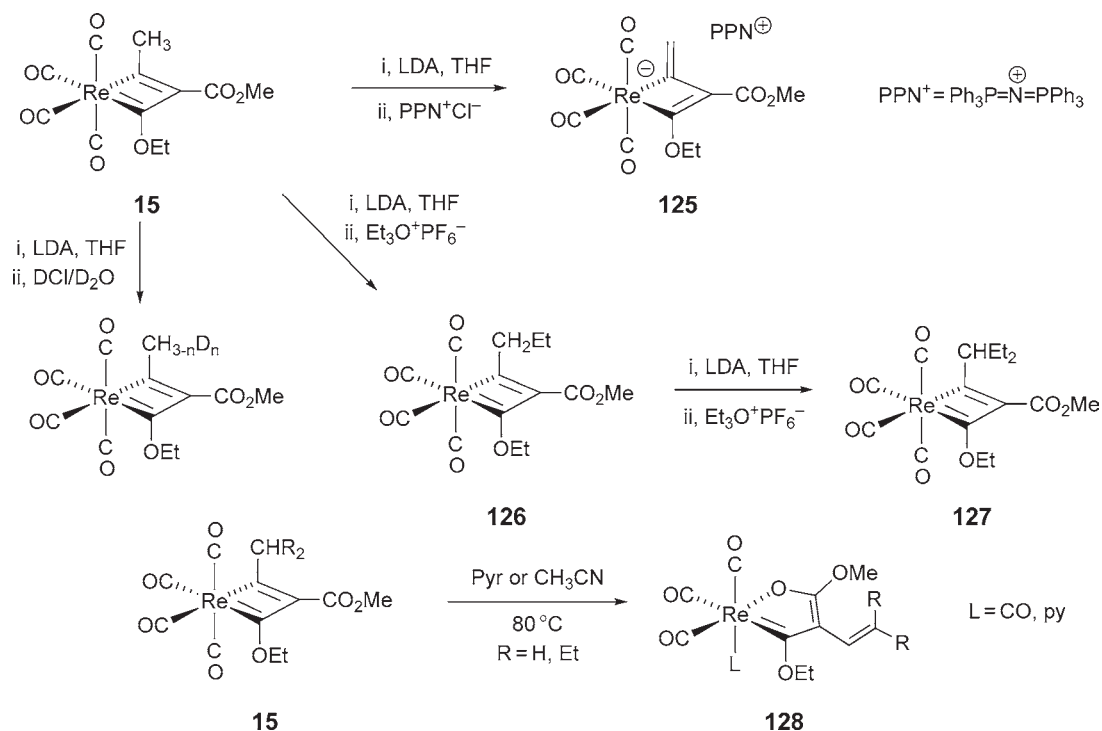


Carbonyl functionality in the 2-position of a metallacycle is conjugated to the metal via $d\pi$ - $p\pi$ orbital overlap. For late transition metals in low oxidation states, significant electron density is delocalized into the acyl group, enhancing the basicity of the oxygen. Thus, 2-rhenacyclobutenones **14** react with hard carbon electrophiles such as $\text{Et}_3\text{O}^+\text{PF}_6^-$ to form 2-alkoxyrhenacyclobutadienes **15** (Scheme 22), but no reaction is observed with softer electrophiles such as methyl iodide <1993JA9986>. For alkyl electrophiles not readily obtained as Meerwein salts, the acetoxyrhenacyclobutadiene complex **124**, prepared by treatment with acetyl chloride, is converted to the 2-alkoxyrhenacyclobutadiene by nucleophilic displacement using a range of primary alcohols <2004JOM2000>.



Scheme 22

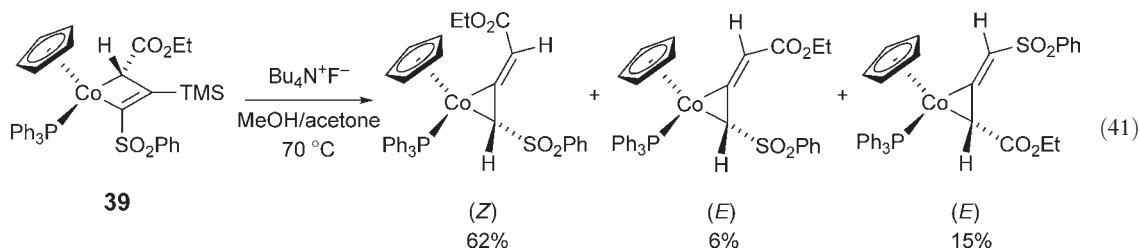
In the rhenacyclobutadiene series, conjugation also acidifies adjacent allylic positions. Kinetic deprotonation of the 2-methyl-4-ethoxyrhenacyclobutadiene complex (**15**: $\text{R} = \text{Me}$, $\text{R}' = \text{Et}$) with lithium diisopropylamide at low temperature gives the exomethylene-substituted rhenacyclobutene anion **125**, which undergoes alkylation with electrophilic reagents to elaborate the rhenacyclobutadiene ring (e.g., **126**, Scheme 23) <2004JOM2000>. The alkylation with Meerwein's salt can be conducted iteratively, giving double alkylation product **127**.



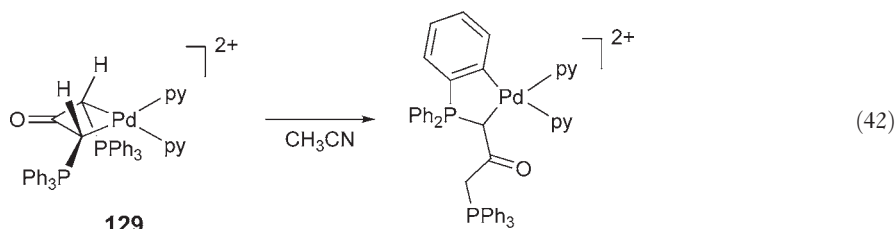
Scheme 23

Deprotonation with a weak thermodynamic base, such as pyridine or even acetonitrile at elevated temperature, leads to skeletal rearrangement, giving the 2-oxa-rhenacyclopentadiene complex **128** <2004JOM2013>.

Among unique transformations on the metallacyclobutene framework, allene complexes of cobalt can be prepared by fluoride-induced desilylation of cobaltacyclobutene complex **39**; three isomeric complexes bearing the same disubstituted allene are obtained (Equation 41) <1998JA1100>.

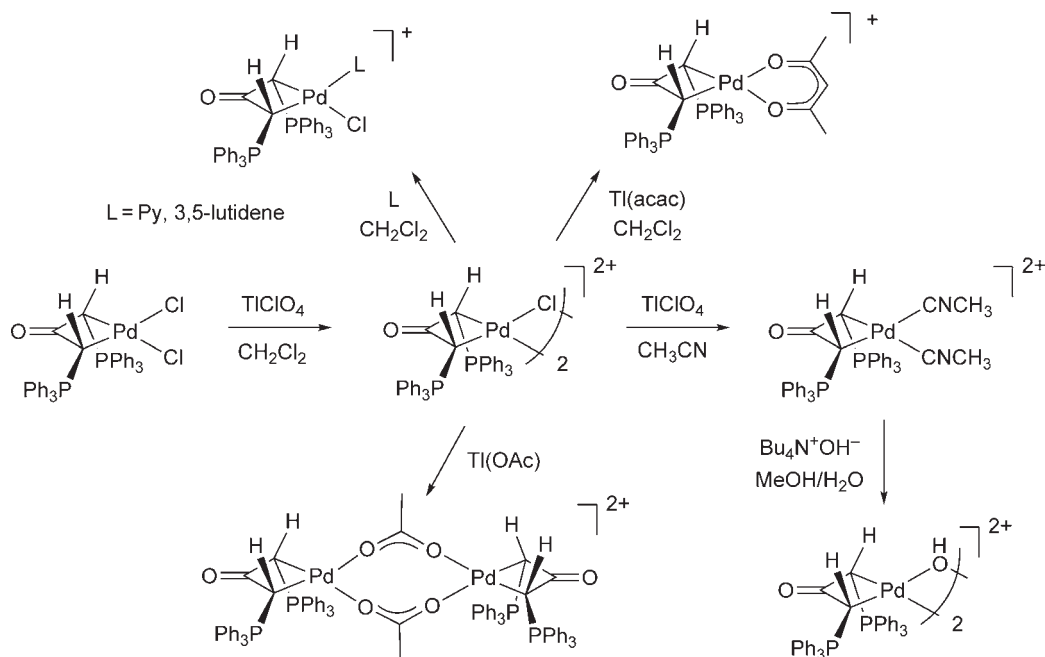


Common reactivity patterns for palladium complexes are also relevant to the chemistry of palladacyclobutane complexes. The arene *ortho*-metallation/reductive elimination cascade observed for palladacyclobutanone complex **129** provide one illustration (Equation 42), hinting at the potential for developing other oxidative transformations of proximal arene functionality <1998OM5887>.

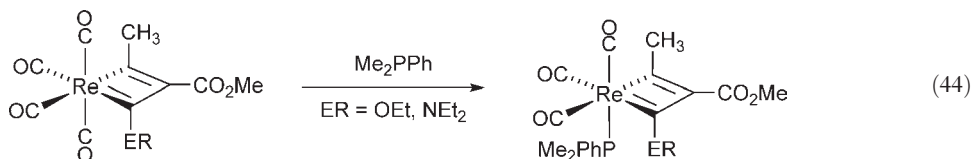
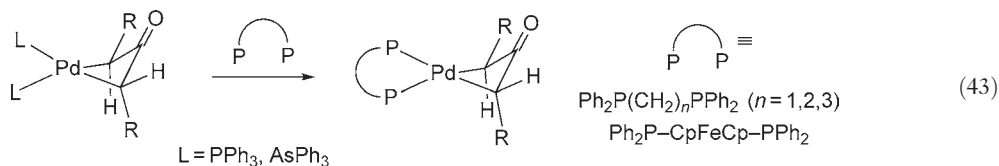


2.12.8 Reactivity of Substituents Attached to Ring Heteroatoms

Considering that the heteroatom in this structural class is a transition metal, the reactivity of substituents attached to the metal amounts to a compendium of typically straightforward ligand substitution reactions, which need not be detailed here. Representative examples from the recent literature are illustrated in [Scheme 24](#) and [Equations \(43\) and \(44\)](#) <1998OM5887, 1998IC6007, 2002POL2653, 1993JA9986, 2004JOM2000, 2004IC7622, 1996JBS75>.



Scheme 24



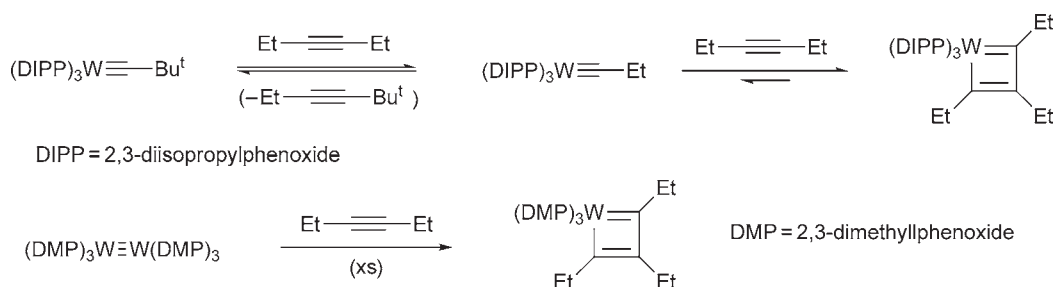
2.12.9 Ring Syntheses from Acyclic Compounds

The synthesis of four-membered ring metallacycles was initially driven by the recognition that low-valent transition metals could mediate cyclopropane carbon-carbon bond cleavage and by the extensive attention devoted to reactivity patterns thought to be relevant to olefin metathesis. More recently, however, organometallic and organic researchers

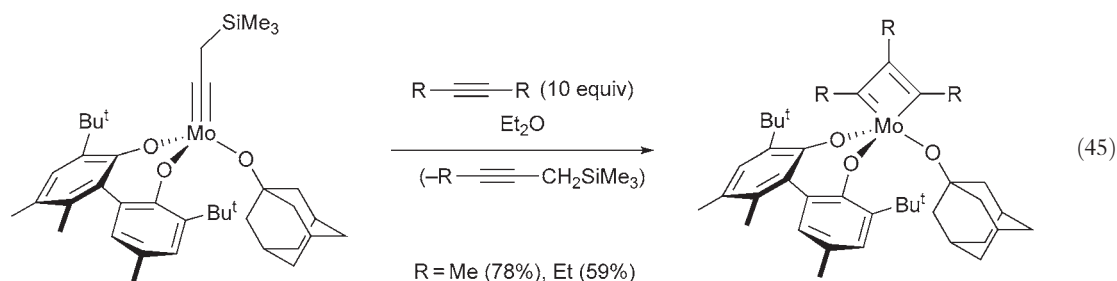
have started to recognize the potential of such strained heterocyclic intermediates for an expanded range of unique transformations and novel synthetic contexts. This is especially true for metallacyclobutene and metallacyclobutane ring systems; the chemistry of four-membered ring boracycles remains rather more esoteric territory, pending the development of more general preparative methodology.

2.12.9.1 Syntheses of Metallacyclobutadienes

The reversible [2+2] cycloaddition of metal alkylidyne or Fischer-type metal carbyne complexes remains the only general methodology for the synthesis of metallacyclobutadiene complexes. Recent literature revolves principally around the heavier group 6 metals and the investigation of intermediates in catalytic alkyne metathesis (Scheme 25; Equation 45) <1996CHEC-II(1b)887> (W: <2005OM4684>, Mo: <2003JOM56>).



Scheme 25



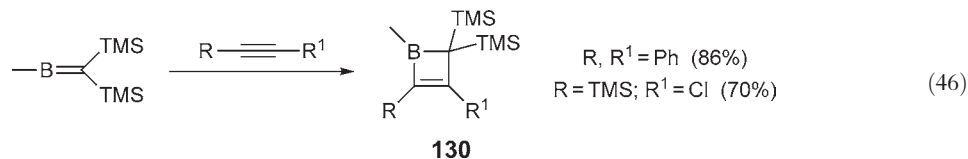
A recent computational investigation of the [2+2] cycloaddition between a hypothetical molybdenum carbyne complex, Cl₃Mo≡CH, and ethyne suggests that the formation of the molybdacyclobutadiene, Cl₃Mo(η²-C₃H₃), is allowed by orbital symmetry. In contrast, the direct formation of the isomeric molybdetetrahedrane (i.e., the η³-cyclopropene complex), Cl₃Mo(η³-C₃H₃), is symmetry forbidden <1993OM1289>; such complexes presumably arise by isomerization subsequent to initial molybdacyclobutadiene formation (Section 2.12.5).

2.12.9.2 Syntheses of Metallacyclobutenes

Although the [2+2] cycloaddition continues to dominate the methodology for the synthesis of boracyclobutene and metallacyclobutene complexes, conceptually new and potentially general alternatives have recently been introduced. In particular, the central carbon alkylation of electrophilic propargyl and allenyl complexes has significantly enriched the palette of available metallacyclobutenes, raising considerable promise for the development of new reactions of relevance to organic synthesis.

2.12.9.2.1 Cycloaddition

Boracyclobutenes **130** are isolated from the [2+2] cycloaddition of boraalkenes (methylene boranes) and alkynes (Equation 46) <2004ZFA508>. Further details and discussion are provided in CHEC-II(1996) <1996CHEC-II(1b)887>.



Diboramethylenecyclopropane **131**, an unusual strained methylene borane, can be depicted in both classical and nonclassical canonicals (Figure 6); the nonclassical structure is shown as a coordinated boraalkyne, with divalent boron bridging the alkyne π -system via a three-center two-electron interaction <1993AGE985>. Sterically isolating substituents are necessary to ensure the viability of this structural class. Given this restriction, however, a remarkably general synthesis of bicyclic diboracyclobutenes **132** has been developed by applying the [2+2] cycloaddition to a range of alkynes (Equation 47).

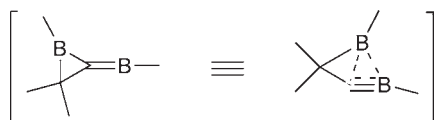
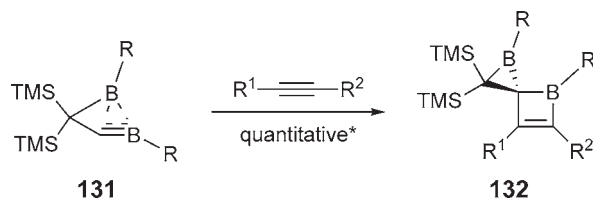


Figure 6 Diboramethylenecyclopropane canonical structures.



*Where determined.

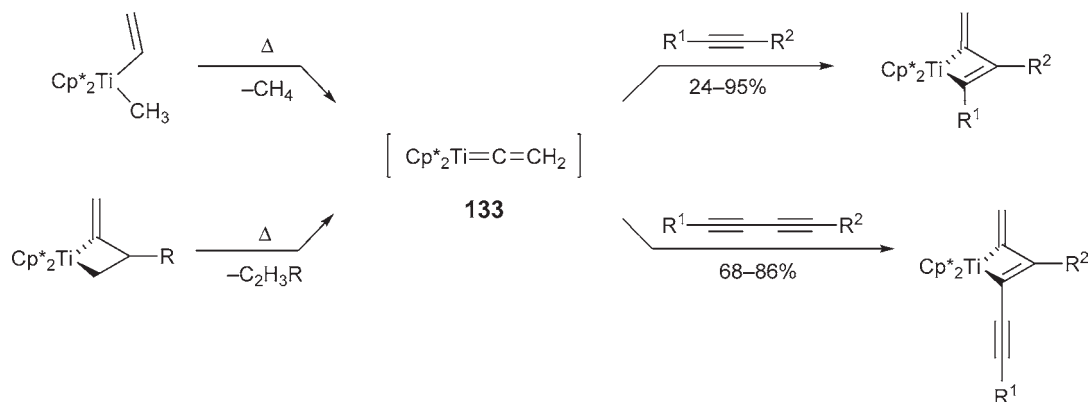
R	R ¹	R ²	Temp. (°C)	Reference
Bu ^t	Ph	Ph	−30	1983AGE877
Bu ^t	Me	Me	−50	1984AGE369
Bu ^t	H	Bu ^t	−50	1984AGE369
Dur	H	TMS	−30	1994AGE1487
Dur	SnMe ₃	3,5-(Bu ^t) ₂ Ph	−20	1994AGE2064
Bu ^t	H	TMS		1994AGE2306
Dur	Et	Et	−30	1995AGE1340
Dur	Me	Me	−30	1995AGE657

Dur = 2,3,5,6-tetramethylphenyl.

(47)

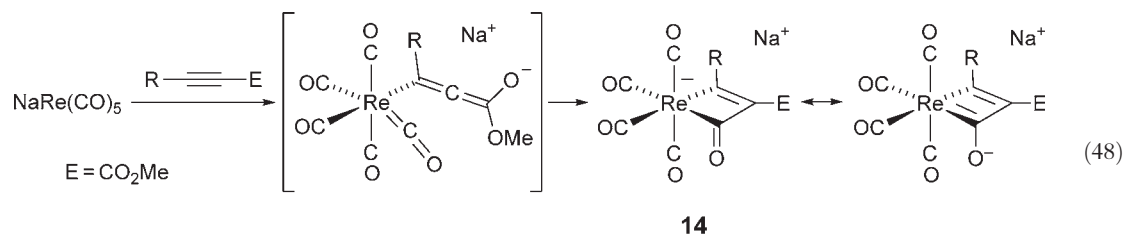
The cycloaddition of alkynes to transition metal alkylidene complexes is very well established for the synthesis of titanacyclobutene and other metallocyclobutene complexes, although the use of unsymmetrically substituted alkynes often returns regioisomeric mixtures <2003ICA27, 1995TL3619, 1993CB1541, 1993OM3776, 1996CHEC-II(1b)887>. Tebbe's reagent [Cp₂Ti(μ-CH₂)(μ-Cl)AlMe₂] can also be used as a pro-alkylidene in titanacyclobutene synthesis, although Negishi *et al.* reported that the reagent must be prepared with great care and the reactions run under basic conditions <1997OM951>.

Titanium vinylidene complexes **133**, generated *in situ*, react with alkynes to yield 2-methylenetitanacyclobutene complexes (Scheme 26) <1996OM1176>. The reaction is often regioselective, preferentially locating the more bulky substituent at the β -position of the titanacyclobutene ring and the alkynyl carbon of greatest electron density, as measured by ^{13}C NMR spectroscopy, on the α -position. The [2+2] cycloaddition of substituted diynes has also been reported, producing the titanacyclobutene regioisomer that places the alkynyl substituent in the α -position. No interaction of the pendant alkyne and the metal is observed <1996OM4731>.



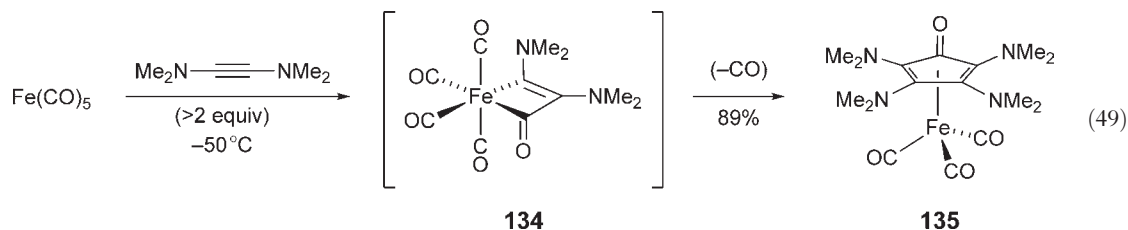
Scheme 26

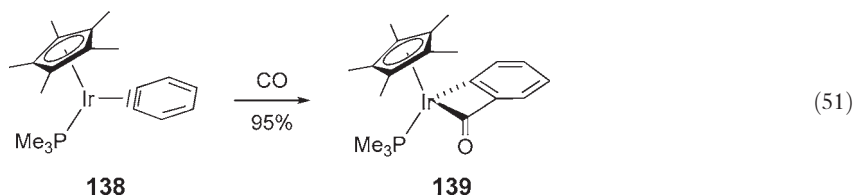
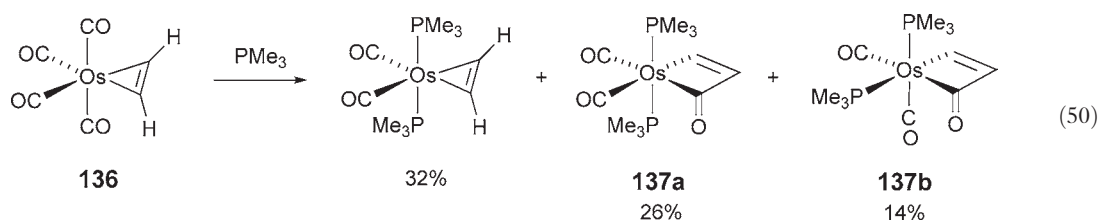
Later in the transition series, the [2+2] reactivity pattern is embedded into the formal [2+1+1] oxidative cycloaddition of alkynes onto a metal carbonyl or isonitrile ligand, a reactivity pattern first reported in the early 1970s <1970JCA2981>, 1996CHEC-II(1b)887>. For the anionic rhenium carbonyl complex (Equation 48), the cycloaddition with alkyne proceeds via initial conjugate addition, leading to 2-rhenacyclobutenone complexes **14** <1990JOMC1, 1993JA9986, 2004JOM2000>. The reaction is regiospecific and requires an electron-deficient alkyne. The physical data for the complex suggest that the product is more rhenacyclobutenone than rhenacyclobutadiene in character. The downstream chemistry of this anionic system is discussed in Section 2.12.5.



R = Me, CO₂Me, H (55–84%) 1993JA9986; R = Ph (80%) 2004JOM2000

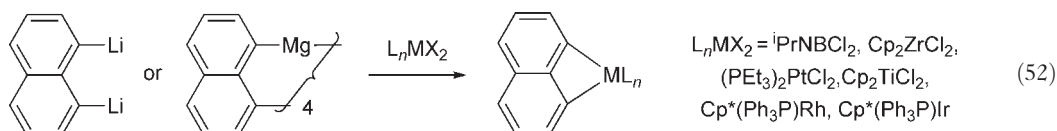
Iron carbonyl complexes also react with alkynes in what can be similarly construed as a [2+2] cycloaddition. The reaction of iron pentacarbonyl with the electron-rich ynamine gives the spectroscopically detected ferracyclobutenone complex **134** in an overall [2+2+1] process leading to the cyclopentadienone complex **135** (Equation 49) <2002AGE2393>. The isolable osmium alkyne complex **136** undergoes a phosphine-promoted oxidative cycloaddition to give a mixture of osmacyclobutene complexes **137**, along with an equivalent amount of nonproductive ligand exchange (Equation 50) <1999OM2331>. A similar net transformation is observed starting from the iridium benzyne complex **138**, producing the 2-iridabenzocyclobutenone complex **139** (Equation 51) <2003OM2134>.



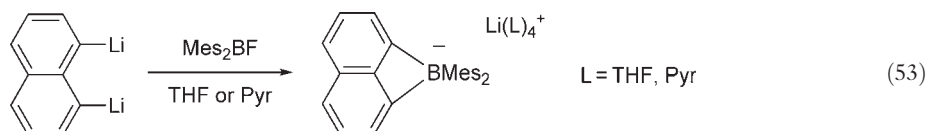


2.12.9.2.2 Nucleophilic and electrophilic alkylation/transmetallation

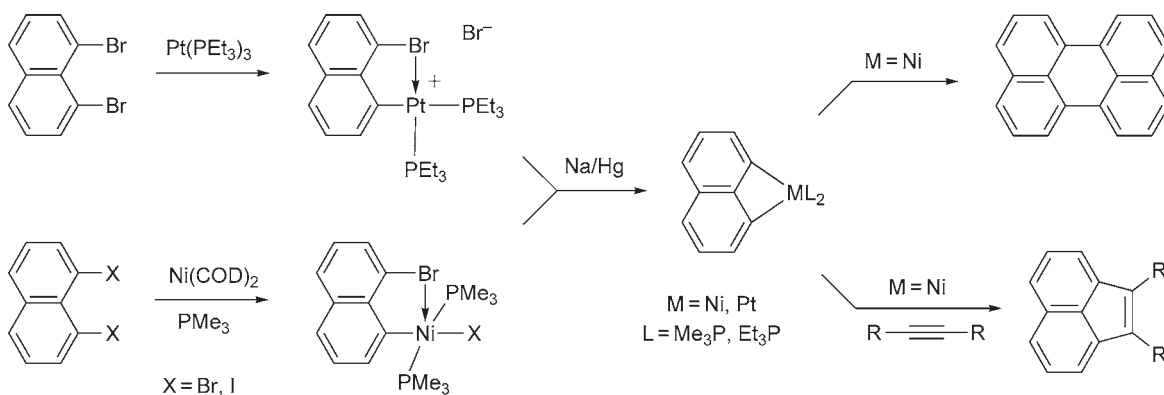
Transmetallation from 1,8-dilithionaphthalene and/or [Mg(1,8-naphthalenediyl)]₄ to a range of boron dihalide and transition metal dihalide complexes affords 1,8-naphthalenediyl complexes, which incorporate an embedded metal-lacyclobutene moiety (Equation 52) (Li/B: <1994AGE1247>, Li/Zr: <1994CB1851>, Li/Pt: <2005JA13494>, Mg/Ti, Rh, Ir, Pt: <1994CB1851>).



The reaction of Mes₂BF with 1,8-dilithionaphthalene in tetrahydrofuran (THF) or pyridine gives the (1,8-naphthalenediyl)borate anion as a lithium salt (Equation 53) <2002OM982>.



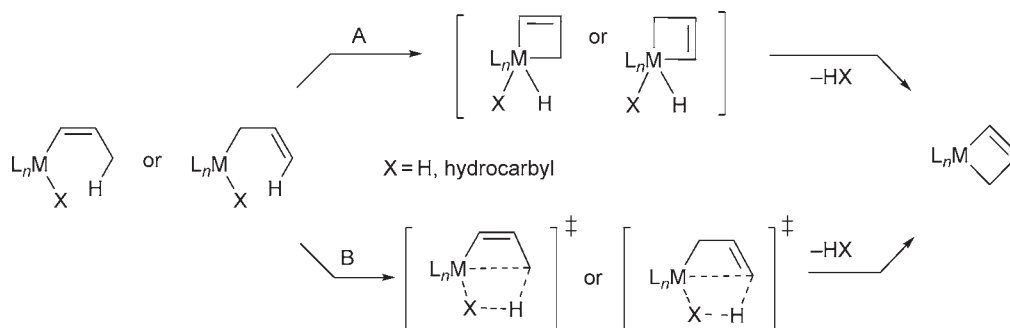
Related complexes of group 10 metals are accessible by an oxidative addition/reductive cyclization protocol, exploiting the inverse electron demand (Scheme 27) (Pt: <2005JA13494>, Ni: <2003OM3604>). The nickel complex is thermally unstable, proceeding to perylene via a bimolecular reductive elimination or, in the presence of alkynes, delivering acenaphthylene derivatives by an insertion/reductive elimination pathway.



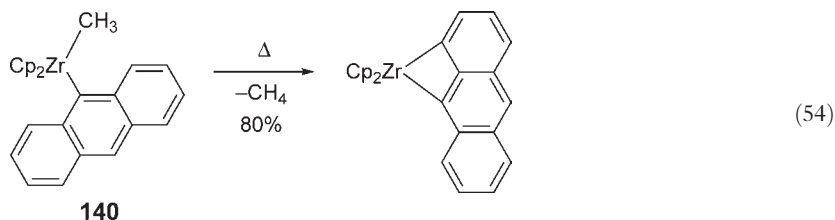
Scheme 27

2.12.9.2.3 γ -Hydrogen elimination

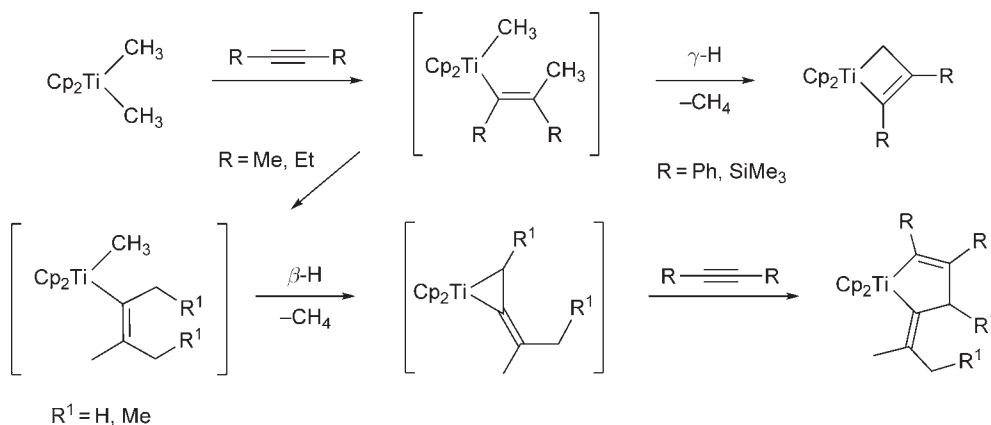
Metallacyclobutene complexes of both early and late transition metals can, in some cases, be prepared by intramolecular γ -hydrogen elimination, although the intimate mechanism of the reaction varies across the transition series. For low-valent late metals, the reaction is generally assumed to proceed via the oxidative addition of an accessible γ -C–H bond (**Scheme 28**, path A), but for early metals and, presumably, any metal in a relatively high oxidation state, a concerted σ -bond metathesis is considered most probable (path B). In this process, the γ -C–H bond interacts directly with an M–X fragment (typically a second hydrocarbonyl residue) to produce the metallacycle with the extrusion of H–X (i.e., a hydrocarbon). Either sp^3 - or sp^2 -hybridized C–H bonds can participate in the γ -hydrogen elimination.

**Scheme 28**

Methyl(9-anthracenyl)zirconocene complex **140** undergoes γ -hydrogen elimination to form the zirconacyclobutene complex, releasing methane (**Equation 54**) <2000JA9880>.

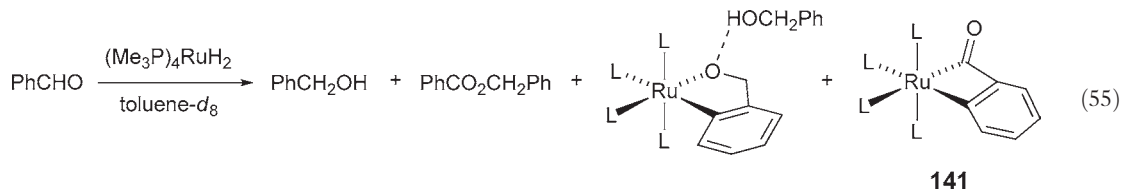


Titanacyclobutene complexes result from the reaction of dimethyltitanocene with alkynes (**Scheme 29**). The reaction can be envisioned to proceed either by initial methane extrusion to form the methyldiene, followed by [2+2] cycloaddition, or by initial alkyne insertion to generate the vinylic intermediate followed by γ -elimination. The evidence suggests that the latter mechanism dominates. Diphenylacetylene and bis(trimethylsilyl)acetylene both provide the corresponding titanacyclobutene complex, preferentially abstracting an allylic γ -hydrogen over the

**Scheme 29**

γ -hydrogen atom on the aryl or silyl substituents. For 2-butyne and 3-hexyne, β -hydrogen elimination is competitive with γ -hydrogen elimination; titanacyclobutene complexes are isolated only as minor products <1993OM4682, 1994JA2147, 2000POL879>.

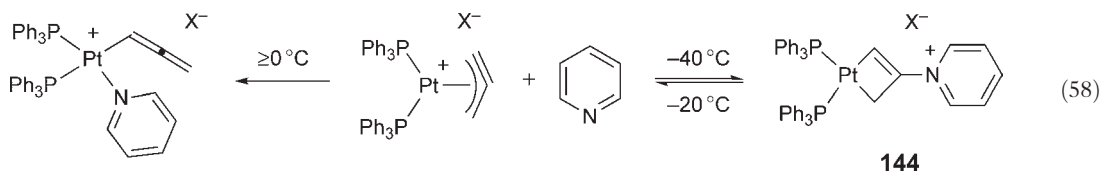
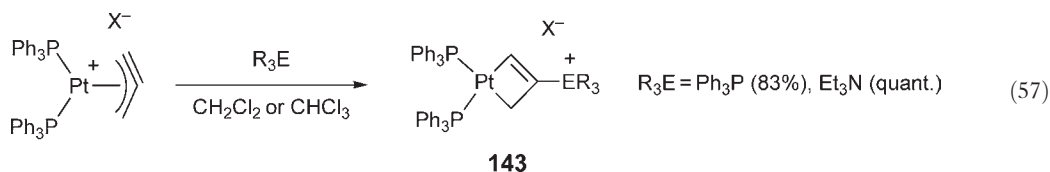
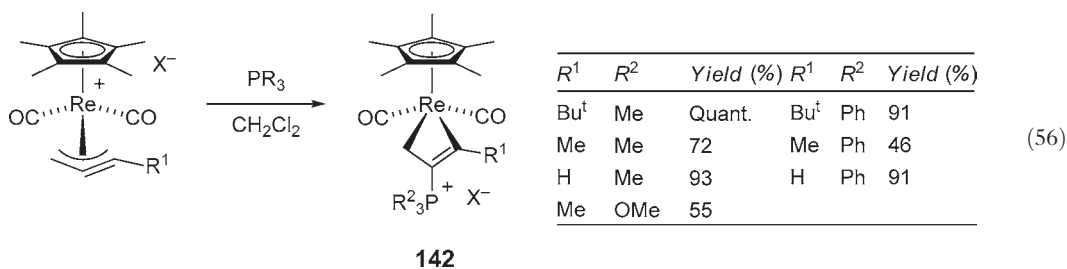
Ruthenacyclobutenone complex **141** is observed as a minor product during the course of the Tishchenko reaction of benzaldehyde catalyzed by $(\text{Me}_3\text{P})_4\text{RuH}_2$; this complex is considered the likely resting state in the catalytic cycle (Equation 55) <1994JOM265>.

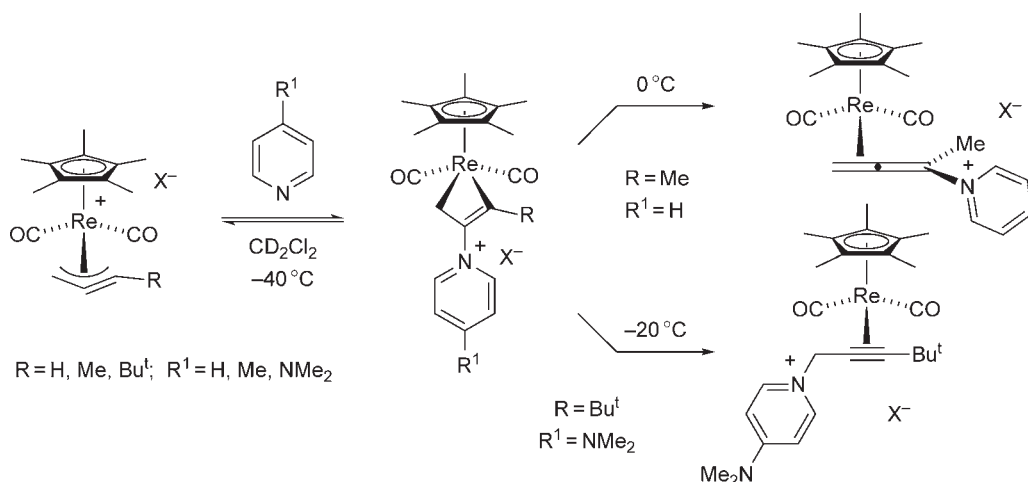


2.12.9.2.4 Central carbon addition to η^3 -allenyl/propargyl complexes

Although the η^3 -propargyl and η^3 -allenyl ligand systems were once considered simple extensions of the corresponding η^3 -allyl system, this functionality is now recognized as quite unique in both structure and reactivity. General reviews of this topic have been published <1994NJC61, 1998BCJ973, 1999CCR1143>. In contrast to transition metal η^3 -allyl complexes, which undergo nucleophilic reactions at either the terminal or central carbon atom (see Section 2.12.9.3.4), η^3 -allenyl/propargyl ligands normally undergo addition at the central carbon. This provides a general, convergent strategy for the regioselective preparation of metallacyclobutene complexes inaccessible from either cycloaddition or γ -hydrogen elimination reactions.

Rhenium and platinum η^3 -allenyl/propargyl complexes undergo central carbon addition with neutral nucleophiles such as amines and phosphines to form cationic metallacyclobutene complexes (e.g., **142** and **143**; Equations 56 and 57) (Re: <1998JA722>, Pt: <1998OM2953>). The amine adducts are typically unstable with respect to reionization and rearrangement: the triethylamine adduct **143** ($\text{E} = \text{N}(\text{Et})_3$), for example, is unstable under vacuum, presumably due to irreversible removal of the volatile amine. The spectroscopically observed platinacyclobutene complex **144**, formed by the addition of pyridine under kinetically controlled conditions, equilibrates in solution to the thermodynamically more stable η^1 -allenyl complex arising from coordination to the platinum center (Equation 58) <1998OM2953>. In contrast, the kinetic rhenacyclobutene adducts obtained from low-temperature reactions with pyridine derivatives undergo equilibration at higher temperatures to give the thermodynamic alkyne or allene complexes from terminal carbon addition (Scheme 30) <1998JA722>.

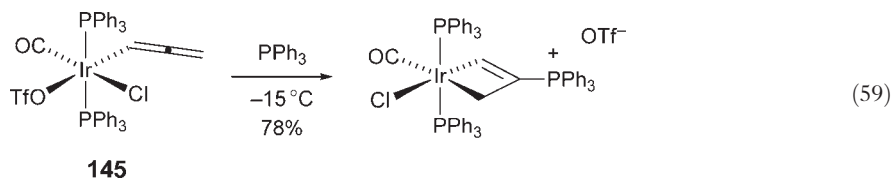




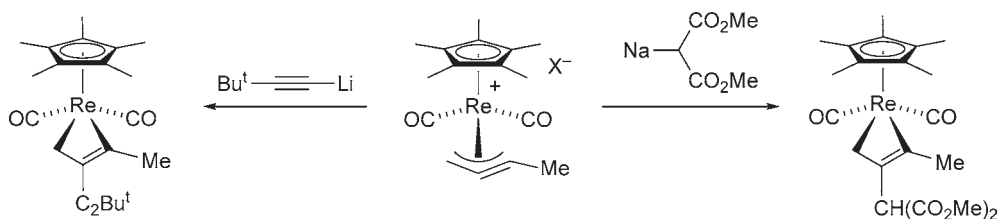
Scheme 30

A recent theoretical investigation of the platinum system suggests that, for this metal, the central carbon of the η^3 -allenyl/propargyl ligand is more positive than that of the η^3 -allyl ligand and concludes that the kinetically controlled nucleophilic addition to the η^3 -allenyl/propargyl central carbon is charge controlled <1999OM837>.

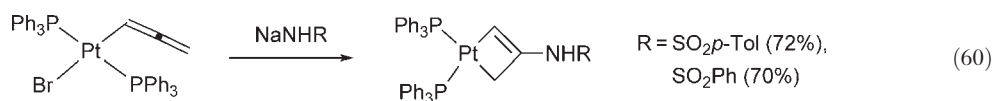
The reaction of η^1 -allenyliridium complex **145** with triphenylphosphine also yields a cationic iridacyclobutene complex (Equation 59), presumably via a cationic η^3 -allenyl/propargyl intermediate formed by dissociation of the inner-sphere triflate <1998OM2953>.



In addition to softer neutral nucleophiles, harder anionic nucleophiles also alkylate the η^3 -allenyl/propargyl central carbon. The rhenium η^3 -2-butyryl complex reacts with malonate and lithium *tert*-butylacetylide to give rhenacyclobutene complexes (Scheme 31) <1998JA722>. The reaction of sodium amide with an η^1 -allenylplatinum complex similarly yields the platinacyclobutene complex, which does not further equilibrate (Equation 60) <1998JOM39>.



Scheme 31



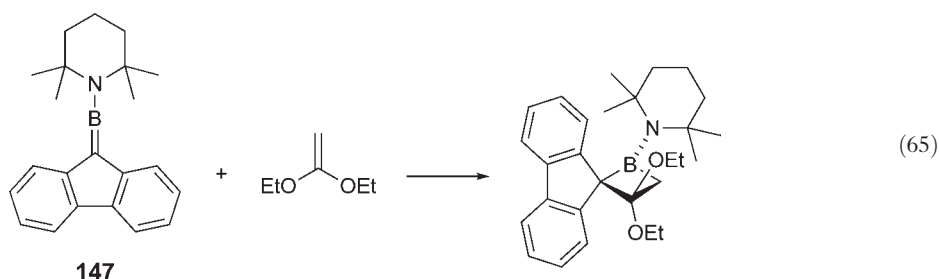
2.12.9.3 Syntheses of Metallacyclobutanes

The preparation of metallacyclobutane complexes in many ways parallels that of metallacyclobutene complexes, with a historical, metathesis-driven bias toward the [2+2] cycloaddition pathway. Cyclopropane oxidative insertion clearly shares this historical pedigree – and persistence – in the recent literature (Section 2.12.10). Nonetheless, valuable new synthetic strategies have recently emerged, with the regioselective central carbon alkylation of η^3 -allyl complexes holding the greatest potential for emergence as the basis for new organic synthesis.

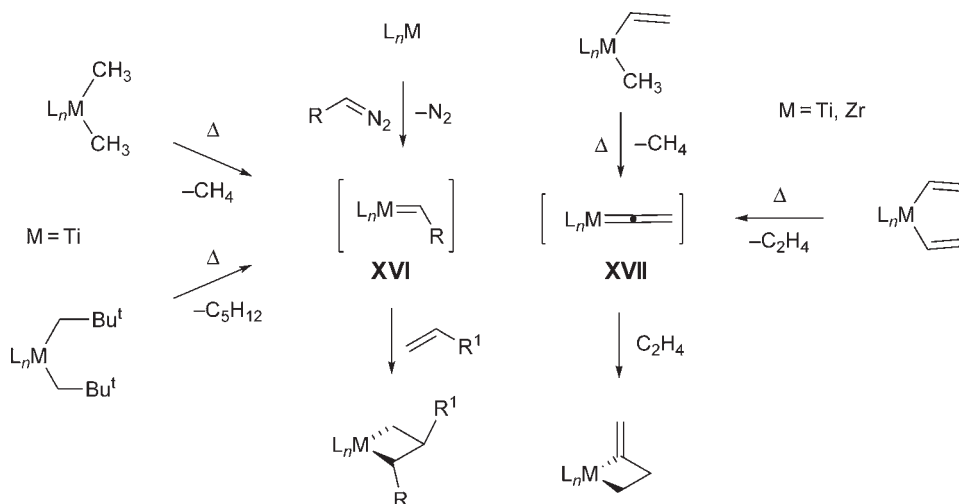
2.12.9.3.1 Cycloaddition

The cycloaddition of alkenes with metal alkylidene complexes remains the most common entry into the metallacyclobutane structural class. Consistent with metallacyclobutane intermediacy in the olefin metathesis reaction, the [2+2] cycloaddition is generally reversible; a propensity for cycloreversion (Section 2.12.6.2.4), however, can significantly limit the utility of metallacyclobutane complexes as intermediates in other synthetic transformations.

In the main group metals, contrasting the generality of boracyclobutene synthesis from borene/alkyne cycloaddition, the corresponding reaction with alkenes is essentially unknown – a single example has been reported in the literature. For the cycloaddition of 2,2,6,6-tetramethylpiperidinylborene **147**, a typical sterically protected borene, the reaction with 1,2-diethoxyethene is unique in affording a boracyclobutene (Equation 65); the use of other polar alkenes led only to nonproductive reactions <1993CB1551>.



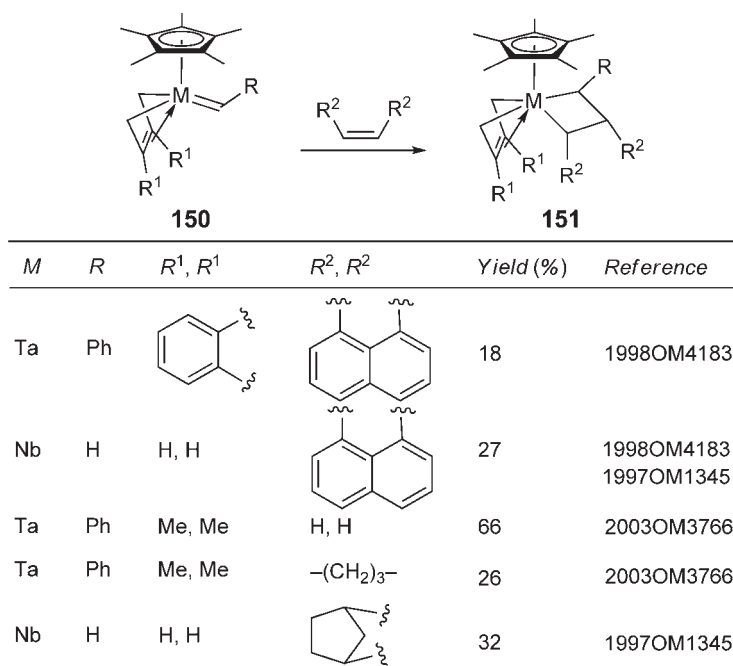
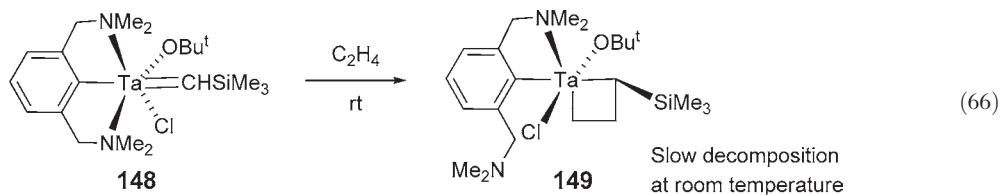
In the group 4 metals, however, the [2+2] cycloaddition is both common and vastly more general. For titanium, the alkylidene or vinylidene intermediate (**XVI** and **XVII**, respectively) is typically generated *in situ* in the presence of added alkene (Scheme 32) <1996CHEC-II(1b)887, 1995OM1278, 1995JOM321, 1996JA8737, 1998JA6316, 1998JA11649, 2003ICA27>. Aside from the use of diazoalkane transfer, the unsaturated intermediates are generated by thermal extrusion, proceeding via α -elimination: the (nominal) deprotonation of one hydrocarbon residue by a proximal alkyl or alkenyl ligand. As such, none of these processes holds much potential for generalization or catalytic transformation. Some corresponding zirconacyclobutane complexes have been similarly prepared <1993JOM75>.



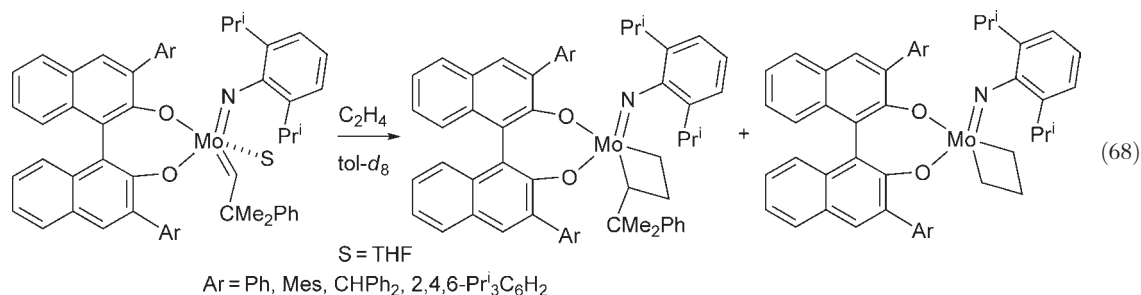
Scheme 32

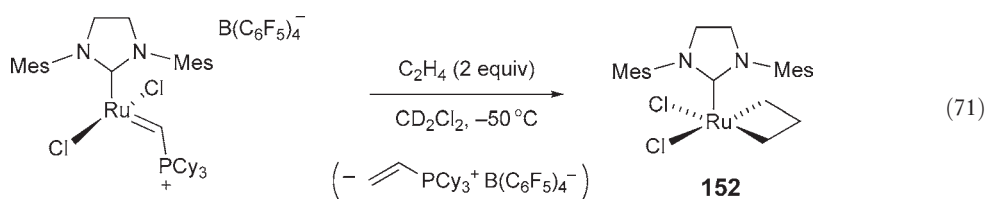
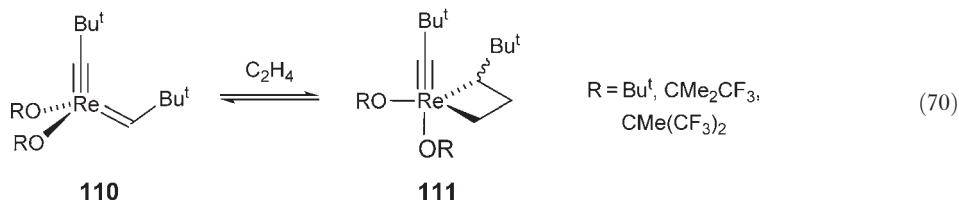
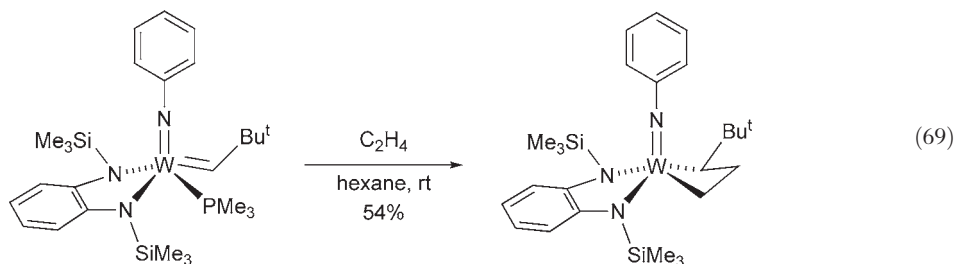
During the course of metathesis-related investigations, a range of metallacyclobutane complexes of other metals have recently been isolated and characterized, at least transiently. The observed complexes are understandably poor catalysts, but the structural and mechanistic insight obtained from such systems has assisted in the development of improved catalysts.

Despite dramatically different ancillary ligand sets, two distinct niobium and tantalum alkylidene systems provide isolable metallacyclobutanes upon reaction with ethylene. In one case, the tantalum aryldiamine pincer complex **148** reacts with ethylene to provide the α -trimethylsilyltantalacyclobutane complex **149** (Equation 66) <1994OM3259>. In a more comprehensive study, alkadiene-supported half-sandwich alkylidene complexes of both tantalum and niobium (the former isolable, the latter generated *in situ*) undergo [2+2] cycloaddition with a range of acyclic and cyclic alkenes, albeit in modest isolated yield (Equation 67).



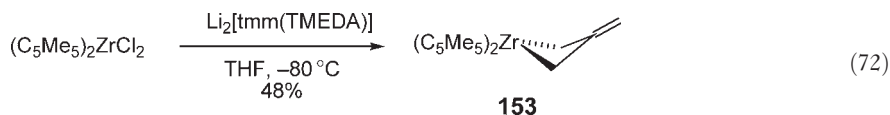
Metallacyclobutane complexes of molybdenum <2001OM5658, 2004OM1997>, tungsten <1998OM2628>, rhodium <1993JA2980>, and ruthenium <2005JA5032> have been isolated or characterized spectroscopically from reactions of ethylene and the corresponding alkylidene complexes (Equations 68–71). Ruthenacyclobutane complex **152** represents the first observable metallacyclobutane intermediate based on the Grubbs's family of metathesis catalysts.



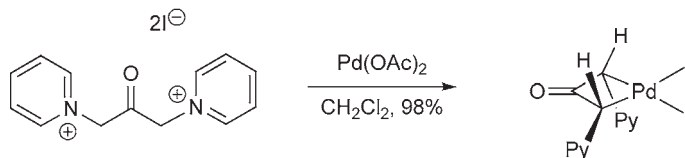


2.12.9.3.2 Nucleophilic and electrophilic alkylation/transmetalation

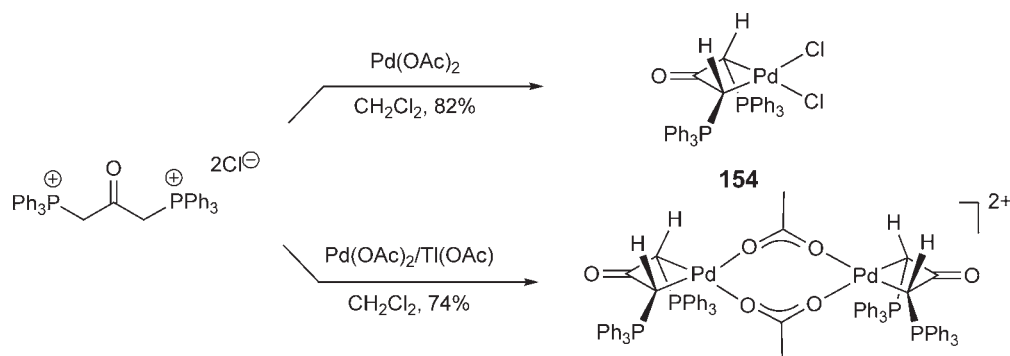
The permethylzirconocene η^2 -trimethylenemethane complex **153** is obtained from the reaction of permethylzirconocene dichloride with $\text{Li}_2[\text{trimethylenemethane}(\text{TMEDA})]$ (TMEDA = *N,N,N',N'*-tetramethylethylenediamine) in moderate yield (Equation 72) <1994AGE2465>. X-Ray crystallography suggests the presence of a weak donor interaction from the β -carbon to the metal, based on the short internuclear distance.



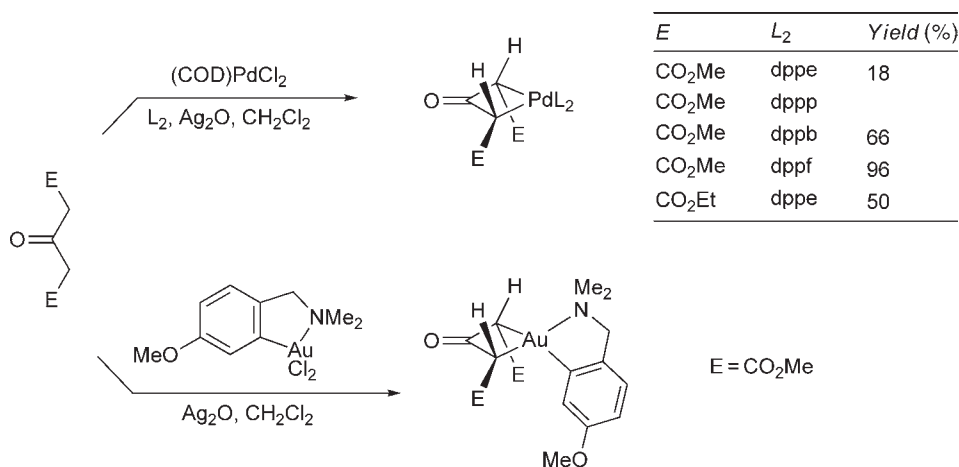
In late transition metals, where the alkylidene/alkene cycloaddition is less accessible, nucleophilic bis(alkylation) provides a general synthesis of substituted metallacyclobutane complexes. The use of highly stabilized carbanions is advantageous, facilitating anion formation. Treatment of 1,3-bis(triphenylphosphonium)-2-propanone with palladium(II) acetate gives palladacyclobutanone complex **154** in good yield, presumably via stabilized phosphorus ylide intermediates formed by *in situ* deprotonation of the highly acidic propanone (Scheme 33). The metal in this palladium(II) product is formally dianionic, balancing the two positively charged phosphorus centers. In the presence of thallium acetate, the reaction proceeds to the corresponding acetate-bridged system <1998IC6007>. Similar reactivity is observed using pyridinium ylide nucleophiles <2001OM995, 2004IC7622>.



Other active methylene compounds also react with both palladium(II) <2002POL2653> and gold(III) <1997JOM243> to produce metallacyclobutane complexes (Scheme 34). The gold complex is not sufficiently stable for isolation. In these reactions, the silver oxide functions both as a base and a reagent for halide abstraction. In the gold series, 1,1,3,3-tetracyanopropane is also a competent pro-nucleophile <1999JOM219>.



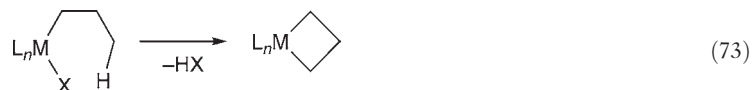
Scheme 33



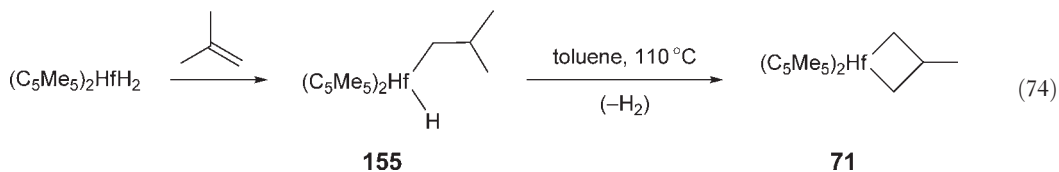
Scheme 34

2.12.9.3.3 γ -Hydrogen elimination

Consistent with metallacyclobutene synthesis, metallacyclobutane complexes can also be prepared by γ -hydrogen elimination (Equation 73), despite the greater entropic disadvantage.

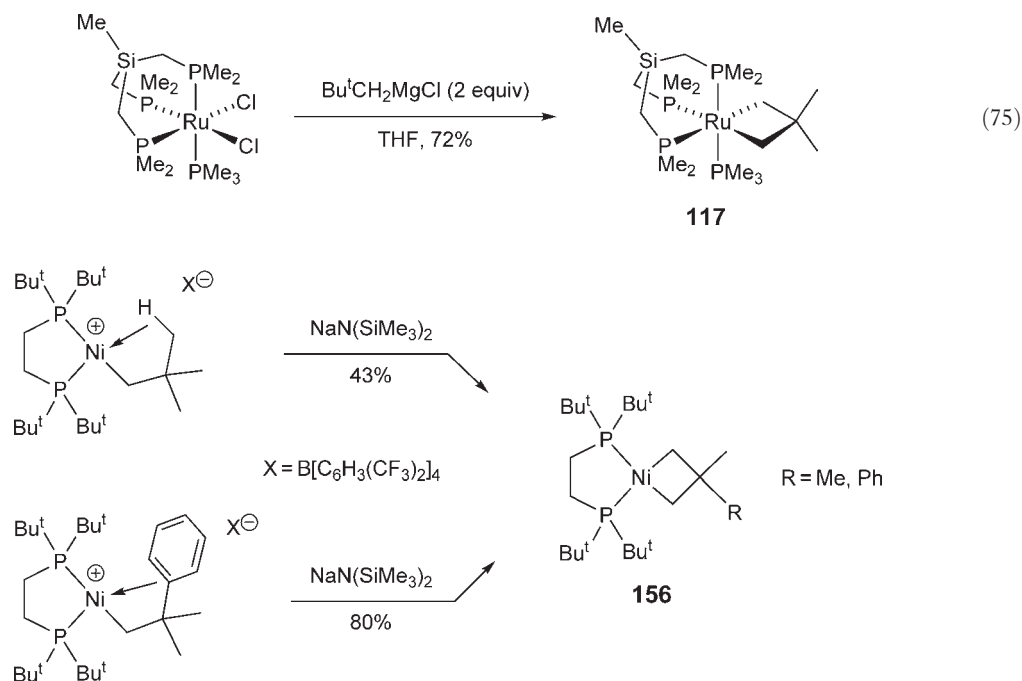


Permethylhafnocene isobutyl hydride **155**, prepared by the insertion of isobutylene into permethylhafnocene dihydride, undergoes γ -hydrogen elimination to give hafnacyclobutane complex **71** with concomitant generation of dihydrogen (Equation 74) <1994OM1424, 1985OM97>.



A similar, albeit more complex, reactivity manifold is reported for the formation of the 'Negishi reagent' starting from bis(*n*-butyl)zirconocene, which *inter alia* decomposes to give the putative zirconocene butene complex. Among the compounds identified in this mixture is a labile 2-methylzirconacyclobutane complex <1997OM1452>.

Bis(neopentyl) complexes of later transition metals also undergo γ -hydrogen elimination; both chromium and ruthenium (Equation 75) mediate this reaction (Cr: <1994OM1326>, Ru: <1995JA3625, 1997JA11244>). Some γ -hydrogen atoms can be activated externally: unsaturated cationic alkylnickel complexes, which display agostic C–H and remote *ipso*-arene donor interactions, are deprotonated by added base to yield nickelacyclobutane complexes **156** (Scheme 35) <2004JA10554>.



Scheme 35

A computational investigation of decomposition pathways for $\text{M}(\text{Np})_4$ complexes ($\text{M} = \text{Ti}, \text{Zr}, \text{Hf}$; Np = neopentyl) revealed that, for zirconium and hafnium, γ -hydrogen elimination leading to metallacyclobutane formation was energetically favored over the corresponding α -hydrogen elimination. However, for titanium, the formation of an alkylidene complex by α -hydrogen elimination was the preferred pathway <1999OM2081>.

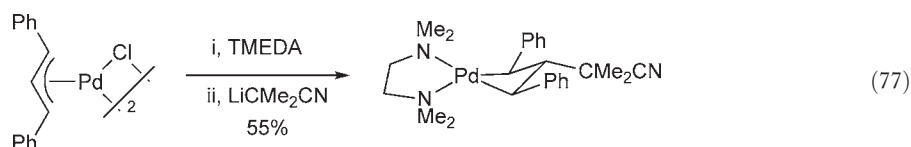
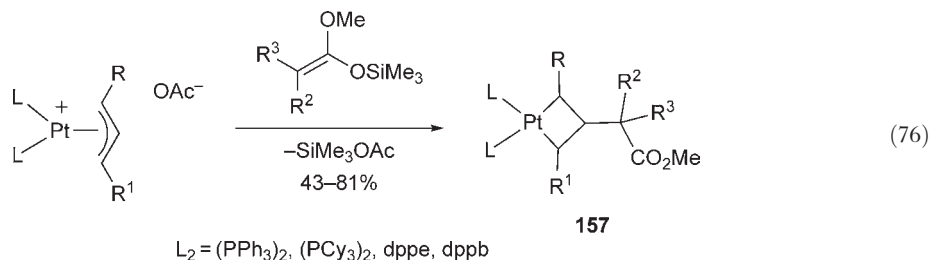
2.12.9.3.4 Central carbon addition to η^3 -allyl complexes

Nucleophilic addition to the terminal carbon of transition metal η^3 -allyl complexes was once considered to be the normal reactivity pattern for allyl alkylation. Recent investigations, however, clearly establish that central carbon alkylation is no less the normal pathway. The regioselectivity of kinetically-controlled η^3 -allyl alkylation is determined by the composition of the lowest unoccupied molecular orbital (LUMO) for the complex; when that metal/ligand hybrid is comprised of substantial π^* (allyl) character, the nucleophile is directed to the central carbon. Initially reported by Green and co-workers for cationic η^3 -allyl complexes of molybdenum and tungsten <1976CC619, 1977JCD1131, 1980JMO15>, the alkylative metallacyclobutane formation has now been observed for early, middle, and late transition metals <1996CHEC-II(1b)887>. Amplifying earlier computational studies, a number of theoretical investigations on the regioselectivity of allyl alkylation have recently appeared <1993OM3019, 2003OM3649, 1995AGE2551>.

Although palladium-catalyzed allylic alkylation represents the archetypical terminal carbon-selective organometallic system, definitive evidence for central carbon alkylation in the η^3 -allylpalladium system was first obtained by Hegedus more than a quarter century ago <1980JOC5193>. For square planar complexes of the form $[\text{L}_2\text{M}(\eta^3\text{-allyl})]^+$ ($\text{M} = \text{Pd}, \text{Pt}$), two unoccupied orbitals of distinctly different composition but nearly equivalent energy compete for the controlling frontier level. The regioselectivity observed for this system is thus dependent on subtle differences in the composition and structure (geometry) of the complex, the character of the nucleophile, and, often, the reaction conditions <1996CHEC-II(1b)887>.

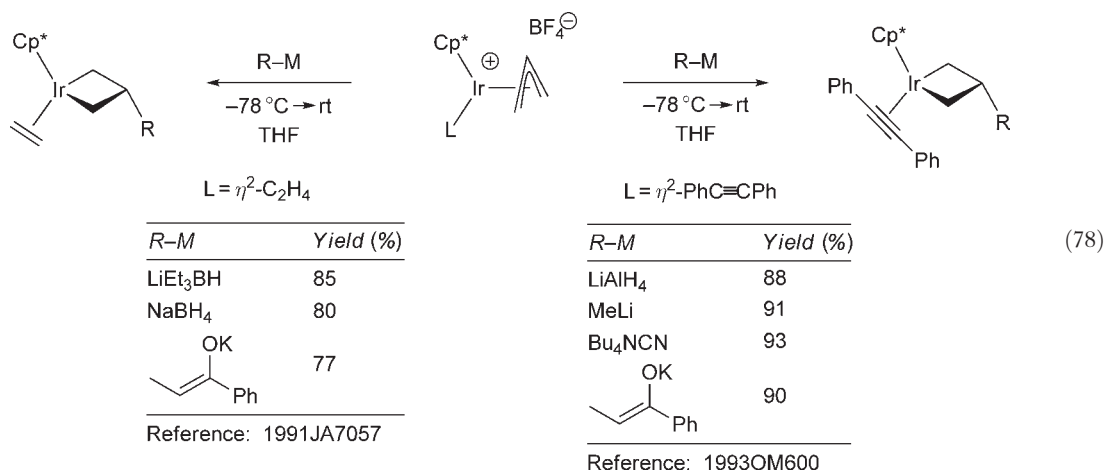
New reports continue to appear, although many pertinent issues remain. Platinacyclobutane complexes **157** have been isolated from the alkylation of cationic η^3 -allyl platinum complexes with ketene silyl acetals and silyl enol ethers

(Equation 76) <1993OM3019>, which react as ester and ketone enolate equivalents, respectively. The latter reaction requires the use of fluoride ion activation (tetrabutylammonium fluoride, TBAF) to actuate the addition. Central carbon alkylation is less common for allylpalladium reactions; despite this, nucleophilic alkylation of TMEDA-stabilized 1,3-diphenylallyl palladium complexes proceeds selectively to the central carbon (Equation 77) <1995AGE100>.

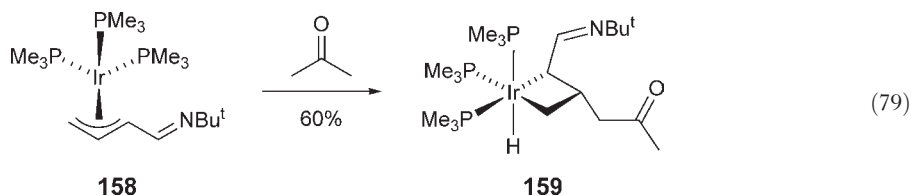


Central carbon alkylation of half-sandwich rhodium and iridium allyl cations has been investigated comprehensively, with initial reports concentrating on pseudo-tetrahedral phosphine complexes <1984JA7272, 1985JA3388, 1986JA7346> and determination of kinetic versus thermodynamic selectivity in this system <1990JA6420, 1992OM16, 1992JA1100>. In general, exclusive alkylation at the central carbon is obtained using hard nucleophiles. For softer nucleophiles, the situation is more complicated: metallacyclobutane complexes result from reactions run under kinetic control, but the thermodynamically more stable terminal adducts are obtained from reactions run under conditions promoting reversible alkylation, such as the reactions of organic enolates. For highly stabilized carbanions and softer nucleophiles, terminal carbon adducts are obtained exclusively, with no direct evidence of intermediate central carbon adducts.

Highly selective central carbon alkylation is also observed for the corresponding *exo*- and *endo*- η^3 -allyl complexes of iridium bearing ancillary alkene and alkyne ligands (Equation 78, illustrated for *exo*- η^3 -allyl cases only) <1991JA7057, 1993OM600>. A similar dependence on the character of the nucleophile has been determined and, for softer nucleophiles, surprising differences in the position of alkylation were noted for complexes differing only in the relative configuration of the allyl ligand (*endo* vs. *exo*): the reaction proceeds in some cases by central carbon alkylation, in others by terminal carbon alkylation, and, in still others, by competitive addition to the ancillary ligand.

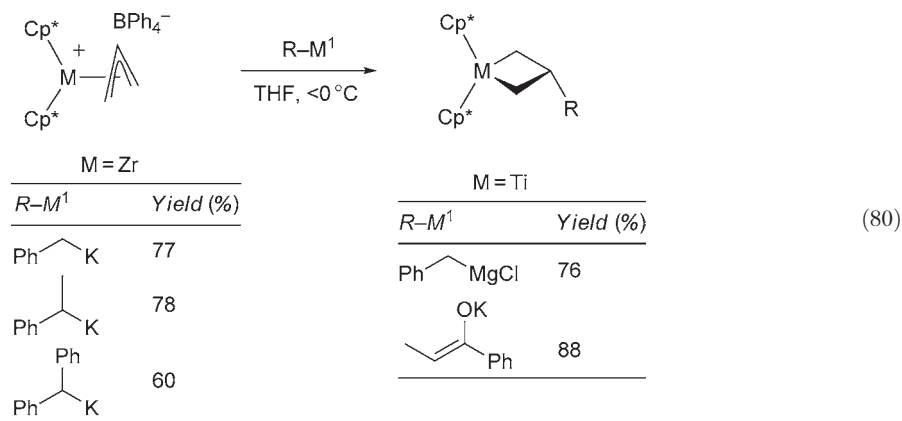


Despite dramatic differences in coordination environment, neutral iridium(I) allyl complex **158** reacts with acetone to form iridacyclobutane complex **159** (Equation 79) <1994OM1592>. This transformation may proceed by nucleophilic addition of the enol tautomer, as the authors suggest, or, plausibly, an acid/base equilibrium induced by the basic Ir(I) center; the cationic hydrido-iridium intermediate thus formed is alkylated at the central allyl carbon by the enolate.

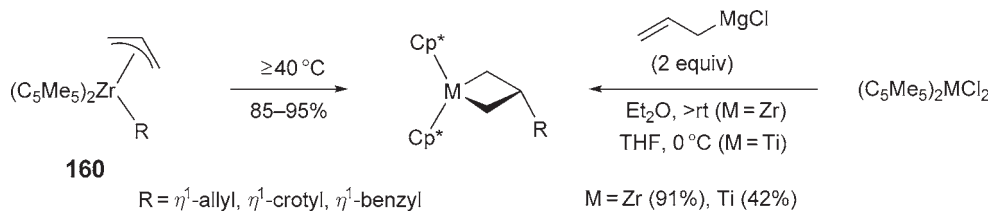


The reaction of the cationic ruthenium complex $[(\text{CO})_2(\text{PhMe}_2\text{P})\text{Ru}(\eta^3\text{-allyl})]^+$ with sodium borohydride produces the corresponding ruthenacyclobutane complex among the principal products [<2003JCD2603>](#).

Directly challenging the assertion that strong $d \rightarrow \pi^*$ back-donation is essential to direct the nucleophile to the allyl central position [<1978T3047>](#), the chemistry of d^0 -allylmethyl systems was investigated. Despite the dramatic reduction in d -orbital occupancy and the coordinatively unsaturated metal center, cationic zirconocene and titanocene η^3 -allyl complexes undergo alkylation with most nucleophiles exclusively at the allyl central carbon to produce isolable metallacyclobutane complexes (Equation 80) [<1993JA9814>](#). For zirconium, the reaction is dependent on the steric profile of the nucleophile; sterically small nucleophiles react competitively at the unsaturated metal center. Alkylation of the inherently more compact titanocene system is correspondingly more general.



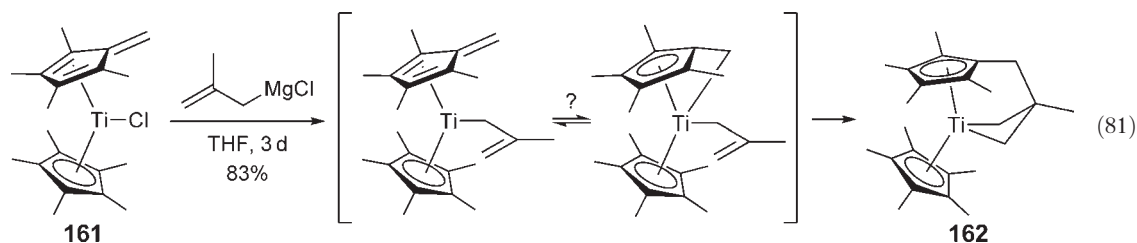
Similar β -substituted zirconacyclobutane complexes have been prepared by intramolecular rearrangements of bis(allyl)permethylzirconocene and related complexes **160** (Scheme 36) [<1993JA2083>](#). The migrating group must be activated by incipient resonance stabilization; simple saturated alkyl ligands do not undergo this rearrangement. Mechanistic investigation strongly supports a free radical mechanism, involving zirconium–carbon bond homolysis followed by radical alkylation of the zirconium(III) intermediate at the η^3 -allyl central carbon. The synthesis of the β -allylzirconacyclobutane complex can also be conducted in one pot starting from the zirconocene dichloride and 2 equiv of allyl Grignard. Under slightly modified reaction conditions, the corresponding β -allyltitanacyclobutane complex has also been prepared [<2003MI1287>](#), although this reaction almost certainly does not involve the formation of the analogous bis(allyl)titanocene intermediate (*vide infra*).



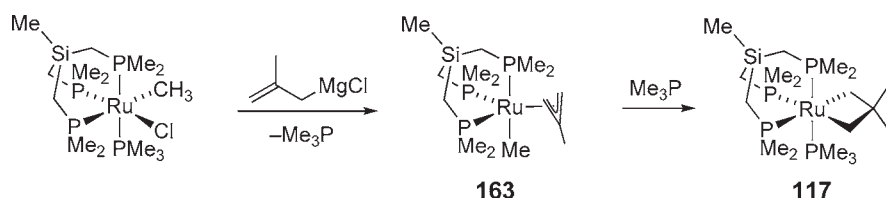
Scheme 36

A mechanistically obscure transformation occurs upon treatment of the tetramethylfulvene titanium complex **161** with methallyl Grignard, producing bridged titanacyclobutane complex **162**. This reaction is proposed to proceed by intramolecular alkylation at the central carbon of an η^4 -fulvene, η^3 -methallyl intermediate, but with due consideration

to the rearrangements above and other recent literature (*vide infra*), it is interesting to posit an internal equilibration to the η^5, η^1 -fulvene, η^1 -allyl form, followed by homolysis of the methylfulvene–metal bond and internal radical alkylation of the resulting η^3 -methallyl ligand (Equation 81) <1995OM5481>.

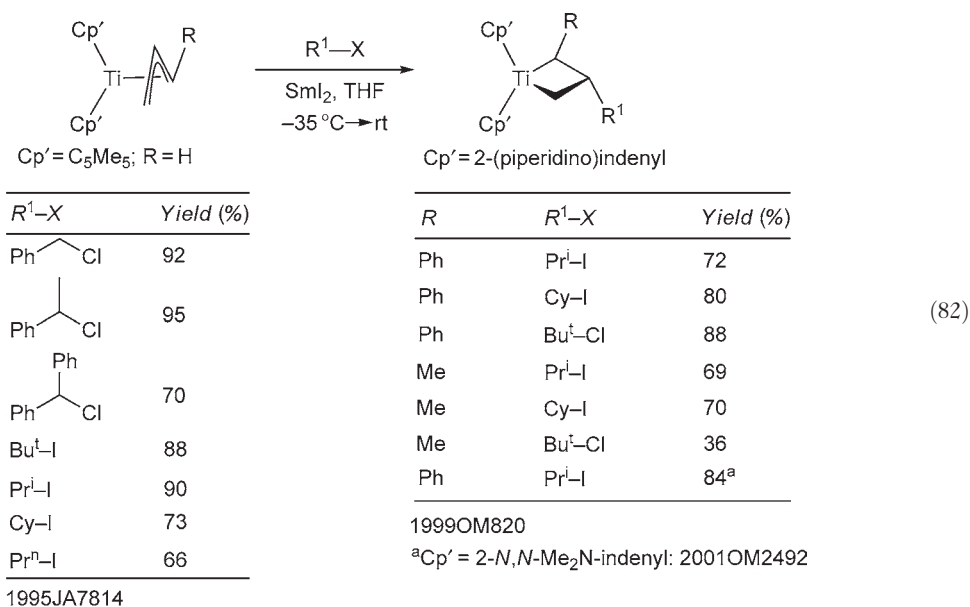


A superficially similar rearrangement has been observed upon treatment of ruthenium methallyl complex **163** with trimethylphosphine, which induces (reversible) methyl migration, providing β, β -dimethylruthenacyclobutane complex **117** in high yield (Scheme 37). The reaction is not considered to involve radical intermediates <1995JA3625, 1997JA11244>.



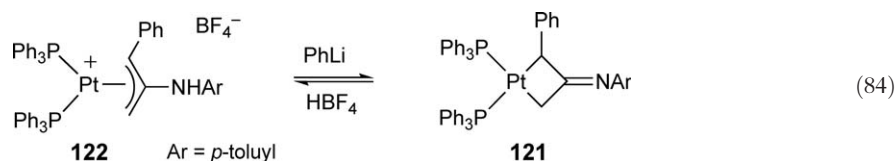
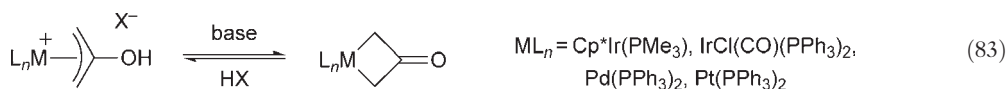
Scheme 37

Definitive, and general, free radical central carbon alkylation of η^3 -allyltitanocene complexes has been demonstrated, using several structurally similar but electronically variable Ti(III) systems <1995JA7814, 1999OM820, 2001OM2492>. Although a number of standard methods for the generation of organic free radicals can be adapted to this process, the use of $\text{SmI}_2 \cdot \text{THF}$ has proved to be the most general and, for some systems, compatible with *in situ* allylation/alkylation procedures. For substituted allyl ligands (crotyl, 1-phenylallyl), the use of electron-rich 2-dialkylaminoindenyl ancillary ligands provides the greatest generality and downstream reactivity. The results summarized in Equation (82) are limited to isolable titanacyclobutane complexes; an extended range of bis(dimethylaminoindenyl)titanacyclobutane complexes have been prepared by this methodology and converted to stereochemically pure 2,3-disubstituted cyclobutaneimine derivatives by *in situ* isonitrile insertion <2002OM1011> (see Section 2.12.6.2).

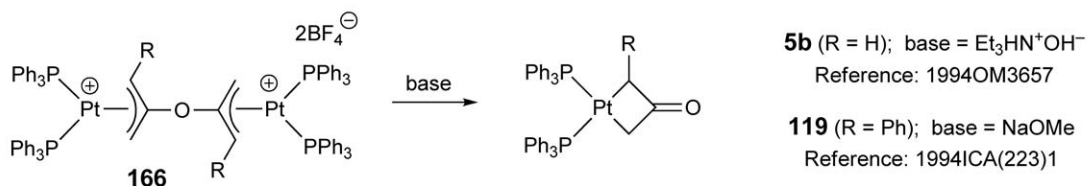
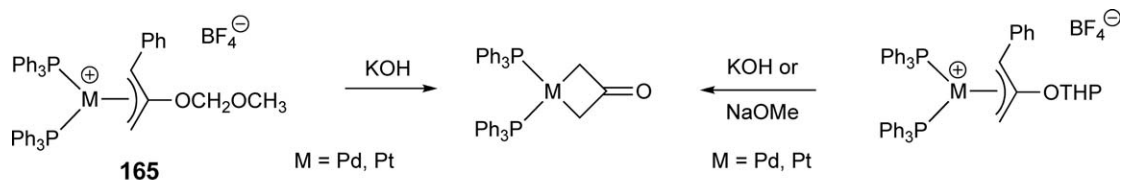
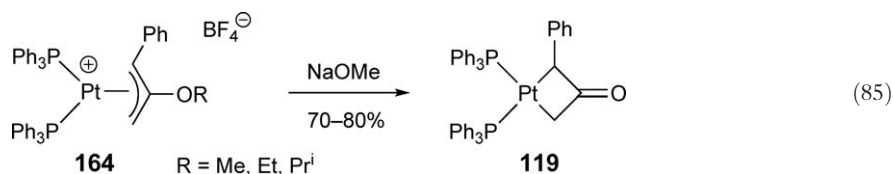


2.12.9.3.5 Deprotonation of 2-hydroxyallyl and 2-aminoallyl complexes

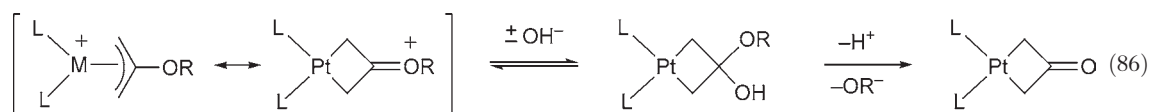
As discussed in Section 2.12.7, deprotonation of 2-hydroxyallyl palladium, platinum, and iridium complexes affords metallacyclobutanone complexes (Equation 83) <1993CC1039, 1995JOM143, 1997OM1159, 1998OM2953>. The reaction of 2-aminoallyl platinum complex **122** with strong base similarly results in the formation of azatrimethylenemethane complex **121**. The aminoallyl complex **122** is regenerated by protonation (Equation 84) <1994ICA1, 1995ICA1>.



Metallacyclobutanones are also obtained from the analogous alkoxyallyl complexes **164** under basic conditions, a reaction that proceeds via nucleophilic addition/elimination to the substituted central carbon (Equation 85) <1994ICA1>. This metal-directed reactivity has been extended to the base-promoted ‘deprotection’ of the corresponding acetal derivatives **165**, a reaction with no counterpart in typical organic acetal chemistry (Scheme 38) <1993CC1039, 1997OM3038>. Similar conversions of oxygen-linked diplatinum complexes **166** have been reported <1994OM3657, 1994ICA1>. The reaction proceeds by reversible nucleophilic addition to the electronically activated central carbon (Equation 86), as confirmed by an ^{18}O labeling experiment <1997OM3038>.

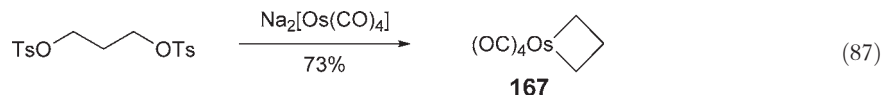


Scheme 38



2.12.9.3.6 Oxidative addition

Double displacement of 1,3-propanediol ditosylate is obtained from the reaction with the strongly nucleophilic dianion $\text{Na}_2[\text{Os}(\text{CO})_4]$, a formal double oxidative addition reaction, providing osmacyclobutane complex **167** (Equation 87) <1992ICA57>.



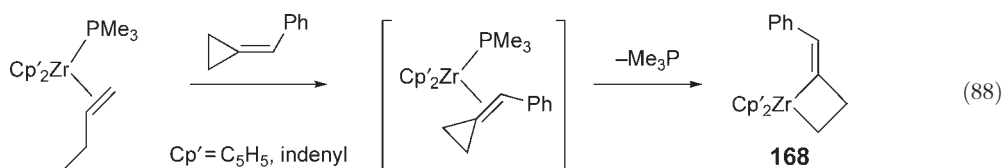
2.12.10 Ring Synthesis by Transformation of Another Ring

In this section, the synthesis of four-membered metallacycles by transformations of larger or smaller rings is discussed. The transmetalation of metallacyclobutene complexes is covered in Section 2.12.6.1.2.

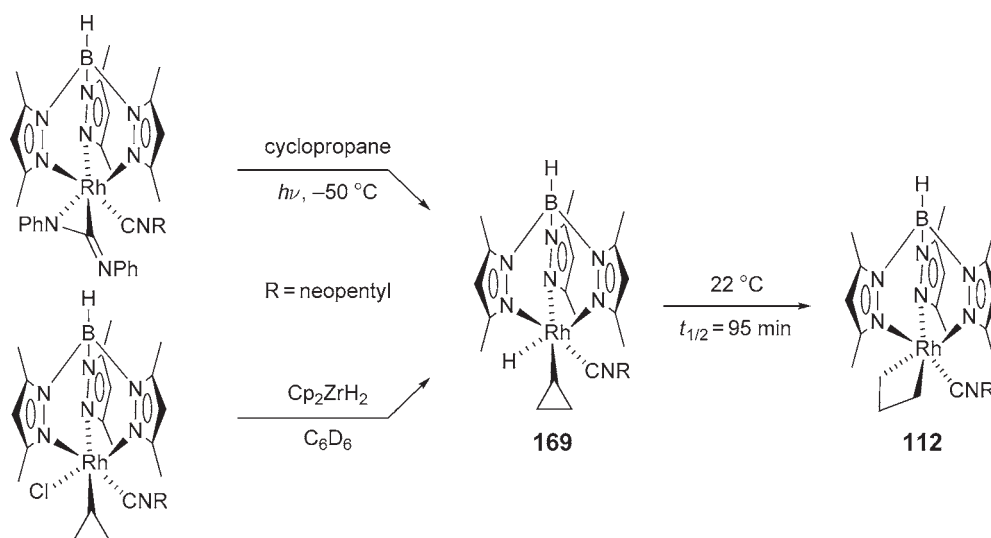
2.12.10.1 Oxidative Addition of Cyclopropanes and Cyclopropenes

Cyclopropane oxidative addition to low-valent transition metals has been intensively investigated in the decades since the first metallacyclobutane complex was prepared by this methodology <1996CHEC-II(1b)887>. Comprehensive reviews on this topic are available <1980CCR149, 1994CRV2241>.

Cyclopropane activation continues to be reported across the transition series. Consistent with earlier results, the insertion of zirconium(II) into a methylenecyclopropane provides the α -methyleneczirconacyclobutane complexes **168**. An intermediate Zr(II) methylenecyclopropane complex is isolated from the reaction of the parent zirconocene complex, but no intermediate is observed using the more reactive bis(indenyl) template (Equation 88) <2002JOM288>.

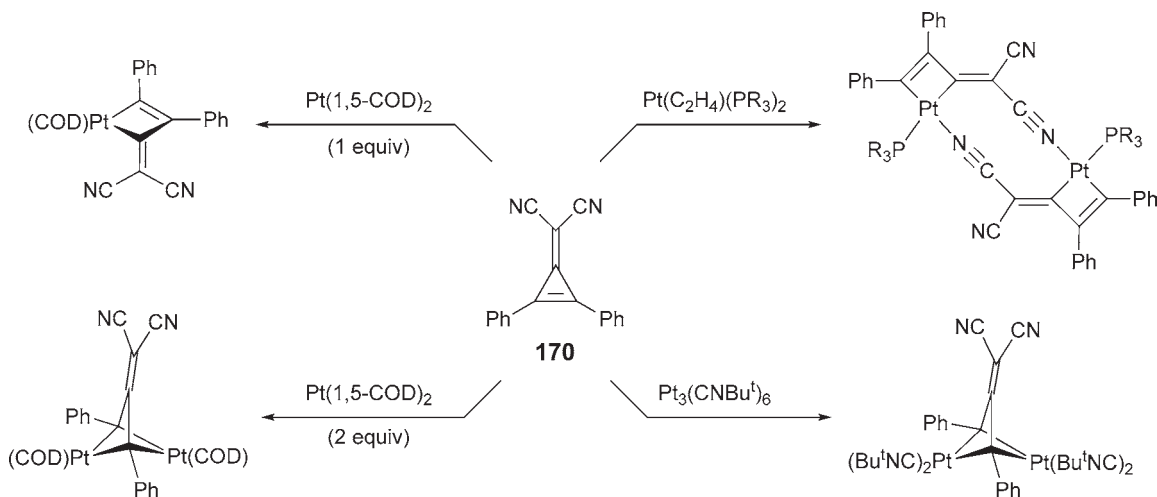


Following Bergman's initial report <1984JA7272, 1986JA7346>, cyclopropane C–H activation and subsequent isomerization of the intermediate σ -cyclopropylrhodium hydride **169** to the rhodacyclobutane complex **112** has been demonstrated for a tris(pyrazolyl)borate analogue (Scheme 39), confirming that net cyclopropane oxidative addition to rhodium follows a rather unexpected indirect mechanistic course <1998OM4484>.



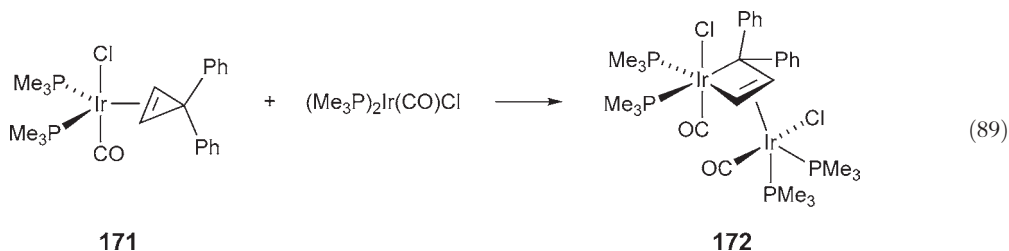
Scheme 39

Oxidative activation of cyclopropenes is much less frequently encountered. The reactions of various platinum(0) complexes with the electron-deficient methylenecyclopropene **170** affords platinacyclobutene complexes, as reported nearly 30 years ago [\[1978ICA19\]](#). More recent investigation has established that in the presence of two or more equivalents of the metal, bicyclic diplatinum complexes can be generated (**Scheme 40**) [\[1996JBS75\]](#).



Scheme 40

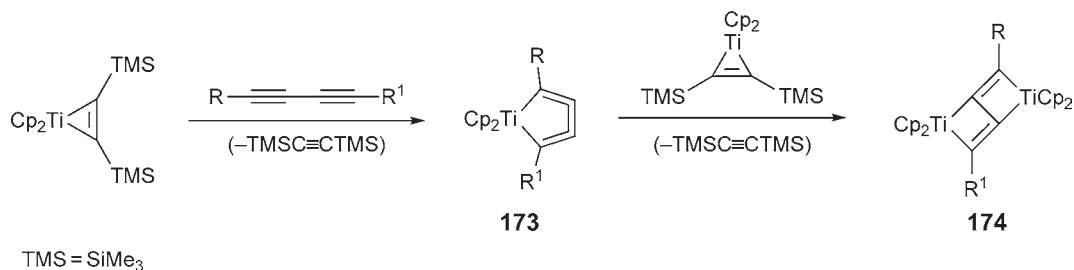
The iridium cyclopropene complex **171** reacts with an additional equivalent of Ir(I) to open the strained ring, affording bimetallic iridacyclobutene complex **172** (Equation 89) [\[1994JA10032\]](#). Labeling experiments were used to establish that the external Ir(I) reagent mediates the oxidative activation of the intact coordinated cyclopropene, with the original Ir(I)–cyclopropene coordination retained throughout the reaction.



2.12.10.2 Ring Contraction

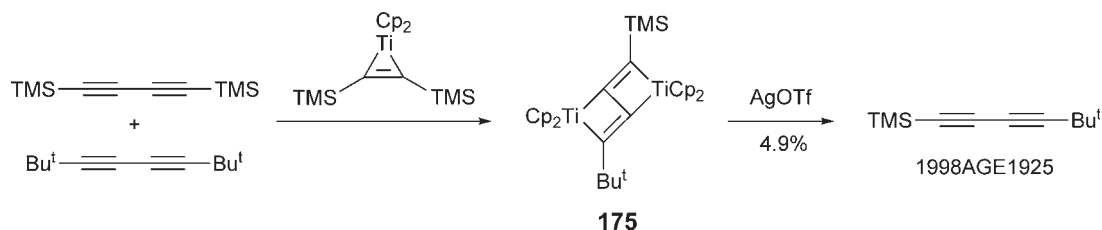
A delightfully odd synthesis of fused dititanabicyclo[2.2.0]butadiene complexes **174** has been intensively investigated. This interesting ring system was originally isolated from reactions of Cp_2TiCl_2 with sodium alkynides [\[1969JOM87, 1976JA1376\]](#). Treatment of disubstituted butadiynes with a preformed titanocene(II) source provides identical products, visualized most easily as not-so-straightforward butadiyne coordination complexes (**Scheme 41**). This subject has been reviewed [\[2003OM884, 2000CRV2835, 2000ACR119\]](#). The initial interaction of the butadiyne with titanium(II) leads to geometrically challenged titanacumulene complex **173**, visualized imperfectly as a titana(IV)cyclopentatriene. This isolable cumulene intermediate captures a second equivalent of Ti(II) and undergoes bond reorganization, reasonably described as an internal redox tautomerization [\[1996AGE1112\]](#). A reaction combining two different diyne derivatives proceeded to end-exchanged titanacumulene complex **175**, an unprecedented σ -bond metathesis reaction, albeit in vanishing low yield (**Scheme 42**) [\[1998AGE1925\]](#). The process has been extended to zirconium and to substrates bearing multiple diyne moieties, leading to homopolymetallic complexes (e.g., **176**) [\[1997AGE2615, 1999OM2906\]](#) and, in some cases, heteropolymetallic Ti/Si and Zr/Si complexes (e.g., **177** and **178**), depending on the substrate and reaction conditions (Zr: [\[1995JA2665, 1997JA12842\]](#), Ti: [\[2001JOM30, 2000OM1198\]](#)). A similar product arises from

the reaction of $\text{Li}[\text{Cp}_2\text{Ti}^{\text{III}}(\eta^1\text{-C}\equiv\text{CBu}^t)_2]$ in the presence of CO_2 , presumably via initial oxidation [<2001OM5289>](#). Protonolysis of the Zr/Si complexes provides the expected silacyclobutenes. The structure, conformation, and reactions of these unusual fused-ring systems have been interrogated computationally [<1997AGE606, 1998JA6952>](#).

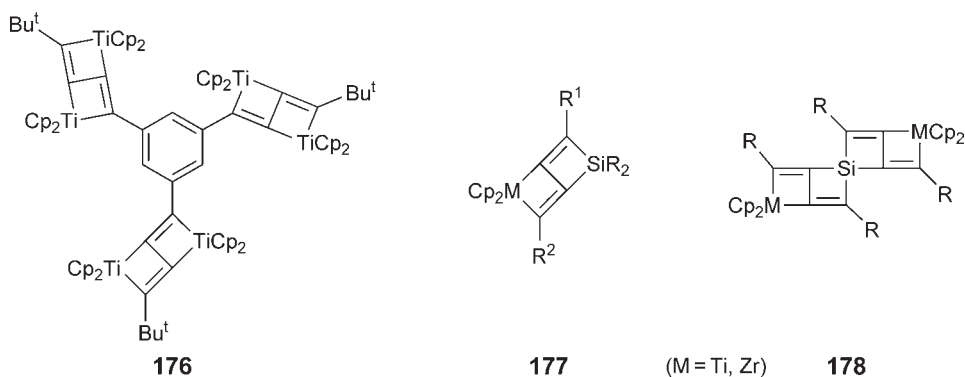


<i>R</i>	<i>R</i> ¹	Yield 174 (%)	Reference
Bu ^t	Bu ^t	41	1994JOMC4, 1995CB967
Bu ^t	SiMe ₃	91	1994JOMC4
Ph	SiMe ₃	33	1994JOMC4, 1995OM2961
Me	Me	60	1999JOM125

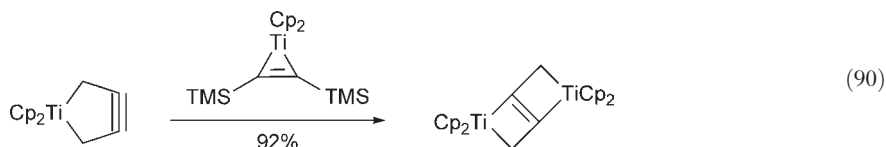
Scheme 41



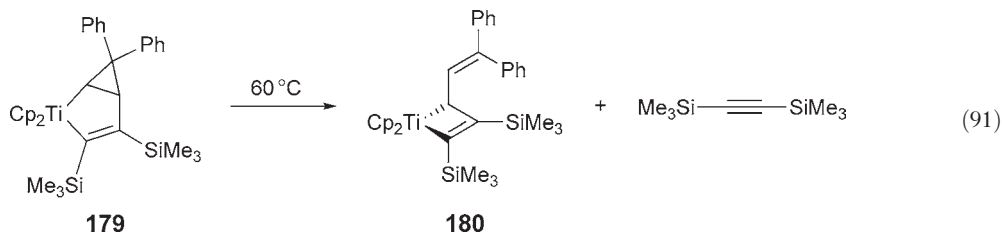
Scheme 42



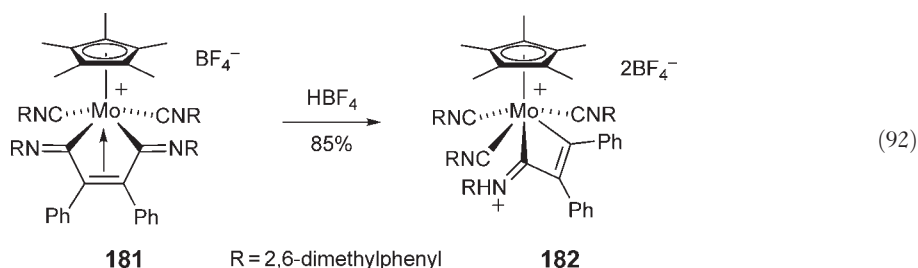
The synthesis of an alternative, less-unsaturated, fused-ring ditanacyclobutene complex has been reported from the addition of $\text{Ti}(\text{II})$ to a titanacyclopentynes complex (Equation 90) [<2004CC2074>](#) or by a borane-induced reductive rearrangement [<2005OM5916>](#).



At 60 °C, bicyclic titanacyclopentene complex **179** rearranges to 2-vinyl-substituted titanacyclobutene complex **180** in indeterminate yield (Equation 91) <1993CB1541>. This transformation proceeds by bis(trimethylsilyl)ethyne extrusion, rearrangement of the residual coordinated cyclopropene to vinylalkylidene, and [2+2] cycloaddition to reincorporate alkyne.



Finally, in an interesting and unique transformation, the de-insertion of isonitrile from the nominally eight-coordinate molybdacyclopentenediimine complex **181** is induced upon protonation with strong Brønsted acid (Equation 92); it is not obvious why the ring-contracted molybdacyclobutenimine product **182** should be thermodynamically more stable than the simple product of protonation <2001JCD1284>.



2.12.11 Synthesis of Particular Compound Classes and Critical Comparison of the Various Pathways

All of the compound classes discussed herein were developed for fundamental purposes: (1) to delineate mechanistic intermediates in important catalytic reactions (e.g., the olefin metathesis); (2) to define the conceptual basis for rational synthetic manipulation; and (3) to introduce novel reactive intermediates and unusual organometallic constructs for potential applications to organic synthesis and materials chemistry (Section 2.12.12). As such, it is almost certainly premature to engage in a critical parsing of the methodology. It should be clear, however, that among the pathways for four-membered metallacycle synthesis discussed in this and earlier reviews <1996CHEC-II(1b)887>, several must be considered sufficiently general to warrant further development. Cyclopropane ring-opening and [2+2] cycloaddition strategies continue to be attractive for further development; both incorporate readily available organic precursors and, typically, inherently high downstream reactivity. The very general [2+2] cycloaddition/cycloreversion manifold, in particular, has enormous potential for being incorporated into new transformations beyond the olefin metathesis and Dötz-derived arene constructions.

Among more recent innovations, the alkylative metallacyclobutane and metallacyclobutene synthesis, involving central carbon addition and addition/elimination reactivity patterns, holds considerable promise for near-term synthetic developments (Section 2.12.12). This is equally true in both the nucleophilic and free radical versions of this process, for both catalytic and stoichiometric transformations and multistep reaction cascades.

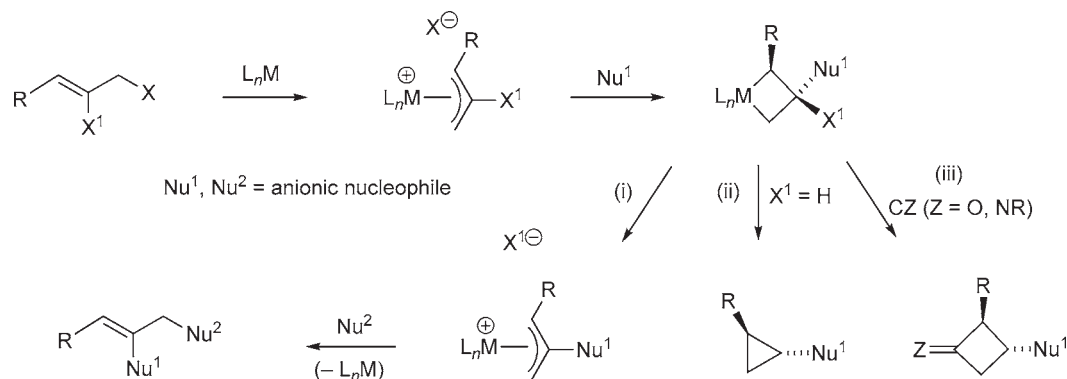
2.12.12 Important Compounds and Applications

In addition to the stoichiometric preparative and reactivity manifolds discussed throughout this chapter, metallacyclobutane and metallacyclobutene intermediates play an essential role in a range of synthetically valuable, or potentially valuable, synthetic transformations, both catalytic and stoichiometric. The tremendous range of

significant applications of the catalytic olefin and alkyne metathesis reaction has been thoroughly reviewed and will not be further discussed here <1995ACR446, 2003AGE1900, 2004T7117, 2005NJC42, B-2003MI1>.

2.12.12.1 Catalytic η^3 -Allyl Central Carbon Addition

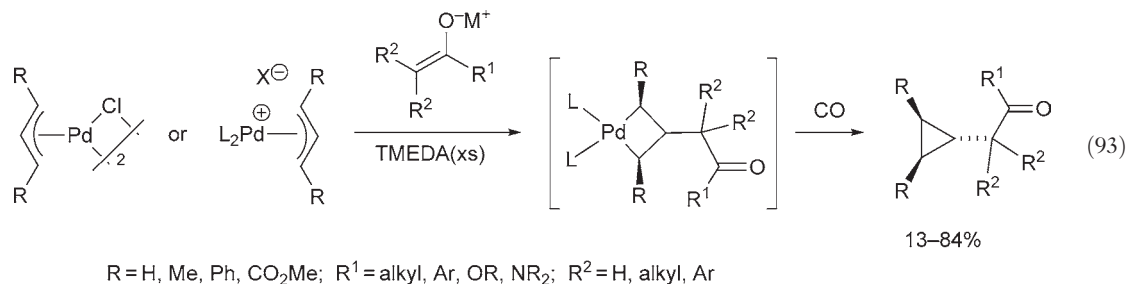
A range of potentially valuable transformations involving central carbon nucleophilic addition has emerged, highlighting the growing attention to applications of metallacyclobutane and metallacyclobutene intermediates in organic synthesis. The most significant developments involve group 10 metals, coupling central carbon alkylation with allylic substitution or reductive processes (Scheme 43, paths i/ii). This has resulted in catalytic syntheses of functionalized cyclopropanes and highly substituted alkenes. A stoichiometric synthesis of cyclobutanone derivatives has also been realized, combining the titanium-mediated free radical alkylative metallacyclobutane synthesis with small molecule insertion (Scheme 43, path iii).



Scheme 43

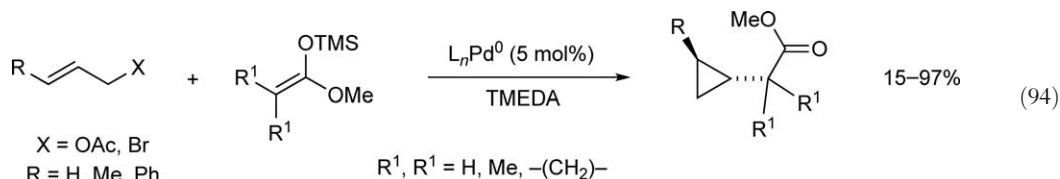
2.12.12.1.1 Alkylative cyclopropanation reactions

Alkylation of the central carbon of allylpalladium complexes with 'soft' nucleophiles results in the formation of palladacyclobutane intermediates. Under appropriate conditions, reductive elimination can be induced to yield substituted cyclopropanes. First identified by Hegedus <1980JOC5193>, the scope of this 'alkylative cyclopropanation' has been expanded to encompass a broad range of pronucleophiles of pK_a 20–30, including anions derived from esters, amides, sulfones, nitriles, and ketones (Equation 93) <1992AGE234, 1993CC615, 1994AGE1280, 1995AGE100>. In stoichiometric form, TMEDA has emerged as the ligand of choice for palladium; this ligand also activates the nucleophile through complexation to the main group counterion. The presence of carbon monoxide is required to promote the reductive elimination, presumably by coordinative destabilization of the palladium(II) intermediate.



Catalytic cyclopropanation reactions can also be accomplished, using nucleophiles generated from silyl ketene acetals (Equation 94) <1991JOC3924, 1992JMOC19, 1993JOMC6, 2000CC771>. The presence of acetate anion, either as an additive or generated *in situ*, is required to activate the silyl acetal toward nucleophilic addition. A platinum-catalyzed version of this reaction has also been reported, although heat or other additives are necessary to

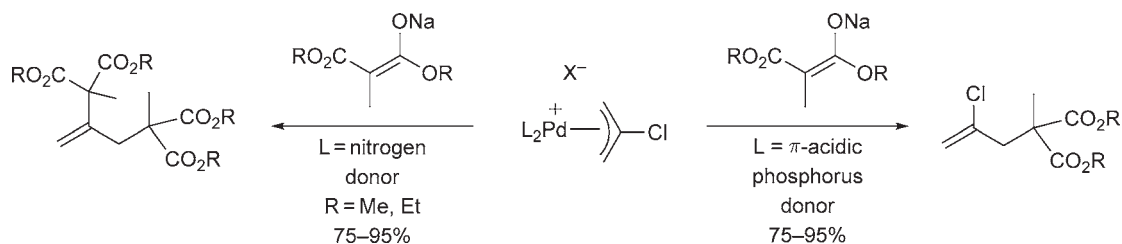
promote the reductive step <1991OM3956>. Platinum, in general, resists the reductive elimination of sp^3 -hybridized alkyl ligands.



By using other chelating bis(amine) ligands, greater regioselectivity for central carbon alkylation over competitive terminal carbon addition has been realized <1998JA10391, 1999CL49>. Intramolecular cyclization has also been demonstrated using a nitrogen nucleophile <2001EJO707>. An asymmetric version of the cyclopropanation reaction, using oxazolidinylpyrazole-based ligands and a palladium catalyst, has been developed <1999TL3597> and reviewed <2000JSO745>.

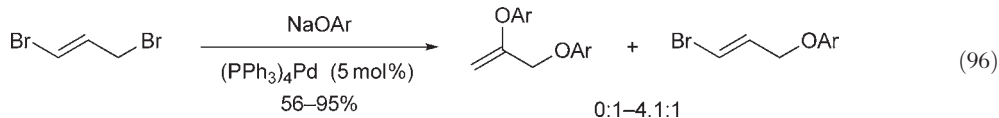
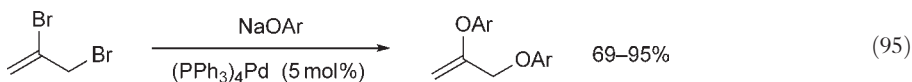
2.12.12.1.2 Double nucleophilic substitution reactions

The presence of a suitable leaving group at the β -allyl position activates this site toward nucleophilic addition/elimination, a net substitution reaction proceeding via metallacyclobutane intermediates <1998JMT205>. In stoichiometric reactions using palladium, the use of nitrogen ancillary ligands was reported to promote the central carbon substitution; π -acceptor phosphine ligands conversely favored terminal substitution (Scheme 44). Thus, using nitrogen ligands, double alkylation was observed, with initial central carbon substitution followed by terminal carbon addition and release of the functionalized alkene. Regardless of the ancillary ligands, the use of slightly more stabilized nucleophiles (e.g., methyl methylacetoacetate) affords products arising from selective terminal carbon attack <1995AGE2551, 1997OM1058>.

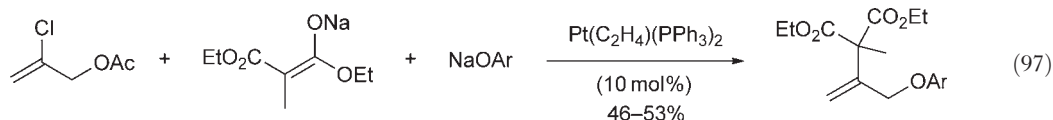


Scheme 44

Regioselectivity issues in allylpalladium and allylplatinum substitution reactions are yet to be completely resolved. Phosphorus rather than nitrogen ligands are required to promote central carbon substitution using harder nucleophiles, such as aryl oxides; in such cases, the use of TMEDA as the ancillary ligand leads to preferential terminal substitution. The incorporation of dense substitution on the allylic substrate disfavors the double substitution. Surprisingly, 1,3-dibromopropene is a good substrate for double displacement (Equation 95), despite the obvious absence of a leaving group at the central position and the general observation that bromide as the leaving group diminishes the propensity for central carbon addition (Equation 96) <1997TL8181, 1998JA9283>. This reaction is proposed to proceed by the rearrangement of the initial 2-bromo-3-aryloxypalladacyclobutane intermediate to the 1-bromo-2-aryloxyallylpropene complex, an isomerization promoted by adventitious water.

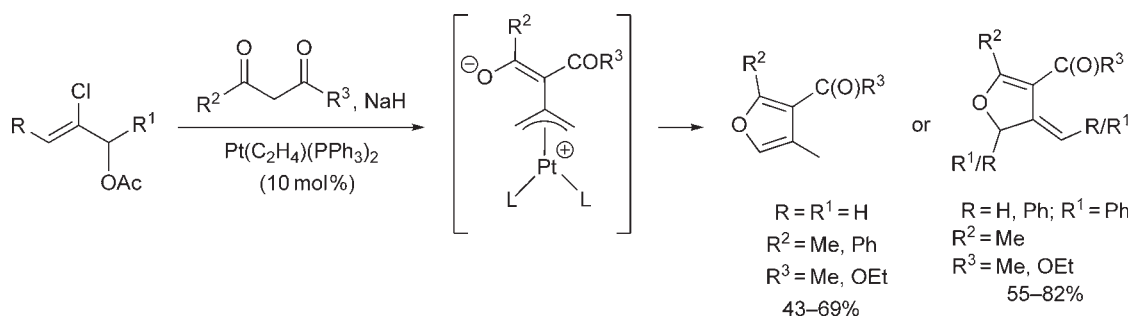


Corresponding platinum catalysts can be used for regioselective double substitution using two different nucleophiles. The dimethylmalonate anion undergoes a selective catalytic central carbon substitution even in the presence of an aryl oxide anion; the aryl oxide subsequently undergoes a standard terminal substitution (Equation 97). Electron-deficient aryl oxide nucleophiles are less effective, giving an increased proportion of malonate-derived double substitution. The corresponding palladium catalyst returns higher overall yields, but diminished regioselectivity <2000OM979>.



A theoretical investigation concluded that central carbon substitution is favored over terminal attack for platinum while for palladium, terminal substitution and the formation of an η^2 -olefin complex is preferred <1999IC370>. Further investigation into the roles played by the ligands and the nucleophile in the double substitution of bifunctional olefins remains ongoing <2004JA16087, 2003JOC3918, 2002TL8989>.

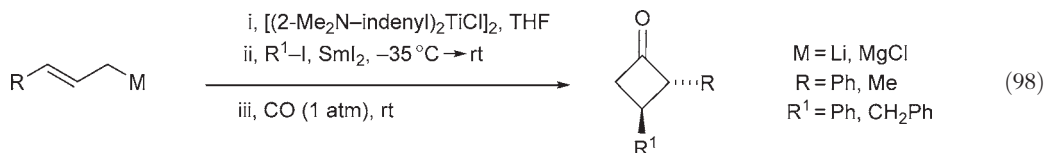
The synthesis of substituted furans has been reported using this platinum-catalyzed double substitution. After initial central carbon substitution, the reaction proceeds by the intramolecular capture of the enolate oxygen by the terminal carbon best capable of stabilizing positive-charge character (Scheme 45). Less-stabilized nucleophiles, including diethylmalonate, exhibit typical terminal alkylation <1994JA4125, 1999JOC7523, 2000OM979>. A similar synthesis of substituted furans has been reported starting from 3-chloro-1,3-diene monoepoxide <2000T2231>.



Scheme 45

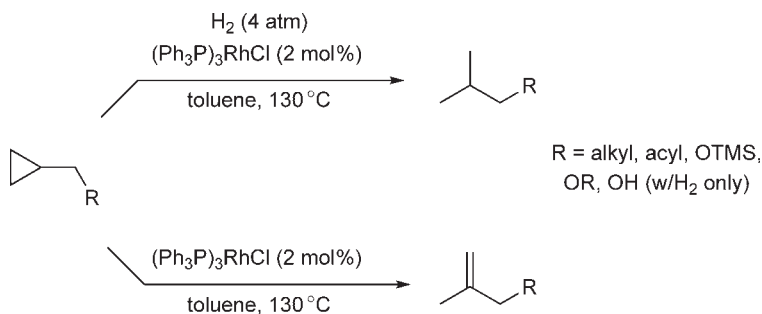
2.12.12.1.3 Cyclobutanone synthesis

Central carbon radical alkylation of η^3 -allyltitanocene complexes (Section 2.12.9.3.4) has been combined with carbonylation into a three-component synthesis of stereochemically pure 2,3-disubstituted cyclobutanones (Equation 98) <2001JA8872>. This cascade can be conducted stepwise in high yield or performed sequentially in a one-pot process, without isolation of the allyltitanium and titanacyclobutane intermediates, albeit in moderate isolated yields.



2.12.12.2 Catalytic Processing of Cyclopropanes

The hydrogenolysis of substituted cyclopropanes to geminal dimethyl-substituted alkanes has been known for nearly half a century, catalyzed by heterogeneous (supported) noble metals. Catalysts for the corresponding homogeneous process have recently been reported (Scheme 46); in the absence of hydrogen, the metallacyclobutane intermediate decomposes by β -hydride elimination/reductive elimination to give the corresponding alkene <2003JA886>.



Scheme 46

2.12.13 Further Developments

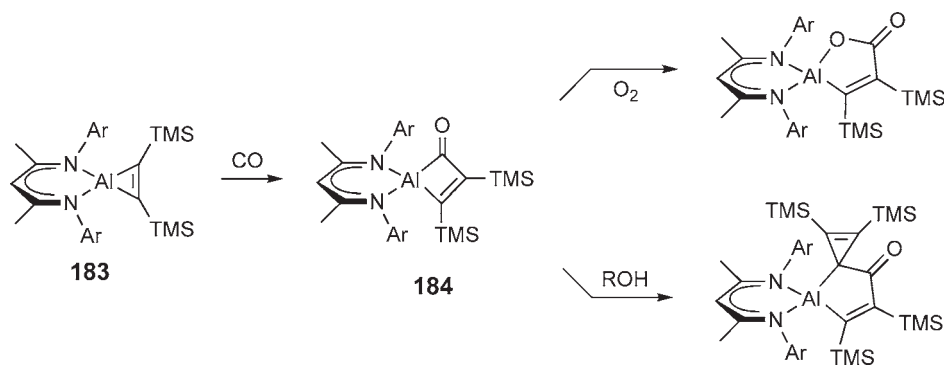
New theoretical/computational investigations pertaining to metalloaromatic systems and the olefin metathesis reaction have appeared, complementing the discussion in Section 2.12.3. Using DFT methodology, the aromaticity of titanacyclobutadiene and tungstacyclobutadiene complexes has been compared <2006OM1924> and the reactivity of both rhenacyclobutane <2007JPO11> and molybdacyclobutane <2007MI2054> intermediates in the olefin metathesis reactions has also been further delineated.

New iridacyclobutadiene intermediates have been isolated in the [2+2+1+1] cycloaddition reaction that yields iridabenzene complexes from two alkynes, carbon monosulfide, and the metal (Section 2.12.5). The iridacyclobutadiene ring can be transformed, alternatively, into the corresponding η^5 -cyclopentadienyl complex or into the iridabenzene product by reaction with additional alkyne, depending on the substituents present on both the iridacyclobutadiene ring and the incoming alkyne.

Further investigation of the equilibrium between titanacyclobutene and titanium vinyl alkylidene complexes, as discussed in Section 2.12.6.1.4, was reported recently <2007CEJ4074>, along with the incorporation of this reactivity pattern into the synthesis of conjugated dienes, homoallylic alcohols, vinylcyclopropanes, and phosphacyclobutenes from γ -chloroallyl sulfides and a source of titanocene(II).

The isolation of coordinatively unsaturated ruthenacyclobutane intermediates in the olefin metathesis reaction has been extended, providing important new mechanistic insights into the ruthenium-catalyzed metathesis (Sections 2.12.6.2 and 2.12.9.3) <2006JA16048, 2007JA1698>. New molybdacyclobutane complexes have been prepared <2006JA9038> that, in some cases, undergo intramolecular C–H activation at the two β -positions to produce both σ -alkyl- π -allyl and conjugated diene complexes. No evidence for metathesis processes was observed. Intramolecular carbon–carbon bond activation was noted for a rhodacyclobutane complex incorporating an agostic carbon–carbon bond interaction to a neighboring cyclopropane moiety <2006AGE452>.

Complementing the transition metal chemistry reported in Section 2.12.9.2, aluminacyclopropene complexes **183** undergo insertion of CO or *t*-butylisocyanide into the carbon–aluminum bond to yield 2-aluminacyclobutenone complexes **184** or the analogous 2-aluminacyclobutenimine complexes, respectively (Scheme 47) <2006CC1763>.



Scheme 47

In the presence of molecular oxygen, oxygenation of the Al–C(O) bond is obtained, whereas the reaction with alcohols affords spirocyclic compounds <2007OM1308>.

Thermally stable polymers containing titanacyclobutene units have been synthesized by central carbon radical alkylation (Section 2.12.9.2.4) of a 1,4-bis(η^3 -propargyltitanium)benzene complex. The reaction is remarkably clean and efficient; subsequent protonation by ethereal HCl produces the unsaturated organic polymer and $\text{Cp}^*_2\text{TiCl}_2$ <2005MI511>.

Finally, a range of platinacyclobutane complexes tethered to biologically relevant amino acid, steroid, nucleoside, and carbohydrate components has been synthesized by oxidative addition of the corresponding cyclopropane derivatives. The complexes were targeted for use as novel prodrugs, presumably capable of delivering cisplatin and its analogues by reductive elimination, have as yet to show significant anticancer activity <2006OM4537>.

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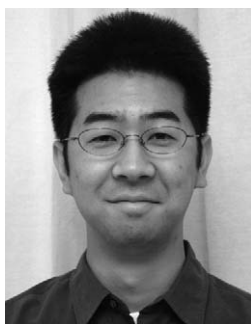
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2.13

Four-membered Rings with Two Nitrogen Atoms

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2.13.1 Introduction

2.13.1.1 Historical Perspective

Four-membered rings containing two nitrogen atoms are known as diazetidines. Depending upon the position of the nitrogen atom in the ring they have been classified into three different categories: (i) diazetidines, (ii) diazetines, and (iii) diazetes. Diazetidines are saturated four-membered rings containing two nitrogen atoms adjacent to each other, whereas, diazetines are four-membered rings with two adjacent nitrogen atoms and one double bond in the ring. In contrast, diazetes are four-membered rings with two nitrogen atoms and two double bonds in the ring.

Historically, Hofmann reported in 1858 the first example of diazetidines by dimerization of phenyl isocyanate in the presence of triphenylphosphine <1858MI349>.

Among all the different four-membered heterocycles containing two nitrogen atoms, diazetidines are the most well-known class of compounds. They have attracted the most attention of the scientific community, due to their close structural similarity to the highly potent β -lactam antibiotics and related antibiotics such as carbapenems, theinamycins, etc. <1983JOC4567, 1984JOC113, 1984JOC2204, 1984JOC4415, 1986JOC1530, 1986JOC1537, 1987JOC4107>. Several studies on the aza analogues of β -lactam antibiotics such as penicillin and cephalosporins have also been reported <1985DEP221735>. Some of the interesting analogues were also explored as anticancer agents <1986ABC1757> and others as antihypertensive and antispasmodic agents <1993MI357>.

An innumerable number of applications in research and industry have led to a continued interest in the area of four-membered heterocycles containing two nitrogen atoms. A detailed account has been compiled in CHEC-II(1996), covering the literature that appeared between 1980 and 1995 <1996CHEC-II(1B)911>. In the present chapter progress in this class of heterocycles during 1995–2006 is described. However, some of the earlier aspects are included to provide continuity and a better understanding of this topic.

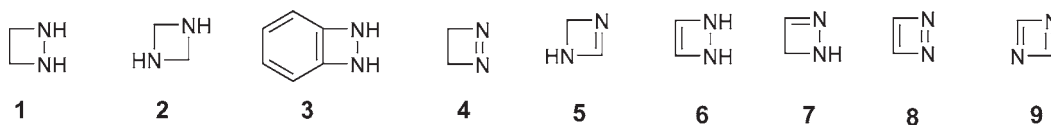
2.13.1.2 Different Structural Types and Nomenclature

The nomenclature and structural types have remained the same during the last decade.

Diazetidines. A saturated four-membered ring containing two adjacent nitrogen atoms is named a 1,2-diazetidine **1**. When the two nitrogen atoms and the two carbon atoms are alternatively present in the four-membered ring, it is named a 1,3-diazetidine **2**, which is also known as uretidine. Fused multinuclear heterocyclic systems are known as diazacyclobutane derivatives. For example, 3,4-benzo-1,2-diazetidine is referred to as 1,2-diaza-3,4-benzocyclobutane **3**.

Diazetines. A four-membered ring with two adjacent nitrogen atoms and one double bond in the ring is called 1,2-diazetine **4** or, less commonly, 1,2-diazene. According to IUPAC nomenclature, 1,2-diazetine is named as Δ^1 -1,2-diazetine or 3*H*,4*H*-diazetine. Similarly, 1,3-diazetine is named as Δ^2 -1,3-diazetine or 1*H*,4*H*-diazetine **5**. When two nitrogen atoms are in 1 and 3 positions, the heterocycle is referred to as 1,3-diazetine **5** or commonly as uretine. The compound **6** is called a Δ^3 -1,2-diazetine or 1*H*,4*H*-diazetine and compound **7** is called Δ^2 -1,2-diazetine or 1*H*,4*H*-diazetine.

Diazetes. A four-membered ring with two nitrogen atoms and two double bonds is called a diazete. These compounds are also described as 1,2-diazacyclobut-1,3-diene **8** or 1,2-diazete and 1,3-diazacyclobut-1,3-diene **9** or 1,3-diazete. This class of compounds is less known in the literature.



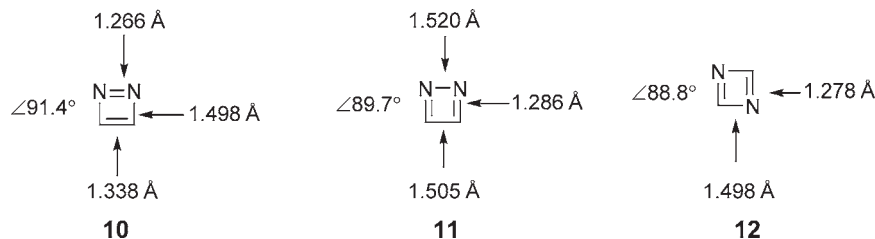
2.13.2 Theoretical Methods

Elucidation of the electronic structure of four-membered heterocycles with two nitrogen atoms has been approached through various theoretical methods. This has been reviewed in CHEC-II(1996) <1996CHEC-II(1B)911>. One of the early *ab initio* calculations by Moffat on the possible formation of diazetidines or diazetes gave interesting insight into ‘dissociative’ and ‘nondissociative’ dimerization of cyanamides <1983JMT(94)261>. Misra and co-workers <1988IJA653> calculated the topological resonance energy (TRE) for several cyclic compounds and predicted that 1,2-diazetidine is more stable than 1,3-diazetidine based on the TRE values. They found that the increase in the TRE value decreases the anti-aromaticity and increases the stability of the molecule. The TRE value of 0.0831 β unit for 1,2-diazetidine indicated some nonaromatic character for this heterocycle. Further, Politzer and co-workers used an *ab initio*-shell self-consistent field (SCF) molecular orbital approach in conjugation with an isodesmic reaction procedure and found that the $\Delta E_{\text{isodesmic}}$ values of 16.7 kcal mol⁻¹ (69.9 kJ mol⁻¹) for 1,3-diazetidine and 25.3 kcal mol⁻¹ (105.9 kJ mol⁻¹) for 1,2-diazetidine, suggesting that 1,2-diazetidines are more stable than 1,3-diazetidines <1990JMT(207)193>.

1,2-Diazete (1,2-diazacyclobut-1,3-diene) and 1,3-diazete (1,3-diazacyclobutadiene) are very high-energy molecules and none of the derivatives have been isolated and fully characterized. There has been considerable interest in exploring the thermodynamic properties of these molecules. Jursic <2001JST(536)143> has employed a high-level *ab initio* and density functional theory (DFT) method to generate the structure and energetic properties for the two-dimensional as well as the three-dimensional structure of diazete. Their stabilities were estimated by computing the enthalpy of formation and the enthalpy of a possible cycloaddition reaction for their preparation. Both two- and three-dimensional isomers should be highly energetic materials and should easily decompose and would be very difficult to prepare. Computed infrared (IR) spectra can be used as guidance for detecting these species in the reaction mixture in low-temperature matrix experiments. It is assumed that the double bond in 1, 2-diazete **8** is localized between the atoms of the same kind, that is, C–C and N–N.

In the early 1990s, Schoeller and Busch calculated bonding parameters and energies at the multiconfigurational SCF (MCSCF) level of the parent 1,2-diazete **10** and **11** and 1,3-diazete **12** <1993AGE617>. The 1,3-diazete can be considered as a ‘push–pull’ cyclobutadiene; its singlet ground state is stabilized relative to that of cyclobutadiene. Its valence isomerization proceeds through a planar transition structure with *C*₂ symmetry. The 1,2-diazetes are higher in

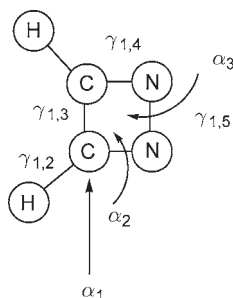
energy than their 1,3-isomers. The 1,2-diazete with two C=N bonds **11** is higher in energy by 12.1 kcal mol⁻¹ (50.7 kJ mol⁻¹), and that with N=N and C=C **10** by 22.5 kcal mol⁻¹ (94.2 kJ mol⁻¹), than the 1,3-isomer **12**.



Facelli has also carried out optimization of geometries for 1,2-diazete (**10** and **11**) and 1,3-diazete **12** using the GAUSSIAN 86 molecular package <1991JMT(236)119>. It is interesting to note that nitrogen atoms in a 1,3-diazete exhibit the largest electronegativity, probably because the electrostatic repulsion of negative and positive centers is reduced on the account of the *trans*-configuration. Bonačić-Koutecký *et al.* have calculated the symmetry state and the energy associated with various levels of protonated 1,3-diazacyclobutadienes <1989JA6140>.

Jursic <2001JST(536)143> found that the C-C bond distance $\gamma_{1,3}$ should be similar to ethylene (~1.33 Å); however, none of the calculations gave a bond distance near to ethylene (Table 1, $\gamma_{1,3}$). On the other hand, the $\gamma_{1,3}$ (C-C) bond computed by B3LYP/6-31G(d)/6-311G(2d,2p) is 1.5 Å which is close to the C-C bond distance in ethane (1.54 Å). The N-N bond distance in 1,2-diazete is even longer ($\gamma_{1,5}$) than the N-N single bond distance in hydrazine 1.47 Å. Therefore, most of the electron density is located between the C and N atom. The computed bond distance between C-N ($\gamma_{1,4}$) is quite close to that observed in methyleneimine (1.271 Å) and 1.284 Å (for 1,2-diazete) based on the B3LYP/6-311G(2d,2p) method.

Table 1 Computed structural properties of 1,2-diazacyclobutadiene^a **10**

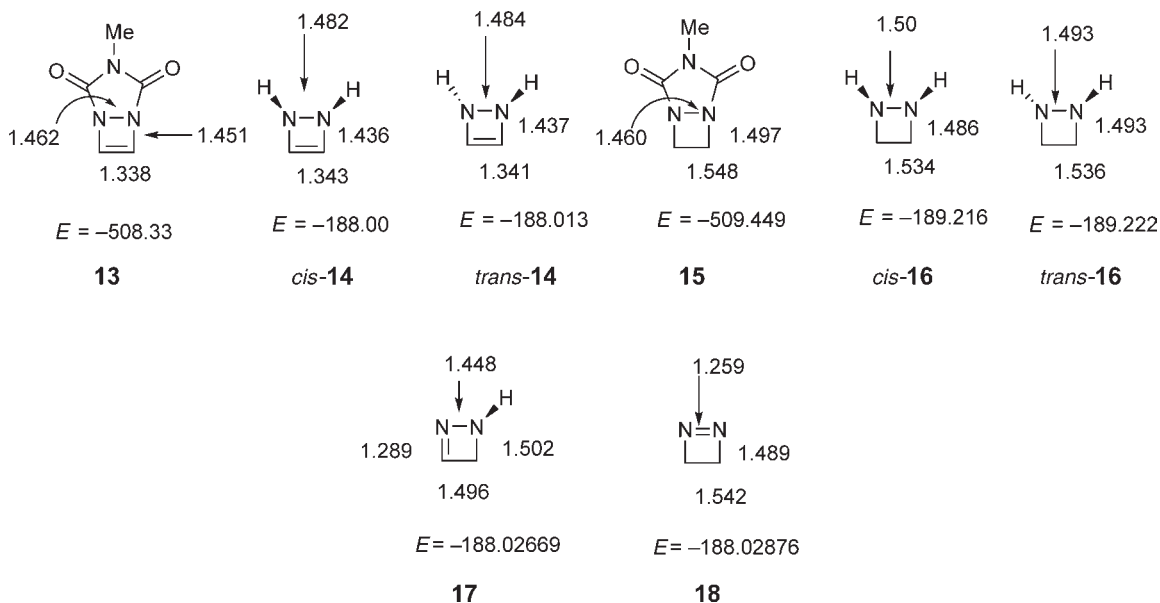


Theory	$\gamma_{1,2}$	$\gamma_{1,3}$	$\gamma_{1,4}$	$\gamma_{1,5}$	α_1	α_2	α_3
MP2/6-31G(d)	1.093	1.482	1.306	1.693	126.6	94.6	85.4
B-3LYP/6-31G(d)	1.092	1.500	1.284	1.651	127.6	93.4	86.6
BLYP/6-31G(d)	1.100	1.496	1.300	1.726	126.6	95.0	84.9
SVWN/6-31G(d)	1.102	1.490	1.285	1.630	127.2	93.00	86.9
B-3LYP/6-311G(2d,2p)	1.087	1.502	1.277	1.645	127.4	93.20	86.8
BLYP/6-311G(2d,2p)	1.095	1.497	1.292	1.720	126.6	95.0	85.0
SVWN/6-311G(2d,2p)	1.097	1.492	1.277	1.624	127.0	95.0	87.0

^a γ values are in Å units and α values are in degrees.

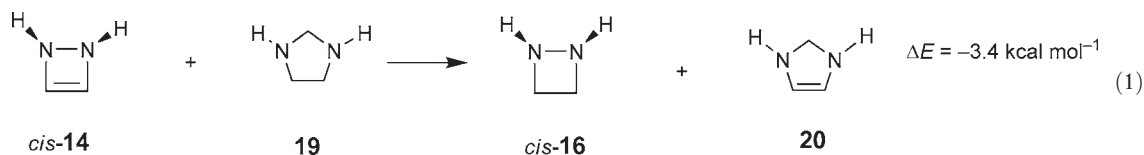
Breton *et al.* <2002JOC6699> have reported some computational studies on a few selected derivatives of 1,2-dihydrodiazete. Warrener performed some semi-empirical intermediate neglect of differential overlap (INDO) molecular orbital calculations on unsubstituted dihydrodiazete, *cis*- and *trans*-**14** <1979AJC2659>.

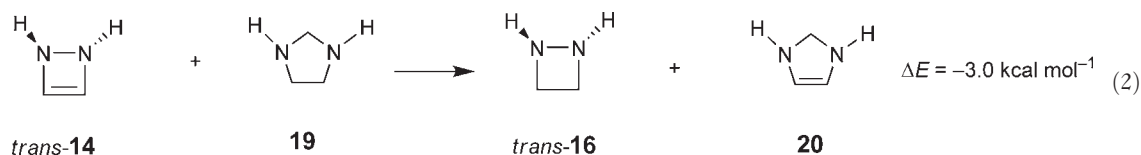
Later, Budzelaar *et al.* <1987JA6290>, Elguero and co-workers <1989JMT(201)17> and Bachrach and Liu <1992JOC2040> investigated a series of such compounds at a higher level of theory (RHF/3-21G*) and all of them concluded that the 1,2-dihydrodiazete system is nonaromatic because of repulsions of the adjacent lone pair of electrons which are not counterbalanced by stabilization from the π -system. Breton *et al.* carried out RHF/6-31G* level geometry optimization of **13** and found a N–N bond length of 1.434 Å, which was shorter than actually observed by X-ray crystallography (1.47 Å) <2002JOC6699>. Further optimization with DFT calculation using RB3LYP/6-311+G(2DP) level lead to a longer N–N bond (1.462 Å) prediction with a lower energy $\Delta E = 8.8 \text{ kcal mol}^{-1}$ relative to the structure at the RB3LYP/6-311+G (2d,p)/RHF/6-31G level. A similar calculation for *cis*-**14** using the RB3LYP/6-311+G(2d,p) level resulted in a longer N–N bond (1.482 Å) and a lower overall energy ($\Delta E = 6.4 \text{ kcal mol}^{-1}$) relative to the RHF/6-31G geometry (N–N bond, 1.457 Å). Based on these observations, Breton *et al.* carried out calculations on several molecules listed (**13**–**18**).



It is interesting to note that compound **13** (N–N bond 1.462 Å) which is nearer to the observed X-ray structure (1.47 Å) is equivalent to the N–N bond distance calculated for nonaromatic saturated diazetidine **15** (1.460 Å) and is much longer than the N=N double bond (1.259 Å) found in 3,4-dihydrodiazete **18**. The bond distance for the C–N single bond in compound **13** (1.451 Å) is similar to the C–N single bond found in nonaromatic compounds and other four-membered heterocycles, such as azetidine (1.428 Å), but longer than in pyrrole (1.372 Å) and the C=N double bond of dihydrodiazete (**17**, 1.289 Å). On the other hand, the C=C bond distance of **13** compares well with the value calculated for nonaromatic C=C double bonds (~ 1.33 Å). The computational studies also reinforced the conclusion drawn from the X-ray crystal structure data and suggested no structural evidence for the effects of aromaticity. Breton *et al.* also studied a series of 1,2-dihydrodiazete ring systems to understand if there is a resonance interaction of the nitrogen lone pair with the C=C bond.

It was found that *cis*-**14** and *trans*-**14** both interacted with 1,3-tetrahydroimidazole **19** to give *cis*-**16** and *trans*-**16**, respectively, and dihydroimidazole **20**. While *cis*-**14** is less stable than *trans*-**14** ($\Delta E = 4.2 \text{ kcal mol}^{-1}$), the *cis*-isomers of **19** and **20** have been found to be more stable. A difference in strain energies has always been found when the double bond in a four-membered ring versus a five-membered ring. This has been estimated to the extent of $-4.0 \text{ kcal mol}^{-1}$. Taking this into consideration, a corrected ΔE for the reactions presented in Equations (1) and (2) has been suggested to be $+0.6$ and $+1.0 \text{ kcal mol}^{-1}$, respectively, which further suggests that there is no additional stabilization of the 1,2-dihydrodiazete ring system over totally nonaromatic dihydroimidazole **20** (Equations 1 and 2).





The calculated relative energies of the three isomeric dihydrodiazetes **14** (0.0) > **17** (−8.21) > **18** (−9.51 kcal mol^{−1}) are in the same order indicating that there is no special stabilization (or destabilization) force in any isomers.

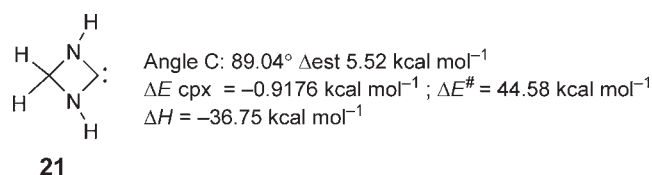
Calculation using RB3LYP/6-311+G(2d,p) suggests two stationary points SP-1 and SP-2 at higher energy for **14**. The SP1 having a single planar nitrogen atom in the ring acts as a transition state for the conversion of *cis*-**14** to *trans*-**14**. The energy of the transition state is 10.4 kcal mol^{−1} higher than the *trans*-**14** which is nearly the same as that predicted by Mo and Yanez (12.9 kcal mol^{−1}) using the MP2/6-31G*//RHF/6-31G* method <1989JMT(201)17>.

The SP-2 structure is fully planar and *cis*-**14** undergoes conversion to its mirror image by a double nitrogen inversion. The energy of SP-2 is 20.2 kcal mol^{−1} higher than that of *trans*-**14** and 9.8 kcal mol^{−1} higher than that of SP-1. However, the predicted bonds for SP-2 are more consistent with what could be expected for a structure in which π -electrons are delocalized with contracted N–N and C–N bonds and an extended C=C bond.

A similar conclusion was drawn based on nucleus-independent chemical shift (NICS) calculations, that is, there is no significant aromatic character to a 1,2-dihydrodiazete. Natural bond orbital (NBO) analysis provides the means of investigating the extent of electron delocalization within a given structure and also indicates the bond order. In ‘Lewis-type’ bonding orbitals electron density is depleted with increase in the occupancy in antibonding or ‘non-Lewis’ orbitals. In the case of *cis*-**14** or *trans*-**14**, there is less occupancy in ‘non-Lewis’ orbitals and the bond order is more like localized bonds: N–N (1.01), C–N (1.06) and C=C (1.76), which are similar to the nonaromatic substances.

From all the above calculations, one arrives at a conclusion that 1,2-dihydrodiazetes are simply constrained nonaromatic heterocycles that do not benefit from aromatic stabilization. Also, these compounds undergo facile Diels–Alder reactions or bromination reactions, with no tendency to regain the π -structure and are thus characteristic for typical nonaromatic compounds.

Su and Chu <1999CPL(308)283> have also carried out B3LYP/6-31G* level calculations for 1,3-diazetidene, especially for carbene generation from this heterocycle. The carbene generated from 1,3-diazetidene is a 4 π electron system. The relative energies of carbene **21** are summarized.



From these calculations, they concluded that four-membered ring carbene species have slightly nonplanar structures resulting in poorer p– π overlap between the carbonic carbon and the adjacent nitrogen atom (Figure 1). This would decrease the LUMO energy and produce a smaller HOMO–LUMO energy gap (and hence smaller ΔE_{est}) (LUMO – lowest unoccupied molecular orbital; HOMO – highest occupied molecular orbital). The barrier of insertion in this four-membered ring carbene is >45 kcal mol^{−1} suggesting a kinetically stable 1,3-diazetidene carbene and may be trapped or isolated perhaps in some reaction.

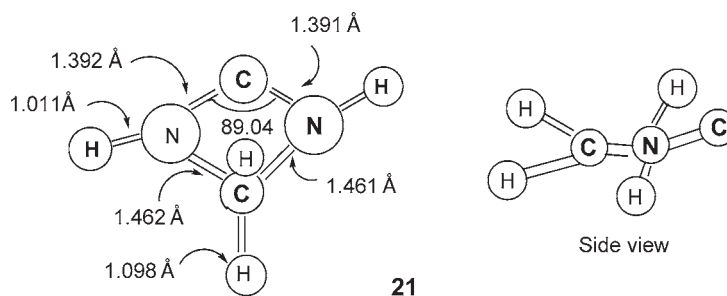


Figure 1

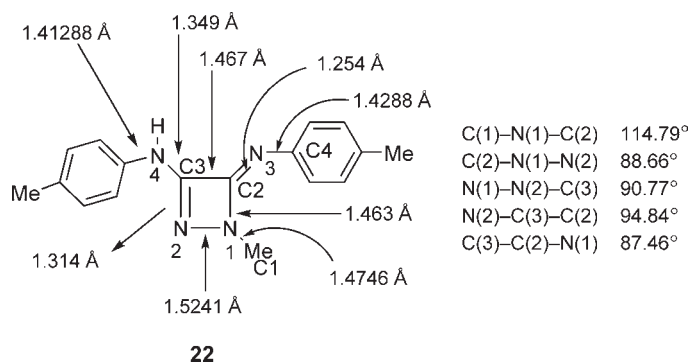
2.13.3 Experimental Structural Methods

2.13.3.1 X-Ray Diffraction Studies

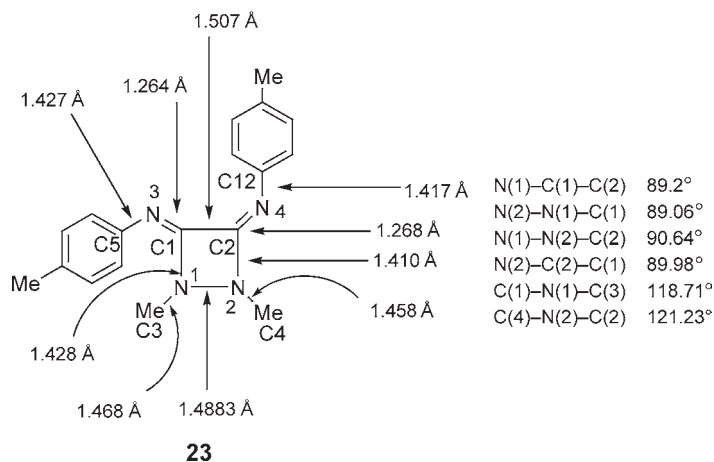
Several X-ray diffraction studies on four-membered heterocycles with two nitrogen atoms have been reported. In CHEC-II(1996) an account of various X-ray studies has been described <1996CHEC-II(1B)911>.

2.13.3.1.1 1,2-Diazetidine derivatives

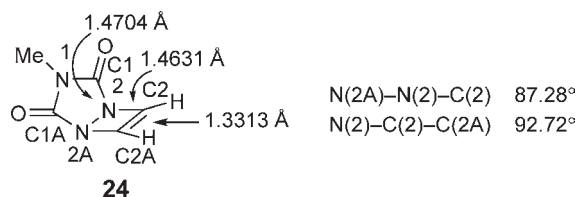
Unlike cyclobutane and its derivatives, many of the four-membered heterocycles usually have planar structures. However, diazetidines are slightly nonplanar or puckered. Earlier, Ruben and co-workers <1974AXB1631> and Loeppky *et al.* <1991JA2308> have reported X-ray crystallography of a few 1,2-diazetidines. Beckert and co-workers <2002H(57)1257>, while carrying out cyclization of amidrazone with bis-imidoyl chloride, isolated a new crystalline compound which was not the expected triazine but Δ^2 -1,2-diazetine or 1*H*,4*H*-diazetine derivative **22** as established by X-ray analysis.



The bond length between N-1 and C-2 is 1.463 Å, whereas the bond between N-2 and C-3 is 1.314 Å and indicated double bond characteristics (1.254 Å) and therefore could be the part of a semicyclic amidine. The four-membered ring is almost planar with a torsion angle of 3.6°. These authors reconfirmed the structure by N-alkylating the Δ^2 -1,2-diazetine derivative **22** with sodium hexadimethyl disilazide and methyl iodide to afford 1,2-dimethyldiazetidene **23** and proving unambiguously the structure **23** by X-ray crystallography.

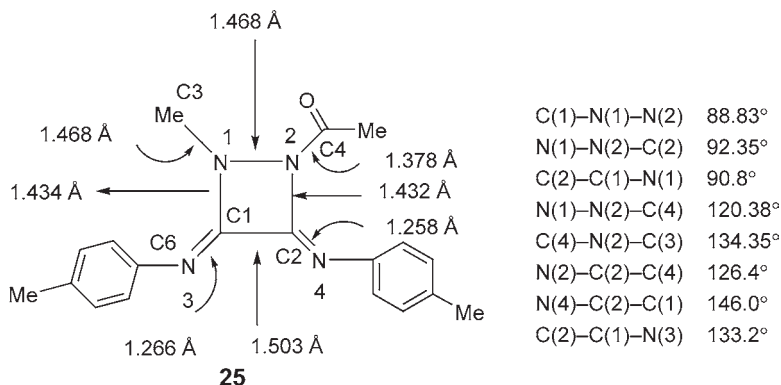


In contrast to the monomethylated derivative **22**, compound **23** is slightly puckered with a torsion angle of 10.8° and both methyl groups are in a *trans*-position with an angle of 121.2° and 118.7°. Breton and Martin <2002JOC6699> synthesized 3-methyl-1,3,5-triazabicyclo[3.2.0]hept-6-ene-2,4-dione **24** and determined its structure unambiguously by single-crystal X-ray crystallography. This is the first structural report on the 1,2-dihydrodiazete.



It is observed that the torsion angle C(1)–N(2)–N(2A)–C(2A) is 120.4°, whereas if nitrogen atoms are planar the torsion angle should be 180°, indicating the pyramidal nature of the nitrogen atom. On the other hand, if the four-membered ring is completely planar, the C(2A)–N(2A)–N(2)–C(2) torsional angle is 0°. The bond lengths N–N, C–N, C=C (1.47, 1.46, 1.33 Å) are very similar to those of hydrazine (N₂H₄, 1.45 Å), methyl amine (1.47 Å), and cyclobutene (1.34 Å).

Fleischhauer *et al.* <2006SS14> have very recently synthesized a number of 1,2-diazetidene derivatives and determined their structure by X-ray crystallography. Δ²-1,2-Diazetidines undergo rearrangement upon acylation to afford ring N-acylation to give 1,2-diazetidene derivatives. In this case, the *N*-methyl and *N*-acyl group are in a *trans*-relation and the ring is almost planar. The tolyl substituents are slightly twisted (*c.* 5°) out of the plane of the ring.

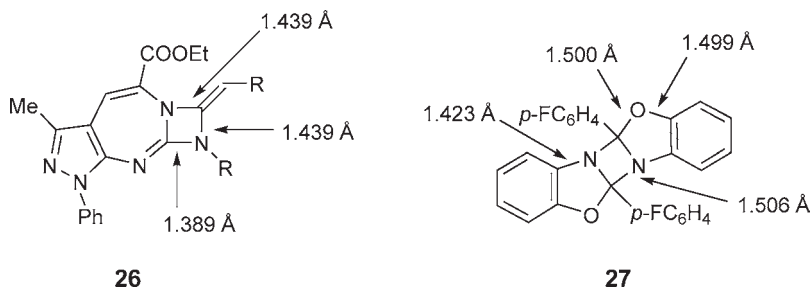


Crystal data: triclinic space group P-1: $a = 7.6472(5)$; $b = 11.0061(5)$; $c = 11.8893(7)$ Å; $a = 117.555(3)$; $b = 94.773(3)$; $\gamma = 101.592(3)$; $v = 851.15$ Å³; $T = -90^\circ$

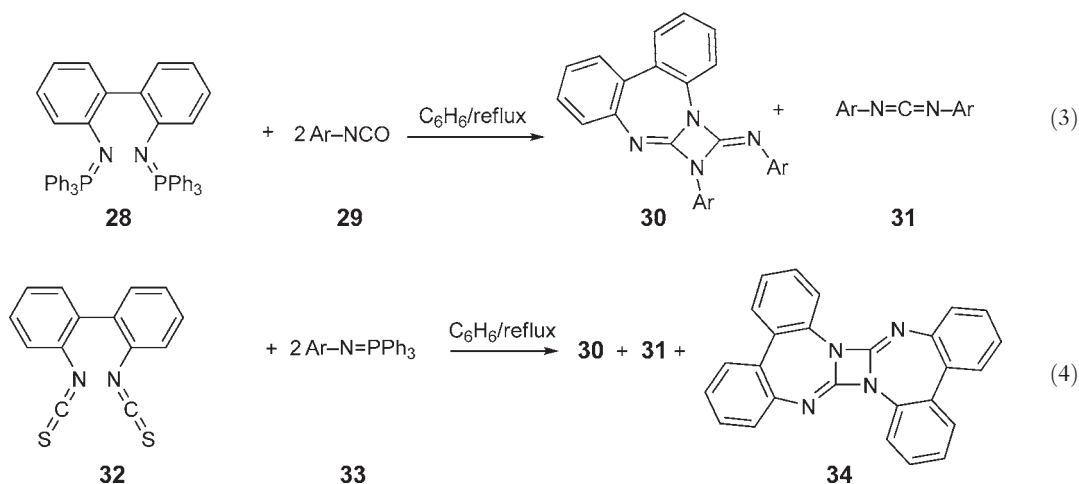
2.13.3.1.2 1,3-Diazetidene derivatives

Fused 2,4-diimino-1,3-diazetidines **26** obtained by aza-Wittig [2+2] cycloaddition of carbodiimide generated in turn from bisiminophosphoranes were confirmed by X-ray diffraction studies <1992CC424>.

An interesting head-to-tail photodimerization of 2-phenylbenzoxazoles leading to a [2+2] cycloaddition to furnish 1,3-diazetidines **27** has been studied and the structures have been finally confirmed by X-ray analysis <1987CC578>.



Molina *et al.* have prepared a number of highly substituted 1,3-diazetidene derivatives and confirmed their structures by X-ray crystallography <1993JPR305>. Some of these studies are covered in CHEC-II(1996) <1996CHEC-II(1B)911>. More recently, Molina and co-workers <1999JOC1121> have carried out intramolecular cyclizations of bis(carbodiimides). The aza-Wittig reaction of bis(iminophosphorane) with aromatic isocyanates gave dibenzo[*d,f*]-1,3-diazetidino[1,2-*a*]diazepine derivatives **30**. Similarly, treatment of bis(isocyanate) with aryliminophosphoranes led to the diazetidine derivative **34** (Equations 3 and 4).



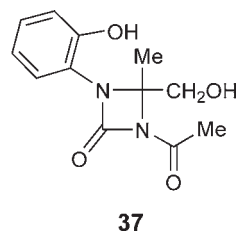
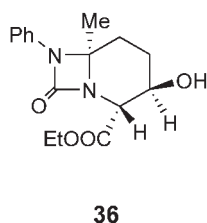
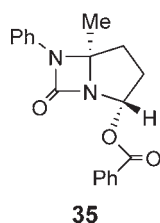
The structure of diazetidines **30** and **34** was confirmed by X-ray analysis. Selected geometrical parameters for **30** and **34** are summarized in Table 2.

Table 2 Selected geometrical parameters of compounds **30** and **34** (Å, deg)

Compound	30	34
C(1)–N(2)	1.440(2)	1.426(2)
N(2)–C(14)	1.457(2)	1.419(2)
C(14)–N(4)	1.405(2)	
C(1)–N(4)	1.392(2)	
N(2)–C(13)	1.431(2)	1.426(2)
N(4)–C(21)	1.415(2)	
C(1)–N(2)–C(13)	114.7(1)	122.3(1)
C(14)–N(4)–C(21)	133.9(2)	
C(13)–N(2)–C(14)	123.0(1)	127.7(1)
C(1)–N(2)–C(14)	87.0(1)	88.8(1)
C(1)–N(4)–C(14)	90.9(1)	
C(1)–N(4)–C(21)	134.3(2)	
N(1)–C(1)–N(2)–C(13)	–56.5(3)	–46.1(2)
C(1)–N(2)–C(13)–C(8)	57.0(2)	40.8(2)
N(2)–C(13)–C(8)–C(7)	–3.2(3)	10.5(2)
C(13)–C(8)–C(7)–C(2)	–37.3(3)	–39.7(2)
C(8)–C(7)–C(2)–N(1)	7.6(3)	3.9(2)
C(7)–C(2)–N(1)–C(1)	30.2(3)	31.8(2)
C(2)–N(1)–C(1)–N(2)	–3.7(3)	–7.5(2)
N(2)–C(14)–N(3)–C(15)	3.7(4)	
C(14)–N(4)–C(21)–C(22)	–1.6(3)	
C(14)–N(3)–C(15)–C(16)	38.6(3)	

In both the compounds **30** and **34**, the N-2 atoms have a distorted tetrahedral environment. $\sum N(2) = 324.7(2)$ and $338.1(2)^\circ$ for **30** and **34**, respectively. The hybridization of the N-4 atoms is sp^2 [$\sum N(4) = 359.1(3)^\circ$]. This behavior is reflected in compound **30** by an elongation of all the bond distances involving N-2. In compound **30**, the four-membered ring and the phenyl substituent at N-4 are coplanar. This indicates that the delocalization of the π -bonding systems across both the rings is aided by C–H–N intramolecular interactions. The sp^2 hybridization of the nitrogen atoms of the diazetidine rings is observed when they are bonded to phenyl rings. In contrast, sp^2 hybridization is presented with cyclohexane rings. The methoxy groups in **30** are almost in the plane of the benzene rings. In compound **34** also C–H–N intramolecular interactions are present. The conformation of the seven-membered rings of both the compounds can be described as distorted boat-sofas, more puckered in **30** than in **34**.

Desiraju *et al.* have prepared some mono and bicyclic-1,3-diazetidine-2-ones with a view to study them as aza analogues of β -lactams and to evaluate their biological activities. The X-ray structure of azacarbapenam **35** and azacarbacepham **36** suggests is that the structural requirement for the biological activities of β -lactams is met. Aza- β -lactam analogue **37** was also crystallized and an X-ray analysis was carried out <1998J(P1)2597>. Only limited X-ray studies have been reported for aza- β -lactams.



Compounds **35** and **36** have been crystallized as monoclinic space group $P2_1/c$, whereas compound **37** crystallized in an orthorhombic form with space group $P2_12_12_1$. The molecules have the (*R*)-configuration. Some of the geometric parameters of the X-ray structure of **35–37** are shown in Table 3.

Table 3 Geometrical parameters for X-ray structure **35–37**

Interaction	<i>d</i> (Å)	<i>D</i> (Å)	θ (°)
<i>Compound 35</i>			
C(16)-H...O(10)	2.760	3.659	140.20
C(20)-H...O(12)	2.535	3.370	133.21
C(22)-H...O(5)	2.690	3.632	145.04
C(23)-H...O(10)	2.529	3.422	139.19
C(23)-H...N(1)	2.771	3.703	144.16
<i>Compound 36</i>			
O(11)-H...O(5)	1.839	2.768	156.46
O(11')-H...O(5')	1.851	2.813	165.34
C(6)-H...O(5)	2.289	3.141	134.10
C(6')-H...O(5')	2.377	3.293	141.34
C(8')-H...O(11')	2.557	3.589	158.92
C(8)-H...O(11)	2.549	3.607	165.26
C(9)-H...O(13')	2.471	3.359	138.41
C(19)-H...O(13)	2.356	3.322	147.64
C(20')-H...O(11)	2.350	3.420	169.38
C(10')-H...O(5)	2.847	3.925	173.45
C(10)-H...O(5')	2.542	3.445	140.22
C(16')-H...N(3')	2.977	3.924	146.26
C(16')-H...O(13)	2.473	3.510	159.87
<i>Compound 37</i>			
O(18)-H...O(7)	1.721	2.681	164.04
O(7)-H...O(17)	1.723	2.694	168.58
C(8)-H...O(5)	2.580	3.626	162.12
C(13)-H...O(18)	2.475	3.364	138.52
C(11)-H...O(18)	2.754	3.691	144.65
C(16)-H...O(5)	2.951	3.960	155.09

The compound **35** possesses *exo*- and *cis*-stereochemistry of the methyl and the benzoate groups based on the nuclear Overhauser effect (NOE) data. Based on the C–N distance (*r*), the Woodward parameter (*h*) and the sum at the N-atom ($\sum N$) value from X-ray data, N-1 is in a pyramidal environment. N-3 is on maximum resonance with the π -framework of the adjacent C=O group. This is reflected in a shorter C(2)–N(3) bond (1.375(2) Å, compared to the C(2)–N(1) bond distance [1.438(2) Å]. $\sum N$ values are as follows: $\sum N-3 = 359.99^\circ$, and $\sum N-1 = 311.74^\circ$ and $h = 0.601$ Å. The X-ray crystallographic data support some of the conclusions derived from AM1 calculations, viz. N-1 and N-3 atoms are in chemically distinct environments and form C–N bonds of different strengths. This would have implications on the

regioselectivity in the cleavage of the diazetidinone ring C–N bond upon attack by the active ser-OH group and other nucleophiles. There is no strong hydrogen-bonding group (OH, NH₂) in **35**. The structure is stabilized by the weaker C–H...O, C–H...N, and C–H... π hydrogen bonds. In the case of compound **36**, the quaternary methyl and the ester groups are *exo* and *cis* to each other while the hydroxyl group is on the *endo* face and *trans* to the ester and the methyl groups. The crystal structure is stabilized by a strong O–H...O and weak C–H...O bond (see Table 3). It is noteworthy that the C–H...O hydrogen bond in which the donor C–H is acidic and is activated by an ester group or part of phenyl C–H group are shorter (<2.4 Å) than the other C–H...O bonds.

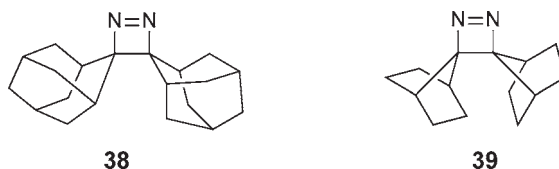
The compound **37** was isolated as an unexpected product and was characterized by X-ray analysis. The single-crystal studies indicate that **37** is in the noncentrosymmetric and enantiomorphous orthorhombic space group P2₁2₁2₁. In **37** the phenolic OH group is intramolecularly hydrogen bonded to the alcoholic OH which in turn is hydrogen bonded to the acetyl C=O in a screw related manner. Additionally, the phenyl C–H is hydrogen bonded to the phenolic O–H and the hydroxymethyl C–H is bonded to the diazetidinone C=O. The geometrical parameters of these interactions are shown in Table 3.

2.13.3.2 Microwave Spectroscopy

The conformation of 1,2-dimethyl-1,2-diazetidene with a dihedral angle of $154^\circ \pm 10^\circ$ between the nitrogen lone-pair orbitals and with both the methyl groups quasi-equatorial has been predicted <1975CB1548, 1975CB1557>. This prediction was tested by electron diffraction and microwave studies <1980J(F2)1293>. Using microwave spectroscopy, rotational constants, quartic centrifugal distortion constants, and quadrupole coupling constants were measured and compared with the calculated values obtained from the force field. Rotational and quartic centrifugal distortion constants were fitted by a least-squares method. Quadrupole hyperfine interactions were fitted with overall standard deviation of 33 kHz. Splitting of the rotational transition because of internal rotation of methyl groups could not be observed. Assuming the lower limit for the rotational barrier in 1,2-dimethyldiazetidene to be 2.5 kcal mol^{−1} (10.5 kJ mol^{−1}), the calculation suggests an average splitting of about 50 kHz with maximum splitting of 110 kHz. This suggests that it is not possible to determine the internal rotational barrier by microwave spectra of the vibrational ground state. However, the hyperfine structure of the rotational transition could be explained by nuclear quadrupole interactions. During the last decade no significant study has been published on the microwave spectroscopy of any of the diazetidine class of compounds.

2.13.3.3 UV–Visible Spectroscopy

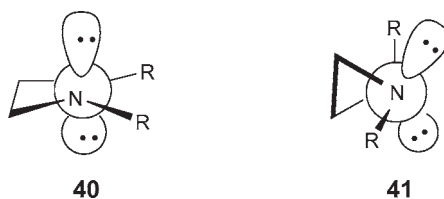
The ultraviolet (UV) spectrum of Δ^1 -1,2-diazetines has been found to give a fine structure arising from the $n\text{--}\pi^*$ transition, unlike other cyclic azo compounds which show a broad absorption at 360 nm without any fine structure. For example, 3,3,4,4-tetramethyl- Δ^1 -1,2-diazetidene showed highly structured transitions at 325, 333, 340, and 356 nm <1975JOC1409>, whereas 2,3-diazabicyclo[2,2,0]hex-2-ene showed λ_{max} at 334, 341, and 350 nm due to $n\text{--}\pi^*$ transitions <1978TL2469>. The absorption and emission spectra of several 1,2- Δ^1 -1,2-diazetidines were studied in various solvents; they showed a blue shift of absorption maxima with increasing solvent polarity, which is typical for an $n\text{--}\pi^*$ transition <1978JA5122, 1981JA7743>. The λ_{max} of compound **38** has been found to be 358 nm ($\epsilon = 95 \text{ mol}^{-1} \text{ cm}^{-1}$) and 355 nm ($\epsilon = 184 \text{ mol}^{-1} \text{ cm}^{-1}$), whereas for compound **39** λ_{max} was 345 nm ($\epsilon = 205 \text{ mol}^{-1} \text{ cm}^{-1}$) <1993JOC5393>.



2.13.3.4 Photoelectron Spectroscopy

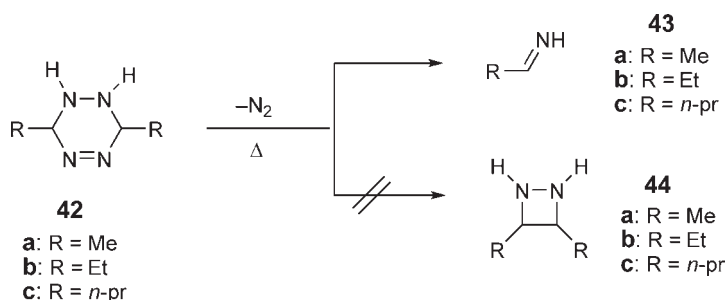
Photoelectron spectroscopy (PS) is employed for the detection of short-lived unstable intermediates. Reactive alkanimines have been prepared through thermolysis of amines and azetidines as well as retrotrimerization of hexahydrotriazines. Thus, tetrahydrotetrazines can extrude dinitrogen in a [2+2+2] cycloreversion or via a diradical pathway, which might either fragment along with an N–N bond or cyclize. <1998JST(471)189>.

Based on photoelectron spectra, an empirical correlation between the interaction energy of the electron lone pairs of the two bonded nitrogen atoms and the dihedral angle between these lone-pair orbitals can be established. Rademacher <1974TL83> predicted a conformation with a dihedral angle of $154 \pm 10^\circ$ between the nitrogen lone-pair orbitals for 1,2-dimethyl-1,2-diazetidines and thus both methyl groups in quasi-equatorial position <1975CB1548, 1975CB1557>.



By increasing the size of the substituents on 1,2-dialkyl-1,2-diazetidines (Me, Pr), the two substituents *trans* to each other seem to push each other further apart. Thus, the two methyl groups exist exclusively in *trans*-equatorial form **40**, whereas in the case of diisopropyl both *trans*-equatorial **40** and axial **41** are possible <1978JA2806>.

More recently, Muchall and Rademacher <1998JST(471)189> have carried out thermolysis of 3,6-dimethyl-, diethyl-, and dipropyl-substituted 1,2,3,6-tetrahydro-1,2,4,5-tetrazine to yield the corresponding N-substituted imines **43a–c** (Scheme 1). They utilized photoelectron spectroscopy to detect the intermediates and the products formed. Thus, PS of tetrahydrotetrazines shows no change up to 400 °C but at 450 °C thermolysis takes place and the bands belonging to ethanimine and nitrogen appear. The ionization potential observed is shown in Table 4.



Scheme 1

Table 4 Experimental vertical ionization potential IP_v (eV) and calculated orbital energies ε (eV) for imines **43a–c**

Imine 43 a ($-\varepsilon$)			Imine 43 b ($-\varepsilon$)			Imine 43 c ($-\varepsilon$)		
IP_v	HF	B3LYP	IP_v	HF	B3LYP	IP_v	HF	B3LYP
10.25	11.37	7.29	10.01	11.31	7.26	9.94	11.27	7.23
11.60	11.74	8.66	11.30	11.73	8.65	11.14	11.66	8.56
13.60	14.97	10.84	12.48	13.65	9.76	11.9	13.12	9.31

No ionization band corresponding to 3,4-dimethyl-1,2-diazetidine **44a** was observed. Even at higher temperature (725 °C), no ionization band of HCN (13.63 eV) was seen. However, the ionization band of HCN as well as of **43a** becomes prominent at 975 °C. Similarly, the ionization spectrum showed a band of imines **43b** and **43c** in the pyrolysis of **42b** and **42c**. In none of the cases was the intermediacy of the diazetidines detected by PS.

The first ionization potential IP^1_v of **43b** was calculated. Using the *ab initio* HF method for geometry optimization and B3LYP for the single point energy calculation, the first IP can be calculated as the energy difference between a molecule and its radical cation. The values of the energies are summarized in Table 5.

Table 5 Total energies (E_T (au)) of imines **43a–c**, diazetidines **44a–c** and their radical cation ($M^{+·}$; n^{-1} electrons) as well as the derived first ionization potential IP^1_v (eV)

	State	HF/6-31+G*		B3LYP/6-31+G*/HF/6-31+G*	
		E_T	IP^1_v	E_T	IP^1_v
43a	M	−133.076101	8.90	−133.957049	10.10
	$M^{+·}$	−132.748877		−133.585762	
43b	M	−172.113532	8.82	−173.273736	9.94
	$M^{+·}$	−171.789352		−172.908487	
43c	M	−211.148759	8.77	−212.588367	9.83
	$M^{+·}$	−210.826490		−212.227186	
44a	M	−266.123035		−267.891395	7.96
	$M^{+·}$	-		−267.598772	
44b	M	−344.193477		−346.520659	7.85
	$M^{+·}$	-		−346.232040	
44c	M	−422.261779		−425.148005	7.78
	$M^{+·}$	-		−424.862184	

From Table 5, it is clear that the value calculated by the HF method ($IP^1_v = 8.90$ eV) is not close to the observed value (10.18 eV), but values obtained by B3LYP ($IP^1_v = 10.10$ eV) are in good agreement. Orbital energies computed for **43a** also show a similar result. If orbital energies are shifted uniformly by 2.8 eV (the difference between HOMO and IP^1_v), the calculated HOMO equals the calculated IP^1_v in energy.

A calculation on 3,4-dimethyl-1,2-diazetidine **44a**, the product of the ring closure from a possible 1,4-biradical generated from **42a**, was carried out. Since the IPs are not known for diazetidine **44a**, the calibration was done using 1,2-dimethyl-1,2-diazetidine. The first ionization reported is 7.95 eV <1978JA2806>, which is quite close to the calculated value IP^1_v value 7.54 eV although an error of 0.4 eV may be admitted based on N-substituted and N-unsubstituted diazetidine. Thus, the value for **44a** can be expected around 8.3 eV. In the pyrolysis of **42a**, the first band of imine **43a** is at about 9.0 eV and any ionization at the lower-energy side of this band should be clearly observed. Thus, it is clear that **44a** is not formed at all in the pyrolysis of **42a** between 450 and 975 °C. A similar conclusion can be drawn from the pyrolysis of **42b** and **42c**, since neither **44b** nor **44c** is formed.

2.13.3.5 IR–Raman Spectroscopy

IR and Raman spectroscopy have extensively been used to determine the cyclic structure of diazetidines and their derivatives. Several studies comparing these cyclic compounds with the related cyclic and acyclic analogues have been reported <1962JCS4840>. Oberhammer and co-workers have carried out detailed IR and Raman spectroscopic studies of 1,2-dimethyl-1,2-diazetidine <1980J(F2)1293>. The IR and far IR spectra were recorded in the ranges 3500–400 cm^{-1} and 50–480 cm^{-1} , respectively. The Raman spectra were recorded in the range 50–3500 cm^{-1} . Frequencies in the range 2700–3000 cm^{-1} can be assigned to the C–H stretching vibrations of methylene and methyl groups. Absorptions around 1450 cm^{-1} are assigned to HCH deformation of methylene and methyl groups. The stretching vibrations of the molecular skeleton are assigned to the absorptions in the range 1100–1220 cm^{-1} . These vibrations are strongly coupled with deformation and rocking vibration of the methyl groups. Eight frequencies have been assigned in the lower-frequency range. The two absorptions at 216 and 219 cm^{-1} are assigned to the torsional vibrations of methyl, two are ring deformations (ring scissoring at 653 cm^{-1} and ring puckering at 140 cm^{-1}), and the remaining four frequencies are assigned to the bending vibrations of the methyl group with respect to the ring.

Jensen carried out a structural determination of 1,3-dichloro-1,3-diazetidine-2,4-dione **45** <2004SAA2719>. Due to its symmetry and unusual bonding, 1,3-dichloro-1,3-diazetidine-2,4-dione is an interesting case for quantum chemical analysis. The vibrational frequencies of **45** were calculated using 6-311G** basis set. The calculation utilized the C_{2h} symmetry of 1, 3-dichloro-1, 3-diazetidine-2, 4-dione molecule (Tables 6 and 7).

Table 6 Normal modes of 1,3-dichloro-1,3-diazetidene-2,4-dione at HF level, DFT level, and MP-2 level of theory assuming a standard 6-311 G** basic set

Sym	NM	Calculated frequencies by			Raman Activity			Assign	Exp. value
		HF	DFT (B3LYP)	MP2	HF	DFT (B3LYP)	MP2		
A_g	ν_1	2213	2028	2018	36	40	51	C=O Str	1952
	ν_2	1396	1170		45	66	41	N–C Str	1200
	ν_3	781	704	704	20	29	29	C–N–C bend	718
	ν_4	503		456	35	64	35	N–Cl Str	465
	ν_5	263		282	1	5	4	N–Cl bend	272
B_g	ν_6	1012		830	4	1	3	N–C Str	850
	ν_7	860		748	2	2	4	C=O bend	750
	ν_8	739		656	2	2	3	C=O bend	655
	ν_9	210		183	5	6	5	N–Cl bend	
IR Activity									
A_u	ν_{10}	2092		1917	1136			C=O Str	1815
	ν_{11}	1161		1029	97			N–C Str	1000
	ν_{12}	182		160	1			N–Cl bend	
B_u	ν_{13}	1456		1192	479			N–C Str	1230
	ν_{14}	889		759	170			C=O bend	750
	ν_{15}	821		683	16			N–Cl Str	705
	ν_{16}	361		320	0			C=O bend	350
	ν_{17}	178		171	17			C–N–C bend	
	ν_{18}	65		65	6			N–Cl bend	

Sym: symmetry; NM: normal modes.

Table 7 Experimentally observed and corrected frequencies of 1,3-dichloro-1,3-diazetidene-2,4-dione at HF level, DFT level, and MP-2 level of theory assuming a standard 6-311 G** basic set

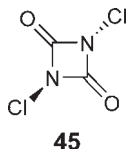
Sym	NM	Exp. value	Assign	Corrected frequencies			Assign	Activity
				HF	DFT (B3LYP)	MP2		
A_g	ν_1	1952	C=O Str	1936	1936	1934	C=O Str	Raman active
	ν_2	1200	N–C Str	1189	1186	1180	N–C Str	Raman active
	ν_3	718	C–N–C bend	718	718	705	C–N–C bend	Raman active
	ν_4	465	N–Cl Str	448	468	469	N–Cl Str	Raman active
	ν_5	272	N–Cl bend	272	272	272	N–Cl bend	Raman active
B_g	ν_6	850	N–C Str	862	841	851	N–C Str	Raman active
	ν_7	750	C=O bend	738	745	757	C=O bend	Raman active
	ν_8	655	C=O bend	634	653	650	C=O bend	Raman active
	ν_9		N–Cl bend	217	177	178	N–Cl bend	Raman active
A_u	ν_{10}	1815	C=O Str	1830	1830	1832	C=O Str	IR active
	ν_{11}	1000	N–C Str	988	1043	1017	N–C Str	IR active
	ν_{12}		N–Cl bend	188	154	157	N–Cl bend	IR active
B_u	ν_{13}	1230	N–C Str	1240	1208	1229	N–C Str	IR active
	ν_{14}	750	C=O bend	763	756	743	C=O bend	IR active
	ν_{15}	705	N–Cl Str	732	701	698	N–Cl Str	IR active
	ν_{16}	350	C=O bend	310	319	322	C=O bend	IR active
	ν_{17}		C–N–C bend	164	174	163	C–N–C bend	IR active
	ν_{18}		N–Cl bend	67	63	60	N–Cl bend	IR active

Each vibrational mode was assigned to one of the six types of motion predicted by theoretical analysis (C=O, stretch, N–C stretch, N–Cl stretch, N–C–N bend, N–Cl bend, and C=O bend). The vibrational frequencies of 1,3-dichloro-1,3-diazetidene-2,4-dione **45** were calculated at Hatree–Fock level, DFT (B3LYP) level, and MP-2 level of theory using a standard 6-311G** basis set. For N–C stretching modes all operators except E have a trace of zero.

Thus, the four N–C stretching modes possess the symmetries A_g , B_g , A_u , and B_u . For the N–Cl stretching modes, σ_h operator has a trace of two and all other operators except E have a trace of zero. Two N–Cl stretching modes possess the symmetries A_g and B_u . For the C=O stretching mode, the C-2 operator has two traces having symmetries A_g and A_u . For N–Cl bending modes possess the symmetries A_g , B_g , A_u , and B_u . The C=O bending modes possess symmetries $2B_g$ and $2B_u$. There are two C–N–C bending modes having A_g and B_u symmetries.

Tables 6 and **7** present the calculated vibrational frequencies of 1,3-dichloro-1,3-diazetidine-2,4-dione. The correction factors for different vibrational modes were calculated. The computed correction factors and geometric parameters for 1,3-dichloro-1,3-diazetidine-2,4-dione **45** at HF, B3LYP and MP-2 levels of theory are summarized in **Table 8**.

Table 8 Correction factors and geometric parameters for 1,3-dichloro-1,3-diazetidine-2,4-dione **45**



Correction factors of 45				Geometric Parameters of 45				
Groups	Hatree-Fock	DFT (B3LYP)	MP2	Groups	Hatree-Fock	DFT (B3LYP)	MP2	Experimentals
C=O Str	0.8748	0.9547	0.958	C=O	115.6	117.7	118.4	117.2
N–C Str	0.8514	1.0134	0.978	N–Cl	167.5	172.6	170.6	169.1
N–Cl Str	0.8916	1.0260	0.965	C–N	141.0	143.5	143.4	142.1
C–N–C bend	0.9027	1.0014	1.004	C–N–C	91.0	91.1	90.8	-
C=O bend	0.8579	0.9954	0.985	N–C–N	89.0	88.9	89.2	-
N–Cl bend	1.0342	0.9645	0.968	C···C=O	0.0	0.0	0.0	0.0
			0	N···N–Cl	15.6	18.2	18.9	32.5
			0	N–C–N–C	0.0	0.0	0.0	0.0

2.13.3.5.1 Vibrational spectra

Gessner and Ball found vibrational frequencies based on the CBS calculations for both the *cis*- and *trans*-conformers of 1,2-diazetidine as well as for *cis*- and *trans*-1,3-diazetidine. They have calculated and compared the vibrational frequencies by G2, G3, CBS-APNO, and CBS-QB3 methods for *cis*- and *trans*-conformers of 1,2-diazetidine as well as for *cis*- and *trans*-1,3-diazetidine and have shown that they differ to some extent in the three methods <2005JST(730)95>. Some of the calculated unscaled vibrational stretching frequencies for the *cis*- and *trans*-conformers of 1,2-diazetidine and 1,3-diazetidines have been compiled in **Table 9**. Some of the salient features worth noting here are: (1) the two conformers of 1,2-diazetidine have markedly different N–H and C–H stretching regions composed of strong absorptions; (2) the *trans*-isomer, in particular, has quite a few absorptions that have a very low (<0.1 kcal mol⁻¹) or even zero intensity, owing to the cancellation of the dipole moment change during the course of the vibration; and (3) the *cis*-isomer has fewer dipole-moment forbidden vibrations due to its symmetry.

A similar pattern is seen for the two isomers of 1,3-diazetidine. For example, (1) for the *trans*-isomer, the CBS-QB3 method shows two variances from the monotonically increasing frequencies; (2) because of their symmetries (both molecules have a C₂ axis), many of the vibrations of both the conformers are predicted to have a very low or exactly zero intensity; and (3) only half or less of the 24 normal modes of vibration have significant intensity.

Thus, the spectra of the two conformers are different enough that unambiguous identification should not be difficult.

Table 9 Vibrational frequencies (in cm^{-1}), absolute intensities (in km mol^{-1}), and approximate vibration description *cis*-1,2-diazetidines (*cis*-**16**), *trans*-1,2-diazetidines (*trans*-**16**), *cis*-1,3-diazetidines (*cis*-**2**) and *trans*-1,3-diazetidines (*trans*-**2**)

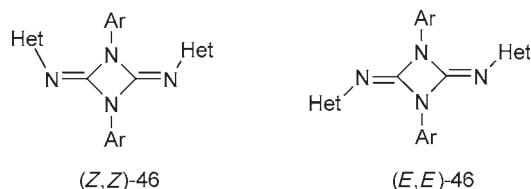
<i>G2, G3</i>	<i>CBS-APNO</i>	<i>CBS-QB3</i>	<i>Approx desc</i>
<i>cis</i> -1,2-Diazetidines			
3276.0 (44.8)	3228.9 (46.7)	3068.3 (54.2)	Sym C–H str
3308.7 (49.9)	3260.5 (56.8)	3113.5 (31.1)	Asym C–H str
3645.7 (13.3)	3646.4 (7.9)	3329.1 (24.0)	Asym N–H str
3757.8 (2.3)	3745.7 (1.1)	3472.9 (2.8)	Sym N–H str
<i>trans</i> -1,2-Diazetidines			
3275.0 (23.4)	3206.9 (102.9)	3003.7 (69.3)	Asym C–H str
3289.2 (91.5)	3212.6 (67.4)	3004.2 (81.7)	Sym C–H str
3741.6 (1.0)	3781.8 (2.9)	3530.1 (<0.1)	Sym N–H str
3749.9 (4.5)	3784.1 (1.2)	3572.5 (1.7)	Asym N–H str
<i>cis</i> -1,3-Diazetidines			
3144.3 (124.8)	3103.2 (134.1)	2916.5 (134.4)	Asym C–H str
3152.4 (133.7)	3110.2 (134.1)	2923.0 (143.2)	Sym C–H str
3256.7 (97.6)	3206.0 (102.9)	3029.4 (97.3)	Asym C–H str
3789.7 (4.3)	3781.8 (2.9)	3534.7 (1.3)	Sym N–H str
3791.9 (0.3)	3784.1 (1.2)	3536.2 (0.1)	Asym N–H str
<i>trans</i> -1,2 Diazetidines			
3197.4 (227.5)	3152.4 (240.2)	2972.9 (243.0)	Asym CH ₂ str
3207.8 (<0.1)	3162.7 (0.1)	2983.6 (0.1)	Sym CH ₂ str
3234.7 (1.1)	3187.6 (1.8)	3003.7 (69.3)	Asym CH ₂ str
3237.5 (173.1)	3190.1 (165.9)	3004.2 (81.7)	Sym CH ₂ str
3786.9 (0.4)	3781.3 (0.5)	3530.1 (<0.1)	Sym N–H str
3787.9 (5.0)	3782.2 (4.5)	3532.5 (1.7)	Asym N–H str

2.13.3.6 Nuclear Magnetic Resonance Studies

Nuclear magnetic resonance (NMR) spectroscopy has been used extensively to study the conformation of a number of diazetidines, their thermodynamic stability, and kinetics of inversion at the N-center in addition to the routine structural elucidation.

2.13.3.6.1 Proton NMR

A detailed account of the use of ^1H -NMR for the measurement of $\Delta G^\ddagger$, the barrier of inversion at the N-center, etc., have been described in CHEC-II(1996) <1996CHEC-II(1B)911>. Only a few salient features have been covered in this. Proton NMR has been used for the structural elucidation and to study the geometrical isomerism of a number of diazetidines and their derivatives. For example, ^1H -NMR has been used to study the inversion of (*Z,Z*)-isomers and (*E,E*)-isomers of 1,2-diazetidines **46**.

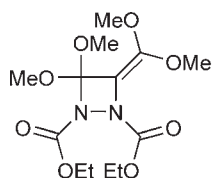
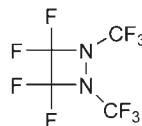


The temperature-dependent NMR studies have been used to calculate the free energy of activation for the amide torsional barrier of diethyl 4,4-dimethoxy-3-dimethoxymethylene-1,2-diazetidene-1,2-dicarboxylate **47** and has been found to be more than 20 kcal mol^{-1} (84 kJ mol^{-1}) and the two methoxy signals at C-3 were found to coalesce at 80°C ,

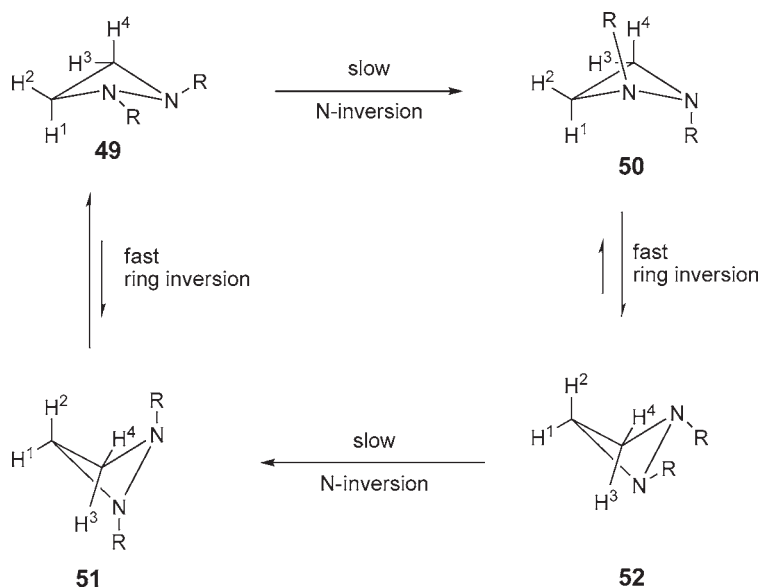
whereas the coalescence of the remaining two signals requires heating to 180 °C due to the methoxy group at the C-4 position <1972CB2437>.

^{19}F -NMR has been used to measure the free energy of activation for the nitrogen inversion of 1,2-bis(trifluoromethyl)-3,4-tetrafluoro-1,2-diazetidines **48**, which has been found to be 7.25 kcal mol $^{-1}$ (30.3 kJ mol $^{-1}$).

The calculation of $\Delta G^\ddagger$ for the inversion at N-1 of *N,N*-diary- or dibenzyl-substituted 1,2-diazetidines-3-one has been carried out through ^1H -NMR measurement <1970TL3605>.

**47****48**

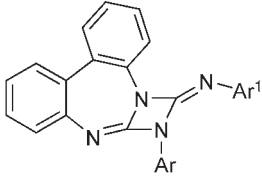
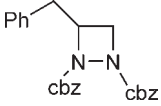
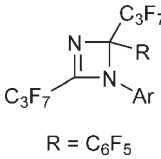
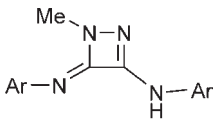
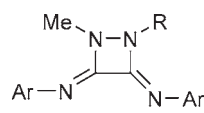
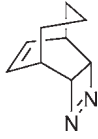
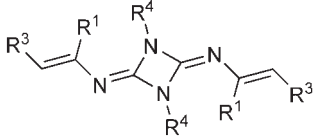
^1H -NMR line shape analysis has been used to measure the ring and N-inversion of diazetidines (Scheme 2) <1978JOC2785>. Temperature-dependent studies suggest that the concentrations of **50** and **51** are small because of the diaxial interaction when R = Me, Et, or Pr ^{i} , whereas they are predominant when R = Bu ^{t} . The temperature-dependent NMR studies indicate the relative ratio for R = Me, Et, Pr ^{i} , Bu ^{t} as 1.0:0.75:0.51:0.74 $\times 10^{-3}$. These data were also used to calculate ΔH and ΔS which suggest that the ring inversion only takes place during heating for di-*t*-butyl-substituted-1,2-diazetidines <1978JA2806>. Some of the examples of ^1H -NMR assignment are summarized in Table 10.

**Scheme 2**

2.13.3.6.2 Carbon-13 NMR

Carbon-13 NMR spectra have been routinely recorded for 1,2- and 1,3-diazetidine derivatives for their spectral assignment. Data for a few diazetidines are collected in Table 11.

Table 10 ^1H -NMR of 1,2- and 1,3-diazetidines derivatives

Compound	^1H NMR chemical shifts (δ)	Reference
 a: Ar = Ar¹ = 4-Me-C₆H₄- b: Ar = Ar¹ = 2,4-diMeO-C₆H₃- c: Ar = Ar¹ = 4-MeO-C₆H₄- d: Ar = Ar¹ = 1-naphthyl e: Ar = Ar¹ = 4-NMe₂-C₆H₄	a: 2.28 (s, 3H, Me), 2.33 (s, 3H, Me) b: 3.58 (s, 9H, Me), 3.64 (s, 3H, Me) c: 3.75 (s, 3H, Me), 3.8 (s, 3H, Me) d: 6.57–7.72 (m, 20H), 8.15–8.29 (m, 2H) e: 2.88 (s, 6H, Me), 2.93 (s, 6H, Me)	1999JOC1121
	2.80 (dd, J = 12.8 and 10.0 Hz, 1H), 2.95 (dd, J = 12.8 Hz, 5.2 Hz), 4.14 (d, J = 10.8 Hz, 1H), 4.18 (d, J = 10.8 Hz, 1H), 4.45–4.54 (m, 1H), 7.50–7.10 (m, 15H), 5.30–5.10 (m, 4H)	2006TL6835
 R = C₆F₅	F¹⁹ NMR: –3.6 (F14), –2.9 (F10), 12.1 (F15), 12.1 (F11), 12.3 (F13), 13.8 (F9), 36.4 (F6'), 36.7 (F6), 44.2 (F5), 47.9 (F5), 82.1 (F7'), 82.8 (F7)	2000JFC(104)263
 a: Ar = 4-Me-C₆H₄- b: Ar = 4-MeO-C₆H₄-	a: 2.27 (s, 3H, Me), 2.32 (s, 3H, Me), 2.59 (s, 3H, Me), 7.16–7.06 (m, 6H), 7.4–7.37 (m, 2H), 9.07 (s, 1H, NH) b: 2.63 (s, 3H, Me), 3.73 (s, 3H, OMe), 3.78 (s, 3H, OMe), 6.92–6.83 (m, 4H), 7.19–7.14 (m, 2H), 8.91 (s, 1H), 7.45–7.40 (m, 2H)	2002H(57)1257
 a: Ar = 4-Me-C₆H₄-, R = Me b: Ar = 4-MeO-C₆H₄-, R = Me c: Ar = 4-Me-C₆H₄-, R = COBu^t	a: 2.30 (s, 6H), 2.63 (s, 3H), 2.97 (s, 3H), 6.49–6.17 (m, 2H), 7.13–6.96 (m, 5H), 7.55–7.52 (m, 1H) b: 2.66 (s, 3H, OMe), 2.96 (s, 3H, OMe), 3.77, 3.76 (2s, 6H, 2Me), 7.72–6.2 (m, 8H, Ar) c: 1.42 (s, 9H, ^tBu), 2.31 (s, 6H, Me), 2.82 (s, 3H, N-Me), 6.25–7.58 (m, 8H, CH, aromatic)	2002H(57)1257 2006S514
	1.1.1.9 (m, 6H, CH ₂), 2.87 (br, m, 2H), 4.43 (dd, J = 2.2, 1.7 Hz, 2H), 5.95 (dd, J = 5.0, 3.0 Hz)	2003JOC8643
 a: R¹ = R² = H, R³ = COOEt, R⁴ = Et b: R¹ = Me, R² = H, R³ = COOMe, R⁴ = Et c: R¹ = Me, R² = H, R³ = COOMe, R⁴ = C₆H₅-	a: 1.23 (t, 6H, J = 7.3 Hz, Me), 1.30 (t, 6H, J = 7.2 Hz, Me), 3.46 (q, 4H, J = 7.3 Hz, CH₂), 4.21 (q, 4H, J = 7.2 Hz, CH₂), 5.83 (d, 1H, J = 13.2 Hz, =CH), 7.85 (d, 2H, J = 13.2 Hz, =CH) b: 1.16 (t, 6H, J = 7.2 Hz, Me), 2.11 (s, 6H, Me), 3.93 (s, 6H, Me), 3.95 (q, 4H, J = 7.2 Hz, 2H), 5.88 (s, 2H, =CH) c: 2.25 (s, 6H, Me), 3.87 (s, 6H, OMe), 6.09 (s, 2H, =CH), 7.42–7.7 (m, 10H)	2001H(55)1641

(Continued)

Table 10 (Continued)

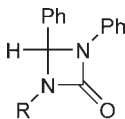
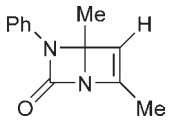
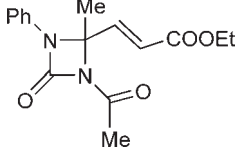
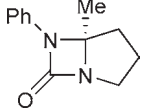
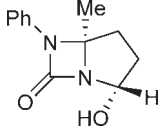
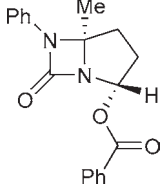
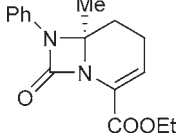
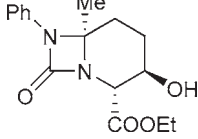
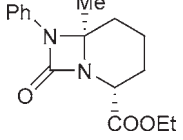
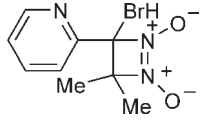
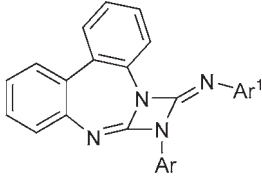
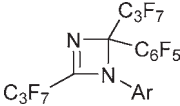
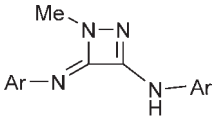
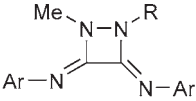
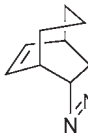
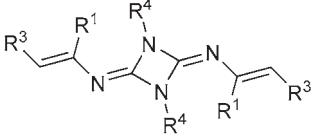
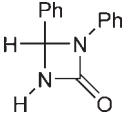
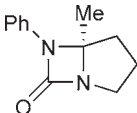
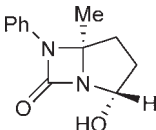
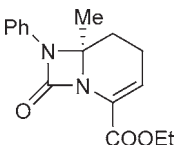
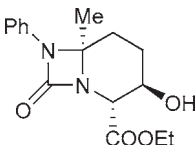
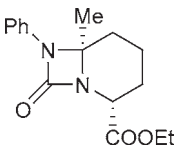
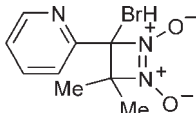
Compound	^1H NMR chemical shifts (δ)	Reference
 a: R = H b: R = Me	a: 6.7 (s, 1H, CH), 7.4–7.1 (m, 10H, Ar), 9.0 (br, s, 1H, NH) b: 1.7 (s, 3H, Me), 6.9 (s, 1H, CH), 7.4–7.2 (m, 10H, Ar)	2003PS1931
	1.86 (s, 3H, Me), 2.12 (d, $J = 2$ Hz, 3H, Me), 6.10 (d, $J = 2$ Hz, Vinyl, CH), 7.38–7.05 (m, 5H, Ph)	1998J(P1)2597
	1.31 (t, $J = 8$ Hz, 3H, Me), 2.41 (s, 3H, Me), 4.28–4.17 (q, $J = 8$ Hz, 2H, OCH ₂), 6.34 (d, $J = 16$ Hz, vinylic, =CH), 7.05 (d, $J = 16$ Hz, vinylic =CH) 7.34–7.05 (m, 5H, Ph)	1998J(P1)2597
	1.72–1.60 (m, 1H, CH ₂), 1.78 (s, 3H, Me), 2.15–1.92 (m, 2H, CH ₂), 3.62–3.51 (m, 1H, CH ₂)	1998J(P1)2597
	1.85 (s, 3H, Me), 2.45–2.05 (m, 4H, 2 $\times$ CH ₂), 2.84 (br, s, 1H, OH), 5.32 (d, $J = 3$, 1H, NCH) 7.35–6.99 (m, 5H, Ph)	1998J(P1)2597
	1.91 (s, 3H, Me), 2.62–1.99 (m, 4H, 2 $\times$ CH ₂), 6.42 (d, $J = 3$, 1H, NCH) 7.65–7.05 (m, 8H, Ph), 8.06 (d, $J = 6$ Hz, COPh)	1998J(P1)2597
	1.38 (t, $J = 9$ Hz, 3H, Me), 1.66 (s, 3H, Me), 1.76–2.55 (m, 4H, 2 $\times$ CH ₂), 4.36–4.42 (m, 2H, OCH ₂), 6.34 (dd, 1H, $J = 6$ Hz, 3, vinyl CH), 6.98–7.36 (m, 5H, Ph)	1998J(P1)2597
	1.30 (t, 3H, $J = 9$ Hz, Me), 1.78 (s, 3H, Me), 2.12–1.62 (m, 2H, CH ₂), 2.45–2.64 (m, 2H, CH ₂), 3.10 (br, s, 1H, OH), 4.12–4.35 (m, 3H, OCH ₂ and CHOH), 4.54 (d, 1H, $J = 2$ Hz, NCH), 6.95–7.35 (m, 5H, Ph)	1998J(P1)2597
	1.30 (t, 3H, $J = 9$ Hz, Me), 1.71 (s, 3H, Me), 1.55–2.28 (m, 4H, 2 $\times$ CH ₂), 4.12–4.28 (m, 2H, CH ₂), 4.59 (dd, 1H, $J = 8.4$ Hz, NCH) 6.95–7.35 (m, 5H, Ph)	
	1.35 (s, 3H, Me), 1.99 (s, 3H, Me), 7.31–7.38 (m, 1H, H ₃ in Py) 7.77–7.81 (m, 2H, H ₄ and H ₅ in Py), 8.67 (dt, $J = 4.5$ and 1.4 Hz, H ₆ in Py)	2003MI395

Table 11 ^{13}C -NMR of 1,2- and 1,3-diazetidines derivatives

Compound	^{13}C NMR (δ) J(Hz)	Reference
 a: Ar = Ar¹ = 4-Me-C₆H₄- b: Ar = Ar¹ = 2,4-diMeO-C₆H₃- c: Ar = Ar¹ = 4-MeO-C₆H₄- d: Ar = Ar¹ = 1-naphthyl e: Ar = Ar¹ = 4-NMe₂-C₆H₄-	a: 20.2, 21.1, 117.3, 118.8, 123.2, 124.9, 125.7, 128.2, 128.7, 128.9, 129.5, 130.0, 131.2, 131.5, 1321.7, 133.3, 134.5, 134.8, 141.4, 141.7, 142.2, 143.8, 151.3	1999JOC1121
	108.4 (C6,6', ¹J_{CF} = 275.4, ²J_{CF} = 30.9), 109.2 (C^{5,5'}, ¹J_{CF} = 264.4, ²J_{CF} = 32.5), 116.6 (C^{7,7'}, ¹J_{CF} = 287.5, ²J_{CF} = 33.6), 130.3 (C⁸, ²J_{CF} = 33.7), 131.5 (C¹¹, ¹J_{CF} = 240.1), 135.7 (C¹⁵, ¹J_{CF} = 240.4), 137.2 (C^{10,14}, ¹J_{CF} = 249.4) 140.5 (C^{9,14}, ¹J_{CF} = 250.4), 155.8 (C-4), 158.4 (C², ²J_{CF} = 25.9)	2000JFC(104)263
 a: Ar = 4-Me-C₆H₄- b: Ar = 4-MeO-C₆H₄-	a: 21.0 (Me), 21.2 (Me), 40.8 (Me-N), 118.7, 124.8, 130.4, 132.1, 136.6, 138.4 (aromatic), 157.1, (C₄ ring), 158.2 (C₄ ring) b: 40.2 (Me-N), 55.4 (OMe), 55.4 (OMe), 114.7, 119.4, 16.4, 134.0, 137.2 (aromatic), 155.8, (C₄ ring), 159.0 (C₄ ring)	2002H(57)1257
 a: Ar = 4-Me-C₆H₄-; R = Me b: Ar = 4-MeO-C₆H₄-; R = Me c: Ar = 4-Me-C₆H₄-; R = COBu^t	a: 20.9 (Me) 21.0 (Me), 38.7 (Me-N), 39.0 (Me-N), 121.2, 122.7, 125.0, 128.9, 129.6, 130.0, 135.2, 136.0, 143.1 (aromatic), 154.9, (C₄ ring), 155.1 (C₄ ring) b: 38.9 (Me-N), 55.3 (MeO), 55.4 (OMe) 113.4, 114.1, 114.6, 114.7, 122.2, 122.3, 124.4, 126.9, 138.6, 138.5 (aromatic), 153.8, (C₄ ring), 158.3 (C₄ ring) c: 21.04 (Me), 21.19 (Me), 26.26 (CMe₃), 38.98 (Me-N), 40.24 (C-Me₃), 123.12, 125.30, 129.95, 130.33, 136.14, 137.37, 141.59, 142.83, 143.77, 152.09 (aromatic) 175.19 (C=O)	2002H(57)1257 2006S514
	22.2, 25.0, 33.6, 82.7, 129.7	2003JOC8643
 a: R¹ = R² = H, R³ = COOEt, R⁴ = Et b: R¹ = Me, R² = H, R³ = COOMe, R⁴ = Et c: R¹ = Me, R² = H, R³ = COOMe, R⁴ = C₆H₅-	a: 13.5 (Me), 14.3 (Me), 38.0 (NCH₂), 60.2 (OCH₂), 114.7 (=CH), 144.8 (=CH), 153.5 (C=N), 167.3 (C=O) b: 13.3 (Me), 23.6 (Me), 36.1 (NCH₂), 55.5 (OMe), 106.2 (=CH), 156.0, 162.4, 163.0 c: 29.8 (Me), 55.8 (OCH₂), 106.8 (=CH), 128–134.7 (aryl and C=) 155.9 (C=N) 163.4 (C=O)	2001H(55)1641
	117–128 (aryl carbons), 154 (CH), 168 (C=O)	2003PS1931

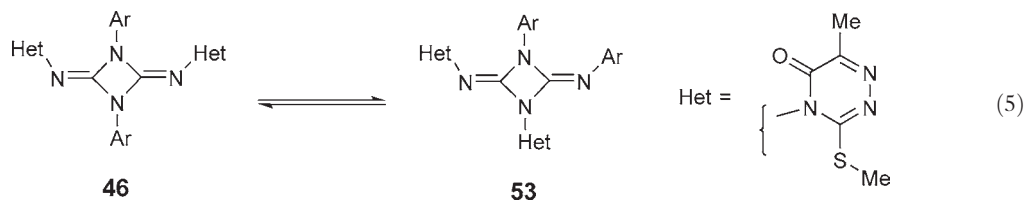
(Continued)

Table 11 (Continued)

Compound	^{13}C NMR (δ) J(Hz)	Reference
	22.86, 26.94, 32.18, 46.41, 84.17, 115.56, 123.04, 129.40, 137.61, 158.12	1998J(P1)2597
	29.46, 33.96, 83.46, 85.46, 115.98, 123.41, 129.39, 136.36, 154.86	1998J(P1)2597
	14.18, 20.89, 21.13, 31.79, 61.46, 74.82, 115.96, 118.82, 122.85, 129.37, 129.90, 136.65, 141.39, 162.48	1998J(P1)2597
	14.12, 23.56, 24.35, 28.19, 60.28, 61.54, 66.38, 76.06, 115.82, 122.37, 129.28, 137.01, 154.21, 170.16	1998J(P1)2597
	17.13, 23.33, 26.87, 35.16, 51.87, 61.25, 115.80, 122.29, 137.19, 153.29, 171.91	
	20.8(q, Me), 22.06 (q, Me), 86.14(s, C4), 90.72 (S, C3), 120.36, 124.58, 137.39, 150.01 (4d, 4CH in Py)	2003MI395

2.13.3.7 Mass Spectrometry

Not many interesting studies related to the use of mass spectrometry for structural assignment have appeared in the last decade. The mass spectra of 1,2-diazetidinones show a typical fragmentation pattern consisting of ketene and azo fragments <1986H(24)885>. However, 1,3-diazetidinones with an *N*-Me group normally gave an $(\text{M}^+ - \text{MeNCO})^+$ fragment <1990OM762>. Chemical ionization mass spectral studies have been used to confirm the dimeric nature of the adduct <1984CC863>. 1,3-Diazetidinones with methyl groups on either or both nitrogen atoms gave a major fragment $[\text{Ar}^2\text{N}=\text{C}-\text{N}-\text{Ar}^2]^+$. The mass spectrum of a structure such as **46** has led to the assumption that an equilibrium exists with that of the nonsymmetric structure **53**, as shown in Equation (5) <1986J(P1)2037>.



2.13.3.8 Electron Spin Resonance Spectroscopy

The electron spin resonance (ESR) splitting constants for the cations of 1,2-dimethyl- and 1,2-diisopropyldiazetidines have been recorded and compared with cyclic and acyclic hydrazine derivatives <1978JA2806>. The ESR spectrum of 3,3,4,4-tetrafluoro- Δ^1 -1,2-diazetidine was recorded and compared with acyclic *N,N'*-perfluoroalkylazo compounds. In the radical cation of this heterocycle, the ring seems to be planar or the conformations are interconvertible in the ESR scale <1970JA2558>. The radical cation of caged diazetidines was generated and was found to be short-lived. No new information has been reported in the last few years.

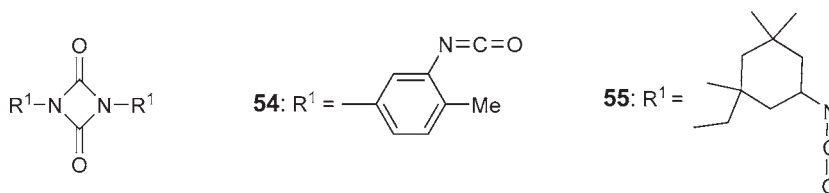
2.13.4 Thermodynamic Aspects

2.13.4.1 Physical Properties

No physical properties of 1,2 and 1,3-diazetes have been reported since they are very energetic molecules and can only be detected by spectroscopic means. On the other hand, 1,2- and 1,3-diazetidines have been found to be mostly solids, depending on their substituents. Decomposition has been observed at the melting points of many compounds, especially in the case of 1,3-diazetidines. These compounds are mostly soluble in the usual organic solvents such as ether, chloroform, acetone, etc. However, dimethyl sulfoxide (DMSO) has been used to dissolve diazetidinium salts. Diazetidines derivatives are mostly good solids that can be purified by recrystallization. Liquid compounds can be distilled under reduced pressure without decomposition.

2.13.4.2 Chromatography

Different members of the class of diazetidines have been analyzed by thin layer chromatography on silica gel plates. Purification of 1,2- and 1,3-diazetidines has normally been carried out either by crystallization (for solid compounds) or by column chromatography. Different stationary phases such as silica gel or reverse phase silica gel can be used for the purification since many of these compounds are quite stable to chromatographic conditions. Oda *et al.* used flash chromatography to purify azacarbapenems derivatives, which are 1,2-diazetidine analogues <1996H(42)577>. Breton and Shugart employed silica gel chromatography for the purification of tricyclic 1,2-diazetidines <2003JOC8643>. Similarly, several 1,3-diazetidines are stable to chromatography and can be purified routinely by this technique. Gas chromatography has also been utilized to detect the formation of diazetidines. Some diazetidines are known to undergo thermal decomposition above 130–150 °C. For example, 1,3-*N,N*-biaryldiazetidine-2,4-dione **54** was subjected to gas chromatographic analysis at 100 °C. Only small amounts of impurities were detected apart from the starting material. When the chromatography was carried out at a higher temperature, there was a slight decomposition at 150 °C whereas almost complete decomposition occurred at 175 °C. The aliphatic 1,3-diazetidine-2,4-dione **55** has been found to be less stable and when subjected to gas chromatography at 50–100 °C, several peaks were observed <1989JCH(472)175>.



2.13.4.3 Stability and Heat of Formation, Combustion, and Vaporization

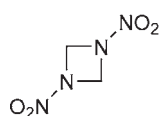
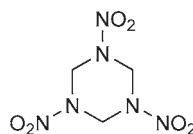
The heat of formation is expressed as

$$\Delta H_f^\circ = \Delta H_{\text{bond}} + \Delta H_{\text{str}} + \Delta H_{\text{steric}} + \Delta H_{\text{thermo}} \quad (\text{I})$$

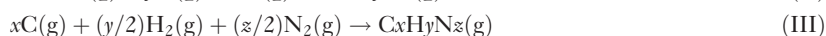
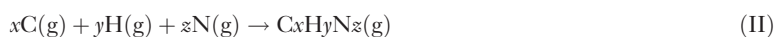
where ΔH_{bond} = sum of bond energy contribution, ΔH_{str} = sum of structural energy contribution, ΔH_{steric} = steric energy, and ΔH_{thermo} = partition function contribution.

For 3,3,4,4-tetramethyl- Δ^1 -diazetidines, the experimental and calculated $\Delta H_f^\circ(\text{g})$ and the differences between the experimental and MOMM values were determined. It was found that the calculated molecular-orbital-based molecular mechanics method (MOMM) results [36.32 kcal mol⁻¹ (152.0 kJ mol⁻¹)] are in excellent agreement with the experimentally observed value [35.92 kcal mol⁻¹ (150.4 kJ mol⁻¹)] <1988JA7286>. Politzer *et al.* found the strain energy of

1,3-dinitro-1,3-diazetidine **56** to be $8.6 \text{ kcal mol}^{-1}$ (39.8 kJ mol^{-1}), which is in good agreement with the HF 3-21G value of $9.5 \text{ kcal mol}^{-1}$ (39.8 kJ mol^{-1}) <1994JCP4706>. The ΔH_f° value for **56** is $6.2 \text{ kcal mol}^{-1}$ and is more than RDX **57**; this is also reflected in strain energies, which is nearly 70% higher for **56** than for **57**. In the case of 1,3-diazetidine and 1,3-dinitro-1,3-diazetidine, ΔE_{act} (activation energy) and ΔE (dissociation energy) were calculated for the decomposition to methyleneimine and the corresponding nitromethyleneimine using a local density functional (LDF) method <1991JCP1668>.

**56****57 (RDX)**

Gessner and Ball performed calculations using Gaussian03 on a Cray X1 supercomputer. The methods used were designed G2 <1991JCP7221>, G3 <1998JCP7764>, CBS-QB3 <1999JCP2822>, and CBS-APNO <1996JCP2598>, and were performed as defined within the GAUSSIAN program. Optimized geometries, vibrational frequencies, the standard heats of formation and enthalpy of formation were determined using the reactions



Reaction (II) is the reverse of the optimization reaction. The energy change was determined using this reaction with the appropriate number of $\Delta H_f^\circ(\text{C})$, $\Delta H_f^\circ(\text{H})$, and $\Delta H_f^\circ(\text{N})$ to determine the enthalpy of formation. Reaction (III) is the slightly modified formation of the cyclic diamines and must only be corrected for the appropriate number of $\Delta H_f^\circ(\text{C})$ s. The proton affinity (PA) is determined using



No symmetry constraints were imposed on the molecules during the geometry optimization. Both the compounds can exist as *cis*- and *trans*-isomers, depending on the relative positions of the hydrogen atoms on the nitrogens in the ring. There was also the possibility that 1,3-diazetidine might have two different *cis*-isomers: with both hydrogens in equatorial-type positions, and with both hydrogens in axial-type positions. In all attempts to optimize in an 'axial-axial' type of conformation, the ring backbone rearranged itself so the hydrogens were in 'equatorial-equatorial' positions and therefore may not occupy a minimal energy position.

2.13.4.4 Enthalpies of Formation

The enthalpies of formation of 1,2- and 1,3-diazetidines have been determined from the calculated energies based on the reactions represented by the Equations (II) and (III) using different methods (see Table 12). For each molecule the predicted ΔH_f° s were fairly consistent from method to method.

Table 12 Calculated enthalpies of formation ΔH_f° s for *cis*- and *trans*-1,2-diazetidines, and *cis*- and *trans*-1,3-diazetidine (in kJ mol^{-1})

Method	G2	G3	CBS-APNO	CBS-QB3
<i>cis</i> -1,2-diazetidines				
Reaction (II)	260.8	257.3	252.7	253.3
Reaction (III)	269.0	254.3	253.3	263.9
<i>trans</i> -1,2-diazetidines				
Reaction (II)	231.9	238.0	234.0	234.8
Reaction (III)	240.1	235.0	243.6	245.5
<i>cis</i> -1,3-diazetidines				
Reaction (II)	172.2	180.1	174.5	175.3
Reaction (III)	180.5	177.1	175.1	186.0
<i>trans</i> -1,3-diazetidines				
Reaction (II)	169.6	177.4	173.4	173.9
Reaction (III)	177.8	174.4	174.0	184.6

In the case of 1,2-diazetidines, in which two nitrogens are bonded to each other, there was a marked difference in the enthalpy of formation between the *cis*- and *trans*-isomer. As expected, the more sterically hindered *cis*-isomer had a slightly higher enthalpy of formation, about 20–30 kJ mol^{−1}. Similarly, for 1,3-diazetidines, although the *cis*-isomer had a slightly higher enthalpy of formation than the *trans*-isomer, the difference (1–3 kJ mol^{−1}) is probably within the expected error limits of the method.

In all cases, the predicted ΔH_f values are within 10 kJ mol^{−1} of each other, despite the difference in the enthalpy of formation.

For the thermal stability of 1,2-diazetidines and their thermodynamic properties, see also Section 2.13.6.

2.13.4.5 Proton Affinity

The 1,2-diazetidine and 1,3-diazetidine isomers have about the same PAs. In the case of 1,2-diazetidine, there is a 20 kJ mol^{−1} difference between the *cis*- and *trans*-isomers in their PA. This should not be surprising, as this molecule also has an NH–NH moiety. For 1,3-diazetidine, the NH groups are on opposite corners of the ring, so the effects on the PA due to *cis/trans*-isomerism should be minimized (Table 13).

Table 13 Calculated PA for *cis*- and *trans*-1,2- and 1,3-diazetidines (in kJ mol^{−1})

Method	G2	G3	CBS-APNO	CBS-QB3
<i>cis</i> -1,2-Diazetidines	933.6	923.9	924.1	920.9
<i>trans</i> -1,2-Diazetidines	904.3	904.6	905.4	902.4
<i>cis</i> -1,3-Diazetidines	914.4	915.7	912.3	915.0
<i>trans</i> -1,3-Diazetidines	911.8	913.1	910.7	913.9

2.13.4.6 Dipole Moment

No systematic studies on dipole moments have been reported on this class of heterocycles. Theoretical calculations on certain tetrazacubanes and 1,3-dimethyl-1,3-diazete indicated a dipole moment of 0.0 debye <1992JMT(256)17>.

2.13.4.7 Aromaticity

According to the Hückel $(4n+2)/(4n)$ rule, four-membered ring compounds should be aromatic with 2π - or 6π -electrons, and antiaromatic with 4π -electrons. A few four-membered rings with 6π -systems are known. The instability of 6π -electrons in four-membered systems has been attributed to large 1,3-repulsive interactions in the π -system <1985JOC5869>. The repulsive interactions in the structures of 1,3-diazetidine, 1,2-diazetidine and related systems are smaller and might be expected to be favorable.

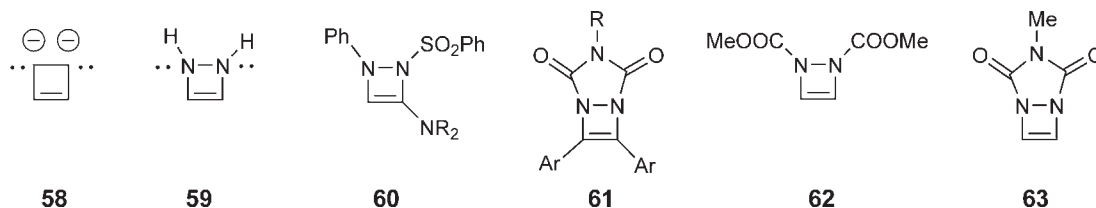
Based on MO calculations, the details of electron density distributions in these molecules were analyzed. The 1,2-diazetidines have completely localized C=C bonds and normal C–N and N–N single bonds. In the case of 1,3-diazetidines, there are two possible electronic configurations differing in the occupation numbers of the π -orbitals π_1 – π_4 . The aromatic occupation π_1^2 , π_2^2 , π_3^2 produces nearly a square structure, but these show no evidence of strong C–N π -bonding. The aromatic character has been measured in terms of absolute hardness and relative hardness <1989JA7371>. The HOMO–LUMO value is taken as a good measure of aromaticity, and this is correlated with absolute hardness.

The aromaticity of 1,2-dihydrodiazete has also been investigated <2002JOC6699>. A thorough experimental and computational investigation of the aromaticity of the 1,2-dihydrodiazete ring system was carried out. The simplest criteria for aromatic compounds consist of the presence of a cyclic conjugated π -system containing the required number of π -electrons (i.e., Huckel's rule). However, complex systems do not always obey this rule of aromaticity. For instance, applying these criteria to the cyclobutadienyl dianion 58, one would predict an aromatic compound since it contains six π -electrons, as in benzene or the cyclopentadienyl anion. The dianion is planar but adopts a structure with C_{2h} symmetry rather than the D_{4h} symmetry expected for a fully delocalised structure.

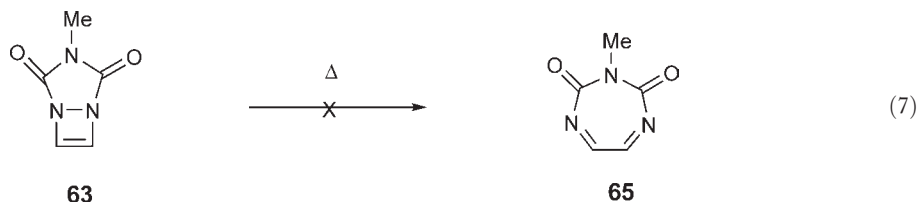
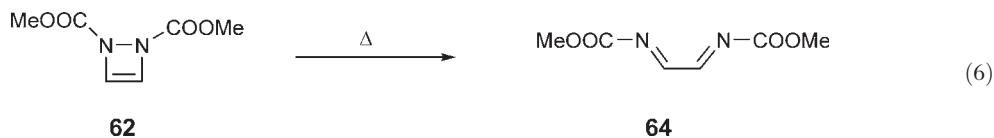
Elguero and co-workers have examined and confirmed the nonaromatic nature of 1,2- Δ^3 -diazetidine <1989JMT(201)17> comparing resonance energies which were of opposite sign to that predicted for benzene, as well as by its high nitrogen inversion barriers <1976J(P2)1222>. The resonance energy of 1,2- Δ^3 -diazetidine was

evaluated by means of a homodesmotic reaction. Although this is described in detail in CHEC-II(1996) <1996CHEC-II(1B)911>, it is important to point out that the HOMO–LUMO barrier of 1,2-diazete and its isomer 1,3-diazete and the π -bond orders clearly indicate the antiaromatic nature of these heterocycles and in several cases π -electrons tend to destabilize these π -bonds.

Recent studies on the cyclobutadienyl dianion, substituted at each carbon of the ring with anion stabilizing substituents such as a trimethylsilyl group, have shown that the dianion is almost square and planar (as determined by X-ray crystallography), suggesting that it could be aromatic <2000JA5652>. It is expected that in the cyclobutadienyl dianion **58** if two negatively charged carbon anions can be substituted by a nitrogen atom, it will result in 1,2-dihydrodiazete **59**. The 1,2-dihydrodiazetes **59** are isoelectronic with the cyclobutadienyl dianion **58**, but with less charge–charge repulsion and therefore might exhibit aromaticity without any need for additional stabilization. A few examples of highly substituted 1,2-dihydrodiazetes have been reported in the literature, such as derivatives **60–63**.



Diazete **60** has been isolated but no data have been reported <1966AGE416>, whereas compounds **61** <1984JOC2917> and **62** <1972CC818> have been characterized and were found to be stable crystalline products, although **62** has been found to have limited thermal stability ($t_{1/2}$ [20 °C] = 6.9 h) <1979AJC2659>. Breton *et al.* <2001OL3185> made **63** as a stable crystalline compound and studied its stability and aromatic character. Thermally, compound **63** was found to be much more stable than **62**. However, the thermal stability of **63** cannot be attributed to the aromatic stabilization relative to **62**, since a similar stability should be present in **62**. It is suggested that compound **62** can undergo a facile thermally concerted conrotatory ring opening leading to **64** (Equation 6), whereas compound **63** cannot undergo a ring-opening reaction since it will lead to inherent strain of ring-opened product **65** (Equation 7).



Therefore, the aromatic character cannot be attributed to six π -electron systems alone and several factors need to be taken into consideration.

2.13.4.8 Conformational Studies

A number of studies have been reported for the conformational analysis of 1,2- and 1,3-diazetidide and diazete derivatives using IR–Raman spectroscopy (see Section 2.13.3.5). The conformational changes may take place as a result of inversion at the nitrogen center or due to the flexibility of the ring. A number of MO calculations suggest that one conformer predominates over the others. Catalan and co-workers have carried out an *ab initio* calculation at the 4-31G level to study the structure and stability of the possible conformers of 1,3-diazetidide. They have found two stable forms: an equatorial–equatorial (*E,E*)-form with a puckered conformation, and an equatorial–axial (*E,A*)-form which is planar. A nitrogen inversion barrier of 4.1 kcal mol^{−1} (17.2 kJ mol^{−1}) <1984JMT(106)251> possibly connects these two stable forms. Gessner and Ball have studied the structures of *cis*- and *trans*-1,2-diazetidide and proposed the minimum energy geometries and specific bonding parameters <2005JST(730)95>. These values are given in Table 14. In the case of *trans*-1,2-diazetidide, it has been found to possess nominal *C*₂ symmetry, with two nitrogen

atoms in equivalent environments. However, in the case of *cis*-1,2-diazetidines, the two nitrogen atoms have been found to be not equivalent because of the puckering of the four-membered ring: one hydrogen is in a more axial position while the other is in a more equatorial position.

Table 14 Optimized structural parameters for *cis*- and *trans*-1,2-diazetidine and 1,3-diazetidine (*r* in Å, angles in degrees)

Parameter	G2, G3	CBS-APNO	CBS-QB3
<i>cis</i> -1,2-Diazetidines			
<i>r</i> (C–H)	1.090, 1.100	1.090, 1.100	1.090, 1.100
<i>r</i> (N–H)	1.010, 1.020	1.010, 1.020	1.010, 1.020
∠(N–N–H)	110.7, 106.3	110.7, 106.5	111.2, 107.0
δ(C–N–N–H)	80.3, 140.3	81.3, 138.8	84.8, 137.2
δ(N–C–C–H)	91.2, 139.1	91.8, 142.7	91.1, 138.3
Ring pucker	22.9	22.1	19.9
<i>trans</i> -1,2-Diazetidines			
<i>r</i> (C–H)	1.090	1.090	1.090
<i>r</i> (N–H)	1.020	1.010	1.010
∠(N–N–H)	106.7	106.9	106.8
δ(C–N–N–H)	134.7	132.4	123.9
δ(N–C–C–H)	91.8, 138.6	94.2, 136.3	99.8, 131.6
Ring pucker	22.5	20.3	15.8
<i>cis</i> -1,3-Diazetidines			
<i>r</i> (C–H)	1.100, 1.090	1.100, 1.090	1.100, 1.090
<i>r</i> (N–H)	1.010	1.010	1.010
∠(C–N–C)	87.0	87.2	88.0
∠(N–C–N)	89.0	89.3	89.5
∠(C–N–H)	114.0	113.4	114.2
δ(C–N–N–H)	94.9, 138.1	95.9, 136.8	99.7, 133.7
δ(N–C–N–H)	136.0	134.2	132.6
Ring pucker	21.0	19.8	17.0
<i>trans</i> -1,3-Diazetidines			
∠(C–N–C)	86.3	88.0	88.4
∠(N–C–N)	91.4	92.0	91.6
∠(C–N–H)	107.9	111.5	112.7
δ(C–N–N–H)	96.4, 136.2	116.5, 118.0	116.7, 118.0
δ(N–C–N–H)	91.1	112.3	114.0
Ring pucker	16.0	<0.1	<0.1

Therefore, there are two different values of the N–H bond distance, N–N–H bond angles, C–N–N–H dihedral angles, etc., for the *cis*-isomer. For both the conformers, the four-membered rings are puckered, as in cyclobutane. However, the *cis*-isomer has *C*₁ symmetry, whereas the *trans*-isomer has *C*₂ symmetry.

In contrast to the 1,2-diazetidines, the structures of *cis*- and *trans*-1,3-diazetidines are very different. Some of the bonding parameters of the minimum energy geometries are listed in Table 14. However, in both CBS calculations (CBS-APNO and CBS-QB-3) for the *trans*-isomer, the minimum-energy geometry is predicted to have a planar backbone. This gives the molecule a nominal *C*_{2v} symmetry instead of the *C_s* symmetry of the puckered geometry. Therefore, the calculated dihedral angles between the hydrogen atoms and the ring backbone are very different for these methods. The *cis*-1,3-diazetidine molecule is puckered with *C*_{2v} symmetry.

2.13.4.8.1 Reactivity

Four-membered heterocycles with two nitrogen atoms are expected to show two different kinds of reactivity: one arising from the ring strain and the other from the presence of heteroatoms. General electrophilic reagents are expected to attack on nitrogen. Several theoretical calculations have explained the reactivity of the ring toward nucleophilic, electrophilic, and radical reagents. The reactivities of several diazetidines and diazetes are summarized in the following sections.

2.13.5 Reactivity of Fully Conjugated Rings

The reactivity of 1,2- and 1,3-diazetes and their derivatives falls under the class of fully conjugated ring systems. It has not been possible to prepare this class of compounds. Because of their high energy, as shown by HF/6-31G* theoretical calculations, neither 1,2-diazetes (total energy = -185.62430 au; relative energy = 79.12 kcal mol $^{-1}$ (331.2 kJ mol $^{-1}$)) nor 1,3-diazetes (total energy = -185.65532 au; relative energy = 59.65 kcal mol $^{-1}$ (249.7 kJ mol $^{-1}$)) were found to be stable <1991JMT(236)119>. Some interesting theoretical aspects have been reported in Section 2.13.2.

2.13.6 Reactivity of Nonconjugated Rings

The reactivity of 1,2- and 1,3-diazetidines and their derivatives falls under the class of nonconjugated ring systems.

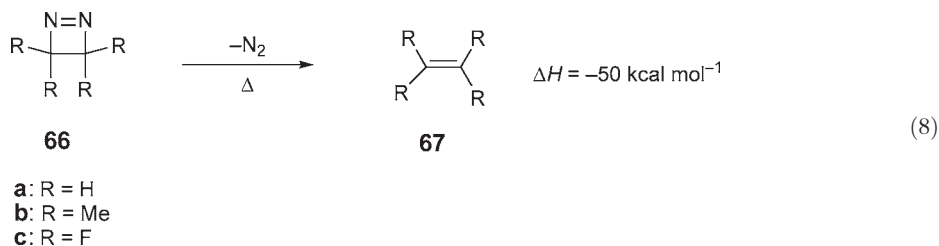
2.13.6.1 Thermal and Photochemical Transformations

Diazetidines and diazetines undergo facile thermal decomposition by a [2+2] cycloreversion pathway either leading back to their parent precursors or to new products. A number of such fragmentation reactions have been compiled by Richter and Ulrich <1983HC(42)443>. These transformations have been covered in detail in CHEC-II(1996) <1996CHEC-II(1B)911>; however, for continuity reasons, a few examples will be quoted here.

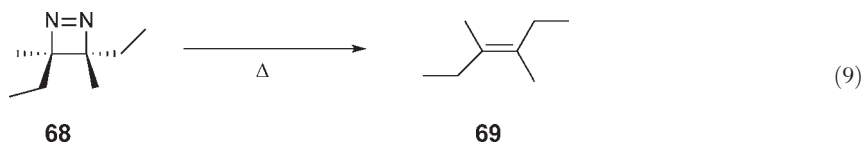
2.13.6.1.1 1,2-Diazetine derivatives

1,2-Diazetines are a class of strained four-membered ring azo compounds <1993JOC5393, 1980CRV99>. Diazetines are thermally quite robust, despite the release of strain energy that would be anticipated upon decomposition <1978JA6760>. The decomposition of diazetines to afford N₂ and the corresponding alkenes is strongly exothermic; however, there is a substantial activation barrier to the process <1978JA6760, 1993JOC5393>.

For example, decomposition of **66** will afford alkene **67** and nitrogen. The reaction is highly exothermic (ΔH -50 kcal mol $^{-1}$), even though it has an activation barrier of $\Delta H^\ddagger \sim 35$ kcal mol $^{-1}$ (Equation 8) <1978JA6760>. The high activation barrier has been attributed to (1) a significant energy required to surmount the symmetry forbidden [2s+2s] cycloreversion reaction and (2) a large increase in strain energy for the molecule to adopt a transition state geometry required for a symmetry allowed [2s+2a] cycloreversion process.

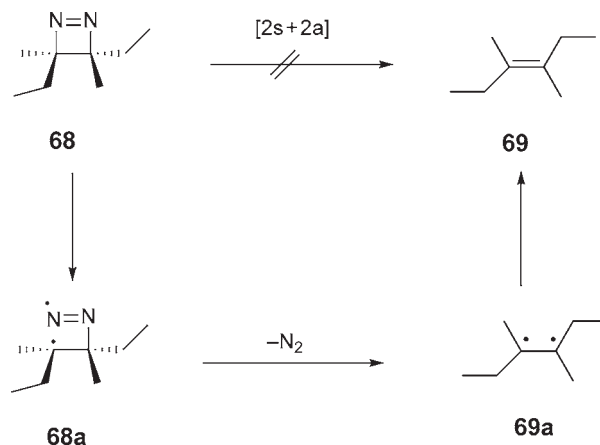


Later, a nonconcerted route was also suggested in which the C–N bond cleavage can take place to form a biradical followed by loss of nitrogen. Green *et al.* have demonstrated that diazetines **68** stereospecifically afford alkene **69** which ruled out the symmetry forbidden [2s(N₂)+2a(olefin)] or [2s(olefin)+2a(N₂)] cycloreversion pathway, since the latter will generate nitrogen in a high energy triplet state (Equation 9).



In contrast, Breton *et al.* <2001OL3185> have reported thermal orbital symmetry allowed conrotatory ring opening of Δ^3 -1,2-dicarbomethoxy-1,2-diazetine **62** to give the cycloreversion product 1,4-dicarbomethoxy-1,4-diazabut-1,3-diene **64** (Equation 6).

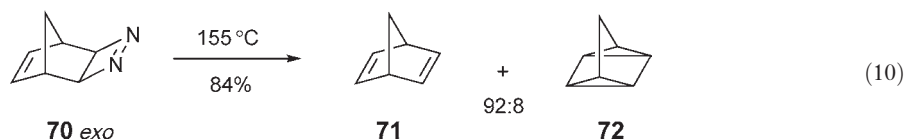
The nonconcerted diradical pathway was still considered viable in the thermal decomposition of 1,2-diazetines assuming that the loss of nitrogen from the intermediate was rapid relative to the C–C bond rotation. Olsen using mono- and dideuterated diazetines provided mechanistic evidence for this process [<1982JA6836>](#). The kinetic isotope effect observed suggested that the transition state was unsymmetrical and should be proceeding via a diradical like pathway ([Scheme 3](#)).



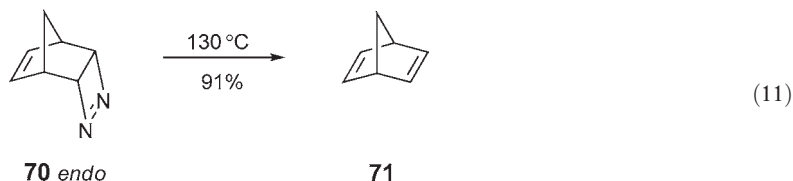
Scheme 3

Theoretical calculations by Yamabe [<2001PCA7281>](#) supported Olsen's conclusion of an unsymmetrical yet concerted biradical as transition state. Theoretical calculations for activation and entropy change for tetramethyl diazetines **66b** are in good agreement with the experimentally observed value ($\Delta H^\ddagger_{\text{cal}} = 35.3 \text{ kcal mol}^{-1}$, $\Delta H^\ddagger_{\text{exp}} = 31.7 \text{ kcal mol}^{-1}$; $\Delta S^\ddagger_{\text{cal}} = 0.94 \text{ cal mol}^{-1}$; $\Delta S^\ddagger_{\text{exp}} = 0.3 \pm 0.8 \text{ cal mol}^{-1}$). Tetramethyl diazetine **66b** was observed to have a higher than expected $\Delta H^\ddagger$ (based on its large strain energy ($24.5 \text{ kcal mol}^{-1}$)) and thus, the transition state energy ($56.0 \text{ kcal mol}^{-1}$) was significantly higher than expected.

Breton *et al.* have reported thermal decomposition of several diazetines such as **70** *exo* at 155°C for 2 h to give a mixture (92:8) of norbornadiene **71** and quadricyclane **72** in 84% yield [<2003JOC8643>](#). It has been demonstrated that quadricyclane is converted into norbornadiene at only 10% conversion under the same reaction conditions ([Equation 10](#)).



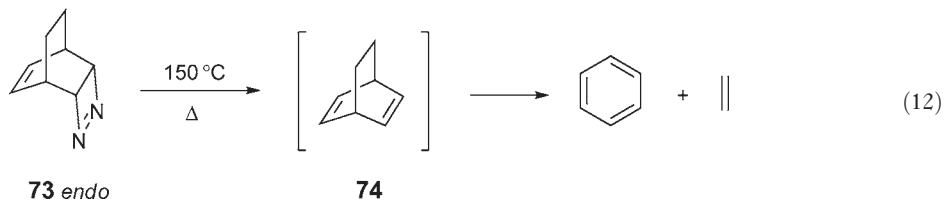
The thermolysis of **70** *endo* at 130°C for 2 h afforded 91% yield of norbornadiene only ([Equation 11](#)).



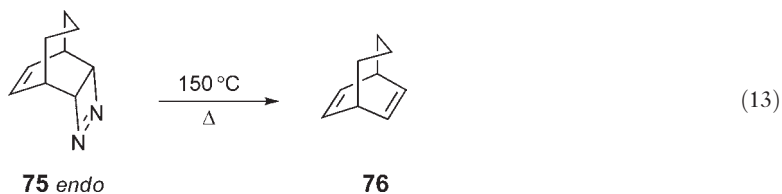
This suggests that the formation of quadricyclane during the thermal decomposition of **70** *exo* results from the competing $[2s+2s+2s]$ retrocycloaddition process rather than via intramolecular trapping of the diradical intermediate by a C–C bond. Thus, the thermal decomposition of **70** *exo* resulted from $[2s+2s+2s]$ cycloreversion reaction rather than from a biradical pathway. If the latter pathway was active, both *exo* and *endo* isomers should have furnished quadricyclane **72**. In fact, **70** *endo* is geometrically incapable to participate in the cycloreversion process.

Diazetine **73** underwent complete decomposition when heated for 10 h at 150°C but no formation of the expected bicyclo[2,2,2]octan-2,5-diene **74** was observed. Instead, further cycloreversion leads to the formation of benzene

(68%) and ethylene (Equation 12). Unlike the case of **70** *exo*, no tetracyclic compound analogous to **72** was observed. Bicyclooctadiene **74** is known to undergo cycloreversion to furnish benzene and ethylene. Thus, it is assumed that in the thermolysis of **73** *endo*, the initially formed bicyclo[2.2.2]octa-2,5-diene undergoes rapid cycloreversion to afford benzene and ethylene.



In contrast, thermolysis of **75** at 150 °C for 10.5 h afforded predominantly bicyclo[3,2,2]nona-6,8-diene **76** (95% yield) (Equation 13). In this case also, no tetracyclic product was detected.



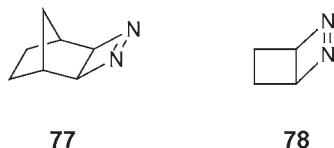
2.13.6.1.1(i) Kinetics of the decomposition of diazetines

The rate of decomposition of 1,2-diazetines **70** *exo*, **70** *endo*, **73** *endo*, and **75** *endo* was carried out using UV spectroscopy and a linear plot $\ln(k/t)$ versus $1/T$ afforded the $\Delta H^\ddagger$ value of the decomposition of diazetines.

The value of $\Delta H^\ddagger$ of **70** *endo* indicates that among all the *endo*-diazetines, **70** *endo* has the lowest $\Delta H^\ddagger$ value. The values of $\Delta H^\ddagger$ for **73** and **75** are also within the error limit. The difference in $\Delta H^\ddagger$ value between **70** *endo* and **75** *endo* is *c.* 7 kcal mol⁻¹, suggesting that the difference in $\Delta H^\ddagger$ may be due to the diazetine ring strain (Table 15).

Table 15 Kinetics of decomposition of diazetines (all energies in kcal mol⁻¹)

Compound	$\Delta H^\ddagger$	ΔH_f calculated	ΔH_f theoretical	E_{strain}
70 <i>exo</i>	30.8 ± 0.8	104.3	58.3	51.0
70 <i>endo</i>	31.7 ± 0.4	109.3	58.3	46.0
73 <i>endo</i>	39.3 ± 1	89.3	53.4	35.9
75 <i>endo</i>	38.8 ± 0.5	82.7	48.5	34.2
66b	35	35.2	11.5	24.4
77		70.6	30.4	40.2
78		91.4	41.9	49.5



2.13.6.1.1(ii) Ring strain of diazetines

The ring strain energies are either determined experimentally or by calculation. Engel has calculated the ΔH_f of a strain-free reference compound (based on Benson's group contribution method) and has subtracted this from the ΔH_f of the compound of interest <1976JA1972>. The difference between these two values is

attributed to ring strain. Breton obtained a group energy term for the N=N bond for several azocompounds for which ΔH_f had already been experimentally determined <2003JOC8643>. Several cyclic and acyclic azo compounds were tested and were found to be in reasonable agreement with the experimental ΔH_f value. For example, ΔH_f for tetramethyl diazetine **66b** (35.2 kcal mol⁻¹) agrees very closely with the experimentally observed value of ΔH_f (35.9 kcal mol⁻¹). The difference between the calculated and the observed values may vary within 1.4 kcal mol⁻¹.

Hence using this method, Breton calculated a ΔH_f value for diazetines **70 endo**, **70 exo**, **73 endo**, and **75 endo** as well as for other diazetines such as **77** (70.6 kcal mol⁻¹) and **78** (91.4 kcal mol⁻¹) for the experimental $\Delta H^\ddagger$ of decomposition which are summarized in Table 16.

Table 16 Calculated strain energies (ΔE_{strain}) localized in the diazetidine ring and transition state energy (E_{TS}) for diazetines (all energies in kcal mol⁻¹)

Compound	ΔE_{strain}	$\Delta H^\ddagger$	E_{TS}
66b	23.7	31.7	55.4
70 exo	24.5	30.8	55.3
70 endo	29.5	31.7	61.2
73 endo	24.1	39.3	63.4
75 endo	21.3	38.8	60.1
77	23.9	33.7	57.6
78	23.3	32.9	56.2

Benson's method used to calculate the contribution to the ΔH_f provides a convenient strain-free reference value. By subtracting the reference ΔH_f from the calculated ΔH_f value, strain energies can be calculated as compiled in Table 16.

The strain energy as calculated for **66b** (24.4 kcal mol⁻¹) compares well with the previously predicted value of 24.5 kcal mol⁻¹ by Engel <1976JA1972>. The successful prediction of both the ΔH_f and the strain energy for tetramethyl diazetine **66b** suggested that the computational approach to obtain the strain energy for diazetines is practical. Thus, both the ΔH_f and the strain energy of diazetines could be predicted with reasonable accuracy.

Breton also calculated the strain energy difference (ΔE_{strain}) which is localized within the diazetine ring itself.

From Table 16, the following observations can be made: (1) substituted diazetine **70 endo** is more strained than the *exo* isomer (**70 exo**) as one would expect ($\Delta E_{\text{strain}} = 5$ kcal mol⁻¹); (2) there is a decrease in the strain energy as the number of bridging carbons in the fused hydrocarbon bicycle increases (**75 endo**, 21.3 kcal mol⁻¹) <**73 endo** (24.1 kcal mol⁻¹) <**70 endo** (29.5 kcal mol⁻¹). Thus, tightening of the bridge-head of the fused hydrocarbon bicycle would result in 'pinching' of the diazetine ring with a corresponding increase in strain energy.

2.13.6.1.1(iii) Transition state energies

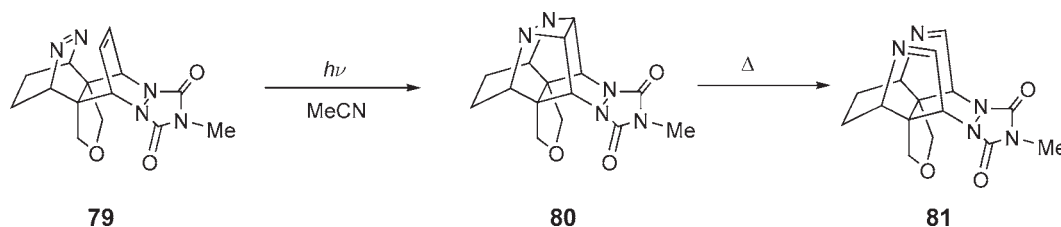
The transition state energy of decomposition (E_{TS}) of diazetines was obtained by addition of the diazetine strain energy and the corresponding $\Delta H^\ddagger$ for decomposition. (Table 16). The E_{TS} is fairly constant for all the diazetines and the average E_{TS} (59 kcal mol⁻¹) agrees well with the estimated transition state energy for decomposition of **66b** (56 kcal mol⁻¹). The overall decrease in strain energy (**70 endo**, **73 endo**, **75 endo**) of 8.2 kcal mol⁻¹ matches with the corresponding increase in $\Delta H^\ddagger$ of decomposition of 7.1 kcal mol⁻¹. The E_{TS} for **73** (63.4 kcal mol⁻¹) is higher than **70 endo** (61.2 kcal mol⁻¹) and **75 endo** (60.1 kcal mol⁻¹) due to a $\Delta H^\ddagger$ value of decomposition higher than expected of 39.3 kcal mol⁻¹ (for **70 endo**, 31.7 kcal mol⁻¹; **75 endo**, 38.8 kcal mol⁻¹). In short, an increase in ground state energy induced by strain is compensated by a decrease in $\Delta H^\ddagger$ of reaction to afford a common transition state of decomposition of diazetines.

Each transition state structure exhibited a single frequency whose motion was consistent with the loss of nitrogen from the hydrocarbon fragment. The TS geometries of all the diazetines were remarkably similar. Each diazetine exhibited a small N(1)–N(2)–C(3)–C(4) dihedral angle of 4.9–5.5° so that the diazetine portion of the ring is not planar. Yamabe established that in 1,2-diazetine **66a**, a symmetry lowering twist of nitrogen fragment relative to C–C bond in the transition state resulted in a lowering of energy of the transition state due to a dual orbital mixing effect possible for a TS exhibiting a strong biradical character <2001PCA7281>. The twisted transition state is of even lower energy than that of the structure allowed by the *Cs* symmetry.

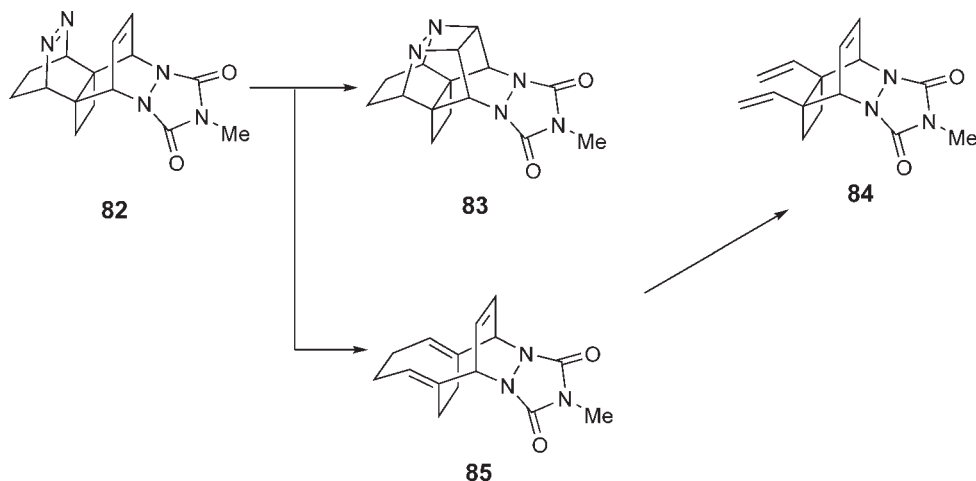
The calculation for the transition state structure and the ground state diazetines structure afforded the transition state barrier (used B3LYP/6-1G* level) at the B3LYP/6-311+G (3df,2p) level. The calculated barrier for **70** *endo* (33.3 kcal mol⁻¹), **73** *endo* (36.9 kcal mol⁻¹), **75** *endo* (37.5 kcal mol⁻¹), and **70** *exo* (34.6 kcal mol⁻¹) compares well with the experimentally observed value (Table 15) which suggests that the mechanism of unsymmetrical yet concerted elimination of nitrogen from diazetines is quite reasonable.

Prinzbach and co-workers <2000EJO743> carried out photochemical and thermal transformations of several diazetine derivatives in a strained cyclic system. They reported the formation of diazetidine **80** by photolysis of diazenelene **79** in acetonitrile.

The diazetidine **80** is thermally unstable and undergoes 2σ–2π cleavage above 100 °C resulting in bispyrroline **81**, which undergoes subsequent polymerization (Scheme 4). In contrast, diazenelene **82** underwent nitrogen elimination to give **84** and **85** along with the [2+2] cycloadduct 1,2-diazetidine **83** (Scheme 5).



Scheme 4



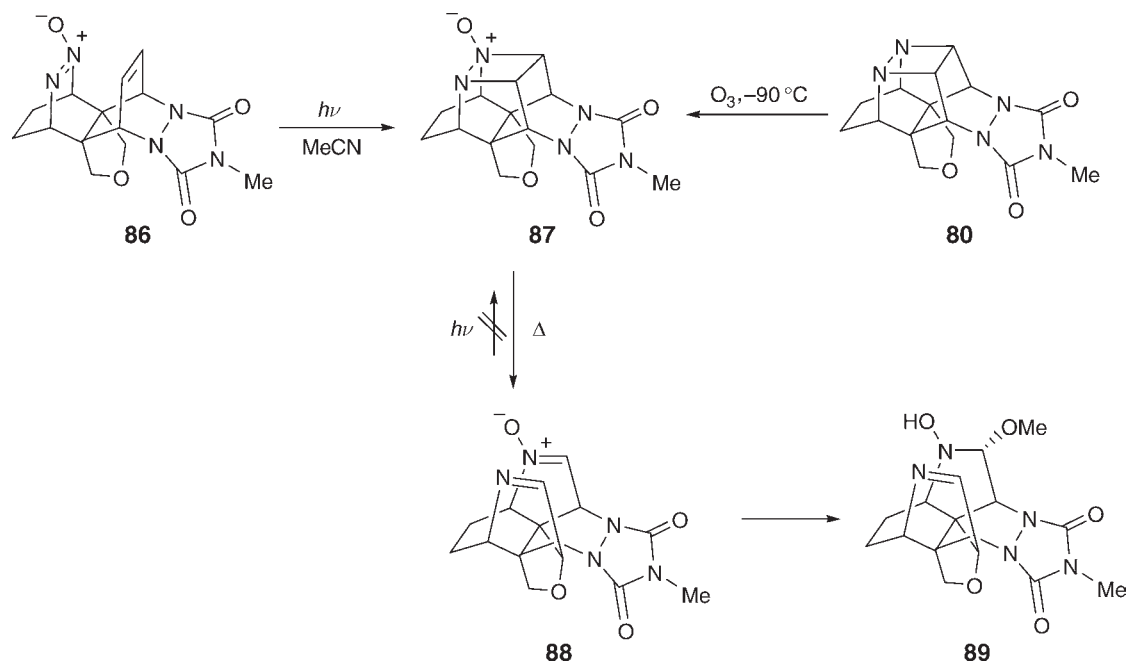
Scheme 5

Similarly, diazeneoxylyene undergoes photoexcitation to give the *N*-oxide of **80**, which undergoes thermal decomposition to nitron **88** and upon further decomposition gave a number of compounds as an inseparable mixture. A sensitized irradiation of **86** in acetone led to **88**. In methanol the product isolated was the 1:1 adduct **89** (86% at 60% conversion). On the other hand, oxidation of **80** with ozone at –90 °C in methanol led to isolation of **88** (85%). In fact, the oxidation of **80** gives **87** at –90 °C, which undergoes thermal opening to **88** at –65 °C (Scheme 6).

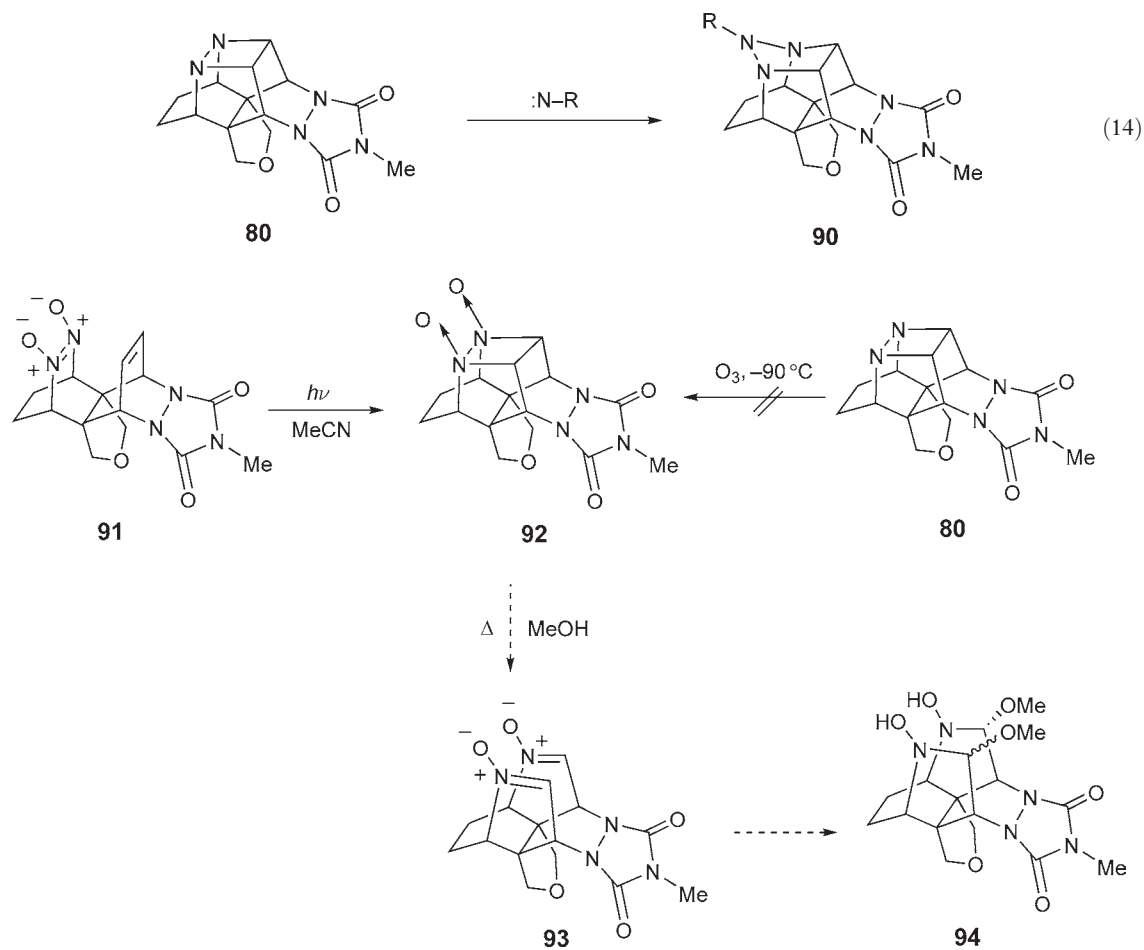
In contrast to the oxidation, **80** can undergo nitrene (R–N) addition across the N–N bond of diazetidine **80** to furnish **90** (Equation 14).

Diazenedioxylyene **91** underwent acetone-sensitized phototransformation to give an inseparable mixture of five to eight products and no compound could be assigned the expected structure **93** by any spectroscopic means.

In the case of oxidation of **80** in methanol by ozonolysis at –90 °C, the *N*-oxide **87** was obtained. Further, extending the reaction time did not afford either **92** or **93** but rather gave a mixture of unidentifiable products (Scheme 7).

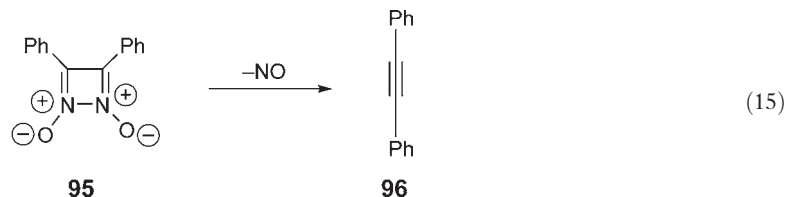


Scheme 6



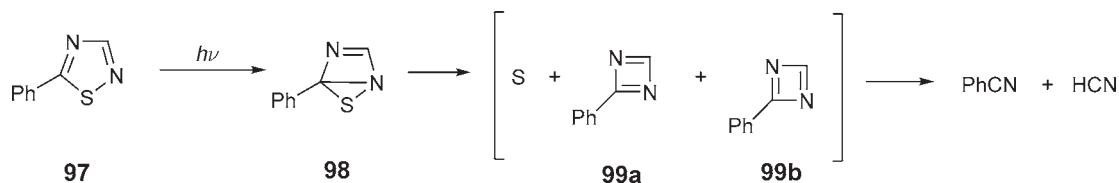
Scheme 7

Tandon and Chhor reported 3,4-diphenyl-3,4-dihydro[1,2]-diazete-1,2-dioxide **95** by the oxidation of diazete with hydrogen peroxide in glacial acetic acid <2004LOC40>. These authors wanted to investigate 'NO' donor properties of these *N,N*-dioxides. The *N,N*-dioxides can undergo thermal exclusion of NO to furnish diphenylacetylene **96** (Equation 15).



2.13.6.1.2 1,3-Diazetidine derivatives

Pavlik *et al.* studied the photochemical transformation of phenyl-substituted 1,2,4-thiadiazoles <2003JOC4855>. When they irradiated a solution of 3-phenyl-1,2,4-thiadiazole in acetonitrile (82% conversion), only benzonitrile (74%) along with elemental sulfur were formed. On the other hand, the photochemical transformation of 5-phenyl-1,2,4-thiadiazole (53% conversion) gave a mixture of benzonitrile (58%), 3-phenyl-1,2,4-thiadiazole (18%), phenyl-1,3,5-triazine (4%), diphenyl-1,3,5-triazine (2%), and traces of diphenyl-1,2,4-thiadiazole. Similarly, 3-methyl-5-phenyl-1,2,4-thiadiazole when irradiated in acetonitrile gave benzonitrile in 50% yield, 5-methyl-3-phenyl-1,2,4-thiadiazole in 10% yield, and dimethylphenyl-1,3,5-triazine (33%) and methyl-diphenyl-1,3,5-triazine (5%). These photochemical transpositions have been rationalized in terms of the intermediacy of **98** and its isomers which undergo either S extrusion to give diazete **99a/b** (Scheme 8) or rearrangement as shown in Scheme 8 to give the observed products. A ¹⁵N-labeling experiment was carried out to understand the mechanism and the transformation pathways.



Scheme 8

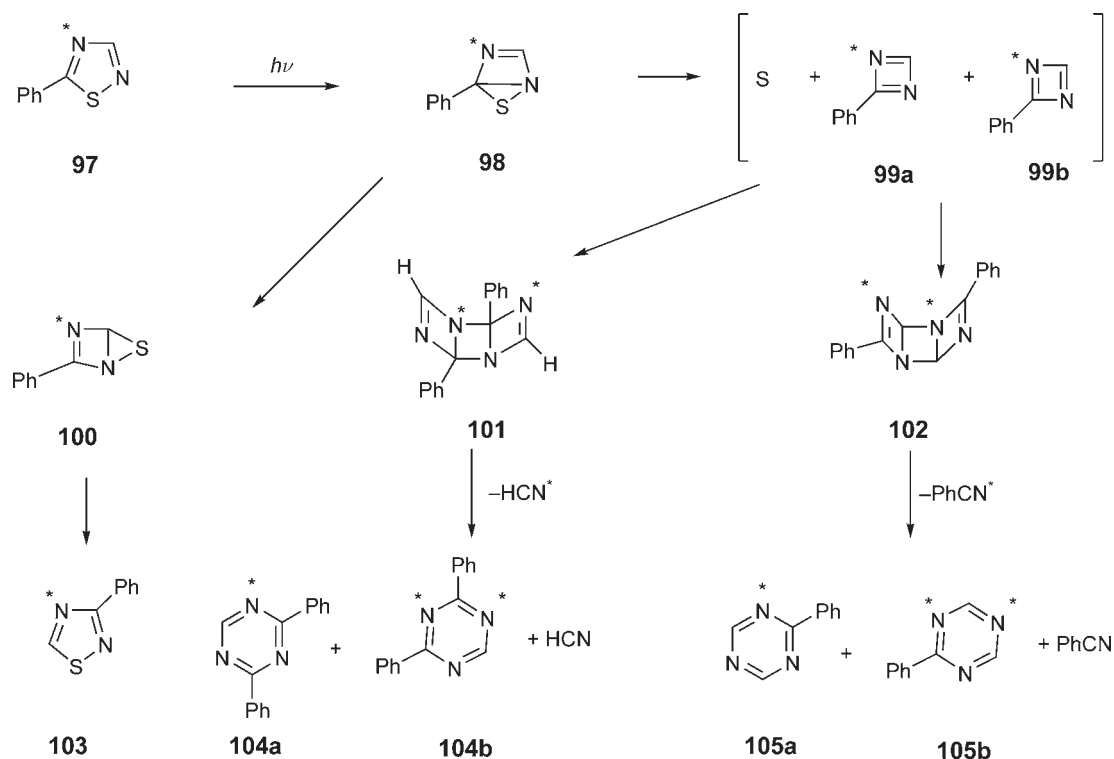
By analogy, diazetine **99a/b** may have various possibilities to undergo [4+2] cycloaddition as shown in Scheme 9.

This explains the formation of various products like benzonitrile, 3-phenyl-1,2,4-thiadiazole **103**, 2-phenyl-1,3,5-triazine **105a/b**, and diphenyl 1,3,5-triazine **104a/b** in the photolysis of 5-phenyl-1,2,4-thiadiazole **97**.

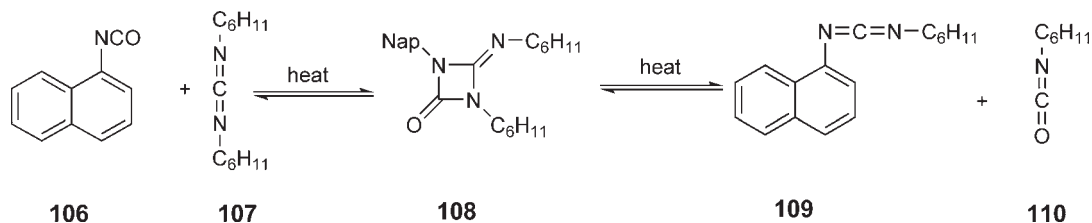
The 1,3-diazetidines are most commonly synthesized by the dimerization of heterocumulenes. At elevated temperature they undergo dissociation and are in equilibrium with their monomers. For example, 1,3-diazetidines **108**, formed by the reaction of α -naphthyl isocyanate **106** with dicyclohexylcarbodiimide **107**, upon thermal dissociation furnished products of its [2+2] cycloreversion reaction, that is, cyclohexyl isocyanate **110** and α -naphthylcyclohexylcarbodiimide **109** (Scheme 10) <1962AGE621>.

2.13.6.2 Acylation Reaction

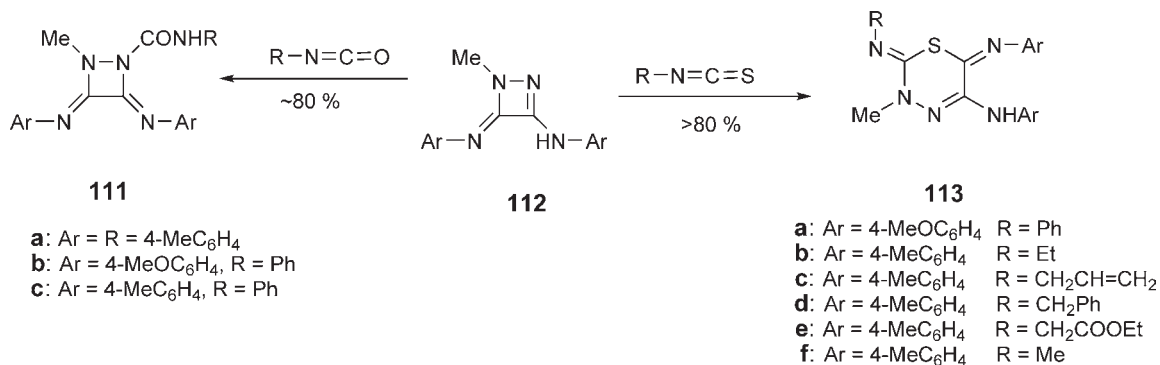
Beckert *et al.* have reported the regioselective acylation reaction of Δ^2 -1,2-diazetines <2005H(65)1311, 2006S514>. Isocyanates react with diazetines to give semicyclic urea derivatives, whereas reaction with isothiocyanates under milder conditions furnishes 1,3,4-thiadiazines **113**. It has been shown that ring acylation occurs at lower temperature, whereas the electrocyclic ring-opening/cycloaddition process is possible at higher temperature (Scheme 11).



Scheme 9

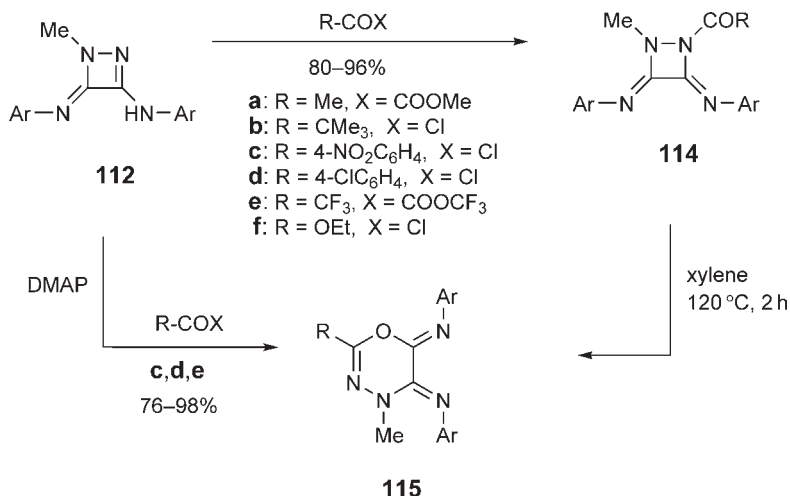


Scheme 10



Scheme 11

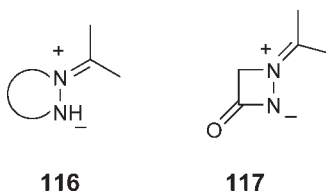
Similarly, treatment of 1,2-diazetines **112** with acyl chloride or anhydride in the presence of DMAP yields acylated 1,2-diazetidines **114** <2006S514> which upon heating give ring-expanded products **115** (Scheme 12).



Scheme 12

2.13.6.3 Cycloaddition Reactions

Cyclic azomethane ylides **116** are useful intermediates in constructing a variety of heterocycles containing bridge-head nitrogen atoms. The lower homologue **117** containing two nitrogen atoms has been shown to be a good 1,3-dipole in cycloaddition reactions <1981JA7659, 1981JA7660, 1981JA7743>. Not many new cycloadditions on azomethane ylides have been reported in recent years.



Breton and Martin <2002JOC6699, 2001OL3185> reported the cycloaddition of 3-methyl-1,3,5-triazabicyclo[3.2.0]hept-6-ene-2,4-dione **63** with a number of different dienes leading to the formation of [4+2] cycloaddition products. Most of the Diels–Alder cycloadditions of **63** were carried out in either benzene or chlorobenzene at a temperature of 100–150 °C.

Thus, cycloaddition of **63** with cyclopentadiene afforded a mixture of *exo*- and *endo*-stereoisomers in 1:15 ratio. In contrast, cycloaddition of **63** with 1,3-cyclohexadiene afforded a single *endo*-stereoisomer. The reaction of **63** with anthracene afforded the expected cycloadduct in excellent yield. When the diene is acyclic, for example, 2,3-dimethylbutadiene, a single cycloadduct was formed in 67% yield (Equation 16). In contrast, 2,4-hexadiene yielded a mixture of two stereoisomers in 2.9:1 ratio, respectively (Table 17).

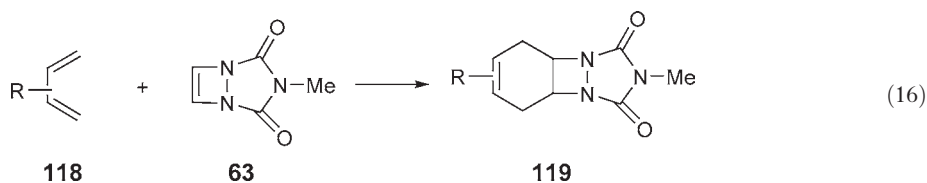
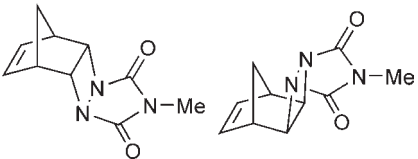
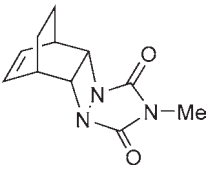
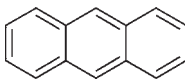
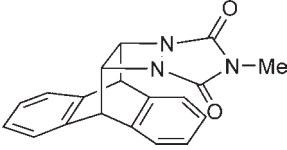
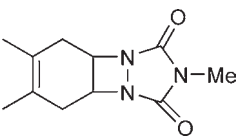
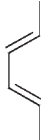
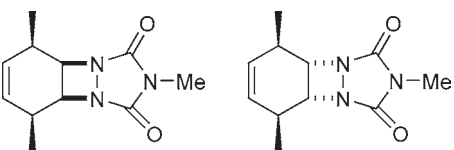


Table 17 Cycloaddition reactions of 3-methyl-1,3,5-triazabicyclo[3.2.0]hept-6-ene-2,4-dione with various dienes

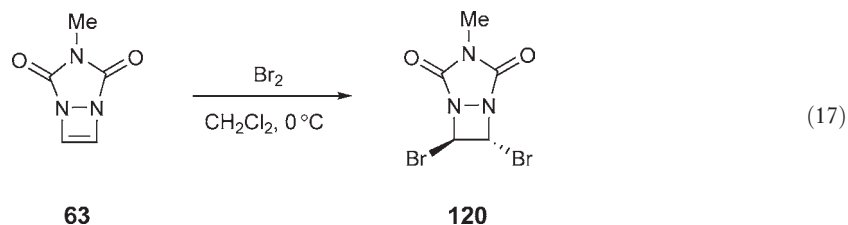
<i>Dienes</i>	<i>Cycloadduct</i>	<i>Yield (%) (ratio)</i>
		82(9.4:1)
		66
		94
		67
		98 (2.9:1)

All the above cycloadducts were converted into the corresponding diazetines via a standard hydrolysis/oxidation sequence in good yield (46–60%).

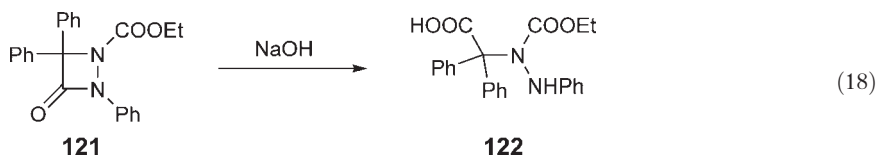
2.13.7 Reactivity of Substituents Attached to Ring Carbon Atoms

2.13.7.1 1,2-Diazetidine Derivatives

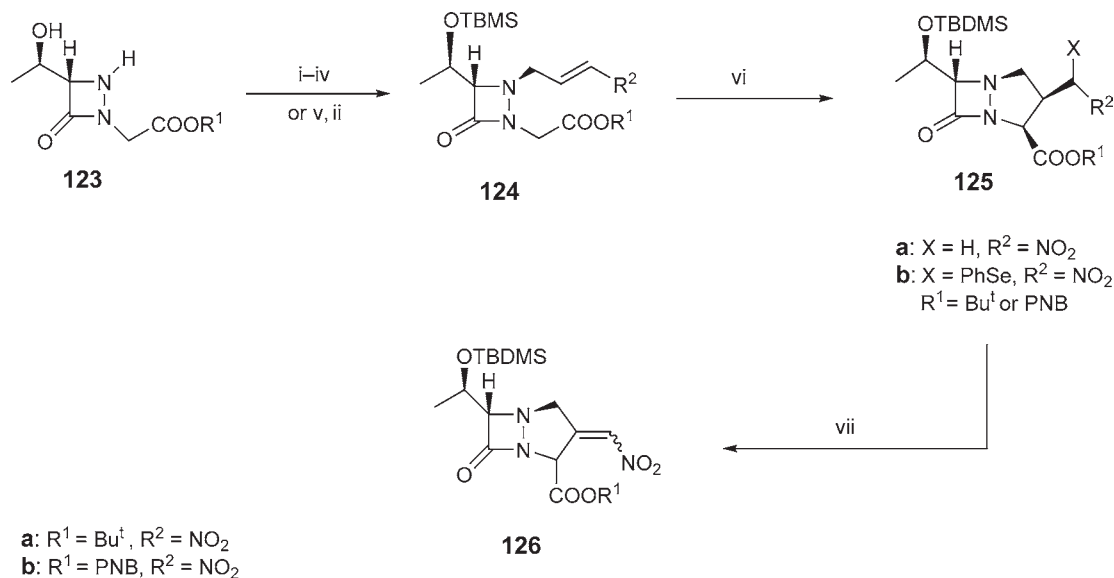
The 1,2-diazetidine are mostly inert at ring carbon atoms unless they are activated by highly electron-withdrawing substituents, such as a carbonyl or CF_3 group. Therefore, not many reactions of 1,2-diazetidines at ring carbon atoms are known. However, if there is a $\text{C}=\text{C}$ bond in the ring it can undergo usual addition reactions. For example, addition of bromine readily takes place on 3-methyl-1,3,5-triazabicyclo[3.2.1]hept-6-ene-2,4-dione **63** in methylene chloride at 0°C (Equation 17) <2002JOC6699>.



The carbonyl groups of the 1,2-diazetidines resemble in their reactivity that of β -lactam carbonyl groups. The four-membered ring opens up when a nucleophile attacks the carbonyl group <1983HC(42)443>. For example, the cyclic amide N–CO bond cleavage takes place in the case of ethyl 2,4,4-triphenyl-1,2-diazetid-2-one-1-carboxylate **121** when treated with dilute ethanolic sodium hydroxide to afford hydrazinodiphenyl acetic acid derivative **122** (Equation 18) <1963JCS674>. Earlier, such examples have been reported in CHEC-II(1996) <1996CHEC-II(1B)911>.



Oda *et al.* have synthesized 5-azacarbenes using the 1,2-diazetidine derivatives **123** (Scheme 13) as intermediates <1996H(42)577>. The diazetidines **123** can be easily prepared in good yield by an intramolecular cyclization of hydrazide followed by catalytic debenzoylation using Pd(OH)₂ on charcoal (Section 2.13.8.1). They developed a more practical and convenient synthetic route to 1,2-diazetidines via hydrazones under very mild acidic conditions (Equation 23, Section 2.13.8.1). Michael cyclization of nitroalkenes **124a/b** obtained from **123** gave the desired bicyclic 5-azacarbenes **125**.



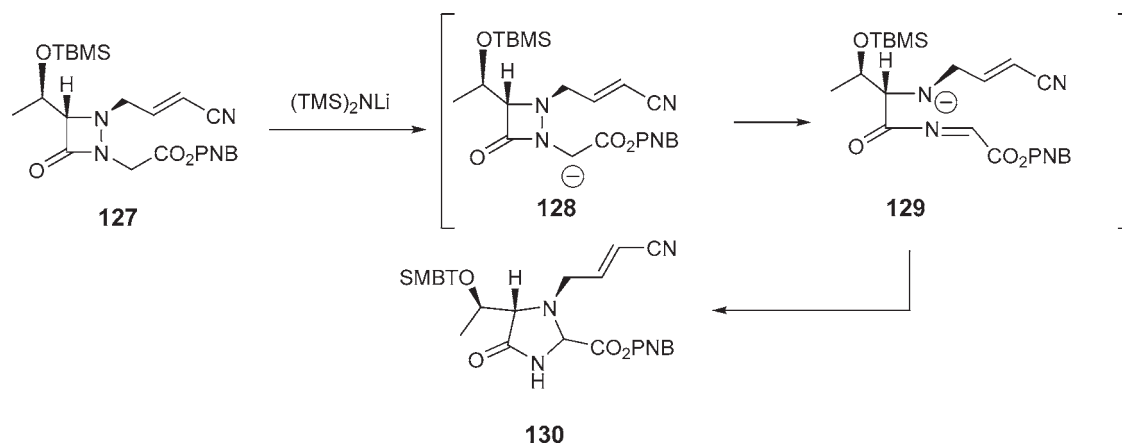
Reagents and conditions: i, allyl bromide, NaI, NaHCO₃, DMF, 92–94%; ii, TBDMS-OTf, 2,6-lutidine, CH₂Cl₂, 0°C, 80–99%; iii, N₂O₄, I₂, Et₂O, 5°C; iv, NaOAc, Et₂O, 56–57% in two steps; v, BrCH₂CH=CHCN, NaI, NaHCO₃, DMF, 59%; vi, (TMS)₂NLi, THF, –78°C, then AcOH or PhSeCl, 40–79%; vii, AcOOH, THF, 0°C, 33–49%

Scheme 13

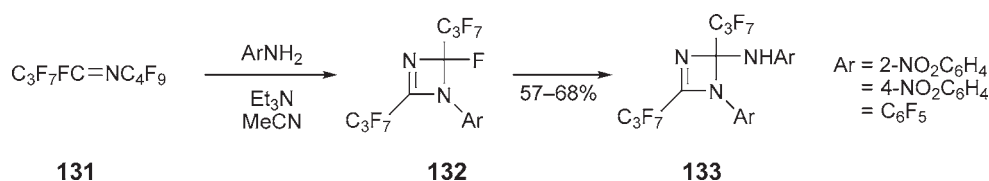
On the other hand, treatment of **127** with lithium hexadimethyl disilazide (HMDS) led to ring expansion and formation of the imidazolidinone **130** (Scheme 14). These results suggest that strong electron-withdrawing groups such as cyano or nitro may favor intramolecular Michael cyclization.

2.13.7.2 1,3-Diazetidine Derivatives

Like 1,2-diazetidines, reactivity at ring carbon atoms of 1,3-diazetidines is also very limited unless activated by strong electron-withdrawing groups, for example, carbonyl, CF₃, or F. Furin reported a reaction of perfluoro compound **131** with 2-nitro-, 4-nitro-, or pentafluoroaniline in the presence of triethyl amine (TEA) in acetonitrile giving kinetically controlled diazetines **132**, which undergoes further substitution reactions at carbon to give the diazetidine derivatives **133** (Scheme 15) <2000JFC(104)263>.

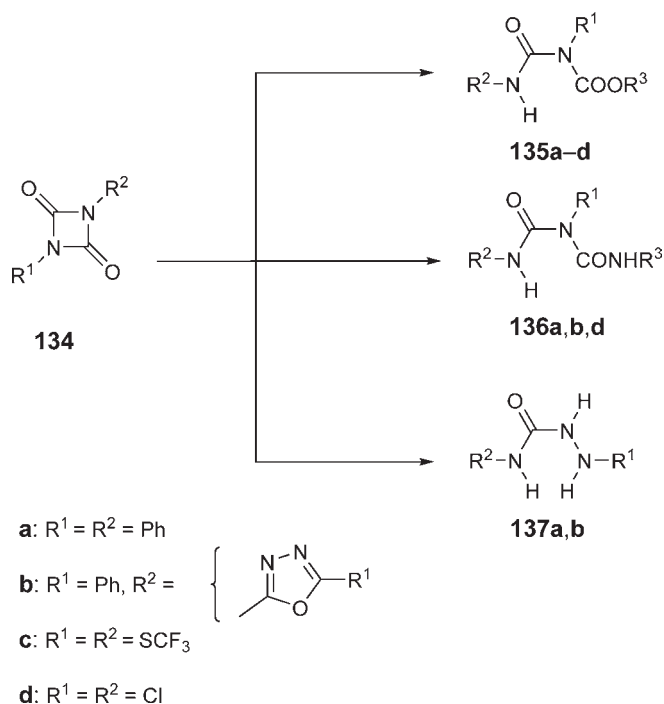


Scheme 14



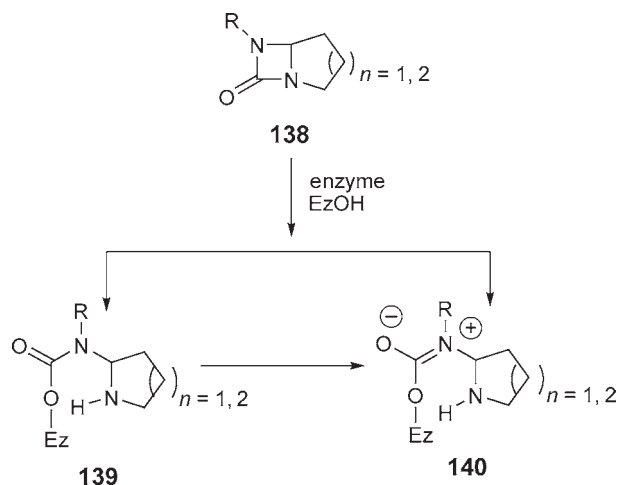
Scheme 15

The most-studied compounds in this class are 1,3-diazetidine-2,4-diones; 1,3-diazetidine-2,4-diones **134** react with a number of nucleophiles, especially oxygen and nitrogen nucleophiles, leading to ring-opened products. The preferred attack by the nucleophile occurs from the most hindered side of the ring. A few representative examples are summarized in [Scheme 16](#).



Scheme 16

Nangia and co-workers have reported the ring opening of several aza- β -lactam analogues with various enzymes as a possible pathway for these aza- β -lactams to act as potential antibiotics [\[1998J\(P1\)2597\]](#). It is expected that a β -lactamase may react at the C=O group leading to the formation of a C=O--enzyme complex by opening of the β -lactam ring to give either [139](#) or [140](#). The hydrolysis of the enzyme complex is expected to be very slow and may, therefore, inhibit the activity of the enzyme ([Scheme 17](#)).



Scheme 17

Similar serine protease inhibition by 1,3-diazetidino-2,4-diones **134** is reported by Aoyama *et al.* <2001BML1691>. A number of derivatives were synthesized (Section 2.13.9.4.3) and their antibacterial potential was evaluated (IC₅₀ in the range 0.85–140 nM).

Molina *et al.* have described the reactivity of 2,4-diimino-1,3-diazetidione which is attacked by several nucleophiles at the electrophilic carbon center [<1993JPR305>](#). Some of these reactions are summarized in CHEC-II(1996) [<1996CHEC-II\(1B\)911>](#). A few representative examples are shown in [Scheme 18](#).

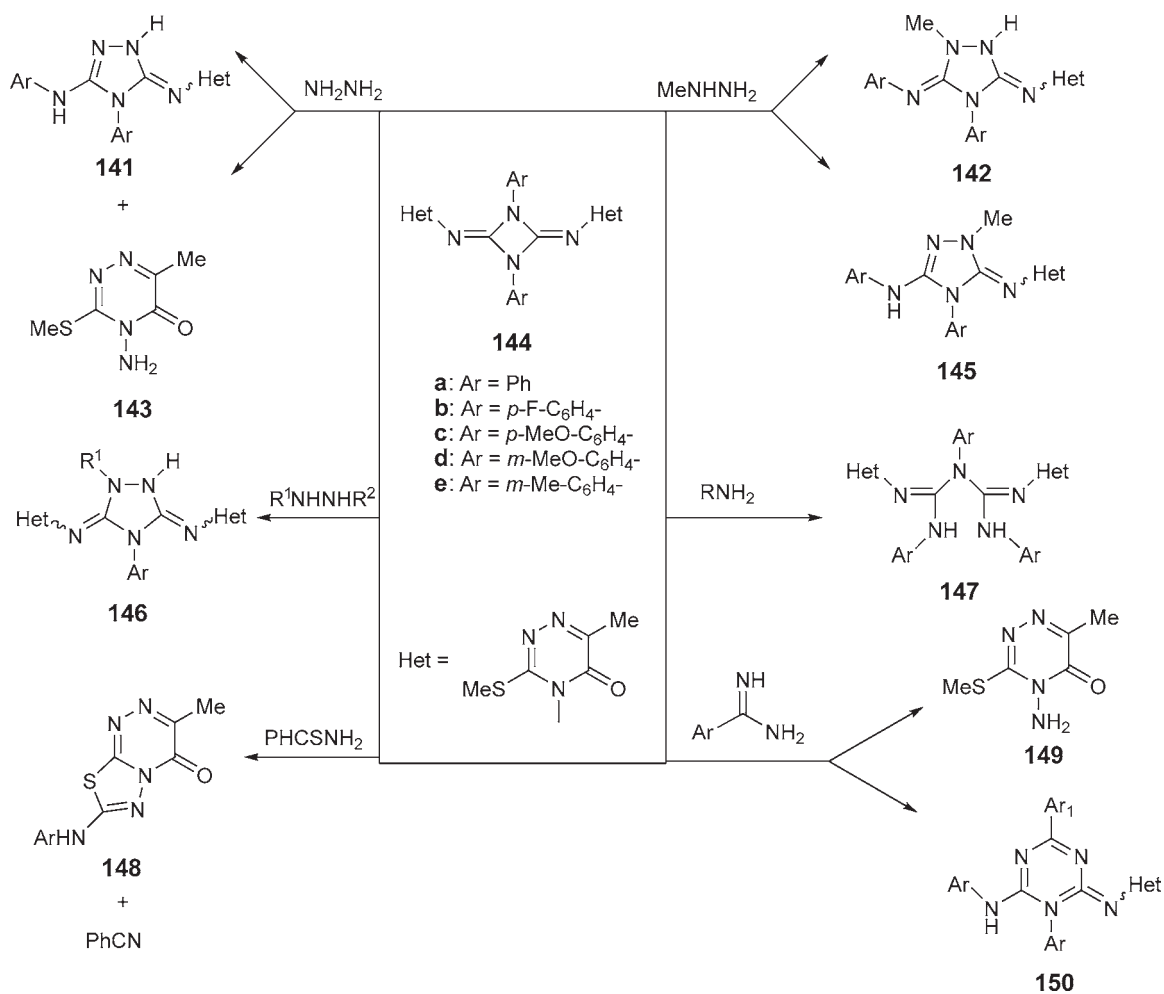
2.13.7.3 Reactivity of the Side Chain Attached to a Ring Carbon

The β -lactams have been widely used as chemotherapeutic agents to treat bacterial infections. A number of analogues have been prepared and evaluated for antibiotic activity. An aza- β -lactam, a mono or bicyclic-1,3-diazetidin-2-one, is a nonnatural analogue of a β -lactam antibiotic which may react with the active site of a serine hydroxyl of the enzyme to form a carbonyl-enzyme intermediate that is sluggish to hydrolyze. This hypothesis was examined with a number of analogues to evaluate their antibacterial properties. Nangia and co-workers have carried out several transformations on the side chain of aza- β -lactam compounds to furnish a number of different analogues <1998J(P1)2597>.

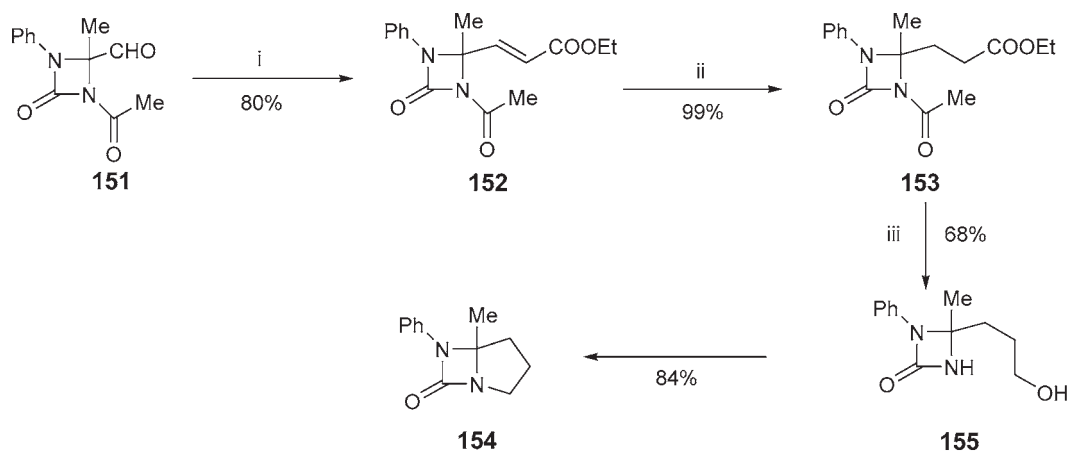
It has been noticed that several organic reactions can be routinely carried out on the side chains of diazetidinones without disturbing the four-membered ring. For example, the aldehyde **151** can undergo a smooth Wittig reaction to furnish **152** which can be reduced using Pd/C in EtOAc to give a 99% yield of **153**. Subsequent reduction with LiAlH₄ in diethyl ether at 0°C gave **155** in 68% yield. A bicyclic ring compound (azacarbepenam **154**) can be prepared through an intramolecular Mitsunobu cyclization reaction on **155** (Scheme 19).

In many of the syntheses, aza- β -lactam aldehyde **151** has been used as a key synthon (**Scheme 20**). For example, aldehyde **151** gives epoxide **157** by treatment with NaH and $\text{Me}_3\text{S}^+\text{I}^-$ in DMSO at low temperature. Similarly, alcohol **156** may be prepared from **151** by reduction with LiAlH_4 in ether. When NaBH_4 is used in methanol a cyclic product **159** was isolated along with alcohol **158** (**Scheme 20**) <1998J(P1)2597>.

Interestingly, the azacarbacepham **162** could not be synthesized from the corresponding aldehyde homologue **161**. Instead, a mixture of products was obtained (Equation 19).

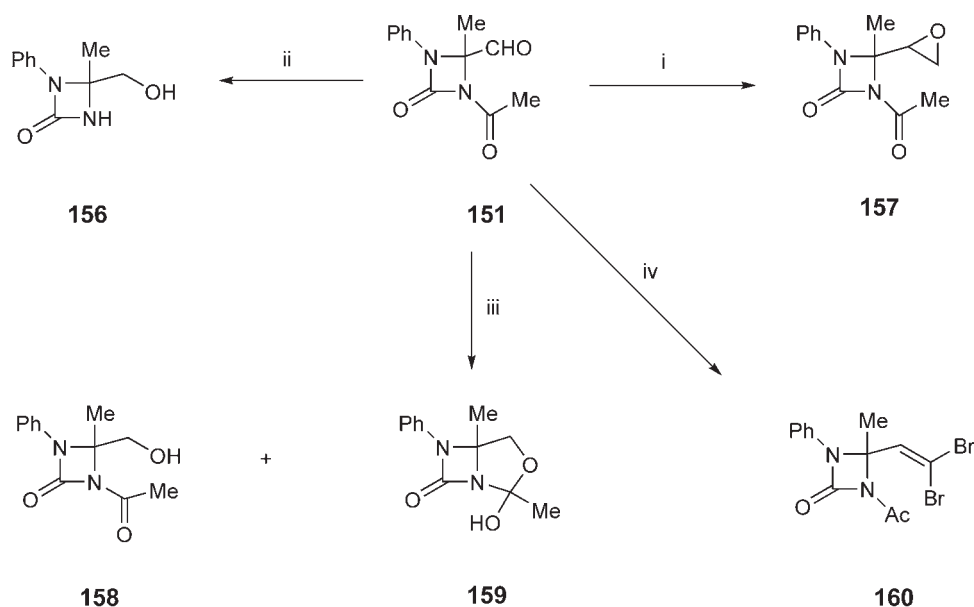


Scheme 18



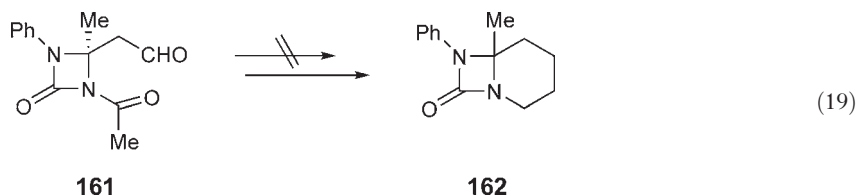
Reagents and conditions: i, Ph₃P=CHCOOEt, benzene, rt, 1 h; ii, Pd/C, 4 h; iii, LiAlH₄, ether, 0 °C, 1 h; iv, Mitsunobu cyclization

Scheme 19

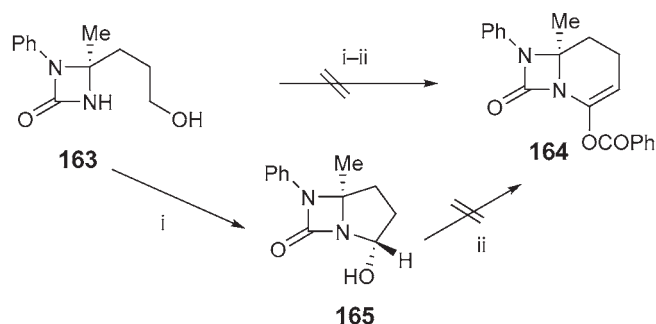


Reagents and conditions: i, Me_3SI , NaH , DMSO , -10 to 0°C , 40 min; ii, LiAlH_4 , Et_2O , 0°C , 1 h; iii, NaBH_4 , MeOH , 0°C , 1 h; iv, Ph_3P , CBr_4 , CH_2Cl_2 , 0°C , 10 min

Scheme 20



Therefore, an alternative synthesis was evaluated using an appropriate amino alcohol **163** which also did not lead to the desired carbacepham **164**. However, an azacarapenam analogue **165** was isolated (Scheme 21) <1998J(P1)2597>.

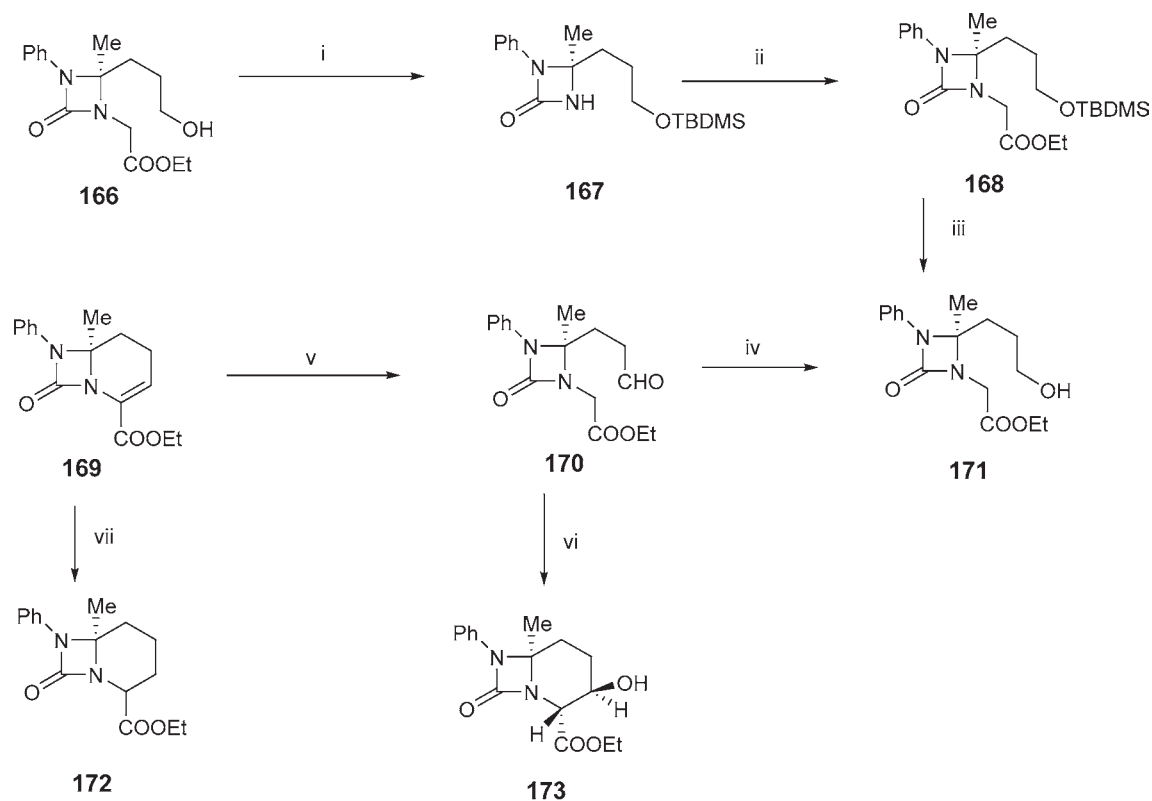


Reagents and conditions: i, PCC , CH_2Cl_2 , rt, 2 h, 65%; ii, PhCOCl , 0°C –rt, 2 h, 62%

Scheme 21

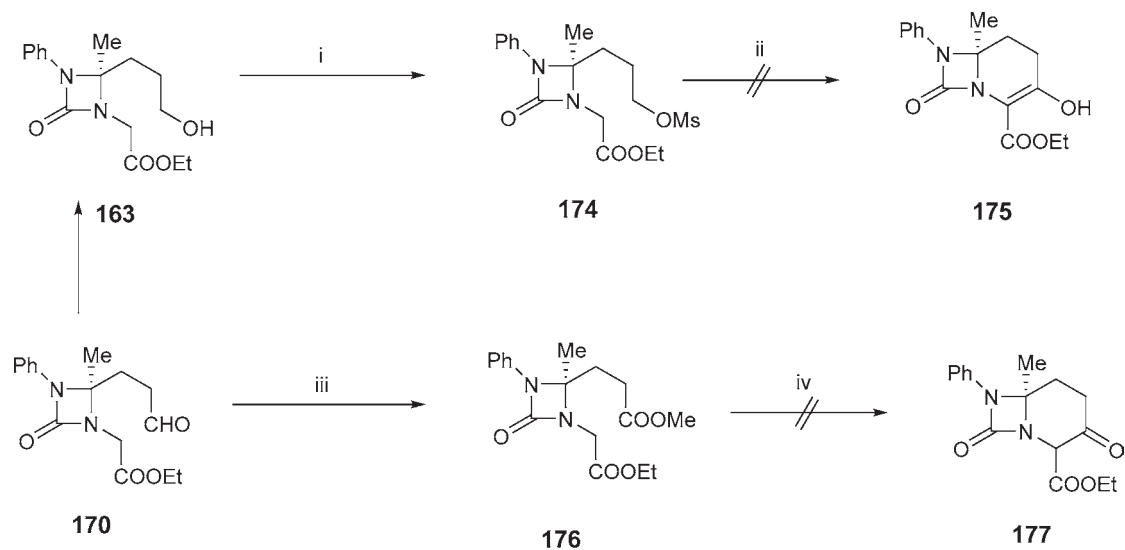
The bicyclic azacarapenams **164** and **165** lack the carboxyl group critical for the recognition and binding between the β -lactam group and the receptor protein. Therefore, a new synthetic strategy was developed from diazetidinone **166** as shown in Scheme 22 <1998J(P1)2597>.

Hydrogenation of the unsaturated ester **169** gave azacarapacepham **172** as the only product. An alternative route to make azacarapacepham analogue from **163** or **170** also failed as shown in Scheme 23 <1998J(P1)2597>.



Reagents and conditions: i, TBDMSCl, TEA, DMAP, 0 °C, 1 h, 90%; ii, NaH, BrCH₂COOEt, THF, 0 °C–rt, 2 h, 98%;
 iii, *n*-Bu₄NF, THF, 0 °C, 1 h, 82%; iv, PCC, CH₂Cl₂, 0 °C–rt, 2 h, 76%; v, NaH, THF, 0 °C, 45 min, 35%;
 vi, NaH, THF, 0 °C, 20 min, 60%; vii, H₂, 10% Pd/C EtoAc, rt, 4 h, 86%

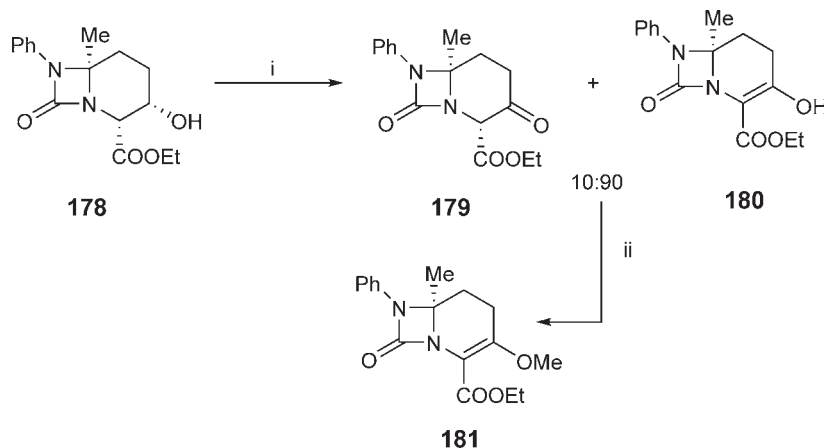
Scheme 22



Reagents and conditions: i, MeSO₂Cl, TEA, CH₂Cl₂, 0 °C, 1 h, 95%; ii, NaH or *t*BuOK, THF;
 iii, PDC, DMF, rt, 8 h, 94%; iv, CH₂N₂ (xs) 0 °C, 80%

Scheme 23

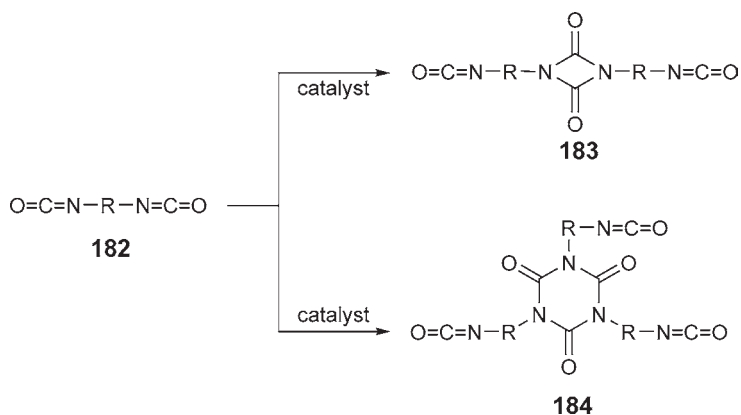
However, carbacepham derivatives **179** and **180** could be generated from **178** by Jones oxidation to furnish a mixture (10:90) of keto-enol isomers **179** and **180**, which can be methylated using diazomethane to give **181** in 63% yield (Scheme 24). Evaluation of various carbacepham analogues as well as carbapenam analogues indicated that some are promising potent antibiotics.



Reagents and conditions: i, 8 M Jones reagent, 0 °C to rt, 2 h, then rt, 2 h, 88%;
ii, CH₂N₂ (xs) 0 °C, 63%

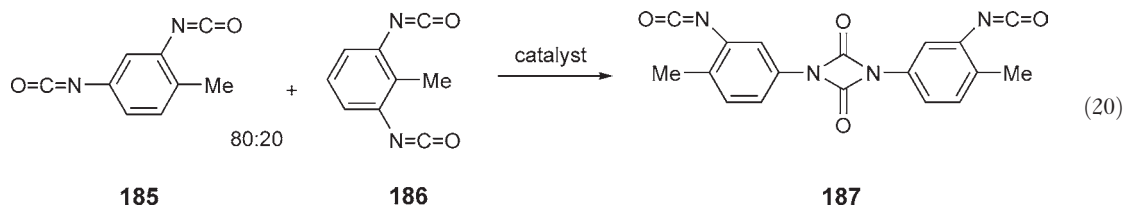
Scheme 24

Risch *et al.* have reported on the reaction of 1,3-diazetidines-2,4-diones, which are used in the preparation of polymers and advanced materials <1999JPR616>. With the help of special catalysts it was possible to dimerize or trimerize diisocyanate to give 1,3-diazetidines-2,4-diones **183** or isocyanurates **184** (Scheme 25).

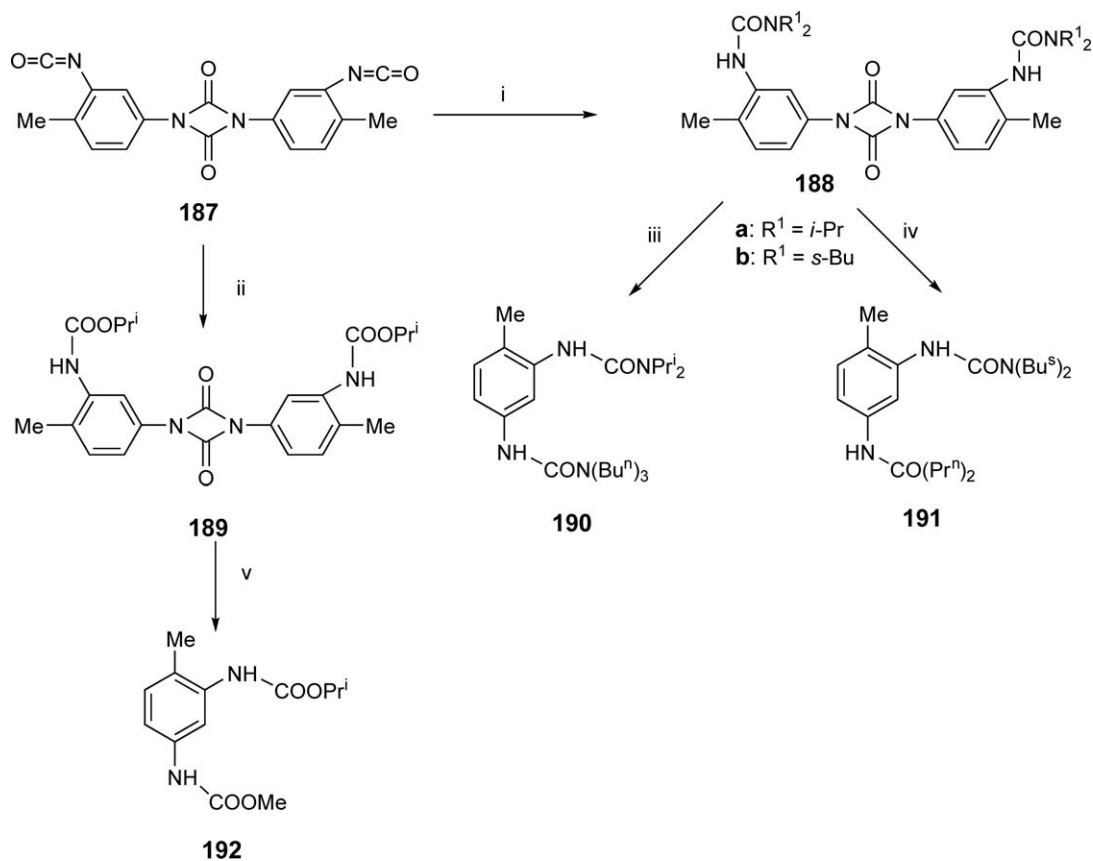


Scheme 25

A dimer **187** was obtained by reacting a mixture of 2,4-toluenediisocyanate (80%) **185** and 2,6-toluenediisocyanate **186** (20%) in the presence of tri-*n*-butylphosphane as a catalyst (Equation 20).

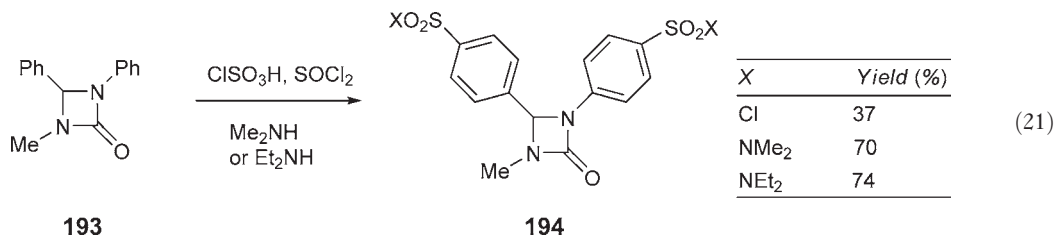


The presence of the isocyanate group on the dimer **187** has been used to functionalize the compound through a number of reactions (Scheme 26).



Scheme 26

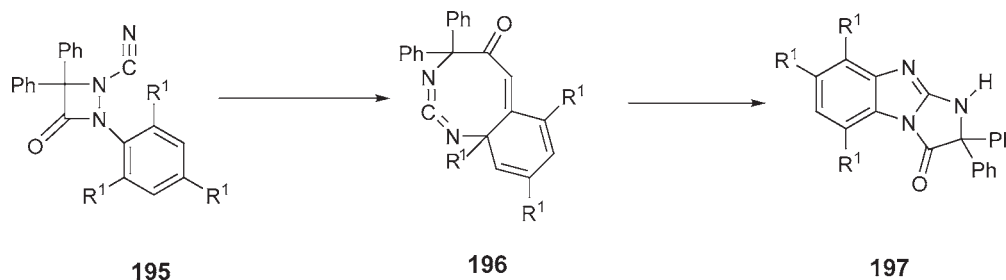
Ellam and co-workers have reported on an interesting chlorosulfonation reaction on the aryl group present on either the nitrogen atom or the ring carbon (Equation 21) <2003PS1931>.



2.13.7.4 Reactions Involving Rearrangements

Several 1,2-diazetidines are known to undergo ring expansions as well as rearrangements to furnish new heterocycles. An account of such rearrangements has been compiled in CHEC-II(1996) <1996CHEC-II(1B)911>. However, one of the most interesting ring expansions and molecular rearrangements was observed in the case of 1,2-diazetidines

195 where N-1 has a cyano substituent and N-2 has an aryl substituent. The compounds **195** undergo sigmatropic rearrangement to yield **197** in refluxing xylene <1964JCS5284> (Scheme 27).



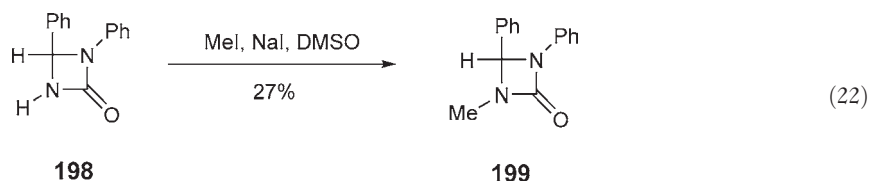
Scheme 27

Beckert *et al.* have reported a ring expansion as well as an N-acylation reaction under mild conditions when 1,2-diazetines **112** were treated with isothiocyanate and isocyanate, respectively <2005H(65)1311>. When an acyl halide is used, N-acylation was observed to give **114** which underwent thermal rearrangement to furnish 4*H*-1,3,4-oxadiazines **115** (Scheme 12) (see Section 2.13.6.2) <2006S514>.

2.13.8 Reactivity of Ring Nitrogens and Substituents Attached to Ring Nitrogen Atoms

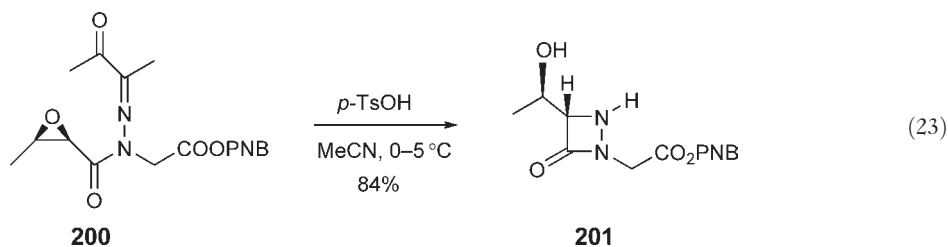
2.13.8.1 Reactivity at Ring Nitrogen Atoms

1,3-Diazetidine-2-one can be N-methylated to give *N*-methyl-1,3-diazetidine-2-one which is stable under acidic conditions (Equation 22).



Oda *et al.* have reported several reactions of 1,2-diazetidinones at the ring nitrogen atom in order to make aza- β -lactam analogues <1996H(42)577>.

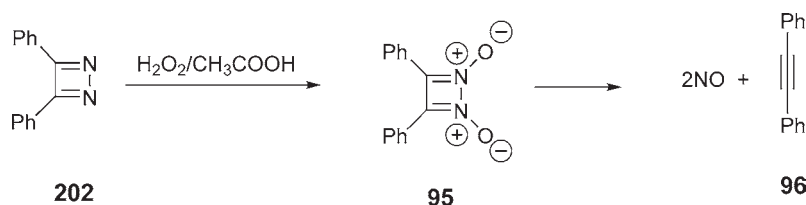
Thus, 1,2-diazetidinone **201**, prepared by the cyclization of hydrazine **200**, was used as a starting building block for several aza- β -lactams (Equation 23).



Michael cyclization of diazetidine **124** gave 5-azacarbapenem **125** in moderate yield.

The oxidative elimination of SePh gave the alkene **126** in moderate yield which was found to undergo gradual decomposition to undesired products (Scheme 13) (see Section 2.13.7.1).

Tandon and Chhor have reported the N-oxidation of 3,4-diphenyl-1,2-diazete using H₂O₂ in acetic acid, furnishing the *N,N*-dioxide which is expected to be a NO donor *in vivo* (Scheme 28) <2004LOC40>.

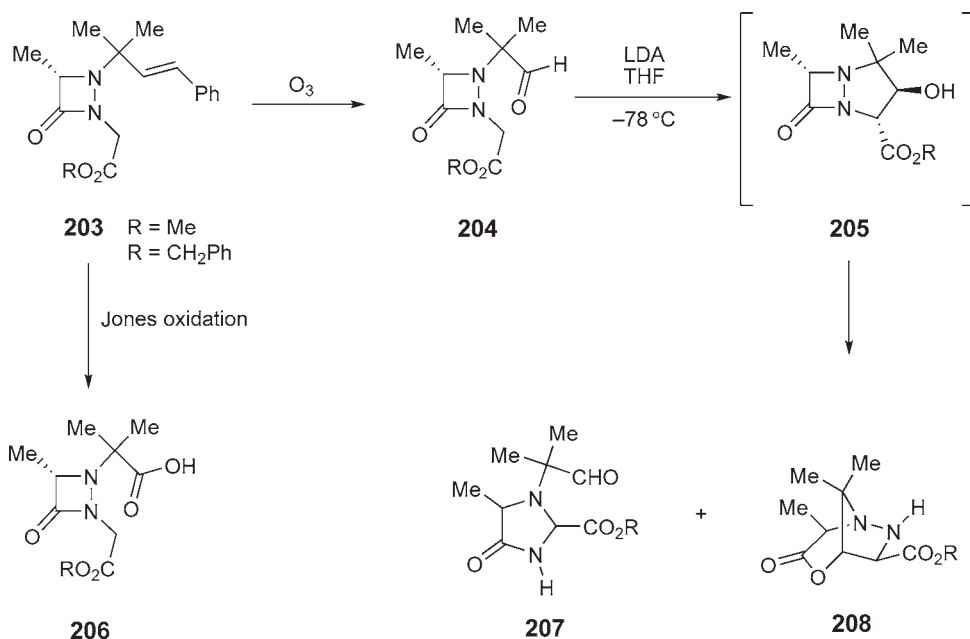


Scheme 28

Beckert and co-workers used an acyl halide for N-acylation of 1,2-diazetidine to give **114** which underwent thermal rearrangement to furnish 4*H*-1,3,4-oxadiazine **115** (Scheme 12) <2006S514>.

2.13.8.2 Reactivity of the Side Chain Attached to Ring Nitrogen Atoms

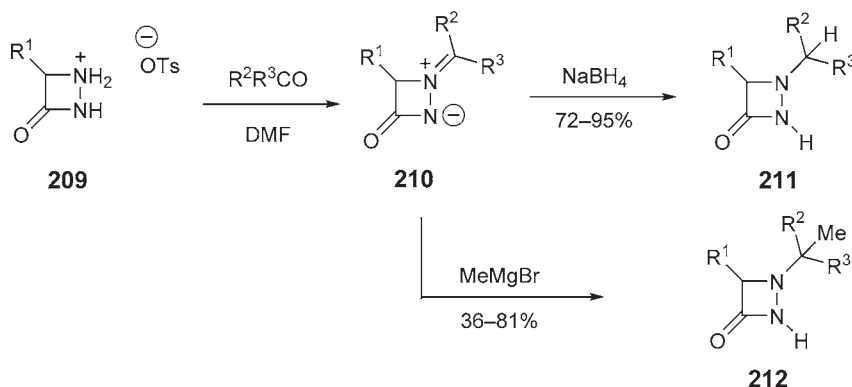
Interest in the development of new carbapenam analogues of the potent β -lactam antibiotics initiated major efforts toward the aza analogues of carbapenam derivatives. Taylor and Davies attempted to synthesize azacarbenams **205** by intramolecular aldol condensation reaction of **204** using LDA as a deprotonating agent, as shown in Scheme 29 <1986JOC1530>. However, an unexpected bicyclic compound **208** was isolated in addition to imidazolidinones **207**.



Scheme 29

Further, Taylor and co-workers carried out reactions to attach a suitable side chain at nitrogen, which subsequently could be cyclized to give aza analogues of β -lactam antibiotics. Thus, the readily available inner salt 1,1-disubstituted-3-oxo-1,2-diazetidinium tosylate **209** was selectively reduced at the side chain attached to N-1 of **210** by sodium borohydride, or was alkylated selectively at the side chain by the reaction of **210** with a Grignard reagent (Scheme 30) <1984JOC4415>.

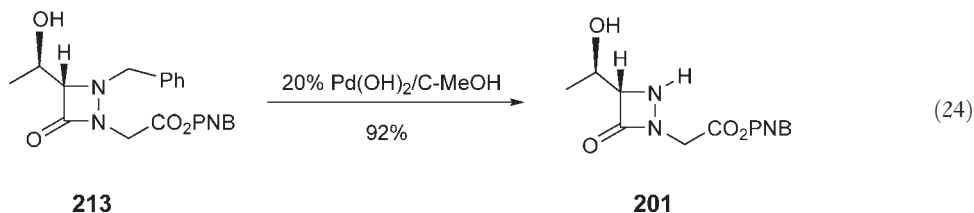
The substitution on the nitrogen exhibited the usual reactivity pattern; for example, the C=C bond in the side chain of **203** could be cleaved by ozonolysis leading to aldehyde **204**.



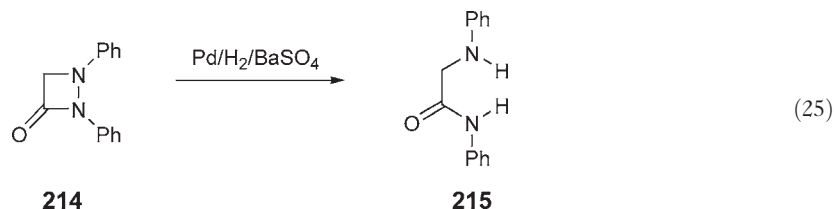
Scheme 30

2.13.8.3 Reactions with Reducing Agents

Diazetidines are quite stable to several reducing agents and various reaction conditions. For example, the *N*-benzyl substituent in diazetidinone could be easily cleaved using $Pd(OH)_2$ in methanol furnishing the *N*-deprotected diazetidinone **201**, without leading to any N–N bond cleavage (Equation 24) <1996H(42)577>.



However, the nitrogen–nitrogen bond in 1,2-diazetidin-3-ones and related systems can be cleaved using a number of reducing agents under mild conditions. For example, 1,2-diaryl-1,2-diazetidin-3-ones **214** underwent N–N bond scission using a Pd catalyst in the presence of hydrogen to give amide **215** <1956AG71> (Equation 25).



Several 1,3-diazetidinones are quite stable to reducing conditions. For example, in compound **152** the $C=C$ bond in the side chain could be easily reduced by $Pd-C$ (10%) in $EtOAc$ in the presence of H_2 yielding quantitatively **153** (Scheme 19). Even lithium aluminium hydride (LAH) could be used for the reduction of the $COOEt$ group in the side chain of **153** without affecting either the ring $C=O$ or the N–N bond under controlled conditions to give **155** (Scheme 19).

Sodium borohydride can also be used for side group transformations without cleaving the four-membered ring (Scheme 20) (see Section 2.13.7.3).

2.13.8.4 Reactions with Metal Carbonyls

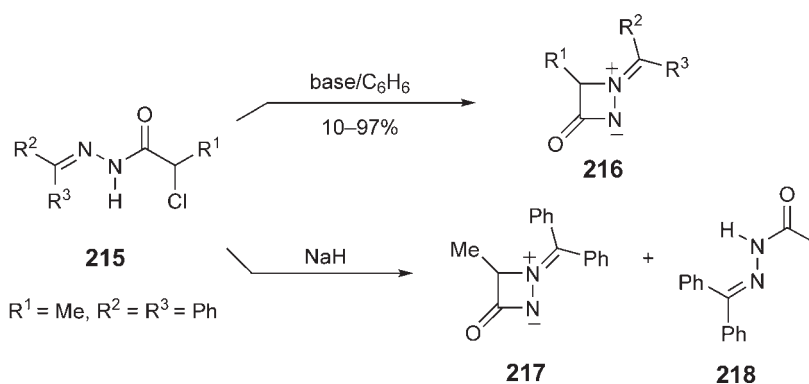
Cyclic diazo compounds are known to form mononuclear σ -complexes with iron carbonyl compounds, which further react to give more stable binuclear complexes containing an Fe–Fe bond <1976TCC105>. However, such complexes are rare in the case of cyclic four-membered diazo compounds. No new examples have been reported in the last decade. For more informations, CHEC-II(1996) should be consulted <1996CHEC-II(1B)911>.

2.13.9 Synthesis from Acyclic Compounds

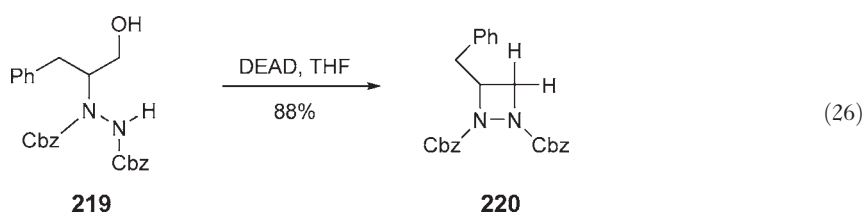
The syntheses of diazetidines are known to proceed via a [2+2] cycloaddition reaction of alkene derivatives with azo compounds. A comprehensive literature overview has been provided in CHEC-II(1996) <1996CHEC-II(1B)911>. This chapter compiles some of the new synthetic methods and examples reported after 1994.

2.13.9.1 Synthesis from Acyclic Compounds via Formation of One C–N Bond

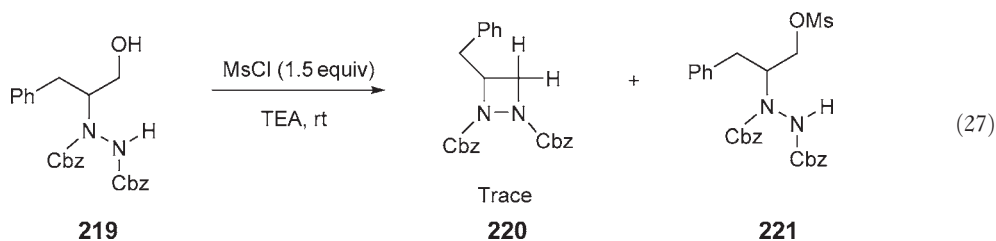
The most general method of synthesis of 1,2-diazetidines is by initial formation of diazetidinium ylides obtained by intramolecular dehydrohalogenation of chloroacetylhydrazones of appropriate carbonyl compounds using a strong non-nucleophilic base, such as sodium hydride or potassium *t*-butoxide in tetrahydrofuran (THF), followed by reduction of the resulting ylide (**Scheme 30**) <1981JA7743>. Interestingly, when R² or R³ are H, Me, or CF₃ groups, the hydrazone **215** does not undergo cyclization. Also, increase in the size of the substituents on the α-carbon atom leads to the formation of side products, originating from the dehydrohalogenation of the side chain (**Scheme 31**) <1981JA7743>. More recently, Ma and co-workers envisioned the preparation of 1,2-disubstituted 1,2-diazetidines **220** by intra-molecular cyclization of a 1(1-hydroxy-3-propane-2-yl)hydrazine derivative **219** under Mitsunobu conditions (**Equation 26**) <2006TL6835>.



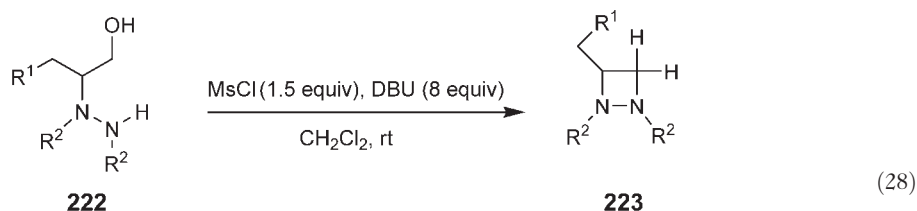
Scheme 31



However, they encountered a problem with the purification of **220** from the by-product, triphenyl phosphine oxide and therefore developed an alternative route for the cyclization. Thus, treatment of **219** in dichloromethane with 1.5 equiv of methanesulfonyl chloride and 3 equiv of TEA gave traces of product **220** along with O-mesylated intermediate **221** as the major product (**Equation 27**).

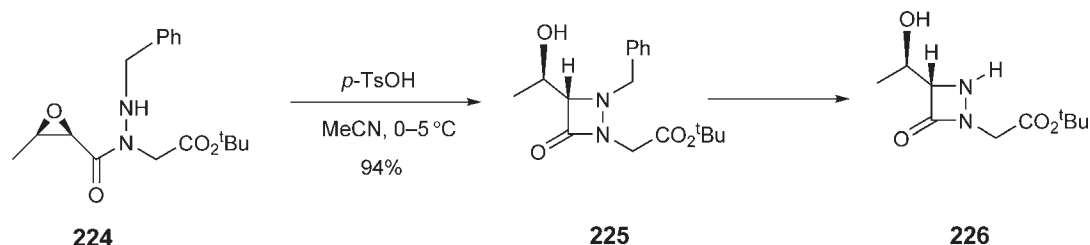


When K_2CO_3 or $CsCO_3$ was used as base in acetonitrile, the desired azetidine was isolated in 85–92% yield. The use of 8 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base in dichloromethane at room temperature gave excellent results (90–96%, yield), whereas TEA or diisopropyl ethyl amine (DIEA) gave poor yields (5–25%). Several substituted diazetidines were synthesized (Equation 28). Use of the corresponding optically pure hydrazines **219** afforded chiral diazetidines <2006TL6835>.

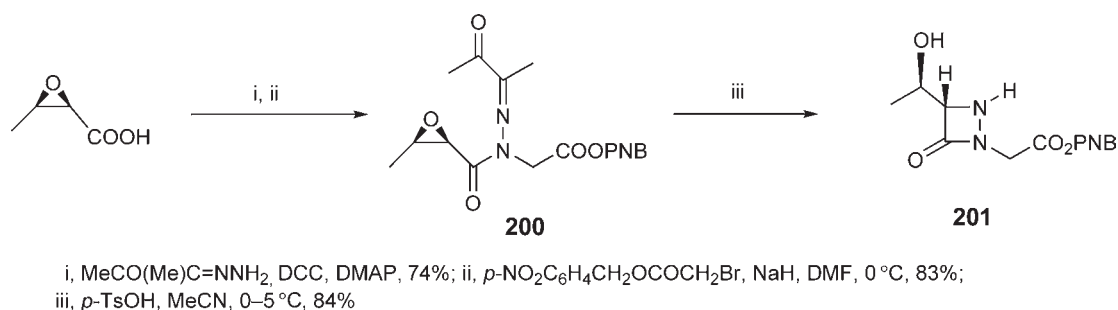


a: $R^1 = \text{PhCH}_2$	$R^2 = \text{Cbz}$	96%	e: $R^1 = \text{Me}$	$R^2 = \text{Cbz}$	96%
b: $R^1 = \text{PhCH}_2$	$R^2 = \text{COOEt}$	90%	f: $R^1 = \text{MeCH}_2\text{CH}_2$	$R^2 = \text{Cbz}$	95%
c: $R^1 = \text{PhCH}_2$	$R^2 = \text{COOPr}^i$	90%	g: $R^1 = \text{Pr}^i$	$R^2 = \text{Cbz}$	93%
d: $R^1 = \text{PhCH}_2$	$R^2 = \text{BOC}$	85%	h: $R^1 = \text{Me}(\text{CH}_2)_3$	$R^2 = \text{Cbz}$	93%

Oda *et al.* reported an interesting hydrazide **224** prepared from (2*R*,3*R*)-epoxybutanoic acid, which undergoes cyclization under mild conditions with the opening of the epoxide ring to furnish the 1,2-diazetidinone **225** (Scheme 32 and 33) <1996H(42)577>. A similar cyclization occurs smoothly to give diazetidinone **201** from hydrazone **200** by removing the protecting group under mild acidic condition (*p*-TsOH) (Equation 23) (Section 2.13.8.1).



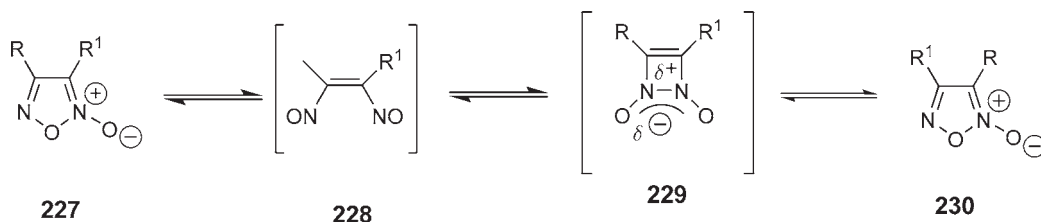
Scheme 32



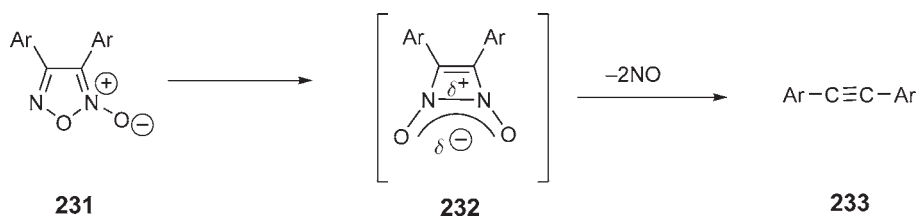
Scheme 33

Auricchio *et al.* have proposed the formation of 1,2-diazetidine-1,2-dioxide as a possible intermediate in the thermal isomerization of furoxanes and benzofuranoxane derivatives (Scheme 34 and 35) <1997T17407>.

Molecular mechanics (MMX) calculation has suggested that ΔE_{strain} (E_{strain} (azodioxide **229**) – E_{strain} (dinitroso **228**)) is actually higher for aliphatic derivatives (ΔE_{strain} 40 kcal mol^{–1} for $R = R^1 = \text{Me}$; ΔE_{strain} 25 kcal mol^{–1} for $R = \text{Me}$, $R^1 = \text{OEt}$) than for aromatic derivatives. Thus, intermediates **232** cannot be isolated. They undergo elimination of NO to give diarylacetylenes **233** and therefore act as an NO donor.



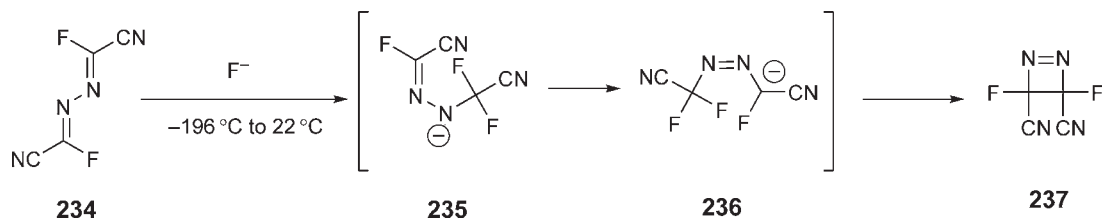
Scheme 34



Scheme 35

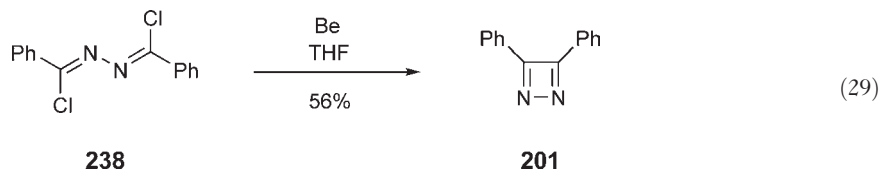
2.13.9.2 Synthesis from Acyclic Compounds via Formation of One C–C Bond

Synthesis of four-membered heterocycles with two nitrogen atoms by C–C bond formation was reported in the early 1990s via a cesium fluoride-mediated cyclization of azine **236** (Scheme 36) <1991IC535>.



Scheme 36

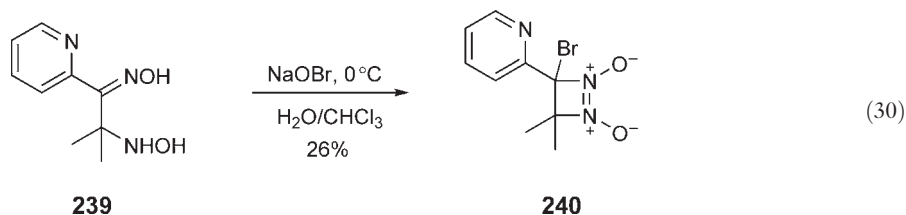
Tandon and Chhor have reported the formation of 3,4-diphenyl-1,2-diazete **201**, a very rare example of an isolated diazete, by C–C bond formation <2004LOC40>. 1,4-Dichloro-1,4-diphenyl-2,3-diaza-1,3-butadiene **238** was treated with beryllium in THF to give a good yield (56%) of 3,4-diphenyl-1,2-diazete **201** (Equation 29). During the last decade, this strategy has not been used.



2.13.9.3 Synthesis from Acyclic Compounds via Formation of One N–N Bond

Oxidation of 2,3-dimethylbutane-2,3-bis-hydroxylamines with bromine or sodium periodate in aqueous solution at room temperature yielded 3,3,4,4-tetramethyl- Δ^1 -1,2-diazetidine-1,2-dioxide <1972JA5077, 1975JOC1409> which can be reduced to diazetidine.

Yelinova *et al.* reported the oxidation of *N*-[2-hydroximino-2-methyl-1-(2-pyridyl)propyl-2]hydroxylamine **239** using sodium hypobromide, generated from bromine and sodium hydroxide in cold condition (0 °C), to furnish 3-bromo-3,4-dihydro-4,4-dimethyl-3-(2-pyridyl)-1,2-diazet-1,2-dioxide **240** in 26% yield (Equation 30) <2003MI395>. These oxides were evaluated for their NO donor activities in biological systems. During the last decade, not many new syntheses of diazetidines have been reported.

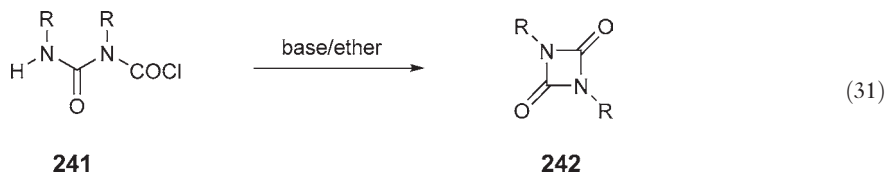


2.13.9.4 Formation of Four-Membered Rings from [2+2] Atom Fragments

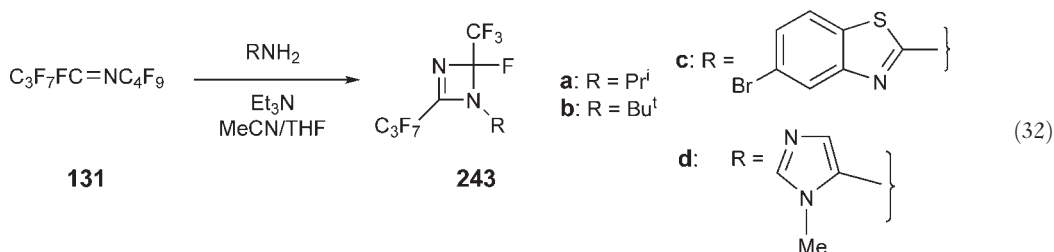
This is the most successful method, which is widely used in the synthesis of the four-membered heterocycles with two nitrogen atoms.

2.13.9.4.1 Formation of two C–N bonds by displacement reactions

Treatment of allophanoyl chlorides **241** with a base, such as triethylene diamine, led to the formation of 1,3-diazetidinediones **242** (Equation 31) <1978JOC4530>.

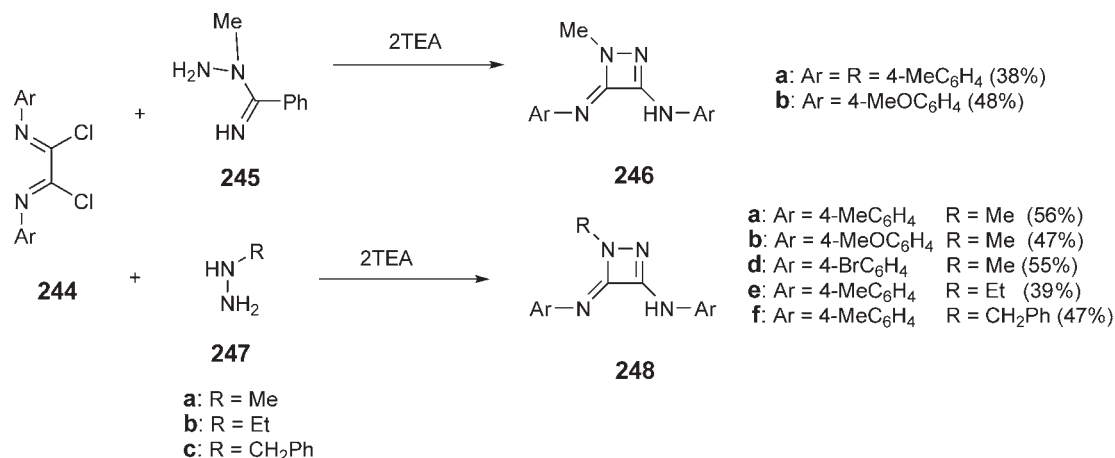


Furin and co-workers prepared several fluorinated diazetines by the reaction of perfluoro compound **131** with isopropyl amine, *t*-butyl amine, 2-amino-6-bromobenzothiazole, and 2-amino-1-methyl imidazole in THF in the presence of triethylamine (Equation 32) <2000RJO109>. The same group also reported the formation of several diazetidines **132** and **133** by the reaction of perfluoro compound **131** with 2-nitro-, 4-nitro-, or pentafluoro-aniline in the presence of triethylamine (Scheme 15, Section 2.13.7.2) <2000JFC(104)263>.



It is expected that perfluoroaniline or nitroaniline first reacts on the C=N bond at the carbon center by the formation of a C–N bond followed by cyclization to furnish 1,3-diazetidines.

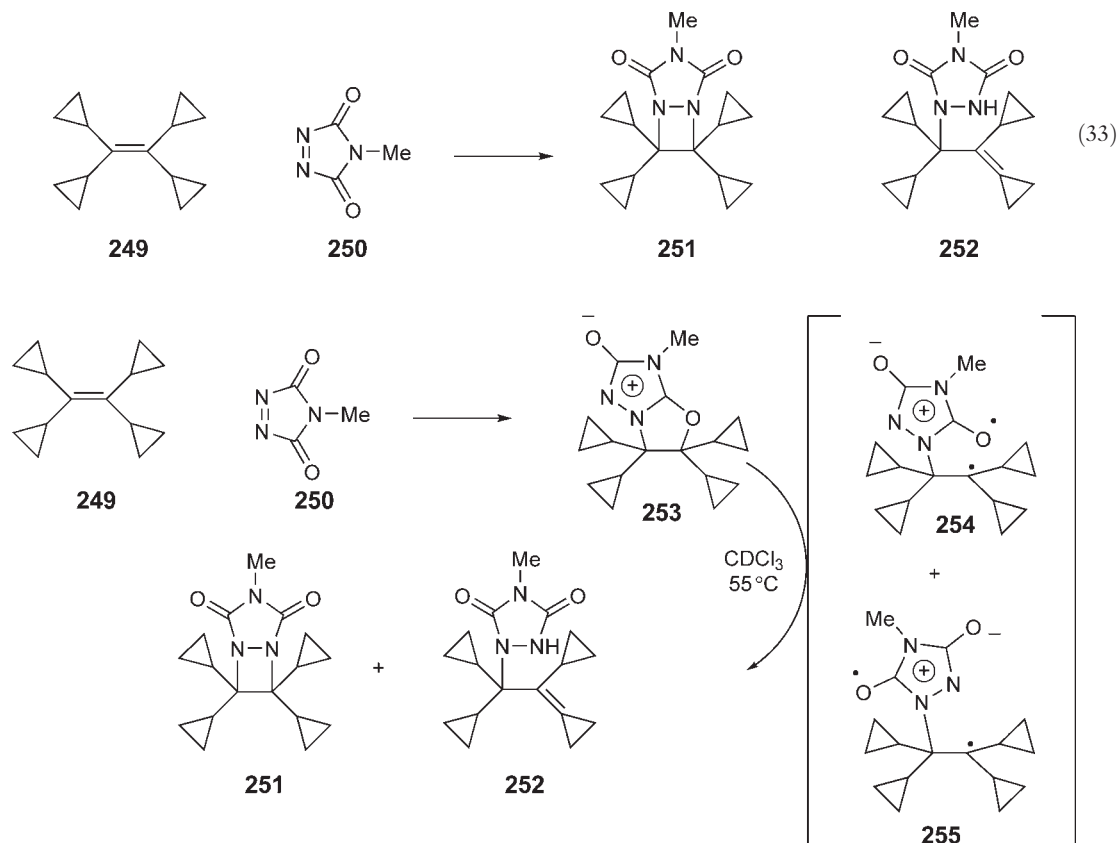
Beckert and co-workers reported the synthesis of 1,2-diazetidine derivatives **246** by the reaction of bis-imidoyl chloride **244** with amidrazone **245** <2002H(57)1257>. The product underwent decomposition during the isolation. Thus, they carried out the isolation at lower temperature to furnish **246a** (38%) and **246b** (48%). On the other hand, reaction of hydrazine **247** with bis-imidoyl chloride **244** gave 1,2-diazetidines derivatives **248** (Scheme 37). Some of the structures were confirmed by X-ray crystallography (Section 2.13.3.1) The reaction is expected to proceed via the formation of a C–N bond with the displacement of a chlorine atom.



Scheme 37

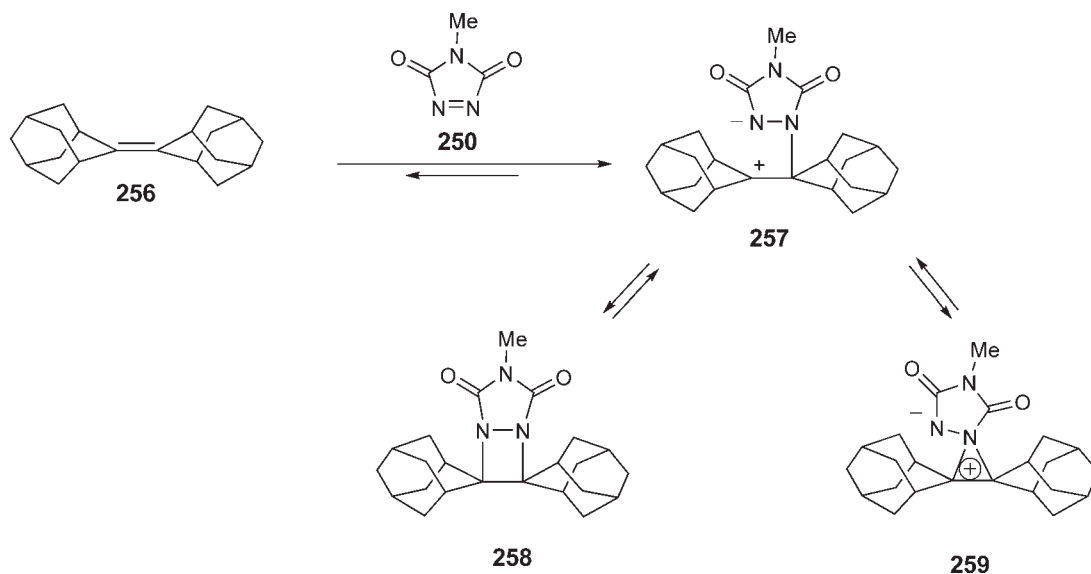
2.13.9.4.2 Formation of two C–N bonds by cycloaddition reactions between C=C and N=N fragments
 The formation of diazetidines by [2+2] cycloaddition can be achieved by a thermal or photoinduced reaction. The reaction may proceed stepwise, either by dipolar or radical intermediates. A large number of 1,2-diazetidine derivatives have been prepared by [2+2] cycloaddition of an alkene to an azo compound. A large number of syntheses involving these types of fragments have been compiled by Richter and Ulrich <1983HC(42)443> and also by Timberlake and Elder <1984CHEC(7)449>.

Kim and O'Shea have reported highly electrophilic additions of 4-substituted 1,2,4-triazoline-3,5-diones with substituted alkenes by [2+2] cycloaddition reactions (Equation 33) <2004JA700>. A possible mechanism is depicted in Scheme 38.



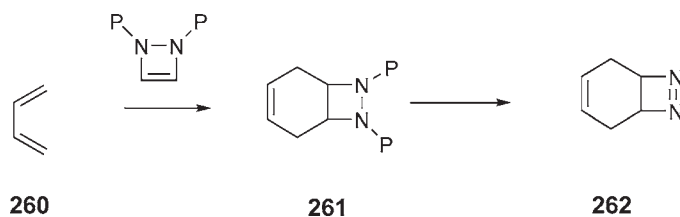
Scheme 38

Nelsen *et al.* reported the preparation of several 1,2-diazetidine derivatives by the reaction of substituted bisadamantylidines **256** with *N*-methyltriazolinediones in chloroform (Scheme 39) <1997JOC6539>.

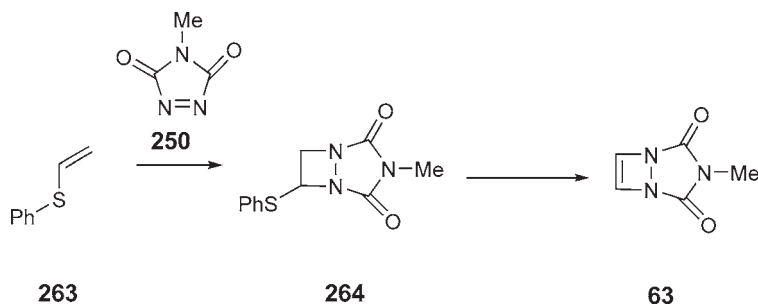


Scheme 39

Breton *et al.* have synthesized Δ^1 -1,2-diazetines by the cycloaddition reaction <2001OL3185>. Δ^1 -1,2-Diazetines are highly strained compounds and are quite unstable and difficult to synthesize (Schemes 40 and 41). Diels-Alder reactions have been widely used as a powerful tool to synthesize a number of compounds from a variety of dienophiles and diverse dienes.

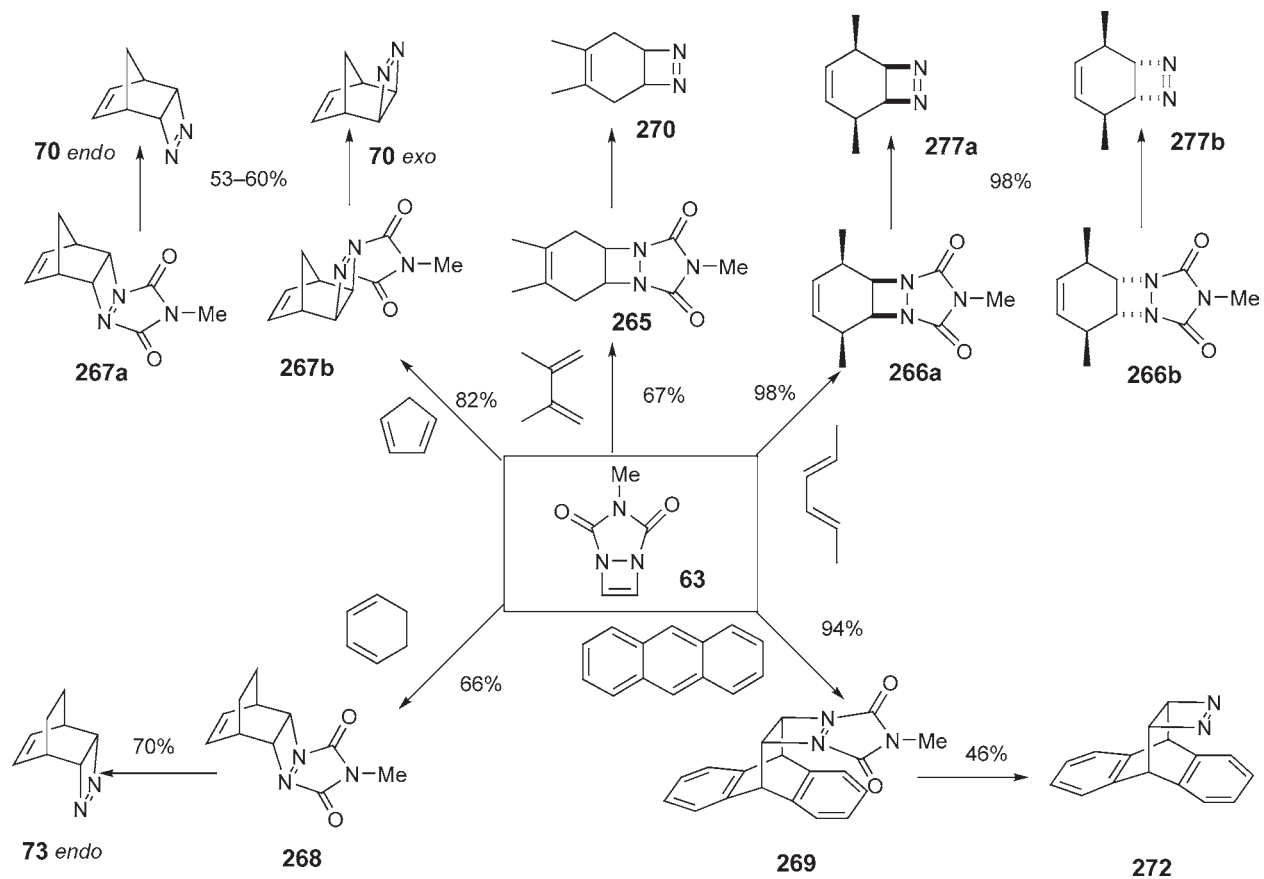


Scheme 40

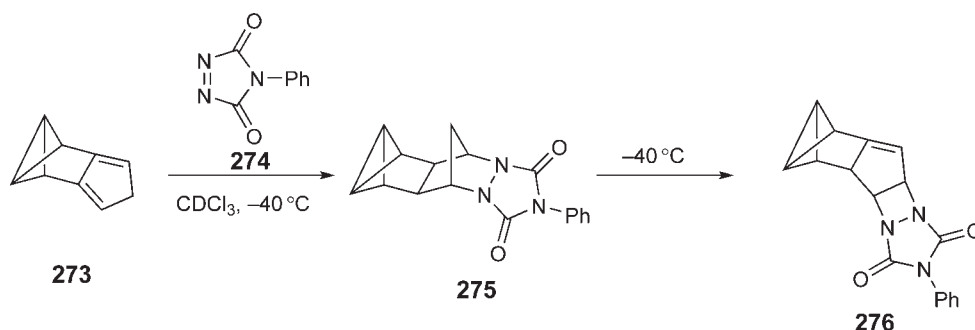


Scheme 41

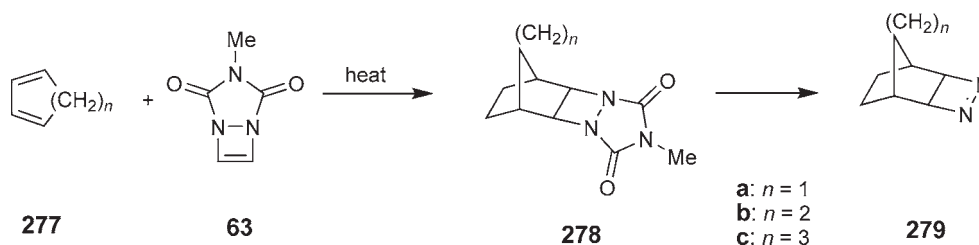
Similarly, a number of dienes have been utilized to give products with yields in the range 66–98%. Some of the cycloaddition products **265–269** could be further hydrolyzed, followed by oxidation to afford the corresponding 1,2-diazetines **270–272**, **70**, and **73** in good yield (Schemes 42 and 44). Similarly, Christle and co-workers have reported an isomerization product of the cycloadduct **275** to diazetidine **276** (Scheme 43) <2002AGE2969>.



Scheme 42

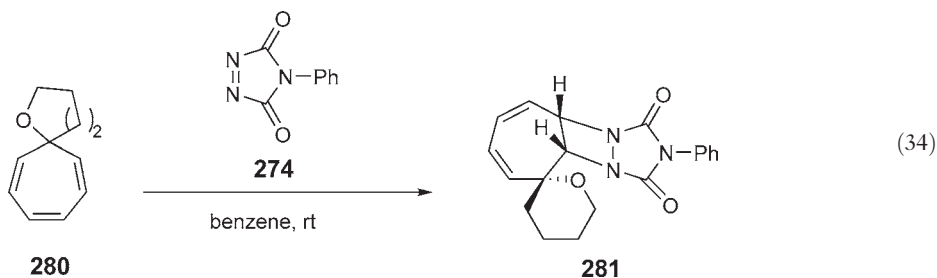


Scheme 43



Scheme 44

Similarly, [2+2] cycloaddition was also observed between *N*-phenyltriazolinedione **274** and oxaspirocycloheptatriene **280** to yield an interesting tetracyclic adduct **281** (Equation 34) <2003OL177>.



2.13.9.4.3 Formation of two C–N bonds by cycloaddition reaction between two fragments containing a C=N function

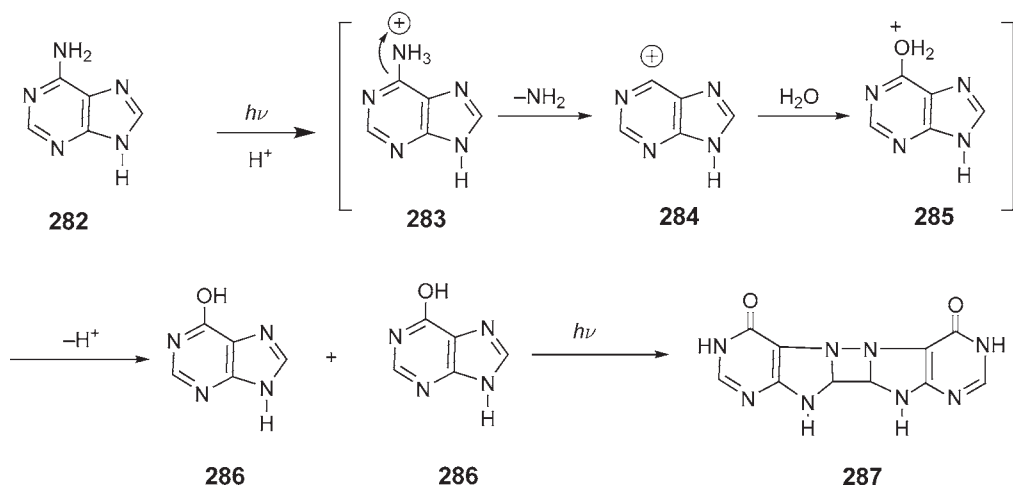
Jain and co-workers prepared highly substituted 1,2-diazetidine derivatives by the photolysis of adenine, which undergoes a [2+2] cycloaddition <1999IJB234>. In aqueous and acidic media adenine undergoes deamination followed by a [2+2] cycloaddition reaction to yield **287**, whereas in alkaline solution it afforded direct the [2+2] cycloaddition adduct **288** (Scheme 45) (Equation 35).

2.13.9.4.3(i) Dimerization of isocyanates

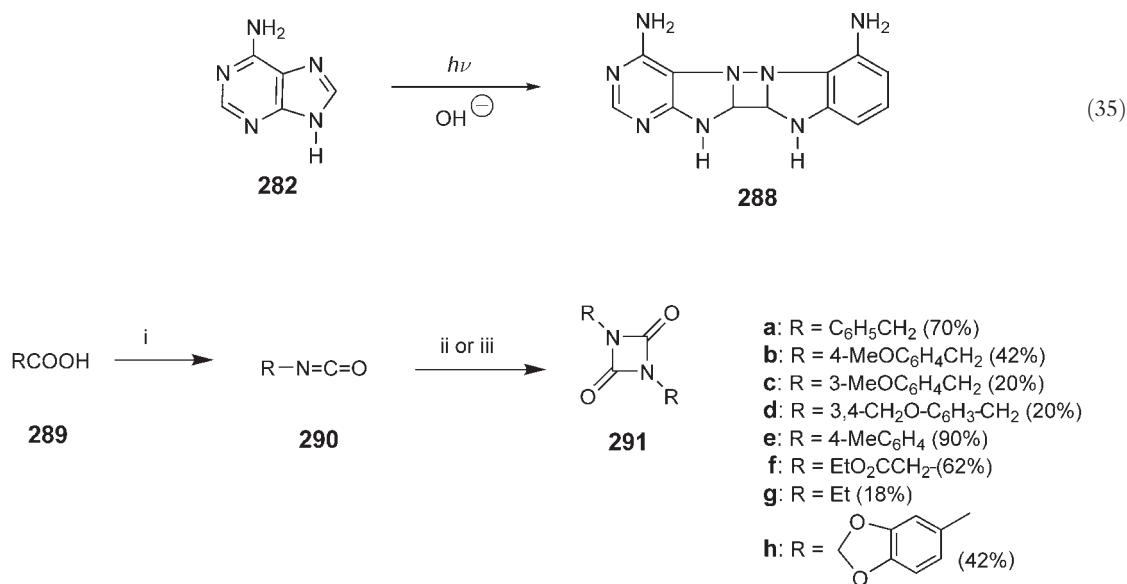
The dimerization of aryl isocyanates to 1,3-diarylazetidin-2,4-diones is one of the classical methods for the synthesis of 1,3-diazetidinones. In 1993 trimerization of phenyl isocyanate catalyzed by a fluoride ion was also reported, and a small amount of 1,3-diazetidin-2,4-dione was obtained at room temperature <1993JOC1932>.

Risch *et al.* reported the dimerization of diisocyanates in the presence of a catalyst to give only 1,3-diazetidine-2,4-dione (uretidiones) (Scheme 25) (Section 2.13.7.3) <1999JPR616>.

Aoyama *et al.* have reported the synthesis of a number of 1,3-diazetidine-2,4-dione analogues with a view to studying their enzyme inhibition activities (Scheme 46) <2001BML1691>.



Scheme 45



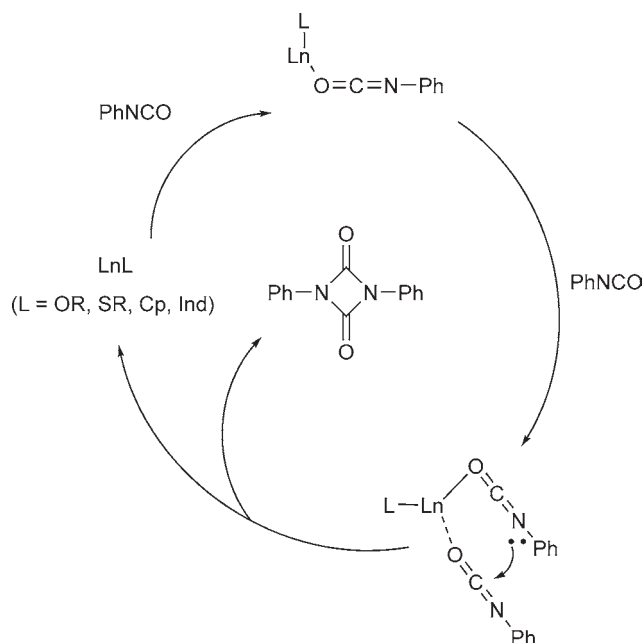
Reagents and conditions: i, TEA, $(PhO)_2P(O)N_3$; ii, 1,2-dimethylimidazole, CH_2Cl_2 ; iii, $SbCl_5$, CH_2Cl_2

Scheme 46

Dimerization of phenyl isocyanate, catalyzed by lanthanide complexes, has been reported by Deng *et al.* <2003CHJ574>. A number of lanthanide complexes were tried and $Sm(SPh)_3(hmpa)_3$ was found to be the most effective catalyst. Conversion was as high as 96% with 2500:1 of substrate to catalyst ratio (Scheme 47).

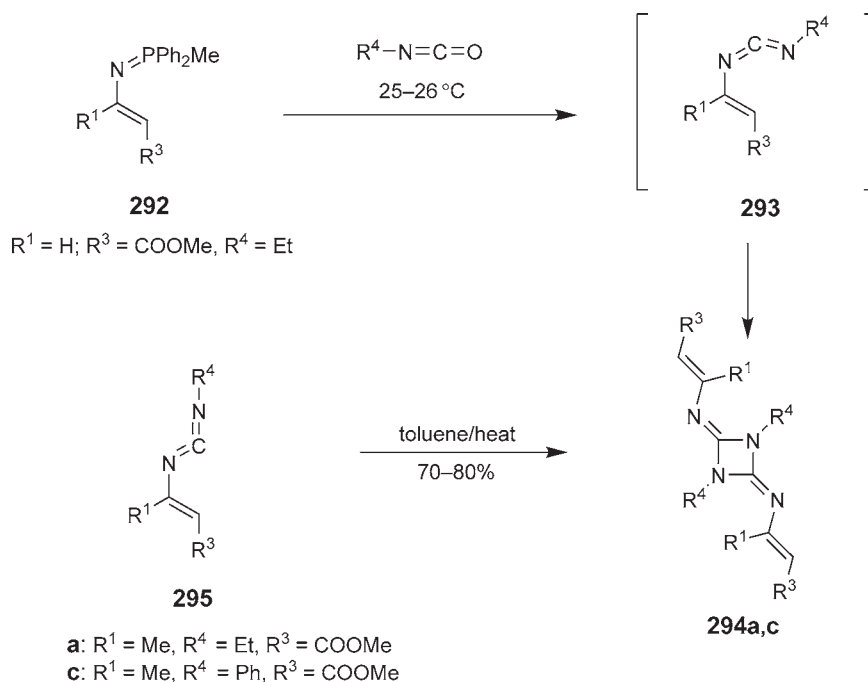
2.13.9.4.3(ii) Cycloaddition of isocyanates with carbodiimides and between carbodiimide moieties

The formation of 1,3-diazetidines by the cycloaddition of isocyanates with carbodiimides has been known since 1957 <1957DEP1012601>. When an equimolar amount of aryl isocyanate or N,N' -diphenylcarbodiimide were mixed with cyclic carbodiimide, a bicyclic 2-imino-1,3-diazetidine-4-one was formed within a few minutes. <1983JOC1694>.



Scheme 47

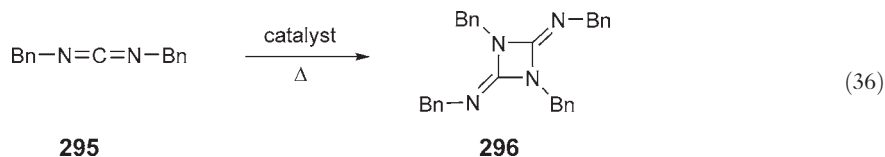
Palacios *et al.* reported the reaction of phosphazenes **292** with ethyl isocyanate to give 1,3-diazetidine-2,4-diimines **294** <2001H(55)1641>. The formation of these four-membered heterocycles could be explained by the *in situ* dimerization of carbodiimide **293**. This hypothesis was proven by the independent dimerization of the corresponding carbodiimides **295** by heating in toluene. Thus, when, *N*-vinyl carbodiimide **295a** ($\text{R}^4 = \text{Et}$) and **295b** ($\text{R}^4 = \text{Ph}$) were refluxed in toluene, 1,3-diazetidines **294a** and **294b** were obtained (Scheme 48). The structures of the products were established based on spectral data.



Scheme 48

2.13.9.4.3(iii) Cycloaddition between carbodiimide moieties

Carbodiimides undergo [2+2] cycloaddition reactions to furnish 1,3-disubstituted-2,4-bisalkyl or arylimino-1,3-diazetidine. For example, dibenzyl carbodiimides undergo dimerization to yield 1,3-diazetidin-2,4-diimines **296** on heating. The reaction can be catalyzed by the addition of tributylphosphine (1%) (Equation 36) <1940CB1114, 1968CB174>.



2.13.9.4.3(iv) Cycloaddition of isocyanates with imines

Aromatic-substituted imines, especially those having electron-donating groups in the *para*-position, undergo a [2+2] cycloaddition reaction with aryl isocyanates <1969CB938, 1978T101>. In the presence of an excess of azomethine, the six-membered triazine derivative is the exclusive product <1970MI149>.

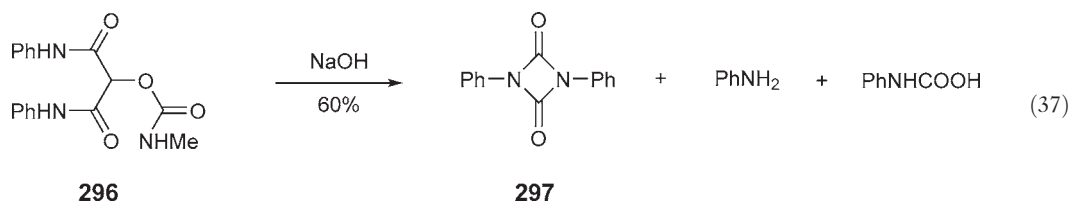
2.13.9.4.3(v) Cycloaddition of iminophosphoranes with isocyanates

Molina and co-workers have synthesized several substituted diazetidine derivatives by intramolecular cyclization of several bis(iminophosphoranes) **28**, which in turn can be generated by the reaction of diazidobiphenyl with isocyanates (Equations 1 and 2) (Section 2.13.3.1.2) <1999JOC1121>.

The diazetidine **30** was isolated in modest yield (20–40%) by the reaction of a carbodiimide with 1 equiv of triphenylphosphine followed by treatment with an aryl isocyanate **29**.

2.13.9.4.4 Miscellaneous methods

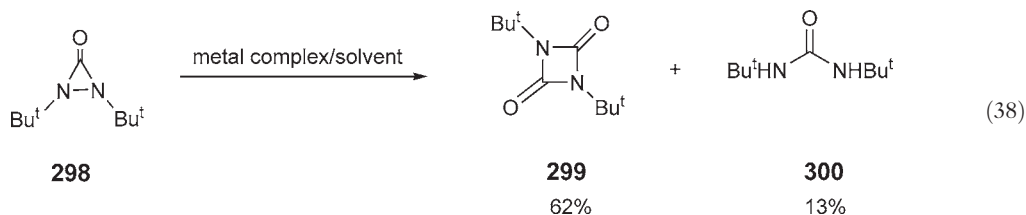
1,3-Diazetidin-2,4-dione derivatives are also obtained by the alkali treatment of 1,5-diphenyl-3-arylcarbamoyloxybiuret derivatives **296** (Equation 37) <1983HCA1011>.



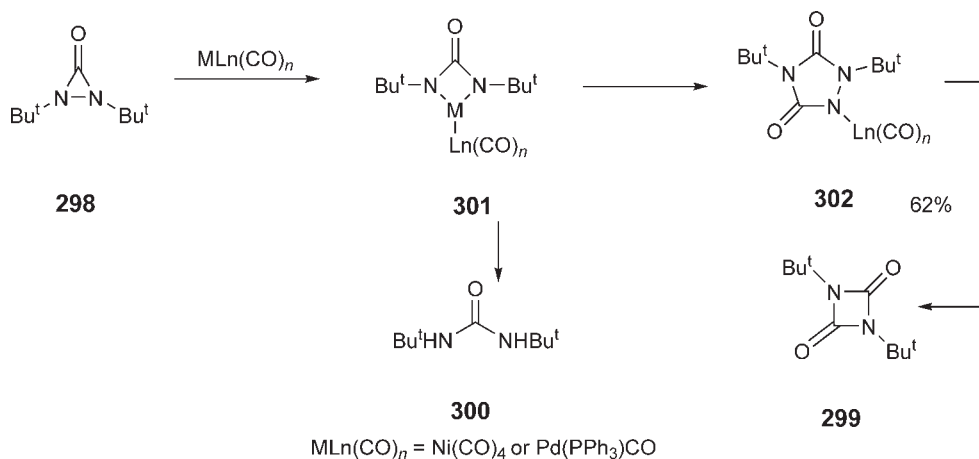
2.13.10 Ring Synthesis by Transformation of Another Ring

2.13.10.1 Synthesis by Ring Expansion

Komatsu and co-workers reported the synthesis of 1,3-diazetidine-2,4-diones by the ring-expansion reaction of diaziridinones <1999H(50)67>. Thus, a ring-expansion reaction of 1,2-di-*t*-butyl-1,2-diaziridinone **298** was carried out by a transition metal-mediated carbonylation reaction to furnish 1,3-diazetidine-2,4-dione **299** (Equation 38).

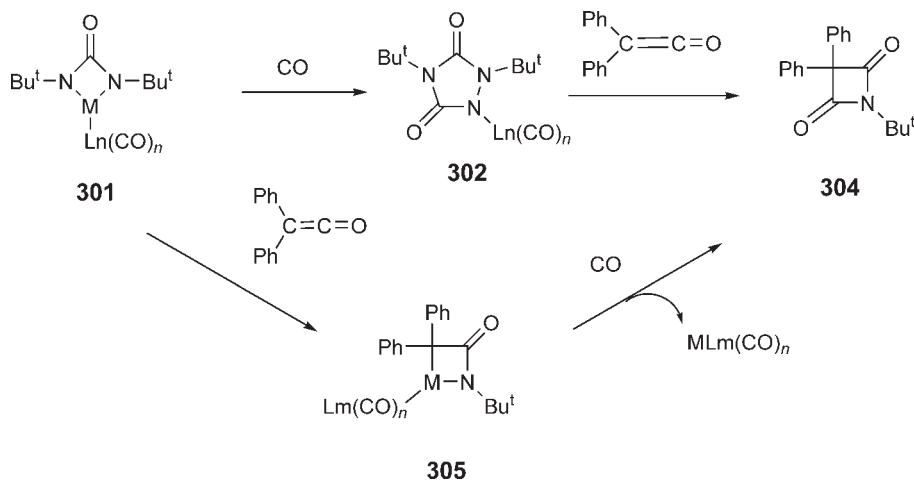


The metal complex used was $\text{Ni}(\text{CO})_4$ under a carbon monoxide atmosphere in DMF at 50°C for 3 h. A suitable temperature was found to be in the range $70\text{--}90^\circ\text{C}$ and the optimum reaction time was 1–3 h. Under an inert nitrogen atmosphere the yield was reduced drastically since the CO atmosphere is essential for the reaction. The use of THF instead of dimethylformamide (DMF) led to a reduction of the yield. Similarly, when 0.1 equiv of $\text{Ni}(\text{CO})_4$ was used as a catalytic metal carbonylating agent, instead of 1 equiv, a low yield of the product was noted. The use of metal carbonyls such as $\text{Fe}(\text{CO})_5$, $\text{W}(\text{CO})_6$ led to a negligible amount of diazetidinediones (**Scheme 49**).



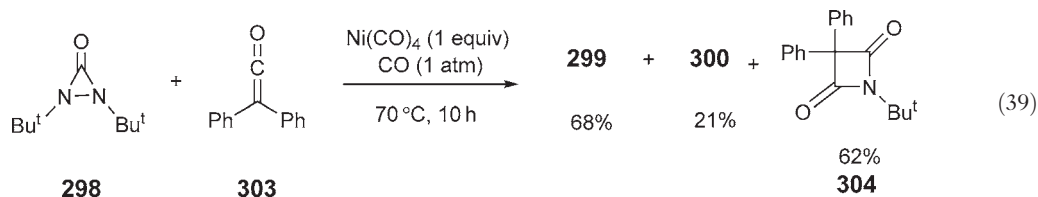
Scheme 49

When $\text{Pd}(\text{PPh}_3)_4$ was used (0.1 equiv) in the presence of carbon monoxide, a 35% yield of the product **299** was obtained. These findings suggest that $\text{Ni}(\text{CO})_4$ and $\text{Pd}(\text{PPh}_3)_4$ are both efficient catalysts for the insertion of CO into the N–N bond of diaziridinone **298**. A possible mechanism suggested by the authors is outlined in **Scheme 50**. The diaziridinone undergoes an oxidative addition on $[\text{Ni}(\text{CO})_4]$ or $[\text{Pd}(\text{PPh}_3)_4(\text{CO})]$ with N–N bond cleavage. Subsequently, CO undergoes an insertion into the N–metal bond complex **301** to furnish metallocycle **302**, which then undergoes a reductive elimination to give **299**. The urea **300** could be rationalized by simple hydrolysis of complex **301** with water present in DMF, or during the workup.



Scheme 50

However, when diaziridinone **298** was treated with diphenylketene in the presence of $\text{Ni}(\text{CO})_4$ under a carbon monoxide atmosphere, a mixture of **299** (28%), **300** (21%), and azetidinedione **304** (27%) was obtained (Equation 39). The formation of azetidinediones **304** may be the result of reaction of diphenylketene with either **301** or **302** followed by reductive elimination to give **304** (Scheme 50).



2.13.11 Synthesis of Particular Classes and Critical Comparison of the Various Routes Available

A number of syntheses of different diazetidines have been reported (Sections 2.13.9 and 2.13.10). However, the synthesis of substituted 1,2-diazetidines developed by Ma and co-workers through intramolecular nucleophilic displacement of a leaving group (such as a mesylate group) by the nitrogen of a hydrazine group of **222** in the presence of a suitable base (K_2CO_3 , CsCO_3 or DBU) has proved to be a very good method (Equations 27 and 28) <2006TL6835>. This methodology has been used to synthesize the corresponding chiral compounds using chiral hydrazines (Section 2.13.9.1.). Yet another interesting method for the synthesis of substituted 1,2-diazetidines is from Oda *et al.* (Schemes 32 and 33) <1996H(42)577>. This method comprising an intramolecular opening of an epoxide **224** is an excellent method to synthesize substituted chiral diazetidines **201**, **225**, **226** (Section 2.13.9.1.).

2.13.12 Applications in Research and Industry

Four-membered heterocycles with two nitrogen atoms are widely used in research and industry. Numerous examples of 1,3-diazetidines are extensively used in the polymer industries.

2.13.12.1 1,2-Diazetidine Derivatives

1,2-Diazetidines have been studied by Taylor and co-workers because of their close structural similarities to the highly potent β -lactam and related antibiotics, such as carbapenams, theinamycin, etc. <1983JOC4567, 1984JOC113, 1984JOC2204, 1984JOC4415, 1986JOC1530, 1986JOC1537, 1987JOC4107>. Later, Oda *et al.* and Desiraju and Nangia have further studied these compounds as potential aza-lactam antibiotics and azacarbenams <1996H(42)577, 1998J(P1)2597> (Section 2.13.7.1).

An application of a diazete has been disclosed in a patent application <1995WO9501347>, as a novel cross-linking agent. Water-soluble cross-linking agents have various applications in separation techniques, that is, chromatography, electrophoresis (separation technique used for peptides and proteins), etc. These water-soluble cross-linking polymers are stable, inert, and are used in solid-phase synthesis of peptides.

Some of the interesting derivatives of aza- β -lactams have been found to induce differentiation of Friend leukemia cells <1986ABC1757>, whereas some diazetidines are antineoplastic agents <1985JPP60239420>. 1,2-Diazetidinium inner salts and 1,2-diazetidine-1-carboxamides have been found to be good medical fungicides <1989USP4826971>. The 4*H*-1,2,4-triazole-4-acetic acid derivative of 1,2-diazetidine has been found to release a development inhibitor with improved abilities in silver halide color photography <1992EPP514896>. 1,2-Diazetidine-1,2-dioxide derivatives show vasodilatory activity. 3-Bromo-4-methyl-3,4-tetramethylenediazetidine-1,2-dioxide was found to possess a spasmolytic effect commensurable with glyceryl trinitrate <1993MI357>. Diazetidine dioxides have been found to be useful as NO donors. They activate guanylate cyclase and inhibit platelet activation and show vasodilatory activity <2005MI687>. Some of the derivatives of the 3,4-dihydrodiazetidine-1,2-dioxide have been found to effectively reduce the arterial pressure in rodent models of hypertension through their ability to donate NO, which is an important signal molecule in animal and human tissues and organs <2003MI395>.

Diazetidine derivatives have been extensively used in the polymerization chemistry to generate cross-linked products that are useful in various industrial applications.

2.13.12.2 1,3-Diazetine Derivatives

Uretidiones containing isocyanate groups on the nitrogen atoms (e.g., 183 and 187) (Section 2.13.7.3) have been extensively used as important building blocks in the polymer industry in manufacturing various kinds of advanced materials with improved properties, such as optical permeability, viscoelasticity, etc. These building blocks are preferred in the synthesis of organic polymers because they do not produce toxic by-products when used as cross-linking agents. Further, the presence of two isocyanate groups helps in making tailor-made polymers. They react with polyhydroxylic compounds to yield polyurethanes and react with polyamines to produce polyureas and hence are used in the manufacture of elastomers, plastics, and coatings.

1,3-Diazetidindiones are used in the preparation of quaternary ammonium polysiloxanes which are useful in the treatment of fibers and are used as fabric softeners <2004WO2004090007>. 1,3-Diazetidine-containing cross-linked polyurethanes are used in ink-jet inks that are suitable for printing on textiles to provide printed materials with improved wash fastedness <2003WO2003016374>. Compounds bearing uretidione groups are useful in forming stable compositions used in coatings, encapsulations, etc. <2000WO2000034355>. Uretidinedione group-containing materials are used in making polyisocyanate compositions with reduced viscosity. Different kinds of polyisocyanate polymers may be obtained based on the catalyst used for this purpose <1999WO9907765>. 1,3-Diazetidinedione diisocyanate dimers are used to prepare pressure-sensitive and peelable adhesive compositions that are used to make protective films for optical component surfaces <2003JPP2003041229>. Uretidione groups containing polyisocyanates are useful in making powder coatings <1999DEP19729262>. 1,3-Diazetidinedione-containing polyisocyanates are used as amine blockers which suppress the formation of toxic *N*-nitrosoamines in rubber processing <1996EPP727458>. Uretidione group-containing polyisocyanates are useful as cross-linkers in polyurethane lacquers for OH-containing binders <1996EPP696606>. Diazetidine-1,4-diones are used in making thermosetting acrylic powder coating compositions. These compositions have been found to possess good acid resistance properties <1995WO9528450>.

1,3-Diazetidin-2,4-dione has been found to be a chymase inhibitor (IC₅₀ 4.0 nM). It has been found that 1,3-diazetidin-2,4-dione derivatives possess high activities against bovine pancreatic α -chymotrypsin, human cathepsin G, and human neutrophil elastase. Some of the derivatives of 1,3-diazetidin-2,4-diones have been shown to be effective as a scaffold for serine protease inhibitors <2001BML1691>. Further, 1,3-diazetidinone containing scaffolds have been found to possess potential antibacterial properties (Section 2.13.7.3).

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Biographical Sketch



Dr. B. B. Lohray is a pioneer drug discovery researcher in the Indian pharmaceutical industry. Several of his new molecular entities have gone to clinical evaluation – Ragaglitazar (went up to phase III), Balaglitazone (entering phase III), ZYH1 (phase II), ZYH2 (phase I), ZYO1 (IND filed) in the area of metabolic disorders and ZYI1 for pain management (phase I).

Dr. Lohray has profound experience in synthetic chemistry and has developed several innovative and noninfringing processes to a number of drug molecules. He has expertise in developing new polymorphs and novel salts of drugs for life-cycle management. He has filed over 150 patent applications and has over 40 granted US patents. He has published 89 papers in peer reviewed journals and authored several reviews and chapters in reference books. He has delivered over 100 lectures in national and international conferences and is a member of several academic and professional societies. In his previous assignment, he has led an interdisciplinary team of 240 scientists comprising chemists, biologists, pharmacologists, biotechnologists, clinicians, and analytical scientists and is responsible for putting four molecules in clinical development and several in preclinical development and several recombinant biotech products in a short span of 5 years.

Dr. Lohray earned his PhD from the Indian Institute of Technology, Kanpur, India under the supervision of Prof. M. V. Gorge in organic photochemistry. He was the recipient of an Alexander von Humboldt Foundation Fellowship at the University of Wurzburg with Prof. W. Adam. Later, he worked with Dieter Enders at RWTH, Aachen, Germany and worked in the area of asymmetric synthesis and developed several asymmetric methodologies using SAMP/RAMP chemistry. He also worked with Prof. K. B. Sharpless (Nobel laureate, 2001) at MIT, Cambridge, USA in asymmetric Catalysis. Presently, he is the CEO of Bhuvud Research Laboratory, Ahmedabad, India (www.bhuvud.com).



Dr. Vidya Bhushan Lohray has extensive experience in drug discovery research. Several drug molecules have emerged from her research – Ragaglitazar (went up to phase III), Balaglitazone (entering phase III), ZYH1 (phase II), ZYH2 (phase I), ZYO1 (IND filed) in the area of metabolic disorders and ZYI1 (phase I) for pain management. Several drug candidates are in preclinical evaluation from her previous work. She has developed several novel and noninfringing processes

to a number of drug molecules. She has expertise in developing new polymorphs and novel salts of drugs. She has filed over 150 patent applications and has over 40 granted US patents. She has published 66 papers in peer-reviewed journals and authored several reviews and chapters in reference books. She has delivered several invited lectures in national and international conferences and is a member of several professional societies. She has technical expertise in intellectual property management. In her previous industrial assignment she has led a team of 40 medicinal chemists and 20 process chemists.

Dr. Vidya Lohray did her PhD in synthetic chemistry from the Indian Institute of Technology, Kanpur, India under the supervision of Prof. S. Chandrasekaran. She worked as a research associate with Prof. W. Adam at the University of Wurzburg, Wurzburg, Germany and with Prof. Dieter Enders at RWTH Aachen, Germany as an Alexander von Humboldt Foundation Fellow. Later, she worked with Prof. T. Ross Kelly at Boston College, Boston, USA as a postdoctoral fellow in synthetic and medicinal chemistry. Presently, she is a director in Bhuvud Research Laboratory, Ahmedabad, India.



Dr. Brijesh Kumar Srivastava did his master's degree in science from Lucknow University in the year 1991 and obtained PhD degree in the year 1999 from the Medicinal Chemistry Department of the Central Drug Research Institute affiliated with Lucknow University, Lucknow, India. During his PhD program, he has mainly worked on antiestrogens and fertility regulating agents.

After obtaining the PhD degree, he worked in the Lucknow Christian College, Lucknow, India to teach postgraduate students and in 2001, he joined the Indian Pharmaceutical Company, Zydus Research Centre, Cadila Healthcare Limited, Ahmedabad, India. Since then, he has been working in the synthesis of novel oxazolidinones and quinolones as antibacterial agents and cannabinoid receptor modulators as antiobesity drug (CB1 antagonist) as well as antipain (CB2 agonist) compounds. His research interests are synthesis of biologically useful and interesting molecules of pharmaceutical importance, stereoselective synthesis of drug and drug intermediates, chiral resolution, drug design, and process development of new chemical entities.

Dr. Brijesh Kumar Srivastava has filed several patent applications and published several papers in peer reviewed journals. He has participated in several international conferences and attended several workshops in the area of drug development.

2.14

Four-membered Rings with One Oxygen and One Nitrogen Atom

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2.14.1 Introduction

Four-membered rings with one oxygen and one nitrogen were covered either as part of a chapter on four-membered heterocyclic rings in CHEC(1984) <1984CHEC(7)449> or in CHEC-II(1996) <1996CHEC-II(1B)969>. The present chapter is intended to update the previous chapters on major new preparations, reactions, and concepts. At the beginning of each main section, a sentence or short paragraph has been provided explaining any omissions in CHEC-II(1996) that have been addressed.

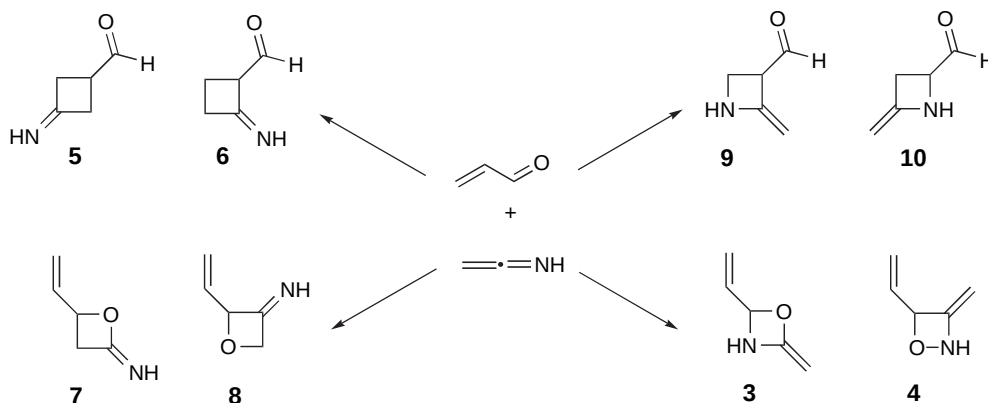
2.14.2 Theoretical Methods

Several papers updating the theoretical calculations on the oxazetidine system have been published since 1996. Strain energies for the two oxazetidine isomers, that is, 1,2-oxazetidine **1** and 1,3-oxazetidine **2**, were reported for the first time by Magers and Davis <1999JMT205> using isodesmic, homodesmotic, and hyperhomodesmotic models. Optimized equilibrium geometries and corresponding electronic energies were computed for all pertinent molecular systems at the MP2 level of theory using the 6-311G(d,p) basis set. Harmonic frequency determinations indicate that both isomers of these oxazetidines are local minima on the ONC_2H_5 potential energy hypersurface at both the self-consistent field (SCF) and correlated levels; a summary of the results is reported in Figure 1.

	Strain energies (kcal mol ⁻¹)		Electronic energies MP2/6-311G(d,p)
	MP2/6-311G(d,p)		
O—NH H₂C—CH₂ 1,2-Oxazetidine 1	Isodesmic	5.6	−208.61274 a.u.
	Homodesmotic	25.2	
	Hyperhomodesmotic	33.0	
O—CH₂ H₂C—NH 1,3-Oxazetidine 2	Isodesmic	−4.0	−208.56307 a.u.
	Homodesmotic	35.2	
	Hyperhomodesmotic	31.8	

Figure 1 Strain and electronic energies of 1,2- and 1,3-oxazetidines.

Fabian examined the geometries of the possible cycloaddition products between ketenimine and acrolein as well as of the respective transition states by *ab initio* calculations at the MP2/6-31G* level <1997JA4253>. Two of the 12 possible products of [4+2] and [2+2] cycloaddition are oxazetidines **3** and **4** (Scheme 1). With respect to the site selectivity of the heterodiene, the [2+2] products resulting from the addition of the ketenimine onto the dienic C=C



Scheme 1

double bond were found to be more stable than those obtained by reaction of the carbonyl group (compare compounds **5** and **6** vs. **7** and **8** or **9** and **10** vs. **3** and **4**) (Scheme 1). Moreover, 1,3-oxazetidine **3** is calculated to be more stable than 1,2-oxazetidine **4** by approximately 38 kcal mol⁻¹ at the MP2/6-31G* level; the activation energy is also lower than that for 1,2-oxazetidine **4** by about 52 kcal mol⁻¹.

An *ab initio* quantum chemical study of the five possible isomers of C₂H₃NO, that is, *trans*- and *cis*-nitrosoethylene, 4*H*-1,2-oxazete, 2*H*-1-azirine-1-oxide, and acetonitrile oxide, was reported by Kolandaivel <1998JMT165>. As far as 4*H*-1,2-oxazete **11** is concerned, geometrical parameters, atomic charges, dipole moment, entropy, rotational constant, and vibrational frequencies with ZPVE correction were reported at the HF and MP2 level of theory. Oxazete **11** was found to be 0.16 kcal mol⁻¹ less stable with respect to *trans*-nitrosoethylene at the HF/63-1G* level, but more stable than *cis*-nitrosoethylene by about 3.64 kcal mol⁻¹; the dipole moment was 4.09 D at the MP2/6-31G* level, and the entropy was 259.2 J mol⁻¹ K⁻¹ at the HF/6-311G* level of theory. Geometrical parameters and atomic charges are reported in Figure 2.

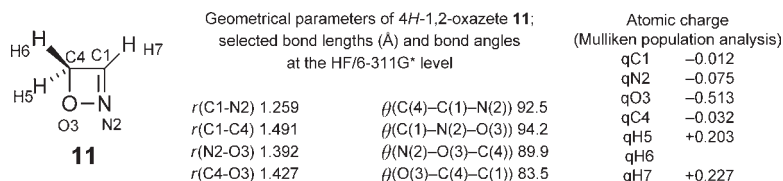


Figure 2 Geometrical parameters of oxazete **11**.

No imaginary frequencies were revealed by vibrational analysis and a value of 1663.2 cm⁻¹ was assigned to the C=N mode, close to that already reported by Ugalde <1992JMT167>.

In the oxidative aromatic substitution of benzene with the nitrosonium cation (NO⁺), the benzene complex with *C*₁ symmetry **12** has been calculated as a local minimum at the B3LYP/6-31G(d) level of theory with an energy of 48 kcal mol⁻¹ above that of the π -complex **13** <1999PCA4261>; therefore, the former should not be relevant for the nitrosation mechanism as was previously proposed (Figure 3) <1985RJOC842>.

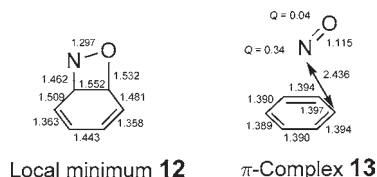
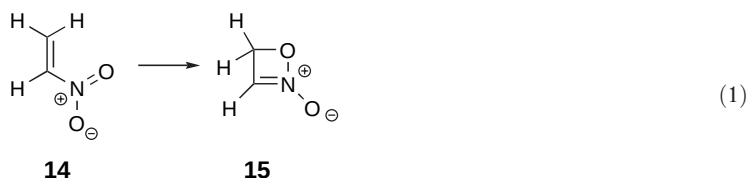
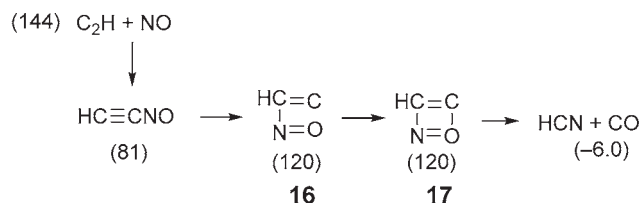


Figure 3 Geometries of the local minimum **12** and of the (C₆H₅...NO)⁺ π -complex **13** in the oxidative aromatic substitution of benzene with NO⁺ at the B3LYP/6-31G(d) level.

4*H*-1,2-Oxazete-*N*-oxide **15** has been postulated as the main intermediate in the mechanism of the unimolecular degradation of nitroethylene **14**. The calculated barrier of 205.6 kJ mol⁻¹, for the reaction shown in Equation (1), at the B3LYP/6-311++G(df,p) level, is close to the experimental energy found in the gas-phase nitroethylene degradation (192.05 kJ mol⁻¹) <2001MC163>.



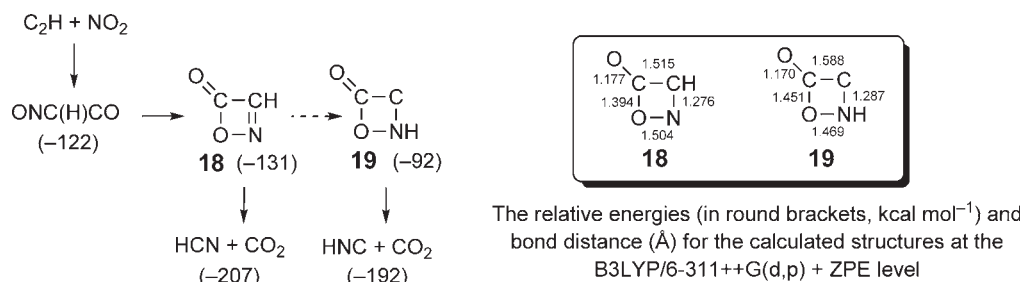
In the study of the potential energy surface [B3LYP/6-311G++(d,p)] for the reaction of the ethynyl radical HC₂ with nitric oxides NO and NO₂, Peeters and co-workers reported that a cyclic 1,2-oxazete intermediate such as **17** may be involved. In the reaction of HC₂ and NO, the four-membered cyclic structure **17**, precursor of HCN and CO, could reasonably be formed from **16** by means of a ring-closing reaction having an activation barrier of 18 kcal mol⁻¹ (Scheme 2) <1998CPL91>.



The relative energies (kcal mol^{-1}) for the calculated structures at the B3LYP/6-311++G(d,p) level are given in round brackets

Scheme 2

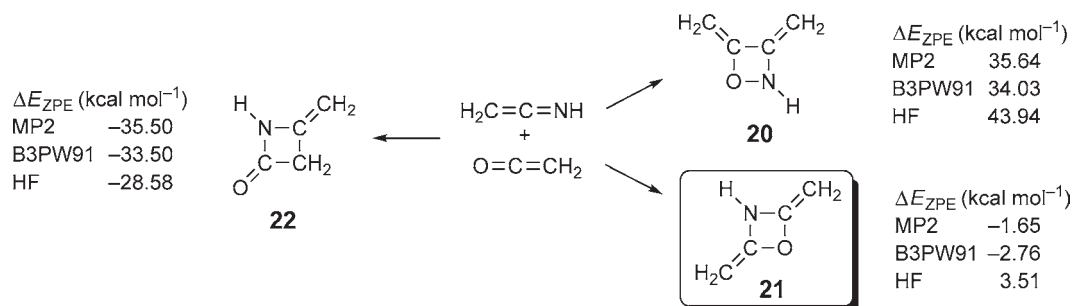
In the case of the reaction of the HC_2 radical with NO_2 , several pathways were considered and the four-membered cyclic structures **18** and **19** were found to be the main intermediates (Scheme 3) <2003JCP10996>.



Scheme 3

Dobrowolski and co-workers reported calculations of the thermodynamic stability of the products derived from cycloaddition of vinylimine and ketene and of isocyanic acid and allene using MP2, density functional theory (DFT) (B3PW91), and Hartree–Fock (HF) methods with the 6-311++G** basis set. Fourteen different structures were calculated for these cycloaddition reactions and the values of the free Gibbs energy showed that only 4- and 3-methylene- β -lactams could be formed in considerable amount.

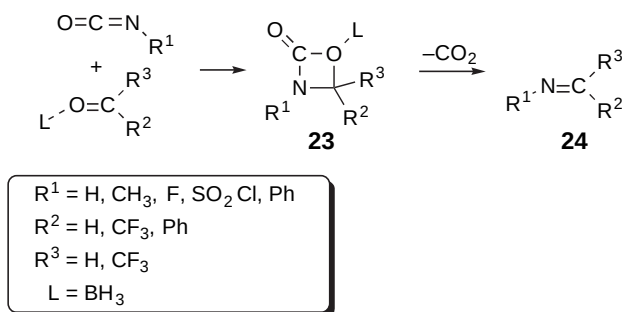
By reacting vinylimine with allene, only product **21**, of the two possible 1,2- and 1,3-oxazetidines **20** and **21**, was considered as a feasible molecule since **20** was found to be unstable at 0 K (Scheme 4) <2002PCP3948>. However, the most stable cycloaddition product was computed to be 4-methylene- β -lactam **22**.



Scheme 4

Fu studied the cycloaddition reactions of aldehydes and isocyanates theoretically by *ab initio* HF and MP2 methods using the 6-31++G** and 6-31G* basis set. It was found that the first step of these reactions led to 1,3-oxazetidin-2-ones **23**, which underwent decarboxylation forming the imines **24** (Scheme 5) <1999JMT15>.

A model reaction ($R^1, R^2, R^3 = H$) was studied at the MP2/6-31++G** level and, in the case of the substituted derivatives, only at the HF/6-31G* level. Transition states were confirmed by vibrational analysis and were characterized only by imaginary vibration modes; energies and geometrical parameters are reported in Figure 4 <1999JMT15>.



Scheme 5

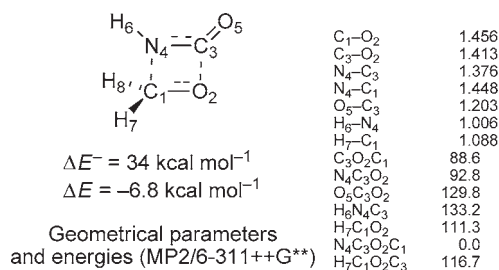


Figure 4 The geometrical parameters and energies for the transition state of the model reaction.

The reaction of substituted isocyanates with aldehydes was also investigated at the HF/6-31G* level of theory <1999JMT15>, and the geometrical parameters are reported in Figure 5.

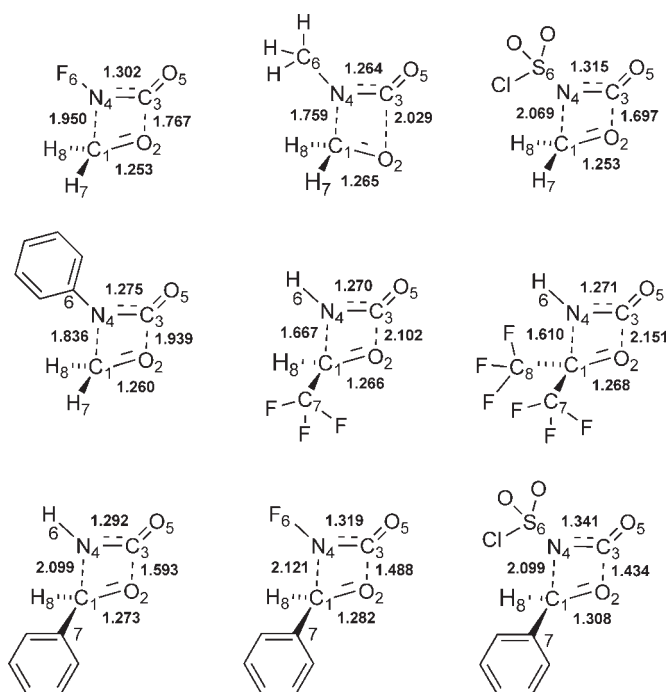


Figure 5 The main geometrical parameters for the transition state of the substituted reactions.

Owing to the similarity to β -lactam derivatives, investigations on the structure of 1,3-oxazetidine-2-one derivatives with potential antibiotic activity were carried out by Munoz and co-workers. PM3 <1999JMT287> and *ab initio* calculations <1999PCA8879> have been used to study the mechanism of alkaline hydrolysis of aza- β -lactams, oxo- β -lactams, and thio- β -lactams. In Figure 6, geometrical parameters and energies at the PM3 and MP2 level are reported in the case of the 1,3-oxazetidine-2-one **25** (oxo- β -lactam).

25	PM3		MP2/6-31+G*	
	C ₇ -N ₄	1.482	C ₇ -N ₄	1.345
	C ₇ -O ₆	1.400	C ₇ -O ₆	1.391
	N ₄ -H ₁₅		C ₅ -S ₁	1.796
	O ₆ -H ₁₅		O ₈ C ₇ N ₄	125.6
	C ₅ -S ₁	1.836	C ₇ N ₄ -C ₅ O ₆	28.2
	O ₈ C ₇ N ₄	139.4	E	-832.81670 a.u.
	C ₇ N ₄ -C ₅ O ₆	2.9	ZPE	0.10047
	ΔH_f	-62.41		
	Imaginary frequency	0		

Figure 6 The main geometrical parameters at the PM3 and MP2 level of theory for the 1,3-oxazetidin-2-one **25**.

Electrostatic potential, structural parameters <2001MI819>, as well as the molecular mechanics <2002JMT19> relevant to 1,3-oxazetidine-2-one derivatives (oxo- β -lactams) as β -lactamase inhibitors have been investigated.

Recently, in a theoretical mechanistic study on the radical-radical reaction between the ketylenyl radical (HCCO $\cdot$) and nitrogen dioxide (NO₂) <2006PCA2527>, a 1,2-oxazetidine derivative (Figure 7) was supposed to be the most likely intermediate in the conversion of the reactants into the products HCNO and CO₂. The geometries of all the reactants, products, intermediates, and transition states were optimized using the hybrid density functional B3LYP with the 6-311G-(d,p) basis set. Figure 7 shows the main geometrical parameters calculated for the intermediate and the relative energies associated with this transformation.

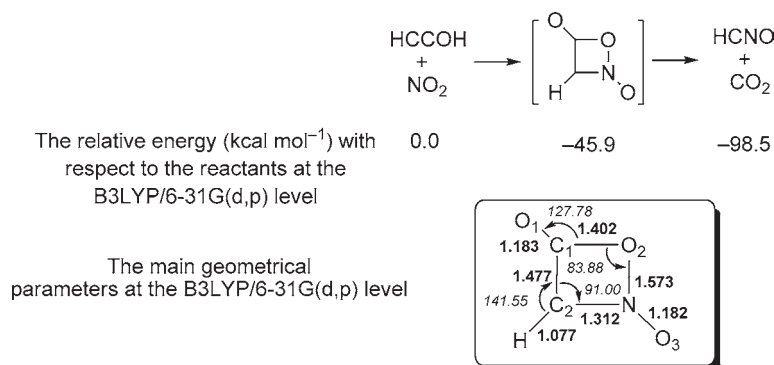


Figure 7 The relative energies and the main geometrical parameters for the intermediate involved in the HCCO + NO₂ reaction.

2.14.3 Experimental Structural Methods

2.14.3.1 X-Ray Diffraction

The first crystallographic data concerning an oxazetidine skeleton, such as that of bicyclic species **26**, was published in 1997 (Figure 8) <1997BSF927>. Other X-ray measurements have only recently been reported by Florio and co-workers in the case of the optically active oxazolinyl-1,2-oxazetidine (-)-**27** (Figure 8) <2003JOC10187> and the hydroxyalkyl 1,2-oxazetidine **29i** (Figure 8) <2006MI1>.

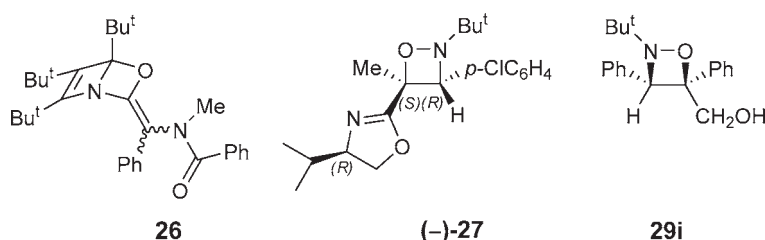


Figure 8 Oxazetidines **26**, **(-)-27**, and **29i** whose crystallographic data have been reported.

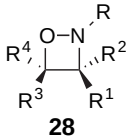
2.14.3.2 NMR Spectroscopy

Relatively few proton and carbon-13 spectroscopic data were reported in CHEC-II(1996) concerning 1,2- and 1,3-oxazetidines; however, much ^{19}F nuclear magnetic resonance (NMR) data were available in the case of perfluoro-1,2-oxazetidines (see, in particular, <1970JOC1607>). Although little followup work has been performed in the last ten years, some solid evidence on predicting the stereochemistry of the oxazetidine system, exploiting established geminal $^2J_{\text{H-H}}$ as well as $^3J_{\text{H-H}}$ and $^3J_{\text{C-H}}$ coupling constant values, has been reported <2003TL3067, 2002EJO2961, 2003JOC10187>.

2.14.3.2.1 Proton NMR spectroscopy

Snider and Duvall published the first geminal coupling constant in the case of the 1,2-oxazetidine carboxylate derivative **28a** (Table 1; Figure 9) and confirmed the formation of the four-membered ring by means of heteronuclear multiple bond correlations (HMBC) (Table 1) <2003TL3067>. Vicinal coupling constant values $^3J_{\text{H-H}}$ are now available in the

Table 1 Proton NMR data for disubstituted 1,2-oxazetidines^a

						Reference
	Compound	R	$R^1 R^4$	$R^2 R^4$	$R^1 R^2$	
a	R = BOC R^4 = Me R^3 = CO ₂ Me R^1 = R^2 = H	1.52			4.36 and 4.68 J = 8.5 Hz	2003TL3067
b	R = Bu ^t R^3 = oxazoliny ^b R^1 = Ph R^2 = R^4 = H	1.14		5.27 and 5.56 J = 10.0 Hz		2002EJO2961
c	R = Bu ^t R^3 = oxazoliny ^b R^2 = Ph R^1 = R^4 = H	1.07	5.16 and 5.22 J = 8.1 Hz			2002EJO2961
d	R = Bu ^t R^3 = oxazoliny ^b R^1 = 4-ClC ₆ H ₄ R^2 = R^4 = H	1.07		5.17 and 5.48 J = 10.0 Hz		2002EJO2961
e	R = Bu ^t R^3 = oxazoliny ^b R^2 = 4-ClC ₆ H ₄ R^1 = R^4 = H	1.07	5.11 and 5.19 J = 8.1 Hz			2002EJO2961

^aChemical shifts in ppm, CDCl₃ as the solvent.

^b4,4-Dimethyl-2-oxazolin-2-yl.

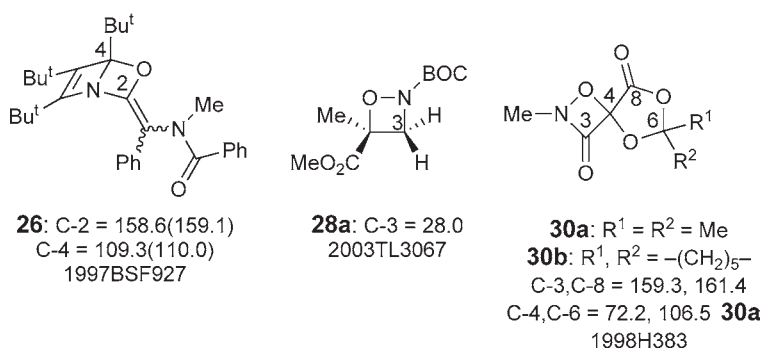


Figure 9 Carbon-13 NMR data of oxazetidines **26**, **28a**, and **30a** and **30b**.

case of *cis*- and *trans*-configured oxazolynyl[1,2]oxazetidines **28b–e**, the *cis* values being always larger than the *trans* values (**Table 1**) <2002EJO2961>. The proton's chemical shift at the C-3 ring carbon atom for trisubstituted (3*R**,4*S**)-configured oxazolynyl[1,2]oxazetidines **28f–l** <2003JOC10187> and 4-hydroxyalkyl-3-aryl-substituted 1,2-oxazetidines **29a–k** <2006OL3923> was always found to fall into the range 5.4–5.7 ppm, whereas that for (3*R**,4*R**)-1,2-oxazetidines **28m** <2003JOC10187> and **29l** <2006OL3923> was 4.90 and 5.22 ppm, respectively (**Table 2**).

Table 2 Proton NMR data for trisubstituted 1,2-oxazetidines^a

Compound	<i>R</i>	<i>R</i> ¹ <i>R</i> ²	<i>R</i> ³ <i>R</i> ⁴	Reference

28

f	R = Bu ^t ; R ¹ = H; R ² = Ph R ³ = oxazolynyl; ^b R ⁴ = Me	1.09	5.47 (R ¹)	1.34 (R ⁴)	2003JOC10187
g	R = Bu ^t ; R ¹ = H; R ² = 4-CF ₃ C ₆ H ₄ R ³ = oxazolynyl; ^b R ⁴ = Me	1.27	5.54 (R ¹)	1.35 (R ⁴)	2003JOC10187
h	R = Bu ^t ; R ¹ = H R ² = 4-MeOC ₆ H ₄ R ³ = oxazolynyl; ^b R ⁴ = Me	1.08	5.41 (R ¹)	1.34 (R ⁴)	2003JOC10187
i	R = Bu ^t ; R ¹ = H; R ² = 4-ClC ₆ H ₄ R ³ = oxazolynyl; ^b R ⁴ = Me	1.05	5.42 (R ¹)	1.31 (R ⁴)	2003JOC10187
j	R = Bu ^t ; R ¹ = H; R ² = Ph R ³ = (<i>R</i>)-oxazolynyl; ^c R ⁴ = Me	1.07	5.47 (R ¹)	1.30 (R ⁴)	2003JOC10187
k	R = Bu ^t ; R ¹ = H; R ² = 4-CF ₃ C ₆ H ₄ R ³ = (<i>R</i>)-oxazolynyl; ^c R ⁴ = Me	0.99	5.54 (R ¹)	1.17 (R ⁴)	2003JOC10187
l	R = Bu ^t ; R ¹ = H; R ² = 4-ClC ₆ H ₄ R ³ = (<i>R</i>)-oxazolynyl; ^c R ⁴ = Me	1.05	5.42 (R ¹)	1.25 (R ⁴)	2003JOC10187
m	R = Bu ^t ; R ¹ = H; R ² = 4-ClC ₆ H ₄ R ³ = Me; R ⁴ = oxazolynyl ^b	1.06	4.90 (R ¹)	1.72 (R ⁴)	2003JOC10187

29

a	R = cumyl; R ² = 4-MeC ₆ H ₄ R ¹ = R ³ = R ⁴ = H		5.41 (R ¹)	3.37 and 3.45	2006OL3923

(Continued)

Table 2 (Continued)

	Compound	<i>R</i>	<i>R</i> ¹ <i>R</i> ²	<i>R</i> ³ <i>R</i> ⁴	Reference
b	R = cumyl; R ² = 2-furyl R ¹ = R ³ = R ⁴ = H		5.44 (R ¹)	3.34 and 3.39	2006OL3923
c	R = cumyl; R ² = 4-ClC ₆ H ₄ R ¹ = R ³ = R ⁴ = H		5.41 (R ¹)	3.38 and 3.43	2006OL3923
d	R = cumyl; R ² = Ph R ¹ = R ³ = R ⁴ = H		5.50 (R ¹)	3.43 and 3.52	2006OL3923
e	R = cumyl; R ² = 4-MeOC ₆ H ₄ R ¹ = R ³ = R ⁴ = H		5.42 (R ¹)	3.39 and 3.47	2006OL3923
f	R = cumyl; R ² = 5-(3-trifluoromethylphenyl)-2-furyl R ¹ = R ³ = R ⁴ = H		5.50 (R ¹)	3.43 and 3.53	2006OL3923
g	R = cumyl; R ² = 4-ClC ₆ H ₄ R ¹ = R ⁴ = H; R ³ = Me		5.55 (R ¹)	0.70 (R ³) 3.60 (R ⁴)	2006OL3923
h	R = cumyl; R ² = 4-ClC ₆ H ₄ R ¹ = R ³ = H; R ⁴ = Ph		5.61 (R ¹)	4.56 (R ³)	2006OL3923
i	R = Bu ^t ; R ² = Ph R ¹ = R ³ = R ⁴ = H		5.61 (R ¹)	3.72 and 3.90	2006OL3923
j	R = Bu ^t ; R ² = 4-ClC ₆ H ₄ R ¹ = R ³ = R ⁴ = H		5.58 (R ¹)	3.70 and 3.85	2006OL3923
k	R = Bu ^t ; R ² = 4-CF ₃ C ₆ H ₄ R ¹ = R ³ = R ⁴ = H		5.68 (R ¹)	3.73 and 3.89	2006OL3923
l	R = Bu ^t ; R ¹ = 4-CF ₃ C ₆ H ₄ R ² = R ³ = R ⁴ = H		5.22 (R ²)	3.54 and 3.97	2006OL3923

^aChemical shifts in ppm, CDCl₃ as the solvent.

^b4,4-dimethyl-2-oxazolin-2-yl.

^c(4*R*)-4-isopropyl-2-oxazolin-2-yl.

2.14.3.2.2 Carbon-13 NMR spectroscopy

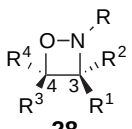
Interestingly, in the case of 4-methyl-substituted oxazoliny[1,2]oxazetidines **28f–m**, the stereochemistry of the oxazetidine ring was established on the basis of the long-range ³J_{C–H} coupling constant: the (*R*^{*},*S*^{*})-isomers, having a *trans*-relation between the hydrogen and the methyl group **28f–l**, showed a smaller ³J_{C–H} coupling constant (in the range 2.8–3.3 Hz) with respect to the isomer **28m** (³J_{13C–H} = 5.7 Hz) having both groups in a *cis*-relation (**Table 2**) <2003JOC10187>, analogously to what was reported in the case of three-membered rings <1978JOC4696>. These relative configurations, in the case of this type of four-membered heterocycles, were also confirmed by means of 2-D nuclear Overhauser enhancement spectroscopy (NOESY) correlations. ¹³C NMR data are also available for *N*-BOC-4,4-disubstituted 1,2-oxazetidine **28a** <2003TL3067>, 4-hydroxyalkyl-1,2-oxazetidines **29a–l** <2006OL3923>, and for the diastereomeric 1,3-oxazetidines **26** having an exocyclic double bond at C-2. Unfortunately, for the latter, the stereochemistry of the two geometric isomers was not specified in the original article (**Table 3**; **Figure 9**). ¹³C NMR data on spirocyclic 1,2-oxazetidin-3-ones **30a** and **30b** have been reported by Katagiri *et al.* The two carbonyl carbons showed two distinct resonances in the range 159–161 ppm, whereas the two quaternary carbons were reported at δ 72.2 and 106.5 ppm in the case of compound **30a** (**Figure 9**) <1998H(47)383>.

2.14.3.3 Infrared Spectroscopy

Infrared data of 1,2-oxazetidines **28b–m** and **29a–k** always include a diagnostic band in the range 1362–1369 cm^{−1}, which can be ascribed to a ring motion <2002EJO2961, 2003JOC10187, 2006OL3923>. Additionally, oxazoliny[1,2]oxazetidines **28b–m** show a sharp band in the range 1657–1679 cm^{−1} due to the C=N stretching <2002EJO2961, 2003JOC10187>. *N*-BOC-4-methoxycarbonyl-substituted 1,2-oxazetidine **28a** absorbs at 1744 and 1714 cm^{−1} <2003TL3067>. Bicyclic 1,3-oxazetidine **26**, bearing an exocyclic double bond at C-2 linked to a tertiary amidic group, gives rise to stretching bands at 1678 (CO) and 1648 cm^{−1} <1997BSF927>. Spirocyclic compounds **30a** and **30b** showed carbonyl absorption stretching bands, due to the 1,2-oxazetidin-3-one and dioxolone moiety, at 1779–1780 and 1805–1807 cm^{−1}, respectively <1998H(47)383>.

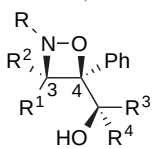
Table 3 Carbon-13 NMR data for trisubstituted 1,2-oxazetidines^a

	<i>Compound</i>	¹³ C NMR				<i>Reference</i>
		<i>C-3</i>	<i>C-4</i>	<i>C-N</i>	<i>C-OH</i>	



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f	R = Bu ^t ; R ¹ = H; R ² = Ph R ³ = oxazolinyll; ^b R ⁴ = Me	65.5	78.1	59.2		2003JOC10187
g	R = Bu ^t ; R ¹ = H R ² = 4-CF ₃ C ₆ H ₄ R ³ = oxazolinyll; ^b R ⁴ = Me	65.4	78.1	59.6		2003JOC10187
h	R = Bu ^t ; R ¹ = H R ² = 4-MeOC ₆ H ₄ R ³ = oxazolinyll; ^b R ⁴ = Me	65.5	78.5	59.4		2003JOC10187
i	R = Bu ^t ; R ¹ = H R ² = 4-ClC ₆ H ₄ R ³ = oxazolinyll; ^b R ⁴ = Me	65.0	77.8	59.2		2003JOC10187
j	R = Bu ^t ; R ¹ = H; R ² = Ph R ³ = (<i>R</i>)-oxazolinyll; ^c R ⁴ = Me	66.0	78.2	59.1		2003JOC10187
k	R = Bu ^t ; R ¹ = H R ² = 4-CF ₃ C ₆ H ₄ R ³ = (<i>R</i>)-oxazolinyll; ^c R ⁴ = Me	65.6	78.0	59.2		2003JOC10187
l	R = Bu ^t ; R ¹ = H R ² = 4-ClC ₆ H ₄ R ³ = (<i>R</i>)-oxazolinyll; ^c R ⁴ = Me	64.4	78.0	59.1		2003JOC10187
m	R = Bu ^t ; R ¹ = H; R ² = 4-ClC ₆ H ₄ R ³ = Me; R ⁴ = oxazolinyll ^b	70.0	80.3	59.1		2003JOC10187



29

a	R = cumyl; R ² = 4-MeC ₆ H ₄ R ¹ = R ³ = R ⁴ = H	66.4	88.3	63.9	66.5	2006OL3923
b	R = cumyl; R ² = 2-furyl R ¹ = R ³ = R ⁴ = H	63.8	87.6	60.3	66.5	2006OL3923
c	R = cumyl; R ² = 4-ClC ₆ H ₄ R ¹ = R ³ = R ⁴ = H	65.7	88.2	63.4	66.4	2006OL3923
d	R = cumyl; R ² = Ph R ¹ = R ³ = R ⁴ = H	66.4	88.2	63.8	66.4	2006OL3923
e	R = cumyl; R ² = 4-MeOC ₆ H ₄ R ¹ = R ³ = R ⁴ = H	66.0	88.3	63.8	66.5	2006OL3923
f	R = cumyl; R ² = 5-(3-trifluoromethylphenyl)-2-furyl R ¹ = R ³ = R ⁴ = H	64.0	87.7	60.2	66.3	2006OL3923
g	R = cumyl; R ² = 4-ClC ₆ H ₄ R ¹ = R ⁴ = H; R ³ = Me	66.2	90.0	63.8	70.2	2006OL3923
h	R = cumyl; R ² = 4-ClC ₆ H ₄ R ¹ = R ³ = H, R ⁴ = Ph	68.1	88.0	64.0	78.9	2006OL3923
i	R = Bu ^t ; R ² = Ph R ¹ = R ³ = R ⁴ = H	66.4	87.0	59.1	67.0	2006OL3923

(Continued)

Table 3 (Continued)

	<i>Compound</i>	¹³ C NMR				<i>Reference</i>
		<i>C-3</i>	<i>C-4</i>	<i>C-N</i>	<i>C-OH</i>	
j	R = Bu ^t ; R ² = 4-ClC ₆ H ₄ R ¹ = R ³ = R ⁴ = H	65.8	87.1	59.4	67.1	2006OL3923
k	R = Bu ^t ; R ² = 4-CF ₃ C ₆ H ₄ R ¹ = R ³ = R ⁴ = H	65.8	87.1	59.4	66.9	2006OL3923
l	R = Bu ^t ; R ¹ = 4-CF ₃ C ₆ H ₄ R ² = R ³ = R ⁴ = H	66.4	83.9	59.3	69.5	2006OL3923

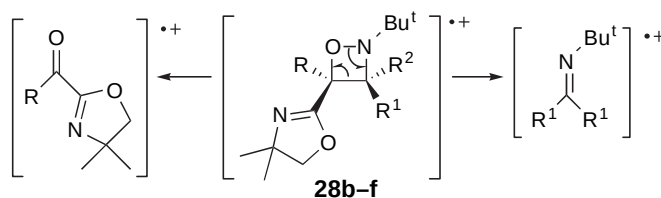
^aChemical shifts in ppm, CDCl₃ as the solvent.

^b4,4-Dimethyl-2-oxazolin-2-yl.

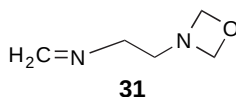
^c(4*R*)-4-isopropyl-2-oxazolin-2-yl.

2.14.3.4 Mass Spectrometry

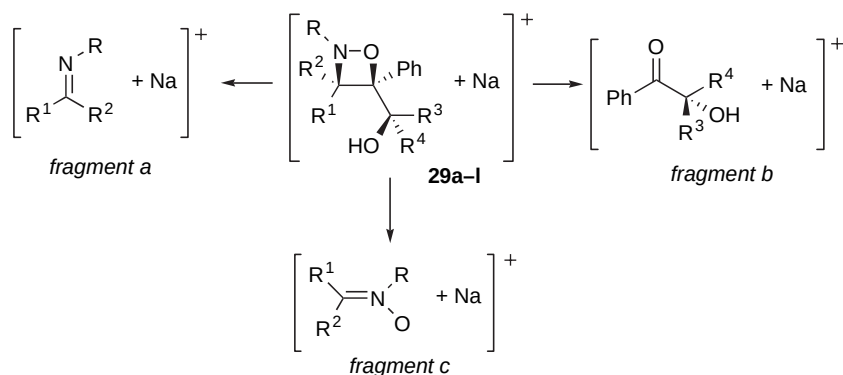
Electron impact (EI) mass spectra of 4-oxazolynyl[1,2]oxazetidines such as **28b–f** never showed molecular ion signals; two complementary fragments of almost equal intensity derived from a formal [2+2] cycloreversion, corresponding either to an oxazolynyl methyl ketone (or an oxazolynylcarbaldehyde) or to an *N*-*tert*-butylarylideneamine, were always detected instead (Scheme 6) <2001TL9183, 2002EJO2961>.

**Scheme 6**

The EI technique was successfully employed in detecting molecular ion signals in the case of the thermally more stable 1,3-oxazetidines **26** <1997BSF927> and **31** (Figure 10) <2005RCB432>; the former gave as base peak $m/z = 118$ [PhCON–H]⁺, whereas that of the latter was $m/z = 56$ [M–OCH₂CH₂N]⁺.

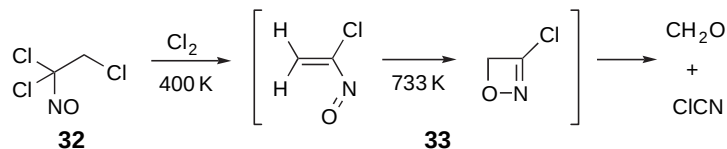
**Figure 10** Chemical structure of 1,3-oxazetidine **31**.

A more gentle technique such as electrospray ionization mass spectrometry (ESI-MS) always favors the detection of molecular ions characteristic of the molecular weight of oxazetidines; indeed, 1,2-oxazetidines **28g–m** and **29a–l** were detected by ESI-MS as their [M + Na]⁺ and [M + H]⁺ adducts <2003JOC10187, 2006OL3923>. Interestingly, in the case of 4-hydroxyalkyl-1,2-oxazetidines **29a–l**, three fragments *a–c* (fragment *b* being the main one), may be formed from the further collision-induced dissociation of their sodium adducts (tandem MS) via competitive retro-[2+2] cycloadditions and other fragmentation pathways (Scheme 7). 1,2-Oxazetidines **29c,g,h** and **29a,b,d,f,i** gave rise to fragments *a* and *c* which were 14–66% and 2–60% of intensity of the fragment *b* ($m/z = 100$), respectively. High-resolution MS was performed in the case of 1,2-oxazetidines **28a** <2003TL3067>, **29b,d,f,k** <2006OL3923>, and **30** <1998H(47)383>.



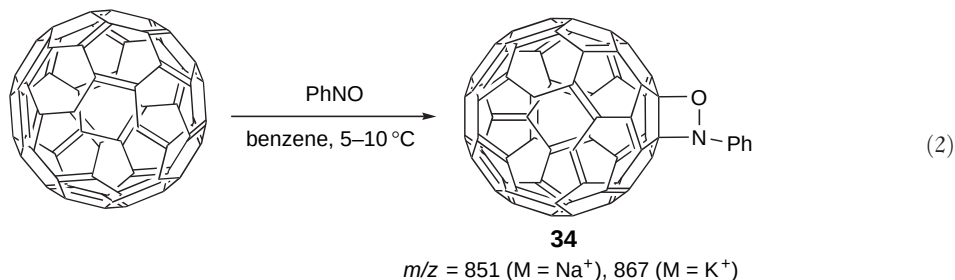
Scheme 7

The pyrolysates obtained at 700–1100 K from 1,1,2-trichloronitroso-ethane **32** and having the ionic peaks at m/z 30 and m/z 62 were determined to be formaldehyde and cyanogen chloride by microwave spectroscopy; the above fragments were supposed to be produced by cleavage of 4*H*-1,2-oxazete **33**, generated by intramolecular cyclization of 1-chloro-1-nitroso-ethene $\text{CH}_2=\text{C}(\text{Cl})\text{-NO}$ (Scheme 8) <2000MI177>.



Scheme 8

ESI-MS of fulleroid 1,2-oxazetidine **34** (Equation 2), obtained by a hetero-Diels–Alder reaction between buckminsterfullerene C_{60} and nitrosobenzene, provided a useful method for the characterization of small neutral organic molecules, otherwise not detectable, as fullerene derivatives <1997USP5635404>.



2.14.4 Thermodynamic Aspects

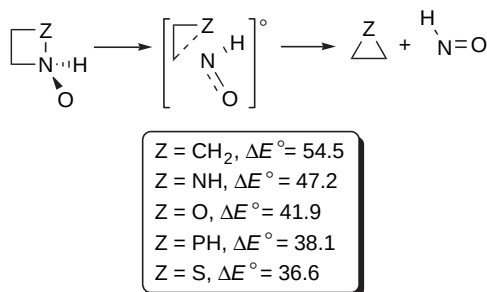
2.14.4.1 Intermolecular Forces

Intermolecular forces in the 1,2- and 1,3-oxazetidine families vary substantially according to the substitution of the four-membered ring. For instance, trisubstituted oxazolinyl[1,2]oxazetidines **28f–m** were all solids with a melting point between 55 and 111 °C and were recrystallized from hexane, whereas disubstituted oxazolinyl[1,2]oxazetidines **28b,c,e** were yellow oils with the only exception being compound **28d** which is a yellow waxy solid <2002EJO2961, 2003JOC10187>. Among 4-hydroxyalkyl-1,2-oxazetidines, only four **29a,g,i,j** were white solids (recrystallized from hexane and with a m.p. ranging from 62 to 139 °C); the others are oils. Bicyclic 1,3-oxazetidines **26** <1997BSF927>

and spirocyclic 1,2-oxazetidin-3-ones **30** <1998H(47)383> were reported to be solids, whereas *N*-BOC-1,2-oxazetidine **28a** <2003TL3067> was an oil. All the above oxazetidines are generally stable on silica gel and can be purified by flash chromatography with a mixture of eluents such as 80–90% hexane (or pentane or petroleum ether) and 20–10% Et₂O (or AcOEt); only in the case of spirocyclic oxazetidines **30** could the crude product not be further purified by recrystallization due to its instability.

2.14.4.2 Thermodynamic Stability

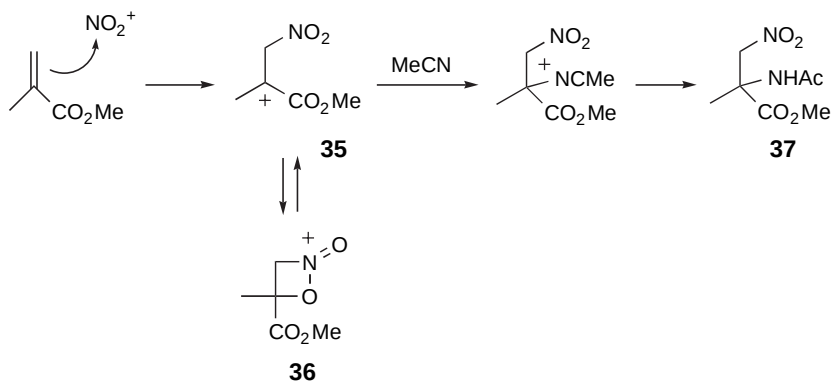
All 1,2-oxazetidines **28a–m** and **29a–l** have been reported to be thermally stable; in particular, 1,2-oxazetidines **28a** <2003TL3067> and **29a–l** <2006OL3923> have been isolated after refluxing of the reaction mixture in the last step of their synthesis. The only exception were 1,2-oxazetidin-3-ones **30**, which, once isolated, could not be further purified due to their instability <1998H(47)383>. The higher computed thermodynamic stability of 1,3-oxazetidines with respect to 1,2-oxazetidines, as well as their ring strain, has been reviewed in Section 2.14.2. The diagonalization reaction (defined by the authors as a concerted bond formation between the diagonal atoms in cyclic saturated compounds) of various 1,2-hetero-azetidine *N*-oxides to produce contracted rings such as those of heterocyclopropanes has been investigated <1999TL8893>. Analysis of the bond interactions at the transition states suggested that the reactivities of the above reactions are controlled by the strain of the incipient rings of the transition structures. Interestingly, the activation energy of 1,2-oxazetidine *N*-oxide ($\Delta E^\ddagger = 41.9 \text{ kcal mol}^{-1}$) and, consequently, its propensity to give an oxirane, was found to be intermediate between that of an 1,2-azetidine *N*-oxide ($\Delta E^\ddagger = 54.5 \text{ kcal mol}^{-1}$) and that of an 1,2-thiazetidine *N*-oxide ($\Delta E^\ddagger = 36.6 \text{ kcal mol}^{-1}$) (Scheme 9).



Scheme 9

2.14.4.3 Ring-Chain Isomerism

The nitration of methyl methacrylate afforded as by-product the nitroacetamide **37** (Scheme 10) <1997J(P1)1559>. Its regiochemistry suggested that the putative α -carbonyl cation **35**, which was then trapped by acetonitrile, may be the intermediate in its formation. However, AM1 calculations showed that the tertiary cation **35** may also be in equilibrium with 1,2-oxazetidin-2-onyl cation **36**, the latter being calculated to be about 1 kcal mol^{-1} lower in energy.



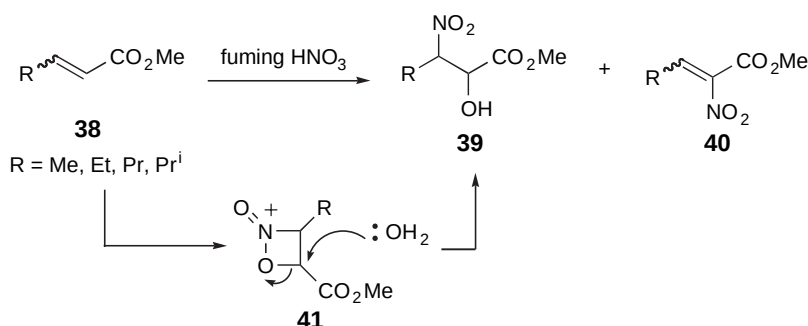
Scheme 10

2.14.5 Reactivity of Unsaturated Rings

From 1996, no literature accounts deal with the reactivity of such unsaturated ring systems. There is just one paper in which a 1,2-oxazetidine skeleton bearing an exocyclic double bond on the nitrogen, and activated toward a nucleophilic attack at the carbon C-4, has been postulated as a possible intermediate in a synthetic pathway (see below).

2.14.5.1 Nucleophilic Attack at Carbon

After nitration of α,β -unsaturated esters of type **38**, Shin *et al.* <1970BCJ3219, 1972BCJ3595> isolated α -hydroxy- β -nitro esters **39** and α -nitro- α,β -unsaturated esters **40** without commenting on the formation of these compounds. According to Murphy and co-workers <1997J(P1)1559>, a possible mechanism that may account for the formation of **39** involves a [2+2] cycloaddition of the nitronium ion to the alkene **38**, giving the four-membered system **41**, which after ring opening by water leads to the isolated β -nitro alcohol **39** (Scheme 11).



Scheme 11

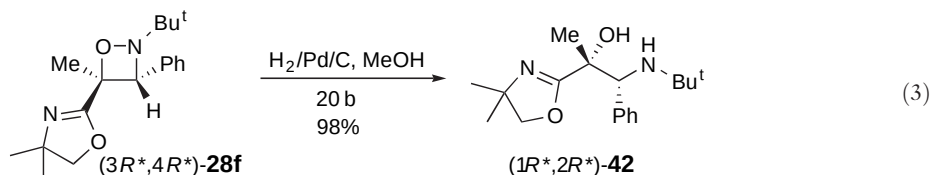
2.14.6 Reactivity of Nonconjugated Rings

2.14.6.1 Tetrahydro Derivatives

Little work has been performed on the reactivity of tetrahydrooxazetidines. The work on the reduction of the N–O bond, however, is certainly worth noting.

2.14.6.1.1 Reaction at surfaces

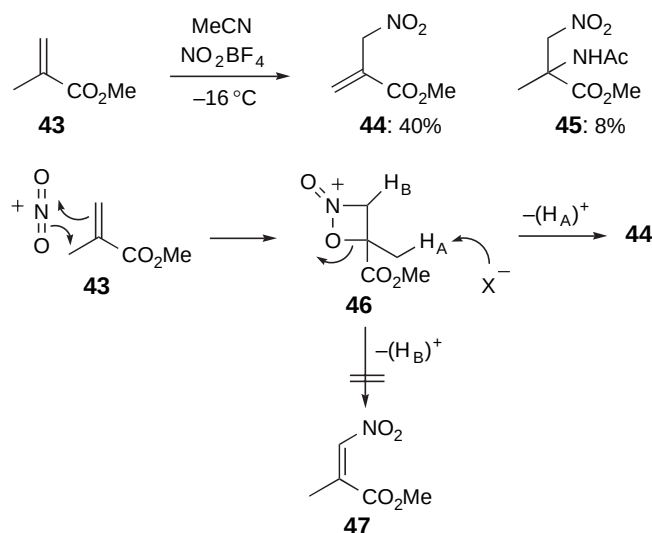
The functionalized oxazolinyl[1,2]oxazetidine **28f** has been transformed quantitatively with high stereoselectivity into the corresponding oxazolinyl- β -amino alcohol **42** (masked form of an α -hydroxy- β -amino acid) upon reduction with H_2 (20 b) on Pd/C (10 wt.%) (Equation 3) <2003JOC10187>.



2.14.7 Reactivity of Substituents Attached to Ring Carbon Atoms

There are no significant reports updating the reactivity of substituents attached to ring carbon atoms. To explain the formation of the allylic nitro compound **44** as the major product of the nitration of methyl methacrylate **43** (Scheme 12) versus nitroacetamide **45**, a plausible mechanism postulated by Murphy and co-workers

<1997J(P1)1559> featured the [2+2] cycloaddition between the nitronium ion and **43** leading to the cyclic cation **46**. Deprotonation may then occur from the exocyclic site H_A rather than the endocyclic site H_B, accounting for the formation of **44** rather than **47**.



Scheme 12

2.14.8 Reactivity of Substituents Attached to Ring Heteroatoms

There are no reports on the chemistry of possible substituents and their removal at both the oxygen and the nitrogen of the oxazetidine system.

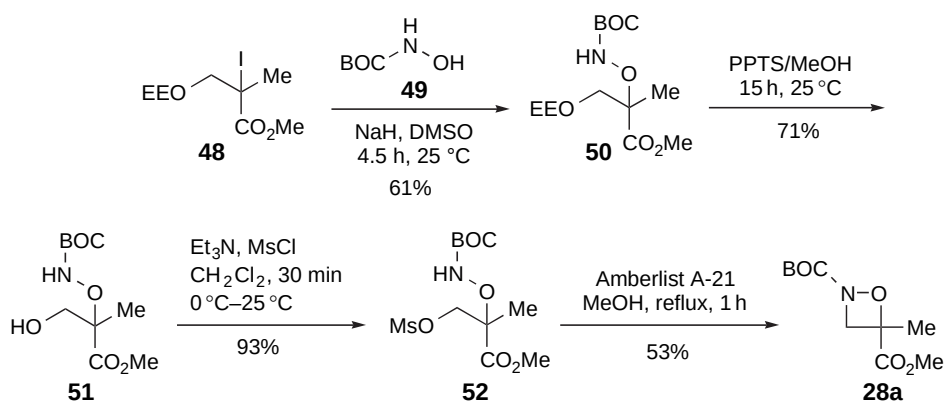
2.14.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

2.14.9.1 Ring Closure of a Single Component

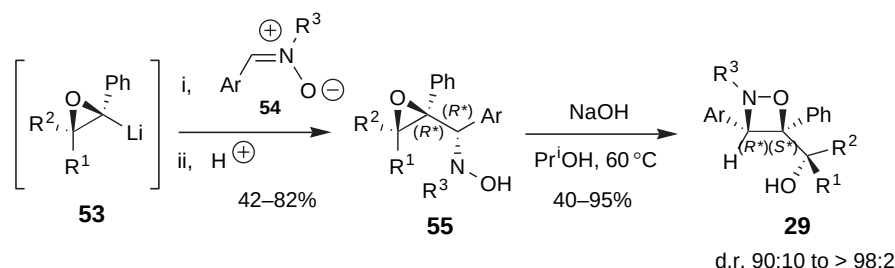
There have been relatively few updates on the synthesis of oxazetidines based on ring-closing reactions involving a single component and they are concerned neither with nucleophilic additions nor with nucleophilic substitutions by oxygen at nitrogen and vice versa. Indeed, intramolecular N-alkylations remain the most widely exploited synthetic method <1972JHC159> such as that recently reported by Snider and Duvall concerning the preparation of a 1,2-oxazetidine-4-carboxylate skeleton <2003TL3067>. *N*-BOC-1,2-oxazetidine **28a** has been prepared by a preliminary O-alkylation of *tert*-butyl-*N*-hydroxycarbamate **49** with iodo ester **48** to give the adduct **50**. Hydrolysis of the ethoxyethyl group of **50** afforded alcohol **51**, which was converted into the mesylate **52**. Treatment of **52** with a weakly basic ion-exchange resin (Amberlist A-21) in MeOH at reflux for 1 h, filtration through Celite, concentration, and flash chromatography afforded the desired oxazetidine **28a** in pure form (Scheme 13). The O-alkylation of tertiary halo ester **48** appears to proceed through an electron-transfer mechanism.

A simple, original, and efficient stereoselective synthesis of 4-hydroxyalkyl-1,2-oxazetidines **29** based on the addition of α -lithiated aryloxiranes **53** to aryl nitrones **54** and subsequent 4-*exo*-tet cyclization of the corresponding intermediates, which are β,γ -epoxyhydroxylamines **55**, has also been described (Scheme 14) <2006OL3923>.

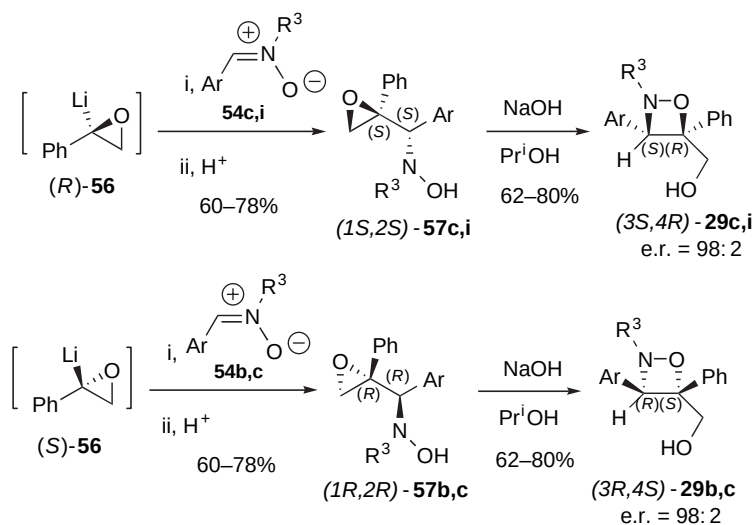
Optically active lithiated styrene oxides (*R*)- and (*S*)-**56** were also found to add to aryl nitrones **54b,c,i** with an excellent diastereo- and enantioselectivity leading to the formation of stereodefined hydroxylamines **57b,c,i** and further to 1,2-oxazetidines **29b,c,i** upon treatment with NaOH/*i*-PrOH (Scheme 15).



Scheme 13



Scheme 14



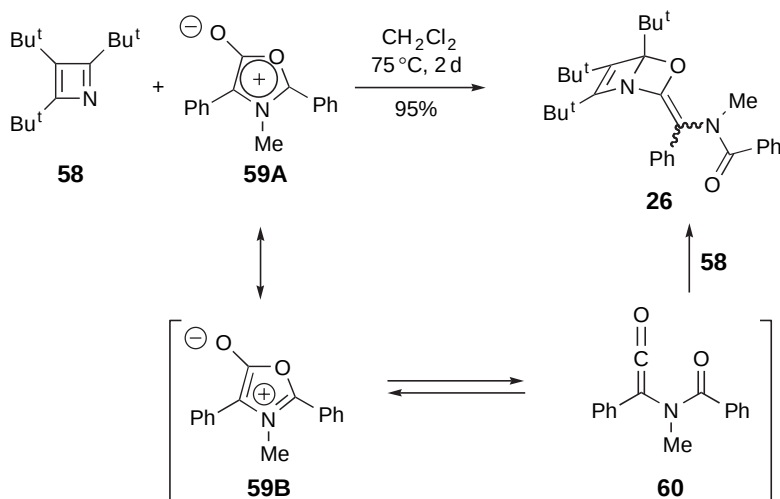
b: R^3 = cumyl, Ar = 2-furyl; c: R^3 = cumyl, Ar = 4-ClC₆H₄; i: R^3 = *t*-butyl, Ar = Ph

Scheme 15

2.14.9.2 Ring Formation from Two Components

[2+2] Cycloaddition is the most common source of 1,2-oxazetidine skeletons, but sometimes it is also useful to construct 1,3-oxazetidine rings. Indeed, in contrast to the usual reactivity exhibited by münchnones, which react with multiple bond systems as azomethine ylides by a [3+2] cycloaddition process, azete **58** was found to react with münchnone **59**, under thermal conditions, to give an isomeric mixture of the oxazabicyclo[2.2.0]hexene (*E/Z*)-**26**,

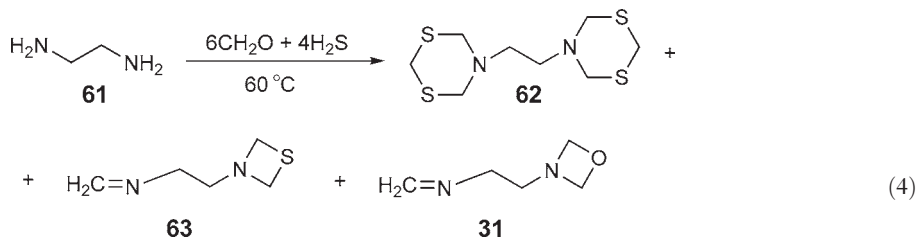
which could be purified but not separated by column chromatography (Scheme 16) <1997BSF927>. The formation of such bicyclic species at the sterically more accessible C/N edge of **58** was preceded by the electrocyclic ring opening of the münchnone (**59A** $\leftrightarrow$ **59B** $\rightarrow$ **60**) which reacted with **58**, via a cycloaddition reaction through its benzoylaminoketene form **60**. However, it should be mentioned that the reaction of diphenylketene with azete **58** is known to proceed by a [4(2)+2] cycloaddition at the carbonyl group <1997BSF927>.



Scheme 16

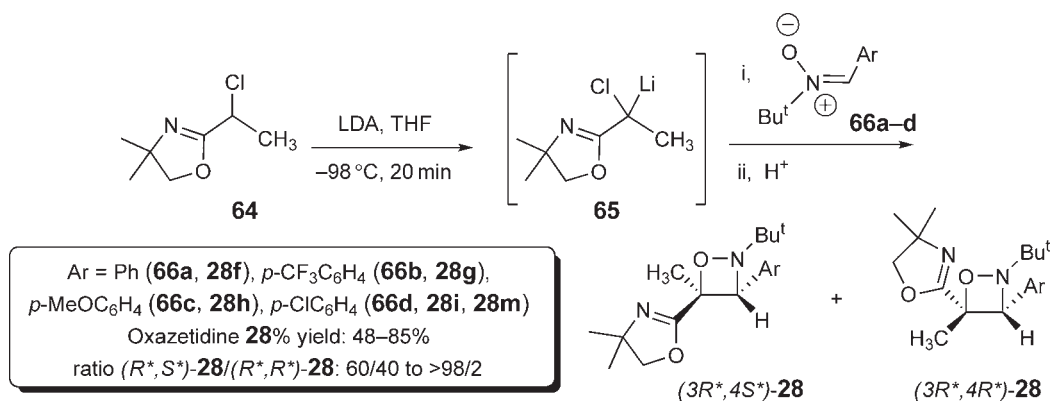
2.14.9.3 Ring Formation from Three Components

The thiomethylation of ethylenediamine **61**, performed by bubbling hydrogen sulfide through a mixture of the above diamine and formaldehyde at 60°C , gave the dithiazine **62** as the main product together with 1,3-thiazetidine **63** and 1,3-oxazetidine **31** as minor products in a 53:25:22 ratio (GC-MS data), respectively (Equation 4) <2005RCB432>. At 80°C , under the above conditions, the only products formed were **62** and **63** in a 90:10 ratio.



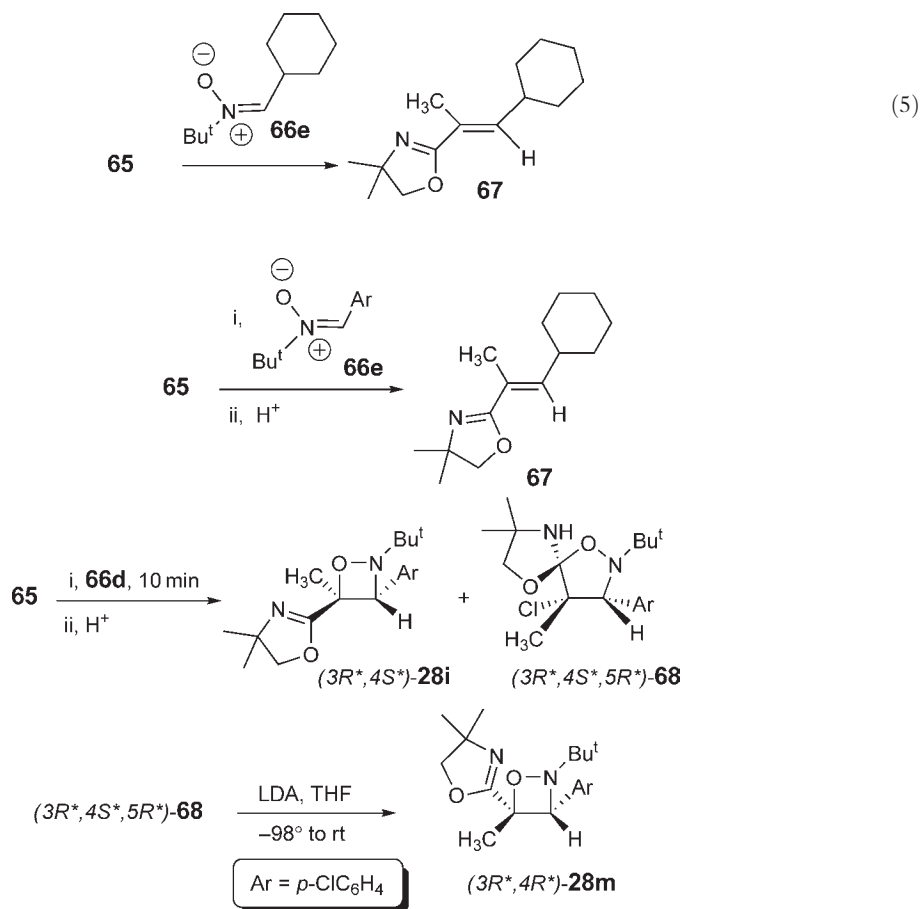
2.14.10 Ring Syntheses by Transformations of Another Ring

The first stereoselective synthesis of oxazolinyl[1,2]oxazetidines, based on the addition of easily available lithiated 2-(1-chloroethyl)-2-oxazolines to nitrones, has been reported <2003JOC10187>. Lithiation of 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline **64** with lithium diisopropylamide (LDA) at -98°C in tetrahydrofuran (THF) generated lithio derivative **65**, which proved to be quite stable. The addition of nitrones **66a–d**, followed by quenching with saturated aqueous NH_4Cl after 3 h, resulted in the diastereoselective formation of oxazolinyl[1,2]oxazetidines (R^*,S^*)-**28f–i** as the main products in quite good yields (48–55%) (Table 2; Scheme 17). Only in the case of the *p*-chlorophenyl-substituted nitron **66d** was an appreciable amount of the corresponding diastereomeric (R^*,R^*)-**28i** oxazetidine also isolated. The oxazetidine formation seems to be limited to aromatic nitrones. In the case of the reaction of lithio derivative **65** with nitron **66e**, the alkenyloxazoline **67** was the only product isolated (Equation 5). An investigation on the reaction mechanism revealed that spirocyclic compounds might be the precursors of oxazolinyl[1,2]oxazetidines from a sort of ring contraction as reported in a previous paper for similar systems <2002EJO2961>. Indeed, in the case of nitron **66d**,



Scheme 17

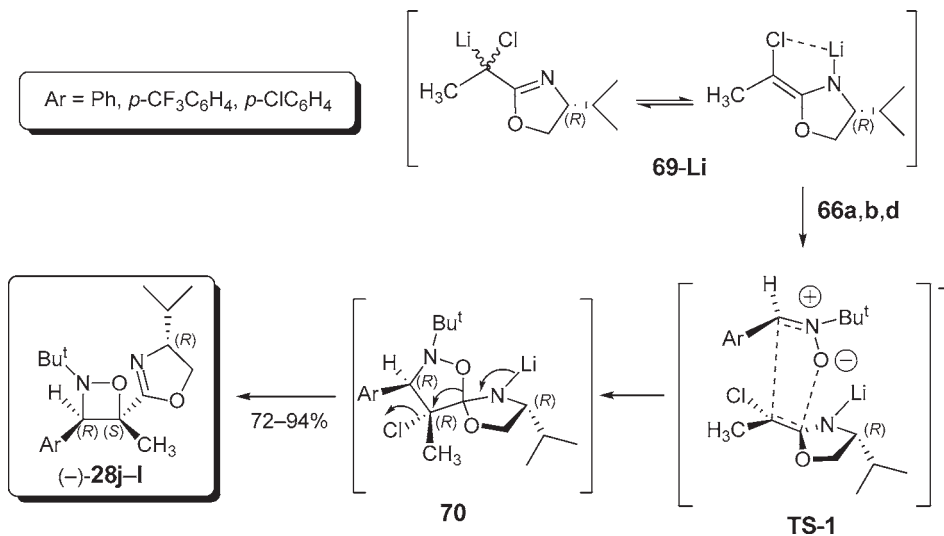
quenching the reaction mixture after a shorter time (10 min) resulted in the oxazetidine (*R*^{*},*S*^{*})-**28i** being formed together with the spirocyclic compound **68**; the latter was isolated and, upon treatment with LDA, was converted into the corresponding oxazetidine (*R*^{*},*R*^{*})-**28m**, proving the reaction stereospecificity (Scheme 18).



Scheme 18

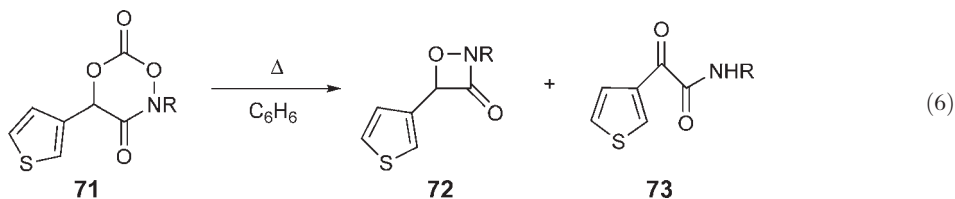
Interestingly, the reaction of a diastereomeric mixture of lithiated 2-(1-chloroethyl)-2-oxazolines such as (*4R*,1'*S*')/(*4R*,1'*R*')-**69-Li** with nitrones occurred with high enantioselectivity <2003JOC10187, 2004CUOC1529>. A plausible explanation might reside in the fact that **69-Li** probably exists as an azaenolate preferentially (*E*)-configured (due to the

internal chelation involving the chlorine atom and the lithium ion) and would be attacked by the nitrones **66a,b,d** on its *si*-face (the less sterically hindered diastereoface) via the transition state **TS-1** to give, through the corresponding lithiated spirocyclic compound **70**, the diastereo- and enantioenriched oxazolinyl[1,2]oxazetidines (–)-**28j-l** (Scheme 19).

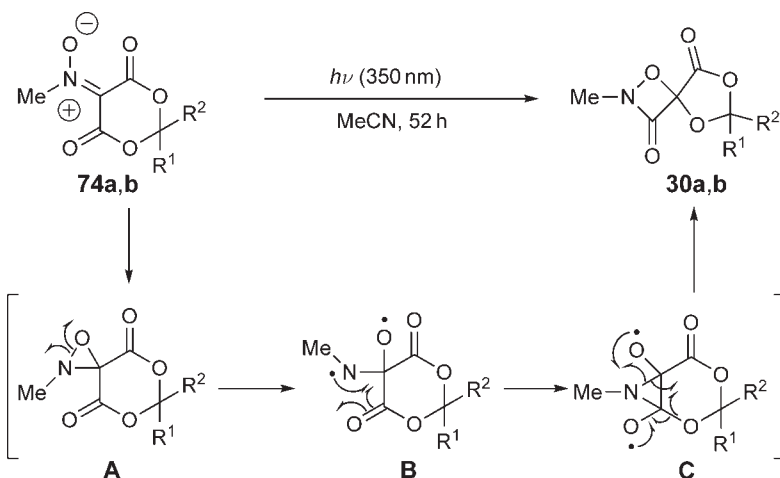


Scheme 19

Dioxazinanediones **71** (R = Me, PhCH₂) underwent a ring contraction based on thermal extrusion of CO₂ on refluxing in C₆H₆ to give 1,2-oxazetidin-3-ones **72** together with α-ketoamides **73** (Equation 6) <1984CZ293>.



Cyclic nitrones **74a** and **74b**, when irradiated by 350 nm rays in acetonitrile at room temperature for 52 h, gave spirocyclic 1,2-oxazetidin-3-ones **30a** and **30b** (85–90% yield) (Scheme 20). A mechanism for the formation of such compounds,



Scheme 20

under the above photochemical conditions, considered that the oxaziridine **A** would be formed first by irradiation of **74a** and **74b**; the former then undergoes radical cleavage to form **30a** and **30b** via intermediates **B** and **C** <1998H(47)383>.

No expansion of three-membered rings has been reported since 1996.

2.14.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

No accounts have been reported in the literature after 1996 describing the general synthesis of particular classes of oxazetidine derivatives with the exception of those described above.

2.14.12 Important Compounds and Applications

2.14.12.1 Medical Applications

FdUMP[10], a 10-mer of 5-fluoro-2'-deoxyuridine 5'-monophosphate (FdUMP), was found to be 338-fold more potent than 5-fluorouracil at inhibiting cell proliferation in the National Cancer Institute 60 cell-line screen. The 5-fluoro-2'-deoxyuridine derivative **75** (Figure 11) showed a Pearson correlation coefficient of 0.781 with regard to the other compounds with the highest correlation which ranked 237th among all the compounds/extracts deposited in the DTP database <2005MI4844>.

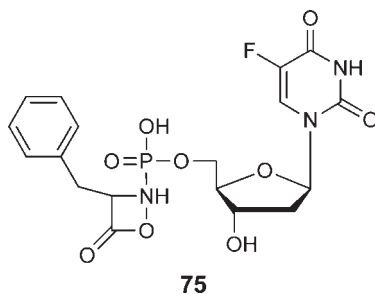


Figure 11 Chemical structure of an FdUMP[10] derivative.

2.14.12.2 Miscellaneous Applications

Low-dielectric-constant films used as interlayer insulation with low dielectric constant, low hygroscopic characteristic, and high temperature resistance were synthesized starting from 3,3'-(1,4-phenylene)bis(1,3-oxazetidine-2,4-dione) <2001JPP2001237241>. Photosensitive polyimide materials for electronic packaging applications have been synthesized by mixing a specified polyimide precursor with a solution of methacrylamide and the catalytic system obtained combining a photoinitiator, a co-initiator, a cationic photoinitiator, and an oxygen scavenger. One of the above materials employed, as a photoinitiator, a 1,3-oxazetidine derivative photosensitive to light with a maximum wavelength of 300 nm <1998USP5756648>. Due to the use of a surface containing sulfate-reducing bacteria in oil fields, the highly toxic and corrosive H₂S can be found in petroleum. Use of a 70% aqueous solution of 1-hydroxy-2-(1,3-oxazetidine-3-yl)ethane (synthesized from paraformaldehyde and monoethanolamine), weakly soluble in petroleum and with good anticorrosion properties, was proposed either for suppression of sulfate-reducing bacteria, or to remove H₂S and mercaptans from gases, crude oil, and petroleum products <2005MI84, 2004RUP2241684, 2003MI15, 2003MI24, 2001RUP2173735>.

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Biographical Sketch



Vito Capriati was born in Bari, Italy, in 1965. He received his degree in chemistry and pharmaceutical technology (with honors) at the University of Bari in 1990 with a two-year experimental thesis in the field of synthetic organic chemistry. In January 1992, after his national service in the Centro Carabinieri Investigazioni Scientifiche in Rome, now known as Reparto Investigazioni Scientifiche (RIS), he returned to the University of Bari where he worked as a fellow in the Centre on Metodologie Innovative di Sintesi Organiche, now Istituto di Chimica dei Composti Organometallici, under the supervision of Prof. Francesco Naso, until December 1993. In 1994, he became assistant professor and joined Prof. Saverio Florio's research group at the Dipartimento Farmaco-Chimico of the University of Bari working in the field of organometallic chemistry, and in 2002 he was appointed associate professor of organic chemistry at the same university. In 2001, he was visiting scientist at the Ohio State University (Columbus, OH, USA) and in 2003 at the Göteborg University (Sweden) working in the field of $^6\text{Li}/^{13}\text{C}$ NMR spectroscopy applied to the study of anionic species in solution. His current research interests revolve around organolithium chemistry, mechanistic studies, asymmetric synthesis of small-ring functionalized heterocycles and stereochemical determination of their relative and absolute configurations, multinuclear NMR investigations on highly reactive organic intermediates, such as oxiranyllithiums, their structures and dynamic behavior.



Renzo Luisi was born in Luxembourg (EU) in 1971. After high-school graduation in 1990, he worked as an analytical chemist for a wine company until 1994. In 1996, he received his degree (with honors) in chemistry and pharmaceutical technology at the University of Bari, and in 2000 he was awarded a Ph.D. in chemical sciences at the University of Bari under the supervision of Prof. Saverio Florio. In 1999, he was visiting scholar at the University of Illinois, spending seven months in Prof. Peter Beak's group. In 2001, after a seven-month fellowship at the Consorzio Interuniversitario sulle Metodologie e Processi Innovativi di Sintesi of the University of Bari, he became assistant professor

at the same university and joined the permanent staff of Prof. Saverio Florio's research group. In January 2005, he was appointed associate professor of organic chemistry at the University of Bari. His current research interests are focused on organolithium chemistry, chemical reactivity of metalated heterocycles and their applications in asymmetric synthesis, and multinuclear NMR techniques aimed at solving mechanistic and stereochemical problems.



Saverio Florio received his 'Laurea' in chemistry at the University of Bari (Italy) and started his academic career there, first as assistant professor (1969) and then as associate professor of organic chemistry (1982). In 1986, he was appointed full professor of organic chemistry at the University of Lecce. In 1990, he returned to the University of Bari and joined the Faculty of Pharmacy as full professor of organic chemistry. His research interests include work in the field of aromatic and heteroaromatic substitution, synthesis and reactivity of heterocyclic compounds, the use of oxiranyl and aziridinyli anions in synthesis, organometallic chemistry, and asymmetric synthesis. Prof. Florio has supervised many dozens of undergraduate and Ph.D. students and published more than 150 papers in international journals. He has been president of the Division of Organic Chemistry of the Italian Chemical Society (1997–2001) and is director of the Consorzio Interuniversitario sulle Metodologie e Processi Innovativi di Sintesi since its institution (1994). Prof. Florio is member of the Board of Consulting Editors of *Tetrahedron* and *Tetrahedron Letters* and member of the Organizing Committee of the International IASOC School. He has been recently awarded with the Ziegler–Natta Lecture for 2004 by the German Chemical Society and with the Gold Medal 'A. Mangini' for 2007 by the Organic Chemistry Division of the Italian Chemical Society.

2.15

Four-membered Rings with One Sulfur and One Nitrogen Atom

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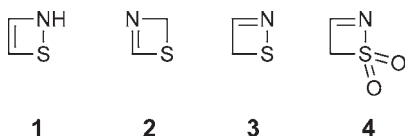
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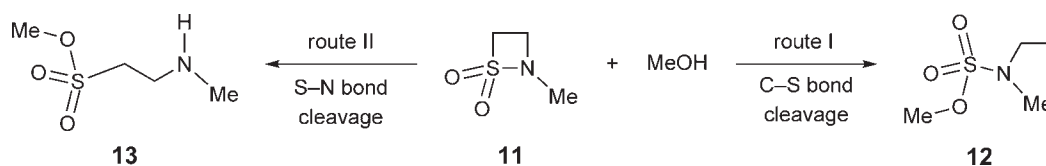
2.15.1 Introduction

Four-membered rings containing one sulfur and one nitrogen atom can be classified under two headings:

1. Unsaturated rings such as 2*H*-1,2-thiazetes **1**, 2*H*-1,3-thiazetes **2**, 4*H*-1,2-thiazetes **3**, 4*H*-1,2-thiazete 1,1-dioxides **4**:



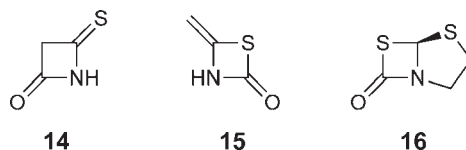
(DFT) at the HF/6-31G* and the B3LYP/6-31G* levels considering the cleavage of S–N and C–S bonds. It was concluded that the nonassisted alcoholysis mechanism of β -sultam **11** proceeds via two routes (Scheme 2). Route I involves C–S bond cleavage and produces sulfonate **12** in a mechanism in which attack of methanol and C–S bond cleavage are concerted. Route II involves cleavage of the S–N bond producing 2-(*N*-methyl) taurine methyl ester **13** by two reaction modes with either a concerted or a stepwise mechanism. In the concerted pathway, the reactant complex directly leads to product **13** through a single transition state in which the methoxy group and the hydrogen from methanol attack the sulfur and nitrogen atoms, respectively, on the β -sultam ring, with concomitant cleavage of the S–N bond. Consequently, the nucleophilic attack and cleavage of the S–N bond occur simultaneously. In the second pathway, the reaction takes place via two steps: first, proton transfer from methanol to the sulfonyl oxygen, and then proton transfer from the sulfonyl oxygen to the nitrogen atom and then ring opening. The energy barrier for the opening of the C–S bond is $230.8 \text{ kJ mol}^{-1}$, which is about 100 kJ mol^{-1} higher than that for the opening of the S–N bond [2003CPL13, 2004JMT199]. The results also show that water- and alcohol-assisted alcoholysis mechanisms are similar to the non-water- and non-alcohol-assisted ones. However, reactions which are alcohol assisted have a slightly higher energy barrier than the water-assisted hydrolysis in the case of compound **11** [2004PCA7702, 2005MI661].



Scheme 2

2.15.2.4 1,3-Thiazetidines

Cycloaddition reactions of thioketene and isocyanic acid forming four-membered ring products have been studied by means of the *ab initio* RHF/6-31G* method. The two alternative reactions are concerted but nonsynchronous, taking place through twisted or planar four-membered cyclic transition states. The activation barriers were calculated to be $150.4 \text{ kJ mol}^{-1}$ and $109.9 \text{ kJ mol}^{-1}$ for formation of β -lactam **14** and 1,3-thiazetidine **15**, respectively, indicating that the second reaction is favored [1999MI108]. The alkaline hydrolysis of thio- β -lactam **15** in the gas phase was examined by means of *ab initio* RHF and DFT calculations. The tetrahedral intermediate was found to be unstable, so the compound evolves directly into the corresponding thioazetidin-2-one via C–S bond cleavage. The stable five-membered ring product obtained by hydrolysis suggests that thio- β -lactam **16** may be an effective inhibitor for β -lactamases [1999JMT287, 2000CPL304].



2.15.3 Experimental Structural Methods

2.15.3.1 X-Ray Crystallography

2.15.3.1.1 4*H*-1,2-Thiazete 1,1-dioxides

The first X-ray crystallographic analysis of the 1,2-thiazete 1,1-dioxide derivative **17** has been described and indicates the presence of two independent molecules A and B in the asymmetric unit (monoclinic, $P2_1/n$ space group) (Tables 1 and 2). The *N*-phenylimino group had (*E*)-geometry across the C=N bond and appeared to be nearly planar in molecule A with a torsion angle of -4.4° , while in molecule B the planarity was lost with a torsion angle of 25.9° [1996T7183]. Crystallographic data of compound **18** showed that the exocyclic C–N bond was significantly shorter ($1.317(2) \text{ \AA}$) (compared with an average value of $1.355(14) \text{ \AA}$ for this kind of bond in the literature) suggesting the

existence of significant conjugation in the amidine moiety. This hypothesis is supported by the marked planarity observed around the nitrogen atom of the diethylamino substituent <2002T5173>.

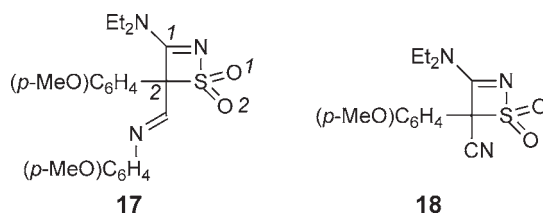


Table 1 X-Ray structure-derived bond lengths (Å) of molecules A and B of the 1,2-thiazete- 1,1-dioxide derivative **17** <1996T7183>

	S–O(1)	S–O(2)	S–N	N=C(1)	C(1)–C(2)	C(2)–S
A:	1.431(3)	1.433(3)	1.652(5)	1.331(8)	1.534(7)	1.877(6)
B:	1.441(4)	1.438(4)	1.647(6)	1.328(8)	1.533(10)	1.866(5)

Table 2 X-Ray structure-derived bond angles (°) of molecules A and B of the 1,2-thiazete 1,1-dioxide derivative **17** <1996T7183>

	<i>Molecule A</i>	<i>Molecule B</i>
O(1)–S–O(2)	117.0(2)	117.4(3)
O(1)–S–N	112.7(2)	113.7(3)
O(2)–S–N	112.3(2)	111.8(2)
O(1)–S–C(2)	113.7(2)	113.5(2)
O(2)–S–C(2)	115.1(2)	114.2(2)
N–S–C(2)	80.7(2)	80.9(2)
N–C(1)–C(2)	106.0(5)	105.8(6)
S–C(2)–C(1)	79.2(3)	79.4(3)
S–N–C(1)	94.0(3)	93.9(4)

2.15.3.1.2 1,2-Thiazetidines

Bond lengths and bond angles from the X-ray crystal structure of 1,2-thiazetidine **19** (monoclinic, $P2_1/c$ space group) are shown in **Table 3**. The C–S (1.874 Å) and S–N (1.791 Å) bond lengths in the 1,2-thiazetidine ring are much longer than the C–S (1.761–1.780 Å) and S–N (1.642–1.698 Å) bond lengths in the corresponding 1,2-thiazetidine 1,1-dioxides. Moreover, the 1,2-thiazetidine ring presents a puckered conformation with a torsion angle of 30.8° and C–C–S–N dihedral angle of 19.6° <2003JA8255>.

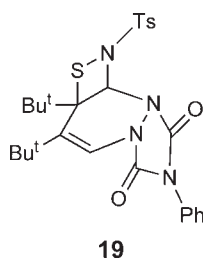
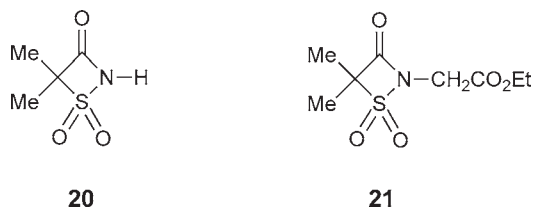


Table 3 X-Ray crystallographic data of 1,2-thiazetidine **19** <2003JA8255>

Bond length (Å)				Bond angle (°)			
S–N	C–N	C–S	C–C	C–N–S	N–S–C	S–C–C	N–C–C
1.791(4)	1.490(5)	1.874(4)	1.533(7)	90.7(3)	76.8(2)	86.3(2)	97.7(3)

2.15.3.1.3 1,2-Thiazetidine 1,1-dioxides

Information on the geometry of 1,2-thiazetidin-3-one 1,1-dioxides has been obtained by single crystal X-ray diffraction (**Table 4**). The four-membered ring of 4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxide **20** (monoclinic, $C2/c$ space group) is almost planar with intra-annular torsion angles between $-3.3(1)^\circ$ and $3.6(1)^\circ$. The carbonyl oxygen atom slightly deviates from the plane of the ring. The methyl groups are nearly perfectly eclipsed with the oxygen atoms of the sulfonyl group. The short C–N bond (1.366(2) Å) and the planarity of the nitrogen indicate delocalization of the lone pair on nitrogen within the lactam group. Moreover, the NH group forms an intermolecular hydrogen bond with the carbonyl group of a neighboring molecule (N $\cdots$ O distance: 2.857(2) Å and N–H $\cdots$ O angle : $158(2)^\circ$). These interactions associate molecules into dimeric units related by a center of inversion <1996HCA2067>. The structure of *N*-benzyl-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxides has also been established by X-ray crystallography (monoclinic, $P2_1/c$ space group) <1999HCA354>. Whereas crystallographic analysis shows that β -sultams are folded structures (the angle between the planes defined by S–N–C(4) and N–C(3)–C(4) lies between 13° and 23°), crystallographic analysis of 2-[(ethoxycarbonyl)methyl]-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxides **21** (orthorhombic, P_{bca} space group) shows a completely planar four-membered ring as a result of better mesomeric stabilization <1997HCA671>. Single crystal X-ray analysis of (3*R*)-*N*-*t*-butyl-3-(2-chlorophenyl)thiazetidine 1,1-dioxides (monoclinic, $P2_1/a$ space group) confirmed the absolute configuration <1999T14089>.

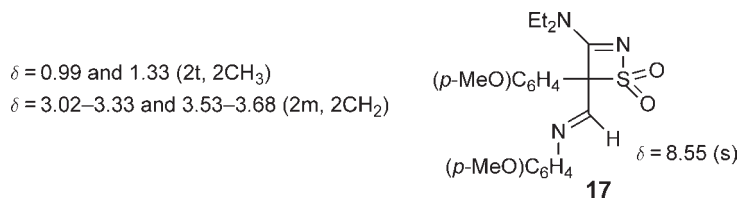
Table 4 X-Ray crystallographic data of 1,2-thiazetidin-3-one 1,1-dioxides **20** and **21**

Compound	Bond length (Å)				Bond angle (°)				Reference
	S–N	C(3)–N	C(4)–S	C(3)–C(4)	C(3)–N–S	N–S–C(4)	S–C(4)–C(3)	N–C(3)–C(3)	
20		1.366(2)			96.3(1)	78.75(7)	84.8(1)	100.0(1)	1996HCA2067
21	1.677(3)	1.360(5)	1.823(4)	1.539(6)	96.6(2)	78.7(1)	84.8(2)	99.9(3)	1997HCA671

2.15.3.2 ^1H NMR Spectroscopy

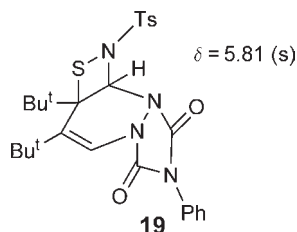
2.15.3.2.1 4*H*-1,2-Thiazete 1,1-dioxides

A striking feature in the ^1H nuclear magnetic resonance (NMR) spectrum of compound **17** was the complexity of the signals associated with the diethylamino group, evidencing the magnetic nonequivalence of the chemically identical hydrogens. This points to a rotational barrier about the C–N bond, which can be explained by extensive conjugation of the amidine system incorporated in the heterocyclic ring <1996T7183>.



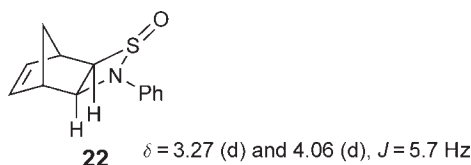
2.15.3.2.2 1,2-Thiazetidines

When the 1,2-thiazetidine ring is fused in a *cis*-manner to a six-membered ring as in compound **19**, the ^1H NMR spectrum shows a downfield singlet at 5.81 ppm for the bridgehead proton <2003JA8255>.



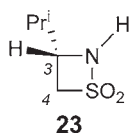
2.15.3.2.3 1,2-Thiazetidine S-oxides

The protons in the 1,2-thiazetidine S-oxide ring **22** appear as a pair of doublets as expected for *cis*-coupling in a four-membered ring, but significantly they are not coupled to the vicinal bridgehead protons of the norbornene component thereby confirming the *exo*-fusion <1997SL167>.

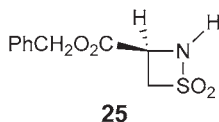


2.15.3.2.4 1,2-Thiazetidine 1,1-dioxides

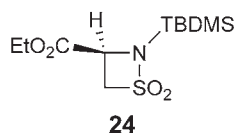
^1H NMR spectra of 3-substituted β -sultams **23–26** are described as ABM(X) systems originating from the protons H-3, H-4, and H-4' <1997LA1261, 2004HCA90>.



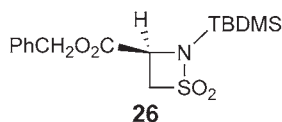
H-3: δ = 3.29 (m)
 H-4 and H-4': δ = 3.89 and 4.18
 J_{AB} = 12.6 Hz, J_{AM} = 11.6 Hz, J_{BM} = 6.1 Hz
 NH: δ = 5.40 (s)



H-3: δ = 4.15 (dd, J = 10.2 and 2.0 Hz)
 H-4 and H-4': δ = 4.32 (dd, J = 13.0 and 2.0 Hz)
 δ = 4.57 (dd, J = 13.0 Hz and 10.2 Hz)



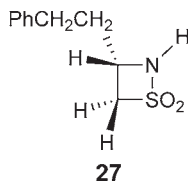
H-3: δ = 4.15 (dd, J = 4.0 and 8.0 Hz)
 H-4 and H-4': δ = 4.30 (dd, J = 12.0 and 4.0 Hz)
 δ = 4.55 (dd, J = 12.0 and 8.0 Hz)



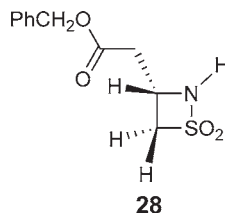
H-3: δ = 4.07 (dd, J = 11.0 and 2.0 Hz)
 H-4 and H-4': δ = 4.18 (dd, J = 13.0 Hz and 2.0 Hz)
 δ = 4.43 (dd, J = 13.0 Hz and 11.0 Hz)

When a methylene group is introduced at C-3 as for compounds **27–29**, the ^1H NMR spectrum is characterized by the superposition of two ABX(M) systems. The first originates from the protons H-3, H-4, and H-4', and the second one belongs to the protons of the methylene group at C-3 (numbered as H-5 and H-5') and H-3 of the β -sultam ring

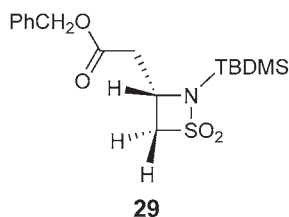
<2002TL5109>. Characteristic coupling constants for compound **29** determined by decoupling experiments are $J_{5,5'} = 16.8$, $J_{4,4'} = 12.2$, $J_{3,4} = 5.5$, $J_{3,4'} = 7.0$, $J_{3,5} = 5.9$, and $J_{3,5'} = 7.6$ Hz <2004M979>.



H-3: $\delta = 3.59$ (m)
 H-4 and H-4': $\delta = 3.81$ (dd, $J = 5.5$ and 12.6 Hz)
 $\delta = 4.22$ (ddd, $J = 3.3$, 7.7 and 12.6 Hz)
 H-5 and H-5': $\delta = 2.67$ (m)
 NH: $\delta = 5.50$ (s)

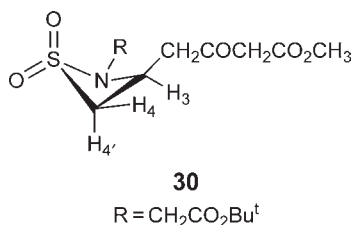


H-3: $\delta = 4.02$ (m)
 H-4 and H-4': $\delta = 3.89$ – 4.01 (ddd, $J = 0.7$, 4.9 , and 12.2 Hz)
 $\delta = 4.36$ (ddd, $J = 3.3$, 7.3 , and 12.2 Hz)
 H-5 and H-5': $\delta = 2.82$ (dd, $J = 5.9$ and 16.8 Hz)
 $\delta = 2.89$ (dd, $J = 7.6$ and 16.8 Hz)
 NH: $\delta = 5.65$ (s)

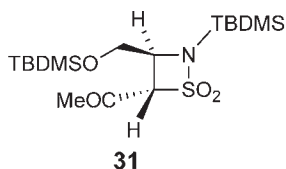


H-3: $\delta = 3.96$ (m)
 H-4 and H-4': $\delta = 3.95$ (dd, $J = 3.7$ and 13.4 Hz)
 $\delta = 4.39$ (ddd, $J = 1.5$, 9.0 , and 13.4 Hz)
 H-5 and H-5': $\delta = 2.81$ (ddt, $J = 2.0$, 10.0 , and 16.4 Hz)
 $\delta = 2.94$ (dd, $J = 3.9$ and 16.4 Hz)

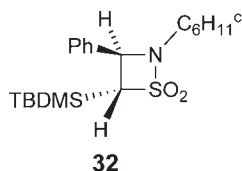
A pseudoequatorial orientation of the protons has been deduced from the ^1H NMR spectrum of β -sultam **30** which is characterized by an ABX system due to the ring protons H3 (A), H-4_{trans} (B), and H-4'_{cis} (X) with coupling constants ($J_{AB} = 6$, $J_{AX} = 8.25$ and $J_{BX} = 12.5$ Hz). The protons of the methylene group at C-3 show a geminal coupling of $J = 15.8$ Hz, and couplings with H-3 of $J = 6$ and 7.5 Hz, while the coupling constant of the methylene protons next to the nitrogen is $J = 18$ Hz <2004M55>.



The ^1H NMR spectrum of the 3,4-disubstituted β -sultam **31** is evidently simplified <2004HCA90>. Configurations of (3*R*, 4*S*)-4-monosilyl β -sultam **32** have been determined from the ^1H NMR spectrum which shows a pair of doublets at 3.80 and 4.08 ppm with a coupling constant of 7.3 Hz due to the H-3 and H-4 protons, respectively, and in agreement with the *trans*-geometry <1998CPB757>.

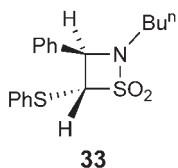


H-3: $\delta = 3.60$ (ddd, $J = 4.0, 5.0, 6.0$ Hz)
 H-4: $\delta = 3.86$ (d, $J = 4.0$ Hz)

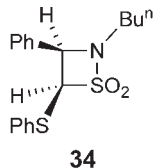


H-3: $\delta = 3.80$ (d, $J = 7.3$ Hz)
 H-4: $\delta = 4.08$ (d, $J = 7.3$ Hz)

The stereochemistry of 3-substituted-4-sulfonyl β -sultams **33** and **34** has also been determined from the coupling constant between the protons H-3 and H-4. In general, *cis*-isomers show greater coupling constants than *trans*-isomers by 1.5–2.0 Hz [\[1998JOC8355\]](#).

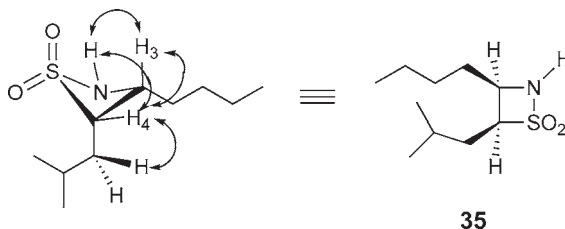


H-3: $\delta = 3.86$ (d, $J = 6.8$ Hz)
 H-4: $\delta = 4.69$ (d, $J = 6.8$ Hz)



H-3: $\delta = 4.69$ (d, $J = 8.3$ Hz)
 H-4: $\delta = 5.65$ (d, $J = 8.3$ Hz)

The *cis*-configuration of the (3*R*,4*S*)-3,4-disubstituted β -sultam **35** was proven by a nuclear Overhauser effect (NOE) experiment. Irradiation of the proton at C-4 showed a strong NOE with the proton at C-3. No interaction was observed between the proton at C-3 with the alkyl side chain at C-4 and the proton at C-4 showed no NOE effect with the alkyl side chain at C-3. Furthermore, the coupling constant between the protons at C-3 and C-4 ($J = 8.4$ Hz) indicates the *cis*-configuration [\[2005SI807\]](#).

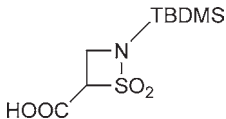
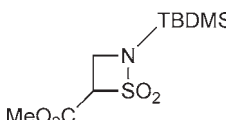
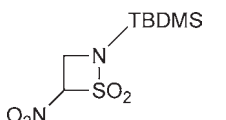


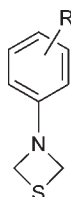
The ^1H NMR spectra of 4-monosubstituted β -sultams **36–38** show an AB(M)X system for H-C(4) and H-C(3). When the substituent at C-4 is an electron-withdrawing group (EWG), the signal for one proton at C-3 shows a significant downfield shift which can be ascribed to the anisotropy effect of the substituent at C-4 on the vicinal proton in the *cis*-position, the *trans*-proton being almost unaffected ([Table 5](#)). This is in agreement with the coupling constants $J_{3',4} = J_{cis} = 7\text{--}8$ Hz, and $J_{3,4} = J_{trans} = 4\text{--}5$ Hz, and with the postulate of a favored pseudoequatorial orientation for the substituent at C-4 [\[2004HCA1574\]](#).

2.15.3.2.5 1,3-Thiazetidines

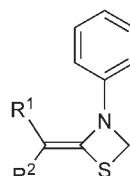
The ^1H NMR chemical shifts of the CH_2 singlet in the *N*-aryl-1,3-thiazetidines **39** are slightly dependent on the nature and position of the substituent of the *N*-aryl group [\[2003RCB1817\]](#). The introduction of 2-ylidene, methyl cyanoacetate, malononitrile, or dimethyl malonate groups onto products **40** [\[2005MI499\]](#) causes a weak downfield shift of the methylene protons when compared to analogous compounds **41** 2-substituted with an arylsulfonylimino group [\[2002SUL105\]](#). The ^1H NMR spectrum of the biheterocyclic triazepine **42** was also described [\[1997TL2087\]](#).

Table 5 Chemical shifts (CDCl₃, in ppm) and constant coupling (in Hz) of 4-substituted β -sultams

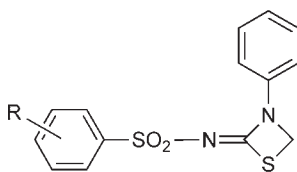
Compound	H'-C(3)	H-C(3)	H-C(4)	<i>J</i> (3,3')	<i>J</i> (3',4)	<i>J</i> (3,4)
 36	3.47	3.65	5.25	6	8	5
 37	3.44	3.67	5.18	5.7	7.5	4.5
 38	3.69	3.94	6.42	8	7	4

**39**

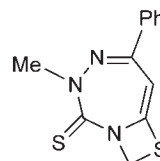
R = 3-Me; δ_{CH_2} = 4.87
 R = 4-Me; δ_{CH_2} = 5.04
 R = 4-OMe; δ_{CH_2} = 4.63

**40**

R¹ = CN; R² = CO₂Me; δ_{CH_2} = 5.17 (s)
 R¹ = CN; R² = CN; δ_{CH_2} = 5.18 (s)
 R¹ = CO₂Me; R² = CO₂Me; δ_{CH_2} = 5.03 (s)

**41**

R = 4-Me; δ_{CH_2} = 4.90 (s)
 R = H; δ_{CH_2} = 4.93 (s)
 R = 2-Me; δ_{CH_2} = 4.92 (s)

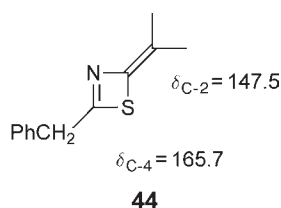
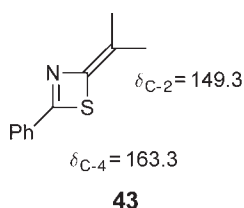
**42**

δ_{CH_2} = 5.31 (s)

2.15.3.3 ¹³C NMR spectroscopy

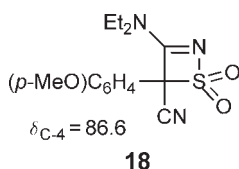
2.15.3.3.1 2*H*-1,3-Thiazetes

Characteristic ¹³C NMR chemical shifts of (2-propylidene)-2*H*-1,3-thiazete derivatives **43** and **44** have been described <1998PJC1915>.



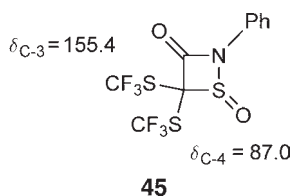
2.15.3.3.2 4*H*-1,2-Thiazete 1,1-dioxides

The presence of a signal associated with a quaternary carbon at $\delta = 86.6$ ppm is the main feature of the 4*H*-1,2-thiazete 1,1-dioxide derivatives **18** <2002T5173>.



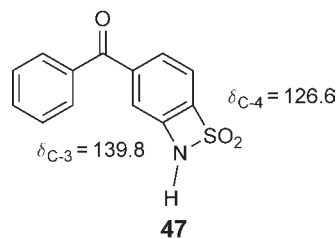
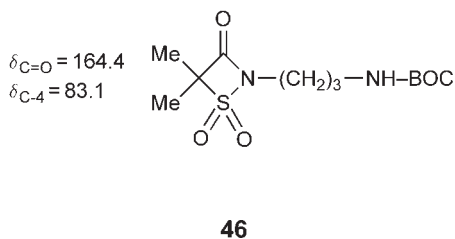
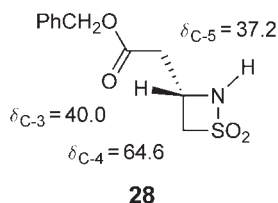
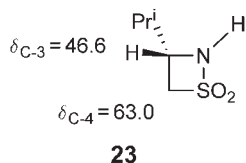
2.15.3.3.3 1,2-Thiazetidine *S*-oxide

Characteristic ^{13}C NMR chemical shifts of the 1,2-thiazetidine-3-one *S*-oxide **45** have been described <1998JFC9>.



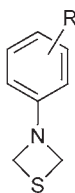
2.15.3.3.4 1,2-Thiazetidine 1,1-dioxides

Characteristic ^{13}C NMR chemical shifts of the 3-substituted β -sultams **23** and **28** <2004HCA90, 2004M979>, 4,4-disubstituted-1,2-thiazetidin-3-one 1,1-dioxide **46** <1996HCA2067, 1999HCA354> in CDCl_3 , and fused aryl β -sultam derivative **47** in CD_3COCD_3 have been described <2002JPH109>.

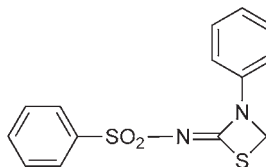


2.15.3.3.5 1,3-Thiazetidines

^{13}C NMR chemical shifts for substituted *N*-phenyl-1,3-thiazetidines **39** and **41** have been reported <2003RCB1817, 2002SUL105>.

**39**

R = 3-Me; $\delta_{\text{CH}_2} = 56.7$
 R = 4-Me; $\delta_{\text{CH}_2} = 56.5$
 R = 4-OMe; $\delta_{\text{CH}_2} = 57.3$

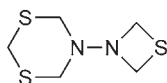
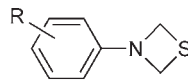
**41**

$\delta_{\text{CH}_2} = 48.6$
 $\delta_{\text{C=N}} = 162.7$

2.15.3.4 Mass Spectrometry

2.15.3.4.1 1,3-Thiazetidines

1,3-Thiazetidine derivative **48** has been characterized by electronic impact ionization (70 eV) with a molecular ion peak $\text{M}^{+\cdot}$ ($m/z = 194$) and fragmentation ion peaks for $[\text{M}-\text{CH}_2\text{S}]^{+\cdot}$, $[\text{M}-\text{CH}_2\text{SCH}_2\text{S}]^{+\cdot}$, $[\text{M}-\text{CH}_2\text{SCH}_2]^{+\cdot}$ as the base peak ($m/z = 102$), $[\text{M}-\text{CHSCH}_2]^{+\cdot}$, $[\text{M}-\text{C}_2\text{H}_4\text{S}_3]^{+\cdot}$, $[\text{M}-\text{C}_2\text{H}_4\text{N}_2]^{+\cdot}$, and $[\text{M}-\text{C}_2\text{H}_4\text{S}_3]^{+\cdot}$ <2006RJO145>. *N*-Phenyl-1,3-thiazetidine derivatives **39** have been characterized by their molecular ion peaks $\text{M}^{+\cdot}$ and fragmentation ion peaks for $[\text{M}-\text{S}]^{+\cdot}$, $[\text{M}-\text{CH}_2\text{S}]^{+\cdot}$, $[\text{M}-\text{CH}_2\text{SCH}_2]^{+\cdot}$, and $[\text{M}-\text{NCH}_2\text{SCH}_2]^{+\cdot}$ <2003RCB1817>.

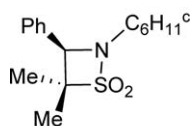
**48****39**

R = 3-Me, 4-Me, 4-OMe

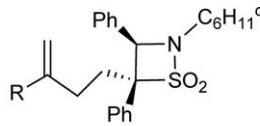
2.15.3.5 IR Spectroscopy

2.15.3.5.1 1,2-Thiazetidine 1,1-dioxides

The infrared (IR) spectrum of a β -sultam ring features a strong C-H stretching band at 3050 cm^{-1} , as well as strong absorptions at 1330 and 1165 cm^{-1} due to the SO_2 group. For compounds not substituted on nitrogen, the IR spectra exhibit an N-H band between 3250 and 3260 cm^{-1} <1997LA1261>. The IR spectra of *N*-acylated β -sultams show a shift of 20 cm^{-1} to higher wave numbers for the sulfonyl bands and they are also characterized by C-H bands around 3040 cm^{-1} <2004M55>. The IR spectra of 4,4-dimethyl-*N*-cyclohexyl β -sultam derivative **49** showed the absorption band for the SO_2 group at 1125 cm^{-1} and a shift to higher wave numbers (1140 – 1160 cm^{-1}) was observed for 3,4-diphenyl analogues **50** and **51** <1998T8941>.

**49**

$\nu = 1125\text{ cm}^{-1}$

**50: R = H****51: R = Me**

$\nu = 1140$ – 1160 cm^{-1}

The IR spectra of β -sultams are characterized by the bands due to the SO_2 group at 1340 – 1295 ($\text{SO}_{2\text{as}}$) and 1200 – 1140 cm^{-1} ($\text{SO}_{2\text{sym}}$), depending on the substituents (Table 6). The data for both bands for the C-3 and C-4 unsubstituted *N*-silyl compounds show a shift to higher wave numbers compared with the data for the *N*-benzoyl analogue. The data for the 4-substituted derivatives usually show no or only a small shift of both bands. Nevertheless,

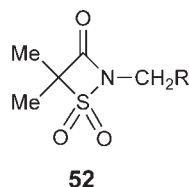
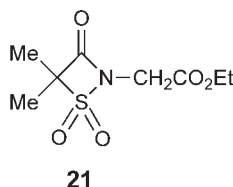
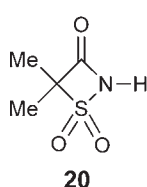
when the substituent at C-4 is an EWG, the shift to higher wave numbers of $\nu(\text{SO}_{2\text{as}})$ is relatively small (0–30 cm^{-1}), but the shift of $\nu(\text{SO}_{2\text{sym}})$ increases by 60 cm^{-1} <2004HCA1574>.

Table 6 IR data for the sulfonyl group of selected β -sultams

	R = PhCO	R = TBDMS	R = TBDMS	R = TBDMS	R = TBDMS	R = TBDMS	R = H
	R ¹ = H	R ¹ = H	R ¹ = COOH	R ¹ = COCl	R ¹ = CON ₃	R ¹ = CO ₂ Me	R ¹ = CO ₂ Me
	R ² = H	R ² = H	R ² = H	R ² = H	R ² = H	R ² = H	R ² = H
$\nu(\text{SO}_{2\text{as}})$ (cm^{-1})	1340	1300	1315	1335	1330	1320	1340
$\nu(\text{SO}_{2\text{sym}})$ (cm^{-1})	1155	1140	1170	1180	1200, 1170	1170	1170

	R = TBDMS	R = TBDPS	R = TBDMS	R = TBDPS	R = TBDMS	R = TBDMS
	R ¹ = CO ₂ Ph	R ¹ = Br	R ¹ = CO ₂ Ph	R ¹ = Br	R ¹ = Et ₂ Si	R ¹ = NO ₂
	R ² = CO ₂ Ph	R ² = Br	R ² = CO ₂ Ph	R ² = Br	R ² = H	R ² = H
$\nu(\text{SO}_{2\text{as}})$ (cm^{-1})	1320	1330	1320	1330	1301	1328
$\nu(\text{SO}_{2\text{sym}})$ (cm^{-1})	1180, 1160	1170	1180, 1160	1170	1161	1184

The IR spectrum (CHCl_3) of an unsubstituted β -lactam is characterized by a strong $\text{C}=\text{O}$ band at 1750 cm^{-1} and an NH band at 3430 cm^{-1} . By comparison, the IR spectrum of the unsubstituted β -sultam **7** in KBr shows an NH band at 3310 cm^{-1} , an $\text{SO}_{2\text{as}}$ band at 1300 cm^{-1} , and an $\text{SO}_{2\text{sym}}$ band at 1150 cm^{-1} . Finally, the IR spectrum (KBr) of 4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxides **20** is characterized by bands at 3405–3385 (NH), 1755 ($\text{C}=\text{O}$), 1335 ($\text{SO}_{2\text{as}}$), and 1160 cm^{-1} ($\text{SO}_{2\text{sym}}$). While the $\text{C}=\text{O}$ group seems not to be influenced significantly by the sulfonamide structure, the SO bands are slightly ($\Delta\nu = 35$ and 10 cm^{-1} , respectively) shifted to higher wave numbers. This might indicate a higher degree of mesomeric stabilization. The spectra of the *N*-alkyl 4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxides **52** show the $\text{C}=\text{O}$ bands at 1760–1785 cm^{-1} , $\text{SO}_{2\text{as}}$ bands at 1325–1335 cm^{-1} , and $\text{SO}_{2\text{sym}}$ bands at 1172–1181 cm^{-1} , indicating that *N*-substitution only influences the $\text{C}=\text{O}$ and the $\text{SO}_{2\text{sym}}$ bands <1997HCA671>.



R = Ph, $-\text{CO}(p\text{-Br-C}_6\text{H}_4)$, $-\text{CO}_2\text{Bu}^t$,
 $-(p\text{-NO}_2\text{-C}_6\text{H}_4)$, $-\text{OMe}$, $-\text{CO}_2\text{CH}_2\text{Ph}$,
 $-\text{CH}_2\text{Br}$, $-\text{CH}_2\text{CH}_2\text{Br}$

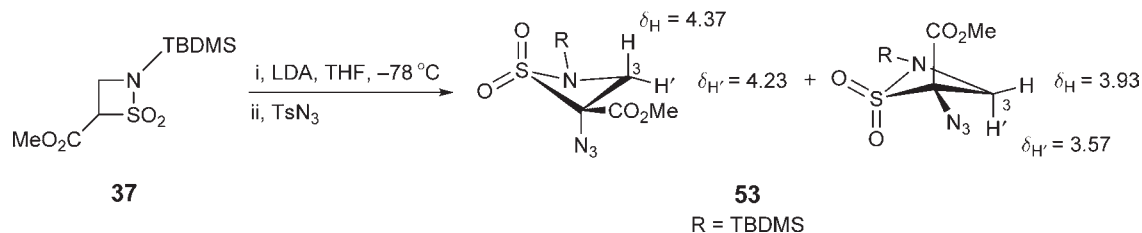
2.15.3.5.2 1,3-Thiazetidines

The IR spectra of 1,3-thiazetidines show stretching bands characteristic of the ring such as the C–N bond (1050 cm^{-1}) and the C–S bond (580–650 cm^{-1}) <2003RCB1817>.

2.15.4 Thermodynamic Aspects

β -Sultams, sulfonyl analogues of β -lactams, are unique four-membered heterocycles containing three different single bonds involving heteroatoms, namely C–N, C–S, and N–S. Stabilization of the β -sultam ring by π -bond overlap between the nitrogen lone pair and the sulfonyl group is much less than the stabilization in a β -lactam ring. In addition, β -sultams are destabilized by the increased distortion of the β -sultam ring due to the C–S and N–S bonds which are longer than the corresponding C–C and C–N of the β -lactam ring <1998JOC8355>.

A remarkable observation was made when the crude 4-disubstituted β -sultam **53** obtained by reaction of compound **37** with tosyl azide was purified by column chromatography on silica gel. Two fractions were isolated which showed identical IR spectra, ^{13}C NMR spectra, and elemental analyses. However, significant differences were exhibited in the ^1H NMR spectra with a downfield shift for both signals, for $\text{H}'\text{-C}(3)$ and $\text{H-C}(3)$ in one of the fractions (**Scheme 3**). It was suspected that two different conformers that were stable at room temperature had been isolated but the activation energy of the interconversion could not be estimated because of decomposition of the compound upon warming <2004HCA1574>.



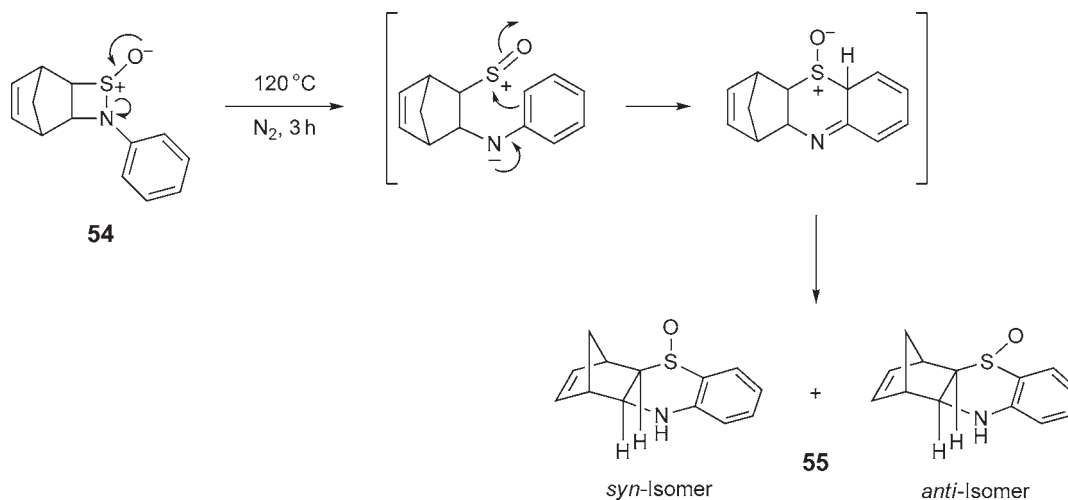
Scheme 3

2.15.5 Reactivity of Conjugated Rings

2.15.5.1 1,2-Thiazetidine S-oxides

2.15.5.1.1 Ring enlargement of 1,2-thiazetidine S-oxides

An interesting aspect of fused 1,2-thiazetidine S-oxides is their propensity for thermal isomerization. Thus, after heating the 1,2-thiazetidine **54** at 120°C , the 1,4-thiazine S-oxide **55** was obtained as a pair of isomeric products (ratio 4:3, 78% yield) which differed only in the configuration of the S-oxide (**Scheme 4**). Irradiation of this 1,2-thiazetidine S-oxide at $\lambda = 300\text{ nm}$ also effected isomerization affording the same ratio of products as that observed in the thermal process <1997SL167>.

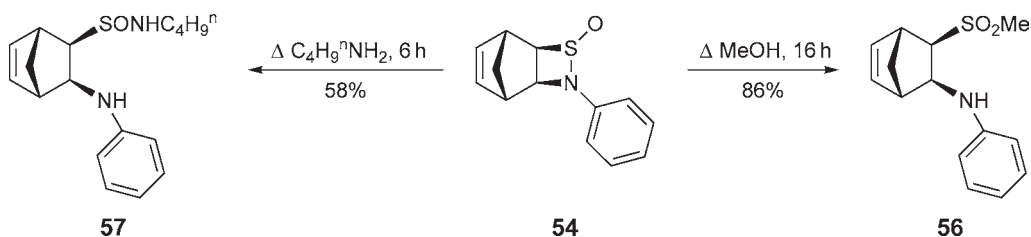


Scheme 4

2.15.5.1.2 Ring opening of 1,2-thiazetidine S-oxides

The facile cleavage of the S-N σ -bond in the 1,2-thiazetidine S-oxide **54** is part of the driving force in its rearrangement and this feature was exploited in reaction with nucleophiles. Thus, treatment with methanol affords the ring-opened alkyl sulfinate **56** in 86% yield while similar reaction using *n*-butylamine leads to the sulfinamide **57**

in 58% yield (Scheme 5). This ring opening with nucleophiles provides direct access to arylamino sulfinates and sulfinamides attached stereospecifically to the norbornene nucleus <1997SL167>.

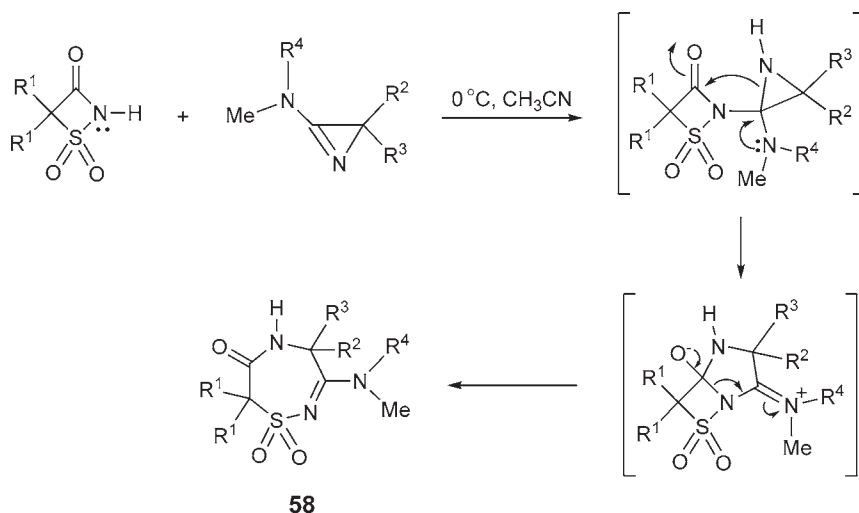


Scheme 5

2.15.5.2 1,2-Thiazetidine 1,1-Dioxides

2.15.5.2.1 Ring enlargement of 1,2-thiazetidin-3-one 1,1-dioxides

3-Amino-2*H*-azirine derivatives react smoothly and rapidly with 1,2-thiazetidin-3-one 1,1-dioxides affording 1,2,5-thiadiazepin-6-one 1,1-dioxides **58** in good yield via ring enlargement (Scheme 6; Table 7). The proposed mechanism for this regiospecific rearrangement to seven-membered heterocycles starts with protonation of the azirine by the NH-acidic thiazetidine compound. Nucleophilic attack at the amidinium carbon atom is followed by a ring enlargement that transforms the aziridine into a zwitterionic intermediate. This rearranges by a second ring enlargement to afford the final seven-membered ring heterocycle (Scheme 6). An alternative reaction mechanism via direct nucleophilic addition to the carbonyl group is excluded as no reaction occurs under analogous conditions using N-benzylated 1,2-thiazetidin-3-one 1,1-dioxide derivatives <1996HCA2067>.

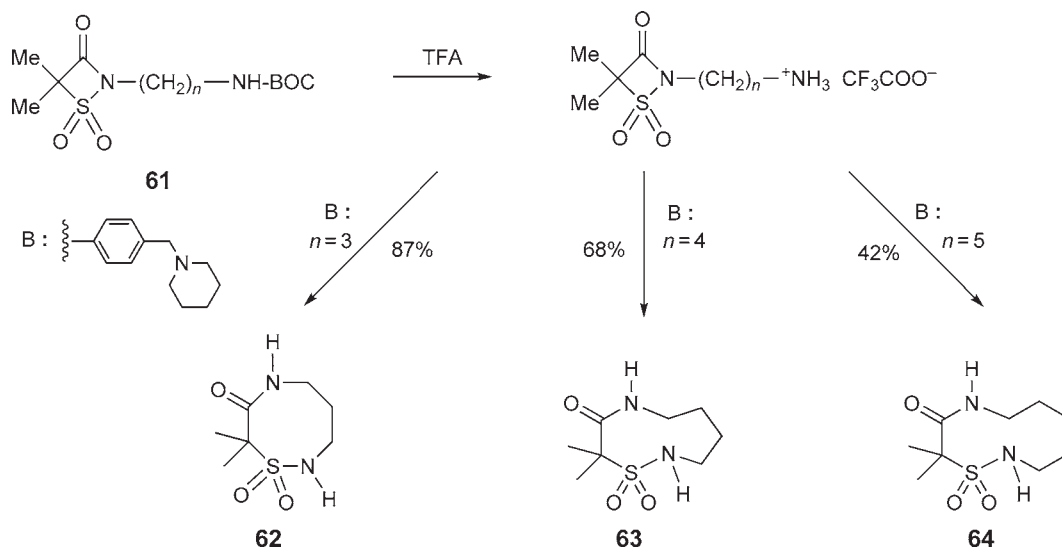


Scheme 6

Table 7 Reaction of 3-amino-2*H*-azirine derivatives with 1,2-thiazetidin-3-one 1,1-dioxides <1996HCA2067>

Entry	R ¹	R ²	R ³	R ⁴	Yield (%)
i	Me	Me	Me	Me	31
ii	Me	Me	Me	Ph	91
iii	Me	-(CH ₂) ₄ -		Ph	79
iv	Me	Me	Bu ⁱ	Ph	80
v	Et	Me	Me	Me	60
vi	Et	Me	Me	Ph	73
vii	Et	Me	Bu ⁱ	Ph	81

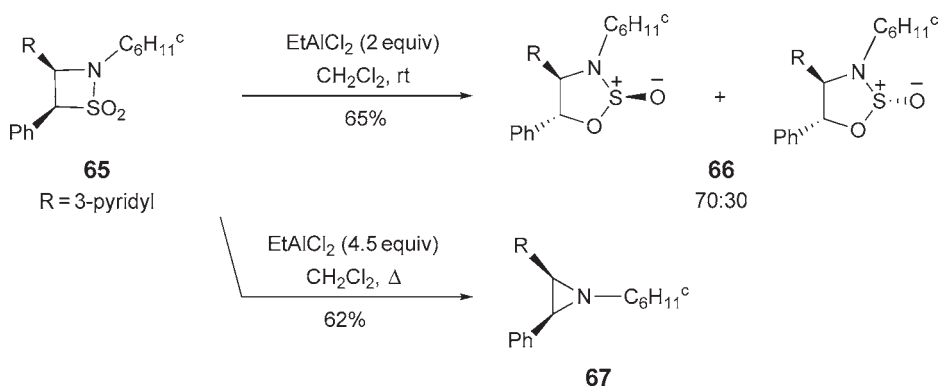
Transamidation-like reactions of 2-(aminoalkyl)-1,2-thiazetidin-3-one 1,1-dioxides proceed via six, seven-, and eight-membered intermediates giving ring-enlarged eight-, nine-, and ten-membered products, respectively, in 42–87% yields (**Scheme 9**). After reaction of the *t*-butoxycarbonyl (BOC)-protected 1,2-thiazetidin-3-one 1,1-dioxides derivative **61** with trifluoroacetic acid (TFA), the resulting ammonium trifluoroacetate was treated with an excess of (piperidino-methyl)polystyrene as base yielding large-membered rings. This transamidation reaction proceeds readily at room temperature giving the eight- and nine-membered ring products **62** and **63**, respectively. Transformation to give the ten-membered analogue **64** occurs when the temperature is increased to 80 °C <1999HCA354, 1999AXC1378>.



Scheme 9

2.15.5.2.2 Ring rearrangements of 1,2-thiazetidine 1,1-dioxides

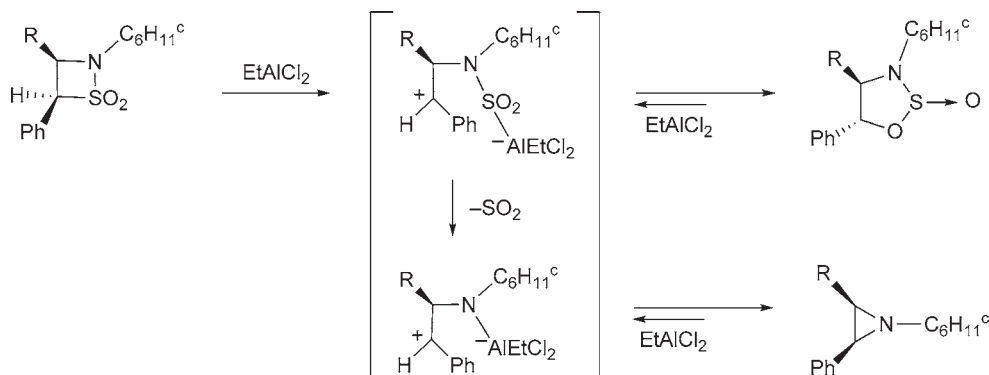
A variety of β -sultams such as **65** with a poorly migratory substituent at C-3 have been treated with ethylaluminum dichloride to afford *trans*-1,2,3-oxathiazolidine-2-oxides **66** as 70:30 mixtures of isomers separable by preparative thin-layer chromatography (TLC) on silica gel. However, *cis*-aziridines **67** are obtained as the major products when the reaction is carried out in refluxing dichloromethane (**Scheme 10**) <1998T8941>.



Scheme 10

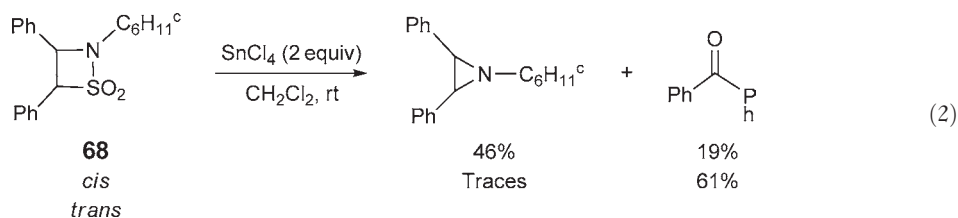
The C–S bond of a β -sultam ring has been cleaved by coordination of a Lewis acid to the sulfonyl group to generate a cationic intermediate. This cleavage is influenced by steric repulsion between the C-3 and C-4 substituents. Cyclization of this intermediate provides stereoselectively *trans*-1,2,3-oxathiazolidine-2-oxides because of the steric repulsion between the C-4 and C-5 substituents. On prolonged reaction, a carbocation is regenerated from the

1,2,3-oxathiazolidine by C–O cleavage with the assistance of the Lewis acid and another cationic intermediate is obtained by elimination of SO₂. The β -amino carbocation then cyclizes to give a *cis*-aziridine which is thermodynamically more stable than the corresponding *trans*-isomer (Scheme 11).

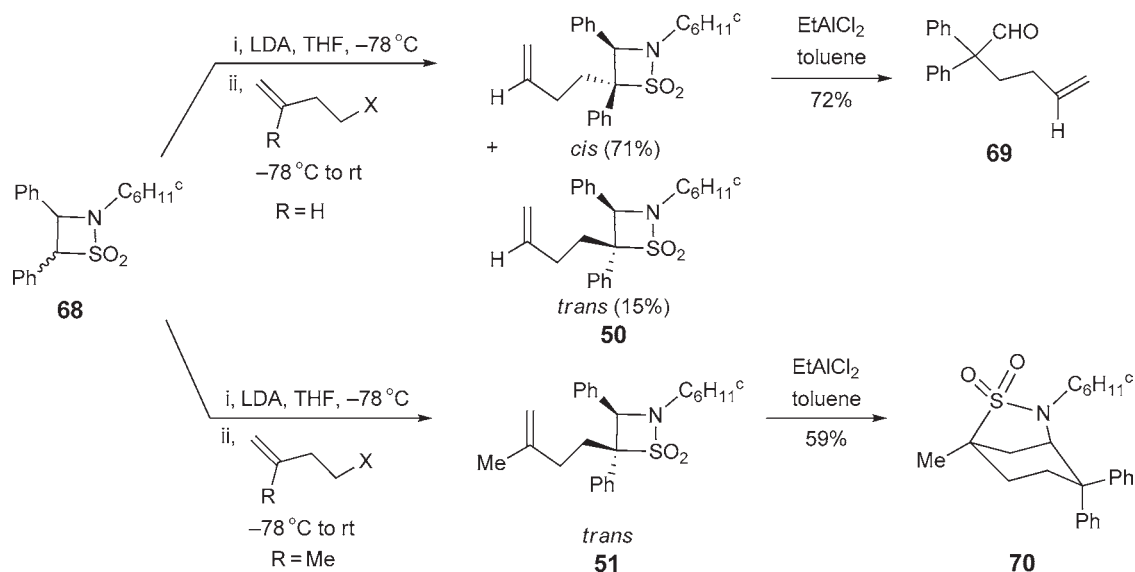


Scheme 11

Reaction of the 1,2-thiazetidine 1,1-dioxide **68** with the weaker Lewis acid, tin(IV) chloride, gives the *cis*-aziridine as a major product together with benzophenone (Equation 2). However, when the reaction is carried out on the *trans*-isomer, it affords essentially benzophenone accompanied by a trace amount of the *trans*-aziridine <1998T8941>.



The 4-alkenyl β -sultams **50** and **51** can be prepared by stereoselective alkylation of the 4-monosubstituted β -sultams **68** with alkenyl halides. Reaction of product **50** with ethylaluminum dichloride in toluene gives the aldehyde **69**. When β -sultam **51** is used, a tandem cyclization is observed yielding the bicyclo[3.2.1] γ -sultam **70** (Scheme 12). In the



Scheme 12

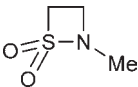
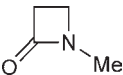
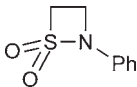
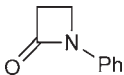
latter case, coordination of the Lewis acid at the sulfonyl group causes the C–S bond cleavage to generate a cationic intermediate. This rearranges by a 1,2-aryl shift to an alternative cation which undergoes an olefinic cyclization followed by tandem recyclization providing the bicyclic γ -sultam **70** thanks to the stabilization of the cation by the methyl group <1998T8941>.

2.15.5.2.3 Reaction of 1,2-thiazetidine 1,1-dioxides with nucleophiles by S–N bond cleavage

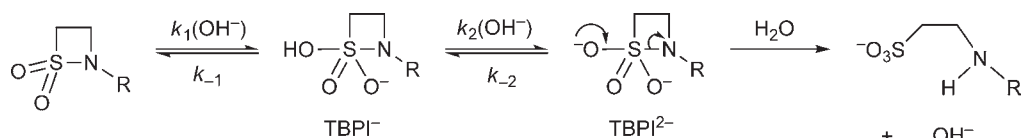
1,2-Thiazetidine 1,1-dioxides (β -sultams), sulfonyl analogues of β -lactams or the cyclized compounds of taurine, are 10^2 – 10^3 -fold more reactive than the corresponding β -lactams. These β -sultams undergo hydrolysis by ring opening and S–N fission to generate the corresponding β -amino sulfonic acids. A detailed kinetic study of the acid- and base-catalyzed hydrolyses of β -sultams has been undertaken <2002J(P2)938, 2004ACR297>. β -Sultams show extraordinary 10^9 - and 10^7 -fold rate enhancements for acid- and base-catalyzed hydrolysis, respectively, compared with the corresponding reactions of acyclic sulfonamides <2000JA3375>.

Whereas it is normally difficult to study the reaction of sulfonamides because of their intrinsic instability, the four-membered β -sultams offer the opportunity to investigate sulfonyl-transfer reactions. For example, *N*-methyl β -sultam undergoes acid- and base-catalyzed hydrolysis in water at 30 °C. This β -sultam presents second-order rate constants for specific acid-catalyzed hydrolysis ($k_{H^+} = 2.79 \text{ M}^{-1} \text{ s}^{-1}$ and for hydroxide ion catalyzed hydrolysis $k_{\text{HO}^-} = 1.38 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ ($6.1 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ for *N*-methyl β -lactam) (Table 8). The entropy of activation for the acid-catalyzed hydrolysis of the β -sultam is $-80 \text{ J K}^{-1} \text{ mol}^{-1}$, which may be indicative of unimolecular ring opening, whereas that for the base-catalyzed reaction ($-184 \text{ J K}^{-1} \text{ mol}^{-1}$) is consistent with a bimolecular process involving hydroxide ion attack on sulfur and probably the formation of a trigonal bipyramidal intermediate (TBPI) <1996J(P2)2245>.

Table 8 Second-order rate constants for hydroxide ion hydrolysis of β -sultam and β -lactam analogues

Compound				
$k_{\text{OH}^-} (\text{M}^{-1} \text{ s}^{-1})$	1.38×10^{-2}	6.1×10^{-5}	5.69	3.87×10^{-3}

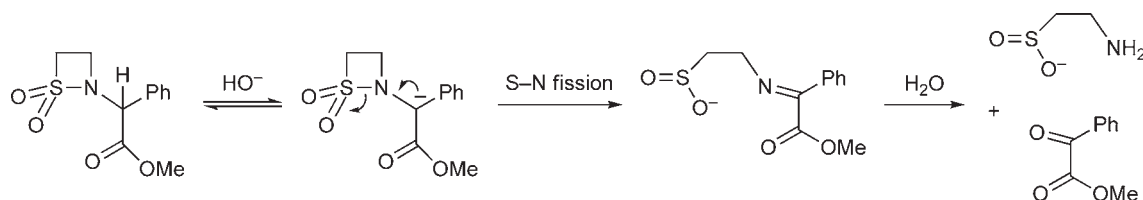
Four-membered rings are strained systems and ring opening is therefore a thermodynamically favorable process. In cyclic β -sultams, the reactant is subject to bond angle strain whereas in the transition state the 90° endocyclic C–S–N bond angle about sulfur has the preferred geometry. Apical attack by nucleophiles on sulfonyl centers generates a TBPI with a 90° bond angle about sulfur, so that the C–S–N bond angle requirement changes from an approximately tetrahedral 109° in the reactant state to an apical 90° in the transition state. Alkaline hydrolysis of β -sultams may be described as an $S_{\text{A}}\text{N}$ bimolecular process with a reaction mechanism aided by the placement of the attacking and leaving groups in the apical positions and this is consistent with the known inversion of sulfonyl centers upon sulfonyl transfer (Scheme 13). The Brønsted β_{lg} value for alkaline hydrolysis of *N*-aryl β -sultams is -0.58 and the kinetic solvent isotope effect $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ is 0.60, compatible with rate-limiting formation of the TBPI. Conversely, $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ for *N*-alkyl β -sultams is 1.55, indicative of rate-limiting breakdown of the TBPI <2002MI19>.



Scheme 13

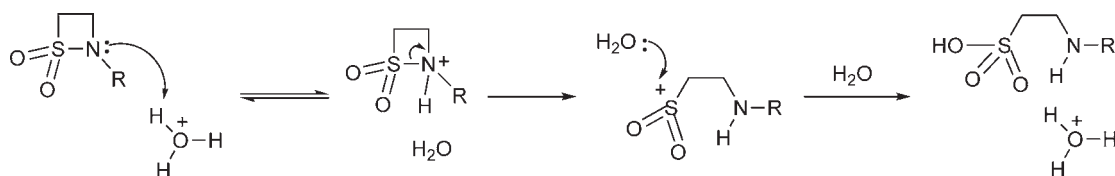
This alkaline hydrolysis shows a rate term that is second order in hydroxide ion concentration, which is indicative of a stepwise mechanism involving a TBPI with a hypervalent sulfur atom. Reversible attack of the hydroxide ion on a β -sultam generates a monoanionic TBPI[−], which requires deprotonation by a second hydroxide ion before the intermediate can collapse to products.

However, an E1cB-type process was reported as a novel mechanism for hydrolysis of a β -sultam. In the case of the *N*- α -methoxycarbonyl β -sultam, deprotonation of the acidic exocyclic hydrogen leads to the formation of a carbanion, which then undergoes a rate-limiting conversion to a ring-opened species with expulsion of a sulfinate anion. Then, hydrolysis of the imine species produces benzoyl formate as the principal product detected (Scheme 14) <2002CC772>.



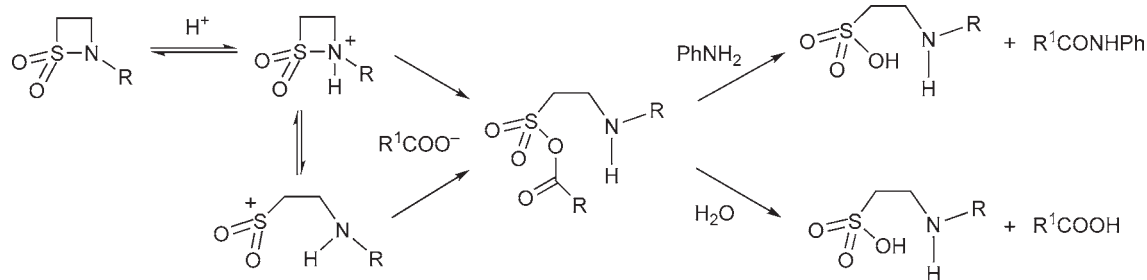
Scheme 14

Now considering acid-catalyzed hydrolysis of β -sultams, a relatively unusual A1-type mechanism occurs (Scheme 15). Rapid and reversible protonation of the ring nitrogen is followed by a rate-limiting ring opening with expulsion of the neutral amine. Electron-withdrawing substituents at the 4-position of the β -sultam ring greatly retard the rates of acid-catalyzed hydrolysis <1997CC2037>. Acid hydrolysis of β -sultam derivatives under mild conditions afforded the taurine derivatives in good yield <2004M979>.



Scheme 15

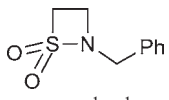
The rate of hydrolysis of *N*-benzyl β -sultam was measured by monitoring changes in its ultraviolet (UV) spectrum at 225–235 nm in a range of carboxylate buffers. The values of the second-order rate constants k_{HA} increased with a decreasing pK_a of the carboxylic acid buffer. The probable mechanism of buffer catalysis involved a specific acid-nucleophilic catalysis. The β -sultam undergoes reversible protonation on nitrogen, followed by direct nucleophilic attack of the carboxylate anion by a unimolecular A1-type process to form a mixed anhydride intermediate that is subsequently hydrolyzed. Nucleophilic catalysis in the carboxylate buffer hydrolysis of β -sultams was confirmed by trapping the mixed acid anhydride intermediate with aniline to give acetanilide (Scheme 16) <1999CC2401, 2000JA3375>.



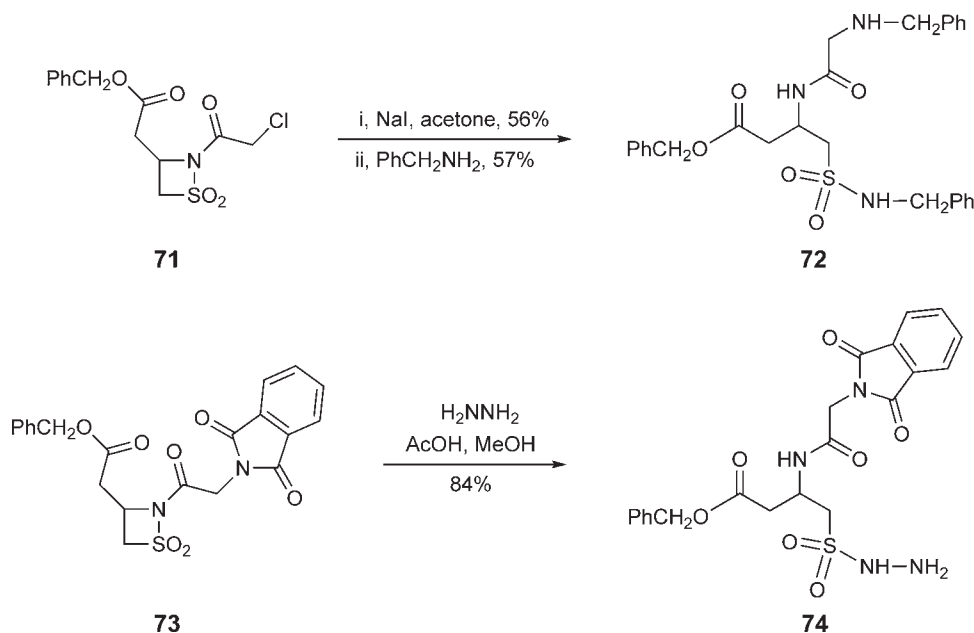
Scheme 16

The Brønsted plot for the carboxylic acid-catalyzed hydrolysis of *N*-benzyl β -sultam gives a good correlation between the values of $\log k_{\text{HA}}$ and the $\text{p}K_{\text{a}}$ for 2-chloroacetic, 2-methoxyacetic, and acetic acids with a slope of -0.67 corresponding to a β_{nuc} of 0.33 for the specific acid-nucleophilic mechanism (Table 9). This is indicative of an early transition state in which there has been a small amount of neutralization of the negative charge on the carboxylate anion. Formic acid shows a positive deviation from this line, which is again indicative of a nucleophilic pathway for catalysis. The solvent isotopic effect $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ of 1.57 for the chloroacetate buffer hydrolysis of *N*-benzyl β -sultam is compatible with a specific acid-nucleophilic process, as is the observed entropy of activation of $-148 \text{ K}^{-1} \text{ mol}^{-1}$ for chloroacetic acid-catalyzed hydrolysis <2000T5631>.

Table 9 Second-order rate constants for the carboxylic acid-catalyzed hydrolysis of *N*-benzyl β -sultam

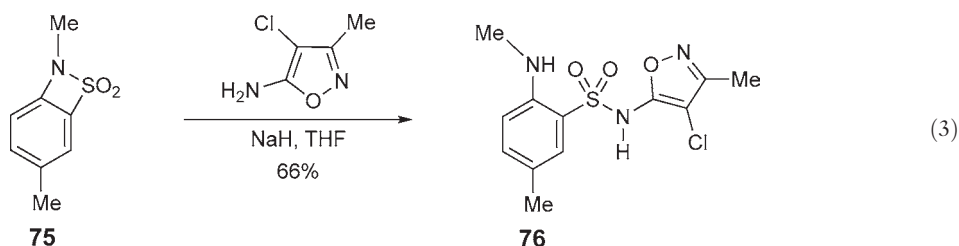
	ClCH_2COOH $\text{p}K_{\text{a}} 2.70$	$\text{MeOCH}_2\text{COOH}$ $\text{p}K_{\text{a}} 3.38$	HCOOH $\text{p}K_{\text{a}} 3.67$	CH_3COOH $\text{p}K_{\text{a}} 4.57$
$K_{\text{HA}} (\text{M}^{-1} \text{s}^{-1})$	7.61×10^{-2}	2.95×10^{-2}	7.53×10^{-2}	4.14×10^{-3}

In the synthetic sequence starting from the β -sultam **71**, chloride is first replaced by iodide, and then nucleophilic substitution with benzylamine is accompanied by concomitant attack on the β -sultam ring, yielding the open-chain sulfonamide **72** (Scheme 17). It was also found that attempted deprotection of the phthalimido group in compound **73** using hydrazine acetate resulted in nucleophilic attack on the β -sultam ring rather than deprotection, affording compound **74** <2004M55>.



Scheme 17

When the β -sultam **75** was treated with 5-amino-4-chloro-3-methylisoxazole, the ring was readily opened via S–N bond fission to give the corresponding sulfonamide **76** (Equation 3) <1998JOC2348>.



Organometallic reagents react as bases and/or carbon nucleophiles with β -sultams to give (*E*)-vinylsulfonamides (Equation 4). For example, reaction of the 4-unsubstituted β -sultams **77** with methyllithium gives only the (*E*)-vinylsulfonamides **78**, whereas reaction with methylmagnesium bromide affords the 2-aminoethyl sulfones **79** as minor products (Table 10). (*E*)-Vinylsulfonamides are obtained by abstraction of the pseudoequatorial proton at C-4 when an organometallic reagent acts as a base. Nucleophilic attack of an organometallic reagent at the sulfonyl group causes ring opening with S–N bond fission to provide an amide intermediate, which reacts in one of two ways, either formation of 2-aminoethylsulfones by protonation during workup or retro-aldol-type reaction to give methyl phenyl sulfone **80** and the imine derivative **81** (Scheme 18) <1998T5507>.

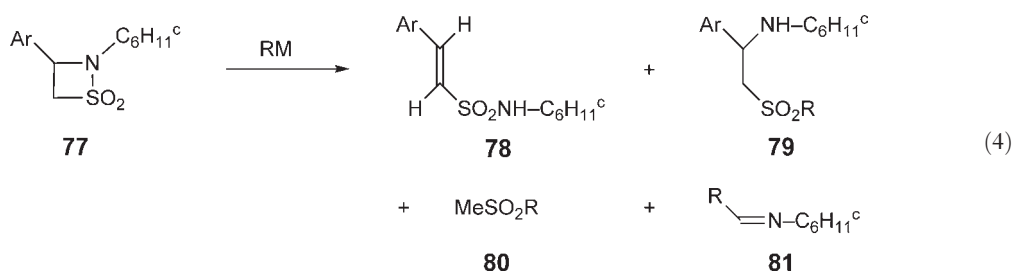
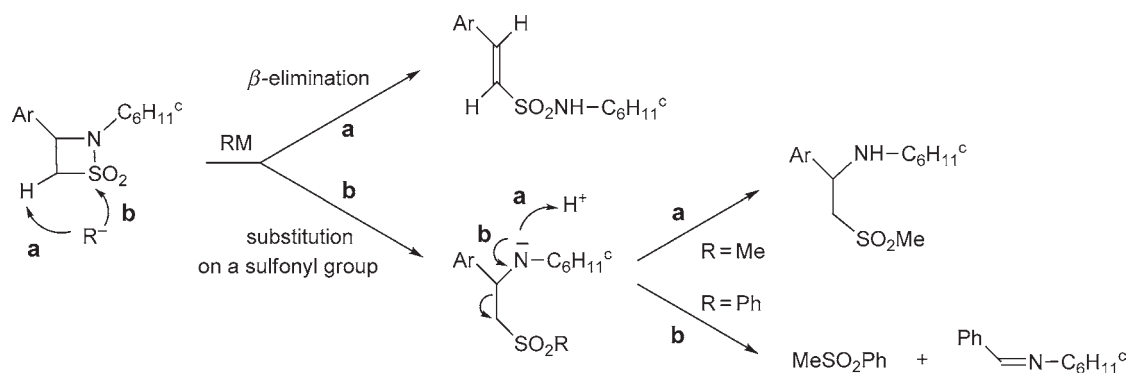


Table 10 Conditions of the reaction of organometallic reagents with 3-monosubstituted β -sultams **77**

<i>Ar</i>	<i>RM</i>	Yield (%)			
		78	79	80	81
Ph	MeLi, THF, 0 °C	70			
Ph	MeLi, TMEDA, THF, 0 °C to rt	84			
Ph	MeMgBr, THF, rt	67	8		
Ph	PhLi, THF, 50 °C	42		10	Traces
<i>p</i> -MeOC ₆ H ₄	MeMgBr, ether, rt	78	11		
<i>p</i> -MeC ₆ H ₄	MeMgBr, THF, rt	68	12		
<i>o</i> -MeC ₆ H ₄	MeMgBr, THF, rt	72	25		



Scheme 18

Reaction of the 3,4-disubstituted β -sultams **82** with organolithium has given the (*E*)-vinylsulfonamides **83** (Equation 5) stereoselectively regardless of the configuration of the 3- and 4-substituents (Table 11) <1998T5507>.

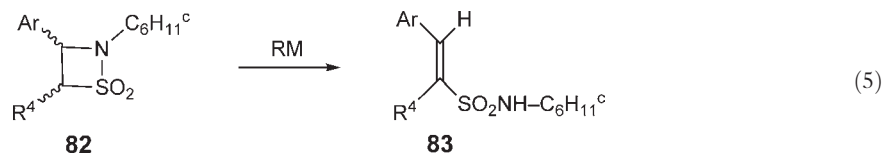
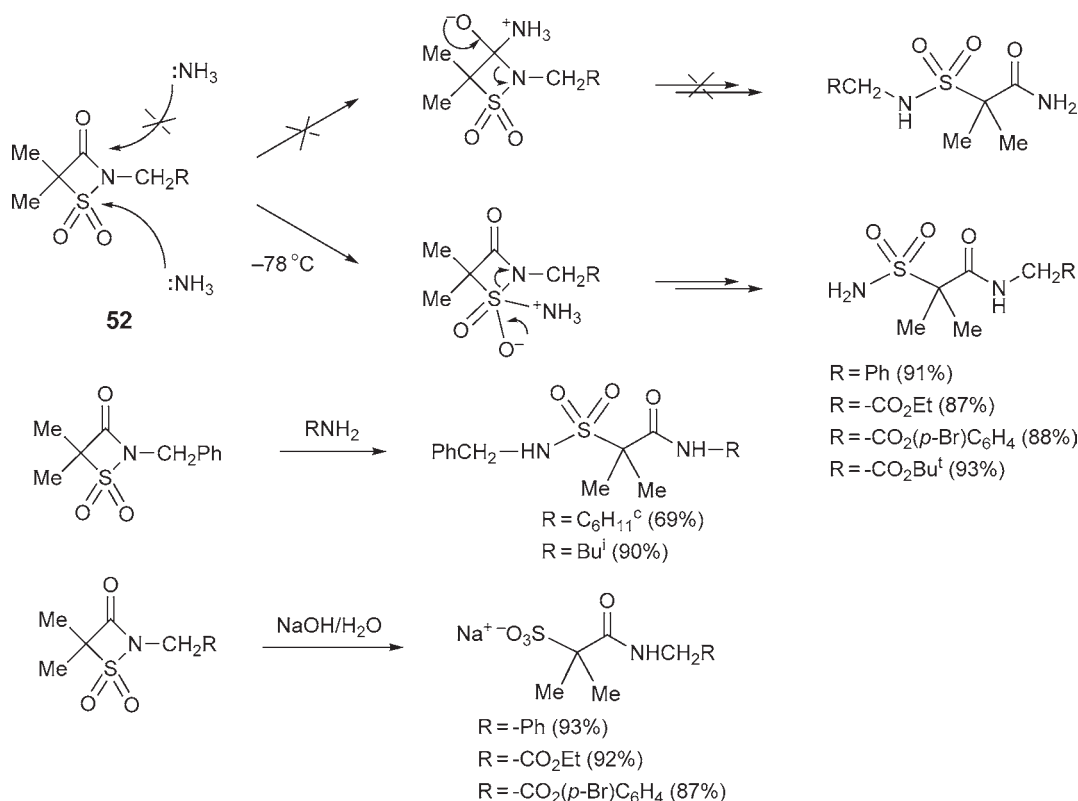


Table 11 Conditions of the reaction of organometallic reagents with 3,4-disubstituted β -sultams <1998T5507>

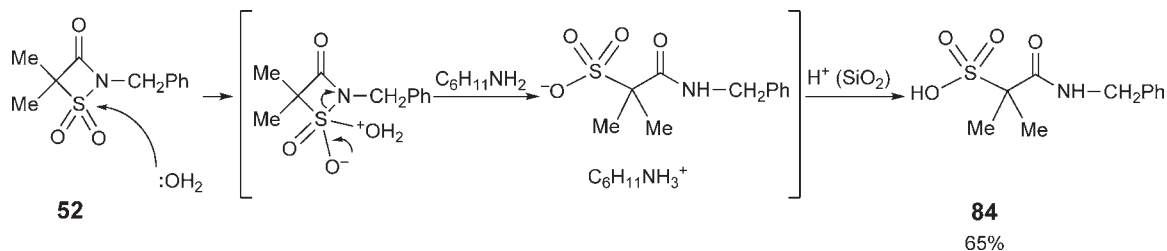
<i>Ar</i> and R^4	<i>RM</i>	Yield 83 (%)
<i>cis</i> : Ar = Ph; R^4 = Ph	MeLi, THF, -78°C to rt	44
<i>cis</i> : Ar = Ph; R^4 = Ph	MeLi, TMEDA, THF, 0°C to rt	86
<i>cis</i> : Ar = Ph; R^4 = Ph	PhLi, THF, 50°C	82
<i>trans</i> : Ar = Ph; R^4 = Ph	MeLi, THF, reflux	78
<i>cis</i> : Ar = <i>p</i> -MeOC ₆ H ₄ ; R^4 = Ph	MeLi, THF, reflux	68
<i>trans</i> : Ar = <i>p</i> -MeOC ₆ H ₄ ; R^4 = Ph	MeLi, THF, reflux	76
<i>cis</i> : Ar = Ph; R^4 = Et	MeLi, THF, rt	67

To obtain further insight into the reactivity of the 1,2-thiazetidin-3-one 1,1-dioxides **52** toward nucleophiles, ammonia and primary amines were reacted with N-substituted and N-unsubstituted derivatives, leading to ring-opening reactions. Reaction of compound **52** with liquid ammonia at -78°C or by refluxing in aqueous NaOH affords the ring-opened adducts from S–N bond cleavage via nucleophilic attack at the sulfonyl group, whereas reaction with primary amines in anhydrous conditions yields products of ring opening in which C–N cleavage was observed from attack at the carbonyl group (Scheme 19) <1997HCA671, 1999HCA354>.



Scheme 19

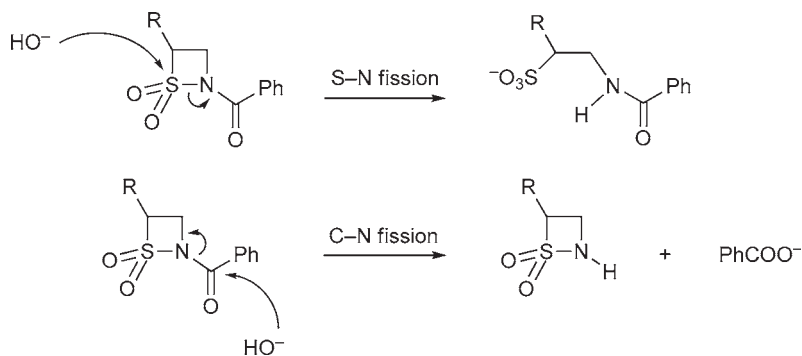
Drastic anhydrous conditions appeared essential for such study since 2-benzyl-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxide **52** was easily hydrolyzed even with only traces of water. Heating compound **52** with cyclohexylamine afforded an intermediate salt which was protonated on silica gel to afford sulfonic acid **84** (Scheme 20) <1999HCA354>.



Scheme 20

2.15.5.2.4 Reaction of 1,2-thiazetidine 1,1-dioxides with nucleophiles by C–N bond cleavage

As with other β -sultams, the *N*-acyl derivatives are at least 10⁶ times more reactive than *N*-acyl sulfonamides. However, the 4-isopropylidene β -sultam **86** is relatively unreactive and undergoes alkaline hydrolysis with C–N fission, leaving the strained four-membered β -sultam ring intact (Scheme 21). This enormous reduction in reactivity at the sulfonyl center is shown to be due to steric hindrance to hydroxide attack by the neighbouring isopropylidene group. A bipyramidal arrangement in the transition state would be formed by apical attack of the hydroxide ion so that the ring S–N bond would also be apical and the two sulfonyl oxygens would adopt equatorial positions. Attack at the sulfonyl center would thus be accompanied by an enormous increase in strain energy with an increasing activation energy so that it becomes larger than required for attack at the acyl center. The (*Z*)-4-ethylidene β -sultam **88** shows similar behavior to the 4-isopropylidene- β -sultam **86** with preferential C–N fission, whereas the (*E*)-4-ethylidene isomer **87** and 4-isopropyl β -sultam **89** showed the expected reactivity of *N*-acyl β -sultam **85** with a hydrolytic ring opening forming β -amidosulfonic acid via the S–N fission. The second-order rate constants for the alkaline hydrolysis of *N*-benzoyl β -sultams at 30 °C were determined (Table 12) <2001J(P2)1503>.

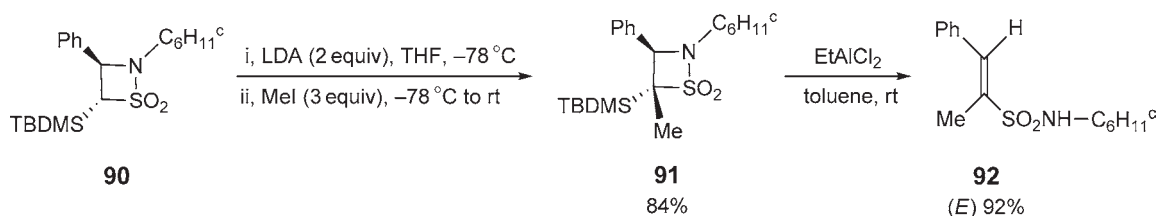


Scheme 21

Table 12 Second-order rate constants for the alkaline hydrolysis of *N*-benzoyl β -sultams

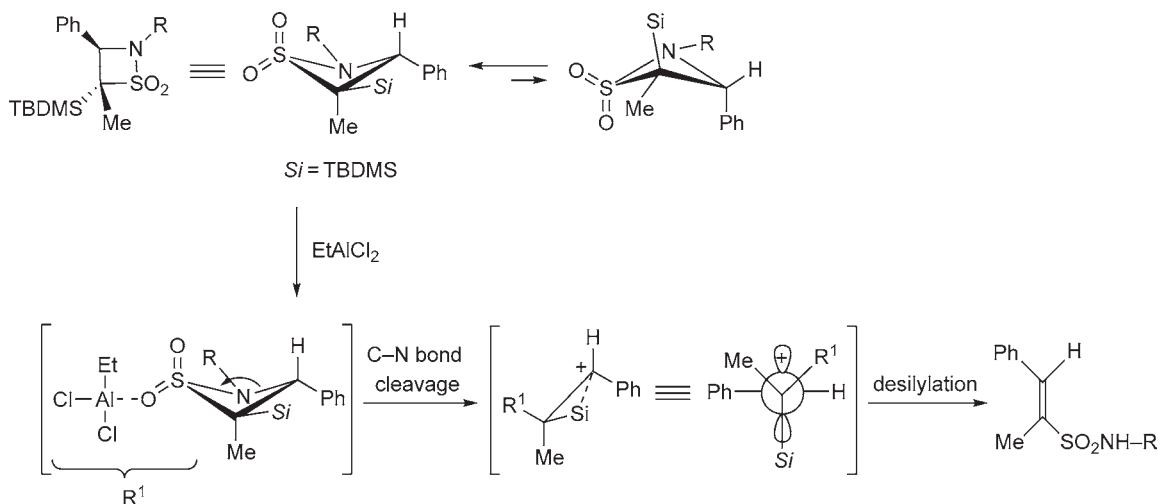
Compound					
	85	86	87	88	89
k_{OH} (dm ³ mol ⁻¹ s ⁻¹)	1.46×10^4	1.18	2.54×10^3	1.72	3.00×10^2

The first C–N bond cleavage of a β -sultam ring leading to the stereospecific formation of a (*E*)-vinylsulfonamide to be observed was due to an anchimeric assistance from a silyl group in acidic medium. 4-Mono- and 4,4-disilylated β -sultams were prepared from 3-aryl β -sultams by basic deprotonation followed by silylation with *t*-butyldimethylsilyl chloride (TBDMSCl) or trimethylsilyl chloride (TMSCl). Stereoselective monosilylation of the appropriate β -sultam furnishes the (3*R*,4*S*)-4-silyl analog **90**. β -Sultam **91** was obtained by stereoselective alkylation of compound **90**. Treatment with ethylaluminum dichloride provided the (*E*)-vinylsulfonamide **92** stereospecifically via selective C–N bond cleavage followed by desilylation <1996TL2257>. Simultaneous C–N bond cleavage and N-dealkylation of 4-silyl β -sultams was noted when using aluminium chloride, suggesting that coordination of the Lewis acid to the sulfonyl group may enhance the polarity of the C–N bond, thus favoring N-dealkylation (Scheme 22) <1998CPB757>.



Scheme 22

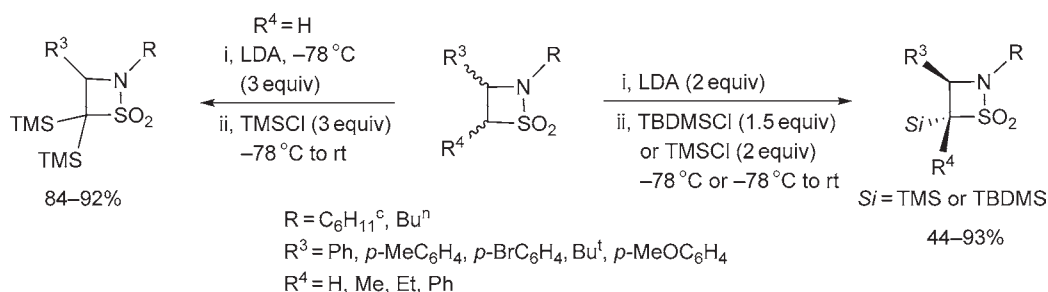
A silylated β -sultam exists predominantly in a conformation where both an aryl substituent and a silyl group are pseudoequatorial, the nitrogen substituent and the pseudoequatorial-oriented silyl group being *anti*-periplanar. The coordination of the Lewis acid to the sulfonyl group would cause selective C–N bond cleavage to generate a carbonium intermediate which should be stabilized by the β -silyl substituent. Elimination of the silyl group from the cation affords stereospecifically the thermodynamically more stable (*E*)-sulfonamide (Scheme 23) <1996TL2257>.



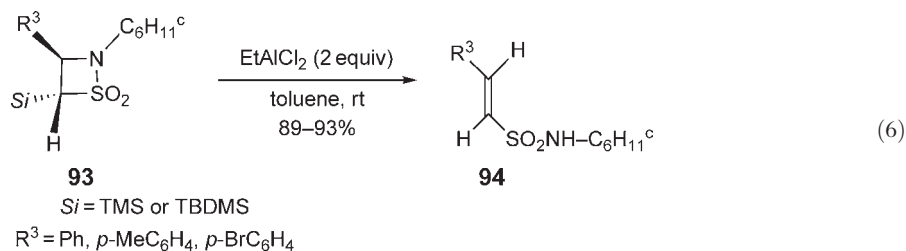
Scheme 23

The 4-monosilyl β -sultams which possess (3*R*,4*S*)-configuration were stereoselectively obtained in high yields as well as 4,4-disilylated β -sultams by the use of TMSCl as a silylating reagent (Scheme 24) <1998CPB757>.

Treatment of 3-aryl-4-silyl β -sultams **93** with ethylaluminum dichloride causes stereospecific C–N bond cleavage to provide (*E*)-styrylsulfonamides **94** (Equation 6). However, reaction of the corresponding 3-*t*-butyl β -sultam proceeds at 40°C , and its low reactivity is explained because of the weaker stabilization of the cationic intermediate by the *t*-butyl group than by the aromatic groups <1998CPB757>.

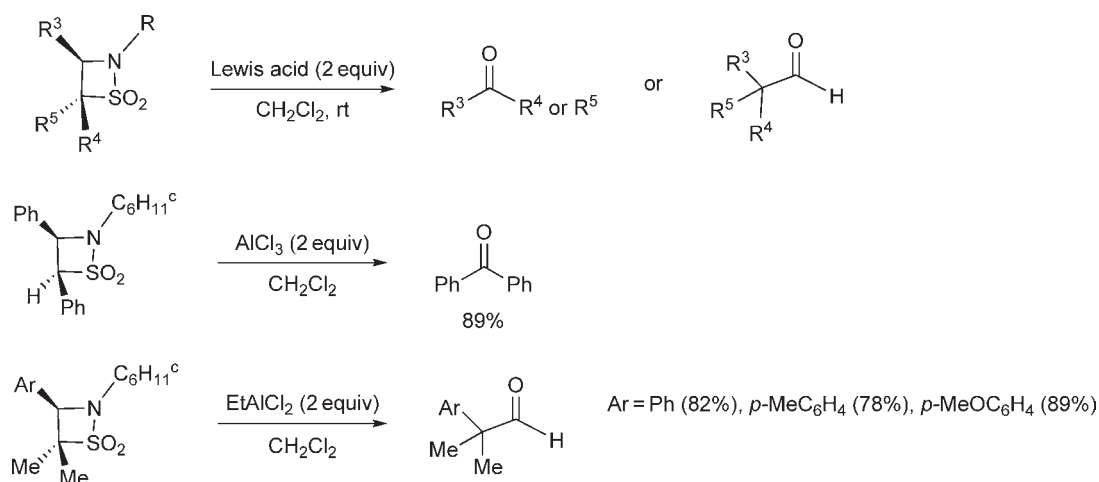


Scheme 24



2.15.5.2.5 Reaction of 1,2-thiazetidine 1,1-dioxides with nucleophiles by C–S bond cleavage

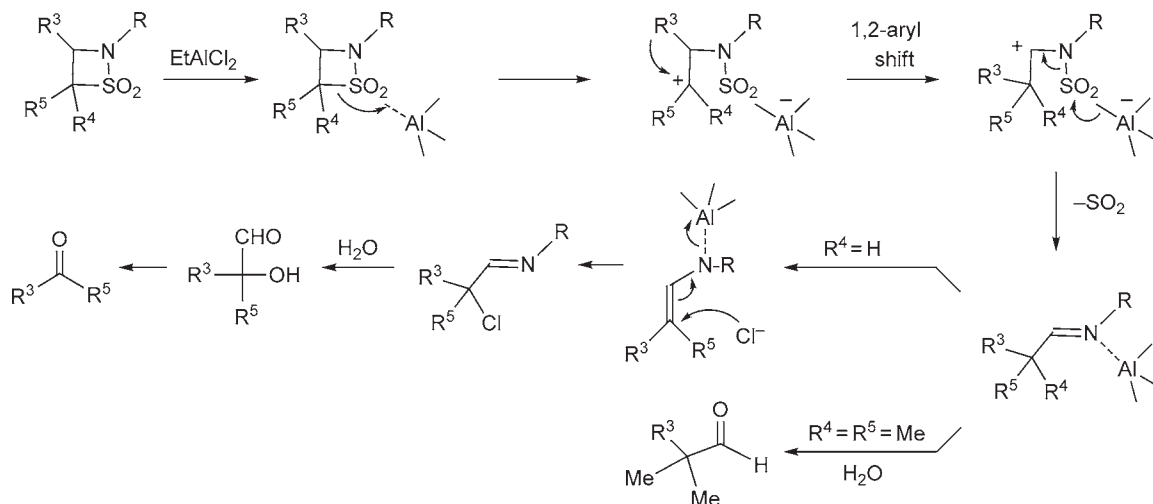
Selective C–S bond cleavage of a β -sultam ring bearing a variety of substituents at C-3 and C-4 can be achieved by reaction with Lewis acids and yields aryl ketones or aldehydes. A solution of ethylaluminum dichloride in hexane is easier to handle than solid aluminium chloride due to their relative moisture sensitivities (Scheme 25) <1998T8941>.



Scheme 25

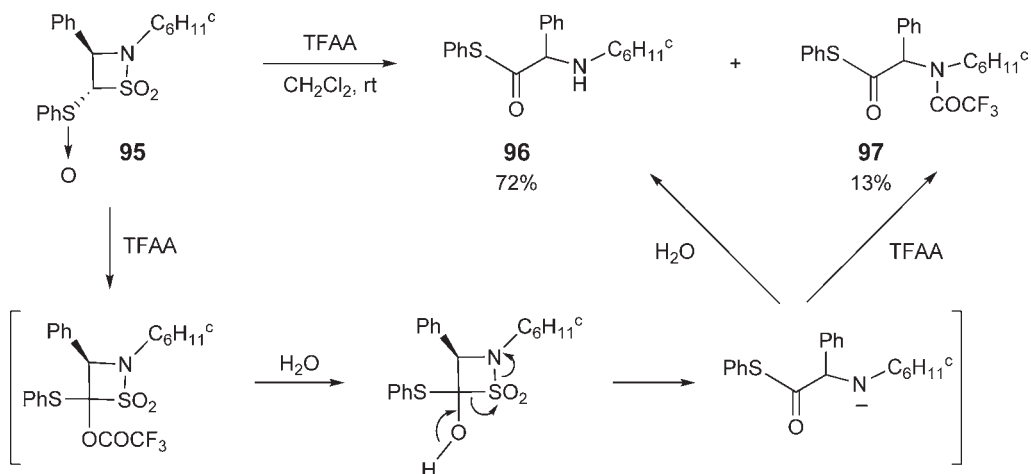
The proposed mechanism suggests the cleavage of the C–S bond of a β -sultam by coordination of the Lewis acid to the sulfonyl group generating a cationic intermediate. Neighboring participation of an aryl group with 1,2-aryl migration provides a further carbocation and an imine is produced by elimination of sulfur dioxide. In the case of $R^4 = \text{H}$, isomerization to an enamine and coordination of the Lewis acid enable a chloride ion to attack at the β -carbon atom. The resulting chloroimine is hydrolyzed to an α -hydroxy-aldehyde which decomposes to an aryl ketone under acidic conditions. For 3-aryl-4-phenyl β -sultams, benzophenone derivatives are obtained in good yields.

It has been shown that an electron-donating group on the aryl substituent promotes C–S bond cleavage because of better stabilization of the benzylic cation. In the case of $R^3 = R^4 = \text{Me}$, the aldehyde is obtained after hydrolysis of the imine (Scheme 26) <1998T8941>.



Scheme 26

α -Amino acid thioesters, activated esters utilized for peptide synthesis as well as for natural product synthesis, are synthesized by the Pummerer reaction of 3-substituted-4-sulfinyl β -sultams with trifluoroacetic anhydride (TFAA). Starting from compound **95**, thioester **96** is obtained in 72% yield accompanied by thioamide **97** (13% yield) by the use of 4 equiv of TFAA (Scheme 27). The proposed mechanism suggests that the hydroxyl intermediate is produced by hydrolysis of the Pummerer product. The amide anion is then generated by C–S bond cleavage followed by elimination of sulfur dioxide to give the thioester <1998JOC8355>.



Scheme 27

Similarly, enantiopure 3-substituted-*N*-methylbenzyl β -sultams have been converted into *N*-methylbenzyl- α -amino acid thioesters via sulfenylation and Pummerer rearrangement with high or complete retention of configuration. Chiral sulfoxides were prepared by sulfenylation followed by oxidation of *trans*-isomers as two separable A and B stereoisomers. Treatment with TFAA gave chiral α -amino acid thioesters in high yields with a de > 90%. Slight epimerization of the α -chiral center of the α -phenyl thioesters has been observed under the reaction conditions whereas no epimerization was observed in the case of α -*t*-butyl thioesters (Scheme 28) <1998JOC8355>.



TBDMS
 PhCO
 SO₂
 EtO₂C
 N
 CO₂Et
 H

TBAF (SiO₂)
 THF, 20 °C

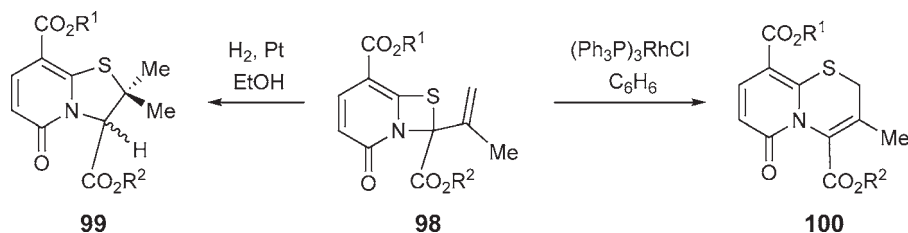
O
 C=O
 OH
 NH₂

33%

+ EtO₂C-NH-NH-CO₂Et

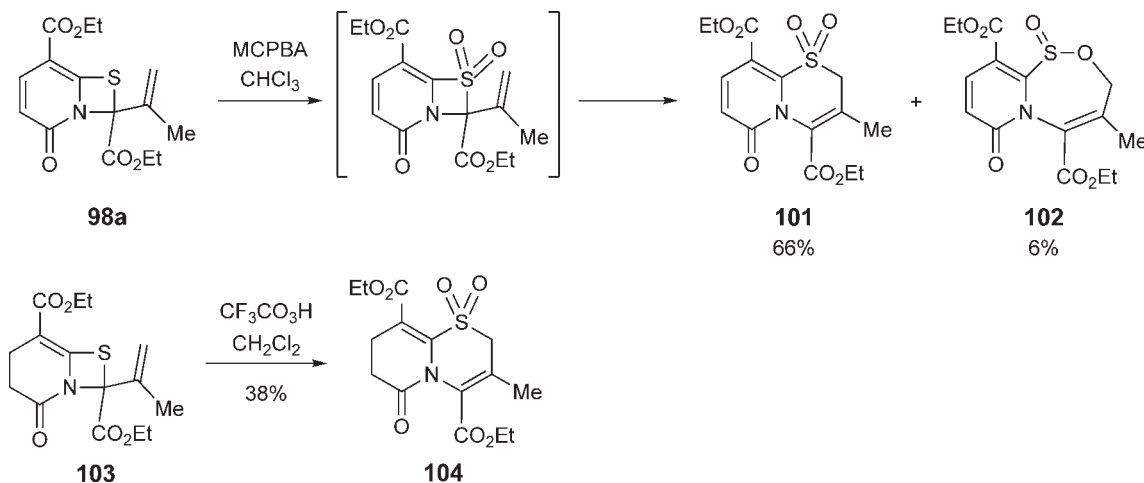
(7)

The chemistry of the 2-vinyl-1,3-thiazetidines **98** is interesting because these compounds undergo rearrangement to the thiazolidines **99** on catalytic hydrogenation and rearrangement to the thiazines **100** on treatment with Wilkinson's catalyst (**Scheme 29**) <1999J(P1)3569>.



Scheme 29

Moreover, the 2-vinyl-1,3-thiazetidine **98a** ($R^1 = R^2 = \text{Et}$) undergoes rearrangement to thiazine sulfone **101** when treated with peracid. A by-product sultine compound **102** was isolated in 6% yield from this reaction. This could be the result of a [2,3]-sigmatropic rearrangement of the sulfone. The reduced 2-vinyl-1,3-thiazetidine **103** is also oxidized with peracid affording the thiazine sulfone **104** but no product corresponding to the sultine was detected (Scheme 30) <1999J(P1)3569>.



Scheme 30

2.15.6 Reactivity of Substituents Attached to Ring Carbon Atoms

2.15.6.1 1,2-Thiazetidine 1,1-Dioxides

2.15.6.1.1 Reactivity at the C-3 position

Substitution of the acetate group at the C-3 position of the β -sultam **105** can occur by reaction with silyl enol ethers in the presence of zinc iodide or zinc chloride. When the diazo compound is used, after desilylation with tetrabutylammonium fluoride (TBAF), photochemical cyclization gives the bicyclic β -sultam **106** as a mixture of two *cis/trans*-diastereoisomers. When silyl enol ethers derived from cyclic ketones are used, the substitution product is stabilized by a retro-Michael-type reaction leading to open-chained sulfonamides **107** (Scheme 31) <1997LA1261>.

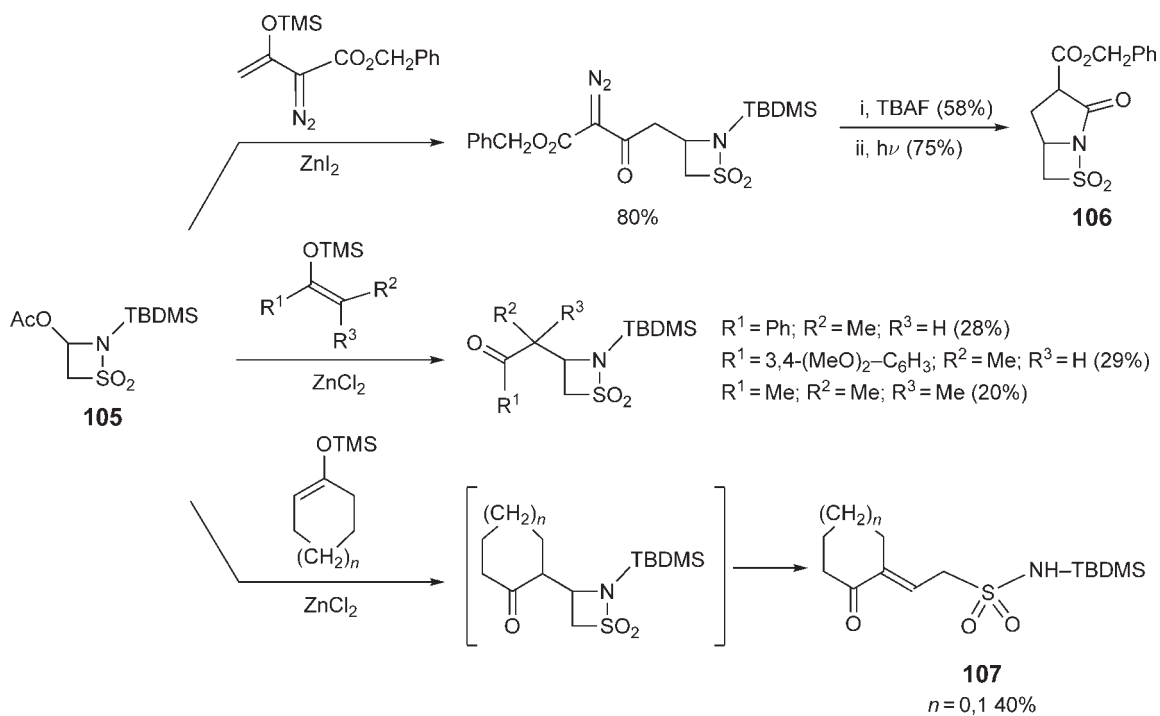
The acetoxy group may also be substituted using N-nucleophiles such as pyrrolidine or morpholine. Since the products of nucleophilic substitution are amins, elimination results in β -substituted ethane sulfonamides **108**. Moreover, while no reaction occurs with phthalimide or sodium azide, trimethylsilyl azide reacts in the presence of Lewis acids such as zinc chloride or tin chloride to give a diazido compound **109** as product (Scheme 32) <1997PHA482>.

N-Alkylated β -sultam peptides have been prepared from the β -sultam **110** by successive hydrogenolytic cleavage of the benzyl ester group and reaction of the resulting unstable carboxylic acid with amino acid esters using peptide-coupling methodology (Scheme 33) <2004M55>.

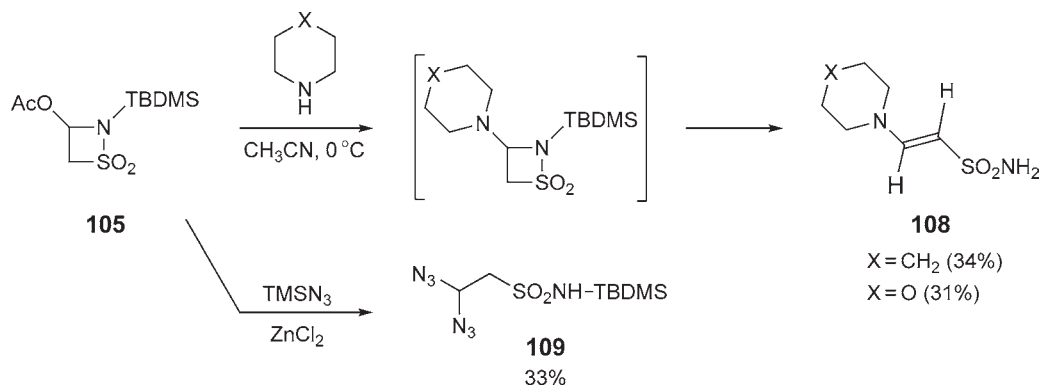
Conversion of the isolated *N*-TBDMS carboxylic acid **111** to the active ester and reaction with amino acid esters yielded after desilylation the β -sultam peptides **112** and **113**. Removal of the protecting groups was also possible with benzylic esters but attempted hydrolysis of alkyl ester groups resulted in hydrolysis of the β -sultam ring. Catalytic hydrogenation of the benzyl esters afforded the *N*-silylated β -sultam peptides **114** in quantitative yields (Scheme 34) <2004M979>.

Simple modifications of the ester group of 3-carboxyalkyl β -sultams can be achieved and aminolysis furnishes the corresponding amides while reduction leads to the corresponding alcohol (Scheme 35) <2004HCA90>.

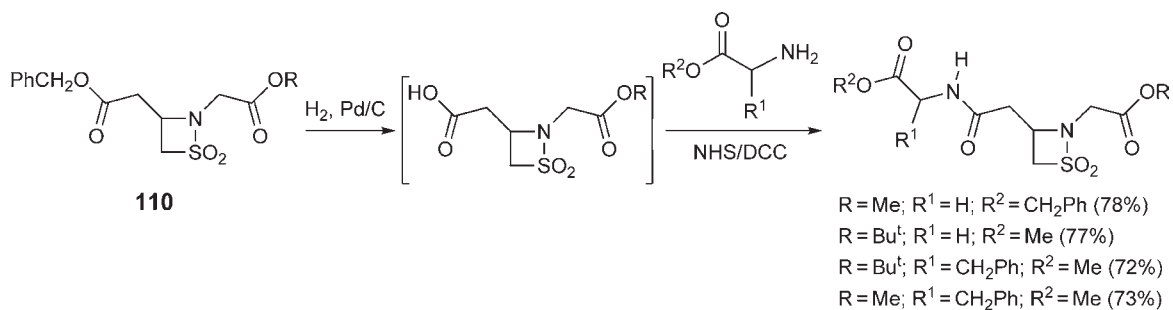
Starting from (*R*)-cysteine, chiral (*3R*)- β -sultam ethyl carboxylate was prepared in three steps. Subsequent reaction with an excess of Grignard reagent from bromobenzene afforded the (*3R*)- β -sultam **115**, which was applied successfully to the enantioselective catalytic reduction of aromatic ketones. This reduction was carried out using oxazaborolidine–borane reagent **116** generated *in situ* from the (*3R*)- β -sultam **115** with borane. Acetophenone was enantioselectively reduced to (*R*)-1-phenylethanol in 81% ee (Scheme 36) <1997TA2033>.



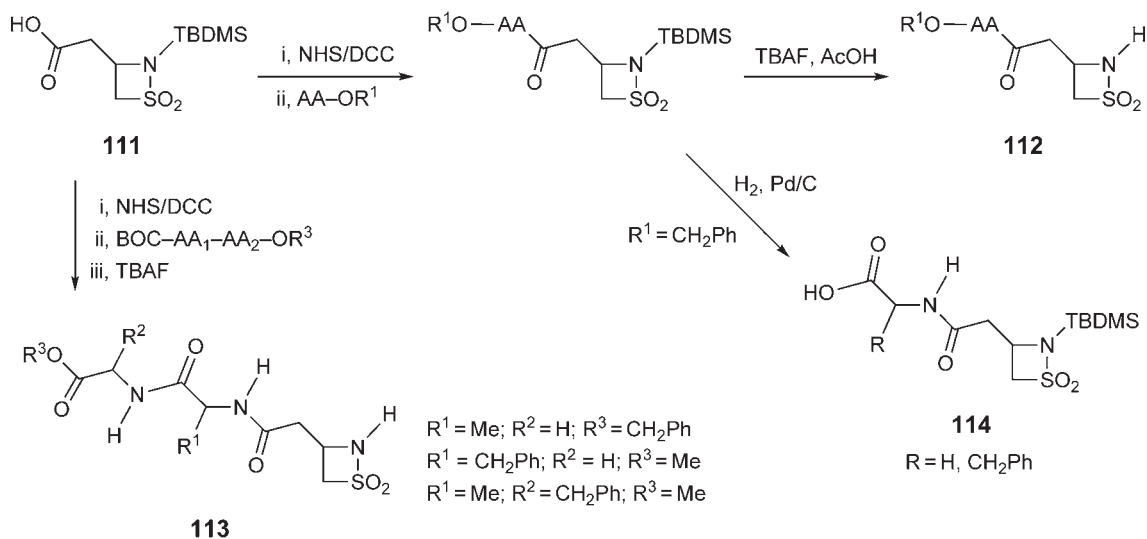
Scheme 31



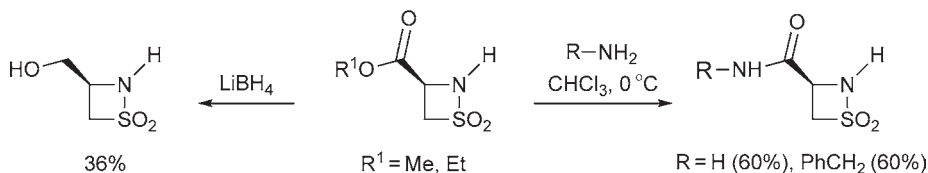
Scheme 32



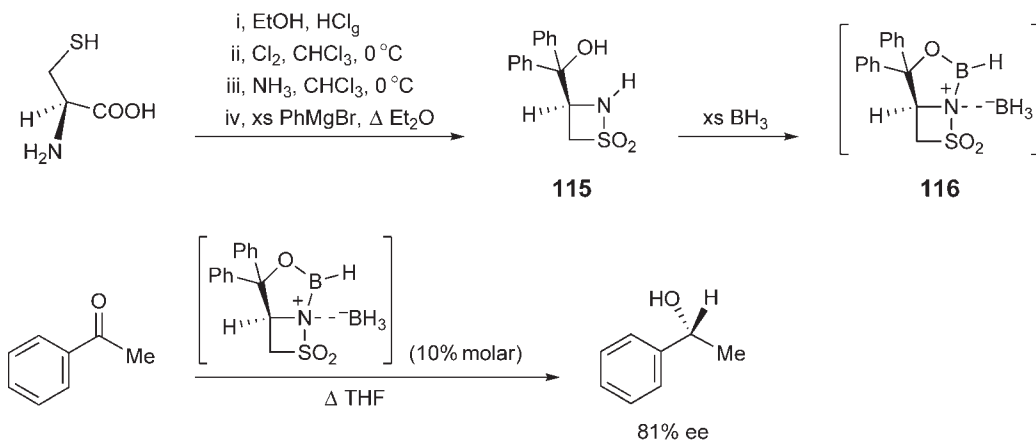
Scheme 33



Scheme 34

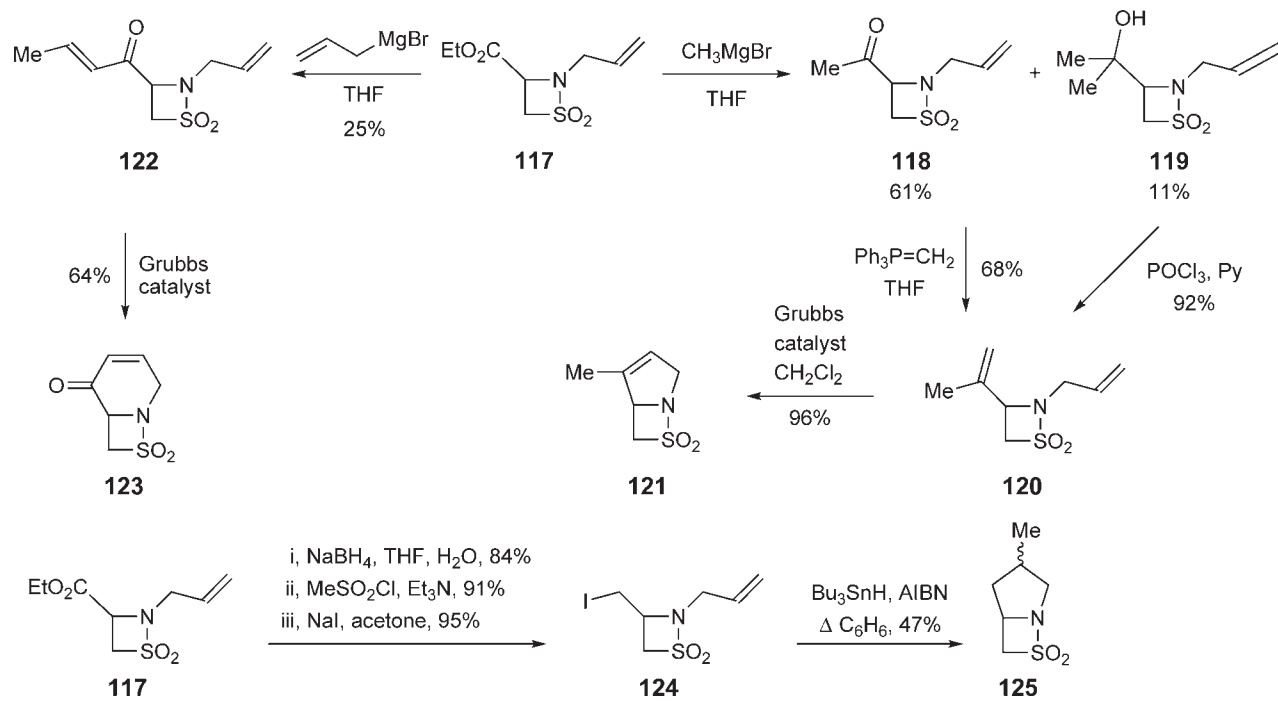


Scheme 35



Scheme 36

The availability of C-3-functionalized β -sultams provides an opportunity to synthesize bicyclic derivatives in a straightforward manner (Scheme 37). The controlled addition of methylmagnesium bromide to ester **117** gave rise to a chromatographically separable mixture of ketone **118** and alcohol **119**. Independent conversion to diene **120** was carried out via Wittig reaction from **118** or elimination using phosphorus oxychloride in pyridine from

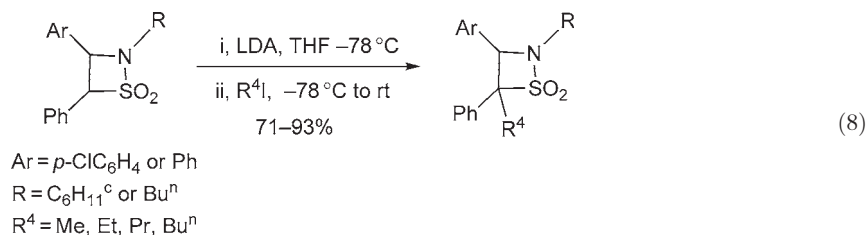


Scheme 37

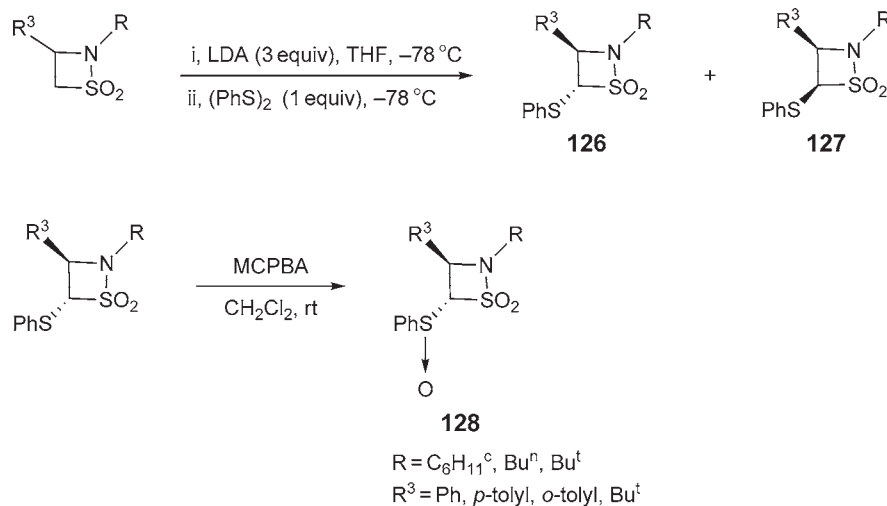
119. Ring-closing metathesis in the presence of Grubbs catalyst was then exploited to generate the bicyclic system **121**. However, the condensation of starting material **117** with 1 equiv of allylmagnesium bromide produced compound **122** which was submitted to a ring-closing metathesis to afford the bicyclic derivative **123**. The ester **117** was also transformed in three steps into the primary iodide **124**, which was treated with tributyltin hydride affording via a 5-*exo*-cyclization the bicyclic β -sultam **125** as a 3:1 mixture of diastereoisomers <2004CJC113>.

2.15.6.1.2 Reactivity at the C-4 position

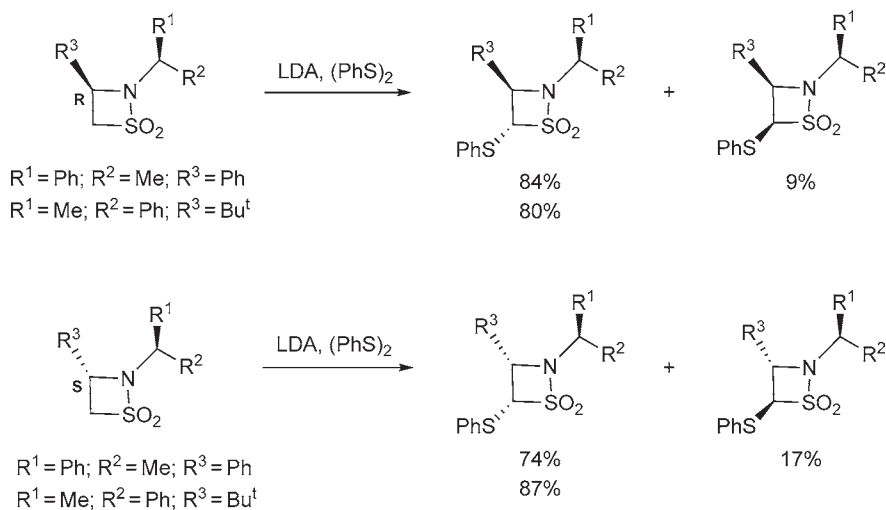
4,4-Disubstituted β -sultams can be prepared by treatment with lithium diisopropylamide (LDA) followed by reaction with an alkyl iodide. Alkylation of 3,4-diphenyl β -sultams proceeds stereoselectively to give products with a *cis*-relationship between the two aryl groups as the major products (Equation 8) <1998T8941>.



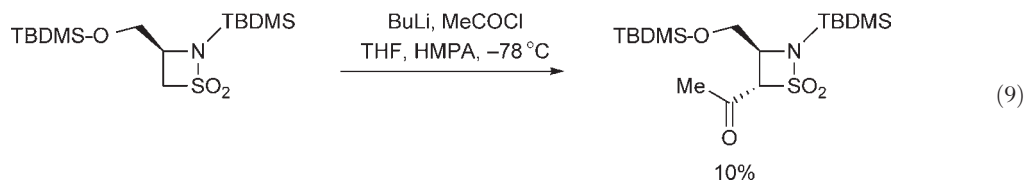
Similarly, the *trans*-3-substituted-4-sulfinyl β -sultams **126** can be synthesized as major products by treatment of 3-substituted β -sultams with LDA followed by reaction with diphenyl disulfide. These are accompanied by the 3,4-*cis*-isomers **127**. It should be noted that these *cis*-isomers can be converted to the *trans*-isomers by treatment with LDA in tetrahydrofuran (THF) at -78°C . Oxidation with *m*-chloroperbenzoic acid (MCPBA) provides *trans*-3-substituted-4-sulfinyl β -sultams **128** as mixtures of stereoisomers at the sulfoxide moiety. This strategy was applied to obtain chiral 3-substituted-4-sulfinyl β -sultams with a high diastereoselectivity (Scheme 38) <1998JOC8355>.



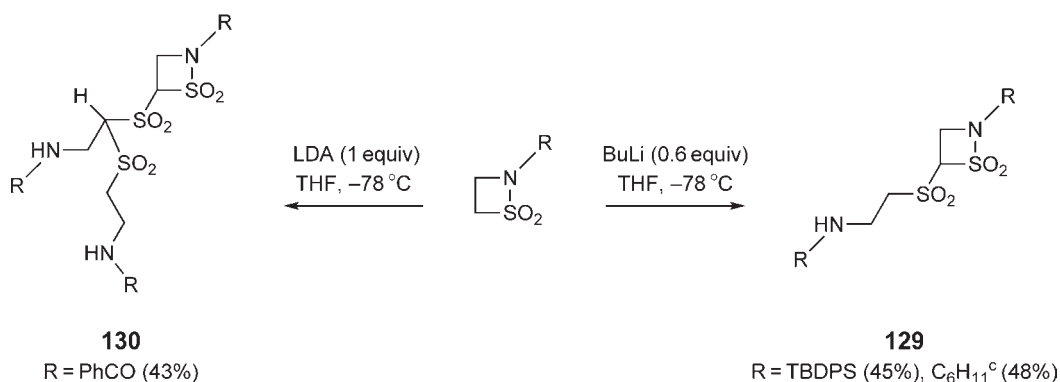
Diastereoselective acetylation at C-4 of 3-substituted β -sultams has been achieved with *trans*-stereoselectivity (Equation 9) <2004HCA90>.



Scheme 38



The introduction of functional groups at C-4 causes special problems, as the introduction of a heteroatom results in an unstable, aminal-like structure, which is readily hydrolyzed. ‘Dimeric’ (aminoethyl)sulfonyl β -sultams **129** were isolated in nearly quantitative yield by addition of a solution of butyllithium at -78°C to a *N*-substituted β -sultam followed by hydrolytic workup. When the reaction was performed on *N*-benzoyl β -sultam, a second deprotonation occurred yielding the ‘trimeric’ compound **130** as a mixture of two diastereoisomers (Scheme 39) <2004HCA1574>.



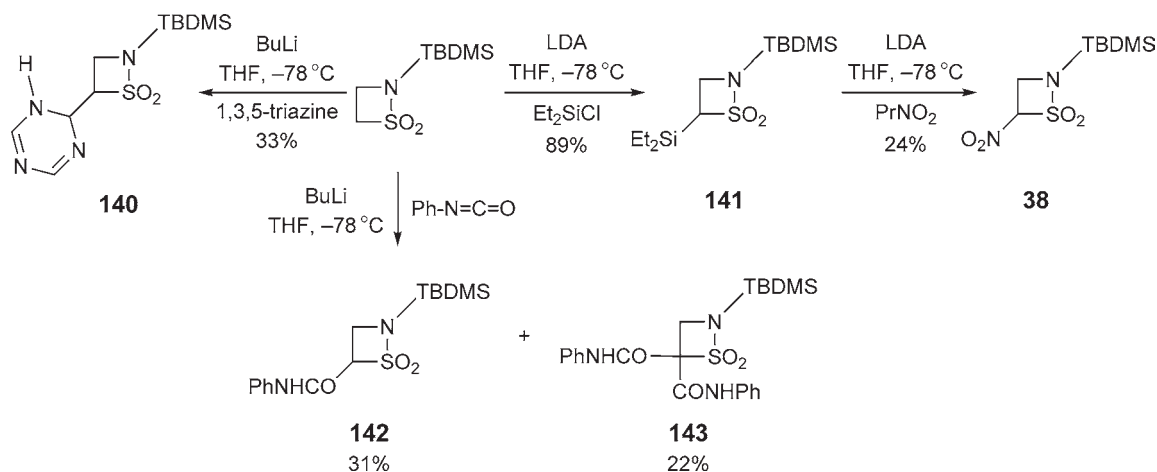
Scheme 39

Substitution at the C-4 position has been described for *N*-TBDPS β -sultam (TBDPS = *t*-butyldiphenylsilyl) by deprotonation followed by reaction with methyl chloroformate or benzophenone yielding only the diacetylated compound **131** and the expected alcohol **132**, respectively (Scheme 40) <2004HCA1574>.

Scheme 40

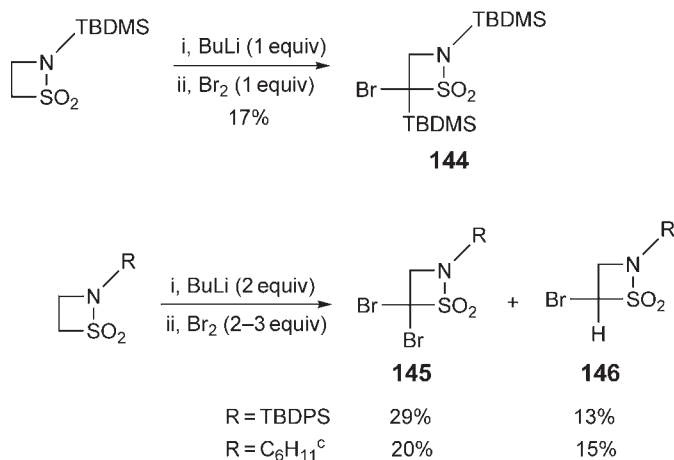
Scheme 41

Following the same strategy, the dihydrotriazinyl derivative **140** has been obtained by deprotonation and the use of triazine as the C-electrophile reagent. 4-Nitro- β -sultam **38** has been prepared for the first time as a very moisture-sensitive and unstable liquid by silylation to the 4-monosilylated product **141**, followed by reaction with nitropropane at -78°C . Reaction of *N*-TBDMS β -sultam with phenyl isocyanate yields mixtures of 4-mono- and 4,4-disubstituted products **142** and **143**, respectively (Scheme 42) <2004HCA1574>.



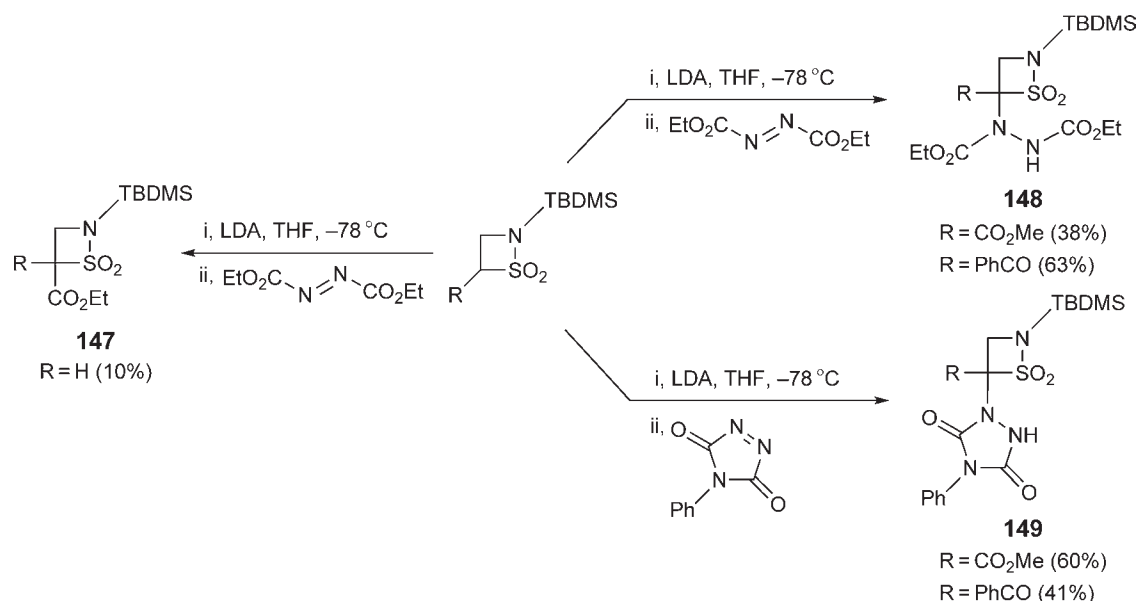
Scheme 42

To explore the possibility of halogenation at the C-4 position, deprotonation of *N*-TBDMS β -sultam with equimolar amounts of butyllithium followed by reaction with bromine leads to a stable compound **144** formed by a *trans*-silylation followed by bromination of the intermediate silylated β -sultam. When an excess of butyllithium is used, mixtures of mono- and dibrominated products **145** and **146** are isolated (Scheme 43) <2004HCA1574>.



Scheme 43

Some unexpected results were obtained when deprotonation with LDA was followed by reaction with diethyl azodicarboxylate (Scheme 44). The ester **147** was isolated suggesting that this reagent could be considered as a C-electrophile rather than a N-electrophile. However, when this reaction was performed with a 4-monosubstituted β -sultam, the expected N-addition products **148** were isolated. N-Addition occurs also with 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)dione leading to compound **149** <2004HCA1574>.

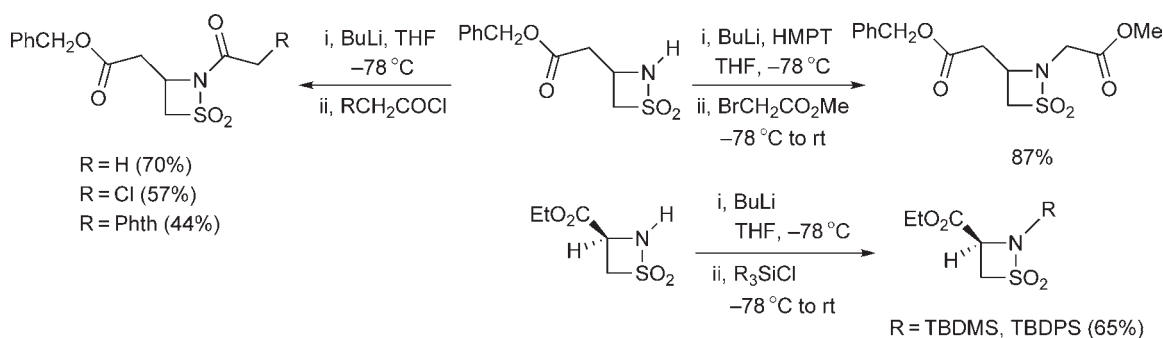


Scheme 44

2.15.7 Reactivity of Substituents Attached to Ring Heteroatoms

2.15.7.1 1,2-Thiazetidine 1,1-Dioxides

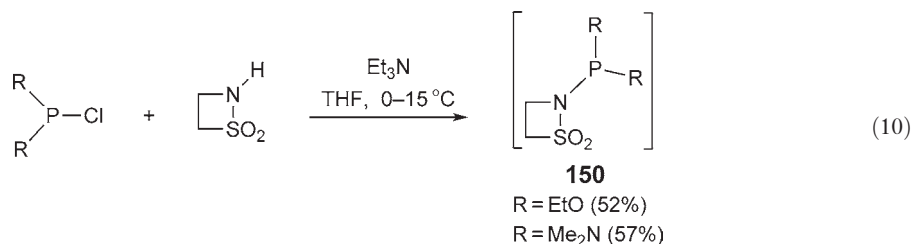
Alkylation at the nitrogen atom of the β -sultam ring has successfully been performed by deprotonation with butyllithium (sodium and potassium hydroxides or amines lead to partial or complete ring opening) followed by reaction with alkyl bromoacetate at -78°C in THF and in the presence of hexamethylphosphoric triamide (HMPT). *N*-Protected β -sultams are isolated after silylation and acylation in the presence of butyllithium (Scheme 45). The latter methodology has been extended to reaction of amino acid derivatives using BOC- or carbobenzyloxy (Cbz) *N*-protected amino acid carboxyanhydrides [2004M55, 2004HCA90].



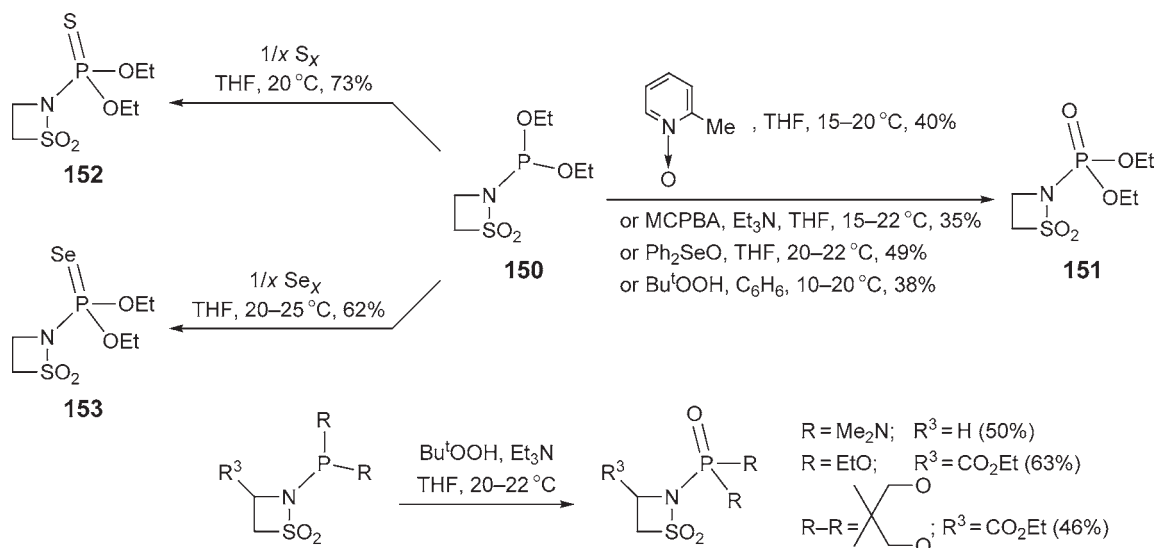
Scheme 45

A synthetic approach to β -sultams containing a direct bond between a tri- or tetracoordinated phosphorus atom and the nitrogen atom of the 1,2-thiazetidine 1,1-dioxide ring has been realized by direct phosphitylation or phosphorylation at nitrogen. Unfortunately, attempts to synthesize *N*-phosphorylated β -sultams by reaction with diethyl phosphorochloridate and diethyl phosphorobromidate, generated *in situ* from diethyl phosphate and carbon tetrachloride or carbon tetrabromide, failed. However, when the β -sultam is treated with freshly distilled diethyl phosphorochloridite or tetramethylphosphorodiamidous chloride in the presence of triethylamine, the expected *N*-diethylphosphito and *N*-phosphorodiamidous β -sultams **150** are obtained (Equation 10). β -Sultams unsubstituted

on nitrogen can also be used as substrates and N-phosphitylated compounds have been isolated from L-(–)-3-carboethoxy-1,2-thiazetidin-3-one 1,1-dioxide. All of these β -sultams show relatively low stability and have not been isolated in their pure form <1999HAC61>.



Oxidation of *N*-diethylphosphito to *N*-diethylphosphono derivatives **151** has been performed using 2-picoline *N*-oxide, MCPBA, diphenyl selenoxide, or *t*-butyl hydroperoxide (TBHP). The latter was selected as the most efficient reagent. Similarly, the N-phosphitylated β -sultams undergo reactions of oxidative addition of elemental sulfur and selenium giving 2-thio- and 2-selenophosphono β -sultams **152** and **153**, respectively, in satisfactory yields (Scheme 46) <1999HAC61>.

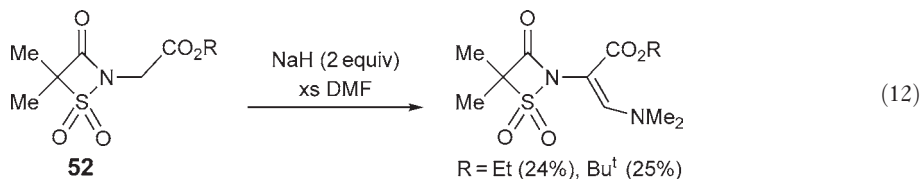


Scheme 46

Commercially available (*1S*)(+)-(10-camphorsulfonyl)oxaziridine (CSO) and (*1S*)(+)-(8,8-dichlorocamphorsulfonyl)oxaziridine (DCSO) were used as oxidizing reagents rapidly furnishing quantitative silyl phosphite derivatives (Equation 11) <1998TL7123>.



Condensation of dimethylformamide (DMF) in the presence of sodium hydride occurs on the N-CH₂ group of the 1,2-thiazetidin-3-one 1,1-dioxide derivative **52**, due to the activation of the methylene group by the electron-withdrawing ester group (Equation 12) <1997HCA671>.

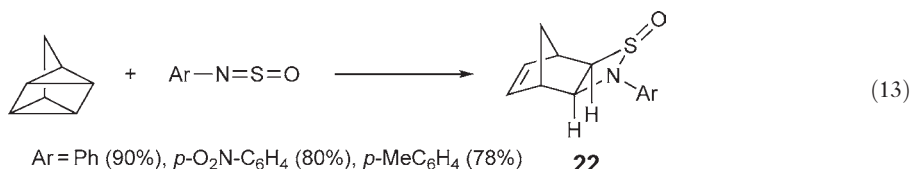


2.15.8 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

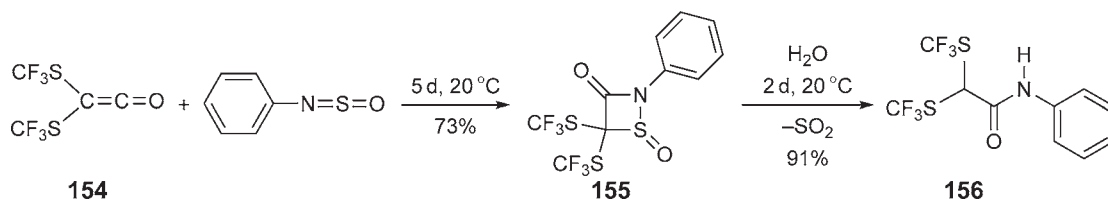
2.15.8.1 1,2-Thiazetidine S-Oxide

2.15.8.1.1 Ring formation by [2+2] cycloaddition

Fused 1,2-thiazetidine *S*-oxides **22** are produced in one step from readily available aryl sulfonamides by cycloaddition with quadricyclane (Equation 13) <1997SL167, 1997SL634>.



Bis(perfluoroorganylsulfonyl)ketene **154** reacts with *N*-phenylsulfonylamine by [2+2] cycloaddition to yield the corresponding 1,2-thiazetidine-3-one *S*-oxide **155** which could be isolated by distillation (b.p. 42 °C). However, compound **155** is sensitive to hydrolysis and is converted in moist air to the amide **156** (Scheme 47) <1998JFC9>.

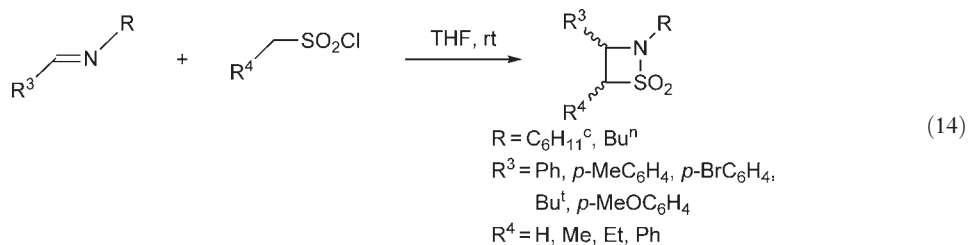


Scheme 47

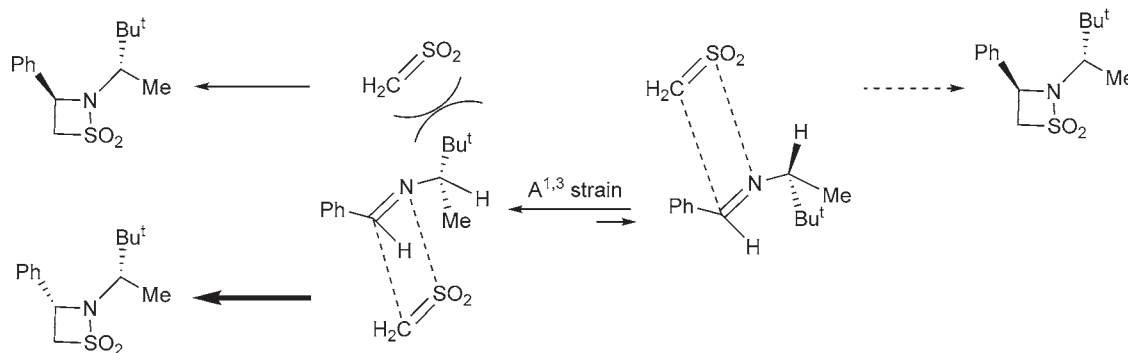
2.15.8.2 1,2-Thiazetidine 1,1-Dioxides

2.15.8.2.1 Ring formation by [2+2] cycloaddition

4-Monosilyl β -sultams are prepared using [2+2] cycloaddition by treatment of methanesulfonyl chloride and an aryl or *tert*-butylimine in THF at room temperature. Better yields are obtained using a *t*-butylimine (83%) than an aryl imine (18–59%) (Equation 14). β -Sultams obtained as a mixture of two isomers are separable by silica gel column chromatography <1998CPB757>.



A diastereoselective synthesis of β -sultams by 1,3-asymmetric induction in [2+2] cycloaddition of a sulfene intermediate and a chiral imine has been described (**Scheme 48**), and it was found that *N*-alkylimines give better diastereoselectivity than *N*-arylimines. The best selectivity was found in the case of *N*-(1-*t*-butylethyl)imine (67% yield, >95% de), and the diastereoselectivity was independent of the size and conformation of the *N*-substituents in the imines. Diastereoisomers bearing an *N*-aryl group were separable by silica gel column chromatography <1998JOC8355>.



Scheme 48

The first solid-phase synthesis of β -sultams to be used for the construction of sulfonyl analogues of β -lactam combinatorial libraries has been reported (**Scheme 49**) <1997JOC8177>. The strategy was based on the [2+2] cycloaddition of activated sulfenes with immobilized imines as its critical step. The imine intermediates generated from polymer-immobilized amino acids and aldehydes were reacted with (chlorosulfonyl)acetates to afford the solid-phase tethered β -sultam products **157**. The latter were released from the support by acidic cleavage or photocleavage, depending on the linker. β -Sultam products **158** are obtained in good yield and purity (58–90% yield, 70–95% purity). Studies employed polystyrene-based Sasrin resin possessing the highly acid-labile alcohol linker or the poly(ethylene glycol)-based TentaGel resin derivatized with an α -methyl-6-nitroveratryl alcohol-based photolabile linker. Immobilized 4-(9-fluorenyl)methoxycarbonyl β -sultams are further functionalized on supports to afford, upon cleavage, the respective carboxy and amido thiazetidine (**159** and **160**) derivatives. This synthetic method is expected to use β -sultam libraries for screening identification of new antibacterial agents.

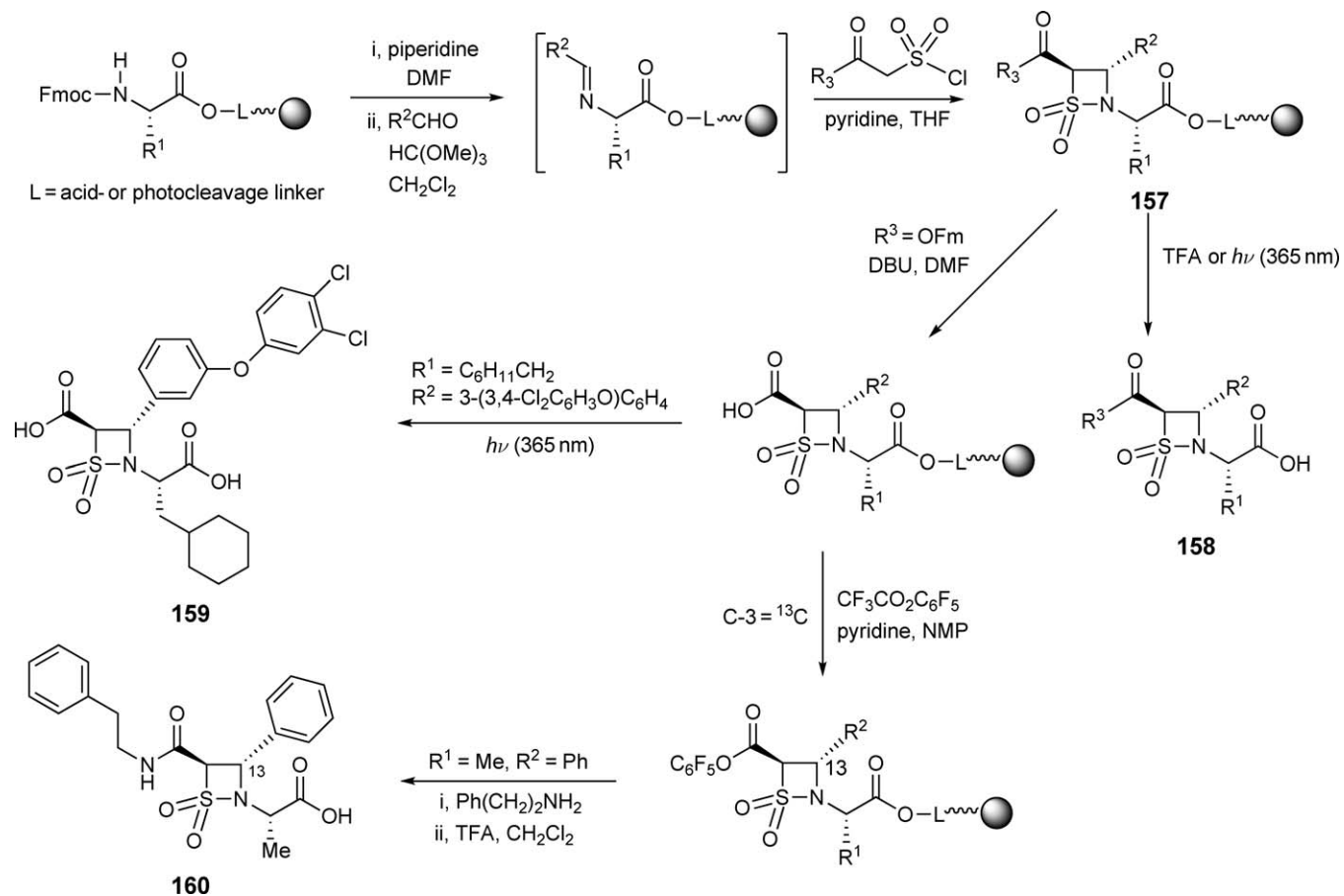
2.15.8.2.2 Ring formation by cyclization with formation of the N–S Bond

The synthesis of 3-alkyl-substituted 1,2-thiazetidine 1,1-dioxides starts by transformation of the amino acids L-Val, L-Leu, L-Ile, and L-Phe into amino alcohols. These are converted via the bromides to the corresponding thiols **161**. Immediate oxidative chlorination affords either sulfonyl chloride hydrochlorides or sulfonic acids **162** which are transformed into the parent β -sultams **163** <2004HCA90>. Similarly, L-cystine derivatives **164** have also been transformed into the parent β -sultams **165** by oxidative chlorination followed by cyclization (**Scheme 50**) <1997LA1261, 2004HCA90>.

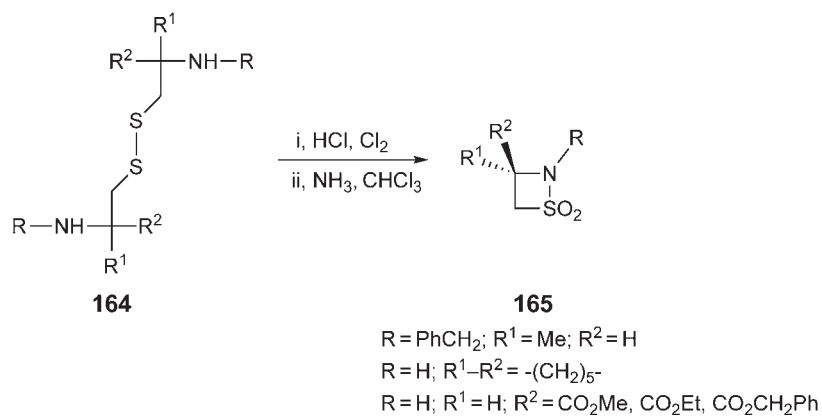
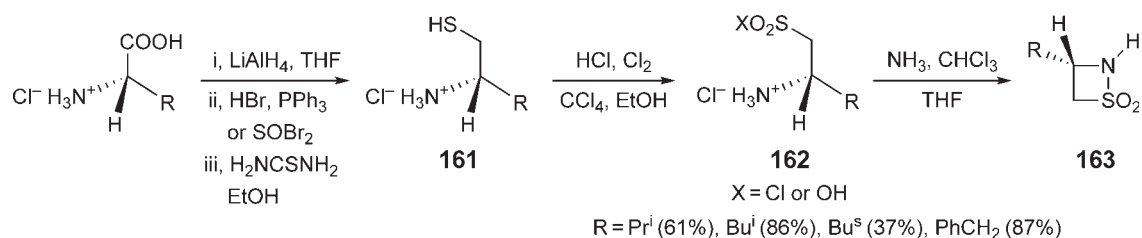
This oxidative chlorination–cyclization strategy has also been applied to the synthesis of the bicyclic β -sultam **166** from chiral morpholine derivatives (**Scheme 51**) <2004HCA90>.

β -Sultam **28** has been prepared using two different routes. In the first route, (*S*)-benzyl- β -homocysteine was obtained by fractional crystallization of the brucine salt of the racemic *N*-formyl derivative **167** followed by deformylation. The resultant amine **168** was then cyclized via the oxidative chlorination route. To prove the stereochemical assignment, a second route was devised starting from BOC-L-Asp(OBn) **169**. Transformation of the carboxylic acid function into a benzylmercaptomethylene group was followed by oxidative chlorination and ring closure with ammonia to yield the identical pure (*S*)-enantiomer (**Scheme 52**) <2004M979>.

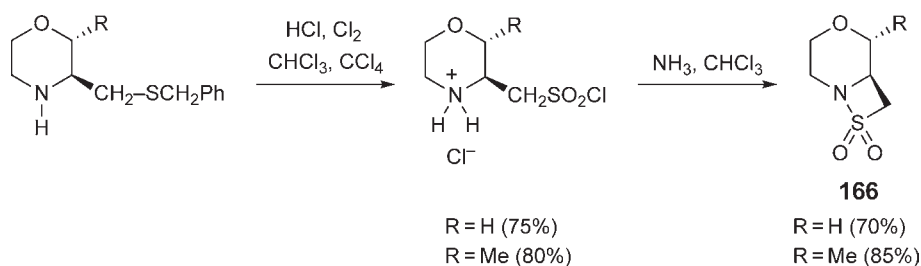
3-Carboxybenzyl-4,4-dimethyl β -sultam **172** has been synthesized stereospecifically from the hydrochloride of D-penicillamine benzyl ester **170**. As oxidative chlorination was not possible, the thiol functionality was oxidized using bromine in acetic acid to give the corresponding sulfonic acid **171**. After chlorination, cyclization of this taurine derivative afforded the (*S*)-enantiomer of the β -sultam **172** (**Scheme 53**). The optical purity was confirmed by ¹H and ¹³C NMR spectroscopy using the chiral shift reagent praseodymium(III) tris[3-heptafluoropropylhydroxymethylene]-*d*-camphorate] (Pr(hfc)₃) and by the circular dichroism spectrum <2004HCA90>.



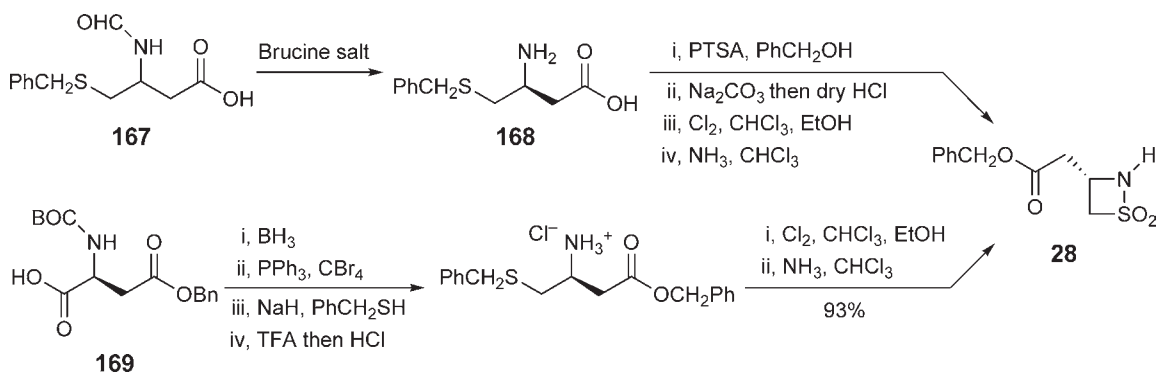
Scheme 49



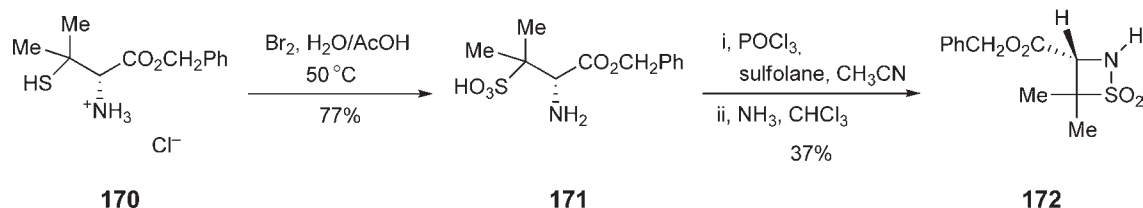
Scheme 50



Scheme 51

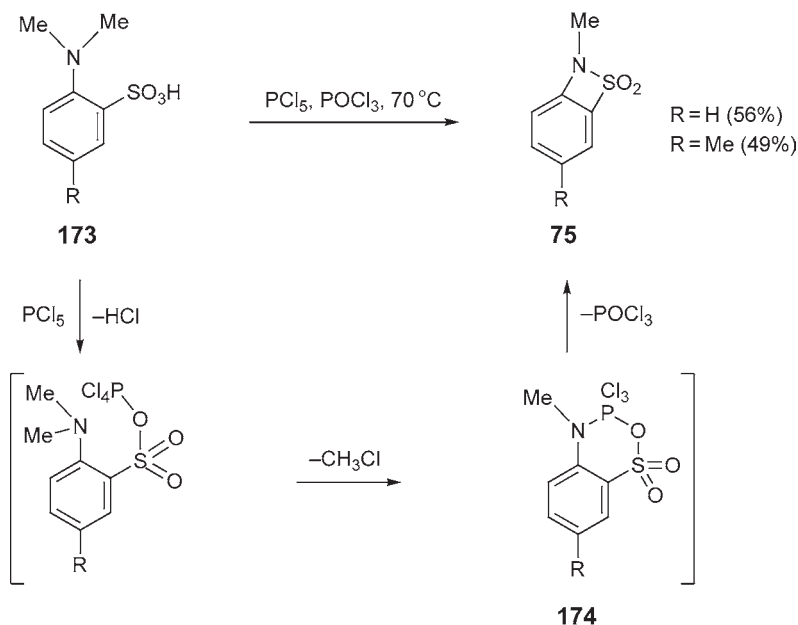


Scheme 52



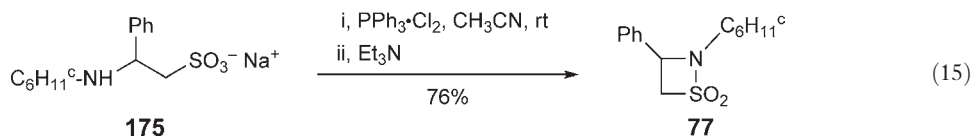
Scheme 53

A novel synthesis of the *N*-methyl-1,2-benzosultams **75** was described using an unexpected demethylative intramolecular cyclization reaction (Scheme 54). When the sulfonic acid **173** was heated at 60–80 °C with phosphorus oxychloride in the presence of phosphorus pentachloride, the β -sultam **75** was obtained instead of the expected (dimethylamino)benzenesulfonyl chloride. The speculated mechanism considers the reaction of the sulfonic acid group with phosphorus pentachloride giving the intermediate **174**, which then forms a six-membered ring with the neighboring dimethylamino group and the final elimination of chloromethane <1998JOC2348>.

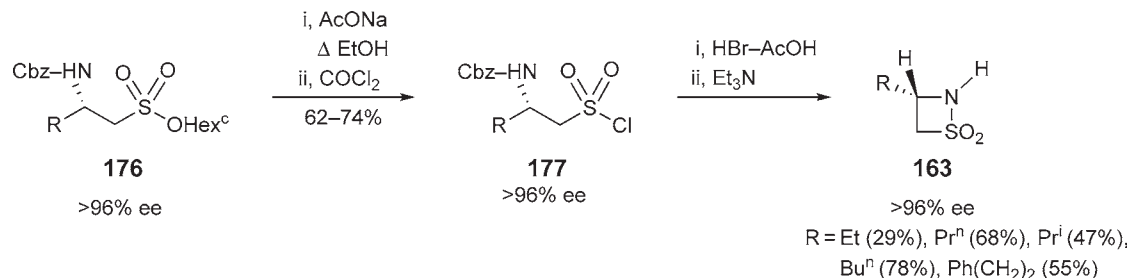


Scheme 54

Triphenylphosphine dichloride was used as a mild halogenating reagent to transform the sodium sulfonate salt **175** into the corresponding sulfonyl chloride. Further treatment using triethylamine gave the β -sultam **77** in satisfactory yield (Equation 15) <1998S423>.

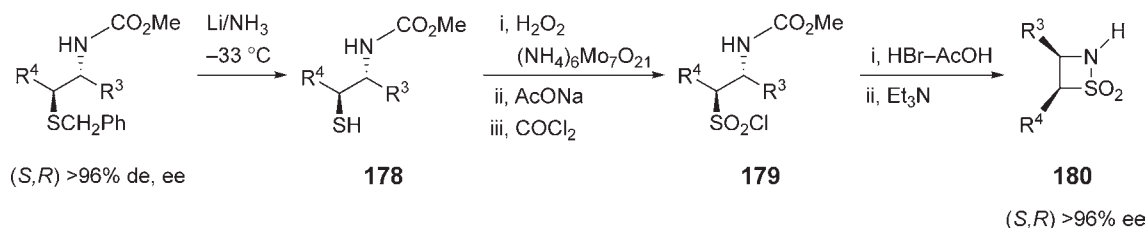


An efficient asymmetric synthesis of the 3-substituted β -sultams **163** has been reported. The key step of the synthesis is the Lewis acid-catalyzed aza-Michael addition of the enantiopure hydrazines (*S*)-1-amino-2-methoxy-methylpyrrolidine (SAMP) or (*R,R,R*)-2-amino-3-methoxymethyl-2-azabicyclo[3.3.0]octane (RAMBO) to the alkenylsulfonyl sulfonates **176**. β -Hydrazino sulfonates were obtained in good yield and excellent enantioselectivity. Cleavage of the sulfonates followed by chlorination resulted in the corresponding sulfonyl chlorides **177**. The (*S*)-3-substituted β -sultams **163** have been obtained in moderate to good yields and high enantioselectivity over two steps, an acidic N-deprotection followed by *in situ* cyclization promoted by triethylamine (**Scheme 55**) <2002TL5109, 2003S1856>.



Scheme 55

The successful application of sulfanyl amines in the diastereoselective and enantioselective synthesis of *cis*-3,4-disubstituted β -sultams has been reported (**Scheme 56**). The protocol is based on the oxidation of the 1,2-aminothiols **178** with hydrogen peroxide and ammonium heptamolybdate. Chlorination of the resulting β -aminosulfonic acids was achieved using phosgene. The β -aminosulfonyl chlorides **179** obtained were cyclized under basic conditions and without epimerization to yield the *cis*-3,4-disubstituted β -sultams **180** (>96% de, ee) (**Table 13**) <2005S1807>.

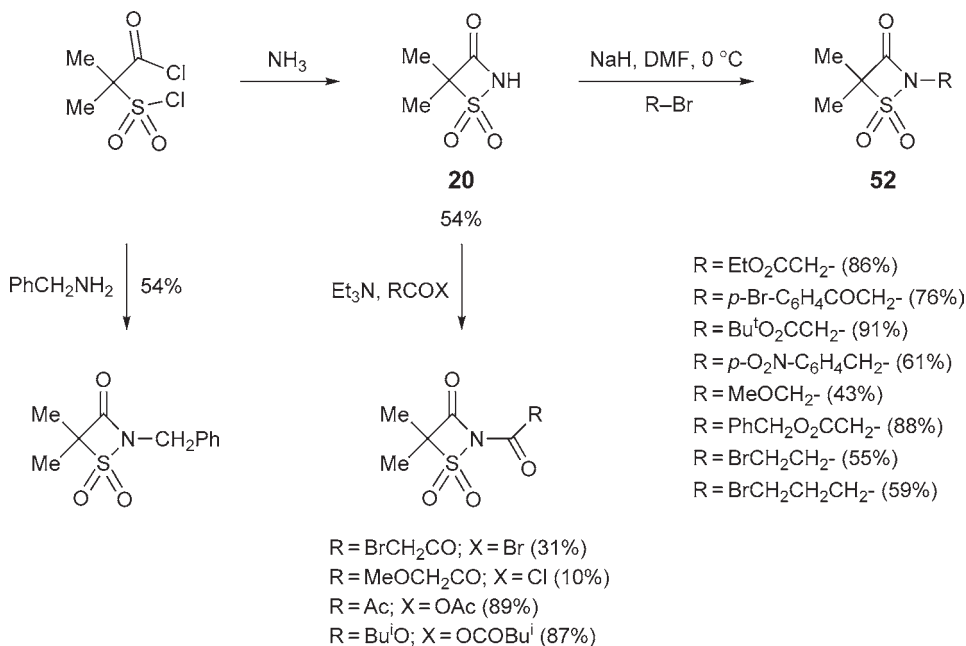


Scheme 56

Table 13 Synthesis of the *cis*-3,4-disubstituted β -sultams **180** by cyclization of the 1,2-aminosulfonyl chlorides **179** <2005S1807>

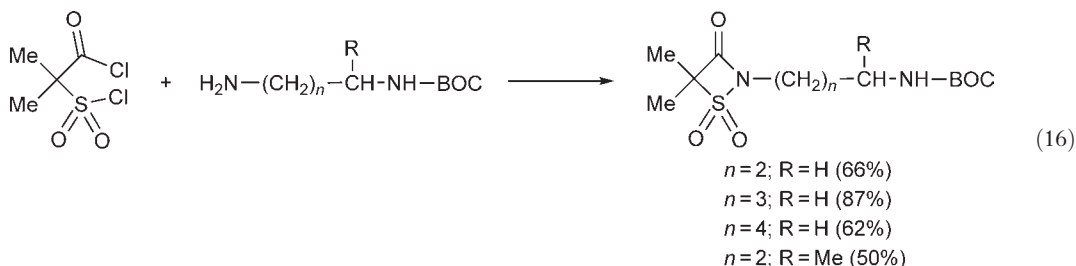
Entry	R ³	R ⁴	Yield (%)	de (%)
i	Bu ⁿ	Bu ⁱ	99	>96
ii	Bu ⁿ	PhCH ₂	44	>96
iii	Me	Ph(CH ₂) ₂	71	>96
iv	Bu ⁿ	Ph(CH ₂) ₂	99	>96
v	Hex ⁿ	Ph(CH ₂) ₂	44	>96
vi	Bu ⁿ	Hex ^c -CH ₂	52	>96

N-Unsubstituted and *N*-benzyl-1,2-thiazetidin-3-one 1,1-dioxides are available by ring closure of 2-(chlorosulfonyl)-2-methylpropionyl chloride, which can itself be obtained from isobutyric acid in improved yields up to 60%. N-Alkylated derivatives **52** have been synthesized in 43–91% yield using sodium hydride in DMF and bromo compounds bearing electron-withdrawing substituents in the α -position (Scheme 57) <1997HCA671>.



Scheme 57

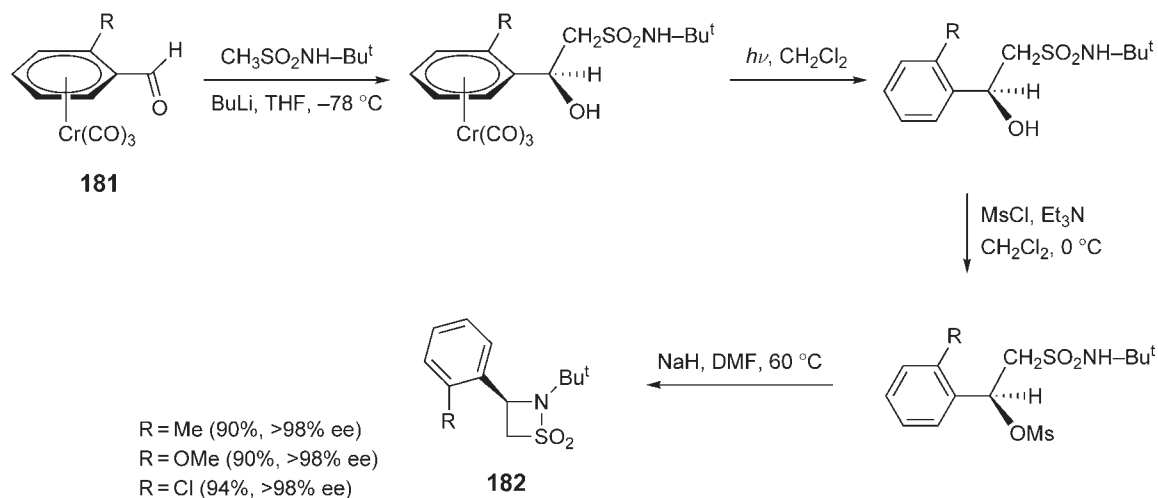
N-(*t*-Butoxyaminoalkyl)-1,2-thiazetidin-3-one 1,1-dioxides have been prepared by ring closure of several mono-BOC-protected diamines (Equation 16) <1999HCA354>.



2.15.8.2.3 Ring formation by cyclization with formation of the C-N Bond

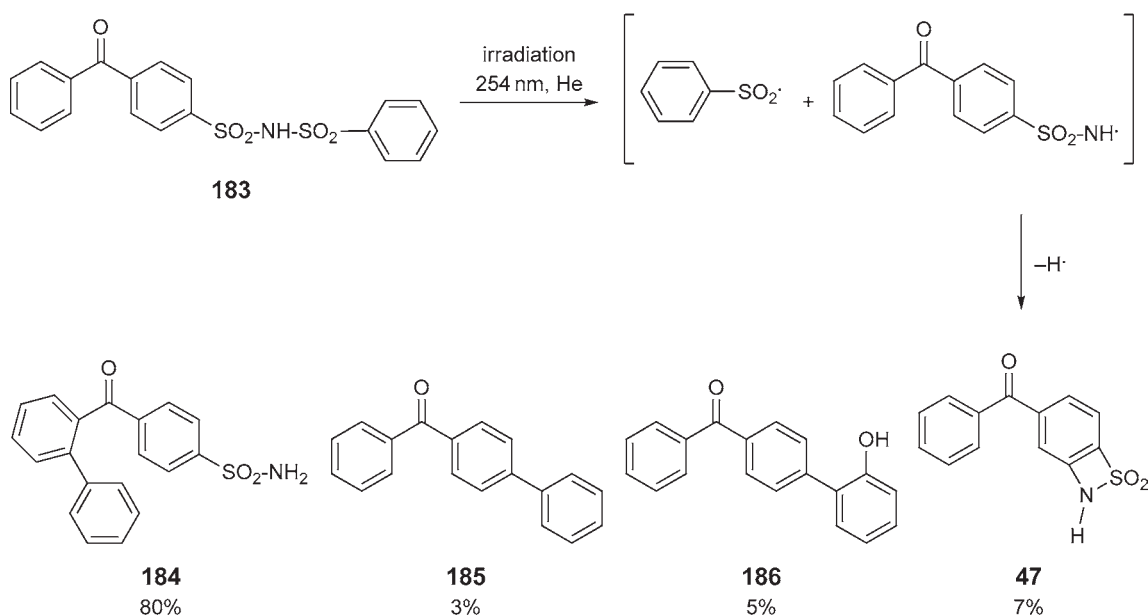
Reaction of the (1*R*), (–) or (1*S*), (+)-tricarboxyl(2-substituted benzaldehyde)chromium complexes **181** with the dianion of *t*-butylmethanesulfonamide affords, after decomplexation and intramolecular cyclization, the enantiomerically pure 3-(2-phenyl-substituted) β -sultam derivatives **182**. The reaction of the dianion on the pro-stereogenic formyl group is key to the diastereoselective formation of the new stereogenic center, and it is controlled by means of

the planar chirality produced by the $\text{Cr}(\text{CO})_3$ unit. After this center is created in high enantiomeric purity, the organic ligand is removed from the complex (**Scheme 58**) <1999T14089>.



Scheme 58

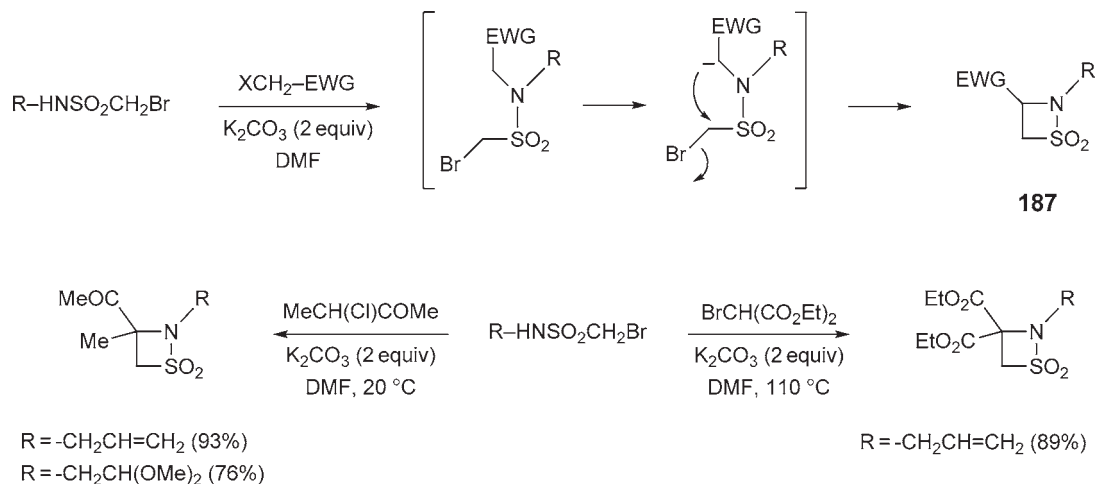
Photodecomposition of the benzenesulfonamide derivative **183** in aqueous solution was investigated by irradiation from a 254 nm low pressure lamp under a helium atmosphere. Homolytic fission of the S–N bond gives arylsulfonyl and arylsulfonylamino radicals. Cyclization from the latter radical via C–N bond formation and hydrogen atom abstraction afforded the β -sultam **47** in 7% yield. Other photodissociation processes resulted in the formation of compounds **184–186** (**Scheme 59**) <2002JPH109>.



Scheme 59

2.15.8.2.4 Ring formation by cyclization with formation of the C–C Bond

Reaction of N-substituted bromomethanesulfonamides with 2 equiv of potassium carbonate and an α -haloketone, ester, or nitrile leads directly to the β -sultams **187** substituted at the C-3 position by an EWG. This base-promoted condensation can be used with α -halo ketones, esters, and nitriles where a second S_N2 intramolecular displacement can operate in tandem fashion (Scheme 60). This domino alkylation sequence exhibits a reactivity order where ketone > nitrile > ester (Table 14). The process is particularly efficient when diethyl bromomalonate or 3-chloro-2-butanone are involved <2004CJC113>.



Scheme 60

Table 14 Synthesis of β -sultams substituted at the C-3 position by an EWG <2004CJC113>

Entry	R	X	EWG	Yield (%)
i	$-\text{CH}_2\text{CH}=\text{CH}_2$	Cl	$-\text{COMe}$	59
ii	$-\text{CH}_2\text{CH}=\text{CH}_2$	Br	$-\text{COPh}$	81
iii	$-\text{CH}_2\text{CH}=\text{CH}_2$	Br	$-\text{CO}_2\text{Et}$	56
iv	$-\text{CH}_2\text{CH}=\text{CH}_2$	Br	$-\text{CN}$	61
v	$-\text{CH}_2\text{Ph}$	Br	$-\text{CO}_2\text{Et}$	70

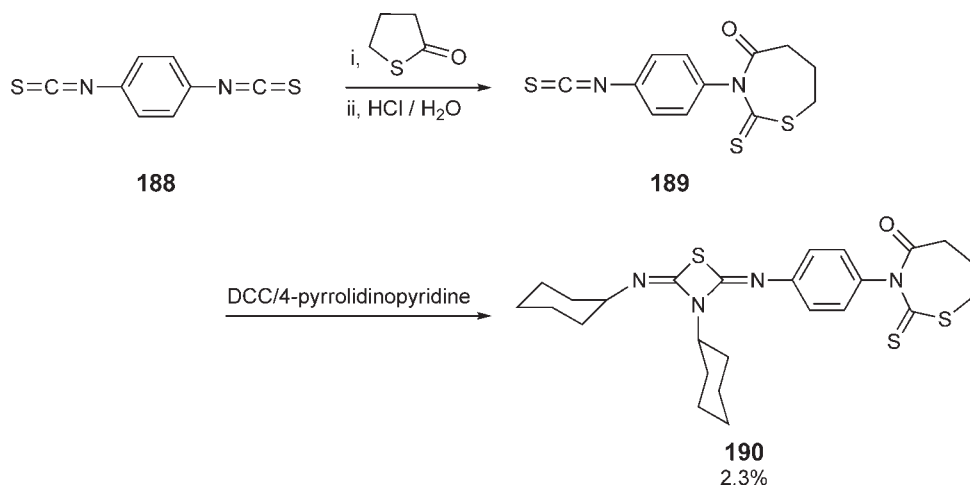
2.15.8.3 1,3-Thiazetidines

2.15.8.3.1 Ring formation by [2+2] cycloaddition

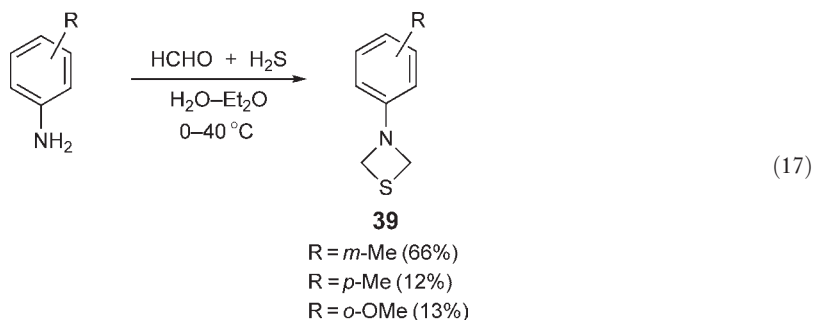
Reaction of *p*-phenylene diisothiocyanate **188** with γ -thiobutyrolactone in an alkaline medium yields a 4-thiocarbamoylthiobutyric acid derivative after acidification. This is cyclized to the 2-thioxo-1,3-thiazepan-4-one derivative **189**. The remaining isothiocyanate functionality is subjected to a [2+2] cycloaddition with *N,N'*-dicyclohexylcarbodiimide (DCC) forming a 1,3-thiazetidine system **190** where both isothiocyanate groups have reacted (Scheme 61) <1999JHC1167>.

2.15.8.3.2 Ring formation by [3+1] cycloaddition

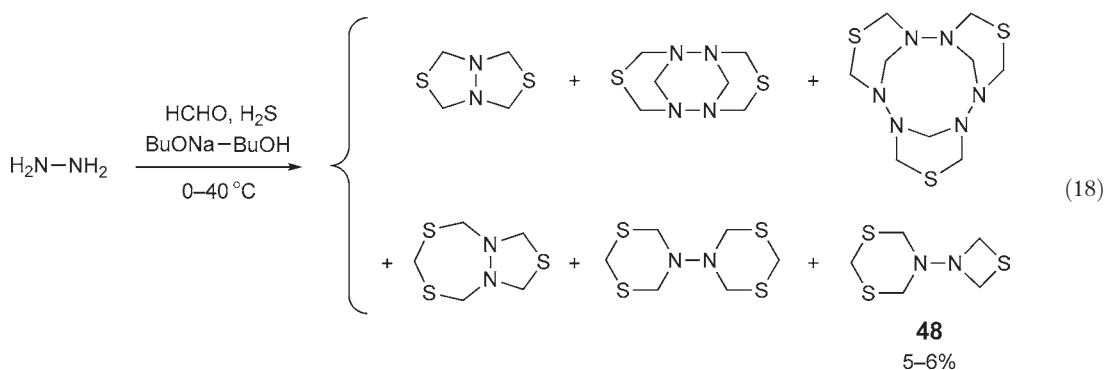
Primary aromatic amines characterized by high mobility of hydrogen atoms may be thiomethylated using formaldehyde and hydrogen sulfide (Equation 17) <2003RCB1817>.



Scheme 61

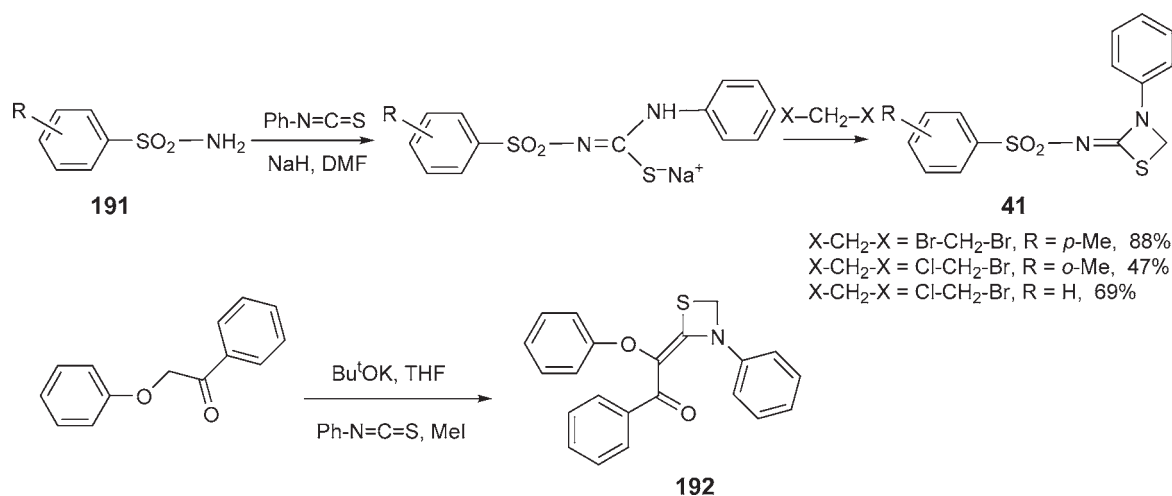


Condensation of hydrazine with formaldehyde (37% solution) and hydrogen sulfide in water in the presence of a sodium butoxide–butanol buffer (pH 10.75–11.5) gives a mixture of products. The reactant ratio is an important factor in determining the product ratio and, when a 6:4:1 ratio of $\text{HCHO}-\text{H}_2\text{S}-\text{H}_2\text{NNH}_2$ was used, the perhydro-*N*-(1,3-thiazet-3-yl)-1,3,5-dithiazine **48** was isolated in 5–6% yield in addition to other S,N-heterocycles (Equation 18) <2006RJO145>.

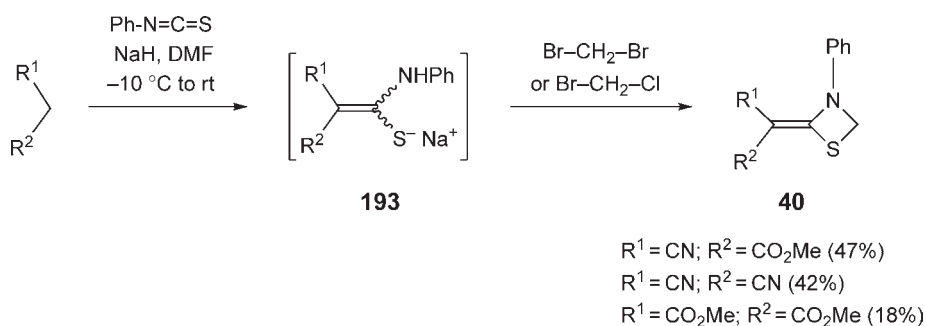


1,3-Thiazetidines may be prepared by alkylation of the sodium salts obtained conveniently by thiocarbamylation of the sulfonamides **191** with isothiocyanates in the presence of sodium hydride in DMF. Alkylation with bromochloromethane or dibromomethane yields the substituted 2-imino-1,3-thiazetidines **41** <2002SUL105>. Phenoxyacetophenone was thiocarbamoylated by treatment with phenyl isothiocyanate in the presence of potassium *tert*-butoxide and methyl iodide to afford 1,3-thiazetidine derivative **192** in 28% yield <1996SUL1> (Scheme 62).

Thiocarbamylation of malonic acid derivatives with phenyl isothiocyanate gives the sodium salts **193** which are not isolated. Alkylation of these salts *in situ* using dibromomethane or bromochloromethane yields the 1,3-thiazetidine derivatives **40** (Scheme 63) <2005MI499>.

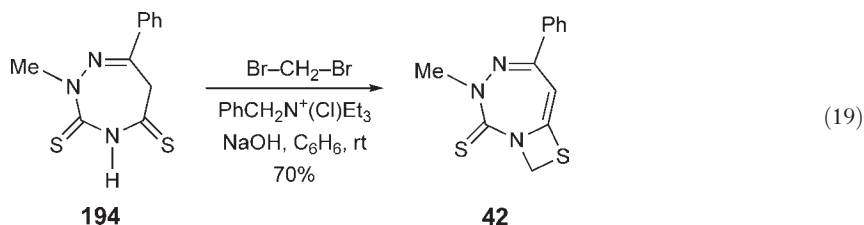


Scheme 62



Scheme 63

Condensation of dibromomethane with the 1,2,4-triazepine **194** in phase-transfer catalysis conditions provides efficient and facile access to the biheterocyclic triazepine **42** with high regioselectivity (Equation 19) <1997TL2087>.



Treatment of 2-thiouracil with diiodo- or dibromomethane in the presence of sodium hydride in DMF gave the dimeric heterocycle **195** as a main product together with small amounts of the 1,3-thiazetidine derivative **196** and the trimeric heterocycle **197** (Equation 20; Table 15) <1996CL1099>.

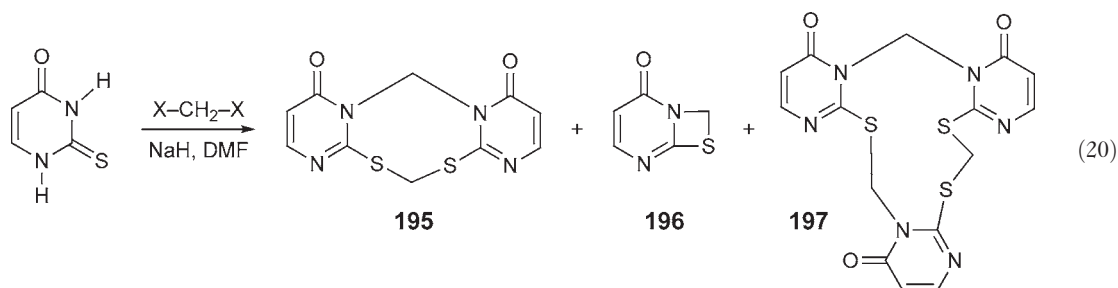


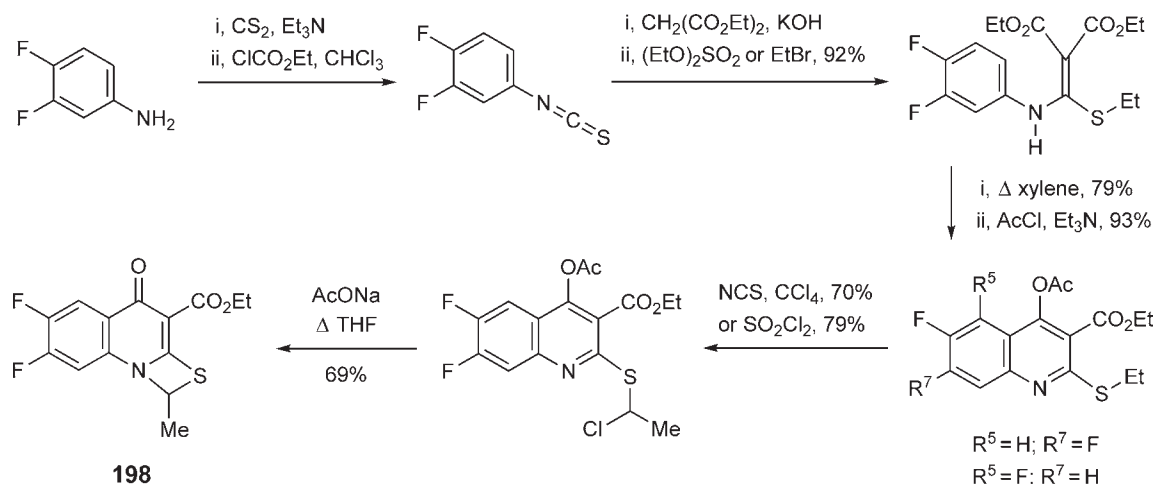
Table 15 Synthesis of the 1,3-thiazetidine derivative **196** <1996CL1099>

Entry	X	Yield (%)		
		195	196	197
i	Br	67	4	5
ii	I	70	3	4

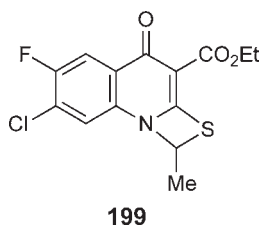
2.15.8.3.3 Ring formation by cyclization with formation of the C–N Bond

A large number of tricyclic fluoroquinolones, in which the 1,3-thiazetidine moiety is fused to the quinolone, have been reported as good antibacterial agents, for example, prulifloxacin, displaying a broad spectrum with low toxicity.

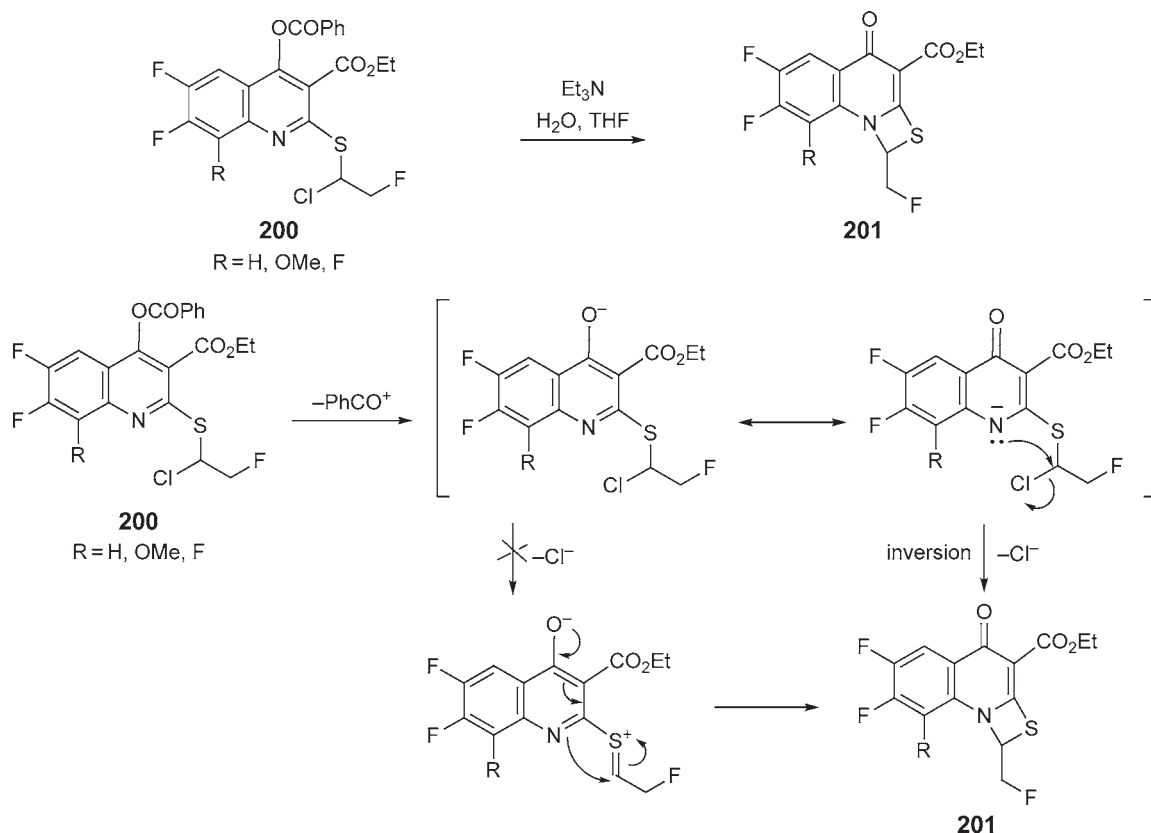
A new synthesis of the 4*H*-[1,3]-thiazeto-[3,2-*a*]quinolin-3-carboxylate **198**, a key for access to prulifloxacin, was developed in order to avoid the disadvantages of a previously reported procedure (Scheme 64). Drawbacks concerned the use of the harmful chloromethyl methyl ether in the sulfur protection step and expensive 1,1-dibromoethane in the final cyclization step. This new synthetic route involved the Gould–Jacobs cyclization of an *N,S*-acetal: yield and regioselectivity were highest when the cyclization was carried out in refluxing xylene instead of diphenylether. After protection of the hydroxyl group, chlorination was effected by treatment with *N*-chlorosuccinimide (NCS) while irradiating with a 500 W lamp. Since the chlorinated intermediate was unstable in water, cyclization was carried out using sodium acetate affording the target compound **198** in 69% yield <1997JHC1773>.

**Scheme 64**

An efficient and less expensive industrial method for preparing the chloro analogue **199** of this tricyclic system has been developed from commercially available 3-chloro-4-fluoroaniline instead of the expensive 3,4-difluoroaniline <2006CCL714>.

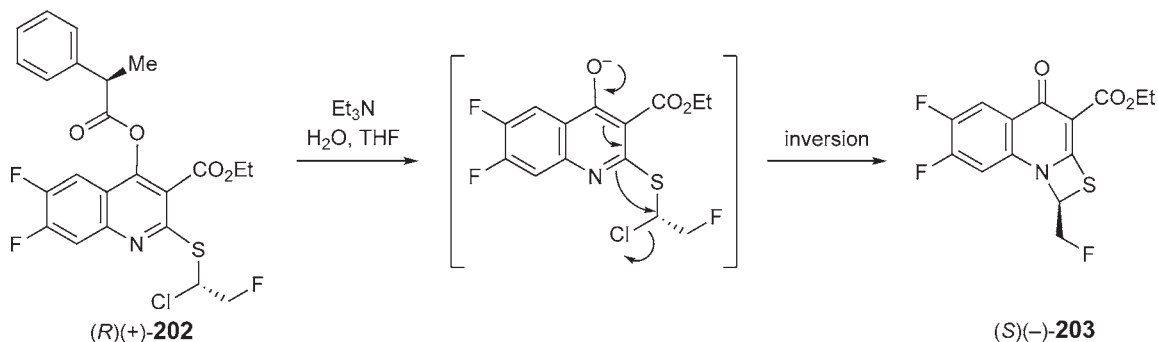


In the synthesis of these compounds, the 2-(1-chloro-2-fluoroethyl)thio compound **200** has been debenzylated and intramolecular cyclization was carried out to afford the 1,3-thiazetidine ring in compound **201** (Scheme 65). The alternative β -elimination reaction is inhibited because the lone pair of electrons on the sulfur atom of the anion is delocalized on the quinolone ring and so cannot attack the α -carbon atom of the chlorosulfonyl group <1999CPB1765>.



Scheme 65

The intramolecular cyclization reaction proceeds with inversion of configuration, thus excluding a mechanism involving the intermediate sulfenium cation (Scheme 66). The (*R*),(+)-enantiomer **202** can be obtained by repeated fractional recrystallizations from the racemic mixture. Cyclization yields the optically pure (*S*),(-)-1,3-thiazetidine derivative **203** <1999CPB1765>. Its absolute configuration was determined by comparing its circular dichroism spectrum with that of an analogous structure for which the absolute configuration was obtained by a single crystal X-ray analysis.



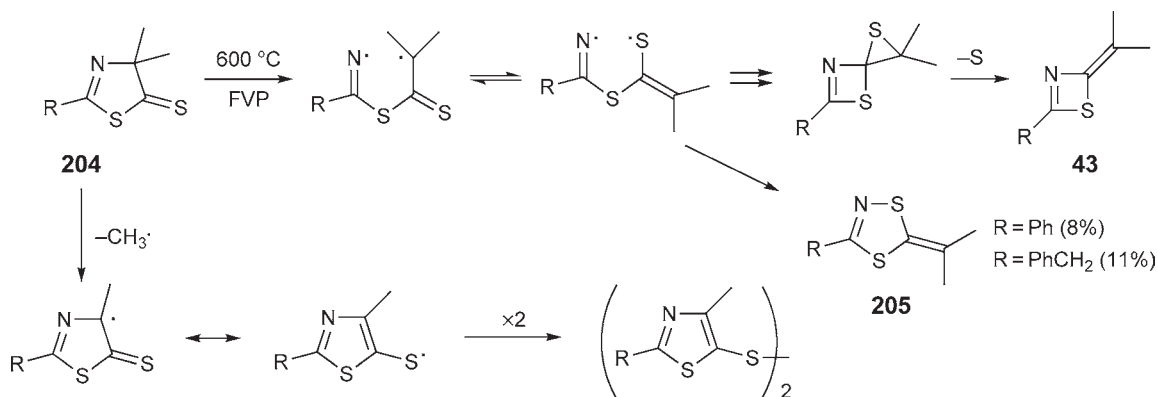
Scheme 66

2.15.9 Ring Syntheses by Transformation of Another Ring

2.15.9.1 2*H*-1,3-Thiazetes

Flash vacuum pyrolysis (FVP) of 2-phenyl-1,3-oxazol-5(4*H*)-one at $600^\circ\text{C}/1.5 \times 10^{-3}$ Torr proceeds via carbon dioxide elimination to give 3-phenyl-2*H*-azirine as the only detectable product isolated in 34% yield. Under similar conditions,

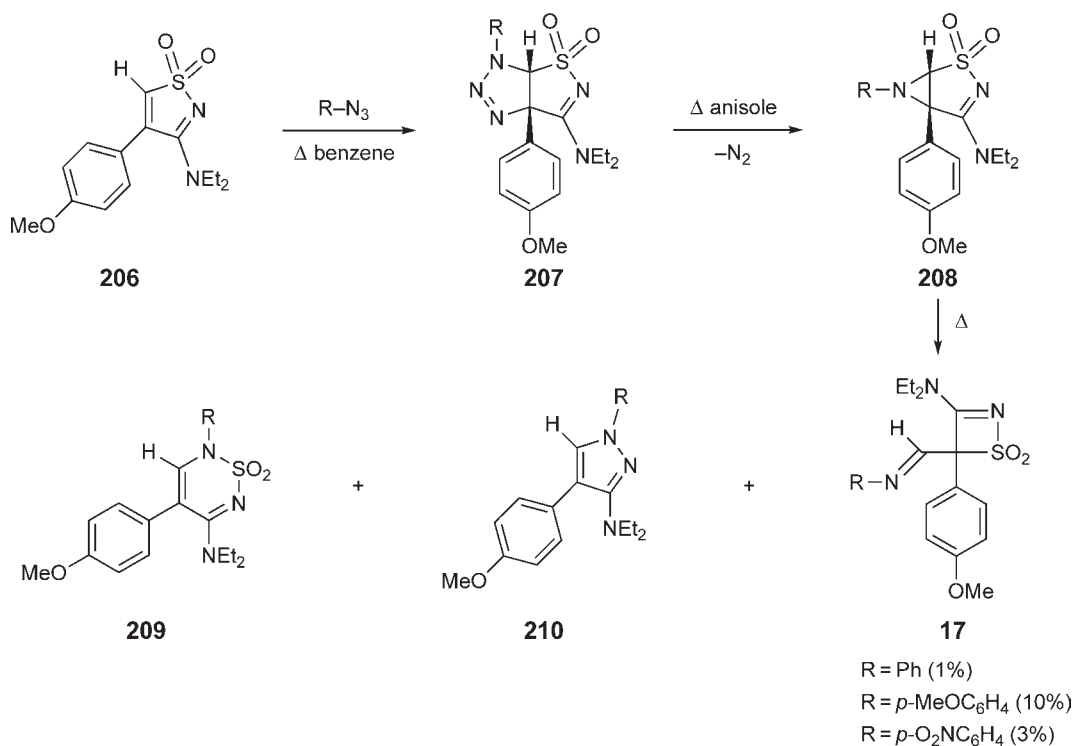
the 4,4-dimethyl-1,3-thiazole-5(4*H*)-thiones **204** yield the isomeric 1,4,2-dithiazole derivatives **205** as the main products. Desulfurization leads to the 2-(2-propylidene)-1,3-thiazetes **43** as minor products (Scheme 67) <1998PJC1915>.



Scheme 67

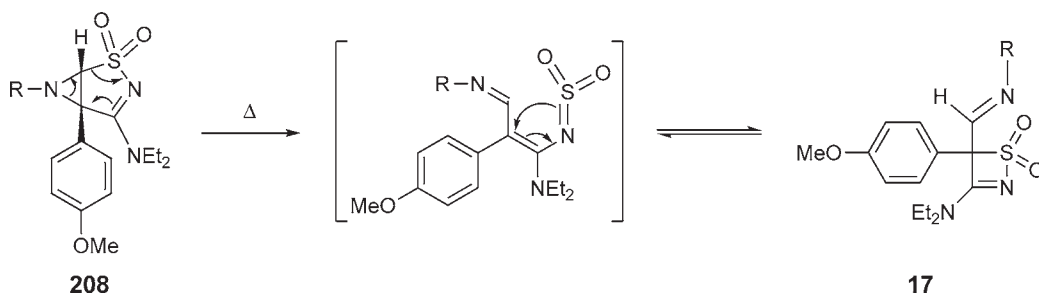
2.15.9.2 4*H*-1,2-Thiazete 1,1-Dioxides

Reaction of the isothiazole 1,1-dioxide **206** with benzyl azide and 2-phenylethyl azide affords the triazole cycloadducts **207**. Refluxing these in anisole or heating at a few degrees above the melting points results in nitrogen elimination and formation of the aziridine derivatives **208**. Further heating produces reaction mixtures containing the thiadiazine dioxides **209** as the main products, together with the pyrazoles **210** and the 4*H*-1,2-thiazete dioxides **17** (Scheme 68). Further heating results in the disappearance of the 4*H*-1,2-thiazete dioxides with transformation to the thiazetidines and pyrazoles as the sole and stable products <1996T7183>.



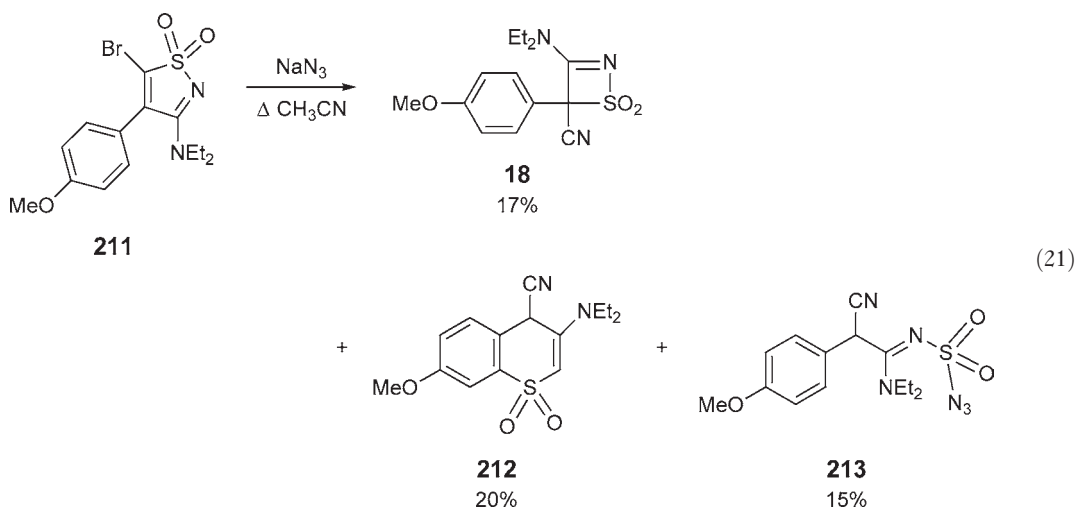
Scheme 68

The thermal transformation reaction of the aziridine derivative **208** has been rationalized by a mechanism involving cycloreversion of the bicyclic system into an open-chain intermediate which cyclizes to the 4*H*-thiazete 1,1-dioxides **17** (Scheme 69) <1996T7183>.



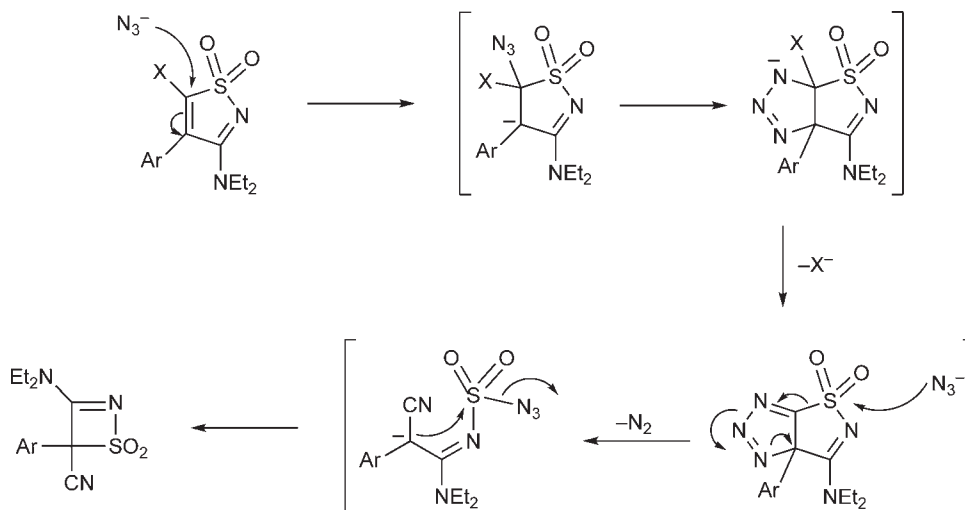
Scheme 69

The isothiazole-1,1-dioxide **211** has been shown to react with 2 equiv of sodium azide affording the corresponding 4*H*-1,2-thiazete carbonitrile **18** accompanied by the [1,2]thiazine carbonitrile **212** and the acyclic sulfamic acid derivative **213** (Equation 21). Prolonged heating of the mixture results only in the formation of the thermally stable 4*H*-1,2-thiazete carbonitrile and the 1,2-thiazine carbonitrile <2002T5173>.

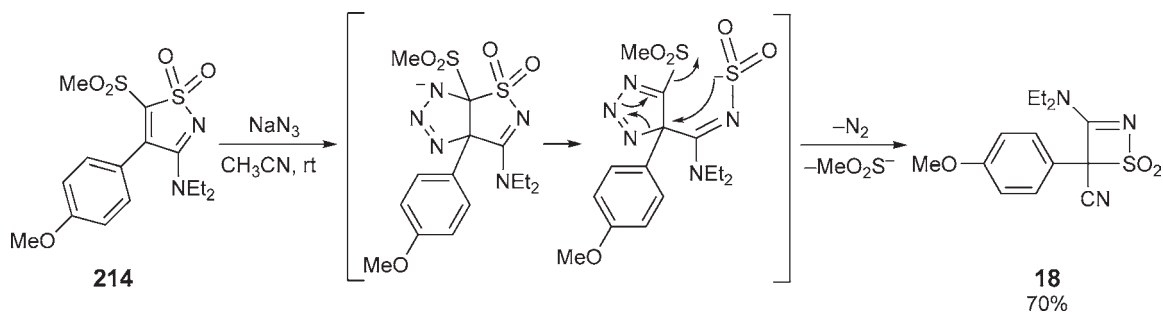


A mechanism has been proposed to account for these results (Scheme 70). Nucleophilic addition of the azide anion to C-5 of the isothiazole-1,1-dioxide ring followed by ring closure affords the triazoline anion. Elimination of bromide then gives the triazole-isothiazole. Opening of the bicyclic system by nucleophilic attack of the azide ion at the electrophilic sulfur atom and loss of nitrogen from the triazole moiety, followed by direct cyclization with concomitant nitrogen extrusion, then leads to the 4*H*-[1,2]thiazete ring <2002T5173>.

When the reaction was carried out on the 5-methanesulfonyl isothiazole 1,1-dioxide derivative **214** using 1 equiv of sodium azide at room temperature, the 4*H*-1,2-thiazete carbonitrile **18** was isolated as the sole stable reaction compound in 70% yield (Scheme 71). In this case, it has been suggested that the triazole-isothiazole ring undergoes ring opening by cleavage of the isothiazole ring affording an unstable 4*H*-thiazole from which the 4*H*-1,2-thiazete carbonitrile is obtained through intramolecular cyclization and loss of nitrogen and the leaving SO₂Me group <2002T5173>.



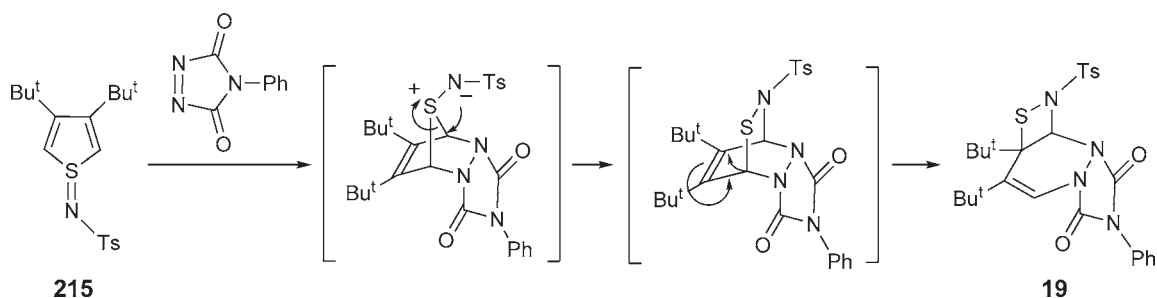
Scheme 70



Scheme 71

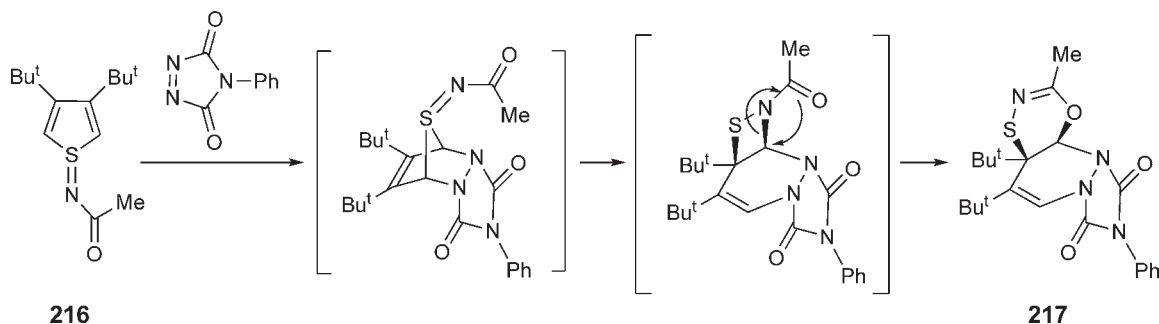
2.15.9.3 1,2-Thiazetidines

[4+2] Diels–Alder reaction of the 3,4-di-*tert*-butylthiophene-1-(*p*-toluenesulfonyl)imide **215** with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) is followed by a rearrangement affording the 1,2-thiazetidine system **19** (Scheme 72). The product is formed in refluxing CH_2Cl_2 for 10 h (81% yield), and also at room temperature for 7 days (65% yield). A mechanism has been proposed for this process, starting from the cycloadduct that results from an *endo*-cyclization with π -face selectivity. Because of electrostatic repulsions between the lone-pair electrons of the three nitrogen atoms, the cycloadduct rearranges to a less-angle-strained bicyclo[2.2.2] ring system. The lone-pair repulsions among the four heteroatoms then cause further rearrangement to the 1,2-thiazetidine **19** <2003JA8255>.



Scheme 72

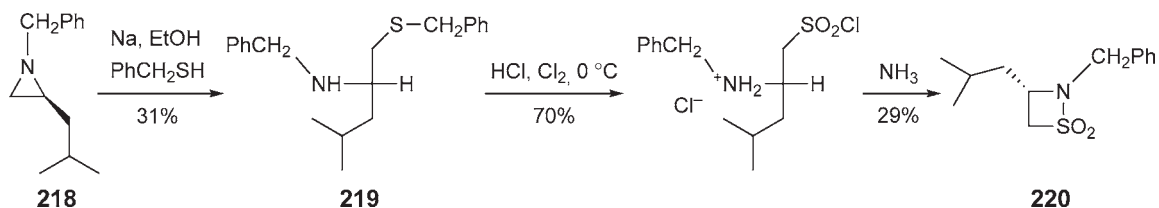
When the corresponding *N*-acetylthiophenimide **216** is used, further rearrangement of the intermediate 1,2-thiazetidine takes place at room temperature to give the 5*H*,6*H*-1,4,3-oxathiazine **217** in 60% yield (Scheme 73) <2003JA8255>.



Scheme 73

2.15.9.4 1,2-Thiazetidine 1,1-Dioxides

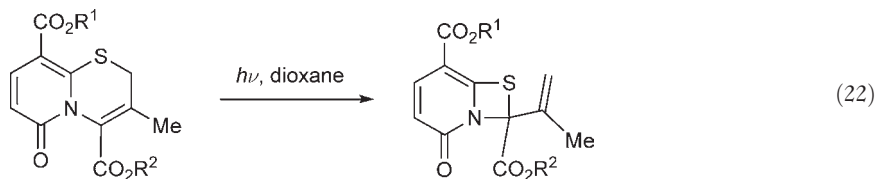
After transformation of the optically active aziridine **218** into the corresponding sulfide **219**, oxidative chlorination and cyclization yields the β -sultam **220** with the same configuration as the parent starting material (Scheme 74) <2004HCA90>.



Scheme 74

2.15.9.5 1,3-Thiazetidines

Vinyl-1,3-thiazetidines have been prepared by novel, high-yielding photochemical rearrangements of the corresponding 1,3-thiazines (Equation 22) <1999J(P1)3569>.



2.15.10 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

2.15.10.1 1,2-Thiazetidines

β -Sultams are accessible using a [2+2] cycloaddition reaction between an alkylsulfonyl chloride and an aryl or *t*-butylimine, better yields being obtained in the latter case. A diastereoselective synthesis of these β -sultams has been described where 1,3-asymmetric induction occurs in a [2+2] cycloaddition between a sulfene intermediate and

chiral imines, better diastereoselectivities being found when *N*-alkylimines are used. This strategy has been usefully extended to the first solid-phase synthesis of β -sultams using activated sulfenes and immobilized imines (see Section 2.15.8.2.1). Nevertheless, the most general method consists in the development of oxidative chlorination–cyclization steps for formation of the final S–N bond. This approach is very efficient when amino acid derivatives are used (see Section 2.15.8.2.2). Concerning cyclization with formation of the C–N bond, an interesting stereoselective synthesis has been reported for 3-substituted β -sultams in which the stereogenic center is created in high enantiomeric purity using chiral chromium complexes (see Section 2.15.8.2.3). A flexible approach to C-3-functionalized β -sultams, bearing an EWG at this position, has been developed. These can be efficiently synthesized via domino alkylation of bromomethanesulfonamides with original formation of the C–C bond (see Section 2.15.8.2.4).

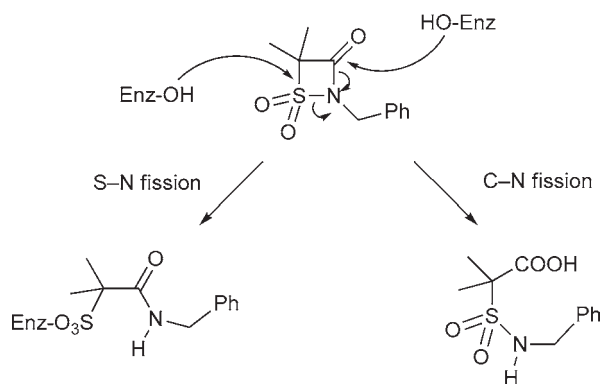
2.15.10.2 1,3-Thiazetidines

Creation of the 1,3-thiazetidine ring can be achieved by [2+2] cyclization of isothiocyanate with DCC in poor yields (see Section 2.15.8.3.1) or by [3+1] cyclization using two different routes. The first approach consists of reaction of aromatic amines with a mixture of formaldehyde and hydrogen sulfide and the second approach involves cyclization of a thiourea with a dihalogenoalkane to give 2-imino-1,3-thiazetidines in high yields. These reactions can also be achieved starting from malonic acid or phenyl sulfonamide derivatives (see Section 2.15.8.3.2). However, formation of the C–N bond, when applied to the synthesis of prulifloxacin intermediates, is certainly the most convenient strategy and this intramolecular cyclization proceeds in a perfectly stereoselective manner through an inversion mechanism (see Section 2.15.8.3.3).

2.15.11 Important Compounds and Applications

2.15.11.1 1,2-Thiazetidine 1,1-Dioxides (or β -Sultams)

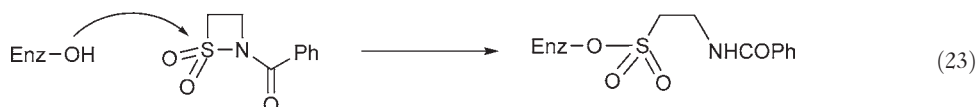
N-Acylsulfonamides usually react with nucleophiles by acyl transfer and C–N bond fission. However, hydrolysis of *N*-acyl β -sultams is a sulfonyl-transfer reaction that occurs with S–N fission and opening of the four-membered ring (Scheme 75) <2004OL201>. Thus, β -sultams are a novel class of inactivators of porcine pancreatic elastase (PPE). Structure–activity effects have been compared between sulfonylation of the enzyme and alkaline hydrolysis. Structural variation in 4-alkyl and *N*-substituted β -sultams causes differences in the rates of inactivation by 4 orders of magnitude <2003OBC67>. It has been reported that 3-oxo β -sultams are unusual since they inhibit elastases by acylation resulting from substitution at the carbonyl center, C–N fission, and expulsion of the sulfonamide <2005JA8946>. It has also been shown that β -sultams are inhibitors of a serine β -lactamase <2001CC497>. Inhibitory properties have been reported with *Streptomyces* R61 DD-peptidase using the same mechanism <2005B7738>.



Scheme 75

Human neutrophil elastase (HNE) is a serine containing enzyme which is one of the most destructive of proteolytic enzymes, being able to catalyze the hydrolysis of the components of connective tissue. It has been implicated in the development of diseases such as emphysema, cystic fibrosis, and rheumatoid arthritis. β -Sultams are excellent candidates for exploring the mechanism of sulfonation and possible inhibition of serine protease enzymes. *N*-Benzoyl

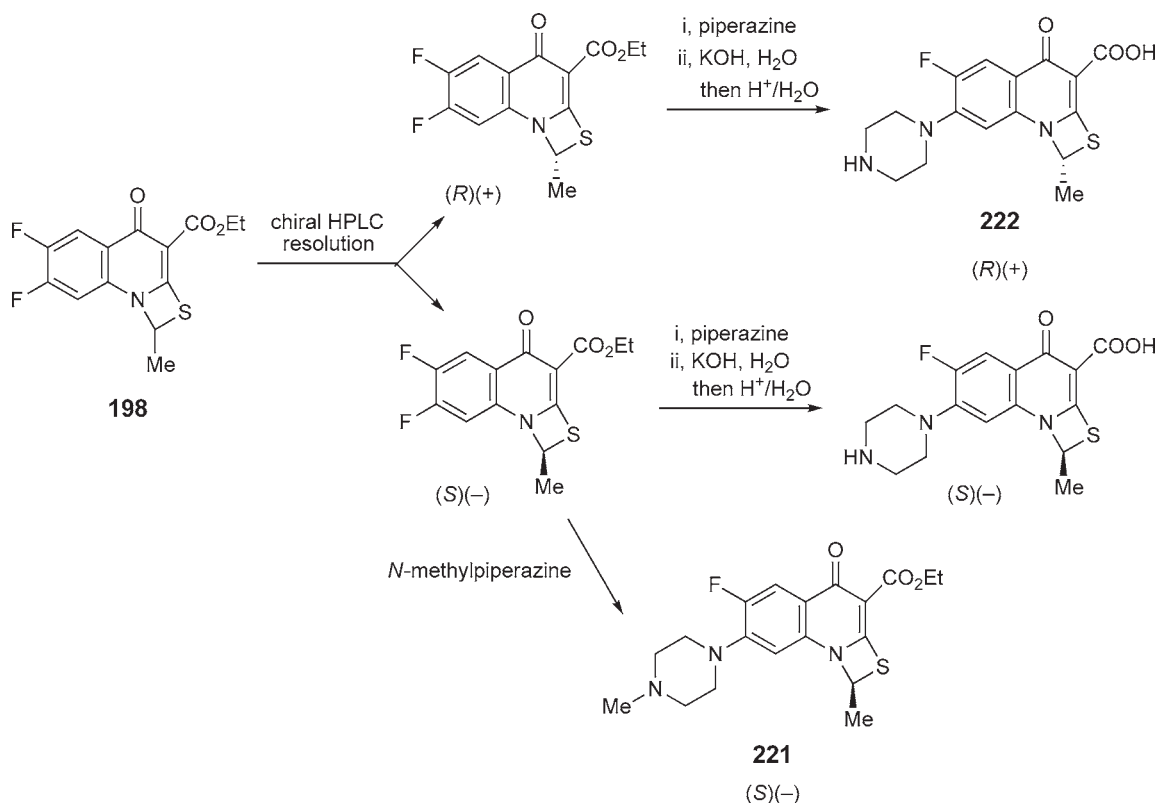
β -sultam has been found to be a time-dependent inactivator of PPE (Equation 23). The enzyme is completely deactivated and shows no sign of recovery after 4 days at 30 °C. Mass spectrometric analysis indicates that the β -sultam reacts with PPE to give both mono- and disulfonated adducts <2001CC497>.



N-Acyl β -sultams have been found to be a novel class of inactivators of class C β -lactamases. They act by sulfonylation as a result of serine nucleophilic attack on the sulfonyl center and displacement of the amide as a leaving group according to a preferential S–N over C–N bond fission. P99 β -lactamase is a serine class C β -lactamase enzyme from the Gram-negative bacterium *Enterobacter cloacae* and it is capable of hydrolyzing a wide variety of β -lactam-based substrates at a rapid rate. At pH 7, the k_i value for the inactivation of P99 β -lactamase by *N*-benzoyl β -sultam is $163 \text{ M}^{-1} \text{ s}^{-1}$ showing that *N*-acyl β -sultams are a novel class of β -lactamase inhibitors. Moreover, the rate of inactivation of P99 β -lactamase by *N*-benzoyl β -sultam shows a sigmoidal dependence on the pH of the incubation solution <2003BML4489>.

2.15.11.2 1,3-Thiazetidines

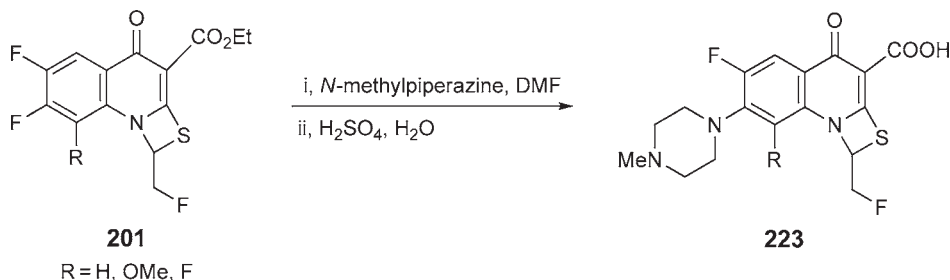
Optically isomers of the 7-(1-piperazinyl)-4*H*-[1,3]thiazeto[3,2-*a*]quinolone derivatives **198** have been prepared by optical resolution of the racemic compound by chiral high-performance liquid chromatography (HPLC) leading to the (*S*)-(–)-enantiomer ($[\alpha]_{\text{D}}^{20} = -148.02^\circ$, $c = 0.96$, DMF) and the (*R*)-(+)-enantiomer ($[\alpha]_{\text{D}}^{20} = +146.96^\circ$, $c = 1.15$, DMF). The absolute configuration at the C-1 position in the thiazetoquinolone ring was confirmed by the X-ray analysis of the *N*-methyl-1-piperazinyl derivative **221**. Treatment with piperazine followed by hydrolysis gave the (*R*)-(+)-enantiomer ($[\alpha]_{\text{D}}^{20} = +140.19^\circ$, $c = 0.93$, 0.1% NaOH) and the (*S*)-(–)-enantiomer ($[\alpha]_{\text{D}}^{20} = +149.65^\circ$, $c = 0.86$, 0.1% NaOH) of the corresponding 7-(1-piperazinyl)-3-carboxylic acid derivative **222** (Scheme 76). The



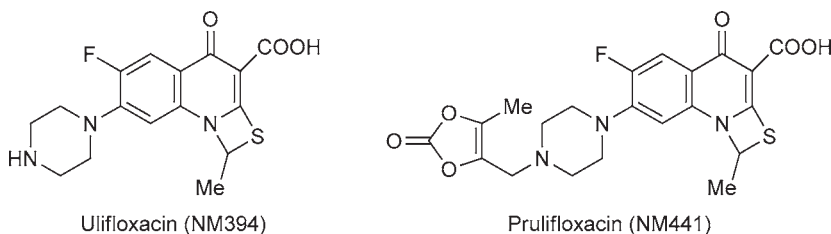
Scheme 76

in vitro antibacterial activity of the (*S*)-(-)-enantiomer was found to be 2–8 times more than the (*R*)-(+)-enantiomer against Gram-positive and Gram-negative bacteria <1995CPB1238>.

The introduction of a fluorine atom at the C-1 methyl group in the thiazetoquinolone **223** should enhance the *in vitro* and *in vivo* antibacterial activity against various bacteria including quinolone-resistant methicillin-resistant *Staphylococcus aureus* (MRSA) and also improve its bioavailability <1999CPB1765>.



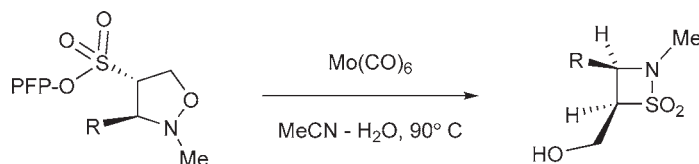
Ulifloxacin (NM394) has been found to have potent, broad-spectrum antibacterial activity *in vitro*, but not *in vivo*. To increase the bioavailability of NM394, various prodrugs were synthesized and tested. The *N*-(5-methyl-2-oxo-1,3-dioxol-4-yl) derivative (NM441) showed potent *in vivo* antibacterial activity and it was confirmed that after oral administration NM441 is readily absorbed and hydrolyzed to NM394 suggesting that NM441 is an effective prodrug of NM394 <1998MI21, 2003MI69>. A liquid chromatographic–tandem mass spectrometric method (LC–MS/MS) for determination of ulifloxacin, the active metabolite of prulifloxacin, in human plasma has been described. It was shown that this method can directly determine the amount of ulifloxacin in human plasma without any need for derivatization <2006JCH280>.



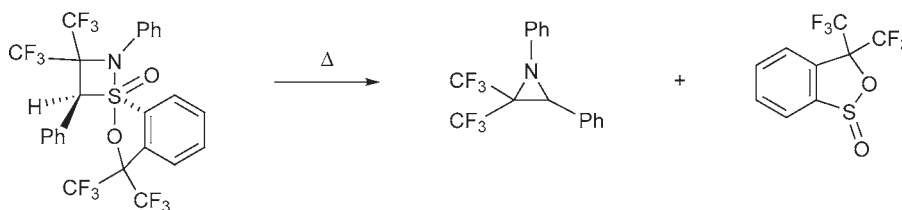
2.15.12 Further Developments

Concerning developments in the synthesis of 1,3-thiazetidine derivatives, it was recently shown that cyclothiomethylation of phenyl hydrazine with formaldehyde and hydrogen sulfide in sodium butoxide medium produced *N*-phenyl(perhydro-1,3-thiazetidin-3-yl)amine in 22% yield <2006RCB1824>.

Synthesis and reactivity of β -sultams were also the subject of recent advances. A stereoselective one-pot synthesis of substituted β -sultams has been achieved from heterocyclic pentafluorophenyl (PFP) sulfonates. This new method for β -sultam formation is based on the selective cleavage of the N–O bond in the presence of the PFP sulfonate motif <2006OL5513>.



Concerning the reactivity of β -sultams, it was recently demonstrated that thermolysis of a pentacoordinate $1\lambda^6,2$ -thiazetidine gave the corresponding aziridine and a cyclic sulfinate almost quantitatively. The potential intermediacy of $1\lambda^6,2$ -thiazetidine was suggested in this aza-Corey-Chaykovsky type reaction <2006OL4625>.



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Biographical Sketch



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2.16

Four-membered Rings with Two Oxygen Atoms

D. K. Taylor

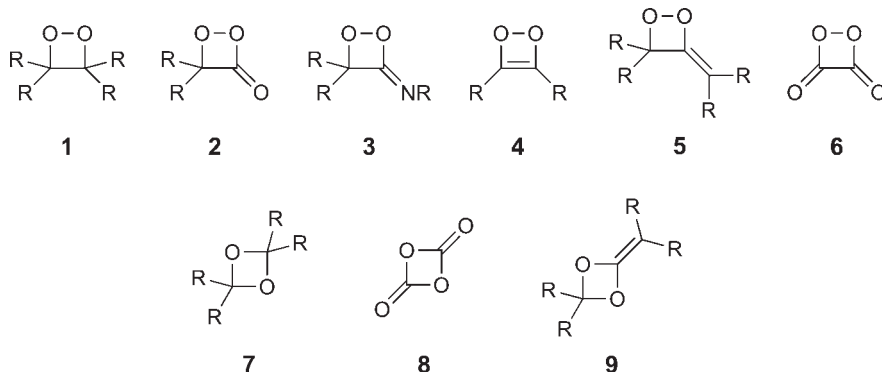
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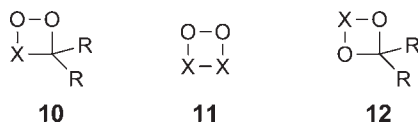
2.16.1 Introduction

The following four-membered ring structures containing two oxygen atoms are known. Of these, the 1,2-dioxetanes **1** are most common and will form the majority of this chapter. 1,2-Dioxetanones **2** (α -peroxy lactones) and dioxetanimines **3** are rare but have been prepared and will be mentioned where relevant. 1,2-Dioxetenes **4**, methylene-1,2-dioxetanes **5**, and 1,2-dioxetane-3,4-dione **6** have not been prepared in stable form and will only be discussed from a theoretical viewpoint. The isomeric 1,3-dioxetanes **7**, 1,3-dioxetane-2,4-dione **8**, and methylene-1,3-dioxetanes **9** have also received attention from the theoretical viewpoint; however, creditable chemical evidence for their existence is still lacking.



This subject was covered previously in 40 pages in CHEC(1984) <1984CHEC(7)449> and CHEC-II(1996) <1996CHEC-II(1B)1041>. The chapter within CHEC(1984) contained a summary of all four-membered rings with two or more heteroatoms while the chapter within CHEC-II(1996) was dedicated only to these systems. Again, this chapter will be solely dedicated to these systems. This chapter is intended to update previous concentration on major new preparations, reactions, and concepts. At the beginning of each main section, a sentence or short paragraph has been provided which explains the major advances or lack thereof since the publication of the earlier chapters. From a historical perspective it should be pointed out that while there was much research being conducted on the synthesis and characterization of the properties of these systems during the period between 1970 and 1995, such interest has waned over the past decade and is now heavily focused on determining the efficiency and wavelength of light associated with intramolecular chemically initiated electron-exchange luminescence (CIEEL) of stable dioxetanes bearing an aryl substituent as an electron donor.

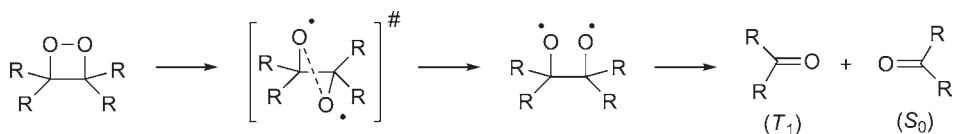
Although reports of heterodioxetanes containing additional heteroatoms **10–12** (X = N, P, S, Si, Ge, etc.) have been cited in the literature over the last decade and indeed were incorporated within the corresponding chapter in CHEC-II(1996) <1996CHEC-II(1B)1041>, they are now more appropriately left for Chapter 2.22 in this edition.



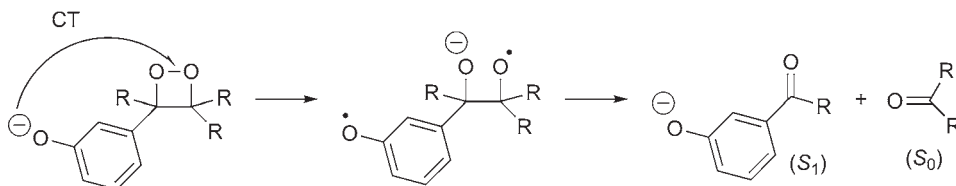
2.16.2 Theoretical Methods

1,2-Dioxetanes **1** contain high strain energy and consequently are inherently unstable and liberate much energy during their decomposition into two carbonyl fragments. This common decomposition process has received great attention from both theoreticians and experimentalists over the last three decades due to the fact that these processes are often associated with light emission. Consequently, 1,2-dioxetanes have unique chemiluminescence properties that may be exploited for the development of bioassays. While much progress has been made over the last decade on the understanding between the structure of the 1,2-dioxetanes and the final chemiluminescence properties, there still remains considerable debate over the plausible mechanistic modes possible. The reader is directed to the previous chapter in CHEC-II(1996) <1996CHEC-II(1B)1041> for a more historical version of the debate and to a recent review <2005BCJ1899> for a detailed account of our current theoretical and experimental understanding of the mechanisms.

The body of evidence summarized within the aforementioned reviews clearly indicates that simple 1,2-dioxetanes decompose thermally through a twisted diradical-like transition state to afford predominantly a triplet-excited carbonyl with no direct emission of light (**Scheme 1**), while dioxetanes bearing an aromatic electron-donor moiety display intramolecular charge-transfer-induced decomposition with accompanying effective emission of light (**Scheme 2**).



Scheme 1



Scheme 2

A recent theoretical study on the effect of substituents on the strain energies of small ring compounds has provided some valuable insight into the differences between 1,2-dioxetanes and 1,3-dioxetanes <2002JOC2588>. The C–H bonds within 1,2-dioxetane have been calculated to be stronger than those within 1,3-dioxetane by some 8 kcal mol^{−1} at the G2 level of theory. Calculations at the same level of theory indicate that 1,2-dioxetane is more strained than 1,3-dioxetane by some 6 kcal mol^{−1}. Somewhat surprising is that this study has also shown that 1,2-dioxetanes are more strained than dioxiranes by some 7–12 kcal mol^{−1}, which is in stark contrast to the case for the parent hydrocarbons and our expectations. The vibrational frequencies and the moments of inertia have also been calculated for the parent 1,2- and 1,3-dioxetanes <1997PCA2471>.

The geometry, ionization energy, and electron affinity have been calculated recently for the parent 1,2-dioxetene **4** at various *ab initio* levels of theory <2005JMT(714)199>. Two theoretical reports also exist that describe the geometries and stability of 1,2-dioxetane-3,4-dione **6** and 1,3-dioxetane-2,4-dione **8** <2000JA5367, 1996JMT(363)1>. Finally, there has been one theoretical report on the possible existence of a methylene-1,3-dioxetane **9** during the cycloaddition of ketenes to tropone <2005HCA1519>.

2.16.3 Experimental Structural Methods

Only experimental information obtained over the last decade has been incorporated within this section and the reader is directed to the previous version of this chapter <1996CHEC-II(1B)1041> for information prior to 1996. Over the last decade, there have only been reports on the characterization of 1,2-dioxetanes **1** and 2-dioxetanones **2** (α -peroxy lactones); consequently, this section contains no information for structures of type **3–9**.

2.16.3.1 Spectroscopic Methods

2.16.3.1.1 IR spectroscopy

Infrared (IR) spectroscopy is not characteristically definitive for the identification and structural proof of the dioxetane core. Dioxetanones **2** (α -peroxy lactones) such as **29** and **30**, depicted in Section 2.16.3.1.4, show carbonyl stretching frequencies at 1835 and 1870 cm^{−1}, respectively <1997JOC1623, 1977JA5768>.

2.16.3.1.2 UV–Vis spectroscopy

Unfortunately, ultraviolet (UV) spectral data for most of the 1,2-dioxetanes prepared over the last decade have not been reported. In the previous version of this chapter, it was highlighted that the absorption maximum (λ_{max}) of 1,2-dioxetanes occurs around 280–300 nm with very small extinction coefficients tailing up as far as 450 nm. Consequently, many 1,2-dioxetanes are pale yellow in color.

2.16.3.1.3 Photoelectron spectra

No new data have been presented within the last decade.

2.16.3.1.4 NMR studies

Typical proton and ^{13}C chemical shift data for ring atoms of dioxetanes from the last decade are collated in [Figure 1](#). For spectral data prior to this, see CHEC-II(1996) <1996CHEC-II(1B)1041>.

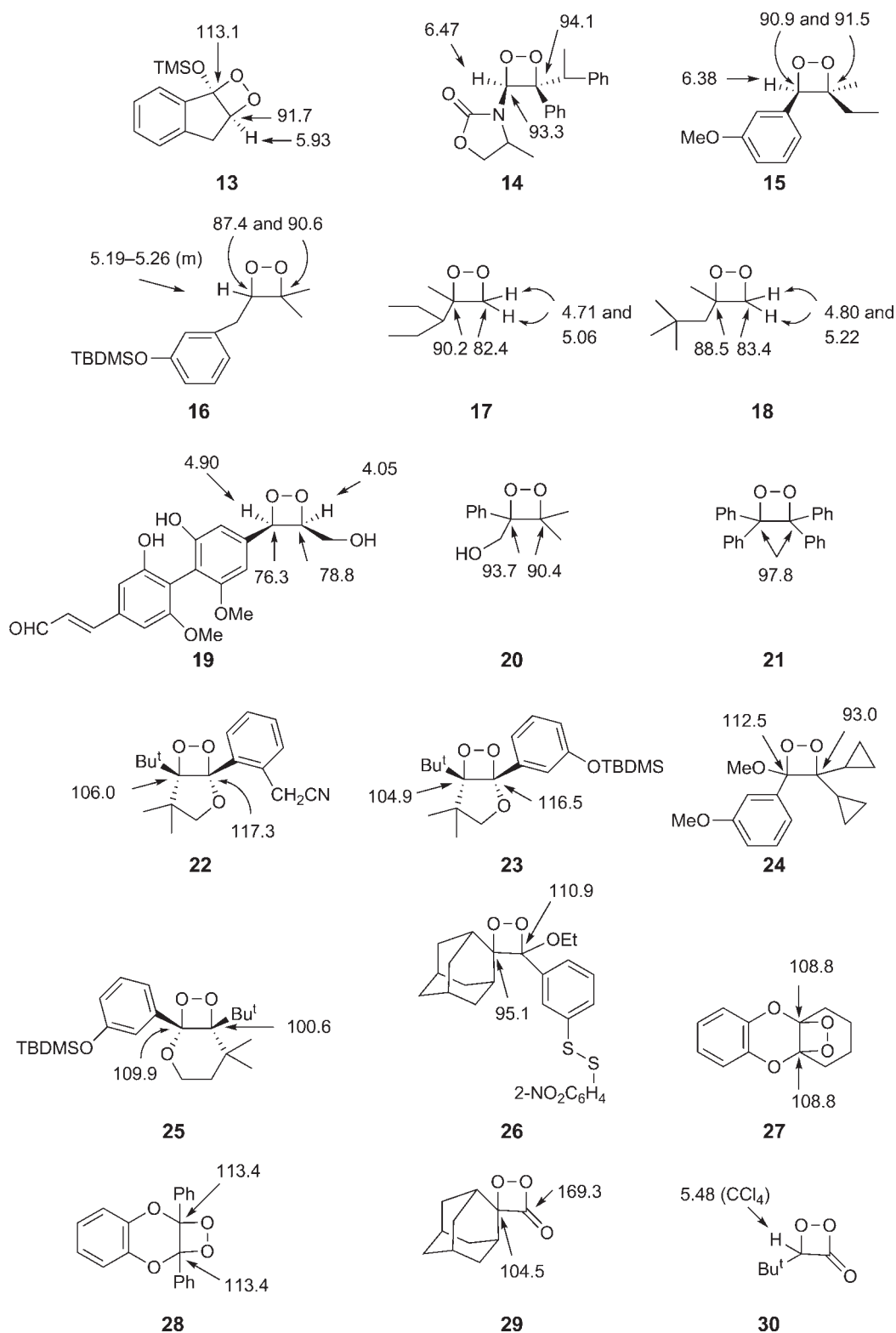


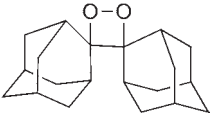
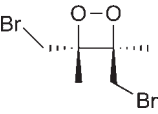
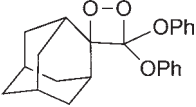
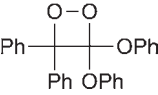
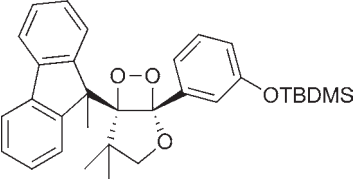
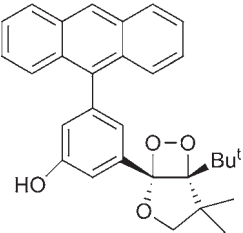
Figure 1 ^1H and ^{13}C chemical shifts of dioxetane ring atoms (ppm with respect to TMS).

Proton resonances directly attached to the dioxetane ring vary considerably ranging from δ 4.0 to 6.5 ppm and therefore provide valuable information regarding the substitution pattern about the dioxetane ring. See structures **13–19** <1999J(P1)2507, 2002JA8814, 2000T5317, 2001HAC459, 2003TL6759> for typical examples of mono-, di-, and trisubstituted dioxetanes. ^{13}C chemical shifts are also diagnostic of the substitution pattern about the dioxetanes core, as exemplified by structures **13–28** <2002OL537, 2005OL4265, 2005T9569, 2000JOC2078, 1999T4287, 2002TL1523, 2002JA4874, 1984JOC3920>. Typical shifts range from δ 76–100 ppm if not substituted by additional heteroatoms to δ 108–116 ppm when containing further oxygen substitution. Spectral data for dioxetanones (α -peroxylactones) are extremely scarce; however, data for two dioxetanones **29** and **30** are available <1997JOC1623, 1977JA5768>.

2.16.3.1.5 Mass spectrometry

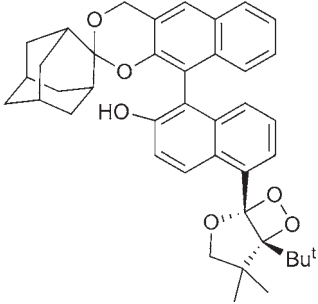
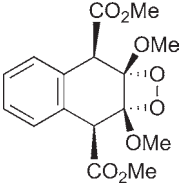
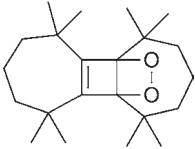
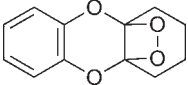
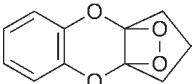
Mass spectrometry remains of limited use for the characterization of dioxetanes; however, numerous relatively stable 1,2-dioxetanes have been prepared over the last decade allowing not only for the detection of their parent ions but also allowing for high-resolution mass spectrometry (HRMS) measurements to be taken. See references associated with structures depicted in **Figure 1** or **Table 1**.

Table 1 X-Ray structural data on dioxetanes

Dioxetane	Torsion angle ^a (deg)	Bond distances (pm)			Reference
		O–O	C–C	C–O	
	21.3	148.0	155.0	147.5	1972TL169
	15.3	144.0	151.0	148.0 149.0	1982TL3251
	11.7	147.0	149.0	149.0 151.0	1982TL3251
	9.6	150.5	155.0	143.0 148.0	1982TL3251
	8.1	149.4	158.4	146.0 148.8	1997TL2863
	8.0	151.7	158.6	146.5 148.8	2004TL8079

(Continued)

Table 1 (Continued)

Dioxetane	Torsion angle ^a (deg)	Bond distances (pm)			Reference
		O–O	C–C	C–O	
	4.7	150.9	158.7	147.0 147.8	2005CC808
	2.5	153.0	156.0	145.0	1994T9009
	0	149.0	155.0	149.0	1980TL3171
	0	149.0	151.0	144.0	1984JOC3920
	0	158.0	158.0	144.0	1984JOC3920

^aTorsion angle in dioxetane ring.

2.16.3.1.6 X-Ray diffraction

The low stability of dioxetanes coupled with difficulties in obtaining crystalline samples have severely limited the amount of crystallographic data available. Success appears to be limited to dioxetanes that are fully substituted about the carbon atoms of the dioxetane core (**Table 1**). The dioxetanes' ring torsion angle (degree of puckering) ranges from 0° for fused polycyclic dioxetanes to 21° for structurally encumbered dioxetanes such as bisadamantylidene-1,2-dioxetane. Puckering of the dioxetane ring is either a consequence of nonbonded repulsions between substituents or a result of lone pair–lone pair repulsions of the peroxide oxygens or a combination of both. Based on current structural data available, there is no clear correlation between bond lengths, bond angles, degree of puckering, and the thermal stability of dioxetanes. Further examples are also tabulated in CHEC-II(1996) <1996CHEC-II(1B)1041>.

2.16.3.2 Chemical Methods

Satisfactory CH microanalyses for 1,2-dioxetanes have been rarely reported over the last decade with preference for the reporting of HRMS data. Presumably, this reflects the belief that 1,2-dioxetanes are always thermally unstable which is clearly not the case. As for any peroxides, iodometric titration can be used to determine the percentage of

oxygen content. Various chemical reactions of 1,2-dioxetanes have been studied in extensive detail and can be utilised to validate their existence (Section 2.16.5).

2.16.4 Thermodynamic Aspects

New sections describing physical data, solubilities, and chromatographic behavior have been incorporated into this edition.

2.16.4.1 Physical Data

While there exists no systematic tabulation of melting points for 1,2-dioxetanes or dioxetanones, the reader is urged to consult the references cited within this chapter for specific examples. It is clearly apparent that simple alkyl and aryl dioxetanes decompose readily and melting points either are not determined or are determined at low temperature. The majority of dioxetanes designed and synthesized for CIEEL studies are stable crystalline substances with sharp melting points. Given the thermal sensitivity of dioxetanes, boiling points are not reported. Occasionally, low-temperature distillation is utilized during purification.

2.16.4.2 Solubilities and Chromatographic Behavior

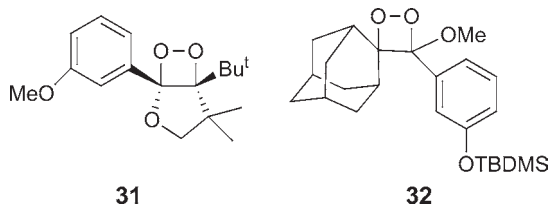
1,2-Dioxetanes and dioxetanones behave chromatographically the same as any organic derivative and as such their R_f will be dependent on the polarity of the substrate as a whole. No special precautions are necessary during chromatography except that one may need to guard against thermal instability. Solubilities will also be subject to 1,2-dioxetane structures; however, there are no notable difficulties with solubilities reported.

2.16.4.3 Stability and Thermochemical Aspects

Traditionally, the research focus on the study of the stability of 1,2-dioxetanes centered on measuring activation parameters (E_A , $\Delta H^\ddagger$, and $\Delta S^\ddagger$) and determining excitation parameters (Φ^S and Φ^T). Indeed the CHEC-II(1996) version of this chapter <1996CHEC-II(1B)1041> contains an extensive tabulation of such parameters for a range of relatively simple 1,2-dioxetanes, and the reader is directed to consult this chapter for useful examples. As highlighted throughout this chapter, research focus has shifted away from measuring such parameters of simple 1,2-dioxetanes and is now heavily directed toward determining the efficiency and wavelength of light associated with intramolecular CIEEL of stable dioxetanes bearing an aryl substituent as an electron donor. Consequently, exhaustive tables on activation and excitation parameters will not be included here but an attempt to highlight some of the key aspects on the stability and thermochemistry of 1,2-dioxetanes will be presented. There are two excellent reviews published recently which detail all current knowledge on the structural aspects of not only simple dioxetanes but also 1,2-dioxetanes active toward CIEEL <2004JPH27, 2005BCJ1899>.

Simple 1,2-dioxetanes decompose thermally through a twisted diradical-like transition state furnishing two carbonyl fragments. Activation energies range between 20 and 30 kcal mol⁻¹ while heats of reaction for these decompositions are between 70 and 90 kcal mol⁻¹ <2004JPH27>.

Nowadays dioxetanes are designed that are extremely stable and it is not until they are activated by a triggering event (see Section 2.16.6.1) that spontaneous emission of light occurs. As a good illustration of this, dioxetanes **31** and **32** have half-lives of 22.1 and 3.8 years, respectively, at 25 °C but upon treatment with fluoride spontaneously decompose with light emission ($\lambda_{\max} = 469$ nm, $\Phi_{\text{CL}} = 0.17$, $t_{1/2} = 4.4$ s for **31**; and $\lambda_{\max} = 465$ nm, $\Phi_{\text{CL}} = 0.25$, $t_{1/2} = 5.0$ s for **32**) <1997TL2863>. As with the simple dioxetanes, activation barriers are again typically between 20 and 30 kcal mol⁻¹.

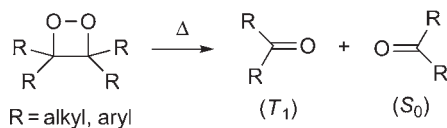


2.16.5 Reactivity of Dioxetanes

The following sections detail examples of the reactivity of 1,2-dioxetanes reported over the past decade and comprise both thermal and photochemical reactions, nucleophilic and electrophilic attack at the ring oxygen atoms, and base attack at hydrogen attached to ring carbon. A new section on the nucleophilic substitution at the ring carbon is also included. It should be emphasized here that the CHEC-II(1996) version of this chapter contains numerous examples on the aforementioned reaction types and the reader is directed to that chapter for further examples <1996CHEC-II(1B)1041>. Given that fundamental studies on the reactivity of 1,2-dioxetanes has become less prevalent in the literature over the past decade, which is presumably due to the research focus being directed toward the design and study of 1,2-dioxetanes displaying CIEEL, fewer examples exist for inclusion within the following sections.

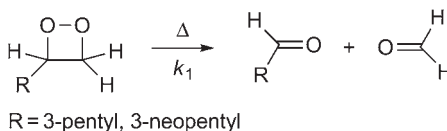
2.16.5.1 Thermal and Photochemical Reactions

As highlighted in Section 2.16.2, simple alkyl-substituted 1,2-dioxetanes are thermally labile compounds and decompose through a twisted diradical-like transition state to afford two carbonyl fragments one of which is predominantly a triplet-excited carbonyl (Scheme 3). Activation barriers are often in the order of 25 kcal mol⁻¹.



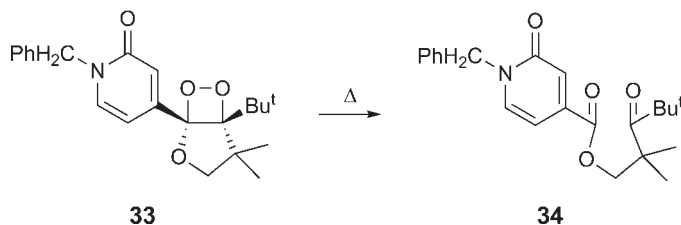
Scheme 3

For example, 3-pentyl- and 3-neopentyl-1,2-dioxetane undergo thermolysis in xylene at 60 °C with first-order rate constants (k_1) of 4.6 and $9.2 \times 10^{-4} \text{ s}^{-1}$, respectively (Scheme 4) <2001HAC459>. Chemiexcitation yields were in the order of 0.02 (Φ^T) and ≤ 0.0005 (Φ^S) for both derivatives.



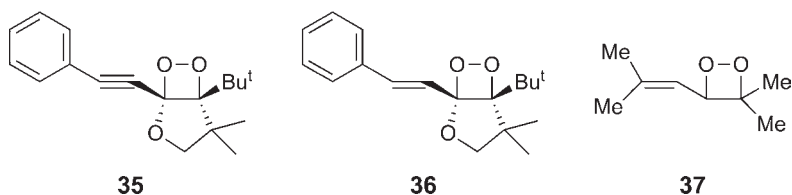
Scheme 4

The thermal stability of dioxetanes can be increased in several ways. As expected, the most useful way to increase the thermal stability of dioxetanes has been to increase the steric bulk around the core. Heavily substituted dioxetane **33** is an example of a stable dioxetane at room temperature and requires elevated temperatures for decomposition. Thermolysis at 90 °C in toluene affords light ($\lambda_{\text{max}} = 411 \text{ nm}$) whose spectrum is in good agreement with the fluorescence spectrum of dicarbonyl **34** (Scheme 5) <2000CC821>.

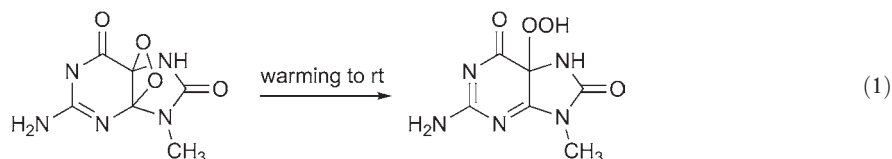


Scheme 5

The increasing of conjugation within the pendant substituents is also another factor that increases the stability of dioxetanes. For example, phenylethynyl dioxetane **35** has been shown to be more thermally stable than the styryl analogue **36**, which in turn is more stable than the simple olefinic dioxetane **37** <1999TL4571>.



Besides the thermal C–C decomposition of dioxetanes into carbonyl fragments, C–O bond cleavage is occasionally seen for specific substrates to afford allylic hydroperoxides (Equation 1) <2004JA16777>.



An alternative thermal decomposition of 1,2-dioxetanes bearing an aromatic electron donor involves a CIEEL mechanism and is described in Section 2.16.6.1.

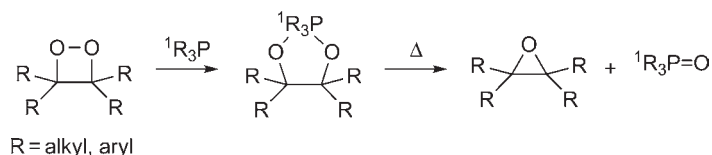
There have been no significant reports in the last decade that report on the outcomes of dioxetanes undergoing photolysis. The reader is directed to CHEC-II(1996) for several studies in the 1970s.

2.16.5.2 Electrophilic Attack at Ring Heteroatoms

In the past decade, there has appeared only one report, which can be classified under this heading, on the monodeoxygenation of spiro-adamantane-1,2-dioxetanes induced by catalytic amounts of tris-(2,4-dibromophenyl)-aminium hexachloroantimonate <1998T6939>. An electron-transfer mechanism from the aminium salt has been proposed for the observed formation of various ketones. Reports citing the electrophilic ring opening of dioxetanes by boron trifluoride, trifluoroacetic acid, and various other Lewis acids have been summarized in CHEC-II(1996) <1996CHEC-II(1B)1041>.

2.16.5.3 Nucleophilic Attack at Ring Heteroatoms

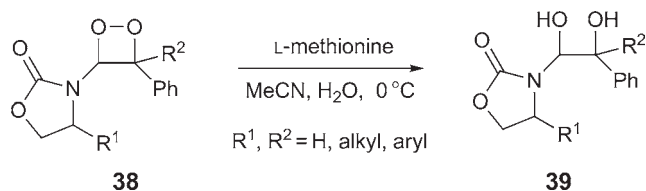
There have been extensive studies on the reaction of dioxetanes and dioxetanones with nucleophiles (C, N, P, and S) and the reader is directed to CHEC-II(1996) for an exhaustive list up to 1996. The most common reactions of dioxetanes have been with phosphorus nucleophiles. The phosphines and phosphites first insert into the O–O bond. The phosphorane intermediate then collapses to afford phosphine oxide or the trialkylphosphate and the corresponding epoxide (Scheme 6). The same is true for the treatment of α -peroxy lactones with phosphines and phosphites except that the so-formed α -lactone intermediate undergoes decarboxylation and ultimately furnishes a ketone <1997JOC1623>.



Scheme 6

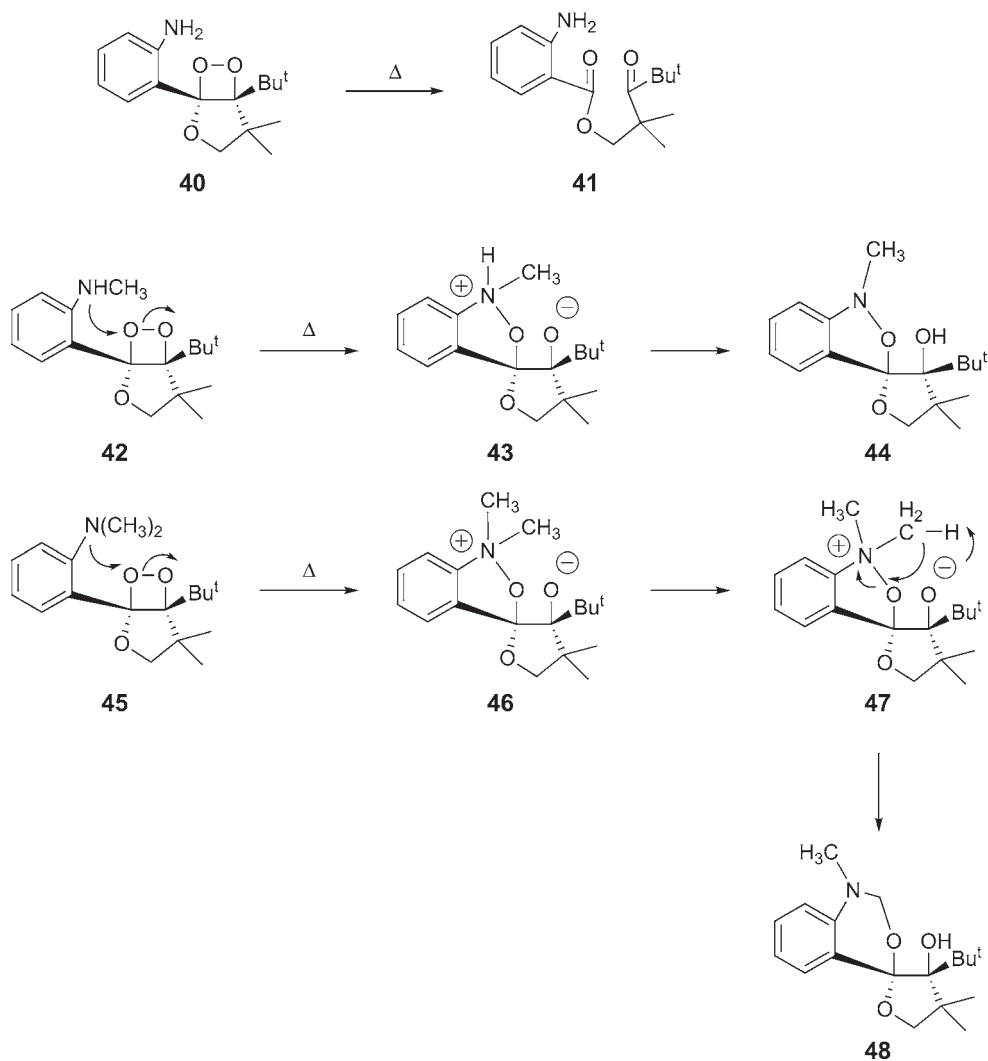
The CIEEL mechanism for dioxetanes was also previously cited within this section but it is now more appropriately left for Section 2.16.6.1.

Dioxetanes are readily reduced to 1,2-diols by lithium aluminium hydride and thiols. However, no notable examples have been reported since 1996. An intriguing and very mild method for the reduction of 1,2-dioxetanes, which utilizes L-methionine as the reductant, has been reported recently. For example, treatment of dioxetanes of type 38 with L-methionine at 0°C produces the desired 1,2-diols 39 (Scheme 7) <2004JOC1704>. Yields ranged from 25% to 41%.



Scheme 7

During the thermal decomposition of a range of 1-(aminophenyl)-5-*t*-butyl-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]-heptanes, an unusual peroxide bond cleavage was found in competition with the normal fragmentation to dicarbonyls that involves intramolecular nucleophilic attack by the amino groupings (Scheme 8) <1998CC2319>. Thus heating of the aminophenyl analogue **40** produced the expected dicarbonyl **41**. In contrast, the thermal decomposition of the *N*-methylamino analogue **42** produced **44**, which has been postulated to be formed via intramolecular attack of the *N*-methylamino group at the O–O moiety of the dioxetane and successive O–O bond fission accompanying a proton exchange in the intermediary zwitterion **43**. Moreover, the thermal decomposition of the *N,N*-dimethylamino analogue **45** furnishes **48**. The same zwitterionic type of intermediate **46** has been postulated to be involved here followed by a Stevens-type rearrangement on **47**. No clear explanation as to the reasons why there is such a difference in reactivity outcomes was given.



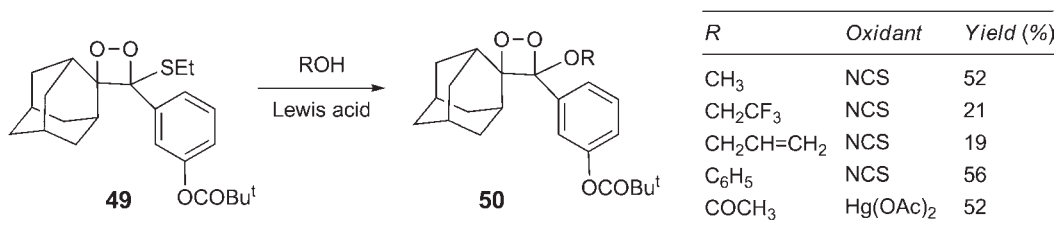
Scheme 8

2.16.5.4 Base Attack at Hydrogen Attached to Carbon

Treatment of dioxetanes with bases such as amines or hydroxide may lead to ring opening via a Kornblum–DeLaMare process with formation of the corresponding hydroxyketones. The observation of this process is extremely rare and no new examples have been cited in the past decade.

2.16.5.5 Nucleophilic Substitution at Ring Carbon

The first examples of a direct substitution upon the carbon atoms of the dioxetane core have now appeared (Scheme 9) <1997JA245>. Thus, treatment of alkylthiodioxetane **49** with a slight excess of a Lewis acid oxidant such as *N*-chlorosuccinimide (NCS) or mercuric acetate in the presence of excess ROH leads to the formation of oxygen-substituted dioxetanes **50** in low to moderate yields.



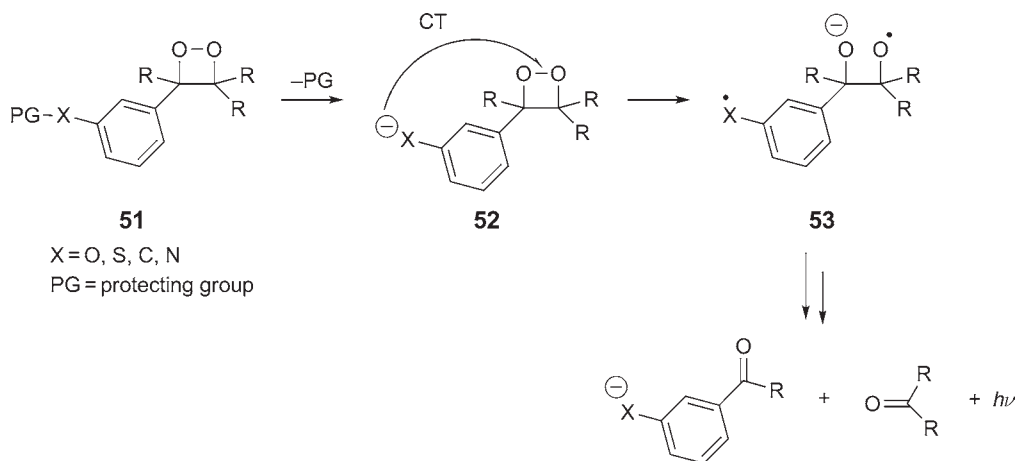
Scheme 9

2.16.6 Reactivity of Substituents Attached to Ring Carbon Atoms

The previous version of this section in CHEC-II(1996) summarized specific examples of the reactions of hydroxy-methyl-substituted dioxetanes and also the deprotection of *N*-acylamino-substituted dioxetanes <1996CHEC-II(1B)1041>. As there have been no new examples over the last decade, the reader is directed to consult the previous chapter for details. It would also be worthwhile to consult reference <1991MI(12)567>, which summarizes basic functional group transformations that can be achieved while leaving the dioxetane moiety intact.

2.16.6.1 Dioxetane Ring Opening by Remote Triggering

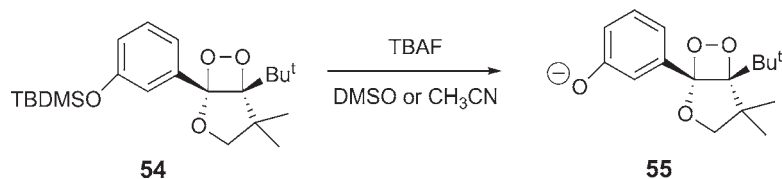
As highlighted in Section 2.16.2 (Scheme 2), dioxetanes bearing an aromatic electron-donor moiety display intramolecular charge-transfer-induced decomposition with accompanying effective emission of light. This mechanistic phenomenon is now well established and is termed chemically initiated electron-exchange luminescence (CIEEL). This ring opening by remote triggering of aryl dioxetanes containing electron-rich substituents relies on a pre-deprotection step and is summarized in Scheme 10. Thus the protecting group within **51** is removed by some



Scheme 10

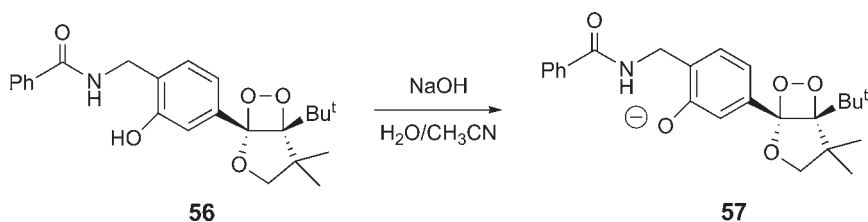
chemical process to trigger the formation of the electron-rich aryl dioxetane **52**, which undergoes intramolecular charge transfer to the peroxide bond to afford intermediate **53**. This intermediate then collapses to ultimately afford the observed carbonyls with accompanying efficient emission of light.

Numerous dioxetanes with varying atom (X) and protecting group (PG) have been synthesized over the last decade in order to study the CIEEL mechanism. The following serve as prototypical examples. The most prevalent trigger is that of a siloxyphenyl substituent such as that incorporated into dioxetane **54**. Tetrabutylammonium fluoride (TBAF) is used in an aprotic solvent, such as dimethyl sulfoxide (DMSO) or acetonitrile, to desilylate to afford the unstable phenolate **55** (Scheme 11) <2002MI305>.



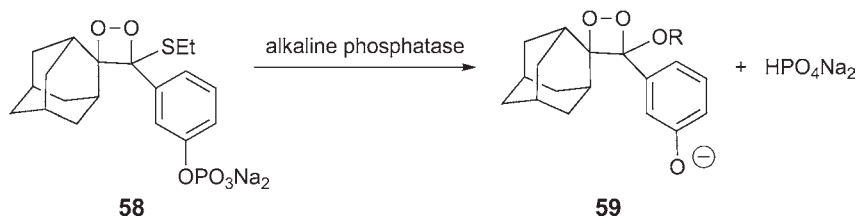
Scheme 11

The parent phenolic dioxetanes can also be employed as suitable precursors to the CIEEL process. Thus, exposure of phenol **56** to NaOH in an aqueous acetonitrile binary mixture results in the triggering for the formation of phenoxide **57** (Scheme 12) <2005TL4871>. These types of derivatives were utilized to study the effects of intramolecular hydrogen bonding on the CIEEL process.



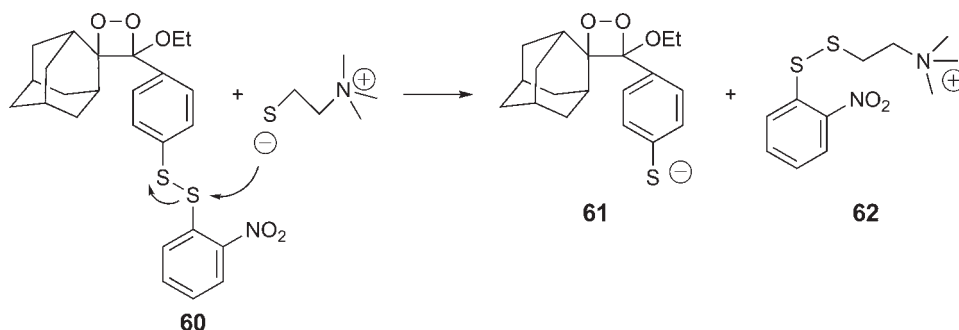
Scheme 12

Protection of the phenolic moiety as a phosphate provides substrates such as **58** that are specifically recognized and cleaved by alkaline phosphatase to afford **59** (Scheme 13) <1998PCA5406>. This type of dioxetane is behind many of the commercial assays that are discussed further in Section 2.16.10.1.



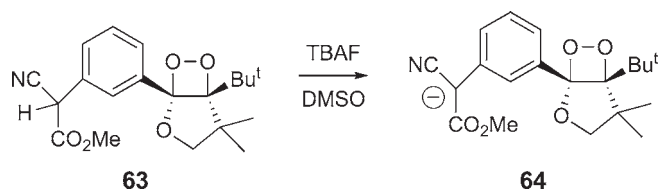
Scheme 13

Chemiluminescent probes based on the dioxetane moiety are now being developed for the detection of cholinesterase activity <2002JA4874>. In this particular case, the nucleophilic thiol generated from hydrolysis of acetylthiocholine iodide triggers the formation of the thiolate **61** and by-product **62** through nucleophilic attack on the disulfide bond of **60** (Scheme 14).

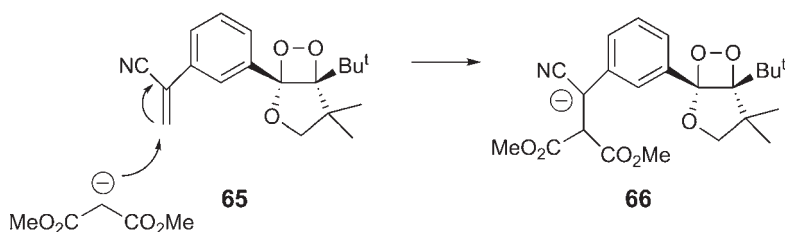


Scheme 14

1,2-Dioxetanes bearing a phenylmethanide anion can be produced in several ways [<2005T9569>](#). Base treatment of dioxetanes containing a phenyl substituent carrying a methine with electron-withdrawing groups triggers formation of the requisite anion **64** (Scheme 15). Alternatively, Michael addition of a malonate anion to an appropriately substituted alkene such as **65** also leads to anions of type **66** which have been triggered to undergo the CIEEL process (Scheme 16).

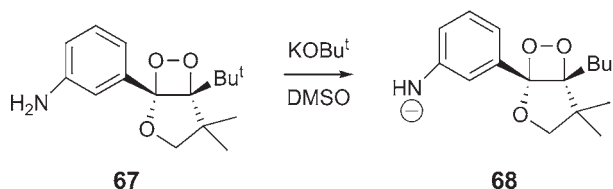


Scheme 15



Scheme 16

1,2-Dioxetanes substituted with anilines also undergo base-induced triggering. For example, it has been reported that treatment of **67** with Bu^tOK in DMSO produces the anion **68**, which decomposes to emit red light via the CIEEL process (Scheme 17) [<2005BCJ1899>](#).



Scheme 17

2.16.7 Ring Synthesis Classified by Number of Ring Atoms in Each Component

This section details the methods of preparation that have been utilized over the last decade for the synthesis of 1,2-dioxetanes **1** and 1,2-dioxetanones **2** (α -peroxy lactones).

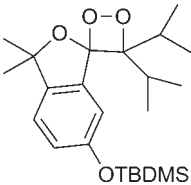
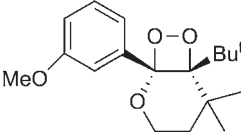
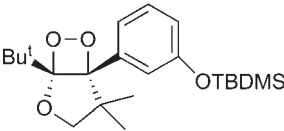
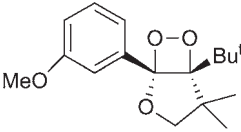
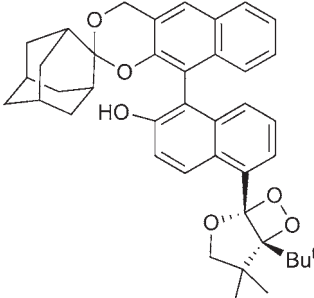
2.16.7.1 Dioxetanes

The singlet oxygen ($^1\text{O}_2$) cycloaddition to electron-rich alkenes is by far the most prevalent method used for the construction of 1,2-dioxetanes. The Kopecky method, which relies on the cyclization of a β -halo hydroperoxide, is rarely utilized these days but was heavily relied upon in the past. The base-catalyzed cyclization of β -epoxy hydroperoxides also appears to be becoming more popular. There are also several miscellaneous methods that have been utilized for specific dioxetane examples and these are summarized in [Section 2.16.7.1.3](#).

2.16.7.1.1 Cyclizations of two-atom components

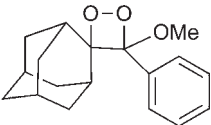
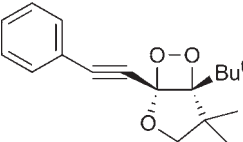
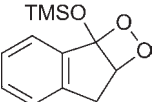
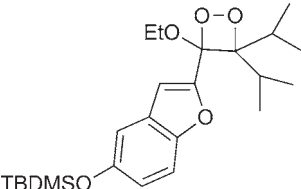
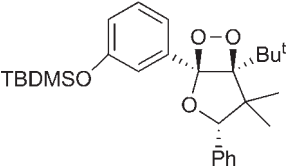
The [2+2] cycloaddition of singlet oxygen ($^1\text{O}_2$) to electron-rich alkenes is the most convenient and versatile method for the preparation of 1,2-dioxetanes. Reactions can conveniently be carried out from low temperature to ambient temperature, in a large range of organic solvents, and employ a range of singlet oxygen sensitizers. [Table 2](#) summarizes the variety of 1,2-dioxetanes that have been prepared via this method over the last decade. The reader is directed to the CHEC-II(1996) chapter [<1996CHEC-II\(1B\)1041>](#) for examples prior to 1996.

Table 2 1,2-Dioxetanes prepared by $^1\text{O}_2$ cycloaddition

<i>Dioxetane</i>	<i>Yield (%)</i>	<i>m.p. (°C)</i>	<i>Reference</i>
	89	a	1997TL5825
	74	a	2002TL1523
	83	42–43	2003T4811
	88	93–93.5	1997TL2863
	88 ^b	a	2005CC808

(Continued)

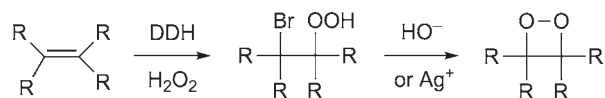
Table 2 (Continued)

<i>Dioxetane</i>	<i>Yield (%)</i>	<i>m.p. (°C)</i>	<i>Reference</i>
	93	85–88	2000J(P1)2243
	80	^a	1999TL4571
	>95	^c	1999JCS(P1)2507
	72	^a	1999MI345
	95	113.5–114	2001TL2349

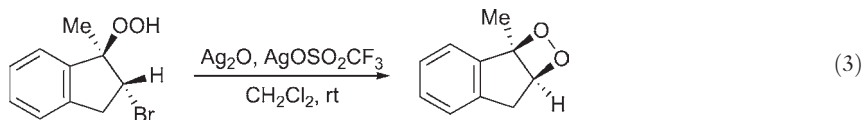
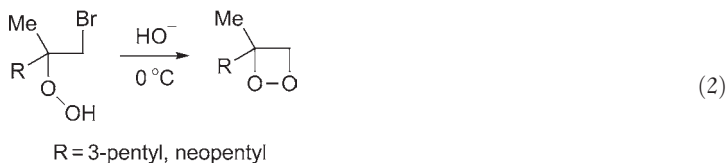
^aOil.^b1:3 Ratio of (Sa, 1*S*, 5*S*)- and (Sa, 1*R*, 5*R*)-isomers.^cStable at 0 °C but unknown if solid.

2.16.7.1.2 Cyclizations of a single four-atom component

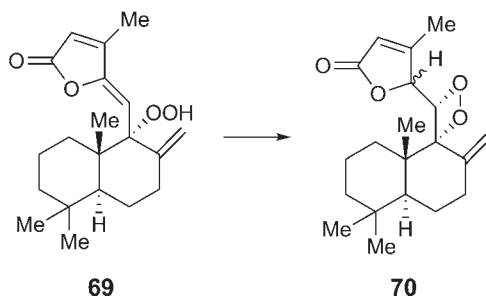
The Kopecky method for the formation of 1,2-dioxetanes involves the dehydrohalogenation of β -halo hydroperoxides and is promoted by the action of a base or a silver salt and was first reported in 1975 <1975CJC1103>. **Scheme 18** depicts the general process in which β -bromo hydroperoxides are prepared by bromination of alkenes with 1,3-dibromo-5,5-dimethylhydantoin (DDH) in the presence of concentrated hydrogen peroxide.

**Scheme 18**

As mentioned above, the Kopecky method is rarely utilized these days but was relied heavily upon in the past with numerous examples tabulated in CHEC-II(1996) <1996CHEC-II(B1)1041>. In fact, only two reports have resulted in the past decade. **Equation (2)** summarizes the preparation of two simple 1,2-dioxetanes in extremely low yield (1–2%) after purification <2001HAC459>, while **Equation (3)** shows that indene derivatives undergo cyclization in excellent yields (88%) <1999H(50)1025>.



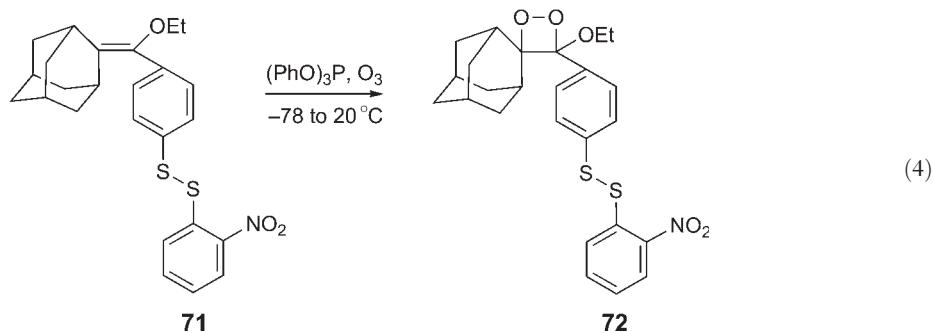
Cyclizations of a single four-atom component are not limited to just the Kopecky method. Diastereomeric 1,2-dioxetanes **70** have also been reported to be formed in excellent overall yield (96%, isomer ratio 1.5:1.0) via the intermediacy of β -ene hydroperoxide **69** (Scheme 19) <2006T5308>.



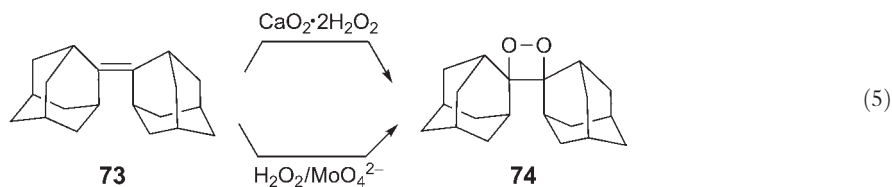
Scheme 19

2.16.7.1.3 Other syntheses

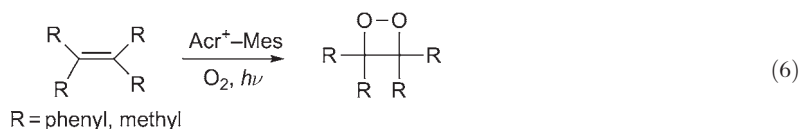
There are a few syntheses outside the reaction categories discussed in the previous sections. Enol ether **71** was successfully transformed into the desired 1,2-dioxetane **72** (25%) utilizing triphenylphosphite ozonide, even though it contains a disulfide bond which would be of great susceptibility to further oxidation (Equation 4) <2002JA4874>.



Recently calcium peroxide diperoxohydrate ($\text{CaO}_2 \cdot 2\text{H}_2\text{O}_2$) has become an environmentally friendly generator of singlet oxygen and was used to generate 1,2-dioxetane **74** from **73** in 75% isolated yield (Equation 5) <2002JOC2418>. The same dioxetane **74** has also been prepared in excellent yield (90%), utilizing a reverse microemulsion of hydrogen peroxide and molybdate ions <1997JA5286>.



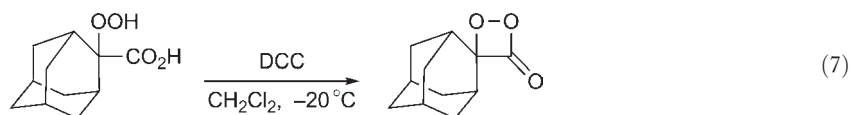
An interesting but under explored method for the formation of 1,2-dioxetanes employing the photocatalytic oxygenation of olefins with dioxygen via selective radical coupling using 9-mesityl-10-methylacridinium ion as an electron-transfer photocatalysis has also appeared (Equation 6) <2004JA15999>.



Section 2.16.5.5 details the preparation of alkoxy-, aryloxy-, and acyloxy-substituted 1,2-dioxetanes via a novel substitution process directly upon the ring carbons of the dioxetane core <1997JA245>.

2.16.7.2 Dioxetanones (α -Peroxy Lactones)

The only method for the synthesis of dioxetanones reported within the last decade relies on the cyclization of α -hydroperoxy acids. This method furnished the desired dioxetanones in reasonable yields and relies on removal of water by the use of a dehydrating reagent such as dicyclohexylcarbodiimide (DCC). For example, spiro-adamantyl dioxetanone was prepared in 55% yield utilizing this method (Equation 7) <1997JOC1623>. The reader is directed to CHEC-II(1996) <1996CHEC-II(1B)1041> for examples prior to 1996.

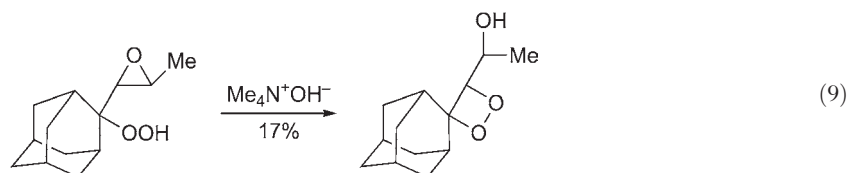
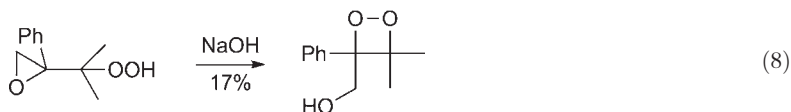


2.16.8 Ring Synthesis by Transformation of Another Ring

As mentioned in the previous edition, the cyclization of hydroperoxides with concomitant ring opening of an epoxide moiety is a viable route to 1,2-dioxetanes. No other syntheses of 1,2-dioxetanes exist which rely upon the transformation of another ring.

2.16.8.1 Transformations of Epoxy Hydroperoxides to Hydroxymethyl-Substituted Dioxetanes

Base-induced intramolecular cyclization of β -epoxy hydroperoxides has recently been exploited by several groups to prepare 1,2-dioxetanes, albeit in low yield (Equations 8 and 9) <2002OL537, 1999JA1834>.



2.16.9 Synthesis of Particular Classes of Compounds

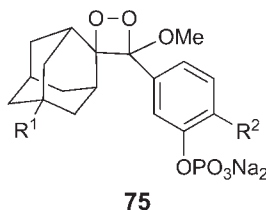
2.16.9.1 Synthesis of Heterodioxetanes

As highlighted within Section 2.16.1, although reports of heterodioxetanes containing additional heteroatoms 10–12 (X = N, P, S, Si, Ge, etc.) have been cited in the literature over the last decade and indeed were incorporated in CHEC-II(1996) <1996CHEC-II(1B)1041>, they are now more appropriately covered in Chapter 2.22 of CHEC-III.

2.16.10 Important Compounds and Applications

2.16.10.1 Applications for Bioanalysis: The Chemiluminescence Immunoassay

CIEEL is of particular interest for the development of modern chemiluminescent bioassays. The most popular clinical bioassays utilize thermally persistent spiro-adamantyl-substituted dioxetanes with a protected phenolate moiety. These designed 1,2-dioxetanes include an energy source, a fluorophore, and a trigger grouping, and are therefore structurally similar to bioluminescent substrates such as firefly luciferin. Three main commercial dioxetanes **75** are available as one-reagent assays for alkaline phosphatase and are sold under the name of AMPPD[®] ($R^1 = R^2 = H$), CSPD[®] ($R^1 = Cl$, $R^2 = H$), and CDP-Star[®] ($R^1 = R^2 = Cl$) <2006S1781, 2003ANA279>. These substrates are sensitive to 10^{-21} mol of alkaline phosphatase in solution.



The design and synthesis of dioxetane-based chemiluminescent probes for the detection of cholinesterase activity <2002JA4874> and for the detection and quantification of singlet oxygen have also recently appeared <2005ANC1200>. Several reports also describe possible oxidative DNA damage by radicals generated in the thermolysis of hydroxymethyl-substituted 1,2-dioxetanes through the α -cleavage of chemiexcited ketones <1998JA3549, 1997JA719>.

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Biographical Sketch



Professor Dennis Taylor, an organic chemist by training and former Head of the Discipline of Chemistry at The University of Adelaide, Australia, has recently been appointed to the Chair of Oenology within the Wine and Horticulture Discipline. Dennis graduated from Flinders University with B.Sc.(Hon.) and Ph.D. in chemistry in 1992 followed by a postdoctoral appointment with Nobel laureate Sir Derek Barton at Texas A&M University. In 1996, Dennis accepted an academic appointment within Chemistry, where he remained until his recent move to the Waite. Dennis is a Fellow of the Royal Australian Chemical Institute and a Member of the American Chemical Society and the Australian Society of Viticulture and Oenology. Awards include the Brailsford Robertson Award, The Rennie Memorial Medal, an RACI Organic Division Lectureship, and a Flinders University Medal. Utilizing his excellent track record in chemistry research associated with 1,2-dioxines, he plans to bring an innovative perspective on issues that influence wine production and quality as well as continuing to develop the field of 1,2-dioxine chemistry.

2.17

Four-membered Rings with One Oxygen and One Sulfur Atom

D. K. Taylor

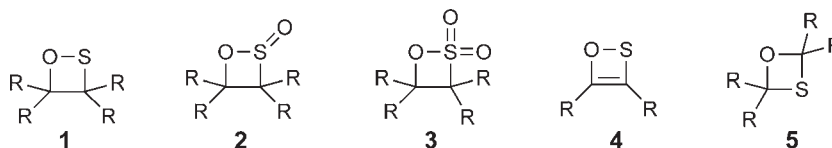
The University of Adelaide, Adelaide, SA, Australia

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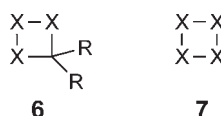
2.17.1 Introduction

The following four-membered ring heterocycles **1–5**, which contain one oxygen and one sulfur atom, are known. Of these the 1,2-oxathietanes are quite common with numerous examples of their oxidised forms, namely the β -sultines and the β -sultones, reported over the decades. These systems will form the major part of this chapter. 1,2-Oxathietes, 1,3-oxathietanes, and their S-oxides are still quite rare but examples have been reported and will be highlighted within the chapter where appropriate.



This subject was covered previously in CHEC(1984) <1984CHEC(7)449> and in CHEC-II(1996) <1996CHEC-II(1B)1083>. The chapter within CHEC(1984) contained a summary of all four-membered rings with two or more heteroatoms while the chapter within CHEC-II(1996) was dedicated only to these systems. Again, the present chapter will be solely dedicated to these systems and is intended to update previous concentration on major new preparations, reactions, and concepts. At the beginning of each main section a sentence or short paragraph has been provided that explains the major advances, or lack thereof, since the previous publication of the topics in question. From a historical perspective it should be pointed out that while there was much research being conducted on the synthesis and characterization of the properties of these systems during the period between 1970 and 1995, such interest has waned over the past decade. As a consequence this chapter is smaller in length to that within CHEC-II(1996), but still covers the same scope.

Although reports of heterooxathietanes containing additional heteroatoms, that is, **6** and **7** (X = N, P, S etc), have been cited in the literature over the last decade, they are more appropriately covered in Chapter 2.22.

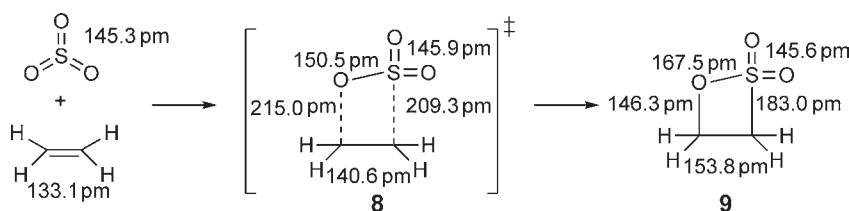


2.17.2 Theoretical Methods

Over the last decade there has been very few theoretical studies conducted on 1,2- and 1,3-oxathietanes and associated derivatives. In fact, there are no new reports for 1,2-oxathietanes, β -sultines, and 1,2-oxathietes. Several reports for β -sultones, a 1,3-oxathietane, and a sulfurane are in existence. The reader should consult the previous version of this chapter <1996CHEC-II(1B)1083> for previous theoretical treatments (mainly low level calculations) of 1,2-oxathietanes, 1,3-oxathietanes, and several 1,2-oxathietes.

2.17.2.1 1,2-Oxathietane-Type Derivatives

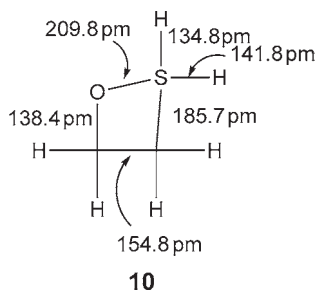
Several detailed theoretical studies have been conducted on the reaction of sulfur trioxide with alkenes to afford β -sultones. The first publication <1998JA6468> details the reaction of sulfur trioxide with ethylene to afford β -sultone **9** via transition state **8** (Scheme 1). Important bond lengths are shown (pm). Density functional and correlated *ab initio* calculations indicate that the reaction proceeds by a concerted [2+2] pathway.



Scheme 1

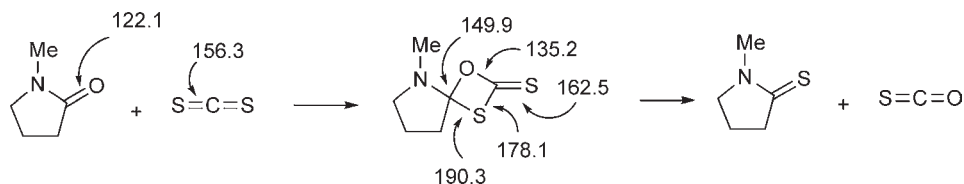
The second publication detailed molecular modeling studies on the reaction of sulfur trioxide with a series of fluoroalkenes and found that the reaction proceeds via formation of stable π -complexes prior to transition state formation <1999J(P2)1819>.

The four-membered ring sulfurane, (*S,S*-H₂)-2-oxa-1-thietane **10**, has also been studied theoretically at the B3LYP/6-31+G(d,p) level of theory <1998PCA4703>. It was found that the S–O bond is long (209.8 pm) and is substantially polarized. The calculated atomic charges on S and O were +0.37 and –0.62, respectively. Consequently, the structure resembles a zwitterionic complex, H₂S⁺CH₂CH₂O[–], rather than a covalent cyclic molecule with a tetracoordinated sulfur atom in a regular oxathietane ring.



2.17.2.2 1,3-Oxathietanes

In the only paper published in the last decade pertaining to theoretical studies of 1,3-oxathietanes, it has been proposed that an intermediate 1,3-oxathietane is formed during the reaction of carbon disulfide with *N*-methyl-2-pyrrolidinone <2006CPL(420)162>. The important bond lengths (pm) are shown in Scheme 2. Optimized structures of all stationary points at the B3LYP/6-31G(d) level were included.



Scheme 2

2.17.3 Experimental Structural Methods

2.17.3.1 Spectroscopic Methods

2.17.3.1.1 IR spectroscopy

Prior to the last decade infrared (IR) spectroscopy was used on a routine basis for the characterization of four-membered rings containing one oxygen atom and one sulfur atom, especially their oxidized forms <1996CHEC-II(1B)1083>. β -Sultones display an asymmetric SO₂ stretch in the region 1400–1470 cm^{–1}, whereas the symmetric mode appears between 1200 and 1230 cm^{–1}. The SO stretch of β -sultines appears around 1150 cm^{–1}. There is only one publication in the last decade that reports IR data for several β -sultones <1999TL7417>.

2.17.3.1.2 UV–Vis spectroscopy

Unfortunately, UV spectral data have not been reported for 1,2-oxathietanes, β -sultines, β -sultones, 1,2-oxathietes, 1,3-oxathietanes, and their S-oxides.

2.17.3.1.3 Photoelectron spectra

No data have been presented on such systems.

2.17.3.1.4 NMR studies

Typical proton and ^{13}C -chemical shift data for ring atoms of β -sultones from the last decade are collated in [Figure 1](#) <1999EJO91, 1999TL7417>. The previous version of this chapter summarized the reported nuclear magnetic resonance (NMR) data (proton, carbon-13 and fluorine-19) for an extensive range of fluorinated β -sultones, non-fluorinated β -sultones, β -sultines, 1,2-oxathietanes, and 1,2-oxathietes that were known up until 1995 <1996CHEC-II(1B)1083>. Given the lack of research on such systems over the last decade, it is not surprising that only limited data are available to report in this edition. No systematic NMR study has been performed on the ring ^1H - and ^{13}C -chemical shifts so general trends are still difficult to highlight.

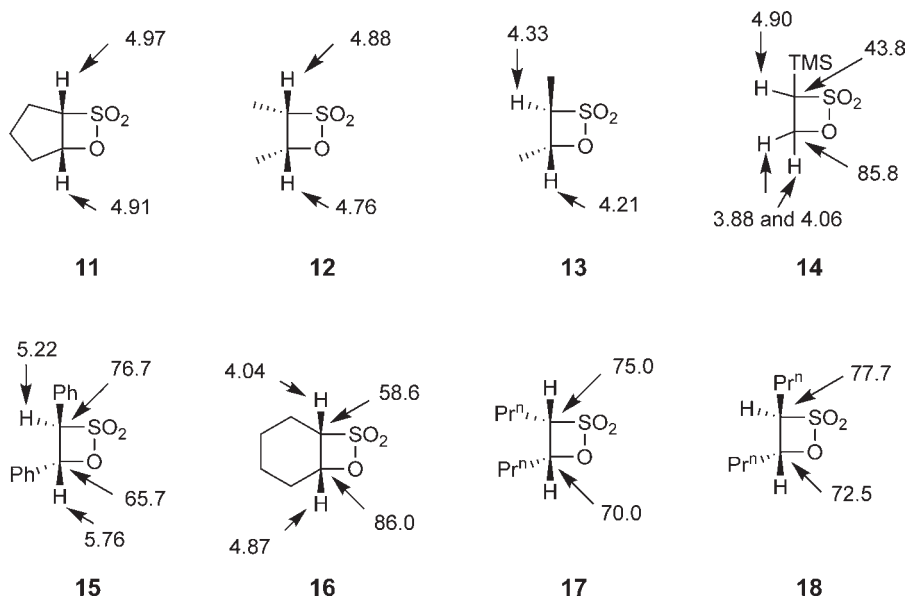


Figure 1 ^1H - and ^{13}C -chemical shifts of β -sultone ring atoms (ppm wrt TMS).

2.17.3.1.5 Mass spectrometry

The previous version of this chapter summarized the reported MS data for a range of fluorinated β -sultones, nonfluorinated β -sultones, β -sultines, 1,2-oxathietanes, and 1,2-oxathietes <1996CHEC-II(1B)1083>. Many different fragmentation routes occur and they appear to be dependent on the substituents that have been incorporated into the system. Electron ionization mass spectrometry (EIMS) data for several β -sultones prepared in 1999 clearly indicate the initial loss of SO_2 from such systems <1999TL7417>. MS dissociation data for several 2-aryl-1,2-oxathietan-2-ium ions generated from arenesulfonyl cations with various acetals and ketals have also been recently reported <2001J(P2)350>. Cycloreversion was clearly a major fragmentation pathway for such systems in the gas phase.

2.17.3.1.6 X-Ray diffraction

The generally low stability of four-membered ring heterocycles containing one oxygen and one sulfur atom, combined with difficulties in obtaining crystalline samples, has severely limited the amount of crystallographic data available ([Figure 2](#)). Despite these problems, data have been reported for two 1,2-oxathietanes **21** and **22** <1996JA697, 1994AGE2094>, two β -sultines **19** and **20** <1981J(P1)1826, 1996JA697>, three β -sultones **23**, **24** and **26** <1990IC3058, 1994IC1273, 1988SUL55>, and one 1,2-oxathiete **25** <1990AGE1128> over the last three decades. No 1,2-oxathietanes have thus far been reported. While there is insufficient data to make meaningful comparisons, it is worthy to note that puckering of the ring can be anywhere from planar to as high as 20° .

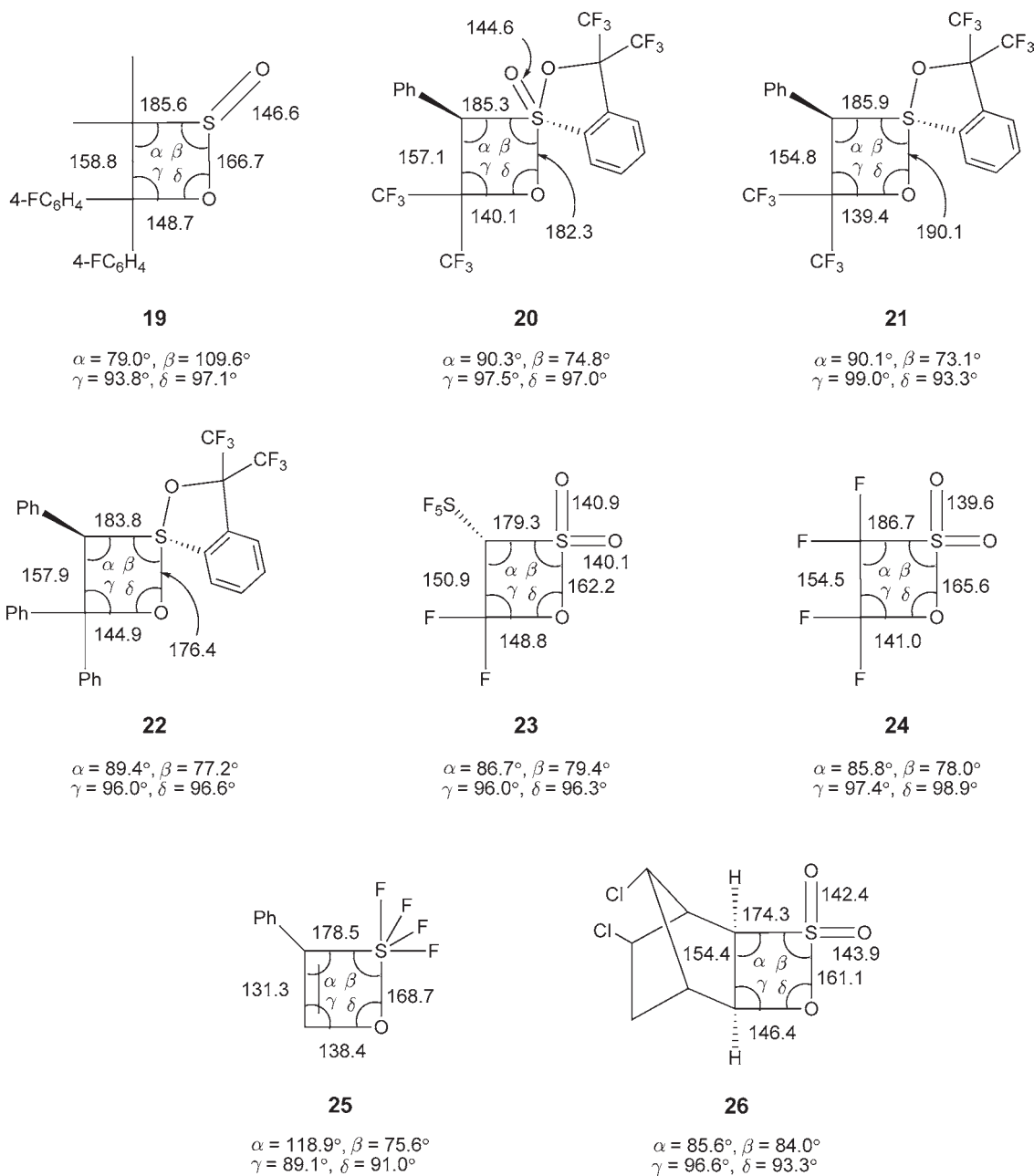


Figure 2 X-ray diffraction data for four-membered ring heterocycles containing one oxygen and one sulfur atom.

2.17.3.2 Chemical Methods

Satisfactory CH microanalyses for several β -sultones <1999TL7417> and several pentacoordinate $1,2\lambda^4$ - and $1,2\lambda^6$ -oxathietanes <1996JA697, 1996JA12455> have been reported over the last decade. While there is no CH micro-analytical data for simple 1,2-oxathietanes, β -sultines, 2-oxathietes, 1,3-oxathietanes, and their S-oxides, occasionally high-resolution mass spectrometry (HRMS) data are reported. Presumably, this reflects the thermal instability of these systems.

2.17.4 Thermodynamic Aspects

2.17.4.1 Physical Data

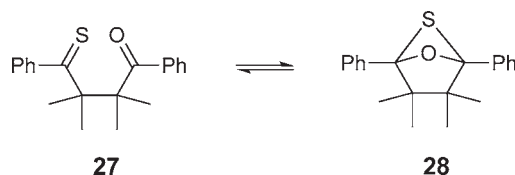
Given that few new 1,2-oxathietanes, β -sultines, β -sultones, 2-oxathietes, 1,3-oxathietanes, and their S-oxides have been prepared over the last decade, there has been no systematic tabulation of melting or boiling points. This also reflects their instability. Only on rare occasions are melting and boiling points reported.

2.17.4.2 Solubilities and Chromatographic Behavior

β -Sultones behave chromatographically the same as any organic derivative and as such their R_f will be dependent on the polarity of the substrate as a whole. No special precautions are necessary during chromatography except that one may need to guard against thermal instability. Solubilities will also be subject to structure; however, there are no notable difficulties with solubilities reported. No data are available for the other four-membered systems highlighted within this review.

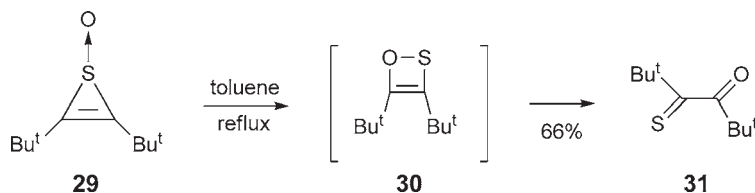
2.17.4.3 Stability and Thermochemical Aspects

The previous chapter in CHEC-II(1996) reported on the stability and derived thermochemical data for the isomerization of β -sultones, the cycloreversion of 1,2-oxathietanes, the relative stability of 1,2- and 1,3-oxathietanes, the isomerization of 1,2-oxathietes, as well as aspects related to stereoisomerization <1996CHEC-II(1B)1083>. Unfortunately, no new studies or information has been presented over the last decade. The only experimental observation worthy of mention is that an equilibrium mixture of the thioketone **27** along with the 6-oxa-7-thiabicyclo[3.1.1]heptane **28** was isolated in 48% yield from the thermal decomposition of a precursor dithiirane oxide <1997BCJ509>. This indicated that the activation barrier for cycloaddition–cycloreversion is low at ambient temperature.



2.17.5 Reactivity of Fully Conjugated Rings

1,2-Oxathietes contain all sp^2 hybridized ring carbons and therefore are considered fully conjugated. Unfortunately, no 1,2-oxathietes have been reported to have been isolated in the last decade. This presumably reflects the fact that their open-chain isomers are thermodynamically more stable. Indeed, in a recent publication on the synthesis and stability of thiirene 1-oxides, it was found that heating of sulfoxide **29** in toluene resulted in an excellent yield of the α -oxothioketone **31** (Scheme 3) <2002HAC424>. The isomeric 1,2-oxathiete **30** was postulated to be a transient intermediate but could not be detected.



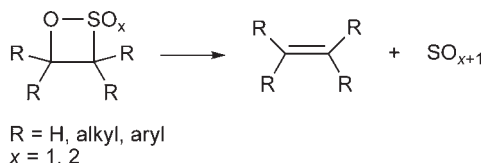
Scheme 3

2.17.6 Reactivity of Nonconjugated Rings

2.17.6.1 Thermal and Photochemical Reactions

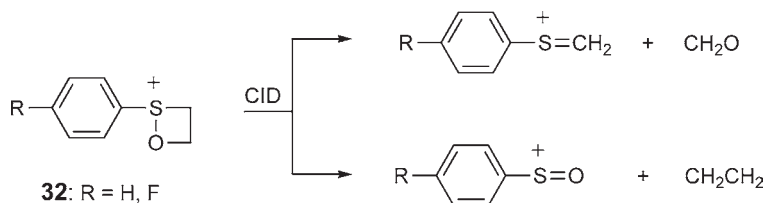
2.17.6.1.1 Cycloreversion

While the previous version of this chapter <1996CHEC-II(1B)1083> detailed numerous cycloreversions of the type depicted within **Scheme 4**, no new chemically useful examples of this type have been reported over the last decade.



Scheme 4

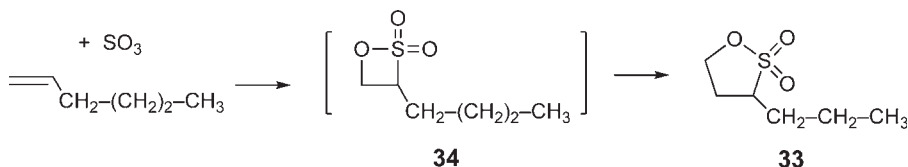
As highlighted in [Section 2.17.3.1.5](#), cycloreversion processes have been described for the collapse of the molecular ion of 1,2-oxathietanes of type **32** (**Scheme 5**) <2001J(P2)350>.



Scheme 5

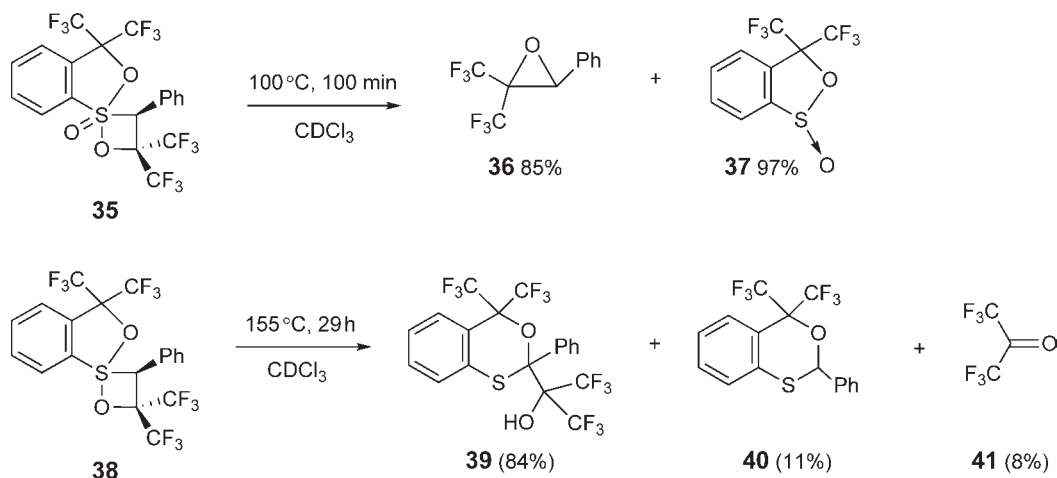
2.17.6.1.2 Rearrangements and isomerizations

A limited number of rearrangements/isomerizations were reported in the previous version of this chapter. Again little has been done in this area of research over the past decade. The most common isomerization involves the ring expansion of β -sultones into γ -sultones and is illustrated by the example below (**Scheme 6**) <1999TL7417>. Thus, treatment of 1-hexene with sulfur trioxide produced the γ -sultone **33** in 68% yield after isomerization of the unstable β -sultone **34**.



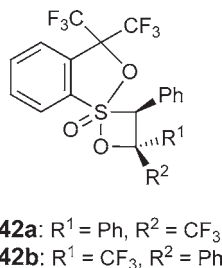
Scheme 6

The thermal rearrangement of several pentacoordinate $1,2\lambda^4$ - and $1,2\lambda^6$ -oxathietanes has been investigated <1996JA697, 1996JA12455>. In the first publication the authors reported that $1,2\lambda^4$ -oxathietane **35** decompose to afford epoxide **36** and cyclic sulfinate **37** while $1,2\lambda^6$ -oxathietane **38** decompose at a higher temperature affording thioacetals **39** and **40** along with some hexafluoroacetone **41** (**Scheme 7**). The contrasting reaction outcomes were explained based on initial S–O bond cleavage followed by loss of the sulfinate **37** for **35**, whereas a 1,3-proton shift followed by a Pummerer rearrangement is favored for **38**.



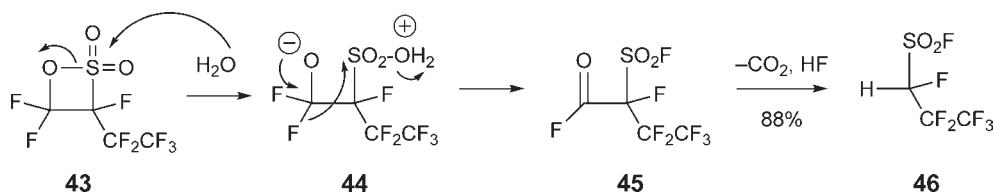
Scheme 7

The second report details the thermal decomposition of a range of stereochemically related 1,2 λ^6 -oxathietanes **42**. Although complex mixtures resulted the products were of the type described above.



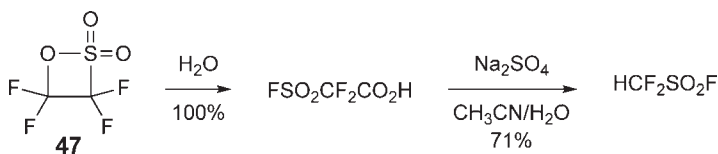
2.17.6.2 Nucleophilic Attack at Ring Sulfur

Nucleophiles, such as F^- , H_2O , ROH , HNR_2 , etc., are known to attack the sulfur atom of β -sultones; however, analogous examples for simple 1,2- and 1,3-oxathietanes are nonexistent. For examples prior to 1996, see CHEC-II(1996) <1996CHEC-II(1B)1083>. Water reacts readily with fluorinated β -sultones to afford sulfonyl fluorides <2004RUP2237659>. The favored mechanism involves nucleophilic attack on the ring sulfur atom in **43** with an S–O bond cleavage. Rearrangement of **44** affords the labile acid fluoride **45**, which upon warming in the presence of water undergoes decarboxylation to afford the observed sulfonyl fluorides **46** (Scheme 8).



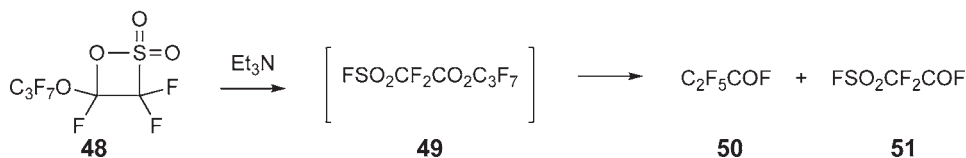
Scheme 8

Another recent example of this type of process involved the formation of fluorosulfonyldifluoroacetic acid from β -sultone **47** in 100% yield. Decarboxylation with Na_2SO_4 in $CH_3CN:H_2O$ (1:1 v/v) afforded difluoromethanesulfonyl fluoride (Scheme 9) <2002CC2098>.



Scheme 9

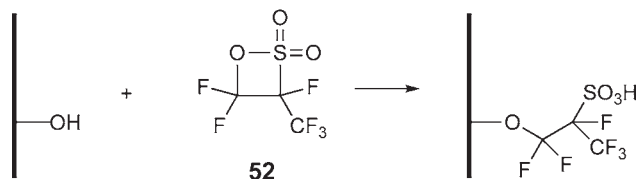
In contrast to other known fluorinated β -sultones, reaction of compound **48** with triethylamine does not give the expected isomer **49**, but only its decomposition products pentafluoropropionyl fluoride **50** and fluorosulfonyldifluoroacetyl fluoride **51** (Scheme 10) <2003JFC(121)147>.



Scheme 10

2.17.6.3 Nucleophilic Attack at Ring Carbon

Nucleophilic attack at the ring carbon within β -sultones has been extensively explored in the past but has only attracted one report in the past decade <2004CC956, 2005JCT48>. In this recent publication, purely siliceous MCM-41 or SBA-15 silicas were functionalized with 1,2,2-trifluoro-2-hydroxy-1-trifluoromethylethane sulfonic acid sultone **52** to furnish sulfonic acid groups anchored to the silanol groups with perfluoroalkyl tethers (Scheme 11). These hybrid organic-inorganic mesoporous materials are structurally analogous to Nafion[®]. If this process really does involve a nucleophilic attack on a ring carbon, then it is unusual as fluorinated β -sultones normally would undergo nucleophilic attack on sulfur.

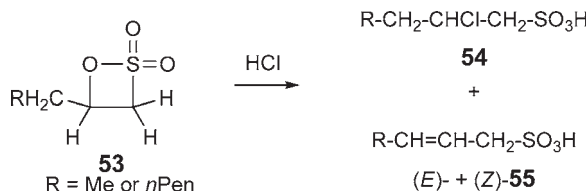


Scheme 11

The reader should consult the CHEC-II(1996) version of this chapter for examples prior to 1993 involving nucleophiles such as water, amines, acids, alkoxides, halides, and various carbon nucleophiles.

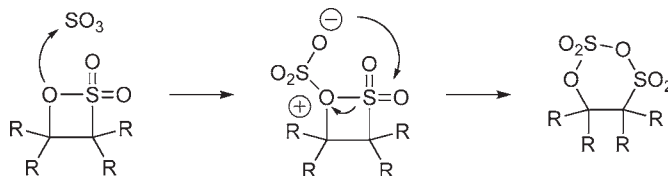
2.17.6.4 Electrophilic Attack at Ring Oxygen

The treatment of β -sultones with hydrochloric acid results in ring-opening products and is initiated by protonation of the ring oxygen atom. For example, Scheme 12 highlights the conversion of the β -sultones **53** into the corresponding 2-chlorosulfonic acids **54** and the (*E*)- and (*Z*)-alkene-sulfonic acids **55** when exposed to HCl <1999EJO91>.



Scheme 12

The CHEC-II(1996) version of this chapter demonstrates that much work has been done on the formation of cyclic pyrosulfates (carbyl sulfates) when β -sultones are exposed to excess SO_3 (Scheme 13) <1996CHEC-II(1B)1083>. Since the early 1990s no new research has been performed in this area, although the existence of a cyclic sulfate has been surmised, based on isolated products <2003JFC(121)147>.



Scheme 13

2.17.6.5 Miscellaneous Reactions

No new miscellaneous reactions have been reported over the last decade. However, several reaction types such as eliminations and reductions were reported in the CHEC-II(1996) version of this chapter <1996CHEC-II(1B)1083>.

2.17.7 Reactivity of Substituents Attached to Ring Carbon Atoms

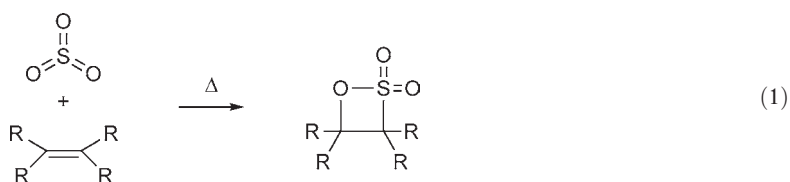
Considering the lack of research being performed on 1,2- and 1,3-oxathietanes and their oxidized forms, it is not surprising that there are no reports in the last decade on the reactivity of substituents attached to ring carbon atoms.

2.17.8 Ring Synthesis Classified by Number of Ring Atoms in Each Component

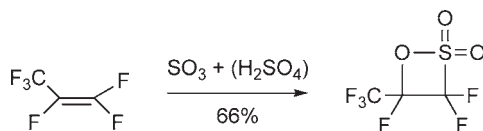
2.17.8.1 Cyclizations of Two-Atom Components

2.17.8.1.1 Cyclizations involving S–C and O–C formation

The only methodology pertinent to the formation of 1,2- and 1,3-oxathietanes and their oxidized forms involving S–C and O–C bond formations is that for the preparation of β -sultones. It is now well established that $[\pi 2s + \pi 2s]$ cycloaddition of sulfur trioxide with an alkene generates β -sultones in moderate to excellent yields (Equation 1). Indeed, the previous version of this chapter detailed numerous examples of the formation of β -sultones (especially fluorinated compounds) by the reaction of SO_3 with an appropriate alkene at elevated temperatures <1996CHEC-II(1B)1083>.

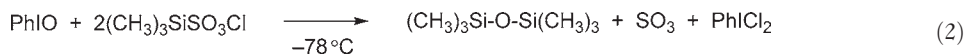


It has been recognized that difficulty in handling sulfur trioxide coupled with the need to reduce its electron-acceptor properties has led to the development of numerous Lewis-base complexed sulfur trioxide reagents such as SO_3 -pyridine <1962CRV549> and SO_3 -dioxine <1954JA3945>. As pure sulfur trioxide readily polymerizes and is difficult to keep dry, researchers have recently investigated the use of fuming sulfuric acid (oleum) as an alternative source of sulfur trioxide for these reactions (Scheme 14) <2003JFC(121)147>. As much as 67 wt.% of monomeric SO_3 is available.

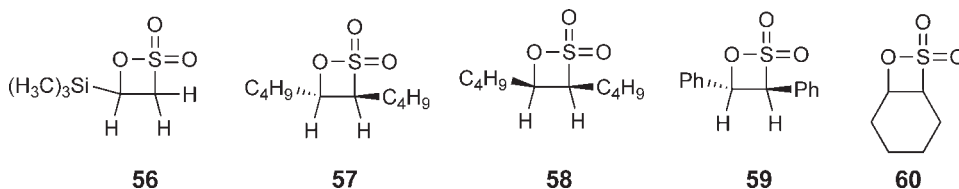


Scheme 14

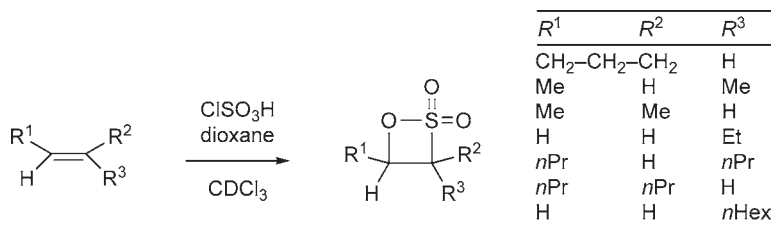
The generation of sulfur trioxide *in situ* in the absence of Lewis bases is also possible and allows the preparation of β -sultones. A novel method for the generation of sulfur trioxide includes the reaction of trimethylsilylsulfonyl chloride with iodosobenzene in dichloromethane (Equation 2) <1999TL7417>.



In this way β -sultones **56–60** were prepared in yields of 50–69% from their respective alkenes.

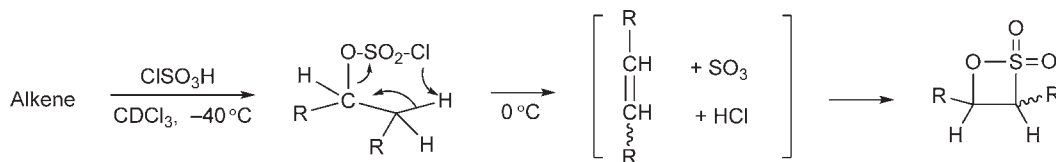


The reaction of various alkenes with chlorosulfuric acid in the presence of dioxane represents a versatile method for the preparation of β -sultones <1999EJO91>. Yields were not reported as these reactions were conducted in CDCl_3 and followed by NMR. However, it was observed that the reactions all went to completion (Scheme 15).



Scheme 15

The same authors also report on the reaction of alkenes with chlorosulfuric acid in the absence of dioxane <1999EJO91>. Thus, treatment of various alkenes at -40°C with chlorosulfuric acid results in the formation of *sec*-alkyl hydrogen sulfates (Scheme 16). From the results presented it appears that the *sec*-alkyl hydrogen sulfates are transformed into a mixture of internal *trans*- and *cis*- β -sultones upon warming to 0°C . Subsequent sulfonation of these alkenes by SO_3 then yields the corresponding β -sultones. Again isolation yields were not reported but the reactions appear to proceed in a quantitative manner. The same paper also describes the use of acetyl sulfate and trifluoroacetyl sulfate for the preparation of β -sultones, but mixtures appear to result.



Scheme 16

No new examples for the formation of β -sultones via S–C and O–C bond formation have been reported in the last decade; however, several examples were cited in the CHEC-II(1996) version of this chapter <1996CHEC-II(1B)1083>.

2.17.8.1.2 Cyclizations involving S–O and C–C formation

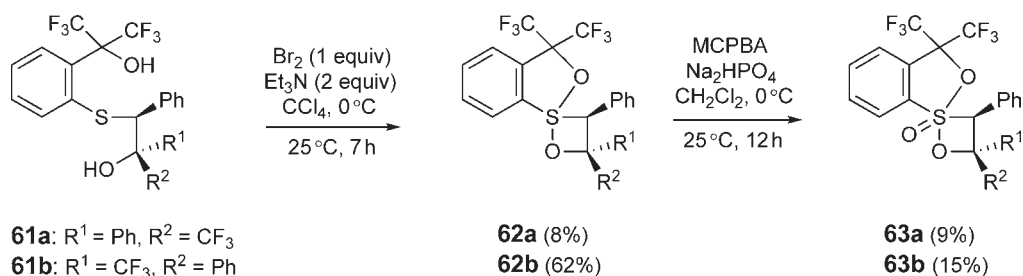
No new methodology pertinent to the formation of 1,2- and 1,3-oxathietanes and their oxidized forms involving S–O and C–C bond formations has been cited in the past decade. The reader should consult the CHEC-II(1996) version of this chapter <1996CHEC-II(1B)1083> for several examples of polyhalogenated β -sultone formations from sulfenes and carbonyl compounds. As the yields are poor, this approach has presumably not been seen to be useful synthetically since the early 1980s.

2.17.8.2 Cyclizations of a Single Four-Atom Component

No new methodology pertinent to the formation of 1,2- and 1,3-oxathietanes and their oxidized forms involving cyclizations of a single four-atom component has been cited in the past decade. The reader should consult the CHEC-II(1996) version of this chapter <1996CHEC-II(1B)1083> for several examples of the formation of simple 1,2-oxathietanes and β -sultines. Yields are reported to vary from poor to excellent (in some cases).

2.17.8.3 Other Syntheses

There is one report on the synthesis of several pentacoordinate 1,2 λ^4 - and 1,2 λ^6 -oxathietanes, which is outside the categories discussed above <1996JA697, 1996JA12455>. Treatment of diols **61a** or **61b** with bromine under basic conditions leads to the formation of pentacoordinate 1,2 λ^4 -oxathietanes **62a** and **62b** in 8% and 62% yields, respectively (Scheme 17). Oxidation of these substrates furnishes the observed pentacoordinate 1,2 λ^6 -oxathietanes **63a** and **63b** in poor yield.



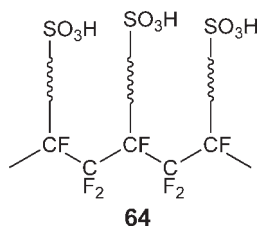
Scheme 17

2.17.9 Synthesis of Particular Classes of Compounds

While the previous version of this chapter contained small sections on the synthesis of fluorinated and nonfluorinated β -sultones along with β -sultines and 1,2-oxathietanes, there has been no major new advances on the synthesis of these types of systems over the last decade. It appears that until practical industrial or medicinal uses are found, new methodologies for the construction of such systems will not be developed.

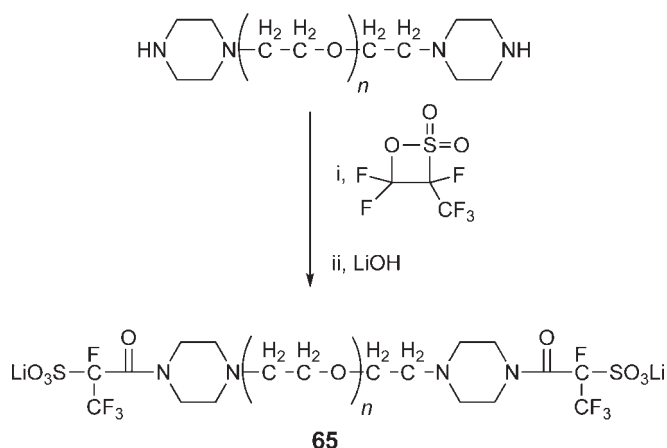
2.17.10 Important Compounds and Applications

The most important use of β -sultones is for the preparation of fluorinated polymers such as Nafion[®] **64**. These solid acid catalysts containing perfluorinated sulfonic acid groups have been known for many years and the presence of the electron-withdrawing F atoms increases the acid strength of the terminal sulfonic acid groups, which become comparable to that of pure sulfuric acid. Prior to the last decade, Nafion[®] had been in use as a superacid, a fuel cell electrolyte and as a membrane-ion separator <1996CHEC-II(1B)1083>.



Attention on designing uses for Nafion[®] has died down in the last decade primarily due to the fact that the polymer catalyst has a low surface area. Focus now appears to be on utilizing β -sulfones for the preparation of hybrid organic–inorganic mesoporous materials with terminal perfluorinated sulfonic acid groupings <2004CC956, 2005JCT48>. The synthetic scheme appears in Section 2.17.6.3. These studies report that these catalysts show higher activity than commercial Nafion[®]-silica composites for the esterification of long chain fatty acids with ethanol.

Molecular salts of type **65** have also been prepared recently by the reaction of a secondary amine with the linear isomer of hexafluoropropane sultone as depicted in Scheme 18 <2003MI1961>. These lithium polymers exhibit high electrochemical stability and cationic conductivity and therefore are ideally suited for lithium polymer batteries.



Scheme 18

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Biographical Sketch



Professor Dennis Taylor, an organic chemist by training and former Head of the Discipline of Chemistry at The University of Adelaide, Australia, has recently been appointed to the Chair of Oenology within the Wine and Horticulture Discipline. Dennis graduated from Flinders University with B.Sc. (Hon) and Ph.D. in chemistry in 1992 followed by a postdoctoral appointment with Nobel Laureate Sir Derek Barton at Texas A&M University. In 1996 Dennis accepted an academic appointment within chemistry where he remained until his recent move to the Waite. Dennis is a Fellow of the Royal Australian Chemical Institute, a Member of the American Chemical Society, and the Australian Society of Viticulture and Oenology. Awards include the Brailsford Robertson Award, The Rennie Memorial Medal, an RACI Organic Division Lectureship, and a Flinders University Medal. Utilizing his excellent track record in chemistry research associated with 1,2-dioxines he plans to bring an innovative perspective on issues that influence wine production and quality as well as continuing to develop the field of 1,2-dioxine chemistry.

2.18

Four-membered Rings with Two Sulfur Atoms

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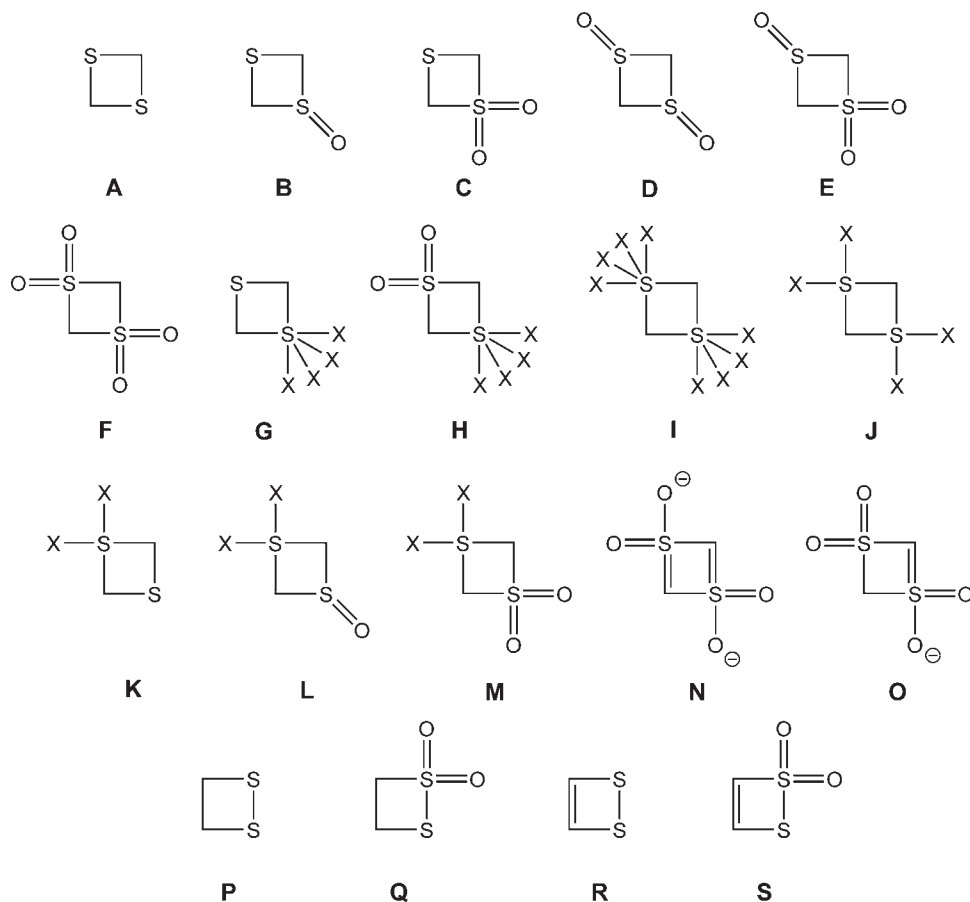
2.18.1 Introduction

2.18.1.1 General Remarks

The corresponding CHEC-II(1996) chapter by Zoller <1996CHEC-II(1B)1113> begins with a concise text entitled “Historical and Future Perspectives”, in which the author gave an excellent overview of the reasons for which small rings, including four-membered rings with two sulfur atoms, have fascinated organic chemists for more than a century. It discussed historical and future perspectives in the chemistry of stable four-membered ring systems with two sulfur atoms. After more than 10 years, which have passed since the publication of CHEC-II(1996), there is no need to update the historical overview of these structures. Simultaneously, the future perspectives mentioned in this text remain alive, and also in this case there is no need to update them. Therefore, we hope that our chapter, which is based on the most recent work in this field, will show how this interesting chemistry has developed after 1994, facilitating answers to the still-open questions related to this group of organic sulfur derivatives.

2.18.1.2 Considered Structures and Scope

The IUPAC systematic name 'thietane' and 'thiete' for the saturated and unsaturated four-membered ring systems containing two sulfur atoms will be followed through this chapter as it was used in the relevant chapter included in CHEC-II(1996) <1996CHEC-II(1B)1113>. Thus, the most recent development in the chemistry of the parent and functionalized 1,2-dithietanes, 1,3-dithietanes, and the 1,2-dithietes and their derivatives having a different oxidation state and/or coordination number of the sulfur atom(s) published after 1994 constitute the main object of this review. However, to make it as comprehensive and useful as possible, the older literature is included when necessary, if it was not mentioned in the relevant chapter of CHEC-II(1996). The preparation of this chapter is based on a literature search through SciFinder Scholar and the Beilstein Database. It gave 324 substances that can be grouped into 15 families of 1,3-derivatives (structures **A–O**) and 4 families of 1,2-derivatives (structures **P–S**). In spite of this large number of considered structures, this update cannot be exhaustive (as the original chapter in CHEC-II(1996)). Due to space limitations, we are forced to discuss only a limited number of examples related to the most important theoretical and experimental problems in the chemistry of four-membered ring systems with two sulfur atoms.

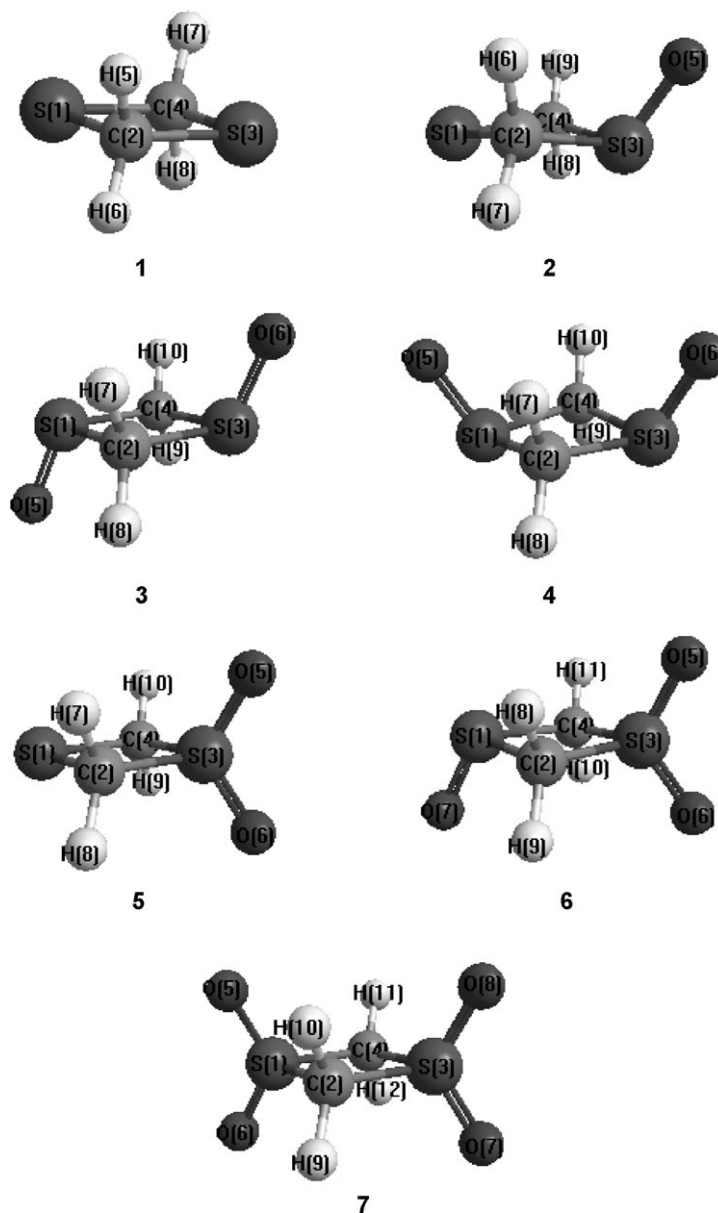


2.18.2 Structure of 1,3- and 1,2-Derivatives with Different Oxidation State and Coordination Number of the Sulfur

2.18.2.1 Theoretical Calculations

A rather limited number of theoretical studies on saturated dithietane systems have been reported during the last 10 years. Most of them are devoted to theoretical calculations of geometries of the 1,3-systems. One can also find *ab initio* calculations of their interconversions and the normal mode frequencies and theoretical predictions of spectroscopic parameters such as infrared (IR) and Raman intensities.

The geometric structural parameters of a number of *S*-oxides generated from 1,3-dithietane and keto and thioketo derivatives generated from 2,2,4,4-tetrafluoro-1,3-dithietane have been recently calculated at the Hartree–Fock (HF)/6-31-G** level, within the molecular orbital (MO) theory framework <1999JMT(466)111>. Structures shown here show the optimized geometries of the parent 1,3-dithietane **1**, its mono- and bis-oxides **2–4**, 1,1'-dioxide **5**, 1,3,3'-trioxide **6**, and 1,1',3,3'-tetraoxide **7**, whereas Table 1 lists the selected bond distances and angles for these compounds.



Analysis of the data from Table 1 shows that the calculated structural parameters for **2** and **7** agree well with the experimental ones <1976JA5715> and allows to draw the following main conclusions:

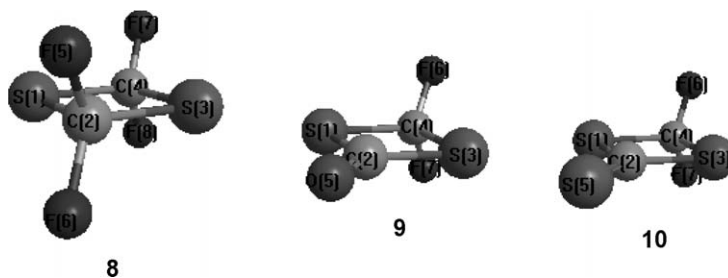
- 1,3-Dithietane derivatives having one or two sulfur atoms with coordination number three have puckered structures.
- The ring of 1,3-dithietane is essentially planar with regular geometry of approximately D_{2h} symmetry.
- Mono-**2**, bis-**3** and **4**, and tri-**5** sulfoxides are puckered with S(1)–C(2)–S(3)–C(4) dihedral angles varying between -24° and 12° .

Table 1 Bond distances and angles for 1,3-dithietane derivatives **1–7**, calculated at the HF/6-31G** level

Parameter ^a	1	2^b	3	4	5	6	7^b
S(1)–C(4)	1.824 8	1.821 7(1.82)	1.820 3	1.819 7	1.830 3	1.838 0	1.804 1(1.808)
S(3)–C(4)	1.824 2	1.817 0(1.81)	1.822 2	1.819 7	1.794 7	1.788 0	1.804 1(1.808)
C(2)–S(3)	1.824 2	1.817 0(1.81)	1.822 1	1.819 6	1.794 7	1.788 0	1.804 1(1.808)
S(1)–C(2)	1.824 8	1.821 7(1.82)	1.820 2	1.819 7	1.830 6	1.837 9	1.804 1(1.808)
S(3)–O(5)		1.471 0(1.473)			1.428 7	1.430 9	
S(3)–O(6)			1.472 1	1.472 0	1.428 7	1.426 0	
S(3)–O(7)							1.426 2(1.433)
S(3)–O(8)							1.426 2(1.433)
S(1)–O(5)			1.477 2	1.471 9			1.426 2(1.433)
S(1)–O(6)							1.426 2(1.433)
S(1)–O(7)						1.470 5	
S(1)···S(3)	2.687 9	2.637 6(2.60)	2.684 8	2.686 5	2.639 8	2.657 9	2.615 8(2.590)
C(2)···C(4)	2.467 9	2.384 7(2.37)	2.363 4	2.368 1	2.368 1	2.437 9	2.485 3(2.524)
S(1)–C(4)–S(3)	94.89	92.92	94.97	95.15	93.46	94.27	92.93
C(2)–S(3)–C(4)	85.13	82.02(81.7)	80.19	81.19	87.61	85.92	87.07
S(1)–C(2)–S(3)	94.89	92.92	94.98	95.15	93.46	94.27	92.93
C(2)–S(1)–C(4)	85.10	87.77(81.1)	80.96	81.19	85.47	83.05	87.07
C(2)–S(3)–O(5)		111.81			110.92	109.23	
C(2)–S(3)–O(6)			110.46	110.80			
C(2)–S(3)–O(8)							110.66(111.2)
C(4)–S(3)–O(5)		111.81			110.92	109.24	
C(4)–S(3)–O(6)			110.46	110.80			
C(4)–S(3)–O(8)							110.66(112.2)
S(1)–C(2)–S(3)–C(4)	0.03	–24.10	–21.53	–20.34	–0.03	12.06	0.00

^aBond distances and angles in Å and degrees, respectively.^bExperimental data in parentheses from <1976JA5715>.

1,3-Dithietane *S*-dioxides can exist in three isomeric forms, **3–5**, (two 1,3- and one 1,1'-isomers). *Ab initio* calculations at various level of theory show that the sulfone **5** is ca. 33 kcal mol^{–1} more stable than the two diastereomeric sulfoxides **3** and **4**. This explains the experimental observation that it is easier to isolate this sulfone than the corresponding sulfoxides. To determine the stability of the bis-sulfoxide species, the detailed *ab initio* calculations were carried out using various basis sets. It showed that *cis*-sulfoxide **4** is only 0.27 kcal mol^{–1} less stable than the *trans*-isomer **3**; this means that the equilibrium between **3** and **4** is slightly shifted to the *trans*-isomer. It is of interest to note that the calculated dipole moments differ substantially (2.5 D for the *trans*-isomer and 3.64 for the *cis*-compounds). Similar calculations were also carried out for tetrafluorodithietane **8** <1999JMT(466)111, 2004JMT(678)189> and its derivatives **9** and **10** in which one of the sp³ ring carbons was converted to a carbonyl or thiocarbonyl group. <1999JMT(466)111>. The data which are collected in Table 2 (taken from <1999JMT(466)111>) show that the calculated bond distances and angles agree well with the experimental values (also refer to Table 3 <2004JMT(678)189>) <1973CRC2023, 1976ACA759>.



Comparison of the appropriate data in Tables 1 and 2 clearly indicates that the changes in the bond distances of the ring in going from **1** to **8** are negligible, whereas the angles vary only about 2°. For structures **9** and **10**, there is a small variation in the bond distances and angles of the rings when compared to **8**. This indicates that perfluorination of the parent dithietane and the change of hybridization of one of the carbon atoms induces no change in the structure

Table 2 Selected bond distances and angles for fluorinated 1,3-dithietanes **8–10**, calculated at the HF/6-31G** level

<i>Parameter</i> ^a	8 ^b	9 ^b	10 ^b
S(1)–C(4)	1.808 8(1.820)	1.814 8(1.821)	1.814 9(1.823)
S(3)–C(4)	1.808 8(1.820)	1.814 9(1.821)	1.814 9(1.823)
C(2)–S(3)	1.808 8(1.820)	1.786 9(1.791)	1.762 6(1.758)
S(1)–C(2)	1.808 8(1.820)	1.787 1(1.791)	1.762 6(1.758)
C(2)–O(5)		1.166 3(1.179)	
C(2)–S(5)			1.599 4(1.598)
S(1)–S(3)	2.718 0	2.727 5	2.690 5
C(2)–C(4)	2.387 2	2.357 2	2.357 2
S(1)–C(4)–S(3)	97.41(97.3)	97.43(97.7)	95.67(94.6)
S(1)–C(2)–S(3)	97.41(97.3)	99.49(100.1)	99.49(99.2)
C(2)–S(1)–C(4)	82.59	81.54(81.0)	82.42(83.1)
C(2)–S(3)–C(4)	82.59	81.54(81.0)	82.42(83.1)
F(6)–C(4)–F(7)		106.37(106.3)	106.47(108.1)
F(7)–C(4)–F(8)	105.92(106.5)		
F(5)–C(2)–F(6)	105.92(106.5)		
S(1)–C(2)–S(3)–C(4)	0.00	0.00	–0.02

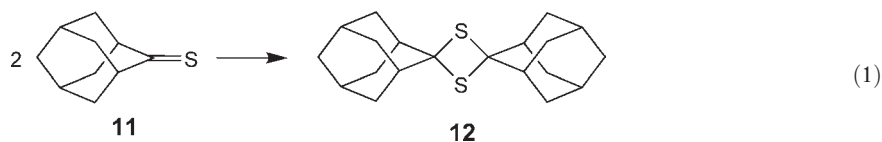
^aBond distances and angles in Å and degrees, respectively.
^bExperimental data in parentheses from <1973CRC2023>.

Table 3 Selected normal modes for tetrafluoro-1,3-dithiethane **8**, calculated by various theoretical methods

		Frequency (cm ⁻¹)						
		Theoretical (method)						
Symmetry	Normal mode	Calc.	Corrected	Experimental	IR ^a intensity	Raman ^b activity	Assignment	
A _g	ν ₁	1336(HF)	1153(HF)	1162	Inactive	13	C–F stretch	
		1163(DFT)	1161(DFT)			7		
		1202(MP2)	1159(MP2)			7		
	ν ₃	570(HF)	506(HF)	516		16	C–S stretch	
		505(DFT)	512(DFT)			18		
		532(MP2)	512(MP2)			15		
B _{1g}	ν ₅	957(HF)	850(HF)	833	Inactive	11	C–S stretch	
		815(DFT)	826(DFT)			7		
		877(MP2)	845(MP2)			5		
B _{2g}	ν ₇	1275(HF)	1101(HF)	1090	Inactive	1	C–F stretch	
		1100(DFT)	1099(DFT)			1		
		1140(MP2)	1099(MP2)			1		
B _{3g}	ν ₉	323(HF)	285(HF)	285	Inactive	4	CF ₂ twist	
		284(DFT)	285(DFT)			5		
		297(MP2)	285(MP2)			4		
B _{1u}	ν ₁₁	1291(HF)	1114(HF)	1118	446	Inactive	C–F stretch	
		1117(DFT)	1116(DFT)					389
		1155(MP2)	1114(MP2)					366
B _{2u}	ν ₁₄	1101(HF)	977(HF)	966	178	Inactive	C–S stretch	
		958(DFT)	971(DFT)					157
		1011(MP2)	974(MP2)					160
B _{3u}	ν ₁₆	1248(HF)	1077(HF)	1076	895	Inactive	C–F stretch	
		1072(DFT)	1071(DFT)					807
		1113(MP2)	1073(MP2)					770
	ν ₁₇	726(HF)	645(HF)	652	14		C–S stretch	
		650(DFT)	659(DFT)					23
		667(MP2)	642(MP2)					19

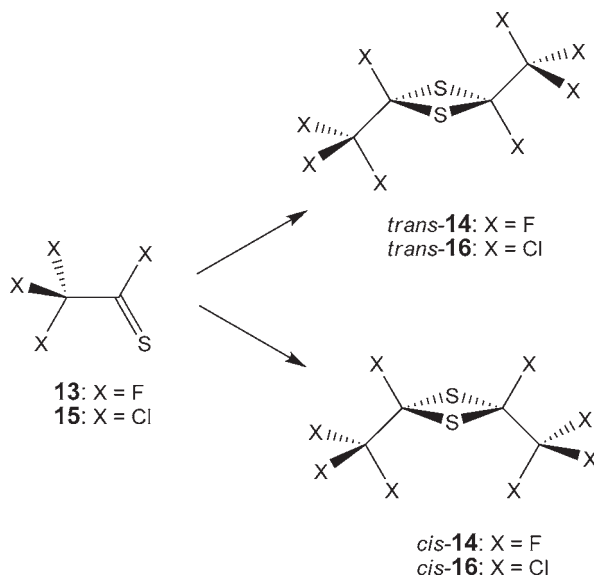
^aUnits of intensity are km mol^{–1}.
^bUnits of Raman scattering activity are Å⁴ amu^{–1}.

of the selected 1,3-dithietane molecules. It is also of interest to note that the calculated long $F\cdots X$ ($X=O$ or S) nonbonded distances (ca. 4.44 and 4.86 Å) are in good agreement with the experimental values (respectively ca. 4.5 and 4.9 Å) <1991JST(249)297>. However, the $S(1)-C(2)-S(3)-C(4)$ dihedral angle found was always zero which indicates the planarity of the rings. This is in contrast with the experimental data which show a small deviation from the planarity in these species and is interpreted in terms of shrinking effects induced by low-frequency out-of-plane vibrations <1991JST(249)297>. Stewart's parametric method number 3 (PM3) has been applied <1989JCC209> for the calculation of the structural parameters of the 1,3-dithietane dimer **11** derived from adamantanethione **12** (Equation 1) <1984J(P1)1869, 1984J(P1)2649, 1999EJO83>. The $C\cdots C$ and $S\cdots S$ distances computed with this method are 2.558 and 2.719 Å, respectively.



The computed CSC and SCS angles have values of 86.5° and 93.5°, respectively, which compare well with the experimental values discussed in Section 2.18.2.2. It is of interest to note that both the calculated frontier molecular orbitals (FMOs) appear to have an antibonding character within the bridge region. The computed ionization potential (IP) is at 9.372 eV while the HOMO–LUMO gap (H–L gap) is at 8.804 eV (HOMO = highest occupied molecular orbital; LUMO = lowest unoccupied molecular orbital) <2004JMT(668)179>.

Ab initio calculations have also been carried out <2003JFC(124)99> for the photodimerization reaction of trifluorothioacetyl fluoride **13** which affords approximately equal amounts of *trans*- and *cis*-2,4-difluoro-2,4-bis(trifluoromethyl)-1,3-dithietane **14** (Scheme 1) <1965JOC1375>. The calculations indicate that both dimers are thermodynamically stable relative to the monomer, and of almost equal stability. The E_c and $G_{298.15}$ values obtained in the G3(MP2) calculations of the dimers relative to monomers gave 115 and 45 kJ mol^{−1} for *cis*-**14**, while the corresponding values for *trans*-**14** were 112 and 44 kJ mol^{−1}. For both isomers, the 1,3-dithietane ring was found to be planar <2003JFC(124)99>.



Scheme 1

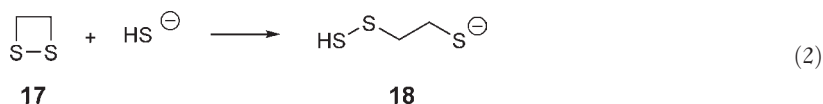
The chlorine analogue of **13**, trichlorothioacetyl chloride **15**, photodimerizes, but only to *trans*-isomer **16**. Investigations of the dimerization reaction first by *ab initio* calculations (HF, MP2) show that the dimers of starting **15**, *trans*-**16** and *cis*-**16**, are both thermodynamically more stable relative to **15** by 57 and 48 kJ mol^{−1}, respectively, and *trans*-**16** isomer is more stable than *cis*-**16**. The difference between their ΔE_c s is 10 kJ mol^{−1} and between their $\Delta H_{298.15}$ and $\Delta G_{298.15}$ is 9 kJ mol^{−1}. These results deviate from these of the fluorine analogues cited above. The results for chlorine *trans*- and *cis*-compounds are consistent with the fact that only the *trans*-isomer is observed in the dimerization <2004MI111>.

According to both HF and MP2 calculations on 1,3-dithietane, the geometry of the 1,3-dithietane ring in *trans*-**16** is almost identical to that of the parent 1,3-dithietane **15**, while this ring in *cis*-**16** is slightly puckered with one C-atom 9.9° out of the plane formed by the other C-atom and the two S-atoms <2004MI111>.

Theoretical calculations on the *anti*-dithietane 1,3-dioxide **3** $\rightleftharpoons$ *syn*-dithietane 1,3-dioxide **4** equilibrium in the gas phase at HF/6-31G** level show that the *anti*-isomer **3** is slightly favored (by ca. 0.27 kcal mol⁻¹) over the *syn*-isomer **4**. The *anti*/*syn*-ratio is 1.6, with a *syn*-concentration of 36%. Due to different dipole moments of the *anti* **3** and *syn* **4**, the solvents of low and medium-high polarity such as carbon tetrachloride, acetonitrile, and dimethyl sulfoxide (DMSO) exert a strong influence on the *anti* $\rightleftharpoons$ *syn* interconversion, producing an increase in the *syn*-concentration <2001BOC57>.

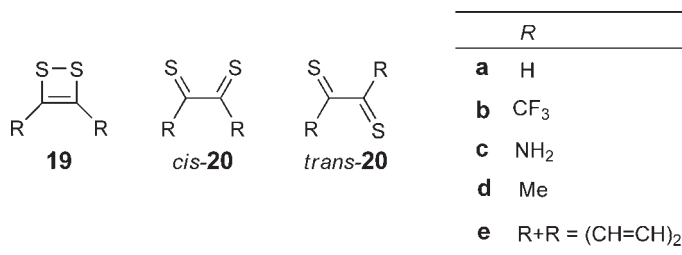
In CCl₄, the *syn*-concentration is ca. 63%, whereas in CH₃CN and DMSO, both *anti*- and *syn*-form concentrations are approximately equal <2001BOC57>.

Bachrach *et al.* investigated the mechanism for the reaction of thiolate (HS⁻) with 1,2-dithietane **17** (Equation 2) by applying B3LYP/ang-ec-pVDZ and MP2/6-31+G* calculations. Both these methods concur on the S_N2-type mechanism for a nucleophilic substitution at the sulfur atom in 1,2-dithietane <2002JOC8983>.



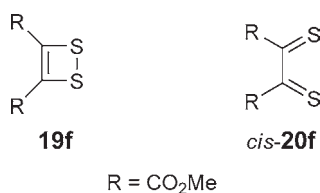
There are some theoretical studies concerning the stability of 1,2-dithietenes and ethane-1,2-dithiones <1996IJQ859>.

The valence isomerization of a series of 1,2-dithietes **19** to the open-chain dithiones **20** was studied by CASSI multiconfiguration methods, including the CASPT2 perturbational treatment <1996IJQ859>.



It was found that the planar 1,2-dithiete parent compound remains only weakly stabilized with respect to the isomeric open-chain dithiones at the highest level of theory employed (CASPT2). More than one set of polarization functions are necessary to describe the S–S bond adequately. In agreement with Jonas and Frenking, the cyclic structure is only then preferred over the acyclic ones if *f* functions on the sulfur atoms are considered. If they are included, the 1,2-dithiete is more stable by 3.8 kcal mol⁻¹ and the barrier amounts to 24.9 kcal mol⁻¹ at the CASPT2(8,8)/6-31G(2df)//MP2/6-31G* level of theory. According to MP2/6-31G* geometry optimizations, substitution of H by NH₂ and Me reduces the stability of the 1,2-dithiete ring structures relative to the open-chain dithiocarbonyl structures, whereas the inverse situation holds for the substitution by CN and CF₃. This is in line with experimental results. Benzodithiete is considerably more stable than the isomeric *o*-dithiobenzoquinone <1996IJQ859>.

Theoretical and experimental studies on the reaction of 3,4-bis(methoxycarbonyl)-1,2-dithiete with alkenes and alkynes yielding cycloadducts have been carried out. The activation energy of the interconversion of the 1,2-dithiete to 1,2-dithione was estimated by MO calculations. These calculations (MP2/6-31G(d)) show that the dithiete **19f** is 5.8 kcal mol⁻¹ more stable than the ethane-1,2-dithione *cis*-**20f**, and the tautomerization energy is 28.5 kcal mol⁻¹ from the thiete **19f** and this value of the activation energy supports the possibility of the tautomerization between the 1,2-dithiete **19f** and ethane-1,2-dithione *cis*-**20f**, at least at high temperature <1996IJQ859>.



Similarly, for sulfur analogues **19b** and *cis*-**20b** (Equation 3), both the HF-level calculations and the addition of MP2 energies (single point) showed that the cyclic structure **19b** is more stable than the acyclic structure *cis*-**20b** (by +9.53 and +3.24 kcal mol⁻¹). HF calculations of the analogues **19d** and *cis*-**20d** showed that in this case the acyclic structure *cis*-**20d** becomes more stable (−2 to −5 kcal mol⁻¹) depending on the level of calculations (Table 4) than cyclic 1,2-dithiete structure **19d** <2000CEJ1153>.

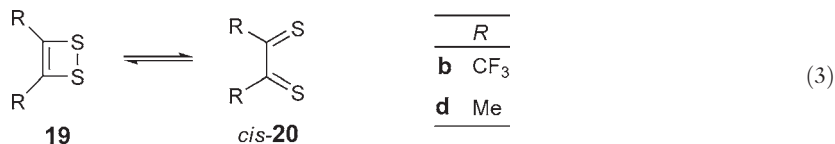


Table 4 Total energies (*E*) of the sulfur-containing compounds *cis*-**26b,d** and **19b,d**, and the differences in the energies for acyclic and cyclic structures (ΔE_{20-19}), from *ab initio* calculations at HF and electron-correlated MP2 levels

Method	<i>E</i> _(acyclic) (au)	<i>E</i> _(cyclic) (au)	ΔE_{20-19} (kcal mol ⁻¹)
	<i>cis</i> - 20b	19b	<i>cis</i> - 20b – 19b
HF/6-311+G*	−1543.33329	−1543.34847	+9.53
MP2/6-311++G**//HF/6-311++G**	−1545.36696	−1545.37213	+3.24
	<i>cis</i> - 20d	19d	<i>cis</i> - 20d – 19d
HF/6-31G*	−949.95122	−949.94715	−2.55
HF/6-31++G**	−949.96433	−949.96103	−2.07
MP2/6-31++G**//HF/6-31++G**	−950.77707	−950.76895	−5.09
HF/6-311++G**	−950.03665	−950.03300	−2.29
MP2/6-311++G**//HF/6-311++G**	−950.88269	−950.87436	−5.23

Theoretical studies on the ring-opening reaction of 1,2-dithiete by using unrestricted density functional theory (DFT) with fractionally occupied frontier orbitals were reported. The topic addressed in these studies was the question of the relative energies of the sulfur species 1,2-dithiete **19a** and dithioglyoxal *trans*-**20a** <1999JCP7705>.

The same subject was also investigated by other authors who realized *ab initio* calculations at HF, MP2, coupled-cluster theory with singles, doubles, and estimated triple excitations (CCSD(T)) and DFT of relative energies of the 1,2-dithiete **19a** and dithioglyoxal *trans*-**20a** <2000JCP8430>. They demonstrated a peculiar dependence of the results on the f-type polarization functions and showed that *ab initio* calculations with 6-31G(nd) basis sets with n = 1–3 incorrectly predict that **19a** is higher in energy than *trans*-**20a**. The relative energies at MP2 and CCSD(T) levels changed by more than 6 kcal mol⁻¹ in favor of **19a** if one set of f functions was added to the basis set. Similarly, the DFT calculations also gave a higher stability of **19a** relative to *trans*-**20a** if the basis set was augmented by f functions, but the change in relative energy was only ~2 kcal mol⁻¹. The large changes in the energies that were calculated at MP2 and CCSD(T) were mainly due to the f functions at the sulfur atom, while the effect on the f functions in the DFT calculations was mainly due to the f functions at the carbon atom <2000JCP8430>.

The IR and Raman spectra of tetrafluoro-1,3-dithietane **8** have also been examined theoretically using the Gaussian 98 set of the quantum-chemistry code <2004JMT(678)189>. Normal modes were calculated at the HF, DFT (B3LYP), and MP2 levels of theory using the standard 6-311G** basis. They were assigned to one of eight types of motion predicted by a group theoretical analysis. The data, which are collected in Table 3, clearly indicate a good agreement between theoretically calculated and experimental values reported for this thietane <1963SAA769>.

2.18.2.2 Experimental Spectroscopic Methods

X-Ray diffraction is one of the best methods for molecular structure determination of four-membered rings with two sulfur atoms, for those having a crystalline form and adequate stability.

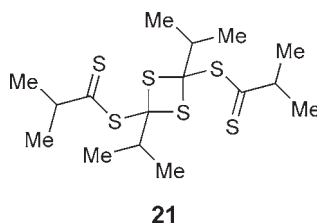
It was determined that the molecules of dispiro[1,3-dithietane-2,2':4,2''-diadamantane] **12** have a crystallographic *C_i* symmetry as well as local *D_{2h}* symmetry and a planar 1,3-dithietane ring <2002AXCo231>. The C–S–C bond angles are significantly less than 90° while the S–C–S angles are correspondingly larger than 90°. The C–S bond length and C–S–C and S–C–S angles in the 1,3-dithietane ring of **12** are similar to those in all of the related

compounds, with the exception of the highly puckered ring of 1,4-diphenyl-2,2,3,3-tetramethyl-5,6-dithiabicyclo[2.1.1]hexane, where the ring strain reduces the C–S–C angles to a mean value of $73.4(1)^\circ$ <2002AXCo231>.

1,1,3,3-Tetrachloro-2,4-dithiacyclobutane also has a crystallographic C_i symmetry, although the molecule of *trans*-2,4-dimethyl-2,4-bis(thioacetylthio)-1,3-dithietane has a pseudo- C_i symmetry and a planar ring <2002AXCo231>.

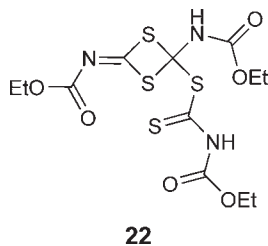
The cyclic sulfone, 1,3-dithietane 1,1-dioxide **5**, was characterized by a single crystal X-ray analysis. In this molecule, the ring is slightly puckered which results in a C–S–C/C–S–C dihedral angle of 163° . This value is slightly larger than those of single substituted thietane 1,1-oxides. The C–S distances to the thioether sulfur atom S-1 (S(1)–C(1) = $1.83(1) \text{ \AA}$, S(1)–C(2) = $1.82(1) \text{ \AA}$) appear to be longer than those of the sulfone sulfur atom S-2 (S(2)–C(1) = $1.77(1) \text{ \AA}$, S(2)–C(2) = $1.81(2) \text{ \AA}$), but the differences are not significant by the 3σ -criterion. IR spectra of **5** show three absorptions in the region characteristic for S–O stretching absorptions: $1375(\text{s})$, $1200(\text{s})$, and 1127 cm^{-1} . The first and last one of these three were assigned to the asymmetric and symmetric S=O stretching vibrations <1999JOM(573)14>.

Determination by X-ray analysis of the structure of **21** was undertaken to confirm the *trans*-conformation of the dithietane molecule and for understanding the process of its formation. The atomic arrangement of the compound **21** is centrosymmetric about the midpoint of S(1)–S(1)ⁱ vector, creating a planar, almost square central ring (*i*: $1-x, -y, 1-z$). The angle S(3)–C(5)–S(3)ⁱ is $95.54(6)^\circ$. The tetrahedral unit C-5, S-2, S-3, C-6, S-3ⁱ is mainly characterized by three very similar C–S distances ranging from 1.827 to $1.839 \text{ \AA}$ and one C(5)–C(6) distance of $1.539 \text{ \AA}$. In spite of this apparent distortion, the average angle C(6)–C(5)–S in this tetrahedron (108.7°) is close to the theoretical value for a regular tetrahedron. The other interatomic distances and bond angles are in accordance with the expected values <2003AXEo545>.



In 1,4-diphenyl-2,2,3,3-tetramethyl-5,6-dithiabicyclo[2.1.1]hexane, the two dithietane ring C-atoms are bridged by an ethylene group, which constrains the C–S–C bonds to be part of a five-membered ring. This produces a severe folding of the 1,3-dithietane ring into a V-shape about both the S··S and C··C axes, the folds being 61.7° and 52.8° , respectively. The C–S bond lengths and C–S–C and S–C–S angles in the 1,3-dithietane ring **12** are similar to those in all of the related compounds, with the exception of 1,4-diphenyl-2,2,3,3-tetramethyl-5,6-dithiabicyclo[2.1.1]hexane, where the ring strain reduces the C–S–C angle to a mean of $73.4(1)^\circ$ <2002AXCo231>.

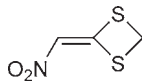
Compound **22**, which can be viewed as an adduct of a dimer of ethoxycarbonyl isothiocyanate ($\text{EtO}_2\text{CN}=\text{C}=\text{S}$) and the ethoxycarbonyl dithiocarbamic acid, contains an imino-substituted four-membered dithietane ring which imposes a highly distorted tetrahedral structure around atom C-2. One of the sulfur atoms of the dithiocarbamyl grouping S-3 is bonded to one of the imino carbon atoms of the EtO_2CNCS dimer at the C-2 atom. Thus C-2 has three sulfur atoms, S-1, S-2, and S-3, bonded to it with bond lengths typical of C–S single bonds. The C–S bonds to C-1 are shorter due to a partial multiple bonding character to C-1 <1998EJI1025>.



This compound dissociates in solution to yield the starting materials, dithiocarbamic acid and ethoxycarbonyl isothiocyanate <1998EJI1025>.

The structure of the heterocycle **23** was confirmed on the basis of the spectral data, and finally by the X-ray crystallographic data analysis <2002SUL207>.

The X-ray crystal analysis of 2-(nitromethylene)-1,3-dithietane **23** revealed a dimeric structure, stabilized through CH–O hydrogen-bonding interactions. It is worth noting that the ^1H nuclear magnetic resonance (NMR) spectrum of **23** reveals the olefinic hydrogen absorption at 7.3 ppm; this observation indicates that the olefinic hydrogen occurs in a shielding environment, which is probably due to increased ring strain <2002SUL207>.

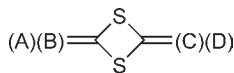
**23**

The X-ray diffraction structure of 2,4-bis(dimesitylmethylene)-1,3-dithietane **24** has been determined and is the first 1,3-dithietane structure having two *exo*-diarylmethylene groups.

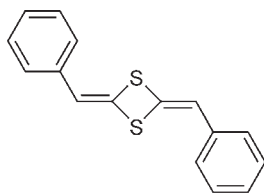
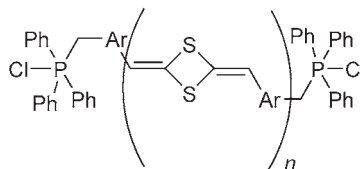
The central ring possesses an inversion center in the middle of the ring exchanging the two pairs of mesityl groups on its both sides. A C_2 -axis passing through the double bonds exchanges two geminal mesityl rings. The Mes–C=C– dihedral angles are 59.8° . The double-bond torsional angle is 8.7° . Static NMR data allowed for the detection of the presence of two enantiomers and one *meso*-form for **24**, formed in the synthesis of **24**. The several aromatic signals observed for **24** at slow exchange at 160 K coalesce to a single signal at higher temperatures. The threshold barrier for these dynamic processes is $12.7 \text{ kcal mol}^{-1}$ and the dynamic behavior was analyzed in terms of flip processes <1996JOC7326>.

**24**

X-Ray diffraction structures of 2,4-diylidene-1,3-dithietane **25**, where A = D and B = C, are centrosymmetric with planar dithiacyclobutane rings with C–S bond lengths of 1.74–1.79 Å in line with C_{sp^2} –S bond lengths in other systems. The S–C–S and C–S–C angles (ca. 98° and 82° , respectively) are in the range of all known structures. The twist in the same direction around the Mes–C=bonds on each side is consistent with the propeller configuration <1996JOC7326>.

**25**

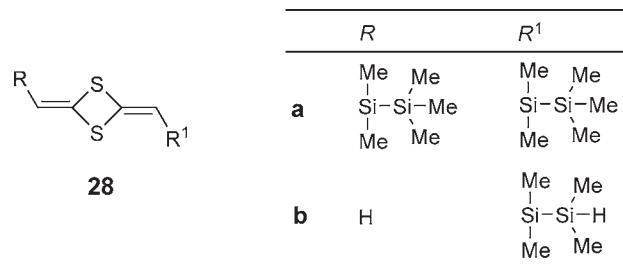
The electric and magnetic properties of 2,4-dibenzylidene-1,3-dithietane **26** and π -conjugated polymers **27** containing these units were reported <2001MM346, 2002MM3806>.

**26****27**

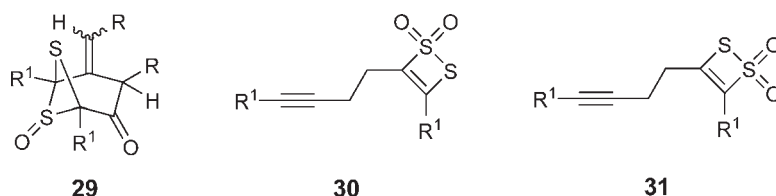
To elucidate the electric properties of **26**, cyclic voltammetry and ultraviolet–visible (UV–Vis) measurements were carried out. The cyclic voltamogram of **26** shows irreversible two-step oxidation peaks (at 0.25 and 0.61 V vs. Ag/Ag^+), indicating that **26** acts as a strong electron donor. Compound **26** shows an absorption in the visible range with a peak at 364 nm (in CH_3CN) due to a π – π^* -transition. This electron donor structure turned out to form charge-transfer (CT) complexes (1:1) with 7,7,8,8-tetracyanoquinodimethane (TCNQ). The CT formation was supported by the appearance of a CT band (600–900 nm) as well as by ^1H NMR and IR spectroscopic data <2001MM346, 2002MM3806>.

The electron-donating properties of the polymers **27** were also confirmed by cyclic voltammetry and were found to depend on aromatic substituents. They also form soluble CT complexes with TCNQ. The degree of CT in the complexes was investigated by UV and IR measurements <2001MM346, 2002MM3806>.

On the basis of theoretical calculations of HOMO and LUMO (using a PM3 Hamiltonian) as well as UV-Vis spectra, it was demonstrated that in the case of 1,3-dithietanes **28** having disilyl moieties, effective σ - π conjugations induce unique CT from the 1,3-dithietane to Si-Si units, even though the Si-Si unit usually acts as an electron donor <2001JA6209>.

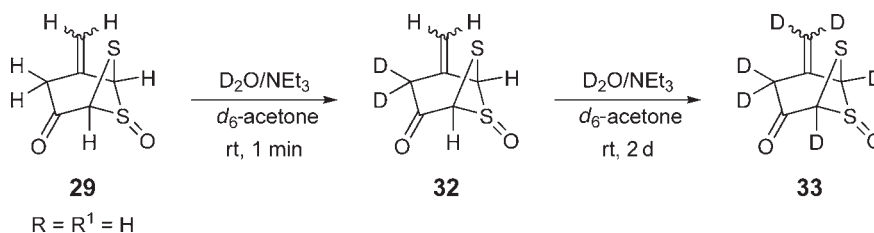


6,7-Dithiabicyclo[3.1.1]heptane-2-one 6-oxide derivatives **29** along with two regioisomeric products **30** and **31** were obtained in multiple rearrangements of propargylic dialkoxy disulfides <2003JA14290, 2003TL777>.



All structures were determined on the basis of a full analysis of ¹H and ¹³C NMR spectra, including several two-dimensional (2-D) techniques such as correlation spectroscopy (COSY), nuclear Overhauser enhancement spectroscopy (NOESY), heteronuclear multiple quantum correlation (HMQC) and heteronuclear multiple bond correlation (HMBC), and were supported by IR and HRMS experiments. These two regioisomers **30** and **31** were distinguished by comparing the chemical shifts of the olefinic carbons (C-1 and C-2), since the main effect of the thiosulfonate function is deshielding for the carbon β to the sulfonyl group and shielding for the carbon β to the disulfide atom <2003JA14290, 2003TL777>.

H/D-exchange was found to occur in dithiabicyclic derivatives **29** and **33** in the presence of NEt₃ and D₂O in *d*₆-acetone (Scheme 2) <2003JA14290, 2003TL777>.



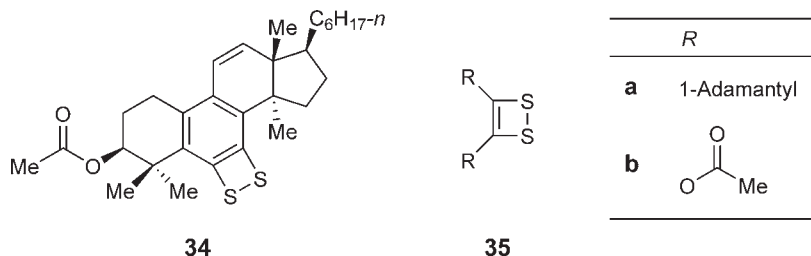
Scheme 2

The experimental and calculated IR spectra of unsubstituted 1,2-dithiete as well as substituted dithietes furnished evidence in favor of the cyclic structure. Only two vibrational modes of the ring skeleton seem to be closely related. These are the symmetric C=C stretch and the antisymmetric S-S stretch vibrations. The vibrational modes of C-S bonds are coupled and not in all cases easy to assign <1996IJQ859>.

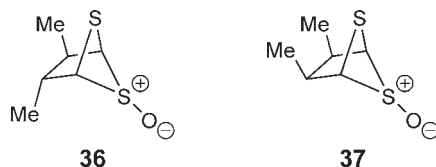
It was shown that 1,2-dithietes have low dipole moments so there is only a slight solvent effect. The highest dipole moment of the studied structures has a 3,4-dicyano-1,2-dithiete with 4.5 D at the MP2/6-31G* level of theory. This led to additional stabilization of the cyclic structure <1996IJQ859>.

Molecular structures of 1,2-dithietes **34** and **35a,b** have also been determined by X-ray crystallographic analysis. The lengths of their C-C double bond are 1.36–1.40 Å and are slightly greater than those of the corresponding strain-free bonds in eight-membered cyclic compounds. The lengths of the S-S bond (2.05–2.12 Å) are normal. The bond angles around the

1,2-dithiete skeletons are, of course, strained. The most interesting point of the structure of the 1,2-dithiete is the planarity of the four-membered ring. The crystal structures of these compounds show an almost planar geometry; for example, the dihedral angle around the S–S bond of dithiete **35b** is 0.1° . The dihedral angle around the S–S bond (0°) is strained (ca. $11.5 \text{ kcal mol}^{-1}$), compared to those calculated for disulfides with strain-free geometries <2000JOM(611)106>.



Oxidation of dialkenyl disulfides gave the stereoisomeric 2,3-dimethyl-5,6-dithiabicyclo[2.1.1]hexane 5-oxides **36** and **37**, which are found in extracts of onion. Further conversion and oxidations afforded a series of various 2,3-dimethyl-5,6-dithiabicyclo[2.1.1]hexane derivatives, which were characterized on the basis of the comparative X-ray structural and NMR and IR spectroscopic data. The ^1H NMR peak assignments for **36** and **37** were facilitated by LAOCOON III analyses of these 10 spin systems and by examination of the shifts induced by $\text{Eu}(\text{fod})_3$ and d_6 -benzene ($\text{fod} = 6,6,7,7,8,8,8\text{-heptafluoro-2,2-dimethyl-3,5-octadione}$) <1996JA2790>.



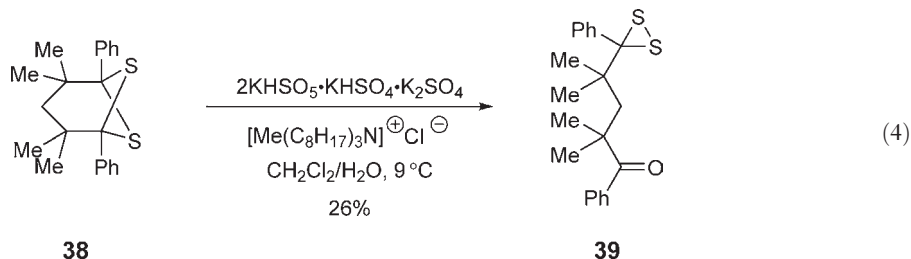
2.18.3 Reactivity of 1,3- and 1,2-Derivatives with a Different Oxidation State and Coordination Number of the Sulfur

2.18.3.1 Reactivity of 1,3-Dithietanes

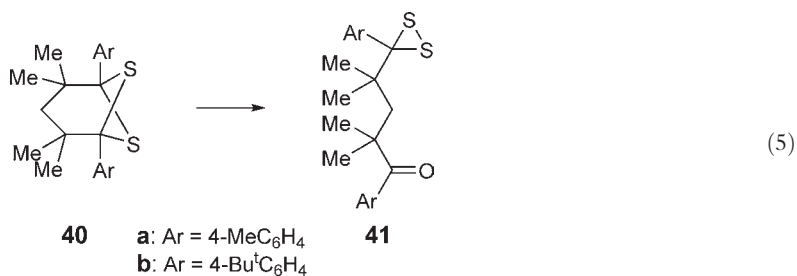
There is a long-standing interest in the chemistry and properties of cyclic compounds containing sulfur atoms in modern materials chemistry <2002MM3806>.

The result of oxidation of 1,3-dithietane systems largely depends on the kind of oxidants and the reaction conditions. Progressive oxidation of dithietane systems with classical oxidizing reagents gives mono-, di-, tri-, and tetraoxides. The application of $\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$ (Oxone[®]) or $\text{NaOCl} \cdot \text{NaClO}_4$ for the oxidation of sulfur atoms in bicyclic 1,3-dithietanes allowed the preparation of dithiirane derivatives. It was found that the successful preparation of stable dithiirane derivatives is largely attributed to steric protection by bulky substituents that hinder the reactive dithiirane ring from intermolecular reactions <1997BCJ509, 1997TL1431>.

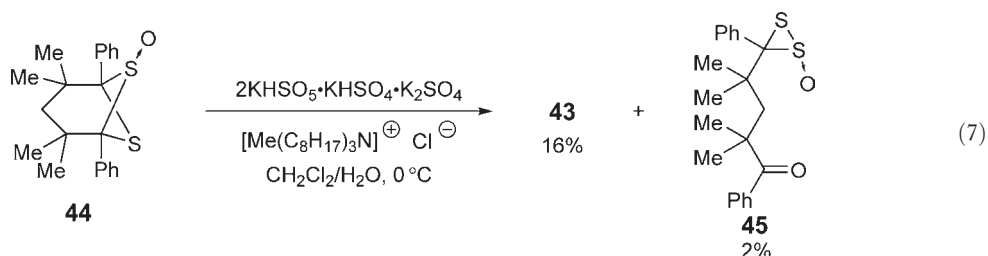
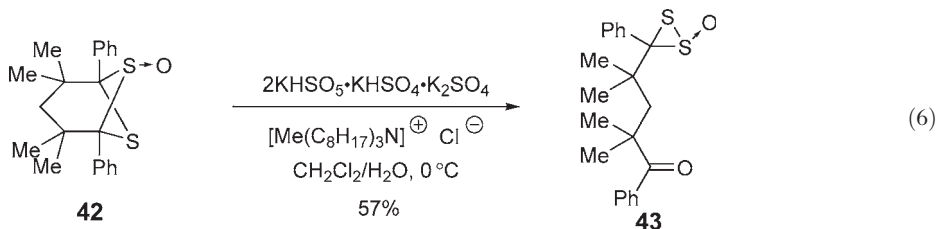
Treatment of unoxidized bicyclic 1,3-dithietane **38** with $\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$ in the presence of a phase-transfer catalyst gave the corresponding unoxidized dithiirane **39** (Equation 4) <1997BCJ509, 1997TL1431>.



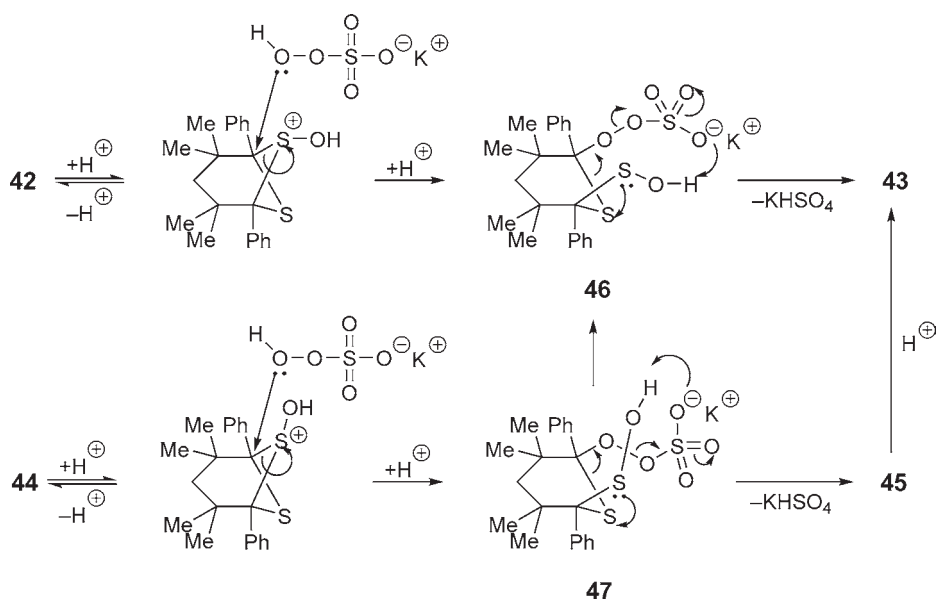
The same product but in higher yield (50%) was obtained by oxidation of **38** with NaOCl with LiClO_4 or NaClO_4 as additive. In a similar manner, dithiiranes **41a** and **41b** were synthesized from the corresponding bicyclic 1,3-dithietanes **40a** and **40b** in 39% and 37% yields, respectively (Equation 5) <1997BCJ509>.



The reaction of the *exo*-sulfoxide **42** with Oxone[®] gave the dithiirane oxide **43** (57%) and other products (Equation 6), while *endo*-sulfoxide **44** gave both **43** (16%) and its isomer **45** (2%), with no other products (Equation 7) <1997BCJ509>.

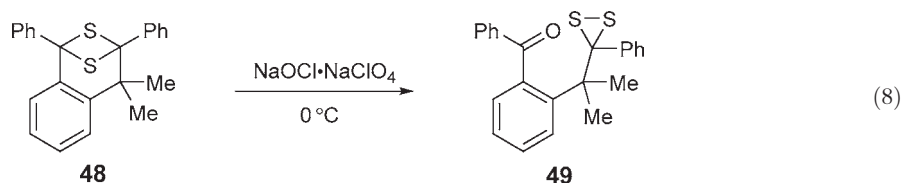


The reaction sequence leading to the formation of the dithiirane oxides **43** and **45** is shown in Scheme 3 <1997BCJ509>.

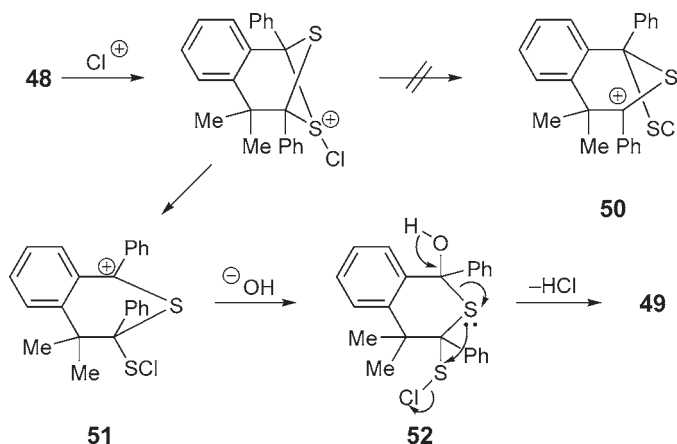


Scheme 3

Treatment of unsymmetrical bicyclic 1,3-dithietane **48** with NaOCl·NaClO₄ furnished the alkylaryldithiirane **49** in good yield (Equation 8) <1997BCJ509>.

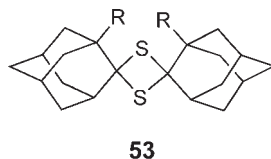


The exclusive formation of the dithiirane **49** is explained by the mechanism shown in Scheme 4 <1997BCJ509>.



Scheme 4

1,3-Dithietanes bearing two adamantyl groups **53** failed to give the corresponding dithiiranes by treatment with Oxone[®] or NaOCl·NaClO₄ <1997BCJ509>.

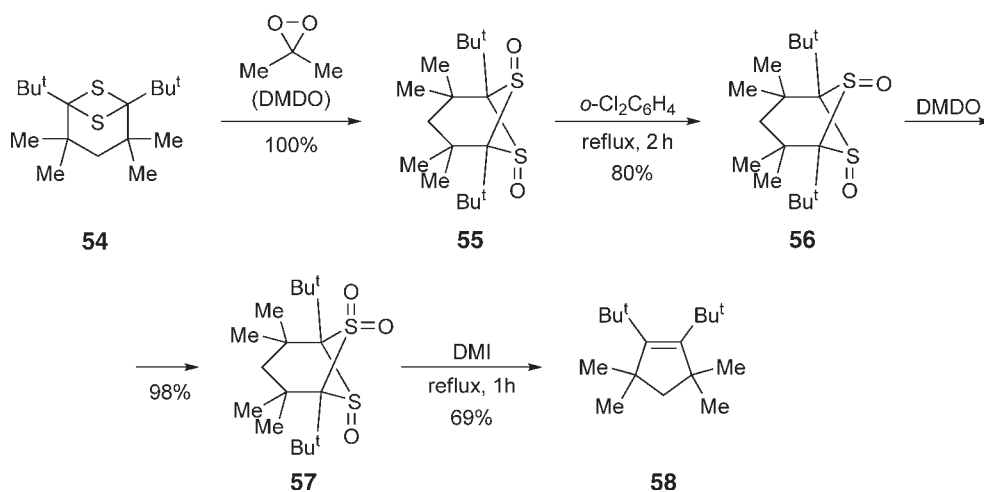


R = H, Me, Et

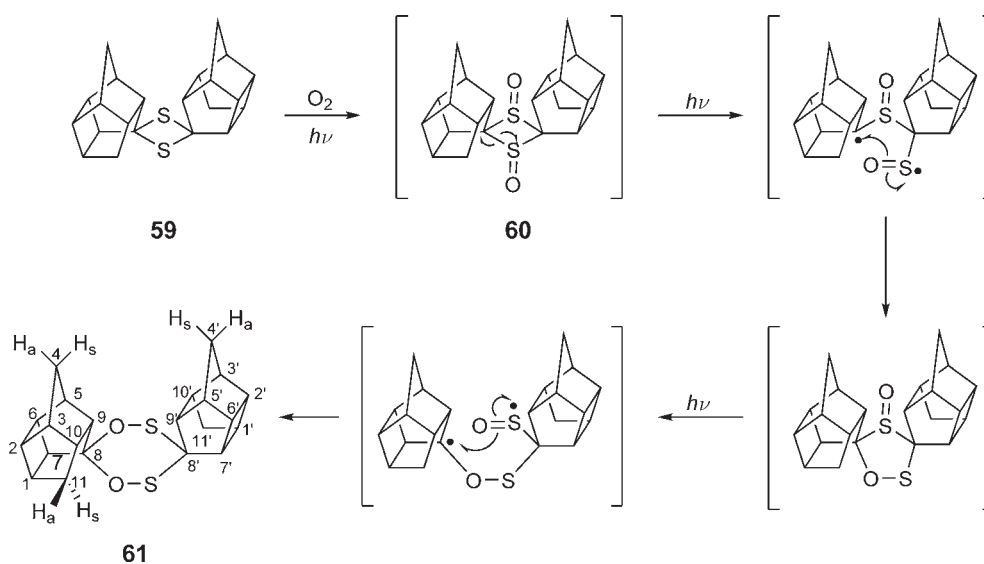
Bicyclic 1,3-dithietane **54** was used as a precursor for the synthesis of the sterically congested cycloalkene **58**, a congener of tetra-*tert*-butylethylene, by a series of reactions involving a twofold extrusion reaction in the final step. Oxidation of the bicyclic 1,3-dithietane **54** with dimethyldioxirane (DMDO) gave the *endo,endo*-disulfoxide **55**, thermal isomerization of which to the *endo,exo*-disulfoxide **56**, followed by oxidation with DMDO gave the trioxide **57**. Heating of **57** in refluxing 1,3-dimethyl-2-imidazolidinone (DMI) (b.p. 224 °C) furnished the corresponding cyclopentene **58** (Scheme 5) <2000JOC1799>.

Photochemical oxidation of the dimer **59** led to an unexpected photochemical oxidation reaction, giving dioxide **60** and its rearrangement to **61**. Exposition of the 1,3-dithietane **59** to oxygen and UV light led to the formation of the stable disulfenate **61**, uncommon in the literature. The proposed mechanism for the transformation **59** → **61** is shown in Scheme 6, but other possibilities are not excluded <2004TL7655>.

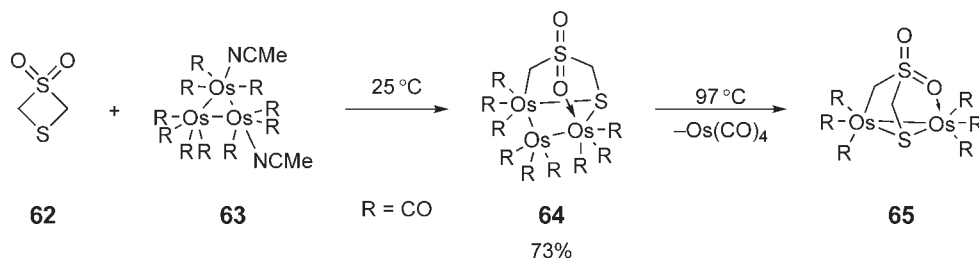
It was found that 1,3-dithietane 1,1-dioxide **62** is able to react with polynuclear metal carbonyls. Thus the reaction of **62** with Os₃(CO)₁₀(NCMe)₂ **63** proceeded with displacement of the two isocyanide ligands (NCMe) in **63** and the addition of 1 equiv of **62** to the cluster with a spontaneous opening of the ring by the cleavage of one of the thioether C–S bonds. One of the Os–Os bonds of the cluster was also cleaved giving the product Os₃(CO)₁₀(μ-CH₂SCH₂SO₂) **64** (73% yield) (Scheme 7). When **64** was heated, the product **65** was formed by the loss of an Os(CO)₄ group from **64** (Scheme 7). One of the sulfone oxygen atoms is coordinated to one of the osmium atoms in both complexes and this results in a substantial weakening of the associated S–O bond, as was determined by IR spectroscopy <1999JOM(573)14>.



Scheme 5

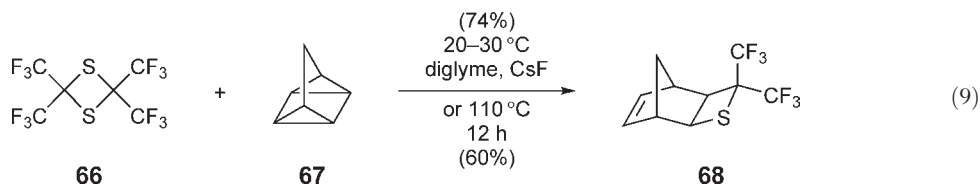


Scheme 6

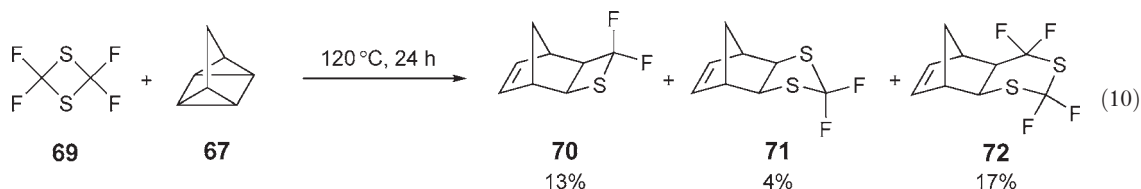


Scheme 7

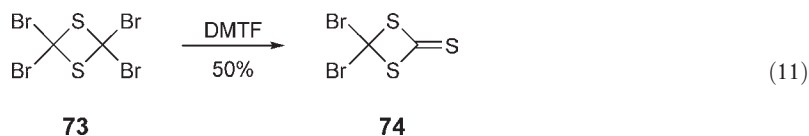
The methodology based on the reaction of 1,3-dithietanes with quadricyclane **67** was applied to the synthesis of polyfluorinated sulfur-containing polycyclic hydrocarbons. The reactions of 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane **66** with quadricyclane **67** under various conditions gave the cycloadduct **68** in high yields (Equation 9) <2005JFC(126)1332>.



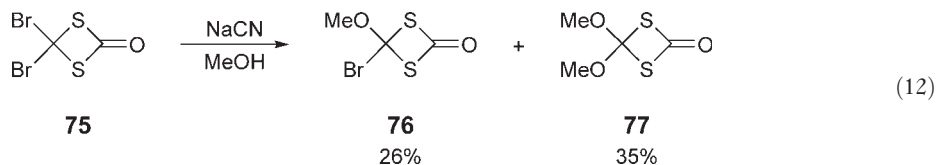
A similar reaction of 2,2,4,4-tetrafluoro-1,3-dithietane **69** at elevated temperature resulted in formation of the mixture of products **70–72** along with some polymeric materials (Equation 10) <2005JFC(126)1332>. The proposed mechanism assumes a single electron transfer from electron-rich quadricyclane to the electron-deficient cyclic sulfides <2005JFC(126)1332>.



It is worth noting, that when 2,2,4,4-tetrabromo-1,3-dithietane **73** was treated with dimethylthioformamide (DMTF), the S-atom from this sulfur-transfer agent replaced the two geminal bromine atoms on C-2 and the 4,4-dibromo-1,3-dithietane-2-thione **74** was formed in good yield (Equation 11) <2002SUL115>.



Treatment of 4,4-dibromo-1,3-dithietane-2-one **75** with sodium cyanide and methanol furnished two products: 4-bromo-4-methoxy-1,3-dithietane-2-one **76** and 4,4-dimethoxy-1,3-dithietane-2-one **77** in 26% and 35% yields, respectively (Equation 12) <2002SUL115>.



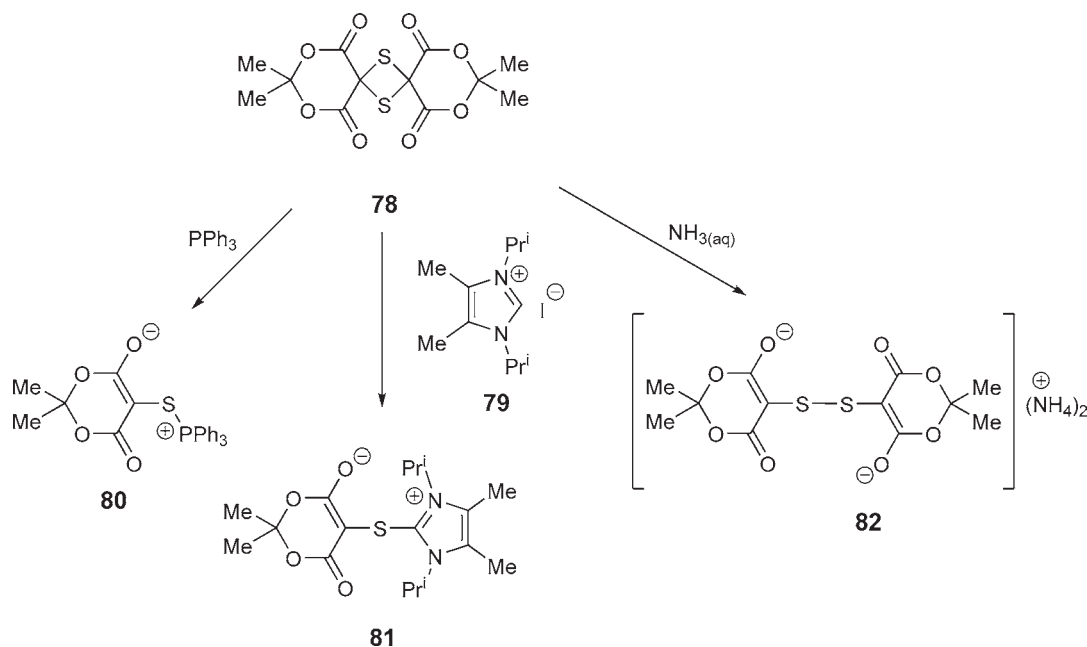
The reaction of dispiro-1,3-dithietane **78** with PPh_3 and 2,3-dihydro-1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene **79** giving the zwitterionic compounds **80** and **81** was described. The use of aqueous ammonia resulted in the formation of the dianionic disulfide **82** (Scheme 8) <2004ZFA1659>.

The cyclic disulfone, 1,3-dithietane 1,1,3,3-tetraoxide **83**, underwent Knoevenagel and substitution reactions to form a new class of unsaturated disulfenes. Thus, its treatment with isobutyraldehyde in the presence of a catalyst gave **84** bearing unsaturated vinylic moieties, the double bonds of which were resistant to all typical olefin reactions. Deprotonation of **84** and subsequent silylation with $\text{C}_4\text{F}_9\text{-SO}_2\text{-OSiMe}_3$ yielded 2,4-disilylated product **85** (Scheme 9) <1996CB161>.

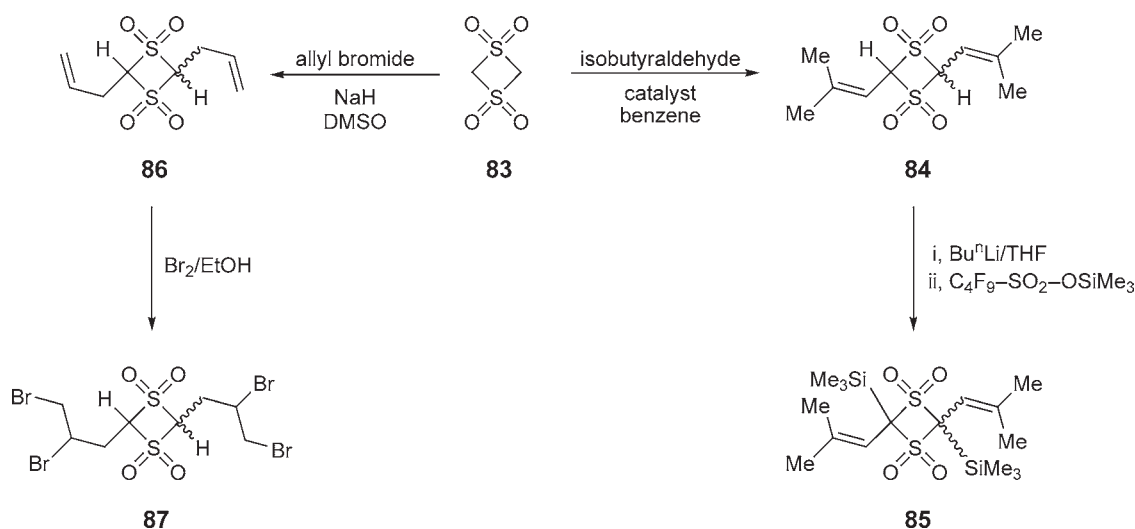
The reaction of **83** with NaH and allyl bromide afforded **86**. In this product, the double bonds are distant from the ring by a CH_2 group, so **86** underwent a typical alkene reaction, for example bromination, affording **87** (Scheme 9) <1996CB161>.

A series of tetrasubstituted sulfoxonium ylides **89a–h** were synthesized from **83** in a two-step reaction via 2,4-disubstituted disulfones **88a–h**, which were converted into the final ylides upon reactions with very strongly silylating agents, such as $\text{C}_4\text{F}_9\text{-SO}_2\text{-OR}$, where $\text{R} = \text{Si}(\text{Alkyl})_3$ (Scheme 10) <1996CB161>.

Dianions of alkyl-substituted sulfoxonium ylides **91a,b,e,f** were prepared from **83** also by a two-step procedure via 2,4-dialkylated disulfones **90a–g**. Deprotonation of **83** and alkylation yielded a family of bis-sulfones **90a–g**, which upon a second deprotonation by treatment with an appropriate base were converted into the corresponding salts **91a,b,e,f** (Scheme 11) <1996CB161>.



Scheme 8

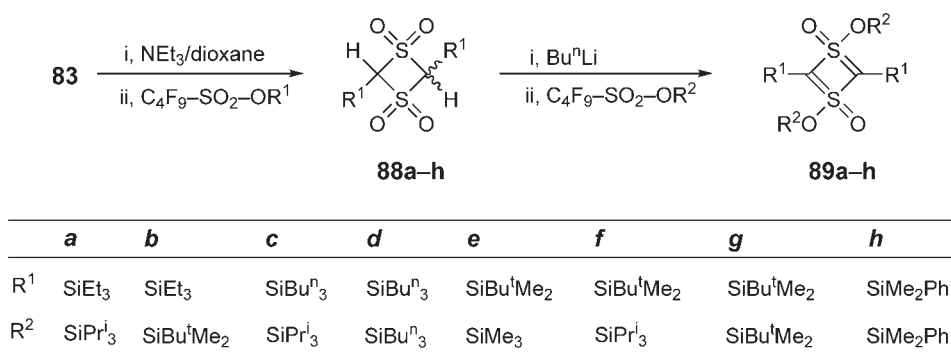


Scheme 9

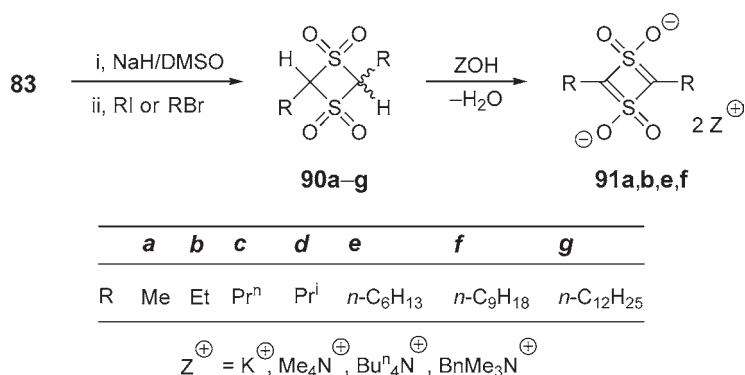
It was reported that 1,3-dithietane-2,4-diylidenebis(cyanomethylphosphonates) and -phenylphosphinates **92** underwent reaction with a variety of substituted acetonitriles **93** to afford phosphono- or phosphino-substituted γ -thiapyrones **94**, in a one-stage process (Equation 13) <1998H(47)221>.

The suggested reaction mechanism assumes an initial nucleophilic attack on the 1,3-dithietane carbon by the α -C-atom of the substituted acetonitriles with subsequent cyclization and transformation of the cyano groups, which lead directly to the observed γ -thiapyrones **94** <1998H(47)221>.

The reaction of 1,3-dithietane **92f** substituted with a diethylphosphoryl group with C-nucleophiles is analogous to the previously reported reaction. Its condensation with different C-nucleophiles, such as cyclic and acyclic α -carbonylmethylenes and α -carbonylhydrazones, gave a number of [2,1-*b*]fused phosphono-substituted thioxopyranes **97**, **100**, **103**, **107**, oxadiazine **109**, and thiazine **105** (Scheme 12), which are of potential biological interest <2002PS1885>.



Scheme 10



Scheme 11

Application of the nitrile oxide method for converting thiocarbonyl groups into carbonyl groups allowed the preparation of desaurines **112** and **113** from the thiodesaurine **110** and nitrile oxide **111** generated from ethyl chloroximidoacetate and triethylamine (Equation 14) <1999JOC4376>.

2.18.3.2 Reactivity of 1,2-Dithietanes

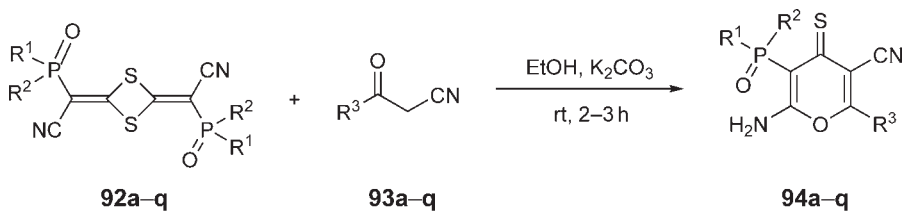
Stereoselective conversion of 3,4-disubstituted-1,2-dithietane 1,1-dioxides **114** into symmetrical (*Z*)-alkenes **115** has been reported. When substituted 1,2-dithietane 1,1-dioxides **114** having a reactive thiosulfonate group in the four-membered ring were treated with lithium cyanide, the alkenes **115a-d** were obtained with high (*Z*)-selectivity and high chemical yield (Equation 15) <1996BSF515>.

2.18.3.3 Reactivity of Other Derivatives

1,2-Dithiete, the smallest unsaturated cyclic system with a disulfide bond, has been the subject of interest since 1960 because of its structure, unique bonding properties, and relation to its valence isomer, ethane-1,2-dithione.

The oxidation of 3,4-di(1-adamantyl)-1,2-dithiete **116a** and 3,4-di-*tert*-butyl-1,2-dithiete **116b** as well as 3',3',7',7'-tetramethylcyclohepteno[1',2'-*c*]-1,2-dithiete **116c** was investigated. It was found that *m*-chloroperbenzoic acid (MCPBA) oxidation of 1,2-dithietes **116** with 1 equiv of the oxidant afforded the corresponding 1,2-dithiete *S*-oxides **117**, while oxidation with an excess (2–3 equiv) of this oxidant produced a mixture of isomeric (*EE*-, *EZ*-, and *ZZ*-) bis-sulfines **119** via the corresponding 1,2-dithiete *S,S'*-dioxide intermediates **118** (Scheme 13). The oxidation

proceeds (**Scheme 13**) via the initial formation of dithiete *S*-oxides **117** and further oxidation to the dithiete *S,S'*-dioxides **118**, which upon ring opening afford the final products, α -disulfines **119** <1995TL8583>.



	R^1	R^2	R^3
a	OMe	OMe	Ph
b	OMe	OMe	C ₆ H ₄ Cl
c	OMe	OMe	Bu ^t
d	OMe	OMe	C ₆ H ₄ Me
e	OMe	OMe	Furoyl
f	OEt	OEt	Ph
g	OEt	OEt	C ₆ H ₄ Cl
h	OEt	OEt	Bu ^t
i	OEt	OEt	C ₆ H ₄ Me
j	OEt	OEt	Furoyl
k	OPr ⁱ	OPr ⁱ	Ph
l	OPr ⁱ	OPr ⁱ	C ₆ H ₄ Cl
m	OPr ⁱ	OPr ⁱ	Bu ^t
n	OPr ⁱ	OPr ⁱ	C ₆ H ₄ Me
o	OPr ⁱ	OPr ⁱ	Furoyl
p	OEt	Ph	Ph
q	OEt	Ph	C ₆ H ₄ Cl

(13)

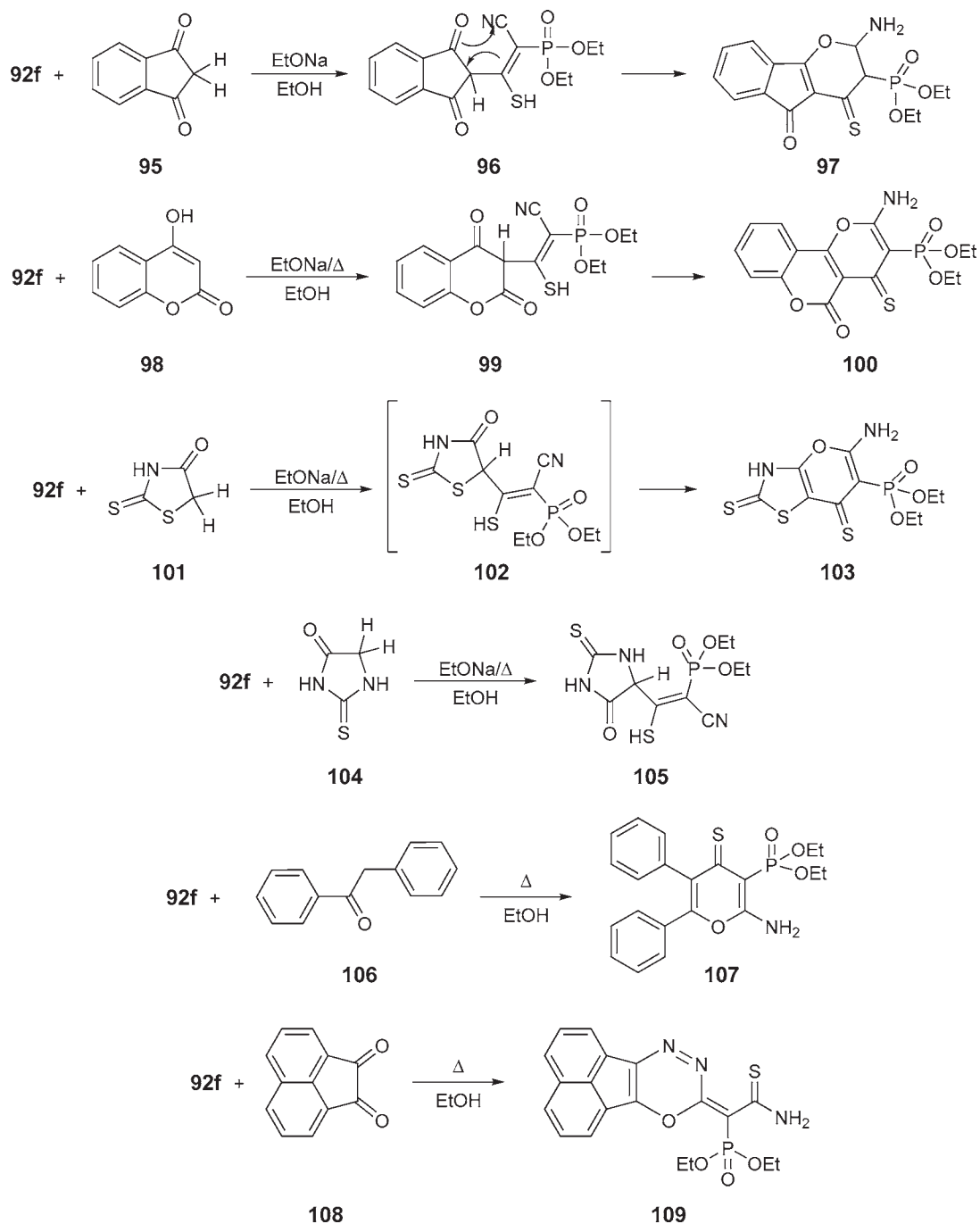
The reaction of 1,2-dithietes with unsaturated compounds has also been investigated. 1,2-Dithietes were found to react with alkenes and alkynes to give the cycloadducts stereospecifically, which indicates the concerted reaction between ethane-1,2-dithione, the valence isomer of 1,2-dithiete, and dienophiles <2000JOM(611)106, 1999JOC8489>.

Thus the reaction of 3,4-bis(methoxycarbonyl)-1,2-dithiete **19f** with alkenes and alkynes gave the corresponding dihydrodithiins or thiophenes **120–126**, respectively (**Scheme 14**). This reaction was considered as a reverse electron-demand hetero-Diels–Alder process (see Section 2.18.2) <2000JOM(611)106, 1999JOC8489>.

Moreover, it was found that tetramerization of 3,4-bis(methoxycarbonyl)-1,2-dithiete **19f** took place selectively to give the unsaturated 16-membered cyclic compound **127** together with a small amount of tetrathiocin **128** under various conditions (**Equation 16**) <2000JOM(611)106>.

It was suggested that this reaction proceeds via the biradical **129** or 1,2-dithione *cis*-**20f**, which is generated as tautomer of **19f** (**Scheme 15**) <2000JOM(611)106>.

1,2-Dithiete can be used as an oxidant for the thiometalates and oxythiometalates, and thus induced internal electron-transfer reactions provide an efficient method for synthesizing selected metal dithiolene and oxo-containing

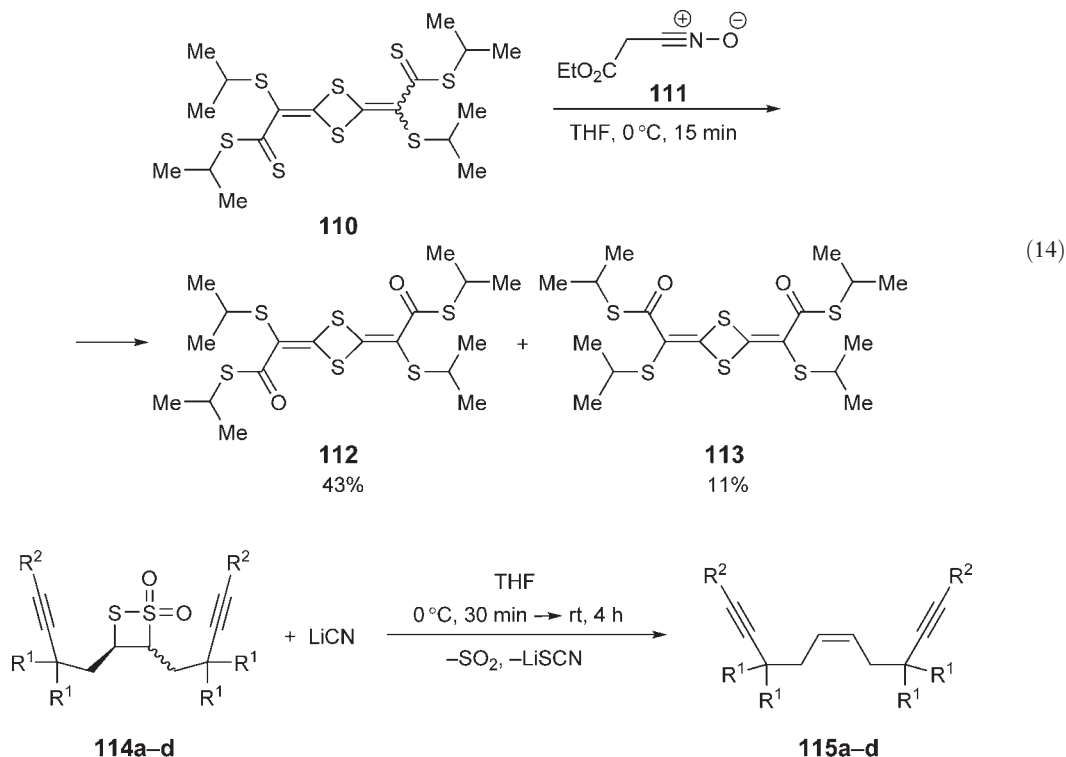


Scheme 12

dithiolene complexes. The reaction of **19b** with tetrathiometalates $\text{MS}_4^{2-} **132** ($\text{M} = \text{W}, \text{Mo}$) resulted in the formation of the tris(dithiolene) complexes **133** (Equation 17). Similarly, treating WOS_3^{2-} and $\text{MoO}_2\text{S}_2^{2-}$ with 1,2-dithiete **19b** gave the respective $\text{MO}(\text{tfd})_2^{2-}$ complexes **134**, where $\text{tfd} = [(\text{CF}_3)_2\text{C}_2\text{S}_2]^{2-}$ and $\text{M} = \text{W}, \text{Mo}$ <1999IC4334>.$

Dithiolene complex **138** (having a 1:1 ratio) was also formed in the reaction of 3,4-di(1-adamantyl)-1,2-dithiete **135** or its valence tautomer **136** with ethylenebis(triphenylphosphine)platinum(0) **137** (Scheme 16) <2003JA12114>.

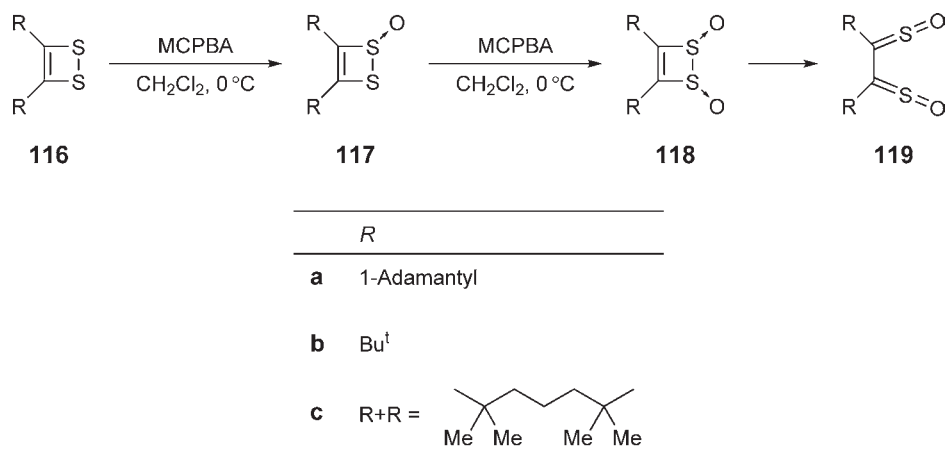
The initial formation of the benzodithiete **19e**, as an intermediate in the reaction of benzyne with elemental sulfur, was suggested on the basis of its secondary reaction that traps another benzyne molecule to give thianthrene **139**, or *o*-C₆H₄S₂ **19e** to give tetrathiocin **140** (Scheme 17) <2004JOC5483>.



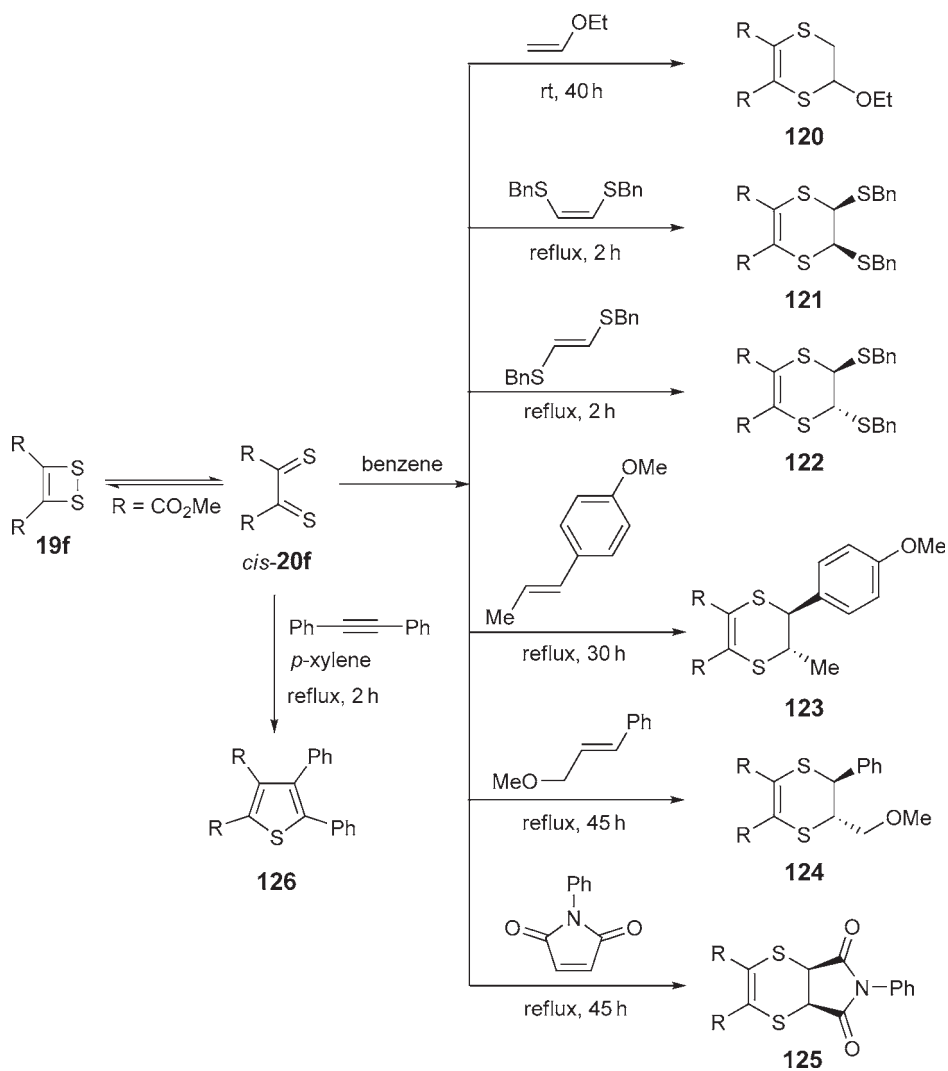
Substrate	R ¹ , R ¹	R ²	Product	Yield (%)	Ratio (E:Z)
114a	Me, Me	Me	115a	90	8:92
114b	Me, Me	Et	115b	90	14:86
114c	-(CH ₂) ₅ -	H	115c	89	6:94
114d	-(CH ₂) ₅ -	Me	115d	93	7:93

It was discovered that 1,2-addition products, **141a,b** and **142a,b**, formed in the reaction of sulfenyl chlorides (or its thio homologues) with cyclic alkenes, are effective in transferring two sulfur units to a diene trap when each of these di- and trithio adducts, **141a,b** and **142a,b**, were heated in the presence of diene **143**. The suggested mechanism for the formation of cyclic tetrasulfide **149** from the thermal decomposition of the dithio reagent **141b** in the presence of **143** is shown in Scheme 18 <1998JOC8654>.

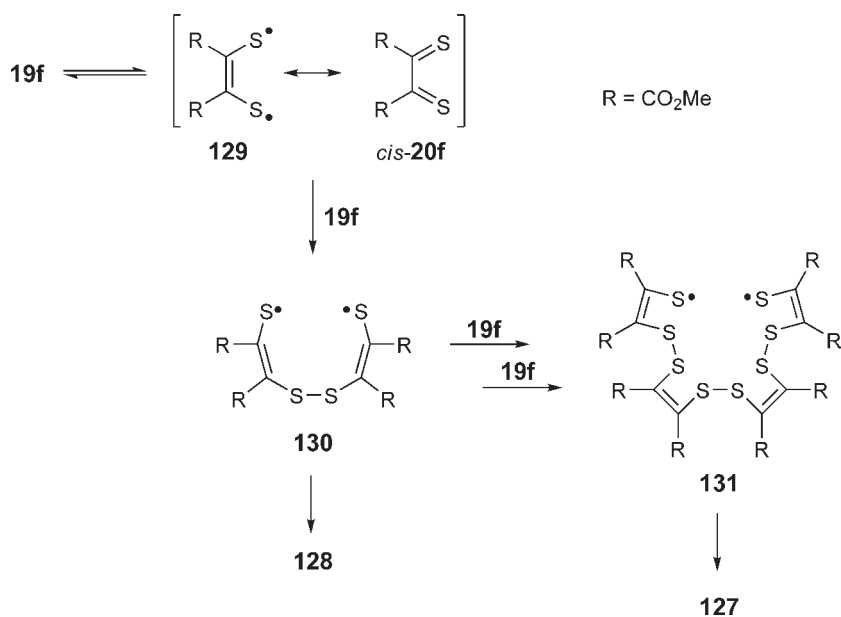
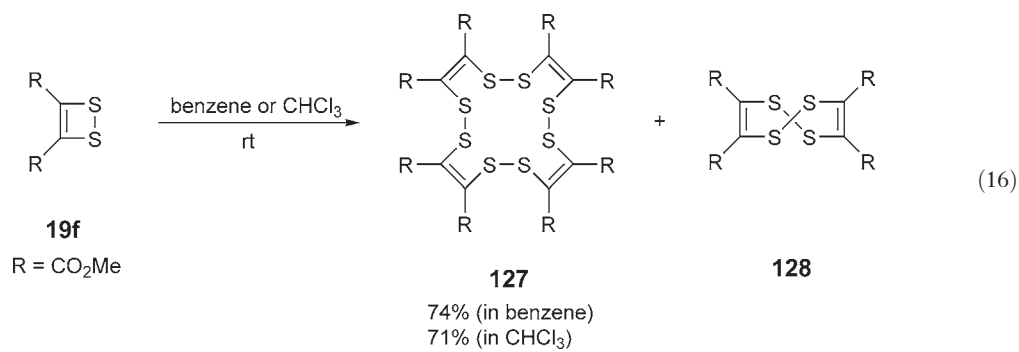
Dithietane intermediate **145** (Scheme 18, path a) either directly transfers its two sulfur atoms to a diene trap **143** to form **147** (Scheme 18, path a₁) or undergoes a cycloreversion to cyclohexene and ¹S₂, which is then trapped by diene **143** (Scheme 18, path a₂). Conversely, intermediate **144** could fragment (Scheme 18, path b) directly to deliver ¹S₂, which is then trapped (Scheme 18, path a₂) by the diene **143** to form cyclic **147**. A second capture of a two-sulfur unit apparently takes place resulting in cyclic tetrasulfide **149** as the major product. It was also found that cyclic tetrasulfide **149** can be converted quantitatively to disulfide adduct **147** by an *in situ* treatment with triphenylphosphine **148**. As a result, this methodology serves to transfer a two-sulfur unit to a diene in high yield <1998JOC8654>.



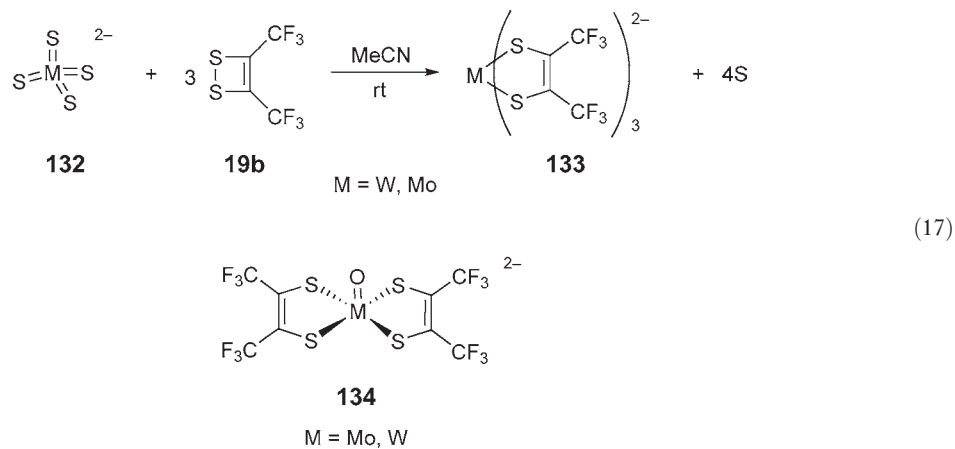
Scheme 13

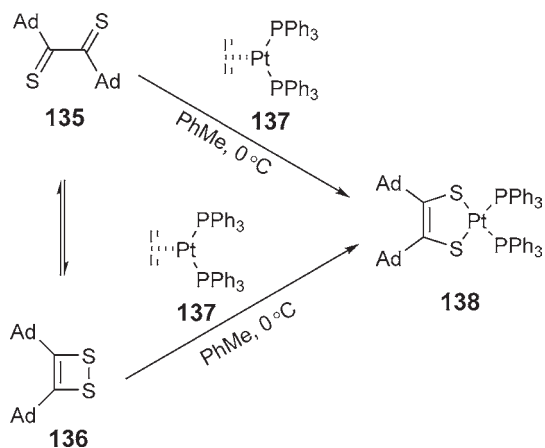


Scheme 14

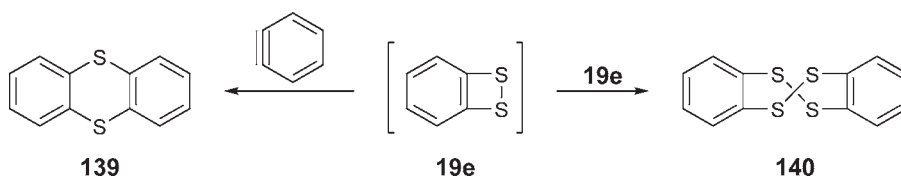


Scheme 15

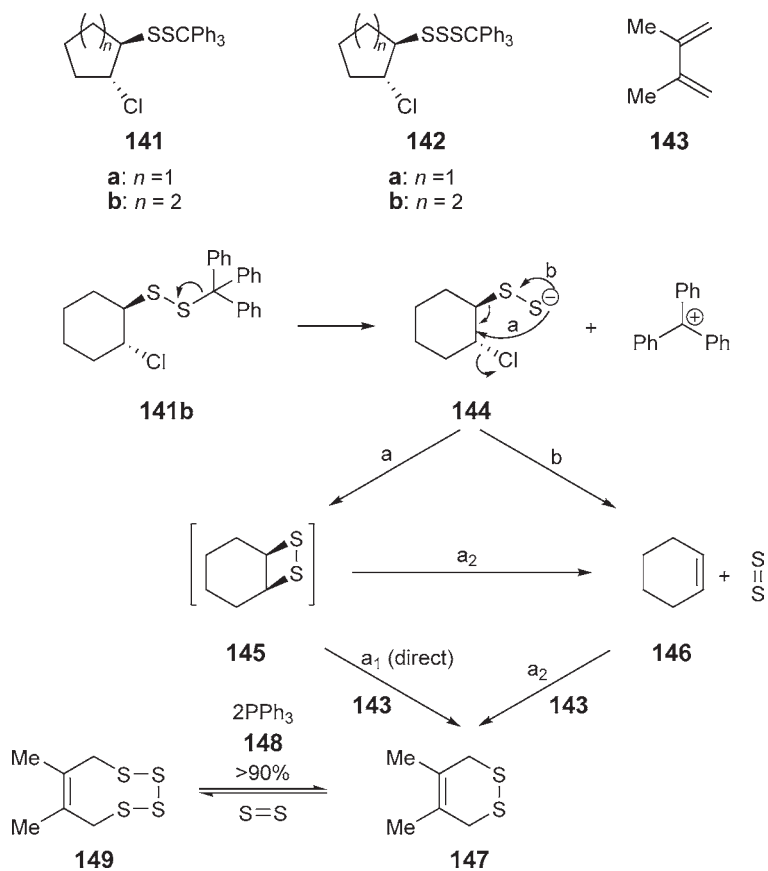




Scheme 16



Scheme 17



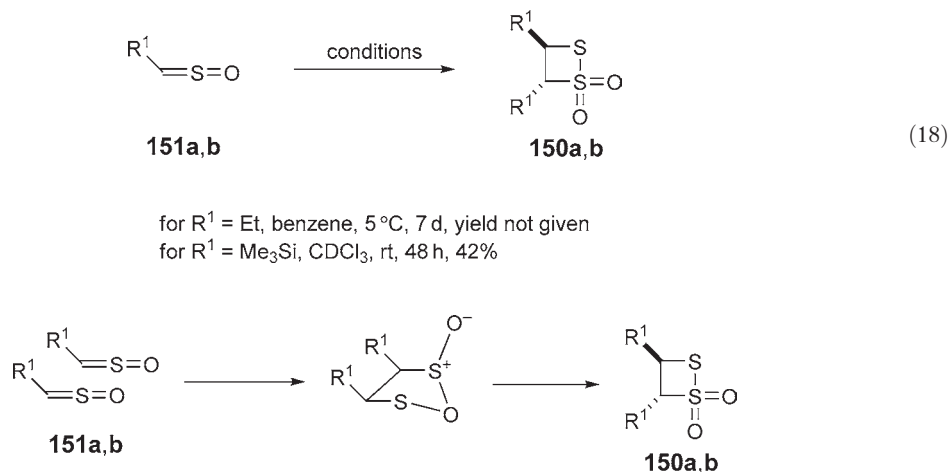
Scheme 18

2.18.4 Syntheses of 1,3- and 1,2-Derivatives with Different Oxidation State and Coordination Number of the Sulfur

2.18.4.1 Syntheses of 1,2-Dithietanes

The synthesis of 1,2-dithietanes has been exhaustively presented by Zoller in CHEC-II(1996) <1996CHEC-II(1B)1113>, where the literature until 1995 has been reviewed. Since this date, only two papers concerning the synthesis of 1,2-dithietanes have been published.

The first paper reported the synthesis of substituted 1,2-dithietane- 1,1-oxides **150a** and **150b** from methanethial *S*-oxides **151a** and **151b** by room temperature cyclization in various solvents, which resulted in the products **150a** and **150b** in moderate yields (Equation 18) <1996JA7492>. The authors suggested a mechanism with a [2+2] cyclization as the first step of the reaction (Scheme 19) <1996JA7492>.



Scheme 19

The second paper described the study of the reaction of propadienyl sulfinates **152** with vinylmagnesium bromide <1996BSF515>. It was found that under certain conditions, the reaction led to the formation of two isomers of 3,4-dibut-3-ynyl-1,2-dithietanes **153** and **154**, which were not separated from the by-products (Equation 19; Table 5).

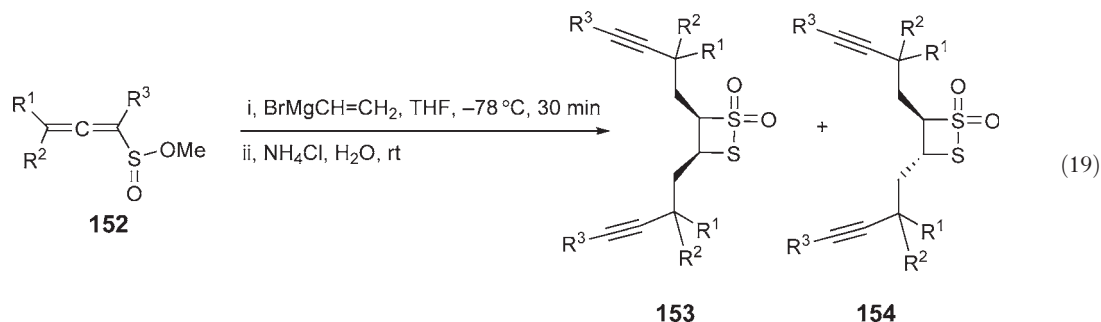


Table 5 Formation of two isomeric 3,4-dibut-3-ynyl-1,2-dithietanes **153** and **154** (Equation 19)

Entry	R ¹	R ²	Yield of 153 + 154 (%)	153/154 ratio
1	Me	Me	86	15:85
2	Me	H	33	5:95
3	Me	Et	62	10:90
4	(CH ₂) ₅	H	67	15:85
5	(CH ₂) ₅	Me	65	15:85
6	Me	Ph	20	15:85

2.18.4.2 Syntheses of 1,3-Dithietanes

Synthesis of 1,3-dithietanes may be performed using several routes. They can be obtained by an intramolecular cyclization of dithiocarbonates <2003CC1408>. The cyclization of the ethoxycarbonylsulfonyl derivatives **155** catalyzed by titanium tetrachloride in dichloromethane at room temperature afforded the corresponding derivatives **156** in satisfactory yields (Equation 20; Table 6).

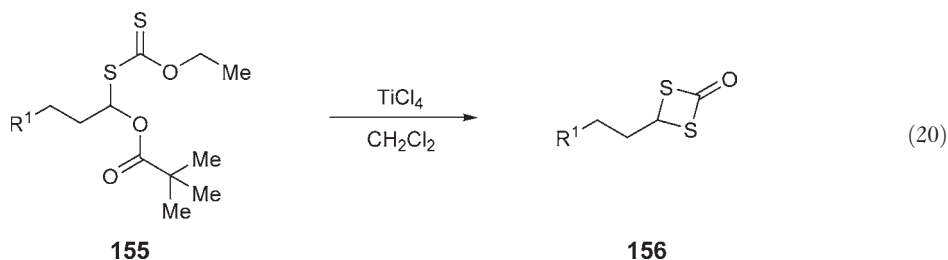
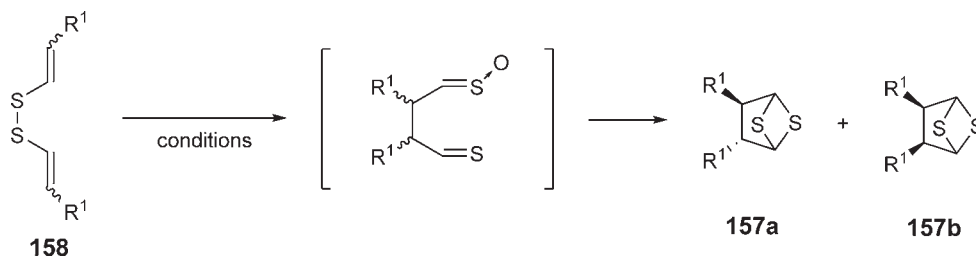


Table 6 Cyclization of ethoxycarbonylsulfonyl derivative **155** catalyzed by titanium tetrachloride (Equation 20)

Entry	R^1	Yield of 156 (%)
1	Bu ^t C(O)	47
2		84
3	<i>p</i> -MeOC ₆ H ₄ C(O)	51
4	<i>p</i> -FC ₆ H ₄ C(O)	67
5		48
6	NC-C(Me) ₂	46
7		10
8	PhC(O)	81
9	<i>p</i> -ClC ₆ H ₄ C(O)	71

The synthesis of two isomers of bicyclic dithietanes **157a** and **157b** is based on the oxidative sigmatropic rearrangement and the [2+2] cyclization of divinylsulfane **158** (Scheme 20; Table 7) <1996JA2790, 1996JA2799>.

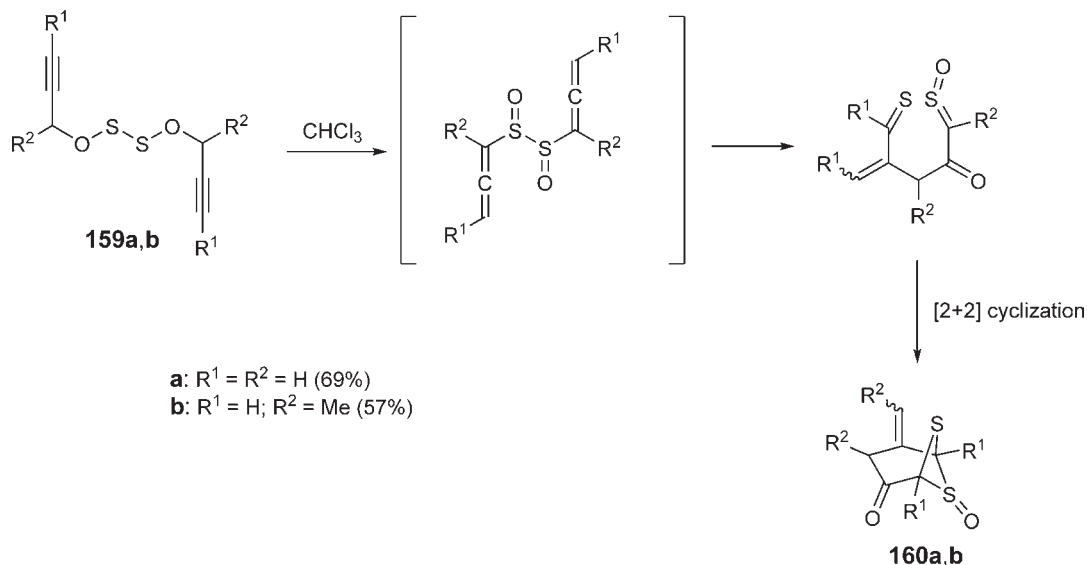
The similar sigmatropic rearrangement and the [2+2] cyclization of dipropargyloxy disulfides **159** in chloroform gave bicyclic dithietane derivatives **160** (Scheme 21) <2003TL777>.



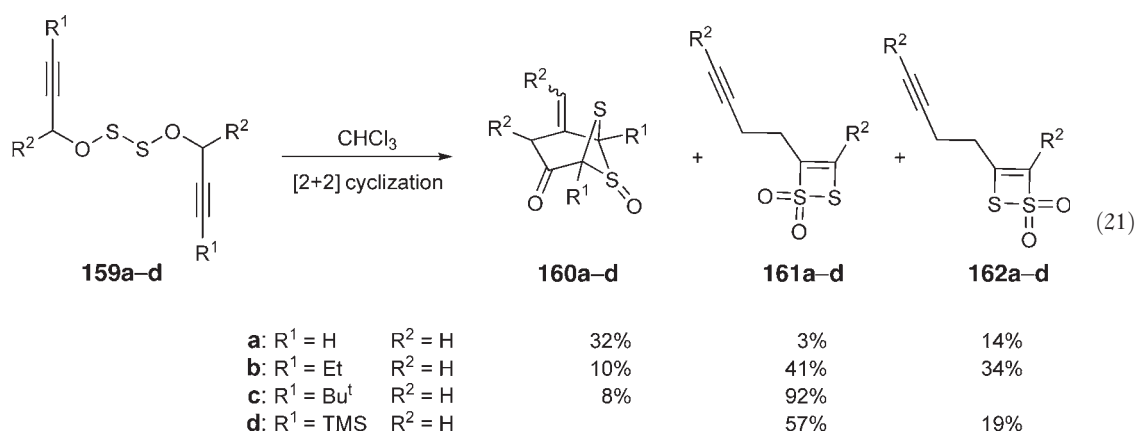
Scheme 20

Table 7 Synthesis of bicyclic dithietanes **157a** and **157b** by the [2+2] cyclization of divinylsulfane **158** (Scheme 20)

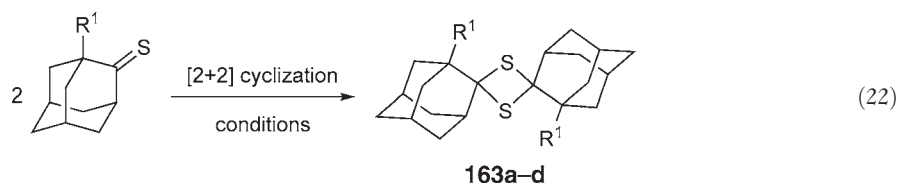
Entry	R ¹	Configuration of 158	Conditions	Yield of 157a (%)	Yield of 158b (%)
1	Me	<i>Z,Z</i>	NaIO ₄ , MeOH, 5 h, 25 °C	26	2
2	Me	Mixture of isomers	AcOOH, AcOH, Na ₂ CO ₃ , CH ₂ Cl ₂ , 18 h, -78 °C	10	11
3	Me	<i>Z,E</i>	AcOOH, AcOH, Na ₂ CO ₃ , CH ₂ Cl ₂ , 18 h, -78 °C		

**Scheme 21**

An analogous reaction, which leads to the bicyclic dithietanes **160** and also to the dithietes **161** and **162** (Equation 21), has also been reported <2003JA14290>.

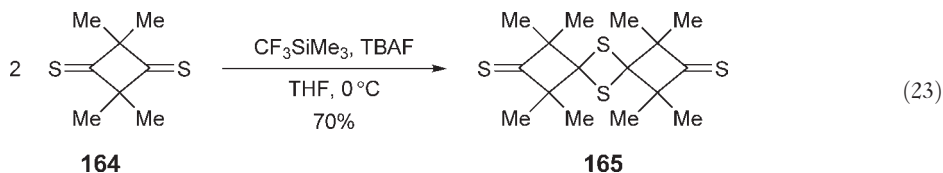


Another reported synthesis of symmetrical spiro-1,3-dithietanes **163a-d** substituted with an adamantyl moiety is based on the [2+2] cycloaddition of two molecules of variously substituted adamantane-2-thiones <1997BCJ509>. With methanesulfonic acid as an acidic catalyst, the reaction provided 1,3-dithietanes **163a-d** in high yields at ambient temperature. A similar reaction was performed with phosphorus pentachloride as the catalyst (Equation 22; Table 8) <2002AXCo231>.

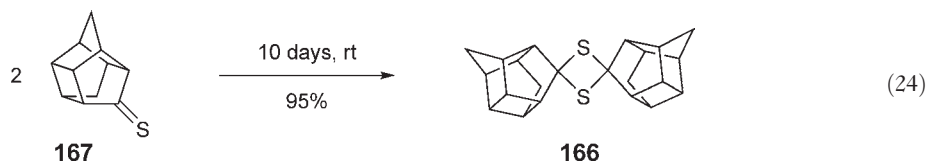
**Table 8** Synthesis of adamantane-derived spiro-1,3-dithietanes **163a–d** (Equation 22)

Entry	R ¹	Conditions	Yield of 163 (%)	Reference
a	H	MeSO ₃ H, 1 h, rt	86	1997BCJ509
b	Me	MeSO ₃ H, 1 h, rt	69	1997BCJ509
c	Et	MeSO ₃ H, 1 h, rt	75	1997BCJ509
d	H	PCl ₅ , CCl ₄ , 7 h, reflux	56	2002AXCo231

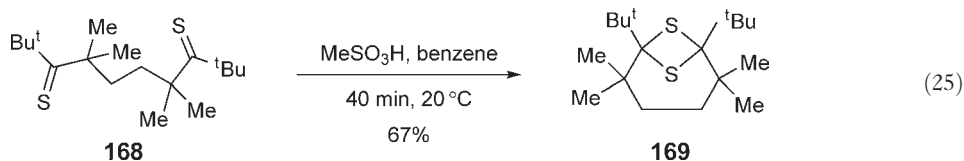
A similar [2+2] cyclization has also been performed with 2,2,4,4-tetramethylcyclobutan-1,3-dithione **164** and trifluoromethyltrimethylsilane in tetrahydrofuran (THF), in the presence of tetrabutylammonium fluoride (TBAF) at 0 °C and led to the formation of spiro-1,3-dithietane **165** in 70% yield (Equation 23) <2002HCA1644>.



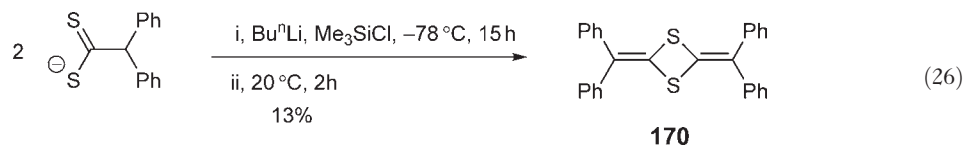
A similar synthesis was performed for the dithietane **166** by the room temperature dimerization of pentacyclo[5.4.0^{2.6}0^{3.10}0^{5.9}]undecane-8-thione **167**. After 10 days, the reaction was complete and dithietane **166** was isolated in 95% yield (Equation 24) <2004TL7655>.



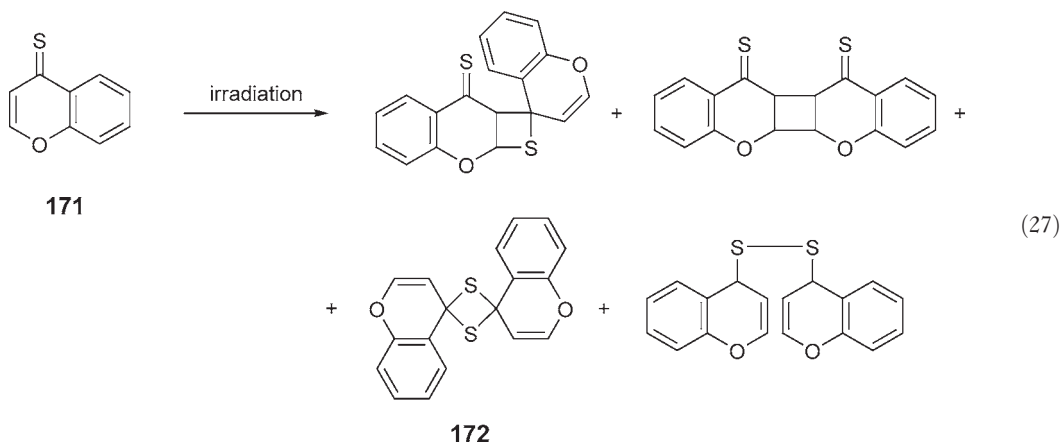
The intramolecular [2+2] cycloaddition of dithione **168**, performed in benzene in the presence of methanesulfonic acid, gives the corresponding 1,3-dithietane **169** in 67% yield (Equation 25) <2000JOC1799>.



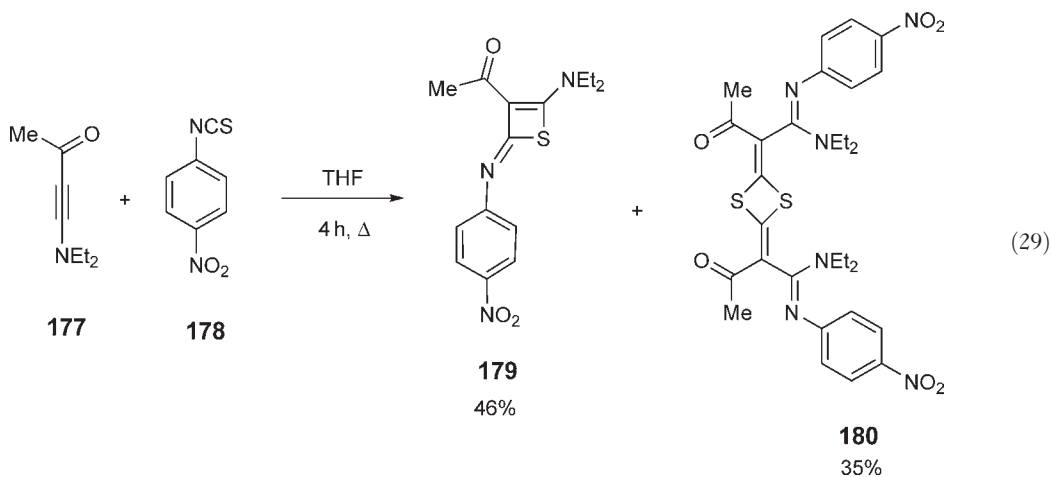
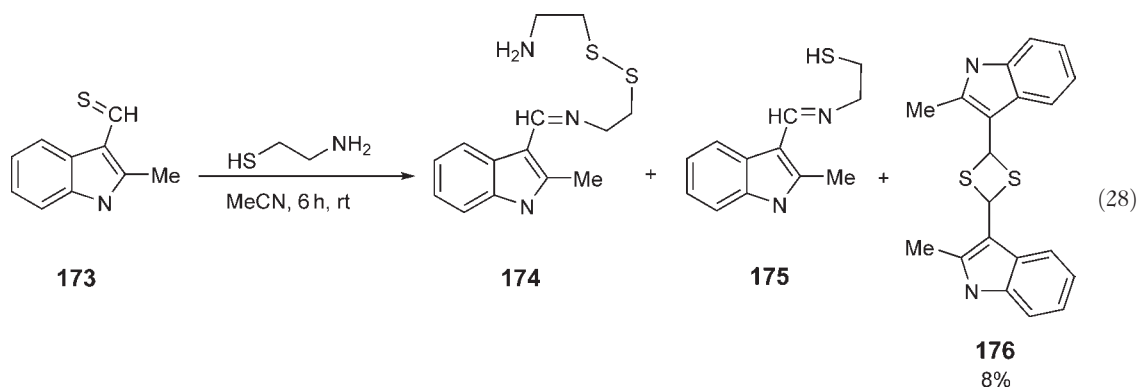
The [2+2] cycloaddition of two molecules of 1,1-diphenyldithioacetic acid carried out in the presence of butyllithium and trimethylsilyl chloride afforded the desired dibenzhydrylidene-1,3-dithietane **170** in 13% yield (Equation 26) <1996CB663>.



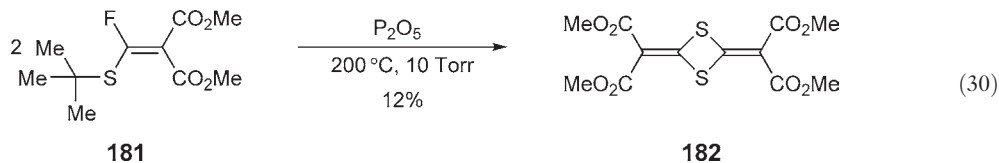
The photoinduced reaction of chromene-2-thione **171** gave four dimerization products, among them the spiro-dithietane **172** (Equation 27) <1999JPO47>.



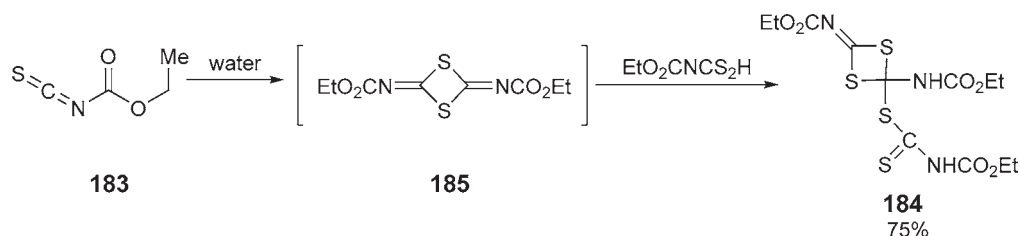
The reaction of 2-methyl-3-thioformylindole **173** with 2-aminoethanethiol led to the formation of the 1,3-dithietane **176** in 8% yield, and also two Schiff bases **174** and **175** (Equation 28) <1999RJO1507>. The rather exotic reaction of 4-diethylamino-3-buten-2-one **177** with 1-isothiocyanato-4-nitrobenzene **178** has also been reported <2001SL361>. After 4 h of heating in THF of the substrates, the substituted thiete **179** and dithietane **180** were isolated in 46% and 35%, respectively (Equation 29) <2001SL361>.



The dimerization of dimethyl 2-(*tert*-butylsulfanylfluoromethylene) malonate **181** in the presence of phosphorus pentoxide gave the corresponding tetramethyl-1,3-dithietan-2,4-diylidene bis-malonate **182** in 12% yield (Equation 30) <2003RCB1198>.



A 2 day reaction of ethyl carbon(isothiocyanatide) **183** carried out in water furnished the 1,3-dithietane **184** in 75% yield (Scheme 22) <1998EJI1025>. The occurrence of the intermediate **185** has been demonstrated.



Scheme 22

As a modification of this procedure, one can consider the reaction of ketones with sulfurating agents leading to thioketones which next react via a [2+2] cycloaddition to furnish 1,3-dithietanes. Thus the reaction of 1,5-diketones with Lawesson's reagent afforded fused 1,3-dithietanes **186** in high yields (Equation (31); Table 9) <1997BCJ509, 2000JOC1799>.

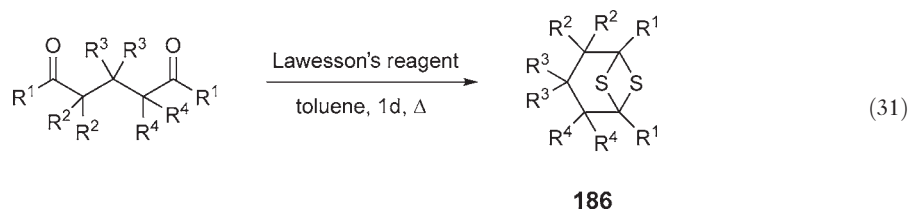
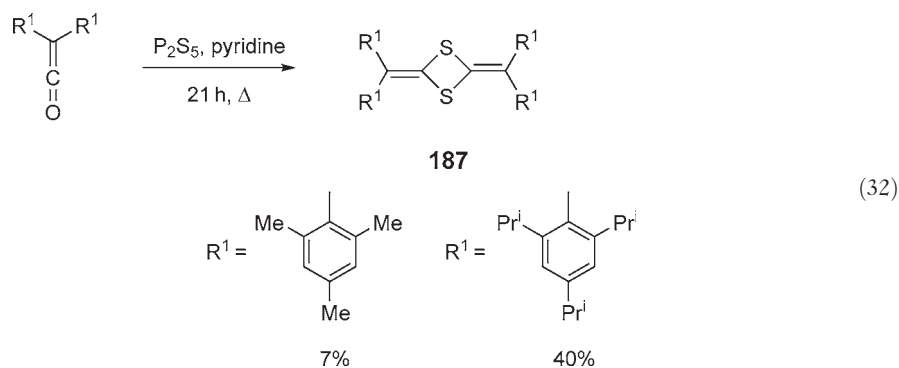


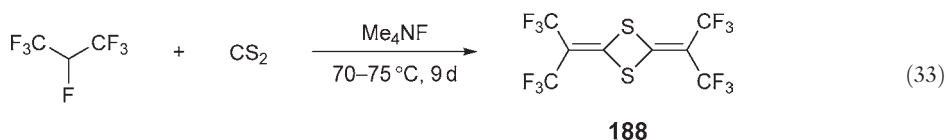
Table 9 Reaction of 1,5-diketones with Lawesson's reagent to form fused 1,3-dithietanes **186** (Equation 31)

Entry	R^1	R^2	R^3	R^4	Yield (%)	Reference
1	<i>p</i> -MeC ₆ H ₄	Me	H	Me	99	1997BCJ509
2	<i>p</i> -Bu ^t C ₆ H ₄	Me	H	Me	72	1997BCJ509
3	Bu ^t	Me	H	Me	75	2000JOC1799
4	Ph	HC=CH	CH=CH	Me	96	1997BCJ509

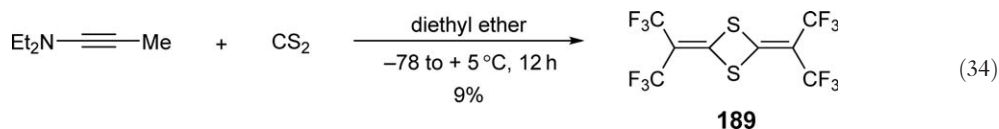
The reaction of diarylketenes with phosphorus pentasulfide in pyridine gave 2,4-dibenzhydrylidene-1,3-dithietane derivatives **187** in moderate yields (Equation 32) <1996JOC7326>.



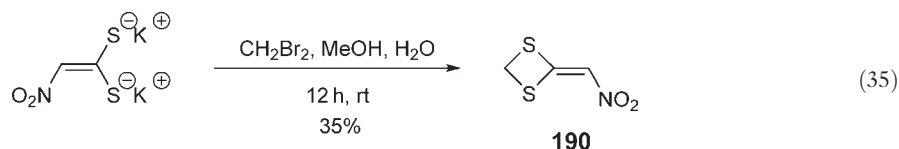
The reaction of carbon disulfide with heptafluoropropane under phase-transfer conditions provided bis-(trifluoromethylidene)-1,3-dithietane **188** (the yield was not reported) (Equation 33) <1997JFC(82)29>.



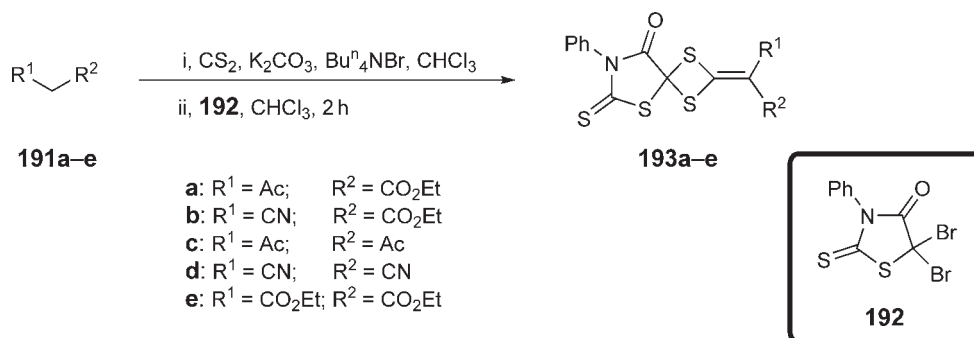
A very similar reaction of carbon disulfide with *N,N*-diethyl prop-1-ynyl amine produced the symmetrically substituted bis-methylidene 1,3-dithietane **189** in only 9% yield (Equation 34) <1998T9849>.



The reaction of nitroketene dithioacetate with dibromomethane in methanol gave 2-nitromethylene-1,3-dithietane **190** in 35% yield (Equation 35) <2000AXC1113, 2002SUL207>.

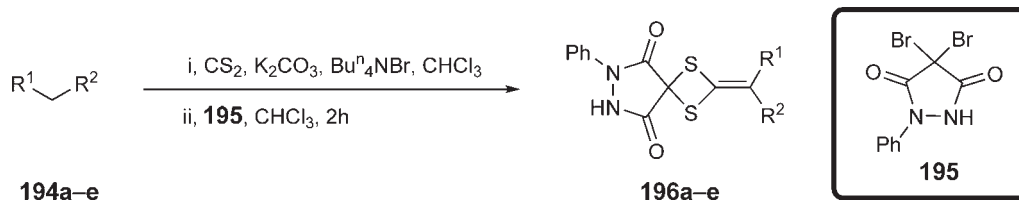


The reactions of carbon disulfide with compounds **191** under phase-transfer catalysis (PTC) conditions followed by the reaction of the formed intermediate with 5,5-dibromo-3-phenyl-2-thioxo-thiazolidin-4-one **192** gave spiro-1,3-dithietane derivatives **193** (Scheme 23) <1997PS173>.



Scheme 23

A similar reaction of the methylene derivatives **194** with carbon disulfide under (PTC) conditions followed by the action of 4,4-dibromo-1-phenylpyrazolidine-3,5-dione **195** produced the spiro-1,3-dithietanes **196** (Scheme 24; Table 10) <2000PS159>.

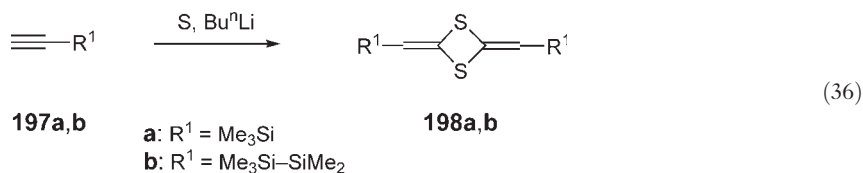


Scheme 24

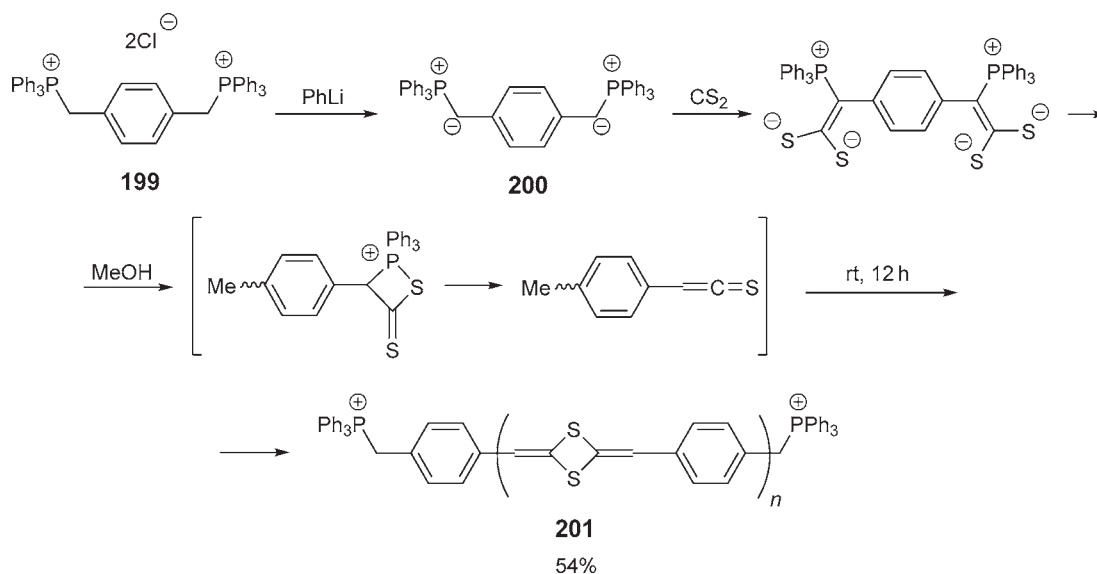
Table 10 Reaction of methylene derivatives **194** with carbon disulfide under PTC conditions (Scheme 24)

Entry	R^1	R^2	Yield of 196 (%)
a	Ac	CO ₂ Et	41
b	CN	CO ₂ Et	70
c	Ac	Ac	60
d	CN	CN	56
e	CO ₂ Et	CO ₂ Et	30

The reaction of the acetylene silanes and disilanes **197a** and **197b** with sulfur in the presence of butyllithium afforded bis-(silanylmethylene)-1,3-dithietanes **198a** and **198b** (yields not reported) (Equation 36) <2001JA6209>.



The synthesis of poly-dibenzylidene-1,3-dithietane **201** is based on the Wittig reaction of *p*-xylene-bis(triphenylphosphonium) chloride **199** with carbon disulfide <2001MM346, 2002MM3806>. The phosphonium salt **199** was converted to the ylide **200**, which reacted with carbon disulfide, yielding, after methanolysis, a thioketene. The latter was stirred at room temperature for 12 h to provide the polymeric compound **201**, bearing 1,3-dithietane moieties in 54% yield (Scheme 25) <2001MM346, 2002MM3806>.



Scheme 25

The synthesis of the selected 1,3-dithietanes is also based on various transformations of other heterocyclic rings. Several reports describe the conversion of the five-membered rings of 4,5-bis-alkylsulfanyl-1,2-dithiole-3-thiones **202a–f** into two isomers of 2,4-dimethylidene-1,3-dithietanes **203a–f** and **204a** and **204b** <1988BSF101, 1998JPR450, 1999JOC4376>. Reactions were carried out in nonpolar solvents and in the presence of phosphines or phosphites as catalysts (Equation (37); Table 11).

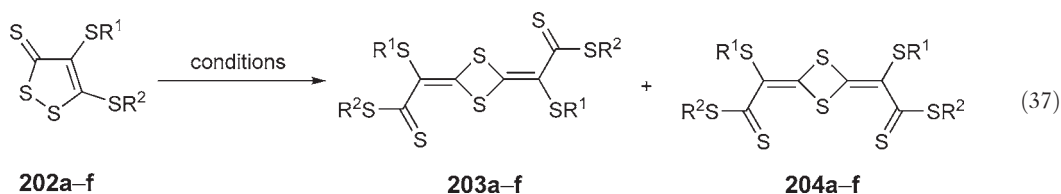
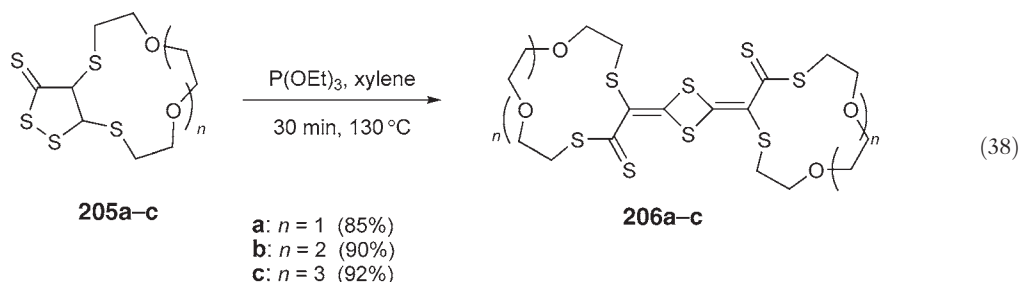


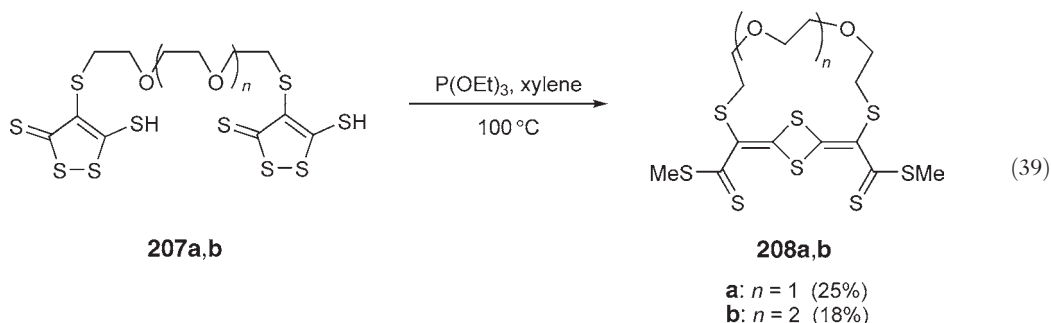
Table 11 Synthesis of 2,4-dimethylidene-1,3-dithietanes **203** and **204** (Equation 37)

Entry	R ¹	R ²	Conditions	Yield of 203 (%)	Yield of 204 (%)	Reference
a	Me	Me	Benzene, PMe ₃ , 30 min, reflux	3	16	1988BSF101
b	Me	Me	Xylene, P(OEt) ₃ , 30 min, 130 °C	50	15	1998JPR450
c	C ₁₂ H ₂₅	Me	Xylene, P(OEt) ₃ , 30 min, 130 °C	85		1998JPR450
d	C ₁₂ H ₂₅	C ₁₂ H ₂₅	Xylene, P(OEt) ₃ , 30 min, 130 °C	71		1998JPR450
e	Pr ⁱ	Pr ⁱ	CH ₂ Cl ₂ , PPh ₃ , 8 h, reflux	83		1999JOC4376
f	Pr ⁱ	Pr ⁱ S	CH ₂ Cl ₂ , PPh ₃ , 5 h, reflux	49		1999JOC4376

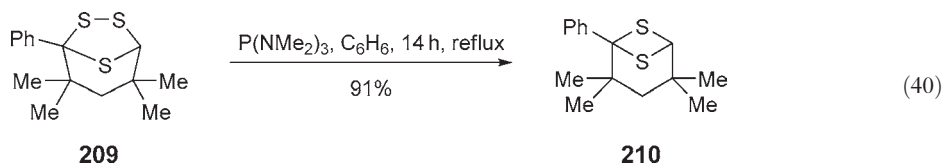
Reaction of the crown ether derivatives **205a–c** of 1,2-dithiole-3-thione in nonpolar solvents, and in the presence of triethyl phosphite as catalyst, gave the 1,3-dithietane derivatives **206a–c** in excellent yields (Equation 38) <1998JPR450>.



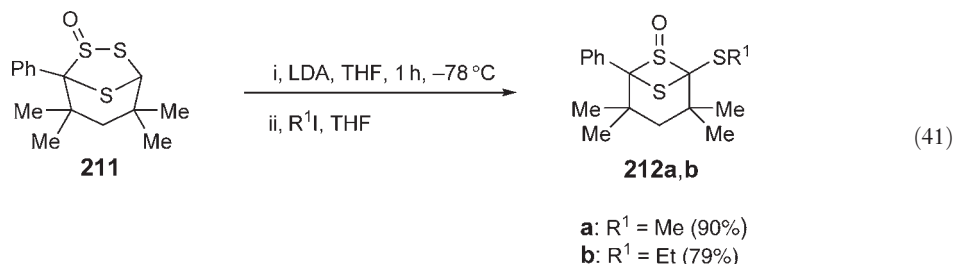
Reactions of bis-(1,2-dithiole-3-thione) polyethers **207a** and **207b**, carried out in xylene at 100 °C in the presence of triethyl phosphite as a catalyst, provided macrocycles **208a** and **208b** bearing a 1,3-dithietane moiety (Equation 39) <1998CC1653>.



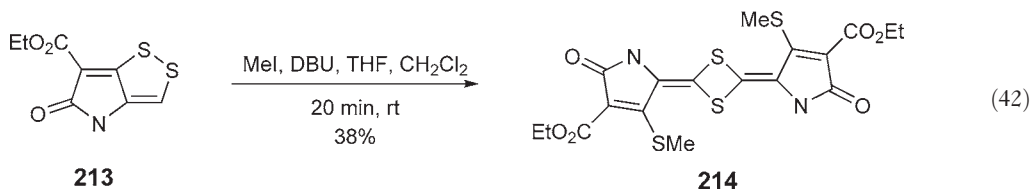
Reaction of the 1-phenyl-6,7,8-trithiabicyclo[3.2.1]octane derivative **209** with hexamethylphosphoric triamide converted it into bicyclic 1,3-dithietanes **210** (Equation 40) <2000BCJ729, 1999T10341>.



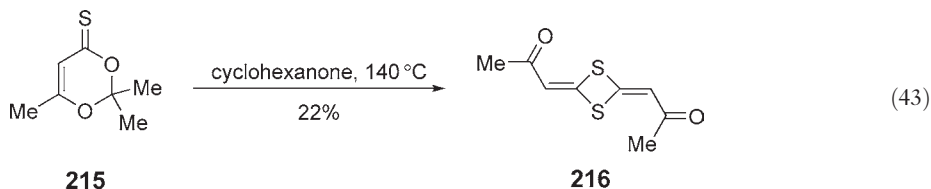
Alkylating transformations of 1-phenyl-6,7,8-trithiabicyclo[3.2.1]octane-6-oxide **211** (lithiation and subsequent alkylation) gave the corresponding fused 1,3-dithietane 1-oxides **212a** and **212b** in good yields (Equation 41) <1999T10341>.



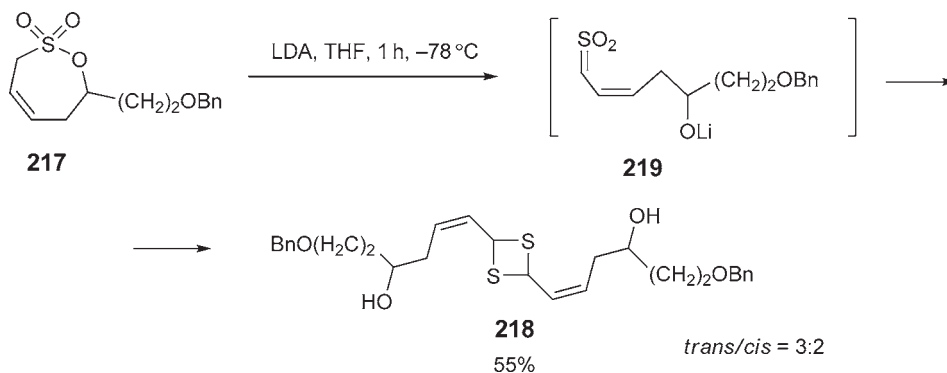
The similar alkylating ring reduction of dithiopyrrole **213** into 1,3-dithietane **214** in 38% yield was realized when this reaction was carried out in THF in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Equation 42) <1999PHA335>.



The conversion of 1,3-dioxine-4-thione **215** into 2,4-di(acetylmethylene)-1,3-dithietane **216** was carried out in cyclohexanone at 140 °C providing the product **216** in 22% yield (Equation 43) <1996CC775>.

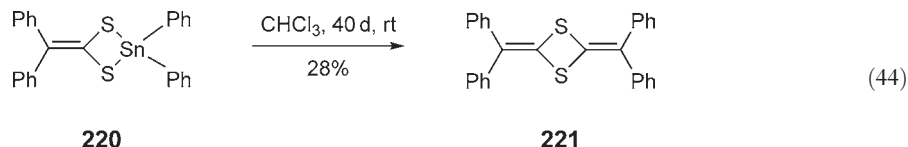


The lithiation of the seven-membered sultone **217** with lithium *N,N*-diisopropylamide at -78 °C led to the rapid formation of the 1,3-dithietane 1,1,3,3-tetraoxide **218** in 55% yield, via the intermediate **219** (Scheme 26) <2003SL667>.

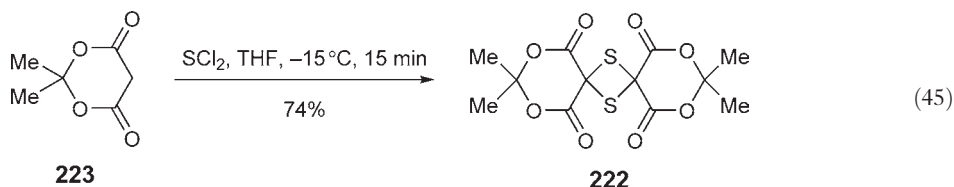


Scheme 26

A slow reaction of 4-benzhydrylidene-2,2-diphenyl-1,3,2-dithiastannetane **220** in chloroform provided dibenzhydrylidene-1,3-dithietane **221** in 28% yield after 40 days of standing at room temperature (Equation 44) <1996CB663>.

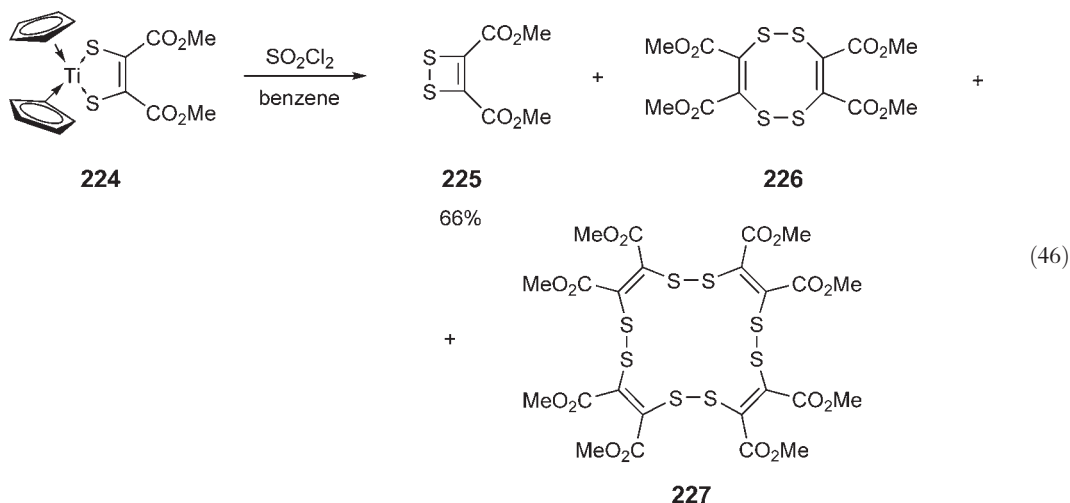


A novel dispiro-1,3-dithietane **222** was isolated in 74% yield after reaction of 1,3-dioxane-1,5-dione **223** with sulfur dichloride (Equation 45) <2004ZFA1659>.

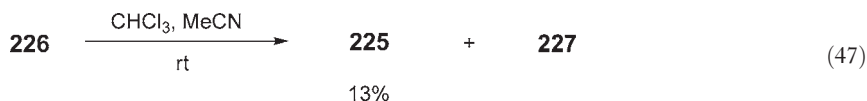


2.18.4.3 Syntheses of 1,2-Dithietes and Other Structures

The synthesis of 1,2-dithietes was extensively described by Zoller in CHEC-II(1996) <1996CHEC-II(1B)1113>, and the literature until 1995 was summarized. Since that time, a few interesting procedures have been reported. The oxidation of the titanium complex **224** with sulfuryl chloride in benzene gave 3,4-dimethoxycarbonyl-1,2-dithiete **225** in 66% yield. Macrocyclic compounds **226** and **227** were isolated as by-products (Equation 46) <1998JOC8192, 1999PS431>.



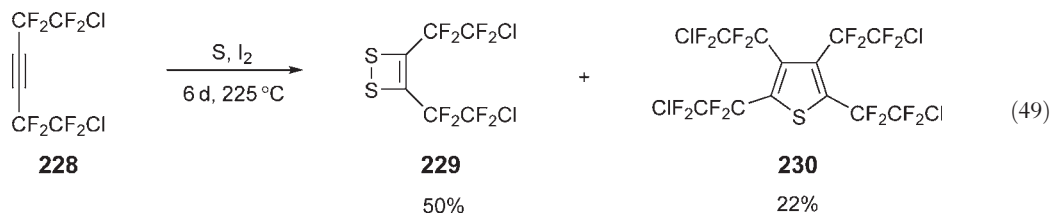
Disproportionation of 3,4,7,8-tetrakis(methoxycarbonyl)-1,2,5,6-tetrathiocine **226** in acetonitrile at room temperature led to the thiete **225** in 13% yield and the macrocyclic compound **227** (Equation 47) <1998JOC8192>.



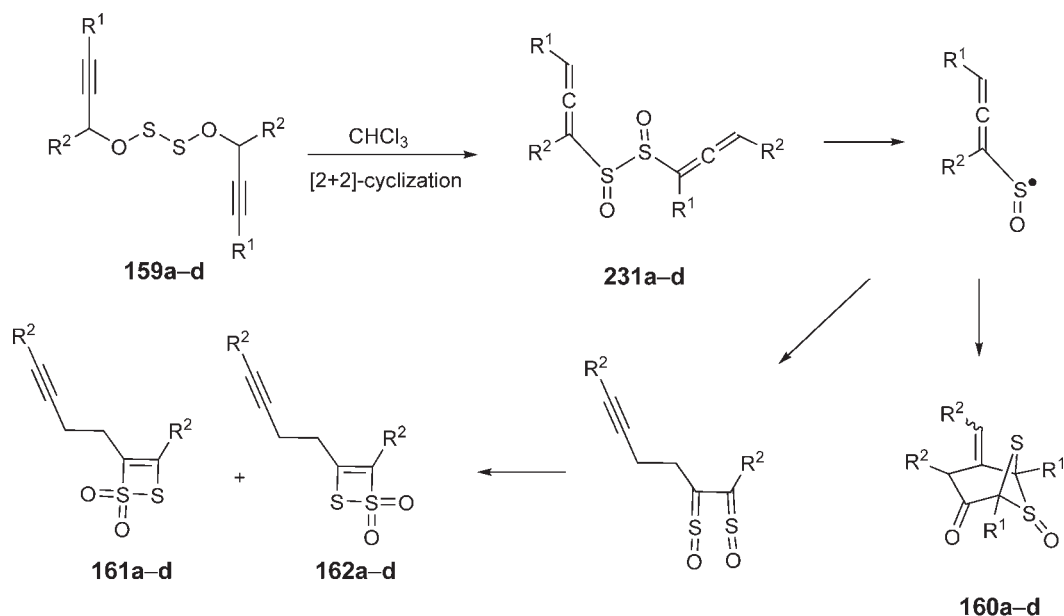
The macrocyclic compound **227** after decomposition in a chloroform/acetonitrile mixture (1:4) gave after 4 h at room temperature the dithiete **225** and thiocine **226** in 6% and 12% yield, respectively (Equation 48) <1998JOC8192>.



The condensation of perfluorinated alkyne **228** with elementary sulfur in the presence of iodine carried out at elevated temperature for 6 days led to the formation of the difluoroalkenyl dithiete derivative **229** and a tetrasubstituted thiophene **230** in 50% and 22% yield, respectively (Equation 49) <2000JFC(102)323>.



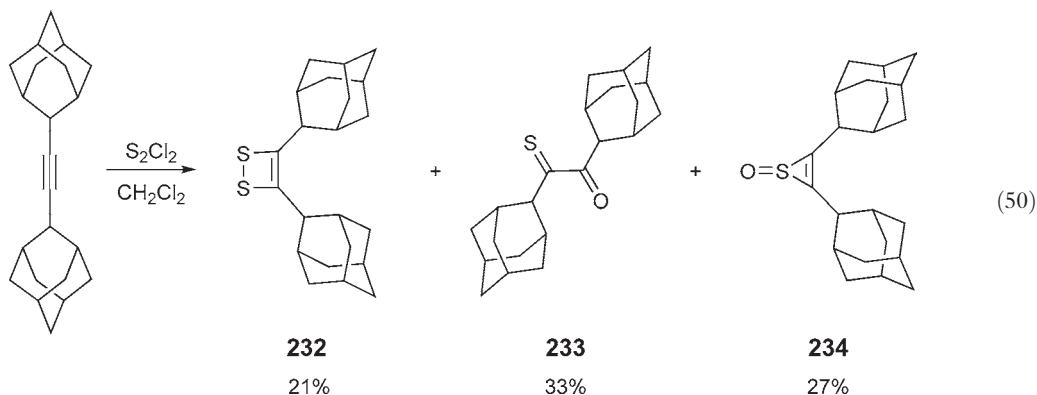
Refluxing of dipropargyloxy disulfides **159a–d** in chloroform for 7 h led to the formation of the bicyclic 1,3-dithietanes **160a–d** and two isomeric 1,2-dithietes **161a–d** and **162a–d** in 3–92% yield (Scheme 27) <2003JA14290>. It was suggested that, in the course of the reaction, the propargyl derivatives **159a–d** are converted into the allenyl derivatives **231a–d**, which undergo a homolytic decomposition. Then, after sigmatropic rearrangement and [2+2] cycloaddition, the formation of derivatives **160a–d**, **161a–d**, and **162a–d**, occurs (Scheme 27) <2003JA14290>.



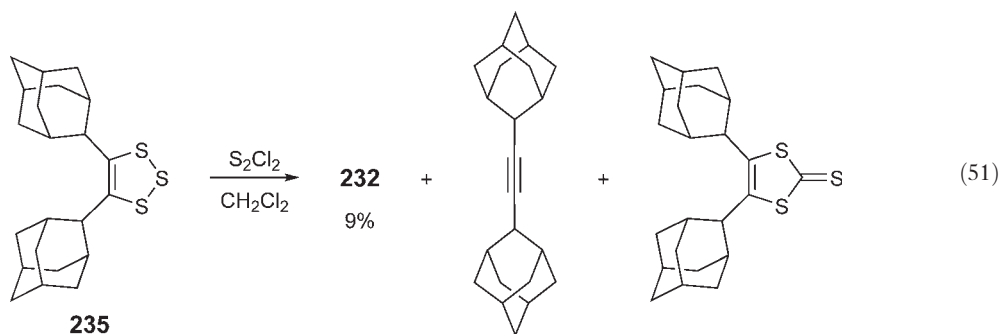
		Yield (%)		
		160a–d	161a–d	162a–d
a:	R ¹ = H; R ² = H	32	3	14
b:	R ¹ = Et; R ² = H	10	41	34
c:	R ¹ = Bu ^t ; R ² = H	8	92	
d:	R ¹ = TMS; R ² = H		57	19

Scheme 27

The reaction of 1,2-diadamantylacetylene with disulfur dichloride led to the formation of the dithiete **232** (mentioned above), 1,2-diadamantyl-2-thiooxoethanone **233**, and the thiirene 1-oxide derivative **234** in 21%, 33%, and 27% yield, respectively (Equation 50) <2000TL8349, 2003JA12114, 1998BCJ1181>.

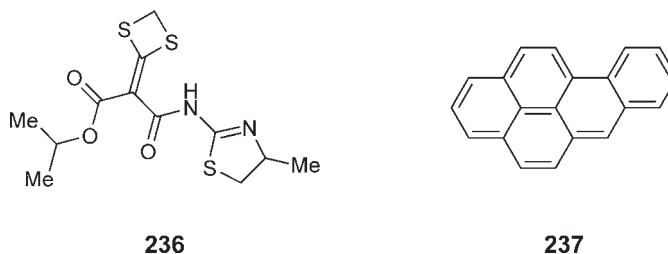


The dithiete **232** was also isolated in 9% yield by the cyclization of trithiole oxide **235** with carbon disulfide (Equation 51) <2003JA12114>.



2.18.5 Important Aspects and Applications

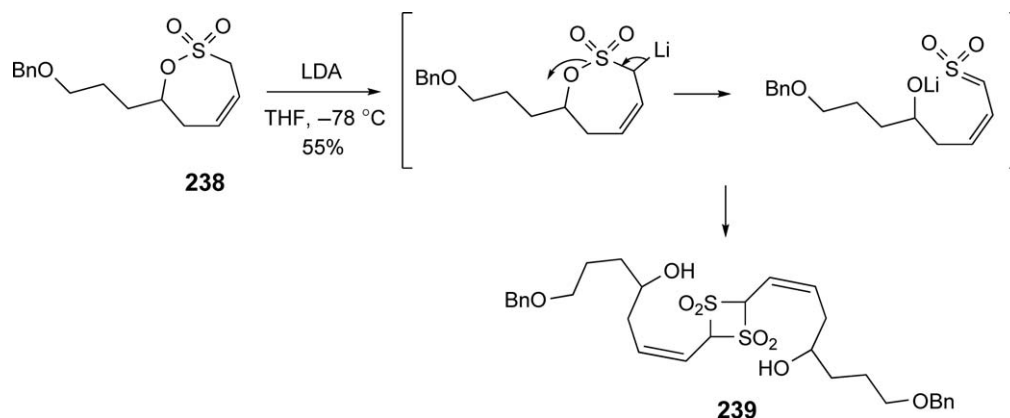
Numerous applications of four-membered rings bearing two sulfur heteroatoms were exhaustively described by Zoller in CHEC-II(1996) <1996CHEC-II(1B)1113>, which covers the literature until 1995. Since this date, several papers reporting pharmacological applications of YH439 have been published. YH439 (chemical name: 2-[1,3]dithietan-2-ylidene-*N*-(4-methyl-4,5-dihydro-thiazol-2-yl)malonic acid isopropyl ester) **236** has been found to be a novel dithioylidene malonate derivative effective in the treatment of hepatic injury <1998MI687>. Authors suggest that compound **236** is able to downregulate the expression of hepatic cytochrome CYP2E1. The chemoprotective effect of YH439 **236** on carcinogenesis of various factors such as carbon tetrachloride, bromobenzene, and dimethylnitrosamine is associated with the inhibition of CYP2E1 <1998MI687>. Similar results were obtained by Yoon *et al.*, who have also studied the metabolic pathways of YH439 **236** <1998MI152>. More recently, Surh *et al.* reported the inhibitory effect of YH439 **236** on skin carcinogenesis induced by benzo[*a*]pyrene **237** <1999MI149, 1996MI219>.



A mixture of **36** and **37** showed a 65–90% inhibition of thrombin-induced TXB2 biosynthesis in human platelet rich plasma at a concentration of 0.1–1.0 mg ml⁻¹ <1996JA2790>.

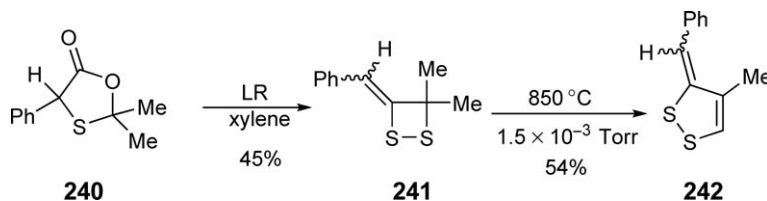
2.18.6 Further Developments

Lithiation of sultone **238** with LDA in THF at -78°C gave the rapid formation of the 1,3-dithietane tetraoxide **239** in 55% isolated yield in the apparent form of a 60:40 mixture of *trans/cis*-diastereomers bearing double bonds with the (*Z*)-configuration <2006T9017>. The authors explained the formation of the 1,3-dithietane **239** by the transformation of the α -lithiated sultone into the corresponding sulfene, which dimerized to give dithietane **239** (Scheme 28).



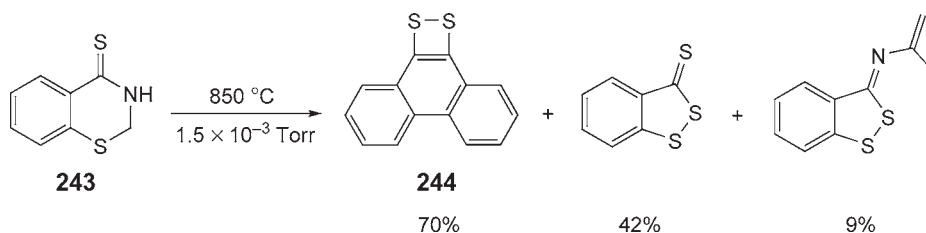
Scheme 28

The thionation of **240** with Lawesson reagent (LR) in boiling xylene led to 1,2-dithietane **241** as a single isomer in 45% yield <2006HCA991>. The dithietane **241** then underwent a gas-phase thermolysis at 850°C under a pressure of 1.5×10^{-3} Torr and 3-benzylidene-4-methyl-3*H*-dithiolane **242** was obtained as a 1:3-*E/Z* mixture in 54% yield (Scheme 29).



Scheme 29

The gas-phase thermolysis at 850°C under 1.5×10^{-3} Torr of **243** led to a mixture of 1,2-dithietane **244** in 70% yield accompanied by two heterocyclic products <2006HCA991> (Scheme 30). The authors suggested a possible mechanism of the reaction.



Scheme 30

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 1965JOC1375
 1973CRC2023
 1976ACA759
 1976JA5715
 1984J(P1)1869
 1984J(P1)2649
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 1989JCC209
 1991JST(249)297
 1995TL8583
 1996BSF515
 1996CB161
 1996CB663
 1996CC775
 1996CHEC-II(1B)1113
 1996IJQ859
 1996JA2790
 1996JA2799
 1996JA7492
 1996JOC7326
 1996MI219
 1997BCJ509
 1997JFC(82)29
 1997PS173
 1997TL1431
 1998BCJ1181
 1998CC1653
 1998EJI1025
 1998H(47)221
 1998JOC8192
 1998JOC8654
 1998JPR450
 1998MI152
 1998MI687
 1998T9849
 1999EJO83
 1999IC4334
 1999JCP7705
 1999JMT(466)111
 1999JOC4376
 1999JOC8489
 1999JOM(573)14
 1999JPO47
 1999MI149
 1999PHA335
 1999PS431
 1999RJO1507
 1999T10341
 2000AXC1113
 2000BCJ729
 2000CEJ1153
 2000JCP8430
 2000JFC(102)323
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Biographical Sketch



Jozef Drabowicz was born in Działoszyn, Poland, in 1946; he studied at the University of Łódź, from where he obtained an M.Sc. in 1969. Since then, he has been employed at the Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences (CMMS, PAS), Łódź. He obtained his Ph.D. under the supervision of Professor M. Mikolajczyk from the Institute of Organic Chemistry, PAS, in 1975 and habilitation from the University of Łódź in 1987. He spent his postdoctoral stay at the University of Tsukuba, Japan, working with Professor S. Oae (1976–77) and worked as a research associate with Professor J. C. Martin at Vanderbilt University (Nashville, USA, 1989–90). Since 1998, he has been professor at the Department of Heteroorganic Chemistry, CMMS, PAS. Since 2002, he has simultaneously been teaching at Jan Długosz University of Częstochowa. He is an author or co-author of one book (*Chiral Sulfur Reagents: Applications in Asymmetric and Stereoselective Synthesis*, CRC Press, Boca Raton, USA, 1998 (with M. Mikolajczyk and P. Kiełbasinski)) and over 150 publications, including several book chapters, among them monographic chapters included in *Houben-Weyl, Science of Synthesis*, and the Patai (*The Chemistry of Functional Groups*) series and *Comprehensive Organic Functional Group Transformations II*. His scientific interests include chemistry and stereochemistry of heteroorganic compounds, synthetic methodology, and asymmetric synthesis.



Professor Jarosław Lewkowski was born in 1966 at Łódź (Poland). In 1990, he obtained his M.Sc. degree from the University of Łódź, Poland, studying the electrochemical oxidation of 5-hydroxymethylfurfural derivatives at the nickel oxide/hydroxide electrode. He then joined Professor Skowroński's group from the University of Łódź, Poland, cooperating simultaneously with Professor Descotes' team from the University of Lyon 1, France. In 1996, he obtained the Ph.D. degree from the University of Łódź, investigating the selective conversions of furfural, 5-hydroxymethylfurfural, and their derivatives. He then joined Professor Vaultier's team from the University of Rennes 1 for his postdoctoral studies, where he worked on conversions of organophosphorus compounds in reactions with boron compounds. After presenting his dissertation entitled "Studies in the Field of Aminophosphonic and Aminophosphonous Derivatives of Furfural, Ferrocenecarbaldehyde and Terephthalic Aldehyde," he received a D.Sc. degree in 2005.

He is the author and co-author of over 40 papers (including book chapters). Now, he is an associated professor at the University of Łódź, Poland. His main areas of scientific interest are the chemistry of furans, the chemistry of ferrocenes, as well as the chemistry of organophosphorus compounds. He is also interested in medicinal chemistry of anticancer drugs.



Wiesława Kudelska was born in Poland (1951); she studied pharmacy at the Medical University of Łódź, Poland (1969–74), where she also carried out her Ph.D. work (1974–82). She joined Professor G. Descotes' group at the Claude-Bernard University of Lyon, France (1985). In 1988, she spent one year in USA working as a postdoctoral research fellow with Professor J. Loz at Laboratory for Carbohydrate Chemistry, Harvard University. From 1974 to 2004, she was employed at the Medical University of Łódź, Faculty of Pharmacy. Since 2004, she is a professor at the Jan Długosz University of Częstochowa, Poland. Her scientific interests are centered on carbohydrate chemistry.



Adrian Zajac was born in Krzepice, Poland, in 1981; he studied at Jan Długosz Academy of Częstochowa, where he obtained an M.Sc. in 2005. Presently he is employed at the Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Łódź. His research interests include chemistry and stereochemistry of hetero-organic compounds and asymmetric synthesis.

2.19

Four-membered Rings with Two or More Heteroatoms including Selenium or Tellurium

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2.19.1 Introduction

Since 1,3-diselenetane was first synthesized in 1920 <1920JCS1456>, various four-membered rings with two heteroatoms including selenium or tellurium have been prepared. 1,2- and 1,3-Diheteroatom-four-membered cyclic compounds, as shown below, are summarized up until CHEC-II(1996) <1996CHEC-II(1B)1139>.

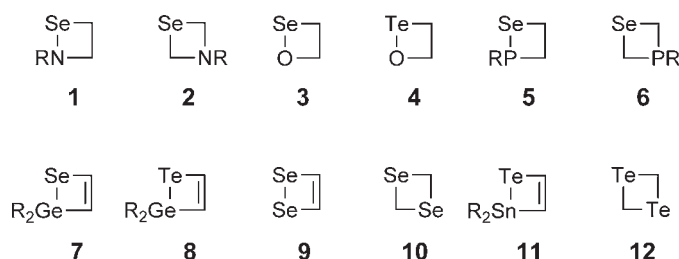


X = Y = Se
X = S, Y = Se
X = R₂Sn, Y = Se

X = Y = Se
X = Y = Te
X = Se, Y = Te
X = Se, Y = NR
X = Se, Y = O

In the last decade, various structures and reactivities of the four-membered cyclic compounds having the skeletons of 1,2-selenazetidine **1** <2001OL691, 2001PS259>, 1,3-selenazetidine **2** <2005HCA766, 2006H(68)1267>,

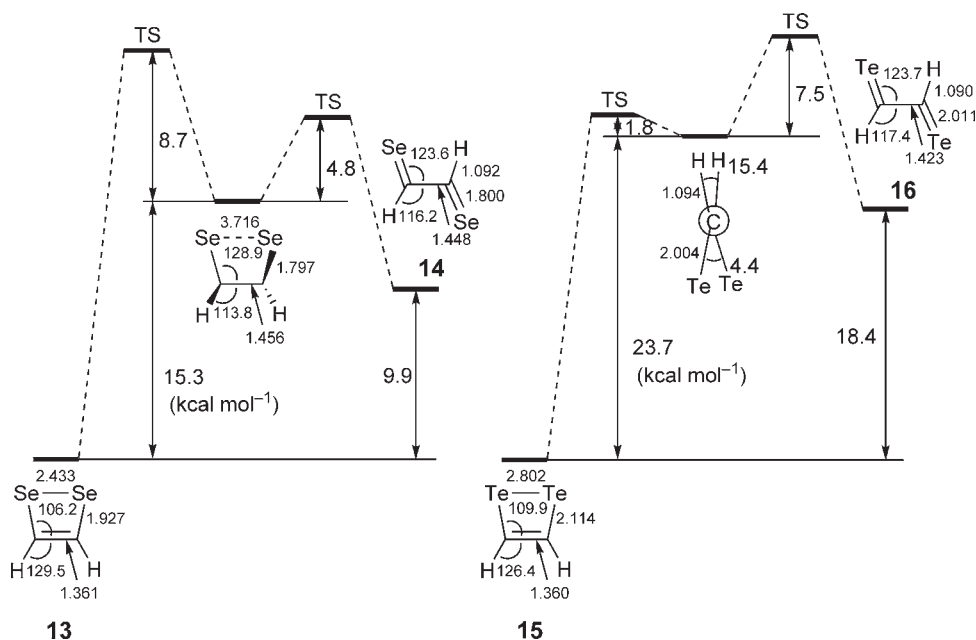
1,2-oxaselenetane **3** <1997CC1671, 1998PS501, 2001CC463>, 1,2-oxatellurethane **4** <1999OM803, 2002TL6775>, 1,2-selenaphosphetane **5** <2001JCD300>, 1,3-selenaphosphetane **6** <2000CC1745>, selenagermate **7** <2005OM612>, telluragermate **8** <2005OM612>, 1,2-diselenete **9** <1996CC2375, 1999JCP7705, 2000CEJ1153>, 1,3-diselenetane **10** <1996POL1847, 1997JA8592, 1997T12167, 2000JOC1799, 2001TL3881, 2003PHC(15)100>, 1,2-stannatellurete **11** <2006OM3552>, and 1,3-ditellurethane **12** <1996JCD4463, 1997TL2501, 1997PS413, 1999ZFA1726, 2000JCD11, 2003TL2397> have been reported.



In this chapter, the theoretical methods, crystal structures, characteristic nuclear magnetic resonances, reactivities, and formation of four-membered rings with two heteroatoms including selenium or tellurium that have appeared in the last decade are described.

2.19.2 Theoretical Aspects

The equilibrium structures and reaction profiles of 1,2-diselenete and 1,2-ditellurete based on density functional theory (DFT) have been reported, together with those of the corresponding oxygen and sulfur analogues <1999JCP7705>. On the basis of the B3LYP method, 1,2-diselenete **13** is calculated to be 9.9 kcal mol⁻¹ more stable than the corresponding ring-opened structure, 1,2-diselone (*trans*-isomer) **14**. Similarly, 1,2-ditellurete **15** is more stable than the corresponding 1,2-ditellone **16**. The equilibrium between the substituted 1,2-diselenetes and 1,2-diselones has also been studied theoretically <2000CEJ1153>.

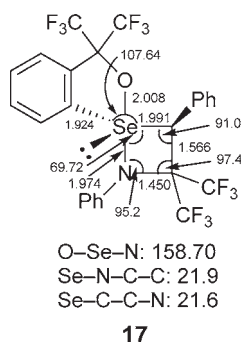


2.19.3 Experimental Structural Methods

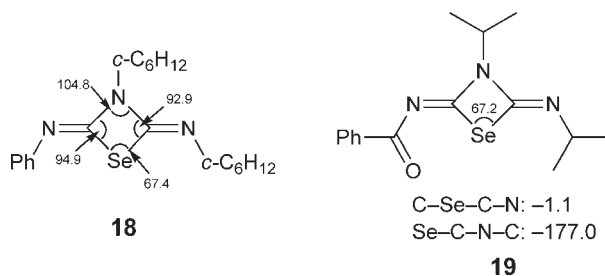
2.19.3.1 X-Ray Diffraction Studies

In the last decade (1996–2006), the crystal structures of 1,2-selenazetidine <2001OL691>, 1,3-selenazetidine <2005HCA766, 2006H(68)1267>, 1,2-oxaselenetane <2001CC463>, 1,2-oxatellurethane <1999OM803, 2002TL6775>, 1,3-selenaphosphetane <2000CC1745>, selenagermate <2005OM612>, telluragermate <2005OM612>, and 1,3-ditellurethane derivatives <1996JCD4463, 1997PS413, 2000JCD11, 2003TL2397> were determined by X-ray crystallographic analysis.

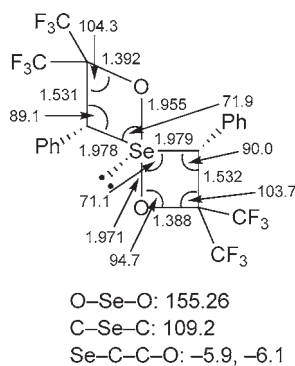
The crystal structure of spiro-1,2-selenazetidine **17** reveals a distorted pseudo-trigonal bipyramidal (TBP) structure at the selenium atom <2001OL691>. The oxygen and nitrogen atoms occupy two apical positions, whereas the two carbon atoms as well as the lone pair occupy three equatorial positions. The nitrogen atom is not trigonal planar. The pyramidal configuration for the nitrogen atom might be explained by the steric repulsion between the Martin ligand and the phenyl group on the nitrogen atom. The four-membered ring significantly deviates from planarity as indicated by the torsion angle (21.6–21.9°). The Se–C bond length of the four-membered ring (1.991 Å) is slightly longer than that of the oxaselenetanes <1993JA10434>. The bond angle between two apical bonds deviates by 21.30° from 180°.



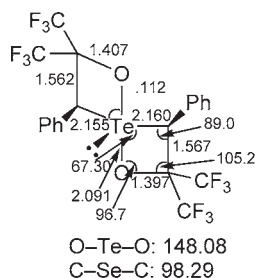
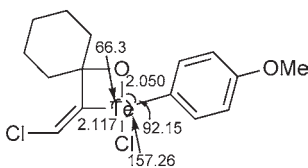
The crystal structure of 1,3-selenazetidine-2,4-diimine **18** shows that both imino groups have a (Z)-configuration, and that the selenazetidine ring is planar with a maximum deviation from the four-atom plane being 0.010 Å for the nitrogen atom <2005HCA766>. The sum of the bond angles around the nitrogen atom of the four-membered ring is 357.3°. The crystal structure of compound **19** has also been determined <2006H(68)1267>. The bond angle of the selenium atom C–Se–C in **19** is 67.2°, which is consistent with the value in diimine **18**. The selenazetidine ring is planar and both imino groups have the (Z)-configuration.



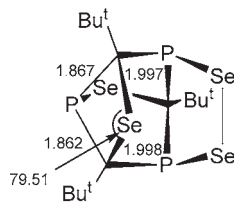
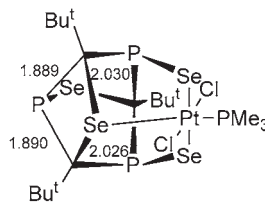
The crystal structure of spiro-selenurane **20** bearing two 1,2-oxaselenetane rings indicates that the asymmetric unit of a crystal contains one and a half molecules, A and B, the latter of which is disordered <2001CC463>. Both molecules have a distorted pseudo-TBP structure with two oxygen atoms at apical positions and two carbon atoms and a lone pair at equatorial positions. Molecule A shows that both the phenyl groups at the 3- and 3'-positions are *cis* to the lone pair of the selenium. The apical Se–O bonds are bent away from the lone pair leading to deviation of the O–Se–O angle by 22.74° from linearity, and the two oxaselenetane rings are almost planar.

**20**

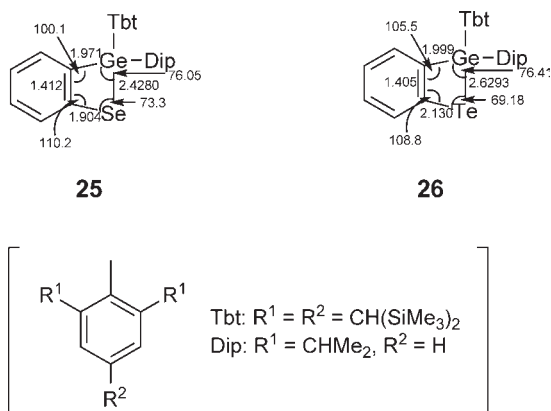
Similarly, the crystal structure of spirotellurane **21** bearing two 1,2-oxatellurane rings has been determined by X-ray analysis <2002TL6775>. The apical O–Te–O bond angle (148.08°), which is much smaller than that (160.53°) of a tellurane bearing two Martin ligands <1984JA7529>, is considerably deviated from linearity. Thus, the structure is intermediate between a pseudo-trigonal bipyramidal structure and a square pyramidal structure. The bond lengths in the four-membered rings are similar to 2-chloro-1,2-oxatellurane <1999OM803>. Both of the four-membered rings are slightly puckered, judging from the torsion angles of Te–C–C–O (12.0 and 10.7° , respectively) and from the sum of the angles of the four-membered rings (358.2° and 358.6° , respectively). Spirotellurane **21** forms a dimer in the crystalline state with intermolecular contacts between two sets of Te $\cdots$ O of two independent molecules (3.195 and 3.676 Å, respectively). The crystal structure of cyclic tellurium oxychloride having a 1,2-oxatellurane ring **22** has also been determined by X-ray analysis <1999OM803>.

**21****22**

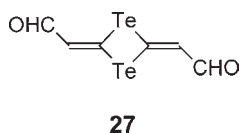
The crystal structure of the cage compound **23** having a four-membered ring including phosphorus and selenium atoms has been determined <2000CC1745>. The bond angle around the selenium atom of the four-membered ring was determined to be 79.51° . The X-ray structure of the Pt complex **24** has also been determined. The bond lengths of the four-membered ring of complex **24** are slightly longer than those of **23**.

**23****24**

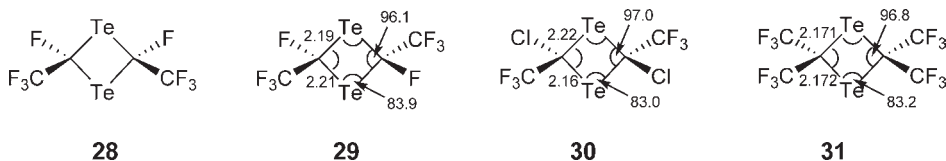
The crystal structures of 2*H*-benzo[*c*][1,2]selenagermate **25** and telluragermate **26** have been determined by X-ray analysis <2005OM612>. Their benzochalcogenogermate rings were found to be completely planar within the error limits. The bond lengths of the Ge–Te, Ge–C, and Te–C bonds of **26** are longer than the corresponding bond lengths of **25**, whereas the C=C bond of the four-membered ring of **26** is slightly shorter than that of **25**.



The crystal structure of the 1,3-ditellurethane derivative **27** shows that the compound is planar <2003TL2397>. The crystal packing, down the crystallographic axis *b*, reveals the formation of columns through π - π stacking interactions. The distance between these molecules in the columns is 6.41 Å.



The crystal structures of *cis*- and *trans*-2,4-difluoro-2,4-bis(trifluoromethyl)-1,3-ditelluretanes **28** and **29** have the same crystal system and space group <1996JCD4463>. The atomic coordinates show only small differences and a slightly enlarged unit-cell volume. Each molecule consists of a planar ditellurethane ring with a center of inversion. The transannular Te...Te distance of only 3.271 Å for **29** is closer to that expected for a Te-Te bond (2.75 Å) than the sum of the van der Waals radii (4.40 Å). The crystal structures of the chlorine derivative **30** and tetrakis(trifluoromethyl)-1,3-ditellurethane **31** have also been determined, and show similar geometries to **28** and **29** <1997PS413, 2000JCD11>.



2.19.3.2 NMR Spectroscopy

Various nuclear magnetic resonance (NMR) data of 1,2-selenazetidines **17** and **32** <2001OL691>, 1,3-selenazetidines **33** and **34** (Tables 1 and 2) <2005HCA766, 2006H(68)1267>, 1,2-oxaselenetanes **35–37** and **20** <1997CC1671, 2001CC463>, 1,2-oxatellurethane **21** <2002TL6775>, 1,2-selenaphosphetane **38** <2001JCD300>, 1,3-selenaphosphetane **23** <2000CC1745>, selenagermate **25** <2005OM612>, telluragermate **26** <2005OM612>, 1,3-diselenetane **39** <2001TL3881>, and 1,3-ditelluretanes **28–30** and **40–43** <1996JCD4463, 1997TL2501> were reported in the period reviewed. Some characteristic NMR data of the four-membered rings are listed below.

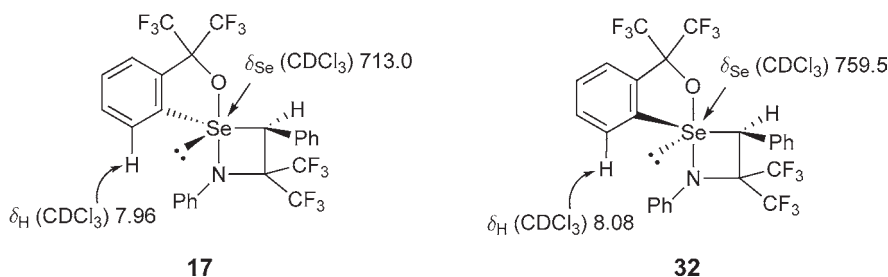
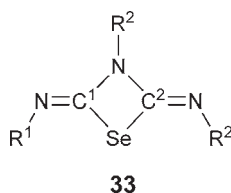
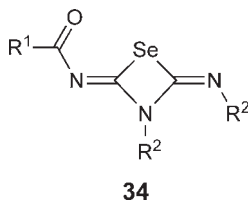
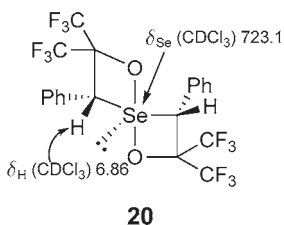
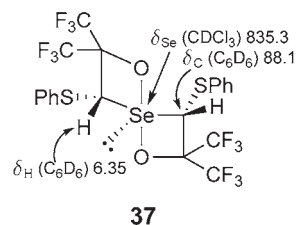
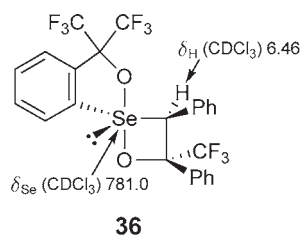
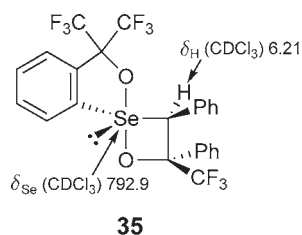


Table 1 Carbon-13 NMR chemical shifts of selenazetidines **33**

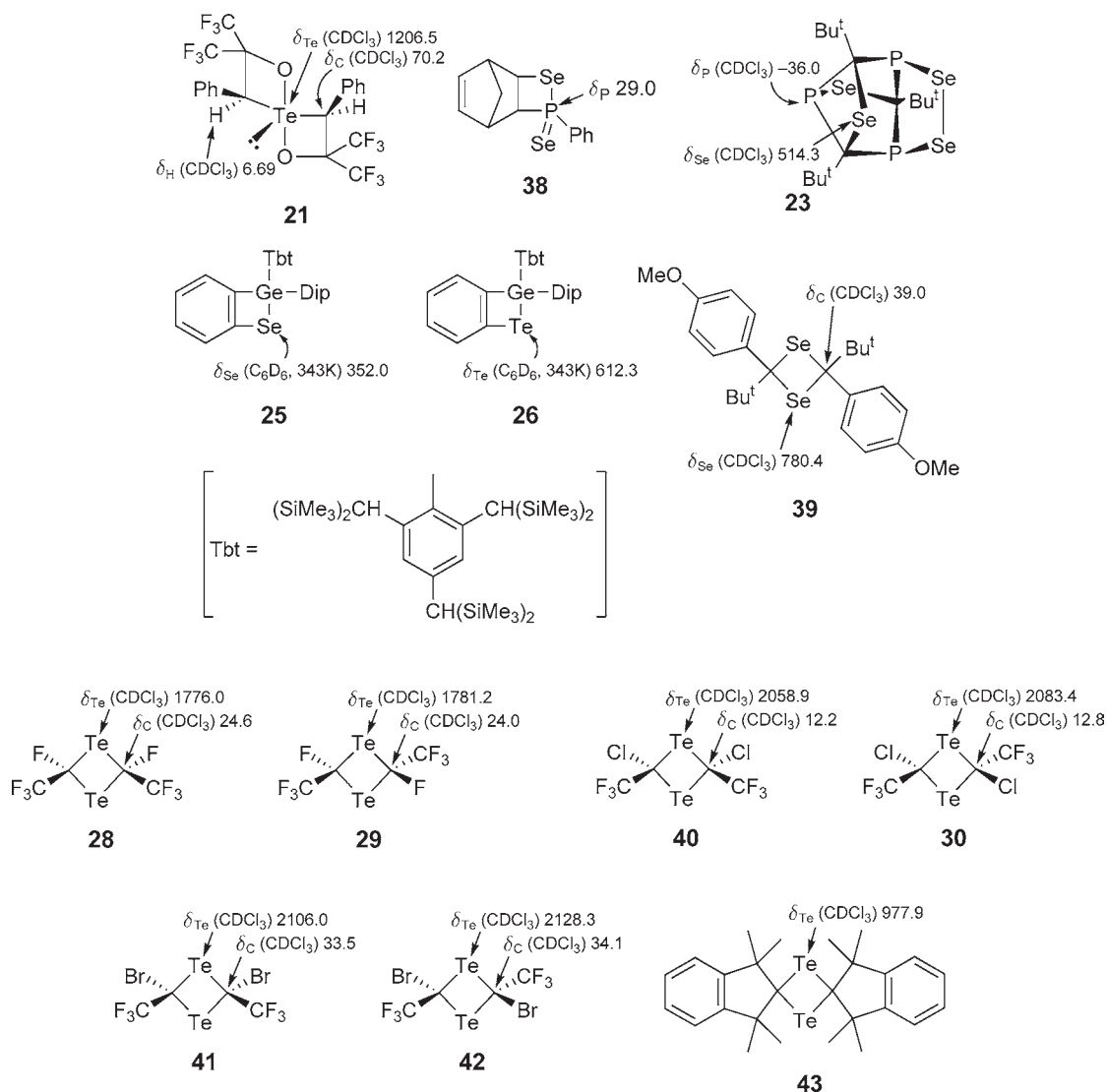
R^1	R^2	$^{13}\text{C NMR } (\delta)$	
		C^1	C^2
Ph	Cyclohexyl	133.1	137.1
Ph	<i>i</i> -Pr	133.0	136.6
4-ClC ₆ H ₄	Cyclohexyl	129.9	132.3
4-ClC ₆ H ₄	<i>i</i> -Pr	130.0	132.2
4-BrC ₆ H ₄	Cyclohexyl	133.1	137.1
4-BrC ₆ H ₄	<i>i</i> -Pr	129.9	137.5
Cyclohexyl	Cyclohexyl	132.5	139.6
Cyclohexyl	<i>i</i> -Pr	131.8	132.7

Table 2 Selenium-77 chemical shifts of selenazetidines **34**

R^1	R^2	$^{77}\text{Se NMR } (\delta)$
<i>t</i> -Bu	<i>i</i> -Pr	752.7
4-ClC ₆ H ₄	<i>i</i> -Pr	756.2
4-MeOC ₆ H ₄	<i>i</i> -Pr	751.8
Ph	<i>i</i> -Pr	754.4
4-MeC ₆ H ₄	<i>i</i> -Pr	753.2
4-MeC ₆ H ₄	Cyclohexyl	750.6



The two oxetane rings of both compounds are observed equivalently.



2.19.4 Thermodynamic Aspects

For the molecules of this chapter, no thermodynamic data have been reported except for the theoretical studies described in [Section 2.19.2](#).

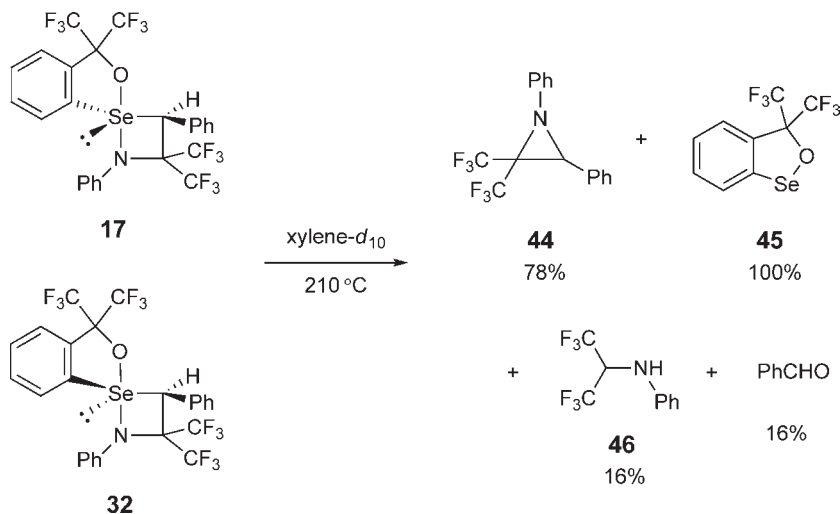
2.19.5 Reactivity of Rings

The reactivities of 1,2-selenazetidine <2001OL691, 2001PS259>, 1,2-oxaselenetane <1997CC1671, 1998PS501, 2001CC463>, 1,2-oxatellurethane <1999OM803, 2002TL6775>, 1,3-diselenetane <1996POL1847, 1997T12167, 2001TL3881, 2004BCJ1933>, and 1,3-ditellurethane derivatives <2000JCD11> have been evaluated during the period under review.

2.19.5.1 Nitrogen-Containing Rings

Thermolysis of 1,2-selenazetidine **17** at 210 °C in xylene-*d*₁₀ yields aziridine **44**, cyclic selenenate **45**, amine **46**, and benzaldehyde in 78%, 100%, 16%, and 16% NMR yield, respectively (**Scheme 1**) <2001OL691, 2001PS259>.

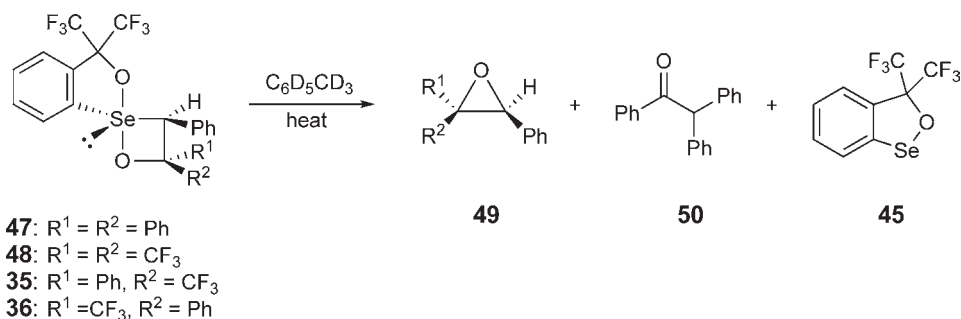
Compound **46** and benzaldehyde are considered to be most likely formed by the ring-opening reaction of aziridine **44**, giving an azomethine ylide, followed by hydrolysis. Thermolysis of **32** also affords **44–46**, and benzaldehyde in 79%, 100%, 15%, and 16% NMR yield, respectively. This is the first example of aziridine formation from heterocyclobutanes with high coordinate main-group elements.



Scheme 1

2.19.5.2 Oxygen-Containing Rings

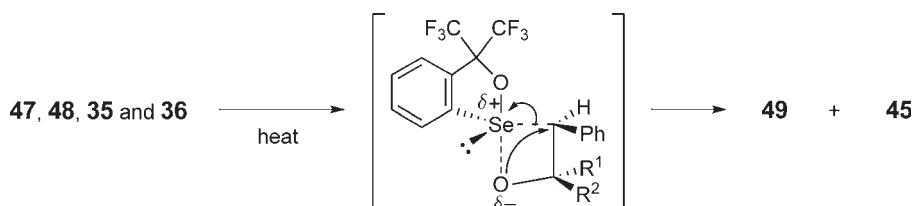
Thermolysis of tetracoordinate 1,2 λ^4 -oxaselenetanes **47**, **48**, **35**, and **36** in $C_6D_5CD_3$ in a degassed sealed tube was found to give oxiranes **49**, ketone **50**, and the bicyclic compound **45**, together with minor products (Scheme 2) <1997CC1671, 1998PS501>. The results are summarized in Table 3 and show that the oxirane formation from 1,2 λ^4 -oxaselenetanes is the reverse of that expected from the back-side attack of the oxide anion, and hence the reaction can be recognized as a carbon–oxygen ligand coupling reaction of λ^4 -selenanes (Scheme 3).



Scheme 2

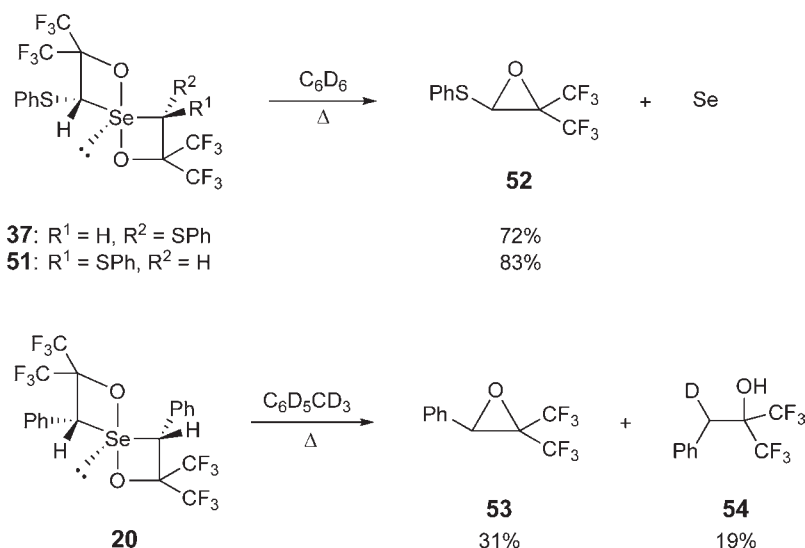
Table 3 Thermolysis of 1,2 λ^4 -oxaselenetanes

Compd	T ($^{\circ}\text{C}$)	Time	Yield (%)		
			49	50	45
47	130	3 d	43	52	95
48	200	6 d	quant.		quant.
35	200	30 h	88		97
36	200	5 h	quant.		quant.



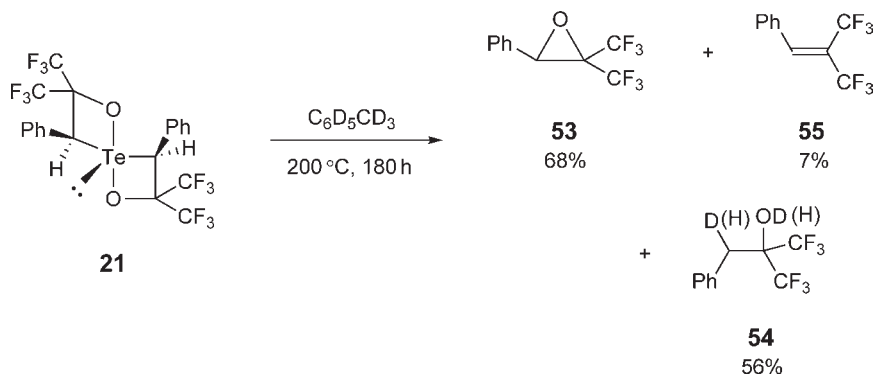
Scheme 3

Thermolysis of spiroseleuranes **37** (C_6D_6 , 120°C , 11 h) and **51** (C_6D_6 , 60°C , 19 h) in a degassed sealed tube yields oxirane **52** in 72% and 83% yields, respectively, with extrusion of elemental selenium (Scheme 4) <2001CC463>. On the other hand, the thermolysis of **20** ($\text{C}_6\text{D}_5\text{CD}_3$, 200°C , 12 d) gives a complicated mixture containing oxirane **53** (31%) and deuterated alcohol **54** (19%).



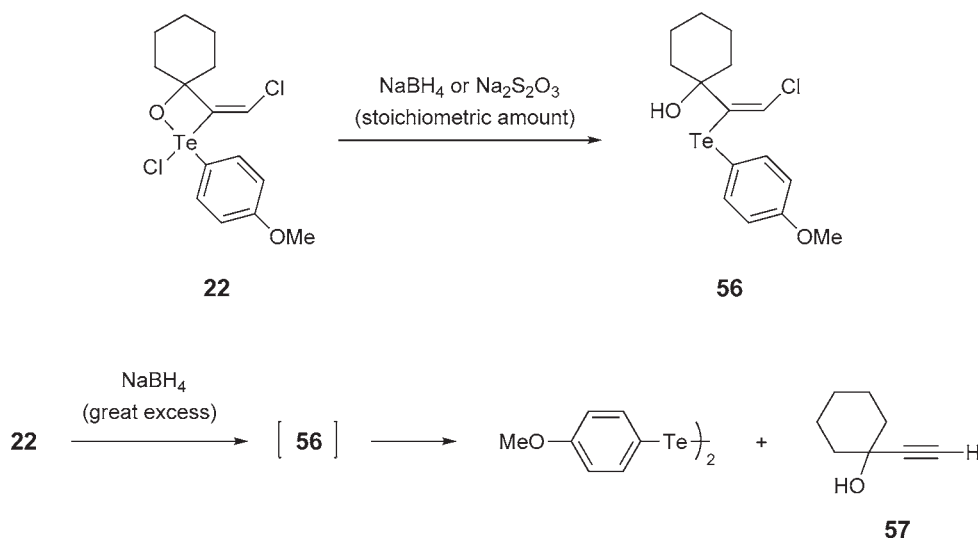
Scheme 4

Thermolysis (toluene- d_8 , 200°C , 180 h) of 1,2-oxatellurethane **21** in a degassed sealed tube gives the corresponding oxirane **53** (68%) and alkene **55** (7%), together with the deuterated alcohol **54** (56%) (Scheme 5) <2002TL6775>.



Scheme 5

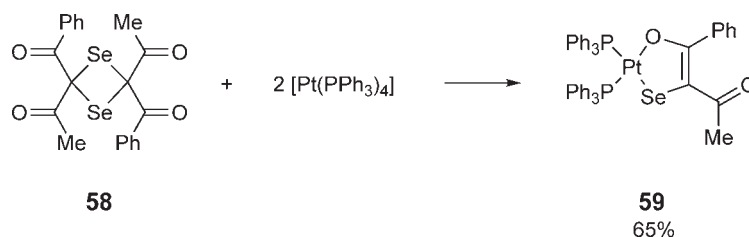
Reduction of cyclic tellurium oxychloride **22** with stoichiometric amounts of sodium borohydride or excess sodium bisulfite yields the telluride **56**, whereas treatment with a great excess of sodium borohydride quantitatively leads to di-*p*-methoxyphenyl ditelluride and alkyne **57** (Scheme 6) <1999OM803>.



Scheme 6

2.19.5.3 Rings Containing Two Selenium Atoms

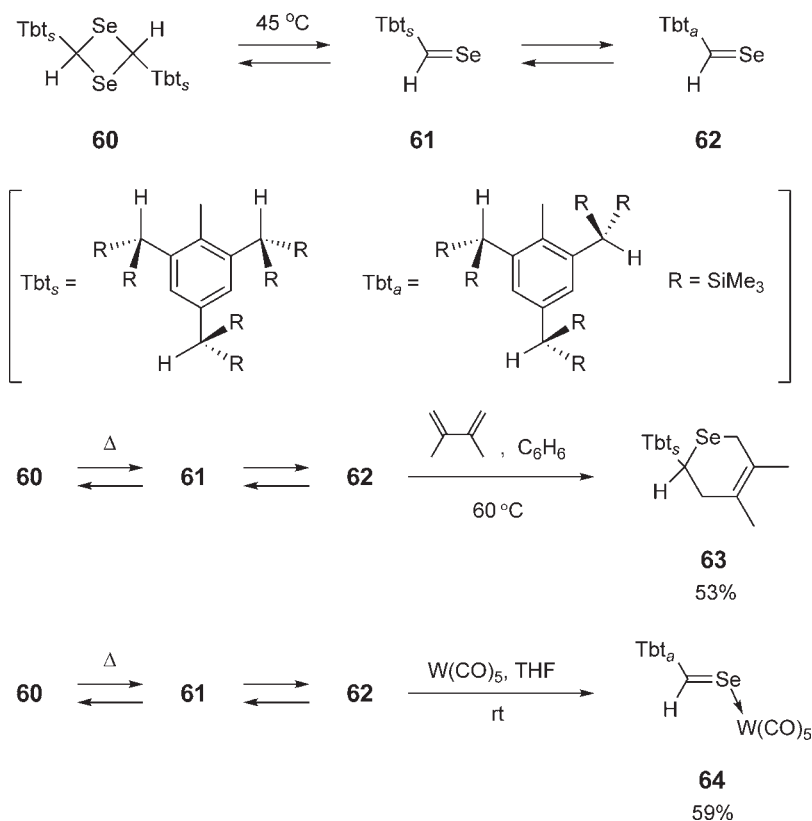
1,3-Diselenetane derivative **58** reacts with 2 equiv of $\text{Pt}(\text{PPh}_3)_4$ affording the platinum(II) complex **59** (Scheme 7) <1996POL1847>.



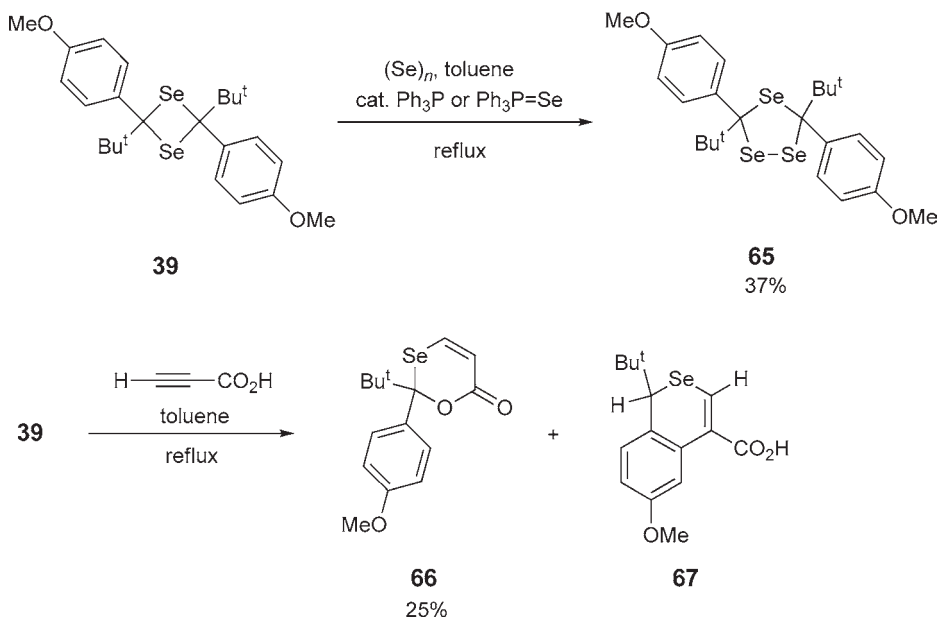
Scheme 7

Heating of the 1,3-diselenetane derivative **60** in a THF or C_6D_6 solution at 45°C affords the selenoketone **61** together with its $\text{Ar-CH}(\text{SiMe}_3)_2$ rotational isomer **62** (Scheme 8) <1997T12167>. Reaction of the equilibrium mixture of **60–62** with 2,3-dimethyl-1,3-butadiene at 60°C yields the [4+2] adduct **63** in 53% yield. Also, reaction with $\text{W}(\text{CO})_5$ affords complex **64**.

1,3-Diselenetane derivative **39** reacts with elemental selenium in the presence of a catalytic amount of triphenylphosphine or triphenylphosphine selenide to give 1,2,4-triselenolane **65** in 37% yield (Scheme 9) <2001TL3881>. The reaction with propiolic acid under reflux conditions in toluene affords selenodioxenone **66** (25%) and trace amounts of compound **67** <2004BCJ1933>.



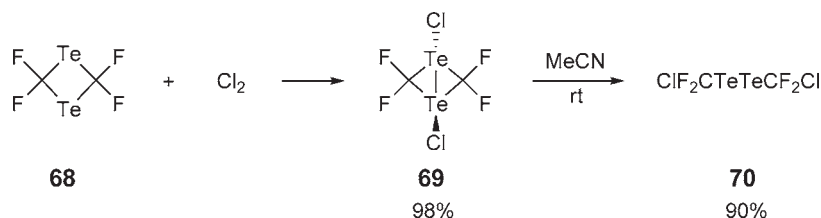
Scheme 8



Scheme 9

2.19.5.4 Rings Containing Two Tellurium Atoms

Oxidative chlorination of tetrafluoro-1,3-ditelluretane **68** leads to the formation of a Te–Te bond yielding bicyclic compound **69** (Scheme 10) <2000JCD11>. When compound **69** is dissolved in acetonitrile at room temperature, the orange-red color changes to dark brown to give ditelluride **70**.



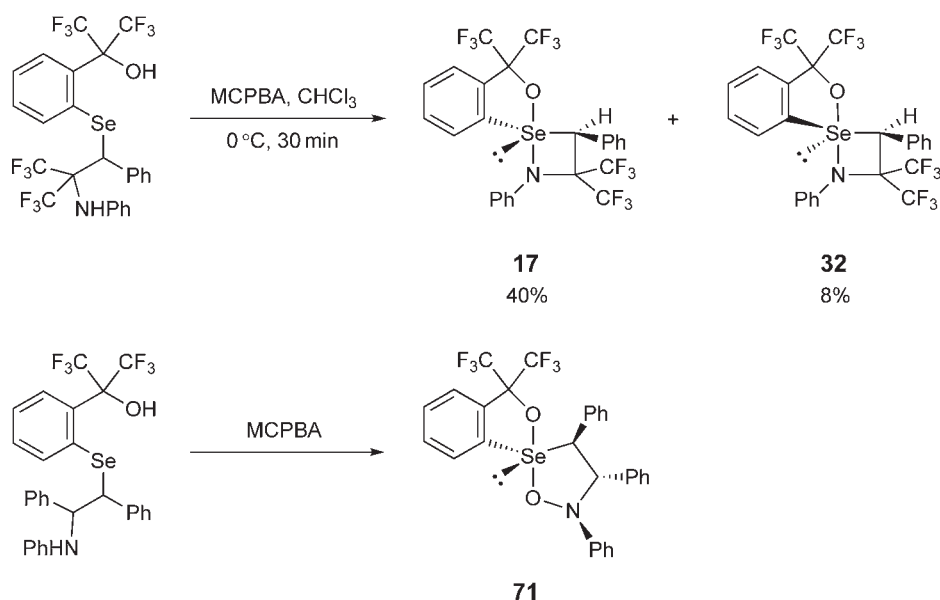
Scheme 10

2.19.6 Ring Syntheses

Formation of 1,2-selenazetidines <2001OL691, 2001PS259>, 1,3-selenazetidines <2005HCA766, 2006H(68)1267>, 1,2-oxaselenetane <1997CC1671, 1998PS501, 2001CC463>, 1,2-oxatelluretane <1999OM803, 2002TL6775>, 1,2-selenaphosphetane <2001JCD300>, 1,3-selenaphosphetane <2000CC1745>, selenagermate <2005OM612>, telluragermate <2005OM612>, 1,2-diselenete <1996CC2375>, 1,3-diselenetane <1997JA8592, 1997T12167, 2000JOC1799, 2001TL3881, 2003PHC(15)100>, 1,2-stannatellurete <2006OM3552>, and 1,3-ditelluretane derivatives <1996JCD4463, 1997TL2501, 1997PS413, 2000JCD11, 2003TL2397> has been reported since 1995.

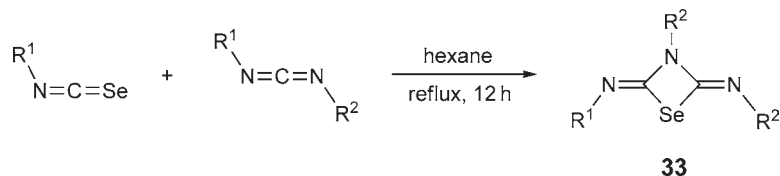
2.19.6.1 Nitrogen-Containing Rings

Oxidation of a β -aminoalkyl selenide bearing the Martin ligand with *m*-chloroperbenzoic acid (MCPBA) affords the novel tetracoordinate 1,2 λ^4 -selenazetidines **17** (40%) and **32** (8%) as a mixture of two diastereomers, which are separated by silica gel chromatography to give stable colorless crystals. However, oxidation of the phenyl derivative yields 1,2,5-oxaselenazolidine **71** (Scheme 11) <2001OL691, 2001PS259>.



Scheme 11

The reactions of isoselenocyanates with carbodiimides in refluxing hexane afford 1,3-selenazetidine-2,4-diimines **33** by a [2+2] cycloaddition in moderate to good yields (Scheme 12 and Table 4) <2005HCA766>. These compounds can be purified by silica gel chromatography and recrystallization. All products **33** are stable and can be stored at room temperature.

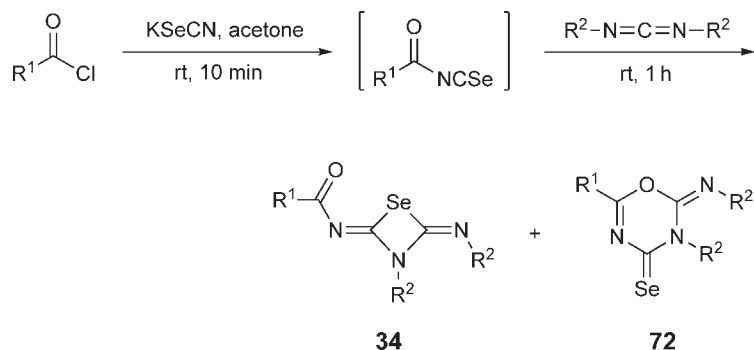


Scheme 12

Table 4 Preparation of selenazetidines **33** from isoselenocyanates

R^1	R^2	Yield (%)
Ph	Cyclohexyl	98
Ph	<i>i</i> -Pr	84
4-ClC ₆ H ₄	Cyclohexyl	88
4-ClC ₆ H ₄	<i>i</i> -Pr	97
4-BrC ₆ H ₄	Cyclohexyl	98
4-BrC ₆ H ₄	<i>i</i> -Pr	99
Cyclohexyl	Cyclohexyl	99
Cyclohexyl	<i>i</i> -Pr	88

1,3-Selenazetidine-2,4-diimines **34** are synthesized in a similar way <2006H(68)1267>. Reactions of acyl isoselenocyanates, prepared from acyl chlorides <1996OM5753, 2005H(65)1903>, with carbodiimides under mild conditions afford 1,3-selenazetidines **34** together with small amounts of the 1,3,5-oxadiazine derivatives **72** (Scheme 13 and Table 5).



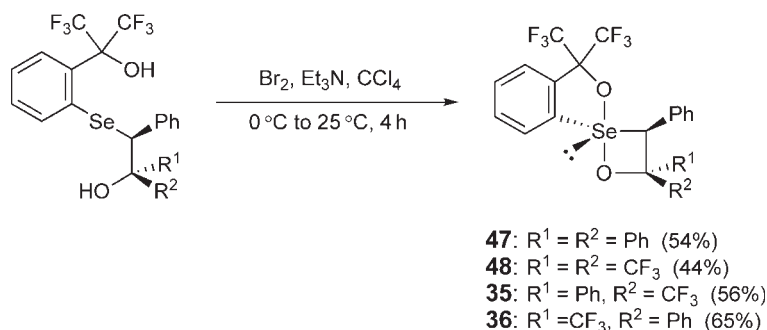
Scheme 13

Table 5 Preparation of selenazetidines **34**

R^1	R^2	Yield (%)	
		34	72
<i>t</i> -Bu	<i>i</i> -Pr	78	0
4-ClC ₆ H ₄	<i>i</i> -Pr	38	Trace
4-MeOC ₆ H ₄	<i>i</i> -Pr	81	11
Ph	<i>i</i> -Pr	62	9
4-MeC ₆ H ₄	<i>i</i> -Pr	86	10
4-MeC ₆ H ₄	Cyclohexyl	72	8
4-MeC ₆ H ₄	Ph	0	0

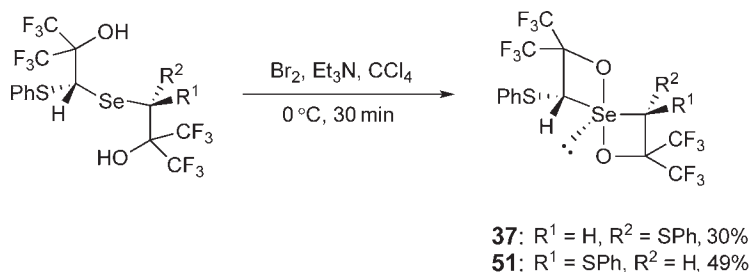
2.19.6.2 Oxygen-Containing Rings

Tetracoordinate 1,2 λ^4 -oxaselenetane **47** is synthesized by a ring-closure reaction of β -hydroxylalkyl selenide in 54% yield [\[1997CC1671\]](#). Similarly, oxaselenetanes **48**, **35**, and **36** are obtained in 44%, 56%, and 65% yields, respectively ([Scheme 14](#)) [\[1997CC1671, 1998PS501\]](#). These compounds were found to be air stable, colorless plates at room temperature, and the relative stereochemistry between the 3- and 4-positions of **35** and **36** has been determined by differential nuclear Overhauser effect (NOE) experiments.



Scheme 14

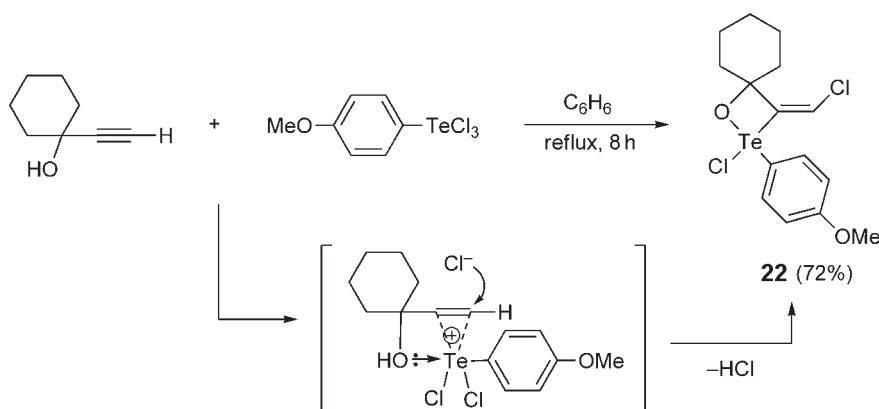
Stable spiroseleuranes bearing two oxaselenetane rings were obtained for the first time in 2001 [\[2001CC463\]](#). Oxidative cyclization of *dl*- and *meso*- β -hydroxylalkyl selenides with bromine in the presence of triethylamine affords the corresponding tetracoordinate 1,5-dioxo-4 λ^4 -selenaspiro[3.3]heptanes **37** and **51** in 30% and 49% yields, respectively ([Scheme 15](#)). Recrystallization from hexane-ether yields colorless plates, respectively.



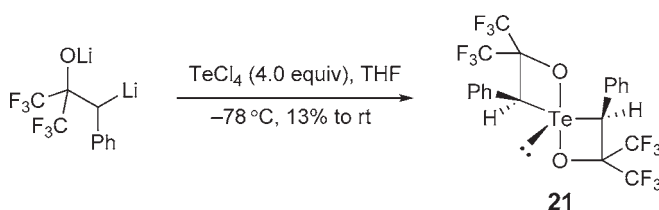
Scheme 15

The reaction of 1-ethynylcyclohexanol with *p*-methoxyphenyltellurium trichloride in refluxing benzene gives cyclic tellurium oxychloride **22** as the major product (72%) ([Scheme 16](#)) [\[1999OM803\]](#). In the reaction, the product resulting from an *anti*-addition is formed. This result can be rationalized in terms of initial formation of a telluronium ion resulting from the attack of *p*-methoxyphenyltellurium trichloride on the triple bond and coordination with the hydroxyl group. This telluronium ion can be opened by the attack of the chloride ion on the less hindered position to form the four-membered ring **22**. The oxybromide and cycloheptyl derivatives are obtained in a similar way, and these compounds were found to show a specific cysteine protease inhibitory activity [\[2005BML755\]](#).

The reaction of excess tellurium tetrachloride with LiCHPhC(CF₃)₂OLi at -78°C and further warming of the reaction mixture to room temperature affords the spirotellurane **21** in 13% yield as an air-stable solid ([Scheme 17](#)) [\[2002TL6775\]](#).



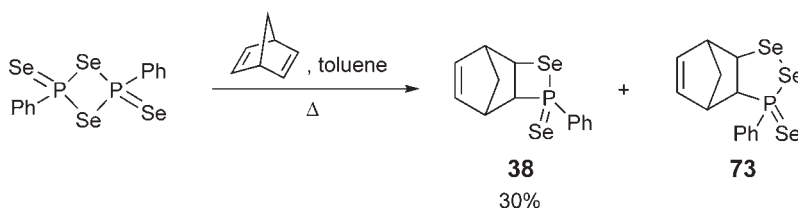
Scheme 16



Scheme 17

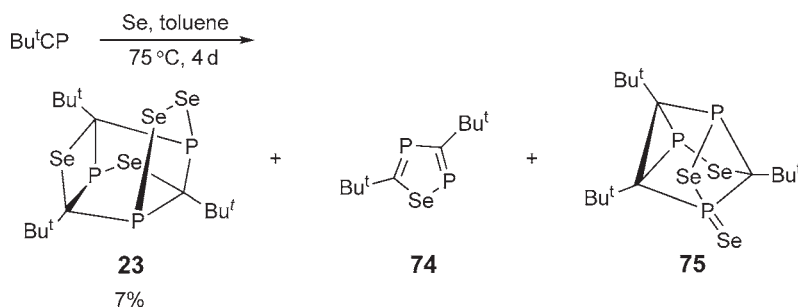
2.19.6.3 Phosphorus-Containing Rings

1,2-Selenaphosphetane derivative **38** is obtained in 30% yield together with compound **73** by the reaction of 1,3-diselenodiphosphetane 2,4-diselenide with norbornadiene (Scheme 18) <2001JCD300>.



Scheme 18

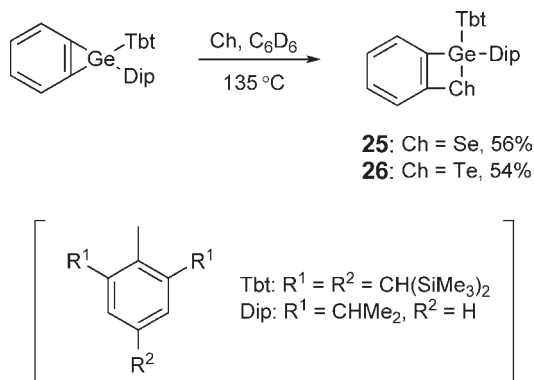
The treatment of a slight excess of selenium with *t*-BuCP in toluene at 75°C affords the novel cage compound $\text{P}_3\text{Se}_4\text{C}_3\text{Bu}_3^{\text{t}}$ **23** (7%), which includes the 1,3-selenaphosphetane unit, together with the cyclic compound **74** and the cage compound **75** (Scheme 19) <2000CC1745>.



Scheme 19

2.19.6.4 Germanium-Containing Rings

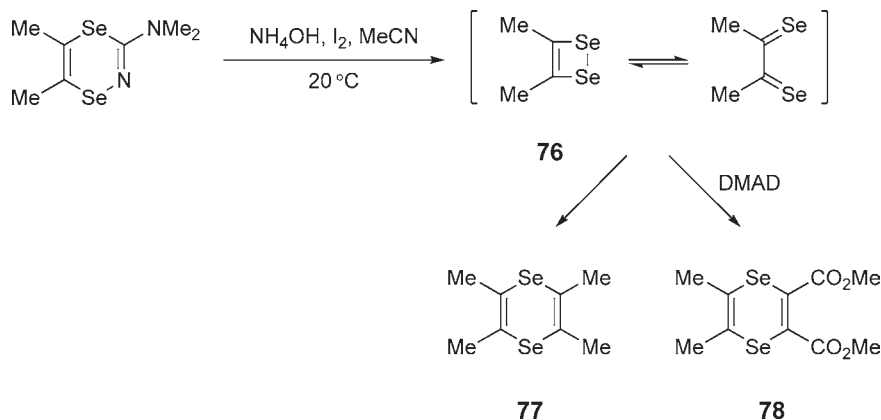
Reaction of germacyclopropabenzene with elemental selenium in a sealed tube at 135 °C in C₆D₆ yields 2*H*-benzo[*c*][1,2]selenagermate **25** in 56% yield as pale yellow crystals (Scheme 20) <2005OM612>. In a similar way, telluragermate **26** is also obtained in 54% yield as orange crystals. These compounds are stable enough to be purified by high-performance liquid chromatography (HPLC) and column chromatographic analysis on silica gel.



Scheme 20

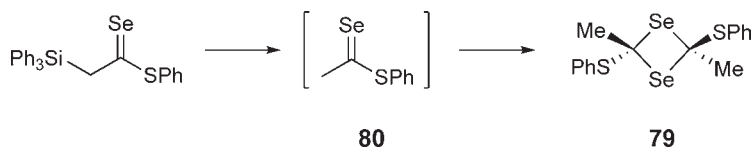
2.19.6.5 Rings Containing Two Selenium Atoms

Unstable 1,2-diselenete **76** is generated by the reaction of a 1,4,2-diselenazine derivative with hydroxylamine and iodine, leading finally to 1,4-diselenin **77** (Scheme 21) <1996CC2375>. In the presence of dimethyl acetylenedicarboxylate (DMAD), 1,2-diselenete **76** affords the 1,4-diselenin derivative **78**.



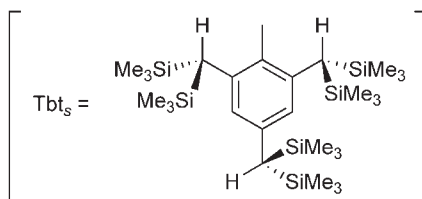
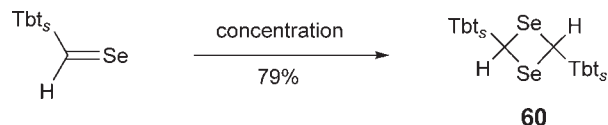
Scheme 21

Selenothioic acid *S*-ester gradually turns from violet blue to yellow within 1 day even when it was stored below −10 °C under an Ar atmosphere. X-Ray analysis of the product reveals that *trans*-1,3-diselenetane **79** is formed, probably via the dimerization of **80**, which is generated by the protodesilylation of the starting material (Scheme 22) <1997JA8592>. A similar dimerization to 2,4-tetraphenyl-1,3-diselenetane from selenoketone was reported to be reversible when it was dissolved in solvent <1989TL2095>. In contrast, 1,3-diselenetane **79** is highly stable in solvent, and no reversible process is observed.



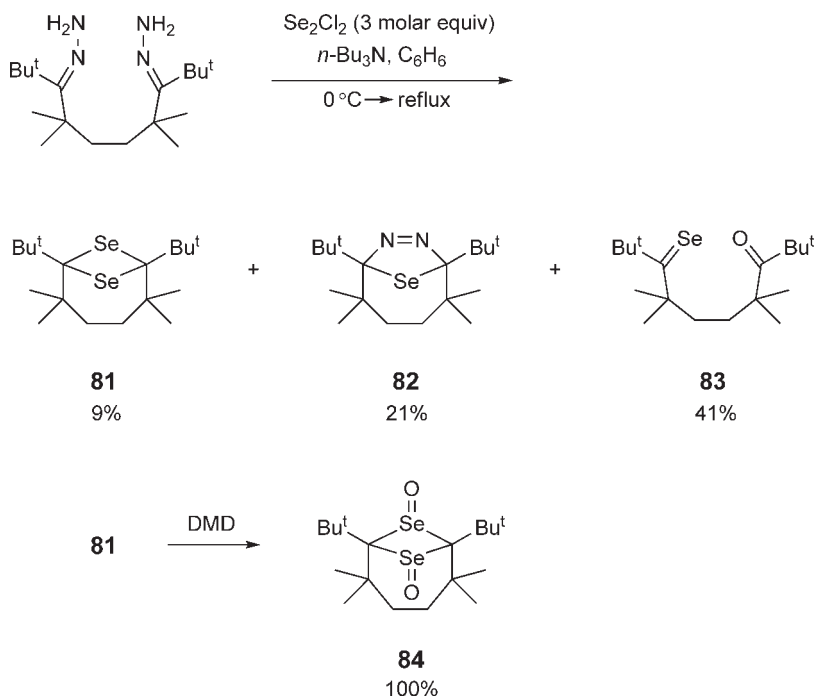
Scheme 22

A selenoaldehyde stabilized by a bulky substituent dimerizes upon concentration of the solution yielding the head-to-tail dimerization product **60** in good yield (Scheme 23) <1997T12167>.



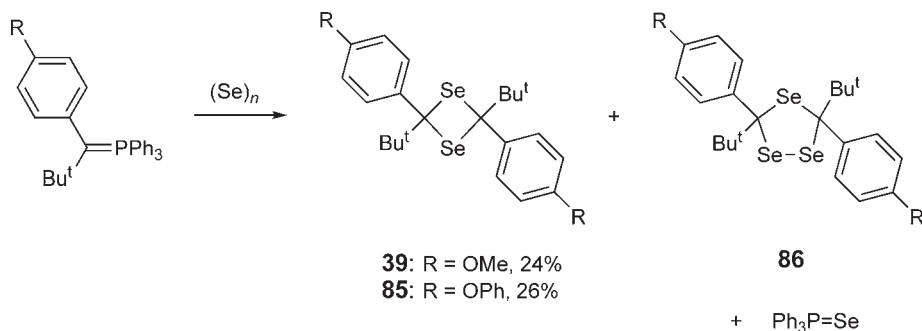
Scheme 23

A dihydrazone derivative reacts with Se_2Cl_2 in the presence of $n\text{-Bu}_3\text{N}$ affording the light-sensitive 1,3-diselenetane derivative **81** (9%) together with the 1,3,4-selenadiazoline **82** (21%) and the monoselenodiketone **83** (41%) (Scheme 24) <2000JOC1799>. Oxidation of **81** with dimethyldioxirane (DMD) yields the corresponding diselenoxide **84** (100%).



Scheme 24

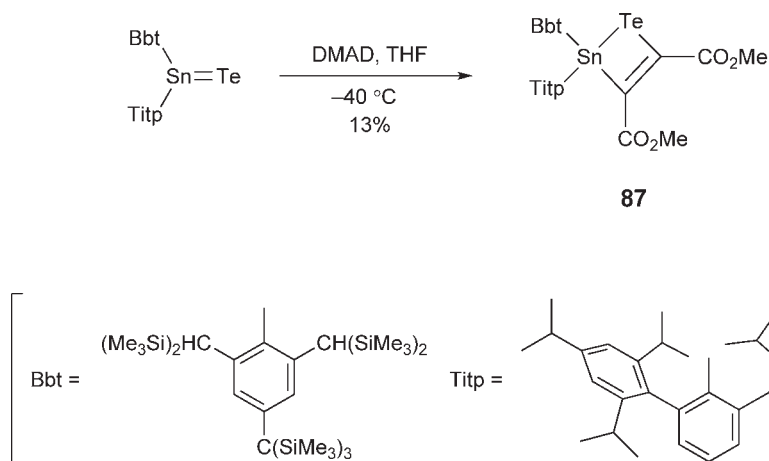
The reactions of *tert*-butylarylmethylenetriphenylphosphoranes with elemental selenium yield the corresponding 1,3-diselenetanes **39** (24%) and **85** (26%) along with the 1,2,4-triselenolane derivatives **86** and triphenylphosphine selenide (**Scheme 25**) <2001TL3881>.



Scheme 25

2.19.6.6 Tin-Containing Rings

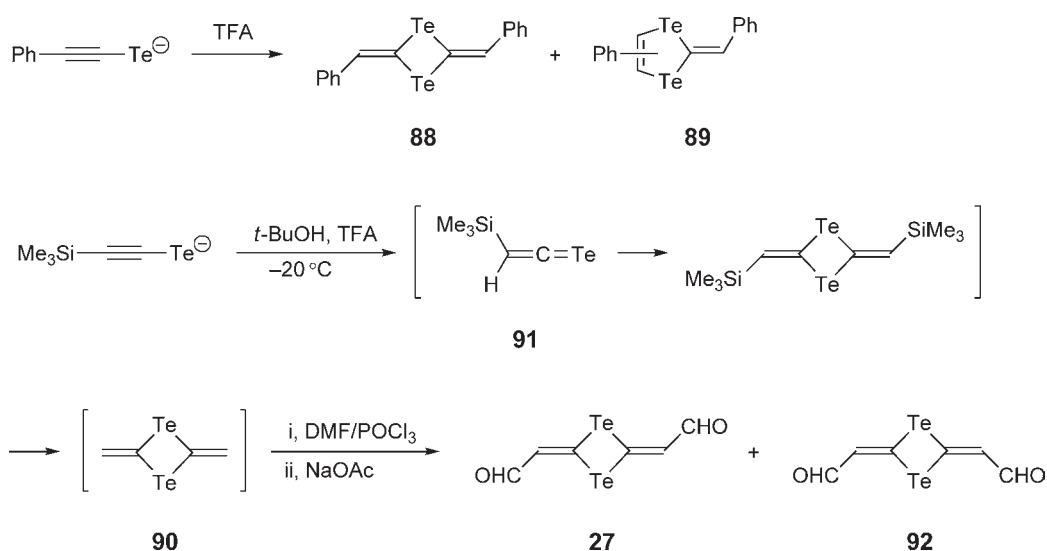
A kinetically stabilized stannanetellone, synthesized by the reaction of stannylene with (*n*-Bu)₃P=Te, reacts with DMAD resulting in formation of the corresponding [2+2] cycloadduct **87** in 13% yield (**Scheme 26**) <2006OM3552>.



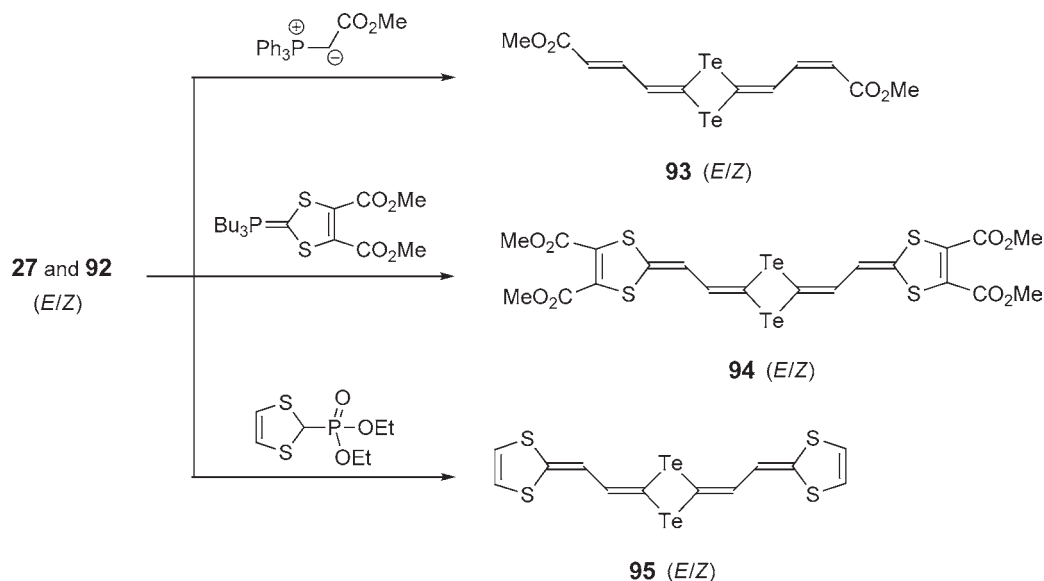
Scheme 26

2.19.6.7 Rings Containing Two Tellurium Atoms

The 1,3-ditellurethane **88** is obtained as a minor product along with the 1,3-ditellurafulvene **89** by the reaction of phenylacetylide with tellurium followed by acidification with trifluoroacetic acid (**Scheme 27**) <2003TL2397>. In the reaction of trimethylsilyl ethynyl tellurolate, use of trifluoroacetic acid in *t*-butyl alcohol at -20°C leads to the formation of the 1,3-ditellurethane **90**, presumably via the telluraketene **91**. Vilsmeier–Haack reaction on the crude ditellurethane **90** furnishes dialdehydes **27** and **92** in 10% yield. 1,3-Ditellurethanes **27** and **92** can be transformed into other derivatives, as shown in **Scheme 28**. An *E/Z* mixture of **27** and **92** condenses smoothly with phosphorane to give diester product **93**. The reaction with diesterdithiole phosphonate or dithiole phosphonate affords 1,3-ditellurethane derivative **94** or **95**, respectively.

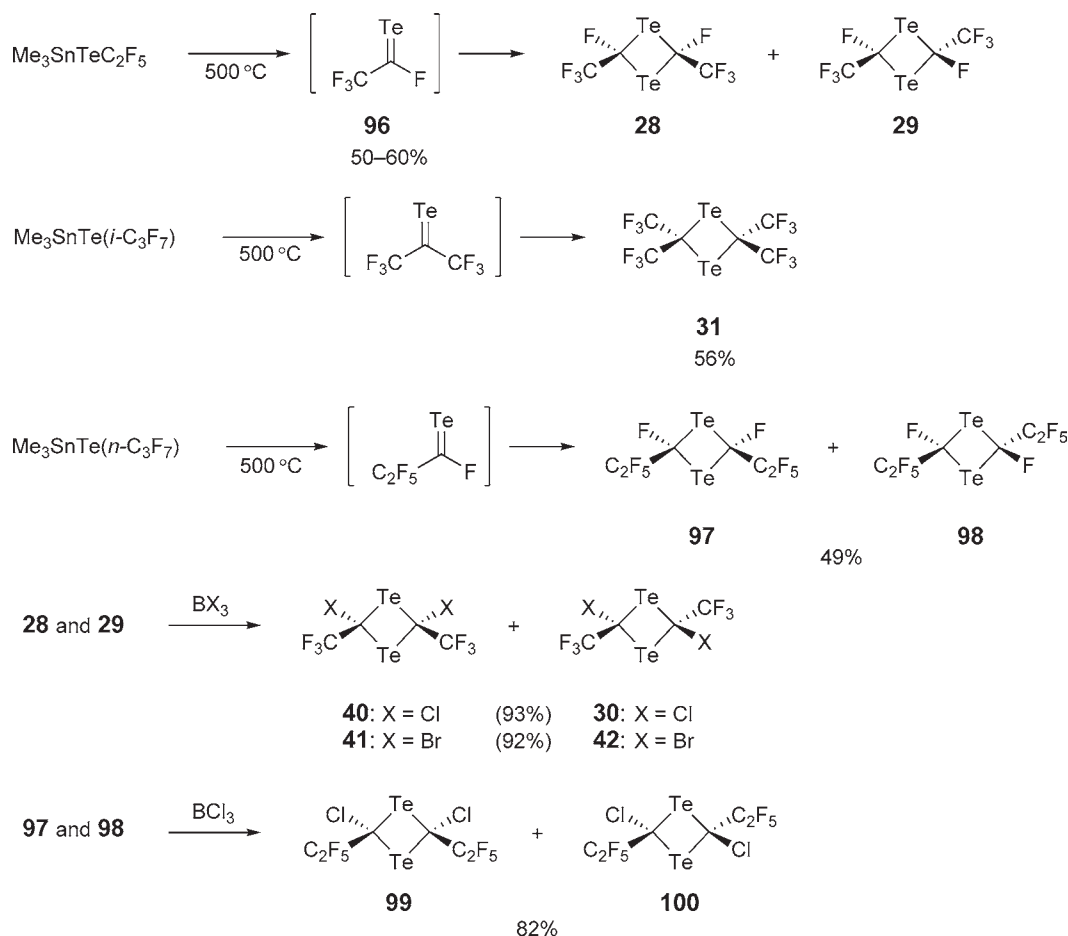


Scheme 27



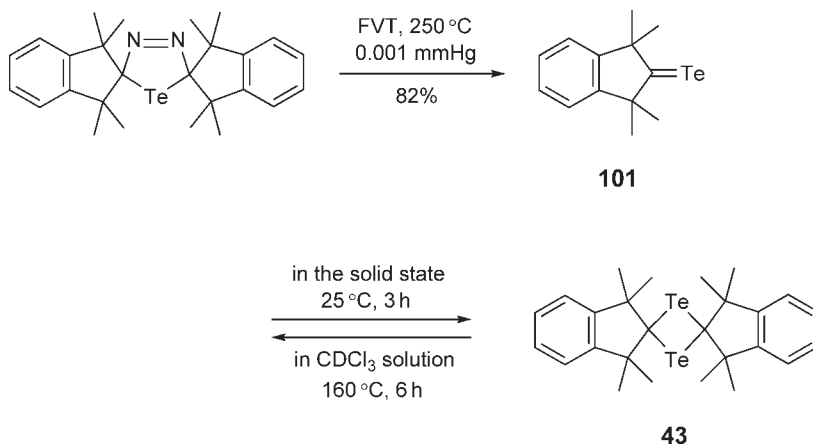
Scheme 28

When trimethylstannyl pentafluoroethyl telluride is allowed to flow through a heated Pyrex tube (500 °C) packed with glass-wool, trifluorotelluroacetyl fluoride **96** is generated in yields of 50–60% (Scheme 29) <1996JCD4463>. Compound **96** is only stable at –196 °C and dimerizes quantitatively a few degrees above this temperature to the corresponding *cis*- and *trans*-mixture of 1,3-ditellurethane **28** and **29**. Similarly, 1,3-ditellurethane derivatives **31**, **97**, and **98** are also obtained by pyrolysis of trimethylstannyl heptafluoroisopropyl telluride and trimethylstannyl *n*-heptafluoropropyl telluride via the corresponding tellurocarbonyl compounds <1997PS413, 2000JCD11>. Halogen-exchange reactions of 2,4-difluoro-1,3-ditellurethanes are also possible. The *cis*- and *trans*-mixture of 1,3-ditellurethane difluoride **28** and **29** reacts with BX₃ (X=Cl or Br) to give a mixture of the corresponding *cis*- and *trans*-dichloro and dibromo derivatives **40–42** and **30** in good yields. A mixture of **97** and **98** affords the chloro derivatives **99** and **100**.



Scheme 29

The green color of the crystalline tellone **101**, which is prepared by flash vacuum thermolysis (FVT) of the 1,3,4-telluradiazoline derivative, gradually fades away within hours at room temperature, and the orange crystalline 1,3-ditellurethane derivative **43** is formed quantitatively (Scheme 30) <1997TL2501>. 1,3-Ditellurethane **43** is stable toward oxygen, water, and light, and the yield of **101** isolated after FVT was estimated to be *c.* 40% on the basis of the yield of **43**. However, 1,3-ditellurethane **43** slowly decomposes in solution when contaminated by oxygen. Dissociation of **43** into **101** proceeds quantitatively in an absolutely deaerated CDCl_3 solution at 160°C in a sealed tube over 6 h.



Scheme 30

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Biographical Sketch



Dr. Toshio Shimizu was born in 1959 in Japan and obtained his PhD at Tokyo Metropolitan University at the Graduate School of Science. After his PhD studies he moved to the University of Tsukuba where he became research associate in 1988 and was promoted to assistant professor in 1990. He then moved back to the Tokyo Metropolitan University in 1993 and was promoted to associate professor in 2001 and full professor in 2006.

2.20

Four-membered Rings with Two Heteroatoms including Phosphorus to Bismuth

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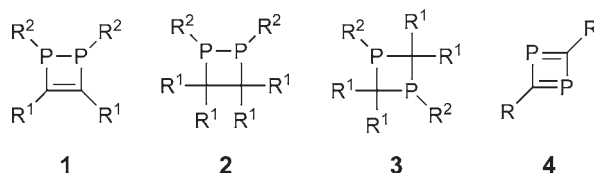
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2.20.1 Introduction

The first example of a four-membered heterocycle with two phosphorus atoms was reported in 1964 by Mahler [<1964JA2306>](#), who prepared a 1,2-dihydro- $1\lambda^3,2\lambda^3$ -diphosphete derivative **1**. The saturated $1\lambda^3,2\lambda^3$ - and $1\lambda^3,3\lambda^3$ -diphosphetane rings **2** and **3** followed when Becker started developing the chemistry of phosphalkenes, as the head-to-head and head-to-tail cyclodimerization, respectively, gave access to both rings [<1976ZFA242>](#). A transition metal-mediated [2+2] cyclodimerization of phosphalkynes leads to the formation of the fully unsaturated $1\lambda^3,3\lambda^3$ -diphosphetes **4**, which are only stable as π -ligands. Free diphosphetes are highly reactive, but may be used as interesting intermediates for the synthesis of organophosphorus cage compounds ([Scheme 1](#)).



Scheme 1

Corresponding phospharsa and diarsa four-membered rings have been synthesized but play a minor role. Related antimony and bismuth compounds are rare.

2.20.1.1 Reviews

The extraordinary synthetic potential of phosphalkynes as precursors of $1\lambda^3,3\lambda^3$ -diphosphetes and of polycyclic P-C cage compounds, which include $1\lambda^3,3\lambda^3$ -diphosphetanes as building blocks, is described in several reviews of Regitz *et al.* [<B-1995MI173, 1999MI199, 1997CB823>](#), Nixon [<1995CRV201, 1995CSR319>](#), and Weber [<1997AMC1, 1997CCR1>](#). Bertrand and Fluck reported on ylidic four π -electron four-membered λ^5 -phosphorus heterocycles [<1998AGE271, 1998PAC819>](#). A monograph by Dillon *et al.* was devoted to organophosphorus chemistry including transition metal complexes of phosphorus heterocycles. It touches the topic of this review at several points [<B-1998MI1>](#). A complete review on four-membered C_2P_2 heterocycles was published in 2001 by Hofmann and Zenneck in a monograph edited by Mathey [<B-2001MI167>](#). Workup to 1996 is surveyed in CHEC-II(1996) [<1996CHEC-II\(IB\)1157>](#).

2.20.2 Theoretical methods

Theoretical calculations utilizing *ab initio* and semi-empirical methods have been applied to all principal C_2P_2 ring structures and reveal details on their relative energy [<1996CB419, 2002CEJ5501, 2003JOM\(686\)257>](#). According to Gaussian calculations, $1\lambda^5,2\lambda^3$ -diphosphetes and 1,2-dihydro- $1\lambda^3,3\lambda^3$ -diphosphetes are higher in energy, but kinetically stabilized when compared to their isomer 1,2-dihydro- $1\lambda^3,2\lambda^3$ -diphosphete **1** [<1997JOM\(529\)177, 1999CEJ274>](#). Ring substituents play a significant role [<2000J\(P2\)2324, 2004CHE676, 2004RJC536>](#). 1,2- and 1,3-Dihydro- λ^3,λ^3 -diphosphetes with peripheral GeR_2 groups have been investigated [<1996OM3070>](#).

In a theoretical search for phosphavinyl cations, the reactivity of protonated P-alkynes toward P-alkynes has been investigated. Among others, monohydro- $1\lambda^3,3\lambda^3$ -diphosphetes have been identified as the potential primary products [<2004OM3701>](#). According to density functional theory (DFT) calculations, unsubstituted 1,2- C_2P_2 is destabilized

by 380 kJ mol⁻¹ with respect to the open-chain 1,4-diphosphabutadiyne isomer [<1999CEJ162>](#). MP2 calculations on conjugated free C₂H₂As₂ lead to a planar molecule, which is only stabilized by ca. 30 kJ mol⁻¹ with respect to two monomeric arsaacetylene molecules As≡CH. The respective diarsatetrahedrane represents the global energy minimum of C₂H₂As₂ [<1998JCD3119>](#).

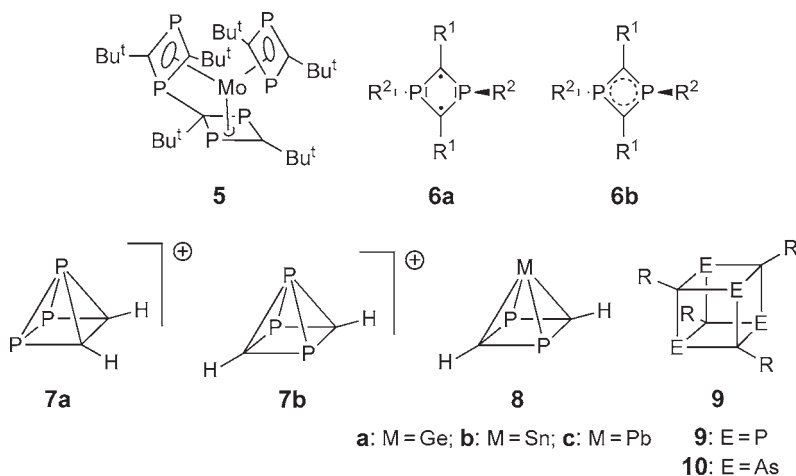
The principal structure of **1** is a trapezoid and that of 1,2-dihydro-1 λ^3 -3 λ^3 -diphosphete is a parallelogram with alternating P–C bond lengths [\[1996JPC6456\]](#). 1,2-Diphosphete is 44 kJ mol^{–1} more stable than the 1,3-isomer **4**. Protonation of hypothetical diphosphatetrahedrane (C₂H₂P₂) in the gas phase leads to trihydro-1,3-diphosphete cations [\[1998JPO678\]](#).

In contrast to the free rings, transition metal π -complexed $1\lambda^3,3\lambda^3$ -diphosphetes **4** have been prepared in many examples. In agreement with the harsh decomplexation reaction conditions, the metal atoms interact strongly with the planar π -ligand [<1996S265>](#). A novel type of amphiphilic reactivity for π -complexed 1,3-diphosphetes was identified and theoretically analyzed for tris($1\lambda^3,3\lambda^3$ -diphosphete)Mo complex **5**. Two unsaturated P-heterocycles, which are attached to the same metal center as π -ligands, are prone to form intramolecular bonds between a P-atom of one ring and a C-atom of the other [<2002AGE4047>](#).

According to *ab-initio* calculations, the electronic structure of 1,3-diphosphetane-2,4-diyl **6** with bulky P-substituents is very complex. A triplet state contributes significantly to the ground state, which might be represented by **6a**, but the P-lone pairs form a cyclic π -system with the two π -electrons of the C-R fragments. An extensive cyclic delocalized π^6 -system can thus be visualized in the alternative representation **6b** <1996PS(111)42, 1998AGE949, 2001PCA10731>. As the phosphorus atoms are not completely planar, the rings are not regarded as fully conjugated. Reduction of **6** leads to an intermediate ring anion radical which is stabilized by homolytic P-aryl substituent bond fission and formation of an aryl radical <2004AGE637>. Deprotonation of a ring carbon atom leads to a planar 1,3-diphosphetane-2,4-diyl-2-ylidenide anion <1999AGE3031, 2000EJI369>, whereas C-protonation results in a strongly puckered structure <2005AGE1405>.

Ring opening of 1,2-dihydro-1 λ^3 ,2 λ^3 - and -1 λ^3 ,3 λ^3 -diphosphetes have been studied by *ab initio* methods <1998EJ951>. Ring-strain energies of possible isomers of 1 λ^3 ,3 λ^3 -diphosphetanes **3** were calculated <1995JPO742>. If the 1,3-diphosphetane unit is fused to two additional three-membered rings, the ring-strain energy decreases with the total number of phosphorus atoms of the resulting tricyclic molecules <2005T2601>.

In agreement with experimental findings, DFT calculations on cationic $\text{C}_2\text{H}_2\text{P}_3^+$ and $\text{C}_n\text{H}_n\text{P}_{(5-n)}^+$ isomers point to square pyramidal ground-state structures. In the case of two P-atoms joining the square, $1\lambda^3, 2\lambda^3$ -diphosphetane substructures **7a** are thermodynamically favored over the alternative isomer **7b**. One of the P-atoms of **7** may be replaced by As- or Sb-atoms. An inversion of the pyramids has been investigated. The formal isoelectronic replacement of the apical P^+ -monocation by a group 14 metal atom results in analogous square pyramids. Theoretical investigations have been focused on the isomers **8a-c** for $\text{C}_2\text{H}_2\text{P}_2\text{M}$ ($\text{M} = \text{Ge}, \text{Sn}, \text{Pb}$) compounds (**Scheme 2**).

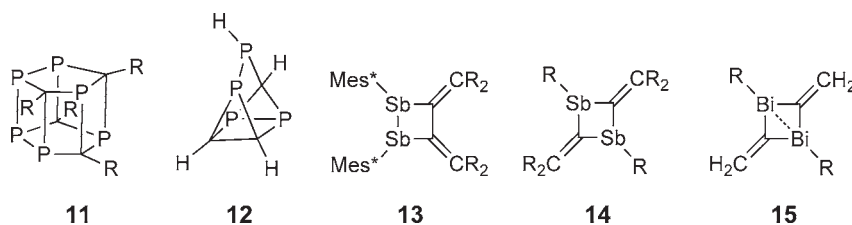


Scheme 2

The ring strain of monocyclic $C_2P_2R_n$ species can be compared to that of tetraphosphacubane **9** which is composed completely of $1\lambda^3,3\lambda^3$ -diphosphetane units. Structure **9** has been calculated to be less stable than its tetraphosphabarrelene isomer <1996JST(368)1>. Upon oxidation of the phosphorus atoms by oxygen or sulfur, the ring strain increases. The same is true for tetraarsacubane **10** <1998TL4211>. The acidity of **9** and its oxidation products have been calculated <1998JA3528>. In the gas phase, **9** is an unexpectedly strong base <1996JOC7813>. MP2 calculations give a hint on the possibility of encapsulating small cations like Li^+ and Be^{2+} <1996CJC901>. DFT calculations helped to identify the reasons for a specific reactivity of the central P–P bond of hexaphosphapentaprismane **11** <2001AGE3474>.

The relative energy of $HC\equiv P$ trimers and $C_4H_4P_2$ isomers have been determined by *ab initio* methods. A spirocyclic species for the trimer forms the energetic maximum, whereas the other structures with C_2P_2 ring moieties, di- and triphosphaprismane and di- and triphosphadewarbenzene, are stabilized by between 125 and 209 kJ mol^{-1} , depending on the number and position of the P-atoms. 1,2,3-Triphosphabenzene forms the most stable species <1999EJO3291, 1999JA4215>. Tetraphosphanorbornadiene is less stable than its tetraphosphaquadricyclane valence isomer **12** with its central $1\lambda^3,2\lambda^3$ -diphosphetane substructure <2001AGE4412>.

The relative energy of several yet to be formed C_2As_2 ring molecules have been calculated <1998JCD3119>. 1,2-Dihydro- $1\lambda^3,2\lambda^3$ -distibetes **13** are folded along the $Sb\cdots C$ diagonal according to PM3 calculations, whereas the 1,3-derivative **14** is planar <2005JOM(690)307>. Semi-empirical calculations on 1,3-dihydro- $1\lambda^3,3\lambda^3$ -dibismutete **15** lead to a puckered ring with very small energy differences for *cis*- and *trans*-isomers and significant $Bi\cdots Bi$ bonding interactions across the ring (Scheme 3) <1999ICA(284)167>.



Scheme 3

Mechanistic investigations of the cyclic addition of 2*H*-phosphole with phosphaketene at the MP2 level point out the preference of the formation of bicyclic P_2 -heterocycles with a C_2P_2 moiety over the formation of four-membered rings <1997JOM(529)15>. A density functional study on the dimerization of phosphaaalkynes in the coordination sphere of transition metals confirms the importance of head-to-head intermediates <1999EJI1281>. P-poor P–C cage compounds with C_2P_2 ring elements are principally accessible by cyclic addition reactions of phospholes; however, *exo*-dimers which block the cage formation are preferred <2003OM5526>.

Gaussian 94 allows the calculation of the ^{31}P -shift tensor of 1,2-dihydro-1,2-diphosphetes. <1999PCA1029>.

2.20.3 Experimental Structural Aspects

2.20.3.1 Structural Aspects

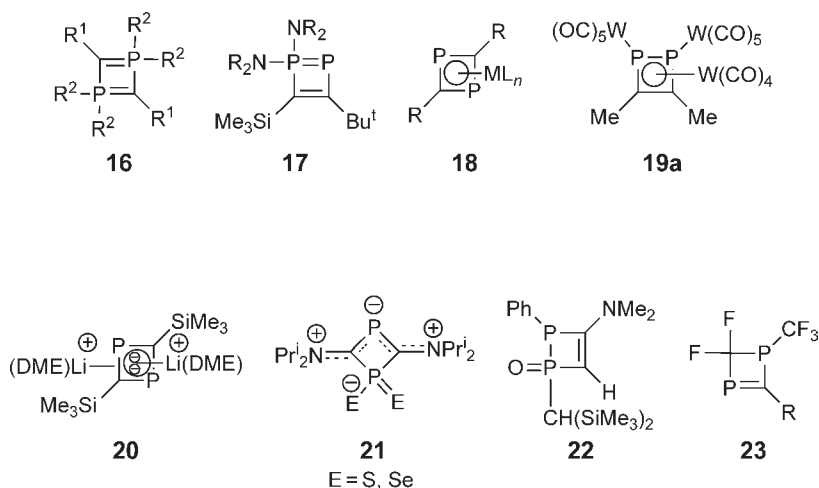
$1\lambda^5,3\lambda^5$ -Diphosphetes **16** are practically planar with intra-ring P–C bond distances in the range of 172–177 pm and P–C–P as well as C–P–C bond angles between 88° and 92° <1995CB959, 1996HAC341>. $1\lambda^5,2\lambda^3$ -diphosphetes **17** are also almost planar as well. The intra-ring distances are P–C 179–183 (λ^5) and 183–192 (λ^3), C–C 136–139, and P–P 217–230 pm, respectively. The parameters suggest a localized C=C bond and a strongly polarized P–P single bond. Oxidation or functionalization of the λ^3 -phosphorus atom causes a more pronounced asymmetry of the rings <1995JA10785, 1996AGE2228, 1997JA9720, 1999CEJ274>.

Structural information on $1\lambda^3,3\lambda^3$ -diphosphetes **4** is accessible exclusively for π -coordinated species **18**. This field has been reviewed extensively (see Section 2.20.1.1). With few exceptions, the coordinated rings generally form slightly distorted squares with identical P–C distances. Depending on the metals, the P–C bond lengths range from 174 to 186 pm, most of them close to 180 pm. Due to the different covalent radii of P- and C-atoms, the intra-ring bond angles are around 84° for C–P–C, and 96° for P–C–P angles. Only a few $1\lambda^3,2\lambda^3$ -diphosphete complexes have been reported to date by Binger (Ti), Jones (W), and Zenneck (Fe) <1995CB1261, 1999OM2021>. Trinuclear

tungsten complex **19a** represents one of the very few examples with methyl substituents on the ring carbons <2006JCD3733>. The great majority of structural information deals with *tert*-butyl groups. As for their 1,3-isomers, coordinated $1\lambda^3,2\lambda^3$ -diphosphete ligands are planar. The P–C bond lengths range from 180 to 182 pm, thus indicating a comparable bonding situation for 1,3- and 1,2-diphosphete ligands. A main group complex **20** of the formal $1\lambda^3,3\lambda^3$ -diphosphete dianion has been obtained with two (DME)Li⁺ units, being attached to the central ring in an inverse sandwich complex fashion (DME = 1,2-dimethoxyethane). As for its transition metal-coordinated neutral counterparts, the ring is planar and the intra-ring bond angles are close by <2004AGE637>.

The 1,2-dihydro- $1\lambda^5,3\lambda^3$ -diphosphete ring of **21** is almost coplanar with its NR₂ substituents, whereas the PE₂ (E = S, Se) plane is arranged perpendicular to them with P–C distances: 180–184 (λ^5) and 175–178 pm (λ^3) <2000T27>.

The P–C bond lengths of 1,2-dihydro- $1\lambda^5,2\lambda^3$ -diphosphete **22** are quite different (λ^5 -P–C = 175 pm; λ^3 -P–C = 185 pm) <1997JOC7605>. 1,2-Dihydro- $1\lambda^3,3\lambda^3$ -diphosphete **23** is almost planar with one pyramidal P-atom (Scheme 4) <1997JOM(529)177>. The principal structural features of 1,2-dihydro- $1\lambda^3,2\lambda^3$ -diphosphetes, which may be viewed as 1,2-diphospha[4]radialenes, have been evaluated previously. An actual example is given by *cis*- and *trans*-**24**. Both are puckered with a stronger effect for the *cis*-isomer <2000JA12507>. 1,3-Dihydro- $1\lambda^3,3\lambda^3$ -diphosphete **25** with exocyclic C=N bonds features a planar central ring with (*E*)-configuration of the P-substituents <1997OM378, 2000JOM(604)260>.



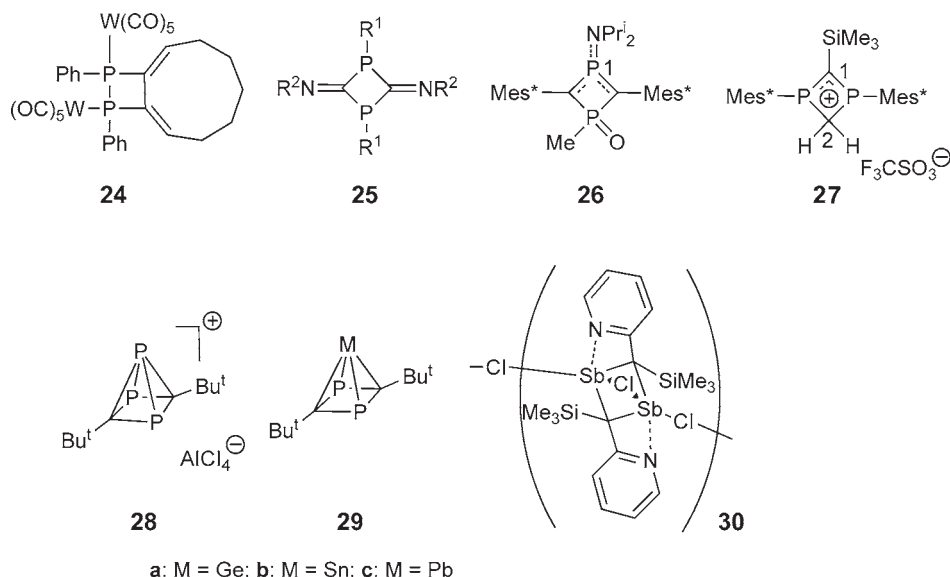
Scheme 4

A specific class of compounds is the puckered 1,3-diphosphetane-2,4-diyls **6** <1995AGE555>. One example allows the selective oxidation of one phosphorus atom to yield the almost planar **26**. Both the nitrogen and its adjacent P-1 atom are planar with P(1)–C intra-ring bond lengths of 183.7 and 182.2 pm <2004CEJ2700>. Protonation is achieved at a C-ring atom to form salt **27** with a planar ring cation. The P–C bond lengths for C-1 are 173.5 and 172.3 pm, respectively, and those for C-2 are 185.5 and 183.8 pm, which are typical P–C single bonds <2005AGE1405>.

Pyramidal cations *nido*-[3,5-*t*Bu₂-1,2,4-C₂P₃]⁺ with a basal $1\lambda^3,3\lambda^3$ -C₂R₂P₂ unit have been investigated as their AlCl₄[−] salt **28** <2003AGE2778>. The basal P–C bonds are almost equal (ca. 180 pm), whereas the P–C bonds to the apical P-atom are significantly longer (200 pm). The structural data for the C₂P₂ ring unit point to a close relation with $1\lambda^3,3\lambda^3$ -diphosphete transition metal complexes. Exchange of the apical P-atom of the pyramid by group 14 metal atoms leads to neutral compounds **29a–c**. The molecular structures of the Ge- and Pb-compounds **29a** and **29c** have been determined by X-ray diffraction <2003OM2891> and that of Sn-species **29b** by gas-phase neutron diffraction <2005JCD1972>. P–C–P and C–P–C angles as well as the P–C bond distances are in close proximity for all investigated derivatives of **28**, **29**, and the related complexes **18** and **20** of $1\lambda^3,3\lambda^3$ -diphosphetes. All share a slight deviation from planarity.

The principal structural features of C₂P₂ heterocycles like diphosphetanes **2**, **3**, and tetraphosphacubanes **9**, for example, have been reviewed and reported earlier.

A crystalline chloro-bridged 1,3-distibetane polymer **30** has been obtained and structurally characterized. The central C₂Sb₂ ring is almost square but buckled (Scheme 5) <1998CC575>.



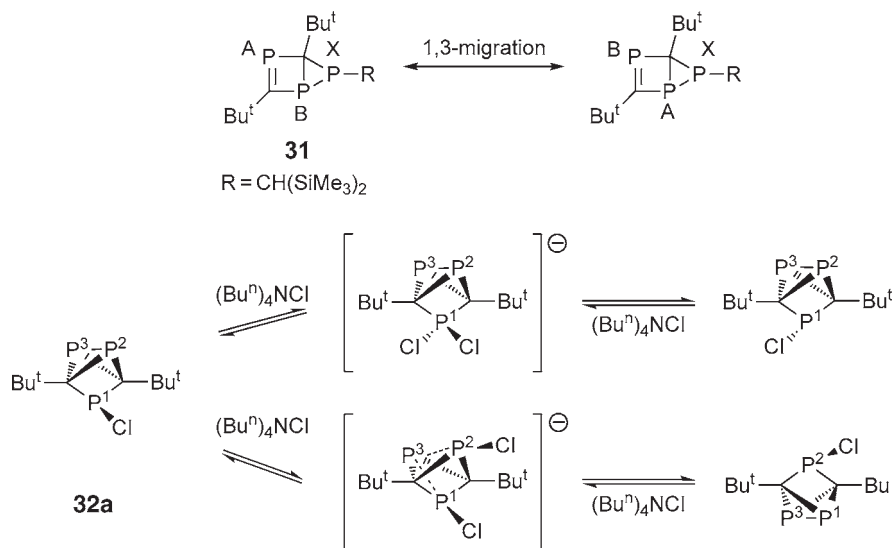
Scheme 5

2.20.3.2 Spectroscopic Aspects

^1H , ^{13}C , and ^{31}P nuclear magnetic resonance (NMR), and mass spectrometry play a dominant role in the characterization of C_2E_2 heterocycles, and carefully investigated spectroscopic parameters are included in the majority of the preparative papers dealing with this chemistry. The general trends can be extracted from earlier reviews <B-1998MI1>.

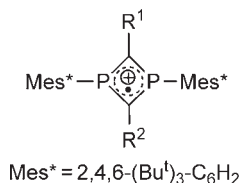
A remarkable effect was observed for salt **28**, as no ^{31}P NMR signals could be obtained between -100 and $+30^\circ\text{C}$. According to theoretical calculations of the ^{31}P NMR shift values and an inversion barrier, this effect is related to molecular dynamics <2003AGE2778>. Dynamic NMR spectroscopic evidence was established for a rapid 1,3-migrational exchange of the phosphorus atoms A and B within the four-membered ring of triphospha bicyclopentene **31** <1998CC1537>.

A nucleophilic chloride exchange reaction was observed by ^{31}P NMR spectroscopy between tetracyclic compound **32a** and $n\text{-Bu}_4\text{NCl}$ in tetrahydrofuran (THF- d_8). The temperature-dependent D NMR spectra were simulated and analyzed theoretically. Evidence was found for a multisided exchange process. One represents a classical $\text{S}_{\text{N}}2$ -type reaction of P^1 , where P^2 and P^3 exchange their identity. On the other side, the incoming chloride may attack P^2 instead and an addition–elimination (AE) mechanism can be proposed. $\text{P}^1\text{--P}^3$ form the two neighboring phosphorus atoms after the chloride exchange (Scheme 6) <2006AGE3628>.



Scheme 6

Stable organophosphorus π -radicals were observed for some derivatives of 1,3-diphosphetane-2,4-diyls **6**. A reversible electrochemical or chemical oxidation of **6c–e** leads to electron paramagnetic resonance (EPR)-active radicals, whose spectroscopic parameters were elucidated (Figure 1) <1996TH1, 1998TH1>.



		$E^{1/2}_{ox_1}(V)$	$a(^{31}P)(G)$	$a(^{35}Cl)(G)$	$a(^{37}Cl)(G)$	$a(^{29}Si)(G)$
6c	$R^1 = R^2 = Cl$	+0.43	30.70	2.56	2.13	
6d	$R^1 = Cl; R^2 = SiMe_3$	+0.41	30.86	2.70	2.25	7.04
6e	$R^1 = R^2 = SiMe_3$	+0.49	22.90			6.98

Figure 1 Selected electrochemical data of 1,3-diphosphetane-2,4-diyls and the related EPR hyperfine parameters of the corresponding cation radicals <1996MI1, 1998MI1>.

The oxidation of a suitable lithium salt precursor leads to isolable and structurally characterized 1-hydro-1,3-diphosphete radical **33**. The EPR ^{31}P and ^{13}C hyperfine parameters were experimentally determined, simulated, and assigned with the help of theoretical calculations (Figure 2) <2006AGE4341>.

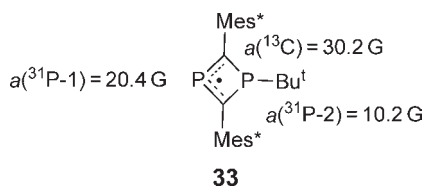
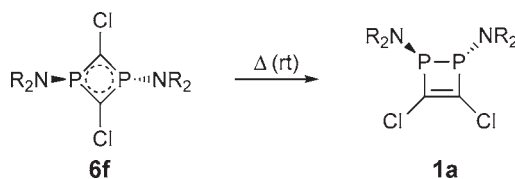


Figure 2 EPR hyperfine parameters of stable neutral radical **33** <2006AG(E)4341>.

Due to its close relation with the electronic structure of the compounds, photoemission spectroscopy (PES) has been applied in some cases of interest and combined with theoretical investigations. This accounts for 1,2-dihydro-1 λ^3 ,2 λ^3 -diphosphetes **1** <1997OM4551> and *nido*-clusters **29a** and **29b** <2003OM2897>, for example.

2.20.4 Thermodynamic Aspects

Thermodynamic properties of C₂E₂ heterocycles have been investigated mainly by theoretical methods and cited there. 1,2-Dihydro-1 λ^3 ,2 λ^3 -diphosphetes are thermodynamically favored over other C₂P₂R₄ derivatives. Therefore 1,3-diphosphetane-2,4-diyl **6**, as well as 1,2-dihydro-1 λ^3 ,3 λ^3 -diphosphete **23**, both rearrange quantitatively to form the corresponding 1,2-dihydro-1 λ^3 ,2 λ^3 -diphosphetes **1** <1997JOM(529)177, 1998AGE949>. 1,2-Dihydro-1 λ^3 ,2 λ^3 -diphosphetes **1** strongly favor the *trans*-configuration. This situation changes and may be reversed, if one or two transition metal fragments, such as W(CO)₅, are linked to the phosphorus atom(s) of the ring molecules <1997OM2506, 1997OM4501>. A spontaneous rearrangement reaction to form 1,2-dihydro-1 λ^3 ,2 λ^3 -diphosphete **1a** takes place upon contact with solvents or even in the solid state if **6f** is allowed to warm up to room temperature (Scheme 7) <1998AGE949>.



Scheme 7

2.20.5 Reactivity of Fully Conjugated Rings

2.20.5.1 Electrophilic Attack at Ring Heteroatoms

The λ^3 -phosphorus atom of $1\lambda^5,2\lambda^3$ -diphosphetes **17** add one or two electrophiles of different kinds, including organometallic species and organyl cations <1997JA9720, 1999CEJ274>.

2.20.5.2 Oxidation of Ring Heteroatoms

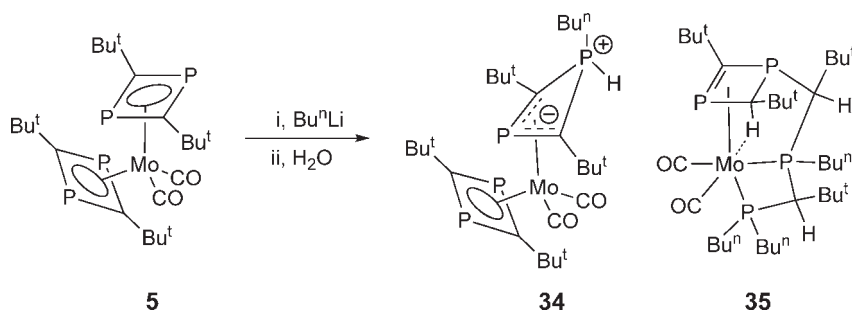
Oxidation of $1\lambda^5,2\lambda^3$ -diphosphetes **17** or its derivatives by chalcogenides or organic oxidants occurs at the λ^3 -phosphorus atom exclusively <1996AGE2228, 1997JA9720>.

2.20.5.3 σ -Complexation of Transition Metals by Ring Heteroatoms

λ^3 -Phosphorus atoms as parts of heterocycles may function as σ -donor ligands of transition metals in many examples. The reviews cited above give an overview. Such metal–ligand units may remain intact over several reaction steps, including open-chain starting materials and products <1997AXC42, 1998CC1537>. π -Coordinated $1\lambda^3,3\lambda^3$ - or $1\lambda^3,2\lambda^3$ -diphosphetes still exhibit ligand properties through the lone pairs of the phosphorus atoms. One or two transition metals may be σ -bonded this way <1999OM2021, 2004ZFA1220, 2006JCD3733>.

2.20.5.4 Reactions with Reducing Agents

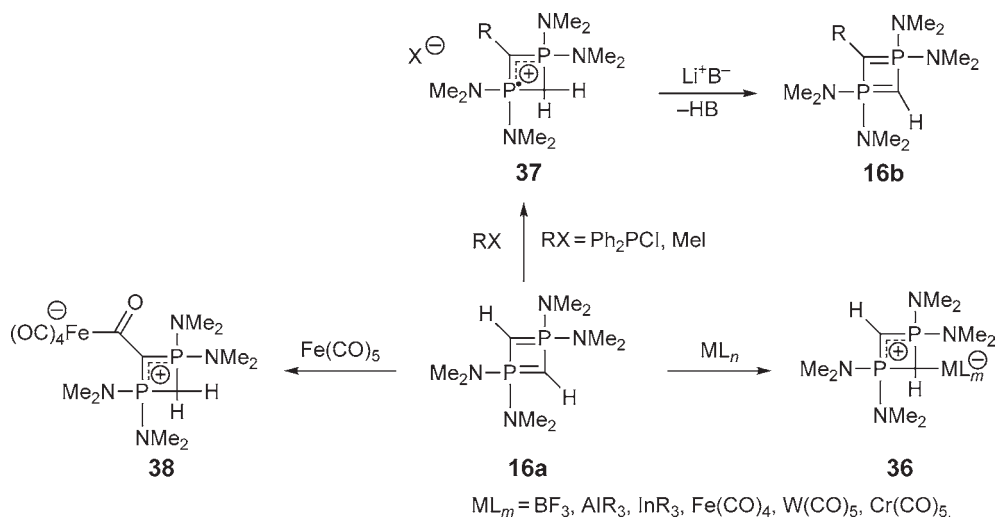
No reports about simple reduction reactions of C_2E_2 heterocycles have appeared in the literature since 1996. In the case of organometallic reductants, the nucleophilicity of the carbanions dominate the course of the reactions. Nucleophilic attack of *n*-BuLi takes place at the phosphorus atom of (2,4-di-*t*-butyl- $1\lambda^3,3\lambda^3$ -diphosphete)₂Mo(CO)₂. Protonation at the same position furnishes a phosphonium-bridged phosphaaallyl ligand of **34**. Using a higher concentration of *n*-BuLi, three carbanions and protons may be added to yield the topologically novel P₄-ligand of complex **35**. The twofold tethered side chain of the 1,2-dihydro- $1\lambda^3,3\lambda^3$ -diphosphete ligand of **35** is a product of the second heterocyclic ligand of the starting material, whose π -system is completely eliminated (Scheme 8) <2002AGE4047>. A comparable nucleophilic attack on a P-atom was also assumed for the addition of water or methanol on a P-atom of Cp'(2,4-di-*t*-butyl- $1\lambda^3,3\lambda^3$ -diphosphete)Mo(CO)Cl (Cp' = C₅H₅, C₅Me₅) <1999CC2147>.



Scheme 8

2.20.5.5 Electrophilic Attack at Ring Carbon Atoms

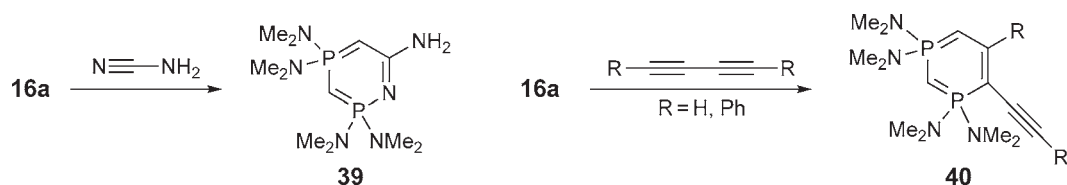
Electrophiles like RX, AlR₃, InR₃, Cr(CO)₅, W(CO)₅, and Fe(CO)₄ add to one of the ring carbon atoms of $1\lambda^5,3\lambda^5$ -diphosphete **16a** and inner salts **36** or addition product **37** are formed <1996HAC341, 1996PS(115)3, 1996ZFA942, 1997ZFA919, 1999ZFA919>. Product **37** may be deprotonated by Li-organyls to receive C-substitution products **16b**. Fe(CO)₅ adds to a carbon atom of **16a** as well and forms inner salt **38**. A successive valence isomerization of the products, however, results in the formation of a dihydrophosphete. The second phosphorus atom moves to an exocyclic position (Scheme 9) <1996PS(115)3, 1996ZFA974>.



Scheme 9

2.20.5.6 Cyclic Addition Reactions

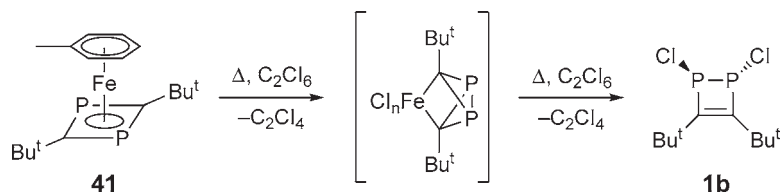
Cyclic addition reactions of **16a** with diynes or cyanamide are interpreted as being initiated by an electrophilic attack of the cyanamide or the terminal carbon atom of a $\text{C}\equiv\text{C}$ bond. Both result in ring expansion and the formation of 2,4- λ^5, λ^5 -diphosphapyridine **39** <1998ZNB443> or 1,3- λ^5, λ^5 -diphosphabenzene **40**, respectively (Scheme 10). The diyne reaction is not limited to conjugated systems. 1,5-Hexadiyne and 1,7-octadiyne can be used as well <1997JOM(529)223>.



Scheme 10

2.20.5.7 Other Reactions

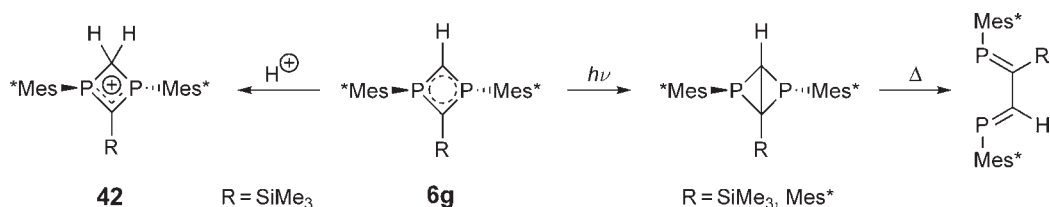
Decomplexation of the $1\lambda^3, 3\lambda^3$ -diphosphete π -ligand of iron complex **41** by C_2Cl_6 results in a 1,3 $\rightarrow$ 1,2-isomerization, most probably via a tetracyclic intermediate and the formation of the *P,P*-dichloro-1,2-dihydro-1 $\lambda^3, 2\lambda^3$ -diphosphete derivative **1b** (Scheme 11) <1996S265>.



Scheme 11

2.20.6 Reactivity of Nonconjugated Rings

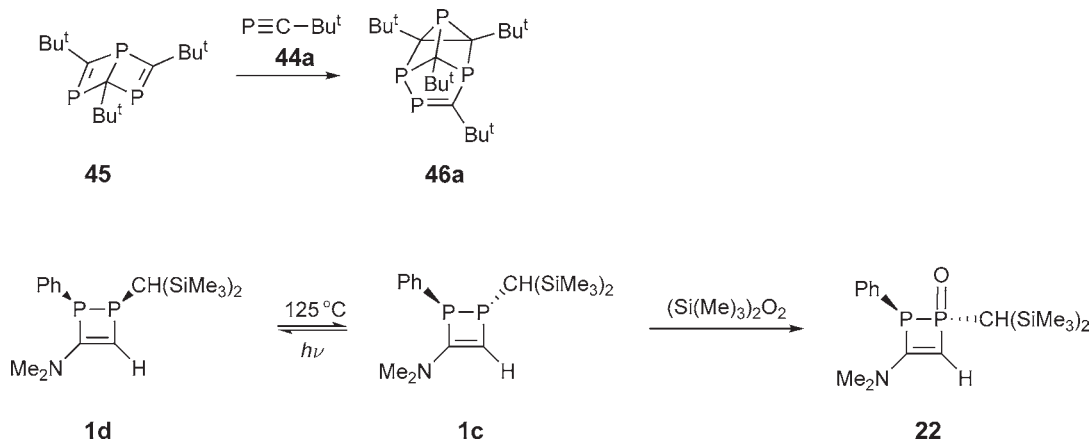
1,3-diphosphetane-2,4-diyls **6** exhibit a unique reactivity. Thermolysis leads to the corresponding 1,2-dihydro-1 λ^3 ,2 λ^3 -diphosphetes **1**. A phosphanylcarbene is believed to be the decisive intermediate <1998AGE949>. An alternative valence isomerization process utilizes a photochemical ring closure of a derivative **6g** to yield a diphosphabicyclobutane and its thermal ring-opening product *gauche*-1,4-diphosphabutadiene <1999AGE3028>. SiMe₃ derivative **6g** may be protonated by HOSO₂CF₃ to obtain **42** (Scheme 12) <2005AGE1405>.



Scheme 12

P-Imino-substituted 1,2-dihydro-1 λ^5 ,2 λ^5 -diphosphetes lose an iminophosphane unit upon heating and rearrange quantitatively to form a 1,2-dihydro-2-aza- λ^3 -phosphete derivative <1996RJO407>. Reduction of 1 λ^3 ,3 λ^3 -diphosphetane-2,4-dion **43** with LiAlH₄ leads only to ring-opened products <1999ZFA919>.

Dienophiles like phosphalkyne **44a** or activated alkynes and triphosphadewarbenzene **45** undergo a [2+2+2] homo-Diels–Alder reaction that leads to C₃P₄ cage **46**. Cyclic dienophiles yield pentacycles (Scheme 13) <1997JOM(529)215, 1999S1363>.

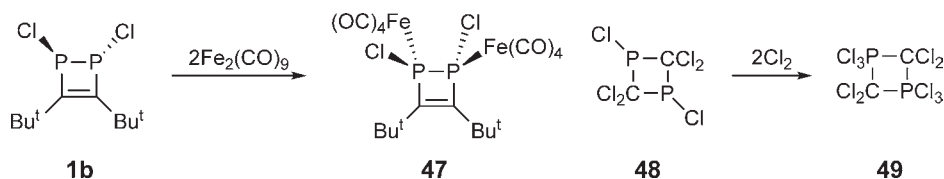


Scheme 13

The P–P bond of a specific 1,2-dihydro-1 λ^3 ,2 λ^3 -diphosphete derivative may be opened selectively by controlled hydrolysis and a phosphalkene is formed <1997JOC7605>.

Oxidation of a λ^3 -phosphorus atom of stable P-heterocycles is a general reaction, which leaves the basic ring structures intact in many cases. This includes the conversion of 1,2-dihydro-1 λ^3 ,2 λ^3 -diphosphete derivatives like **1c**, for example, to form 1,2-dihydro-1 λ^5 ,2 λ^3 -diphosphete **22**. Oxidation agents used are elemental selenium or [(CH₃)₃Si]₂O₂ <1997CB1519>. Upon photolysis **1c** rearranges partly into its *cis*-isomer **1d**. The mixture of isomers can be reconverted completely into the *trans*-isomer **1c** by heating <1997JOC7605>.

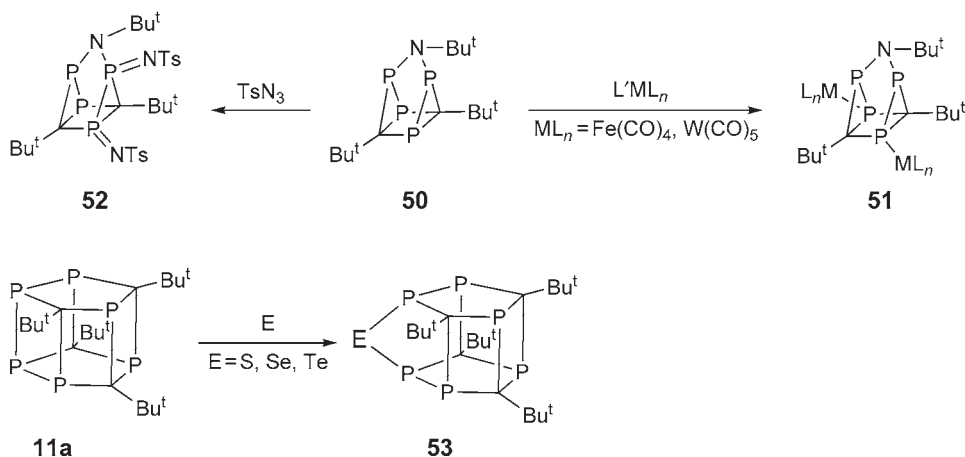
1,2-Dichloro-1 λ^3 ,2 λ^3 -diphosphete **1b** adds one or two Fe(CO)₄ or other transition metal carbonyl fragments under mild conditions <1997JOC7605>. Diiron complex **47** allowed the first targeted preparation of a 1,2-diphosphete derivative (see Section 2.20.10) <1999OM2021>. Oxidation of compound **48** with Cl₂ leads to perchloro-1 λ^5 ,3 λ^5 -diphosphetane **49** (Scheme 14) <2002RJC151>.



Scheme 14

One or two phosphorus atoms of tetraphosphacubane **9** can be reacted with suitable electrophiles. Those may be transition metal fragments <1996PS(113)15> or cationic organic groups <1999PS281>. The same counts for aza-tetraphosphatetradicyclane **50**, which yields a complex family **51** or Staudinger reaction products like **52**, for example <2001ZNB951>.

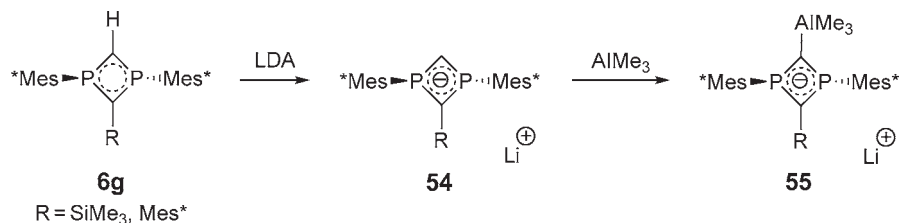
Hexaphosphapentaprismane **11a** exhibits a specific reactivity at the central P–P bond. Chalcogene atoms insert into the bond to form cages **53** (Scheme 15) <2001AGE3474>.



Scheme 15

2.20.7 Reactivity of Substituents Attached to Ring Carbon Atoms

1,3-Diphosphetane-2,4-diyls with a ring carbon hydrogen substituent are acidic; thus **6g** may be deprotonated by lithium diisopropylamide (LDA) to yield the diphosphacarbene lithium salt **54**. Addition of AlMe_3 to salt **54** results in the formation of a stable alane adduct **55** (Scheme 16) <1999AGE3031, 2005AGE1405>.

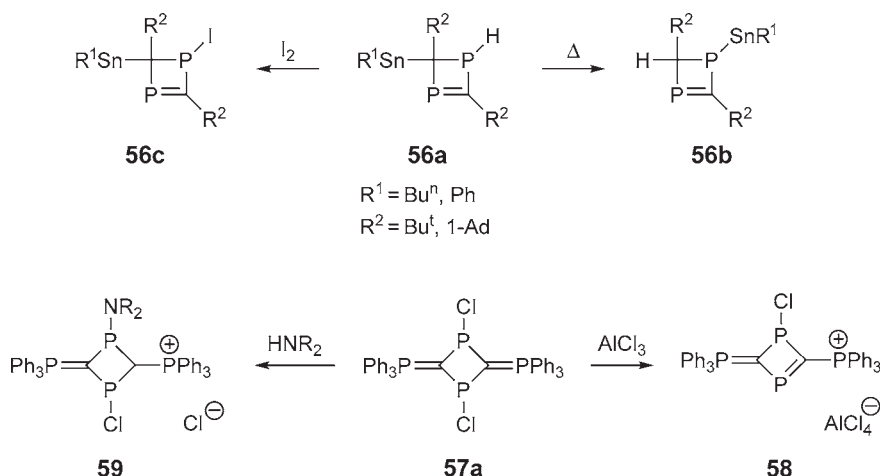


Scheme 16

2.20.8 Reactivity of Substituents Attached to Ring Heteroatoms

Quantitative ring substituent exchange between the neighboring phosphorus and carbon atoms of 1,2-dihydro-2-stannyl- $1\lambda^3,3\lambda^3$ -diphosphete **56a** to form **56b** is achieved by heating at 90°C for 6 h. I_2 reacts with **56a** at room temperature by substitution of a hydrogen atom to yield **56c** <1998EJI227>.

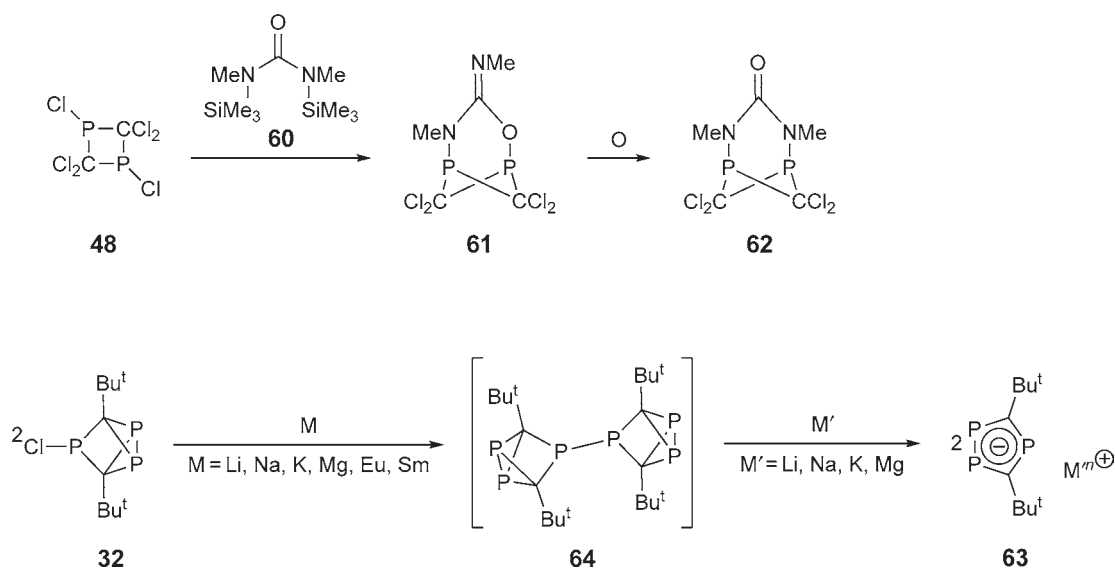
One or both chloro substituents of 2,4-diphosphoranediy-1 λ^3 ,3 λ^3 -diphosphetane **57a** may be removed as chloride anions by AlCl_3 or other chloride scavengers. The resulting electronic deficiency of one phosphorus atom causes an electronic rearrangement, which imports the exocyclic double bond into the ring and 1,2-dihydro-1 λ^3 ,3 λ^3 -diphosphete salts like **58** are formed. Salt **58** gives access to several derivatives. Derivative **57a** combines the potential of nucleophilic substitution reaction at the PCl units with the basicity of the ylide moieties. Protic nucleophiles like secondary or primary amines may thus substitute one or both chlorides to form **59**, for example (Scheme 17) <1997CB1519>.



Scheme 17

Perchloro-1 λ^3 ,3 λ^3 -diphosphetane **48** reacts with urea derivative **60** to form tricyclic species **61**, which can be rearranged to the symmetric isomer **62** <2002ZFA1903>.

The tetracyclic P_3 -species **32** can be dechlorinated by several metals to form 1,2,4-triphospholide salts **63**. The process occurs stepwise and a P-P coupled intermediate **64** was observed by NMR spectroscopy (Scheme 18) <2005OM5789>.

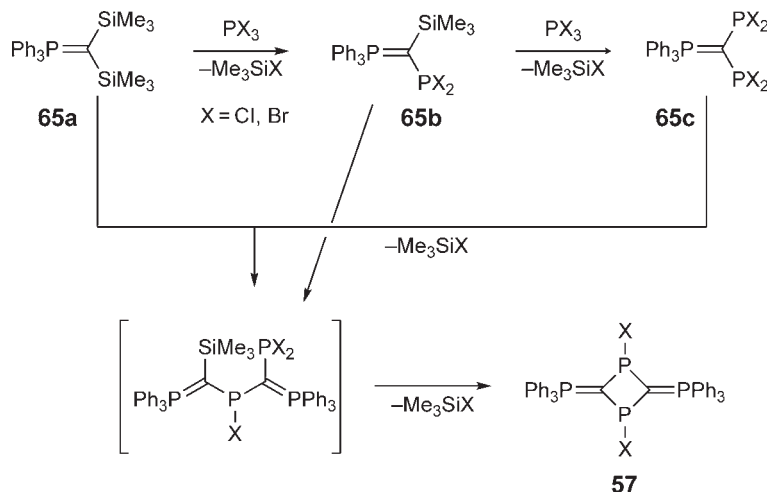


Scheme 18

2.20.9 Ring Syntheses from Acyclic Compounds

2.20.9.1 Ring Syntheses by Formation of One E–C or E–E Bond

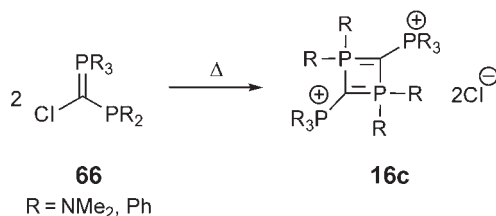
Bis(trimethylsilyl)ylide **65a** reacts with phosphorus trichloride or tribromide to give dihalophosphino(trimethylsilyl)ylide **65b**. In a two-step self-condensation, 2 equiv of trimethylsilyl (TMS) halogenide are eliminated and *P,P*-dihalogeno-2,4-diphosporandiyl-1 λ^3 ,3 λ^3 -diphosphetanes **57** are formed (Scheme 19) <1997CB1519>.



Scheme 19

2.20.9.2 Ring Syntheses by Formation of Two C–E Bonds

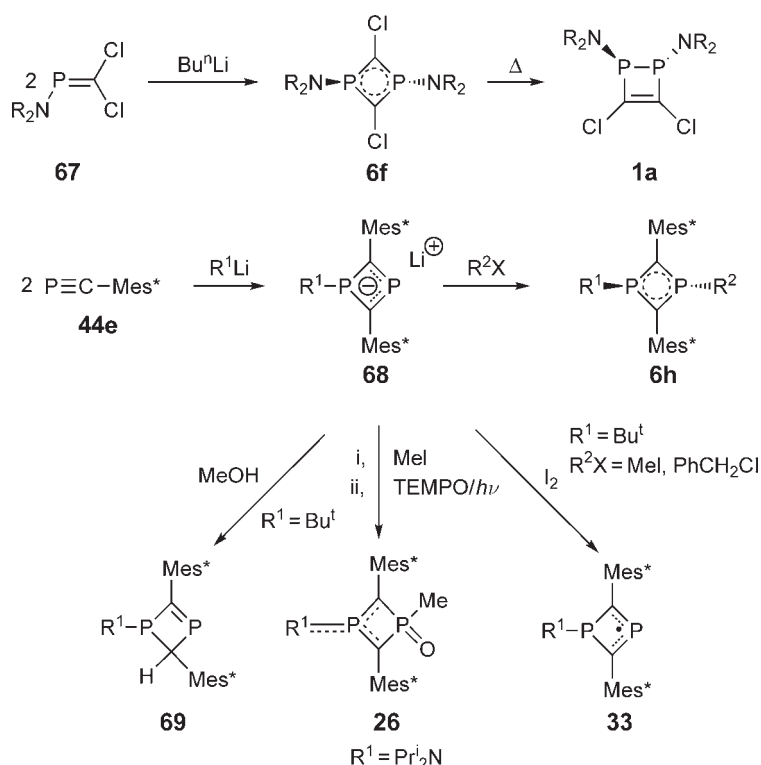
In a 1,3-cyclosubstitution reaction of λ^5 -phosphaalkenes **66**, the lone pairs of the λ^3 -P-atoms attack the carbon atoms of the other molecule and chloride is eliminated to form 1 λ^5 ,3 λ^5 -diphosphetes **16c** (Scheme 20).



Scheme 20

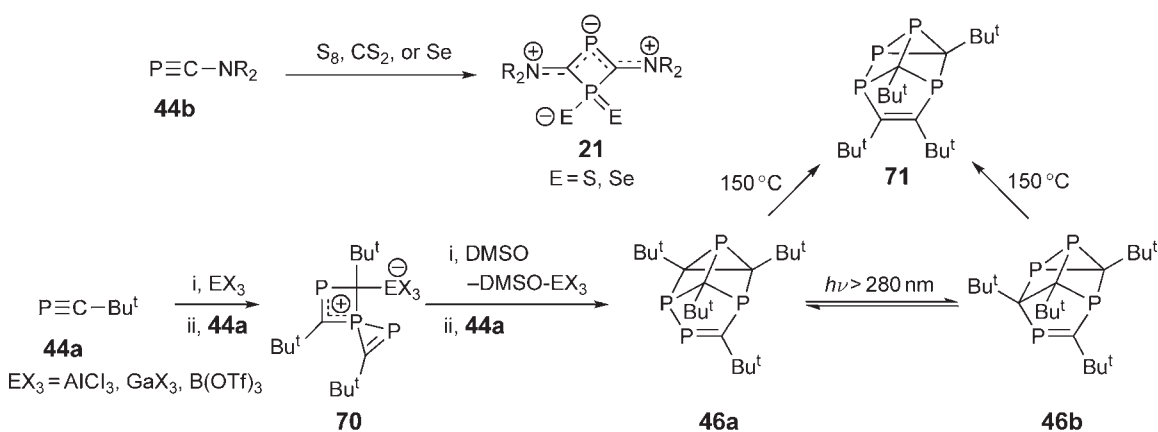
Dehalogenation of dichloro-*P*-diorganylamino phosphaalkenes **67** at low temperature leads to 1,3-diphosphetane-2,4-diyls **6f**. A spontaneous rearrangement reaction to form 1,2-dihydro-1 λ^3 ,2 λ^3 -diphosphetes **1a** takes place by contact with solvents or even in the solid state if **6f** is allowed to warm up to room temperature <1998AGE949>. However, if **67** is dehalogenated by a group 4 metallocene, **1a** is formed directly <1997OM4551>. Supermesitylphosphaalkyne **44e** may be reduced by R¹Li to furnish Li-salts **68**. Subsequent reactions with organic halides yield 1,3-diphosphetane-2,4-diyls **6h** <2003AGE3802, 2005JOM(690)2515>, oxidation by I₂ leads to stable radical **33** <2006AGE4341>, protonation by methanol gives 1,2-dihydro-1 λ^3 ,3 λ^3 -diphosphete **69** <2002CC1744>, and methylation with a subsequent photooxidation by a suitable *N*-oxide leads to 1,3-diphosphetane-2,4-diyl **26** with one λ^5 -phosphorus atom (Scheme 21) <2004CEJ2700>.

If the P-TMS derivative of **68** is reacted with M(CO)₆ (M = Cr, W), a C=O unit inserts and forms five-membered diphospha heterocycles <1999PS41, 2002CEJ2188, 2002PS1605>. A partial oxidation of amino-substituted phosphaalkyne **44b** by sulfur or selenium leads to the quantitative formation of 1,2-dihydro-1 λ^5 ,3 λ^3 -diphosphetes **21** <2000T27>.



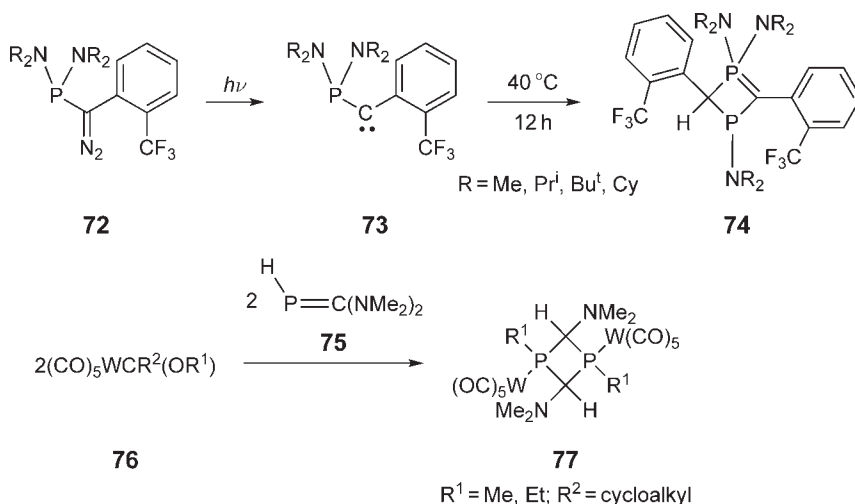
Scheme 21

The reaction of electrophiles $\text{E} = \text{AlX}_3$, $\text{B}(\text{OTf})_3$, and GaX_3 with two *tert*-butyl phosphalkyne molecules **44a** leads almost quantitatively to the spirocyclic inner salts **70**. Bases like dimethyl sulfoxide (DMSO) remove the electrophiles and activate **70** to form the tetracyclic isomers **46a** and **46b** which exist as a 1:1 mixture in equilibrium upon irradiation of one or the other. Heating each of the valence isomers at 150°C gives access to a third isomer **71**. All three contain $1\lambda^3,3\lambda^3$ -diphosphetane ring elements (Scheme 22) <1996CB489, 1997AGE1337>. Photochemical activation of **46b** causes additional rearrangement processes, which give access to more polycyclic tetramers of **44a** <2001HAC406>.



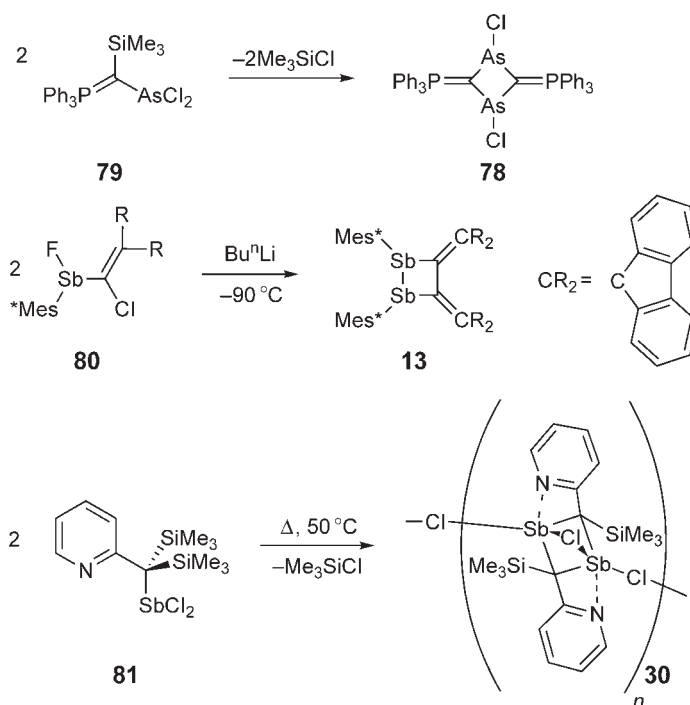
Scheme 22

Photolysis of diazophosphane **72** leads to isolable phosphinocarbene **73**. Mild thermolysis of **73** furnishes 1,2-dihydro- $1\lambda^3,3\lambda^3$ -diphosphate **74** <2003JA124>. The cyclization of P-alkene **75** can be initiated by $\text{W}(\text{CO})_5$ -carbene complexes **76** to yield tungsten-complexed $1\lambda^3,3\lambda^3$ -diphosphetanes **77** (Scheme 23) <2003OM5063>.



Scheme 23

Me_3SiCl abstraction provides the driving force for the formation of 1,3-dihydro-1 λ^3 ,3 λ^3 -diarsete **78** from arsa-substituted λ^5 -phosphaalkene **79** <2000CEJ3531>. Double dehalogenation of vinylstibane **80** gives access to 1,2-dihydro-1 λ^3 ,2 λ^3 -distibete **13** <2005JOM(690)307>. Mild thermolysis of (2-pyridyl)(SiMe_3) $_2\text{CSbCl}_2$ **81** affords the chloro-bridged polymeric 1 λ^3 ,3 λ^3 -distibetane compound **30** (Scheme 24) <1998CC575>.

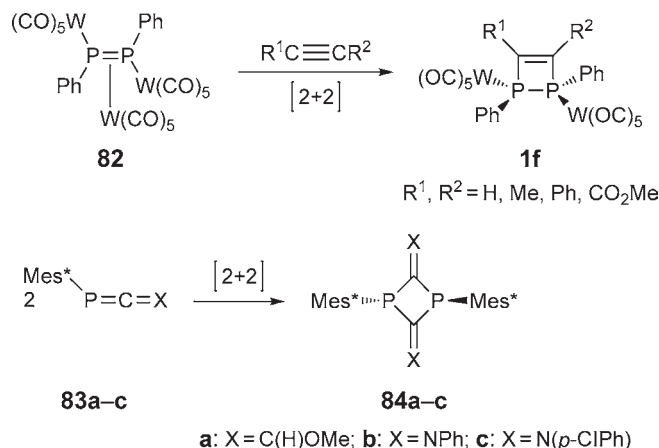


Scheme 24

2.20.9.3 Ring Formation by Organic Cyclic Addition Reactions

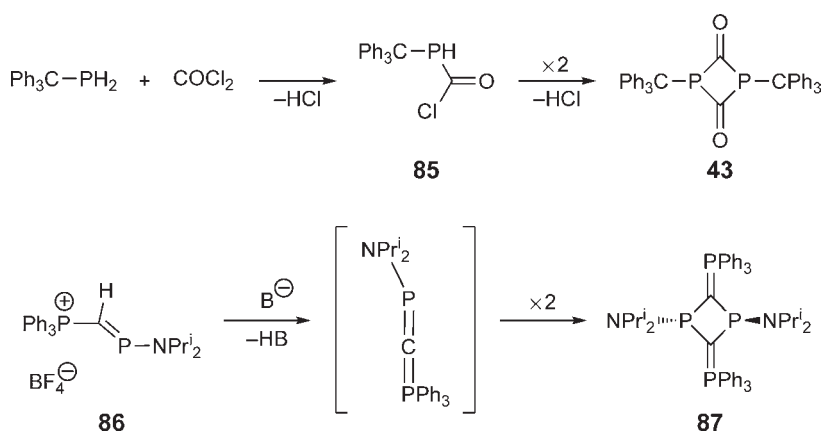
Dehalogenation of P-fluorinated λ^5 -phosphaalkenes and cyclodimerization of the resulting intermediates is a useful route for the preparation of 1 λ^5 ,3 λ^5 -diphosphetes **16** <1998ZFA1116>. Cycloaddition reactions of unsaturated organophosphorus compounds and their heavy atom analogues are the most frequently used preparative route to

4-ring heterocycles containing two pnictogene atoms. 1,2-Dihydro-1 λ^3 ,3 λ^3 -diphosphetes **1** should be principally accessible by direct [2+2] cycloaddition of diphosphenes $\text{RP}=\text{PR}$ and alkynes RCCR . Due to their high reactivity, the diphosphenes must be stabilized by bulky substituents or suitable transition metal complexation. The latter approach was successful for tris- $\text{W}(\text{CO})_5$ complex **82** which adds alkynes at elevated temperatures to form the target ring molecules **1f** <1997OM2506>. Supermesityl substituted 1-phosphaallene **83a** requires heating without solvent at 120 °C to form 1,3-dihydro-1 λ^3 ,3 λ^3 -diphosphete **84a** by [2+2] cycloaddition <2003EJO4838>. A head-to-tail [2+2] cycloaddition of two phosphazaallenes **83b** leads to 1,3-dihydro-2,4-diimido-1 λ^3 ,3 λ^3 -diphosphete **84b**. The same starting material **83b** yields the related azaphosphaheterocycle in the presence of a $\text{Pd}(0)$ catalyst <1997OM378>. The *N*-phenyl substituent may be replaced by a 4-chlorophenyl group (Scheme 25) <2000JOM(604)260>.



Scheme 25

In a very basic approach to C_2P_2 ring synthesis, Schmutzler and co-workers reacted triphenylmethylphosphine with phosgene to obtain 1,3-dihydro-1 λ^3 ,3 λ^3 -diphosphetane-2,4-dione **43** in good yield simply by leaving the components at room temperature for 18 h without stirring. Intermediate triphenylmethyl(chloroformyl)phosphine **85** can be isolated after a short reaction time <1999ZFA1979>. Phosphaalkene phosphonium salt **86** can be deprotonated by lithium hexamethyldisilazide to yield a short-lived diphosphaallene which dimerizes spontaneously to form 1,3-dihydro-1,3-diphosphete **87** (Scheme 26) <2005EJI2619>.

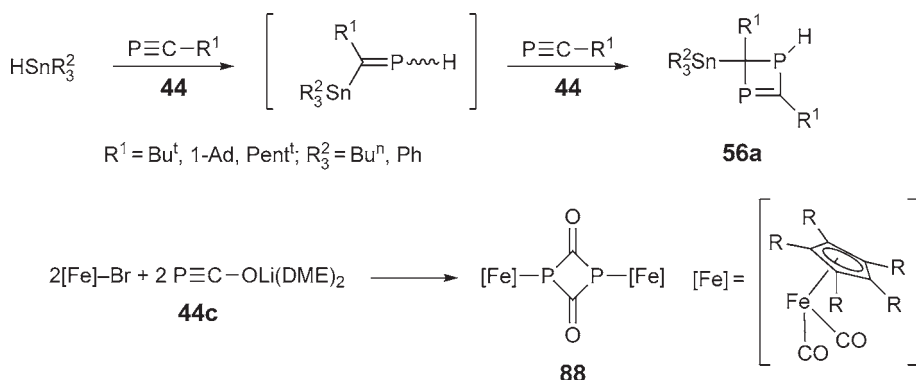


Scheme 26

Hydrostannylation of a *P*-chloro phosphalkene and subsequent R_3SnCl elimination is a low-yield route to specific 1 λ^3 ,3 λ^3 -diphosphetanes <1998HAC453>. Hydrostannylation of the *P*-alkynes **44** generates the related stannylphosphaalkenes which react with the starting phosphalkynes in a [2+2] cycloaddition to form

2-stannyl-1,2-dihydro-1 λ^3 ,3 λ^3 -diphosphete derivatives **56a**. A side reaction leads to a pentacyclic SnC_4P_4 cage compound with 1 λ^3 ,3 λ^3 -diphosphetane units, which is formally derived from tetraphosphacubane **9** where an SnR_2 group has inserted into a P–C bond <1998EJI227>.

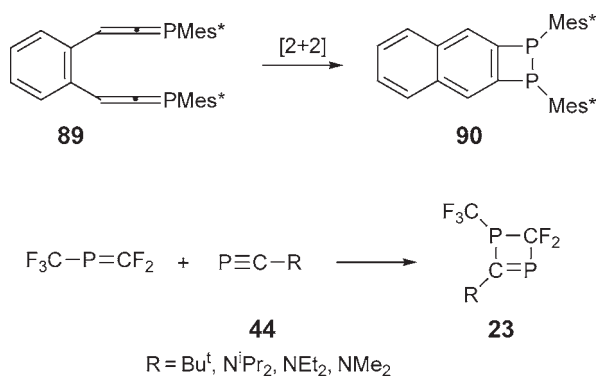
The preparative potential of phosphalkenes, including *in-situ*-prepared species, was explored soon after the first access to this class of compounds and an early review by Appel *et al.* in the early 1980s outlines the most important facts. The preferred route of cyclodimerization is head-to-tail, which yields 1 λ^3 ,3 λ^3 -diphosphetanes. This includes fluorinated species $\text{RP}=\text{CF}_2$ (R = alkyl, aryl, CF_3) <1996AXC1919>. Lithoxyphosphaalkyne $(\text{DME})_2\text{LiOC}\equiv\text{P}$ **44c** reacts smoothly with $\text{Cp}^{**}(\text{CO})_2\text{FeBr}$ ($\text{Cp}^{**} = \text{C}_5\text{Me}_5$ or other bulky substituted Cp derivatives) to afford 1,3-diferrio-1 λ^3 ,3 λ^3 -diphosphetane-2,4-diones **88** by a [2+2] cycloaddition reaction of a phosphaketene intermediate (Scheme 27) <1996OM128, 2000T27>.



Scheme 27

An intramolecular [4+2] addition between a diphosphirene and a *P*-cyclopentadiene substituent is believed to result in the formation of a tetracyclic P–C cage compound with a 1,2-diphosphetane moiety <1997PS545>.

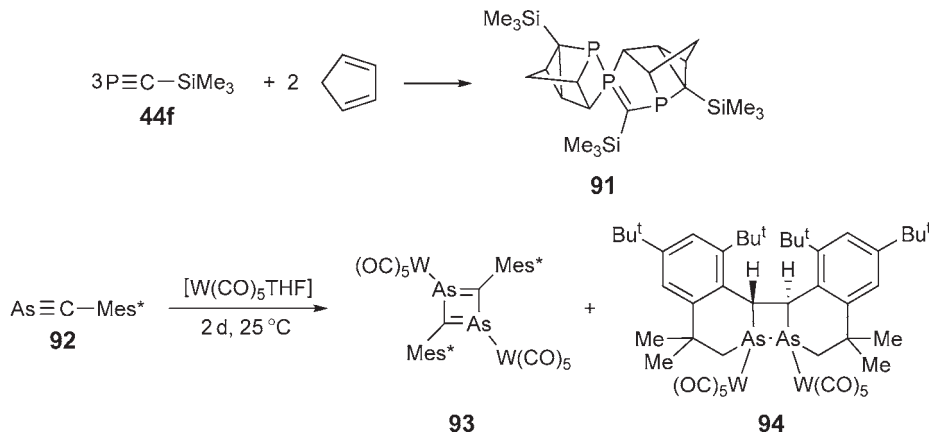
Bisphosphaallene **89** is a spectroscopically observable intermediate, which undergoes an intramolecular [2+2] addition reaction at room temperature effectively forming 3-naphtho-1,2-dihydro-1 λ^3 ,2 λ^3 -diphosphete **90** <1997LA121>. The same reaction topology was postulated for an allylphosphine pyrolysis product <1997HAC91>. The head-to-tail [2+2] cycloaddition of perfluorophosphaalkene and phosphalkyne derivatives yields 1,2-dihydro-1 λ^3 ,3 λ^3 -diphosphetes **23** (Scheme 28) <1997JOM(529)177>.



Scheme 28

In situ-prepared 1-adamantyl-2-diphenyl-phosphaalkene dimerizes spontaneously and forms an 1,2-diadamantyl-1 λ^3 ,2 λ^3 -diphosphetane <2006IC5225>. Repetitive cycloaddition reactions between trimethylsilylphosphaalkyne **44f** and cyclopentadiene, in a molar ratio of 3:2, lead to formation of the polycyclic triphospha compound **91** <1999EJO363>. $[\text{W}(\text{CO})_5\text{THF}]$ triggers [2+2] cycloaddition reactions of Mes^* -arsaalkyne **92** by σ -complexation

to yield binuclear $1\lambda^3,3\lambda^3$ -diarsete σ -complex **93** and a mixture of stereoisomers of $1\lambda^3,2\lambda^3$ -diarsetane complex **94**, both in low yield. The formation of **94** includes the insertion of an arsenic atom of a primary head-to-head cycloaddition product into a C–H bond of a *tert*-butyl group of the Mes* substituent and a subsequent hydrogen migration (Scheme 29) <1996CC631>.



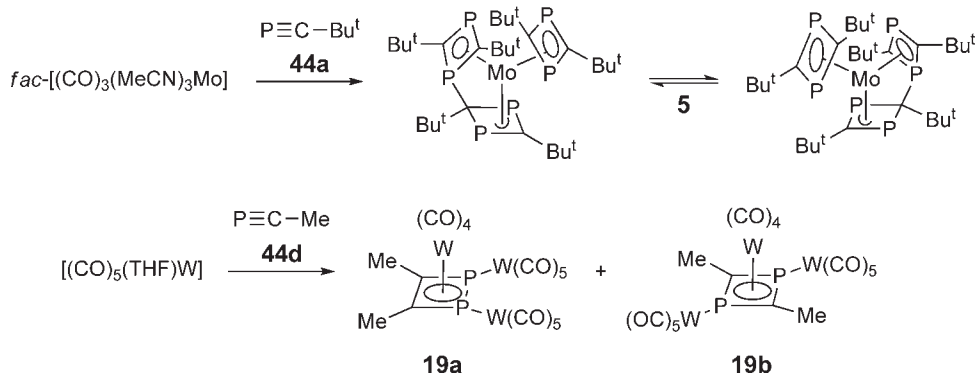
Scheme 29

2.20.9.4 Ring Formation in the Coordination Sphere of Transition Metals

Kinetically stabilized phosphalkynes can be used very successfully for the synthesis of transition metal-coordinated $1\lambda^3,3\lambda^3$ -diphosphetes in complexes of the type **18**. This field was opened by Binger, Nixon, Regitz, and others in 1986 and has been reviewed several times <B-1998MI1, B-2001MI167>. The phosphalkyne/transition metal complex combinations used since 1996 for this purpose are: **44a**/M(CO)₃L₃ (M = Mo, W; L = CH₃CN) <1998ZFA399, 2002AGE4047>, **44a** and mesitylphosphalkyne **44g**/W(CO)₅THF <2000EJI1869>, **44g**/Fe₂(CO)₉, **44g**/Ru(CO)₄(C₂H₄), **44a**/Cp*Mo(CO)₃Cl, **44a**/KMn(CO)₅, **44a**/(1,5-COD)₂Ni <2004ZFA1220>, and diisopropylaminophosphalkyne **44b**/(1,5-COD)₂Ni (COD = cyclooctadiene) <1996ZFA24>.

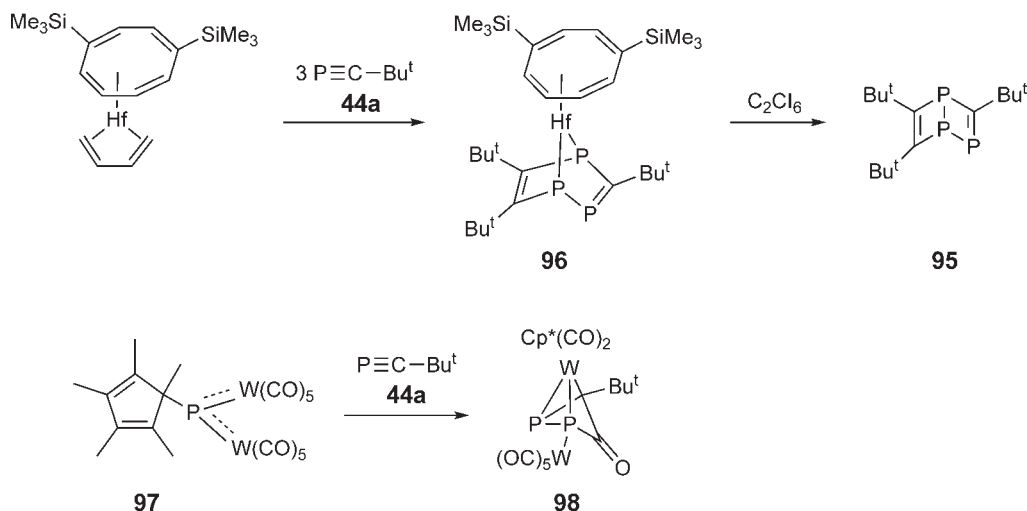
The homoleptic complex tris(2,4-di-*tert*-butyl- $1\lambda^3,3\lambda^3$ -diphosphete) Mo **5** was obtained by reacting [*fac*-(CO)₃(MeCN)₃Mo] with *P*-alkyne **44a** <2002AGE4047>. The compound exhibits a unique temperature-dependent, reversible P–C bond formation between two of the heterocycles in the solid state. A related close contact between a P-atom of one π -coordinated $1\lambda^3,3\lambda^3$ -diphosphete ligand and a C-atom of another one at the same metal center has also been observed for the tungsten analogue of **5** <2000TH1>.

Highly reactive methyl *P*-alkyne **44d** reacts in a slightly different way to its *tert*-butyl analogue **44a** in organometallic cycloaddition reactions where $1\lambda^3,3\lambda^3$ -diphosphete complexes are formed preferably. Two trinuclear complexes can be isolated from the reaction mixture of **44d** with [(CO)₅(THF)W]: 80% $1\lambda^3,2\lambda^3$ -diphosphete complex **19a** and 20% of its $1\lambda^3,3\lambda^3$ -isomer **19b** (Scheme 30) <2006JCD3733>.



Scheme 30

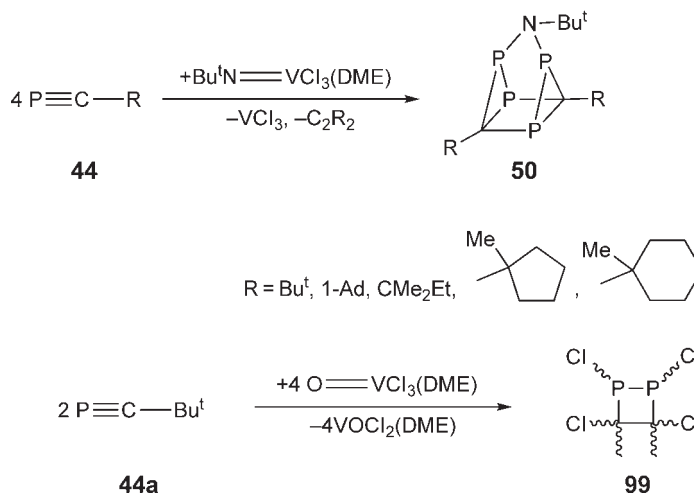
Free 1,2,5-triphospha Dewar benzene derivative **95** is formed in two steps from 3 mol of **44a** by oxidative decomplexation of the triphosphacyclohexa-1,4-diyl-2,5-diene ligand of the Hf complex **96** <1997CB1491>. An organometallic [2+1+1] cycloaddition reaction between the phosphinidene complex **97**, **44a**, and a coordinated CO gives access to the 1,2-diphosphacyclobutenone complex **98** (Scheme 31) <1998CEJ1917>.



Scheme 31

Cyclotetramerization of a series of phosphalkynes at a vanadium(v) center, metal-to-phosphorus transfer of a ^tBuN -fragment, and subsequent elimination of alkyne are the main steps in the formation of azatetraphosphaquadricyclanes **50** with their $1\lambda^3,3\lambda^3$ -diphosphetane basic ring <1998AGE1233, 2000CEJ4558, 2001ZNB951>.

If $\text{VOCl}_3(\text{DME})$ is used, the cyclization of P -alkyne **44a** leads to a mixture of isomers of tetrachloro- $1\lambda^3,2\lambda^3$ -diphosphetane **99** (Scheme 32) <2003ZNB44>. A twofold $\text{W}(\text{CO})_5$ -complexed $1\lambda^3,2\lambda^3$ -diphosphetane was obtained as a side product in low yield from a specifically substituted (phosphanorbornadiene) $\text{W}(\text{CO})_5$ complex in the presence of CuCl <2005OM2930>.

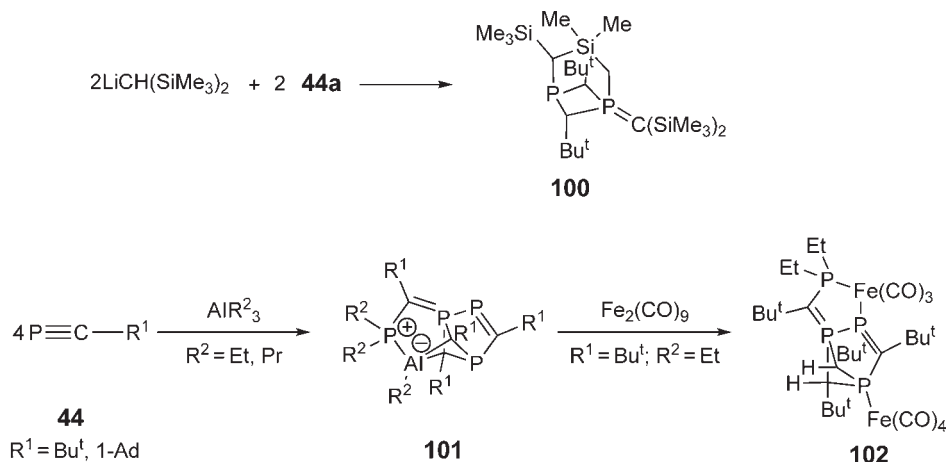


Scheme 32

A platinum-mediated coupling of diphosphastibolyl anions takes place, if they are allowed to react with *cis*- $[\text{PtCl}_2(\text{PETe}_2)_2]$. The resulting polycyclic P_4Sb_2 organic cage ligand contains a 1,3-diphosphetane ring <1997JCD4321>.

2.20.9.5 Ring Formation by Other Routes

Two moles of $\text{LiCH}(\text{SiMe}_3)_2$ and **44a** each form in a reasonable (64%) yield the sila-bridged $1\text{-}\lambda^5,3\lambda^3\text{-1,3-diphosphetane}$ **100** in an as yet unclear reaction sequence <2002JOM(645)256>. A P,P-based phosphalkene bridge across the ring of a $1\lambda^5,3\lambda^3\text{-diphosphetane}$ subunit is the common feature of the polycyclic aluminatetraphospha cage **101**, diiron follow-up product **102**, and a structurally related Mg-compound **103** (*vide infra*). Product **101** is generated from 4 mol of *P*-alkyne and AlR_3 . Cage **101** loses its Al-atom and adds two $\text{Fe}(\text{CO})_n$ complex fragments to furnish **102** when reacted with $\text{Fe}_2(\text{CO})_9$ (Scheme 33) <1997JOM(539)61>. GaEt_3 reacts in a related manner with *P*-alkynes and gives access to more metalladiphosphapropellane derivatives <1998EJI1597>.



Scheme 33

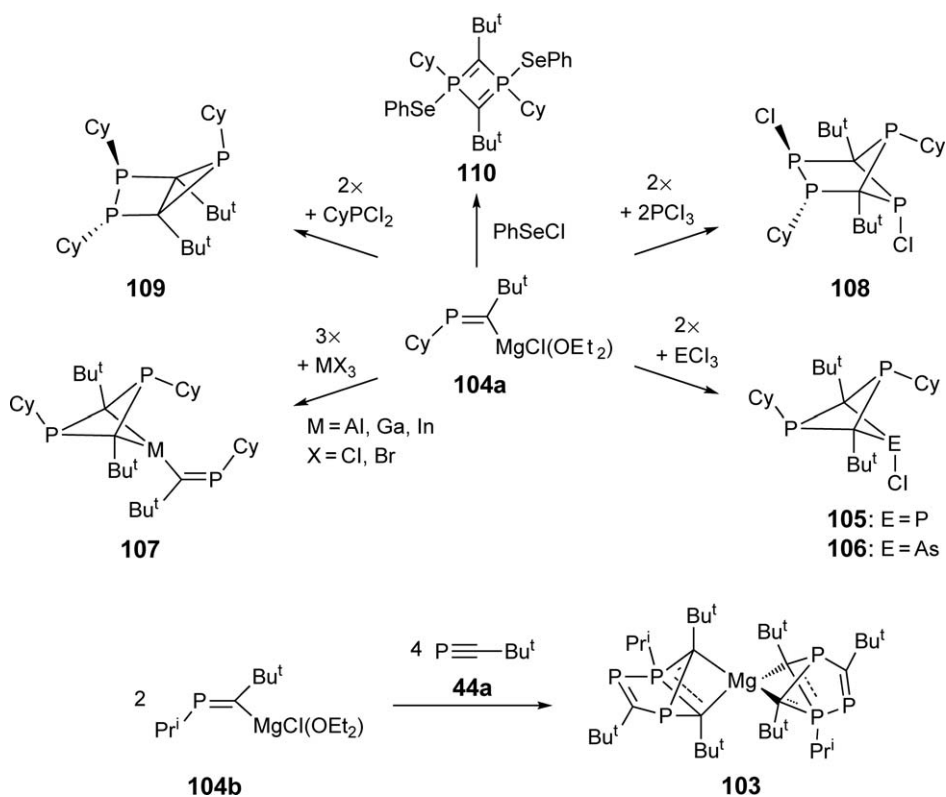
2-Phospha-1-vinylmagnesium chlorides **104** are useful starting materials for the preparation of C_2E_2 heterocycles as part of polycyclic compounds. Two moles of the cyclohexyl derivative **104a** and 1 equiv of PCl_3 or AsCl_3 yield triphosphapropellane **105** or arsadiphosphapropellane **106**, respectively <2002NJC1209>. Three moles of derivative **104a** and 1 mol of MX_3 ($\text{M} = \text{Al}, \text{Ga}, \text{In}$) result in the formation of diphosphametallapropellanes **107** <2001JOM(629)109>. The addition of equimolar amounts of PCl_3 , however, leads to tetraphosphabicyclo[2.1.1]hexane **108**, but cyclohexyldichlorophosphine and 2 equiv of **104a** form 2,3,5-triphosphabicyclo[2.1.0]pentane **109** <2002NJC1209>. A 1,2-dihydro- $1\lambda^3,3\lambda^3\text{-diphosphete}$ derivative was observed as a side product of the reaction between **104a** and Cp^*NbCl_4 <2002OM438>.

Addition of PhSeCl leads to a completely different product, namely $1\lambda^5,3\lambda^5\text{-diphosphete}$ **110** <2003JOM(665)127>. The combination of the two highly reactive P–C species **104b** and *P*-alkyne **44a** allows the formation of Mg-connected spiropolycyclic hexaphospha species **103** with two triphosphabicyclo[2.1.1]hexene structure elements in a reasonable 72% yield (Scheme 34). The bonding situation of the central part of the molecule is complex. It may be viewed either as *i*-PrP–C single bonds in combination with a negatively charged magnesium atom or as *i*-PrP–C interactions with partial double-bond character and a neutral Mg-atom. If TaCl_5 is combined with **44a** instead of **104b**, the same structure element is formed and spanned by a $\text{TaCl}_2\text{OTaCl}_5$ unit <2000EJI2337>.

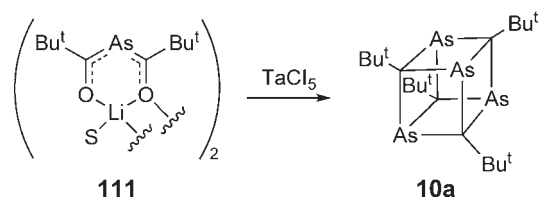
Jones and Williams accidentally found a novel route to tetraarsacubane **10a** when reacting 2-arsa-1,3-dionato lithium compound **111** with TaCl_5 . A transient $t\text{-BuC}\equiv\text{As}$ is believed to play an important role in the cage formation (Scheme 35) <2004JOM(689)1648>.

2.20.10 Ring Syntheses by Transformation of Another Ring

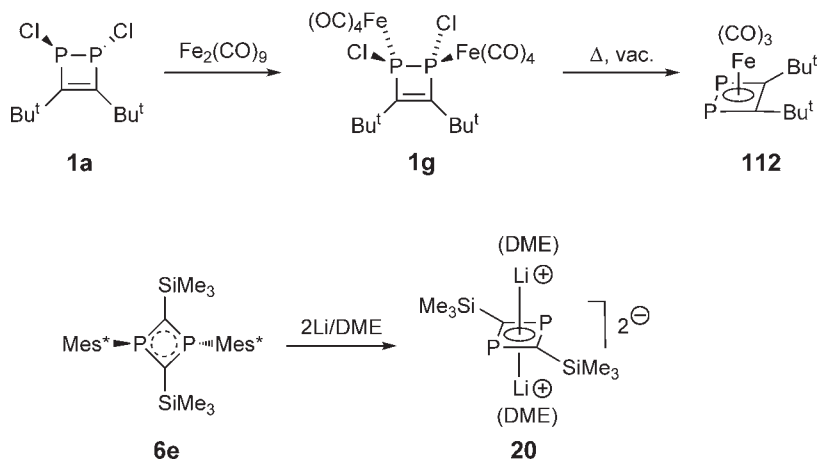
The only targeted preparation of a $1\lambda^3,2\lambda^3\text{-diphosphete}$ complex is based on a thermal-induced chloride abstraction by a transition metal and rearrangement of the isolable intermediate (*trans*-1,2-dichloro- $1\lambda^3,2\lambda^3\text{-diphosphete}$) $\text{Fe}_2(\text{CO})_8$ σ -complex **1g** which leads to the ($1\lambda^3,2\lambda^3\text{-diphosphete}$) $\text{Fe}(\text{CO})_3$ π -complex **112** <1999OM2021>. Bis-trimethylsilyl-1,3-diphosphetane-2,4-diyl **6e** <1999AGE3028> may be reduced by K or Li to form aromatic 1,3-diphosphetediide salts, for example, **20** (Scheme 36) <2004AGE637, 2004PS779>.



Scheme 34

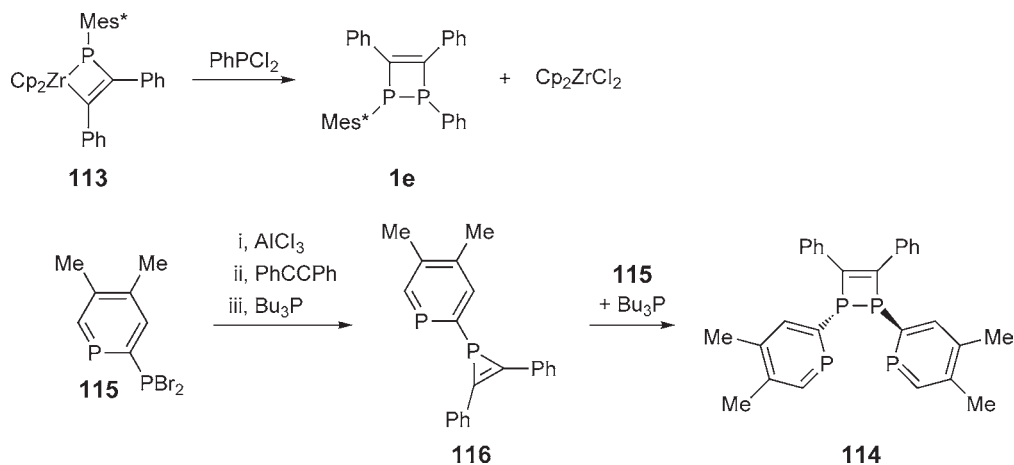


Scheme 35



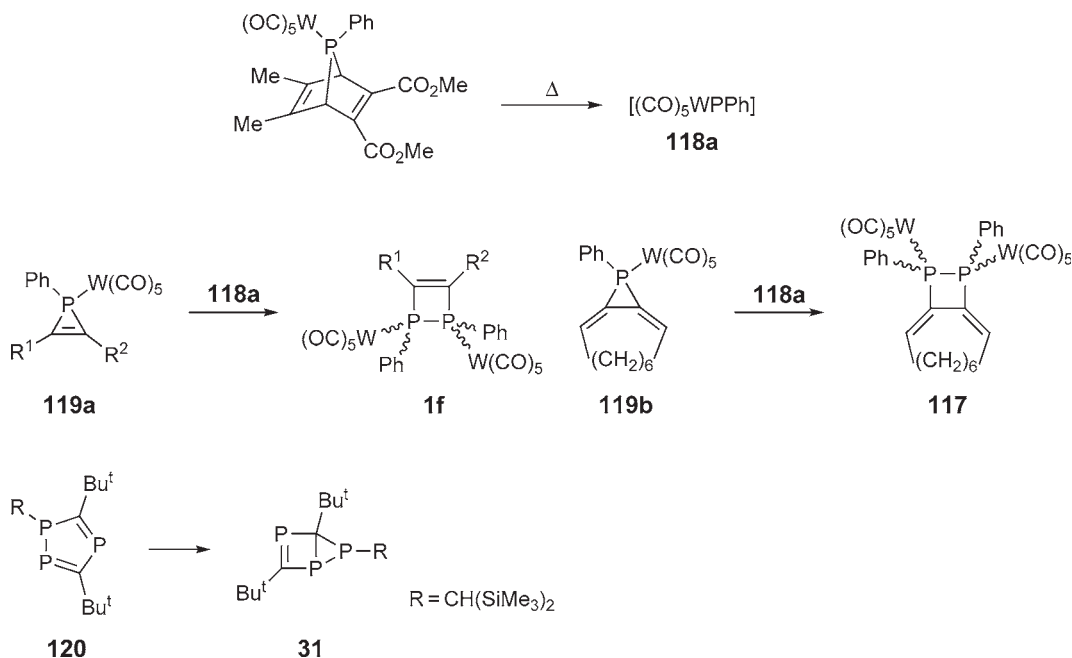
Scheme 36

Zirconacyclic compound **113** can be transformed into 1,2-diorganyl-1 λ^3 ,2 λ^3 -diphosphate **1e** with two different P-substituents by reaction with PhPCl₂ <1997OM365>. 1,2-Bisphosphinine-1 λ^3 ,2 λ^3 -diphosphate **114** possesses a high potential as a chelating bidentate ligand. It is accessible through 2-dibromophosphino-4,5-dimethylphosphinine **115**, AlCl₃, toluene, and tributylphosphine <1996OM1597>. A phosphinine-substituted phosphinidene inserts into the phosphirene intermediate **116** to form the 1,2-diorganyl-1 λ^3 ,2 λ^3 -diphosphate ring of derivative **114** (Scheme 37).



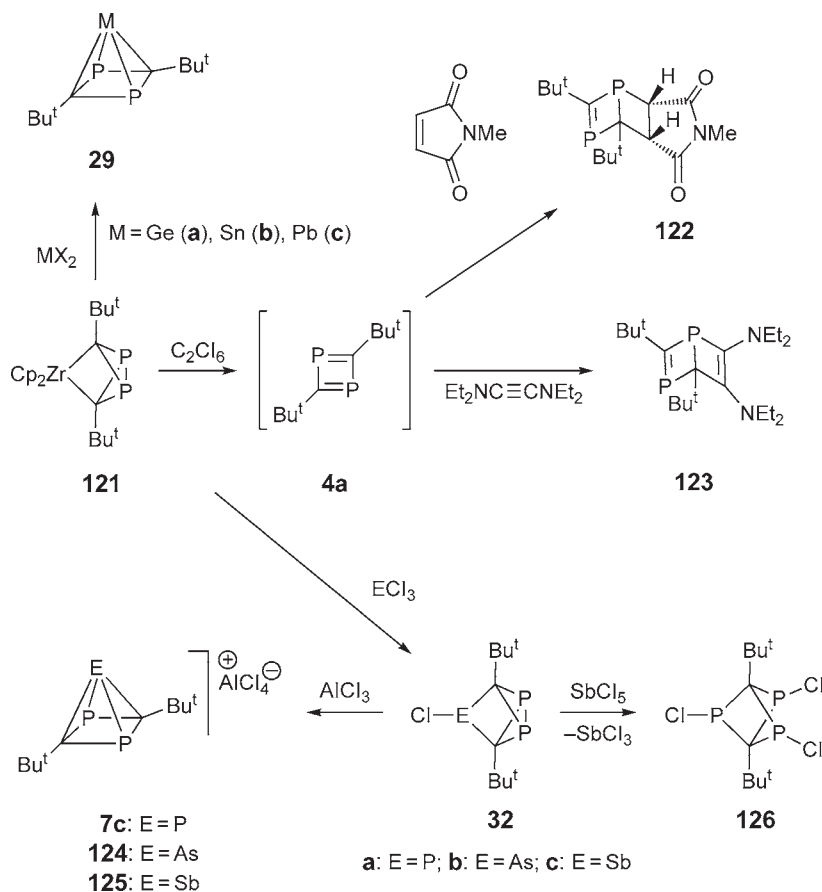
Scheme 37

Bis-tungstenpentacarbonyl μ -1,2-dihydro-1 λ^3 ,2 λ^3 -diphosphate σ -complexes **1f** and **117** are formed upon insertion of transient phosphinidene complex PhPW(CO)₅ **118a** into one of the P–C bonds of W(CO)₅-stabilized phosphirenes **119a** and **119b** in good yield. The substituents R¹ and R² of **1f** and **119a** may contain functional groups such as C $\equiv$ C bonds <1997OM4501, 1999OM796, 2006OM4799> or form a cyclo-1,3-diene as in **117b** and **119b** <2000JA12507>. Photochemical electrocyclicization of triphosphol **120** affords triphosphabicyclopentene **31** with a 1,2-dihydro-1 λ^3 ,3 λ^3 -diphosphate substructure (Scheme 38) <1998CC1537>.



Scheme 38

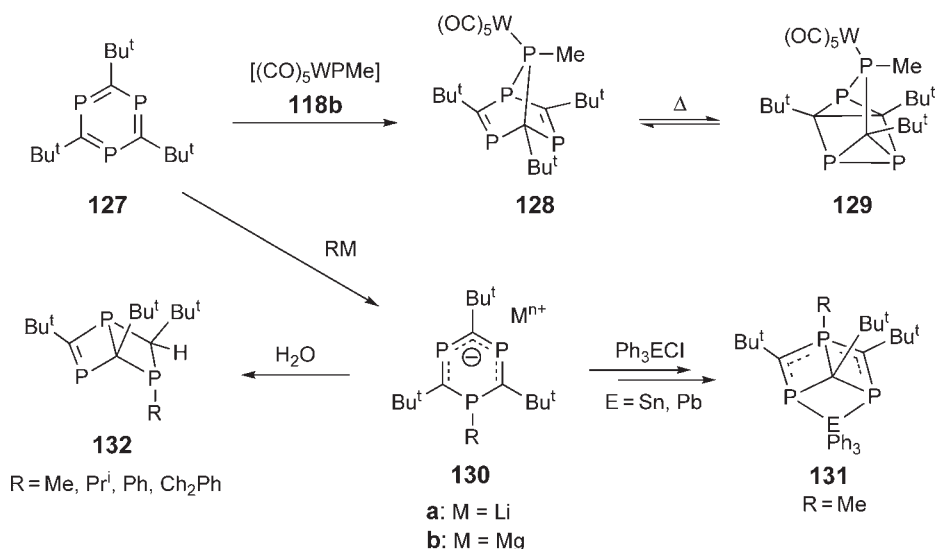
1,2-Dichloro-1 λ^3 ,2 λ^3 -diphosphete **1a** can be prepared by a rearrangement and oxidation reaction of (1,3-diphosphete)(toluene)iron **41** (see also Section 2.20.5.7) <1996S265>. Tetracyclic (diphosphabicyclobutanediyl)ZrCp₂ complex **121** can be utilized for the transformation of its P₂-ligand by oxidative decomplexation into transient free 1 λ^3 ,3 λ^3 -diphosphete **4a**. Cycloaddition with reactive multiple bond systems leads to di- and tricyclic products **122** and **123**, respectively <2002JOM(643)409>. Compound **121** reacts with ECl₃ (E = P, As, Sb) to yield tetracyclic P₂E species **32a–c**. The chlorine atom of **32a** may be exchanged by iodine <2006AGE3628>. Dechlorination by chloride scavengers transforms them into salts **7c**, **124**, and **125**, respectively, with their square pyramidal C₂R₂P₂E⁺ cations. If **121** is reacted with MX₂ (M = Ge, Sn, Pb; X = Cl, I), neutral C₂R₂P₂M pyramids **29a–c** with apical metal atoms are formed <2002CCC86, 2003OM2891>. Dichlorination of derivative **32a** yields triphosphapropellane **126** (Scheme 39) <2003AGE2778, 2006CC1375>.



Scheme 39

2,4,6-Tri-*tert*-butyl-1,3,5-triphosphinine **127** adds short-lived tungsten methylphosphinidene complex **118b** at positions 1 and 4 to furnish tetraphosphanorbornadiene tungsten complex **128**, which is in thermal equilibrium with tetraphosphaquadracyclane **129** <2001AGE4412>. The *P*-phenyl derivative of **129** has also been reported <2001CEJ3545>.

P-alkylated 2,4,6-tri-*t*-butyl-1,3,5-triphosphacyclohexadienide anions **130a** and **130b** are useful starting materials for four-membered diphospha heterocycle synthesis. A complex rearrangement reaction takes place upon stannylation or plumbylation of **130a**. It proceeds via isolable tricyclic intermediates, which rearrange under mild conditions to form unsaturated tricyclic compounds **131**, which include two P₂C₂ units each <2006OM4799>. Hydrolysis of the magnesium salt **130b** leads to triphospha-dihydro-Dewar benzenes **132** (Scheme 40) <2003AGE1863>. If **130a** is reacted with FeCl₂, a ferratetraphosphaheterocubane with three 1 λ^3 ,3 λ^3 -diphosphetane units has been observed as a side product <2005OM4216>.



Scheme 40

Hexaphosphapentaprismane **11a** is accessible by several routes. All are based on five-membered $\text{C}_2\text{R}_2\text{P}_3$ rings: potassium salt **133** or 1,2,4-triphosphol derivatives **120**. Two equivalents of salt **133** and HgCl_2 form **11a** in 20% yield. A trinuclear mercury insertion product of **11a** with a close structural relationship to **53** has been isolated and structurally characterized. Alternatively, the stannyl derivative of triphosphol **120** can also be reacted with HgCl_2 to form 72% hexaphospha-bis-phosphaalkene **134**, which rearranges slowly in daylight to **11a** in 40% isolated yield. A P–P-bond-opened triplet radical has been identified as the decisive intermediate for the last step <2002CEJ2622>. UV photolysis of **11a** leads to valence isomers <2003ICA(356)103>. Salt **133** and GeI_4 or SiI_4 lead to formal insertion products of **11a**. A GeI_2 or SiI_2 unit bridges the two central P-atoms in products **53d** and **53e** <2000CC879>. The bis-trimethylsilyl-methyl derivative of **120** gives access to the two cages **135a** and **135b**, where a CHX-group takes the same place as the EI_2 units of **53d** and **53e**. Thermolysis of **120** leads to hexaphospha-homopentaprismane cage **135a**, where a $\text{CH}(\text{SiMe}_3)$ group occupies the place between the two central P-atoms <2002JBS555>. Addition of cobaltocene to the reaction mixture leads to the additional formation of another cage **135b** together with **135a** in low yield. A cobaltocene unit is connected in this case to the bridging methylene carbon atom by a σ -bond with a C–H moiety of one of the Cp ligands <2001CC2720>.

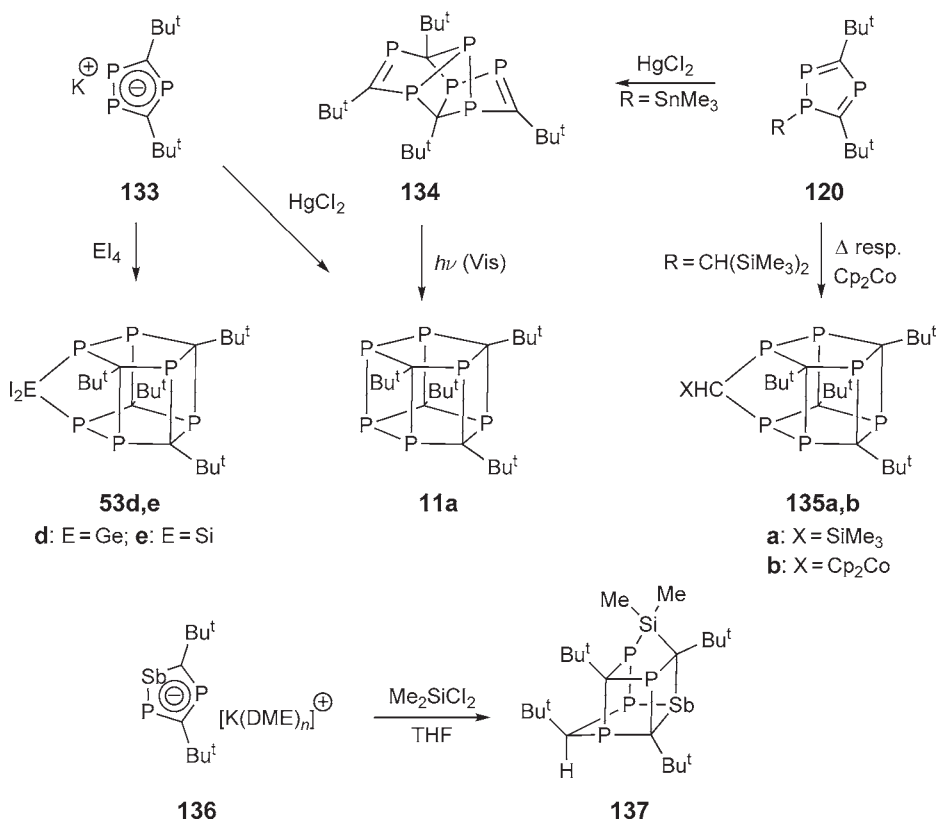
A complex reaction sequence results from a primary redox reaction between Me_2SiCl_2 and potassium diphosphastibolyl salt **136**. The tetraphosphastibolyl salt **137** is formed in reasonable 41% yield and contains fused $1\lambda^3$ -stiba- $3\lambda^3$ -phosphetane and $1\lambda^3,3\lambda^3$ -diphosphetane subunits (Scheme 41) <2001JOM(622)61>.

2.20.11 Synthesis of Particular Classes of Compounds

All relevant reactions leading to C_2E_2 heterocycles are described in Sections 2.20.9 and 2.20.10. This section highlights the most useful preparative routes to ring compounds of interest that have appeared in the literature since 1996. Earlier work has been reviewed <B-2001MI167>.

2.20.11.1 Fully conjugated 1,2- and 1,3-diphosphetes

P-SePh substituted $1\lambda^5,3\lambda^5$ -diphosphete **110** is accessible in 78% yield from 2-phospha-1-vinylmagnesium chloride **104a** and PhSeCl <2003JOM(665)127> (Section 2.20.9.5). $1\lambda^5,2\lambda^3$ -Diphosphete **17** can be obtained in a good 90% yield from *in situ*-prepared C-diazo diaminophosphane precursors and *t*-butyl phosphalkyne **44a** <1997JA9720>. Only one targeted synthesis of a $1\lambda^3,2\lambda^3$ -diphosphete π -complex has appeared in the literature. It is based on a thermally induced chloride abstraction of *trans*-1,2-dichloro- $1\lambda^3,2\lambda^3$ -diphosphete **1a** by $\text{Fe}_2(\text{CO})_9$ and rearrangement of an isolable intermediate σ -complex to form $(1\lambda^3,2\lambda^3\text{-diphosphete})\text{Fe}(\text{CO})_3$ π -complex **112** in 44% yield <1999OM2021>. Two trinuclear diphosphete complexes can be isolated from the reaction mixture of *P*-alkyne



Scheme 41

44d with $[(\text{CO})_5(\text{THF})\text{W}]$: 80% of $1\lambda^3,2\lambda^3$ -diphosphete tritungsten complex **19a** and 20% of its $1\lambda^3,3\lambda^3$ -diphosphete isomer **19b** <2006JCD3733> (Section 2.20.9.4). Aromatic 1,3-diphosphetediide dilithium salt **20** results from the reaction of bis-trimethylsilyl- $1\lambda^3,2\lambda^3$ -diphosphetane-2,4-diyl **6d** through alkaline metal reduction in more than 90% isolated yield (Section 2.20.10) <2004AGE637>.

Free $1\lambda^3,3\lambda^3$ -diphosphetes **4a** exist only as reactive intermediates and can be trapped by suitable reaction partners. They can be obtained by an oxidative degradation of Zr-diphosphabicyclobutane complex **121** <2002JOM(643)409>.

2.20.11.2 $1\lambda^3,3\lambda^3$ -Diarsete

Reaction of Mes^* -arsaalkyne **92** with $[\text{W}(\text{CO})_5\text{THF}]$ yields the antiaromatic free $1\lambda^3,3\lambda^3$ -diarsete ditungsten complex **93** in low yield (Section 2.20.9.3) <1996CC631>.

2.20.11.3 1,3-Diphosphetane-2,4-diyls

2,4- Mes^*_2 -substituted 1,3-diphosphetane-2,4-diyl **26** with one λ^5 -phosphorus atom is accessible by two different alkylation steps and one oxidation from Mes^* -phosphaalkyne **44e** in 45% yield <2004CEJ2700>. Without the oxidation, $1\text{R}^1,3\text{R}^2$ -2,4- Mes^*_2 -1,3-diphosphetane-2,4-diyl derivatives like **6h** are formed almost quantitatively (Section 2.20.9.2) <2003AGE3802, 2005JOM(690)2515>.

2,4-Dichloro-1,3-diorganylamino-1,3-diphosphetane-2,4-diyl **6f** can be prepared in 98 % yield from dichlorophosphaalkene **67** and $n\text{-BuLi}$ <1998AGE949>.

2.20.11.4 1,2-Dihydro- $1\lambda^3,2\lambda^3$ -diphosphetes

1,2-Diorganylamino-3,4-dichloro- $1\lambda^3,2\lambda^3$ -diphosphete **1a** is formed by an effective and spontaneous rearrangement of 1,3-diphosphetane-2,4-diyl **6f** <1998AGE949>.

Free 3-naphtho-1,2-dihydro-1 λ^3 ,2 λ^3 -diphosphete **90** is formed effectively by [2+2] cycloaddition rearrangement of bisphosphaallene species **89** (Section 2.20.9.3) <1997LA121>. Free 1,2,5-triphospha Dewar benzene derivative **95** is furnished in 50% yield by oxidative decomplexation of the triphosphacyclohexa-1,4-diyl-2,5-diene ligand of Hf-complex **96** (Section 2.20.9.4) <1997CB1491>. Access to the 1,2-diorganyl-1 λ^3 ,2 λ^3 -diphosphete ring family **1e** with two different P-substituents is provided by the transformation of zirconacyclic compound **113** by reaction with PhPCl_2 (53%) <1997OM365>. 1,2-Bisphosphinin-1 λ^3 ,2 λ^3 -diphosphete **114** is generated by the reaction of 2-dibromophosphino-4,5-dimethylphosphinine **115** with AlCl_3 , toluene, and tributylphosphine (75%) <1996OM1597>.

Ditungsten complexes **1f** of 1,2-dihydro-1 λ^3 ,2 λ^3 -diphosphetes are accessible in 25–27% yield by direct [2+2] cycloaddition reactions of diphosphene ditungsten compound **82** and several alkynes at elevated temperatures <1997OM2506>. Alternatively **1f** and related species **117** are obtained from W(CO)_5 -stabilized phosphirenes **119a** and **119b** by insertion of transient phosphinidene complex PhPW(CO)_5 **118a** in 47% yield (Section 2.20.10) <1997OM4501>.

2.20.11.5 1,2-Dihydro-1,3-diphosphetes

Amino-substituted 1,2-dihydro-1 λ^5 ,3 λ^3 -diphosphetes **21** are formed by oxidative cyclodimerization of aminophosphaalkyne **44b** (93–95%) <2000T27>. 1,2-dihydro-1 λ^3 ,3 λ^3 -diphosphetes **69** with *C*-Mes* substituents are accessible from Mes*-phosphaalkyne **44e**, organolithium compounds, and protonation of the intermediate (41%) (Section 2.20.9.2) <2002CC1744>. 1-Stannyl-1,2-dihydro-1 λ^3 ,3 λ^3 -diphosphete **56a** can be obtained by [2+2] cycloaddition of one stannylphosphaalkene with a phosphaalkyne (23–48%) <1998EJI227>. 1,2-Dihydro-1 λ^3 ,3 λ^3 -diphosphetes **23** with CF_2 and P-CF_3 ring elements are accessible by cyclic addition of a perfluorophosphaalkene and phosphaalkynes (34–65%) (Section 2.20.9.3) <1997JOM(529)177>. Diphospha-Dewar benzene derivative **123** can be formed by cyclic addition of the intermediates of $\text{Cp}_2\text{Zr(diphosphabicyclobutane-diyl)}$ complex **121** and bis(diethylamino)acetylene (47%) <2002JOM(643)409>.

2.20.11.6 1,3-Dihydro-1 λ^3 ,3 λ^3 -diphosphetes

1 λ^3 ,3 λ^3 -Diphosphetane-2,4-dione **43** is accessible by mixing solutions of triphenylmethylphosphine and phosgene and leaving the components at room temperature for 18 h without stirring (94%) <1999ZFA1979>. 1,3-Diferrio-1 λ^3 ,3 λ^3 -diphosphetane-2,4-diones **88** are generated by reacting $(\text{DME})_2\text{LiOC}\equiv\text{P}$ **44c** with $\text{Cp}^{**}(\text{CO})_2\text{FeBr}$ (32–38%) <1996OM128>. Mes*-substituted 1-phosphaallene **83a** forms 1,3-dihydro-1 λ^3 ,3 λ^3 -diphosphete **84a** with exocyclic double bonds by dimerization (41%) (Section 2.20.9.3) <2003EJO4838>.

2.20.11.7 1,3-Dihydro-1 λ^3 ,3 λ^3 -diarsete

1,3-Dihydro-1 λ^3 ,3 λ^3 -diarsete **78** is formed in 18% yield by the abstraction of Me_3SiCl from arsa-substituted λ^5 -phosphaalkene **79** (Section 2.20.9.2) <2000CEJ3531>.

2.20.11.8 1,2-Dihydro-1 λ^3 ,2 λ^3 -distibete

Double dehalogenation of vinylstibane **80** gives access to 1,2-dihydro-1 λ^3 ,2 λ^3 -distibete **13** (49%) (Section 2.20.9.2) <2005JOM(690)307>.

2.20.11.9 1 λ^3 ,2 λ^3 - and 1 λ^3 ,3 λ^3 -Diphosphetanes

PH-phosphaalkene **75** can be activated by W(CO)_5 -carbene complexes **76** to yield a tungsten-complexed 1 λ^3 ,3 λ^3 -diphosphetane **77** (60–72%) (Section 2.20.9.2) <2003OM5063>. Two moles of P-alkyne **44a** and 4 equiv of $\text{VOCl}_3(\text{DME})$ form a mixture of isomers of tetrachloro-1 λ^3 ,2 λ^3 -diphosphetane **99** (93%) (Section 2.20.9.4) <2003ZNB44>. Cyclohexyldichlorophosphine and 2 equiv of phosphaalkene Grignard compound **104** form 2,3,5-triphosphabicyclo[2.1.0]pentane **109** (62%) (Section 2.20.9.5) <2002NJC1209>.

2.20.11.10 $1\lambda^3,2\lambda^3$ -Diarsetane

Mes^{*}-arsaalkyne **92** generates a racemic mixture of enantiomeric 1,2-diarsetane as [W(CO)₅THF] complex **94** in low yield (Section 2.20.9.3) <1996CC631>.

2.20.11.11 $1\lambda^3,3\lambda^3$ -Distibetane

Thermolysis of (2-pyridyl)(SiMe₃)₂CSbCl₂ **81** affords chloro-bridged polymeric $1\lambda^3,3\lambda^3$ -distibetane compound **30** (63%) (Section 2.20.9.2) <1998CC575>.

2.20.11.12 C₂E₂ units (E = P, As, Sb) as Parts of Polycyclic Compounds

Several polycyclic compounds with C₂E₂ units have been prepared in reasonable to good yield in the last decade. This accounts for spiro and polycyclic triphospha compound **91** (72%) (Section 2.20.9.3) <1999EJO363>; aza tetraphospha quadricyclanes **50** (47–76%) (Section 2.20.9.4) <1998AGE1233>; sila-bridged $1\lambda^5,3\lambda^3$ -diphosphetane **100** (64%) <2002JOM(645)256>; polycyclic aluminatetraphospha cage **102** (74%) <1997JOM(539)61>; triphospha-propellane **105** (36%) and arsadiphosphapropellane **106** (41%) <2002NJC1209>; diphosphametallapropellanes **107** (15–49%) (Section 2.20.9.5) <2001JOM(629)109>; tetracyclic P₂E species **32a–c** (E = P, As, Sb) <2006AGE3628>; salts **7c**, **124**, and **125** with square pyramidal C₂R₂P₂E⁺ cations (E = P, As, Sb) <2003AGE2778, 2006CC1375>; neutral C₂R₂P₂M pyramids (M = Ge, Sn, Pb) **29a–c** (30–86%) <2002CC86, 2003OM2891>; hexaphosphapentaprismane **11a** (40%) <2002CEJ2622>; tetraphosphasilastibaorganic cage **137** (41%) <2001JOM(622)61>; and stannylated unsaturated tricyclic compound **131** (86%) (Section 2.20.10) <2006OM4799>.

2.20.12 Important Compounds and Applications

To the best of our knowledge, no technical applications of C₂E₂ heterocycles with the elements discussed in this chapter have appeared in the literature.

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Biographical Sketch



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2.21

Four-membered Rings with Two Heteroatoms including Silicon to Lead

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2.21.1 Introduction

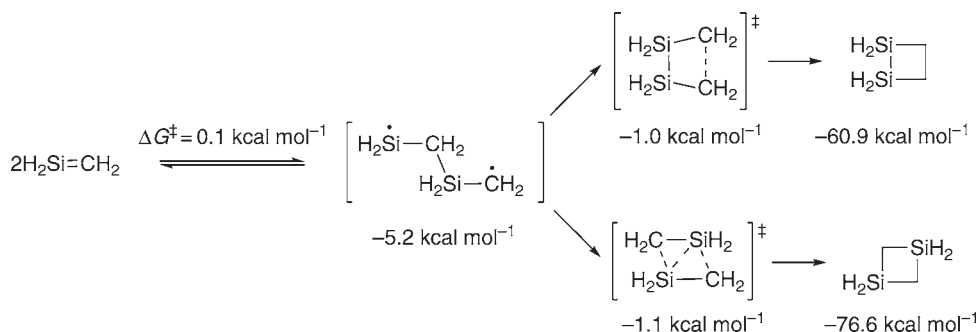
This subject was covered previously in CHEC(1984), together with other heterocyclic systems containing silicon, germanium, tin, or lead <1984CHEC(1)573>, and in CHEC-II(1996) <1996CHEC-II(1B)1175>. The present chapter is intended to update the previous editions with emphasis on major new preparations, reactions, and concepts. We have provided at the beginning of each main section a short summary of the major advances since the publication of the earlier chapters and also any omissions in CHEC-II(1996). This chapter, as the previous one by Conlin and Meagher

<1996CHEC-II(1B)1175>, deals with saturated and unsaturated cyclobutane ring systems containing two heteroatoms, one or two of which are from group 14. A number of important books and reviews have appeared which discuss the synthetic methods and reactivity of four-membered heterocycles, mainly those including silicon (Chapters 2.11 and 2.22; <B-1998MI857, B-2001MI949>), but there are some reviews covering germanium heterocycles <1998CCR593> and also heterocycles containing heavier elements of this group <B-1995MI453, B-2002MI283>.

2.21.2 Theoretical Methods

Early theoretical work concerning small rings containing silicon has been comprehensively reviewed <B-1989MI57, 1996CHEC-II(1B)1175>. Due to the dynamic development of theoretical methods, the number of papers in this field has rapidly expanded in recent years. *Ab initio* molecular orbital studies on the structure and thermodynamic stability of silacyclobutadienes have been discussed <B-1998MI1>. Theoretical and electronic aspects of [2+2] cycloaddition of silenes to multiple bonds have been thoroughly reviewed <B-1998MI857>. Theoretical results concerning compounds containing Si, Ge, Sn, and Pb, including also four-membered heterocyclic rings, have been discussed <B-2001MI1>. Germanium, tin, and lead heterocycles have been comprehensively treated <B-2002MI169, B-2002MI221-09>.

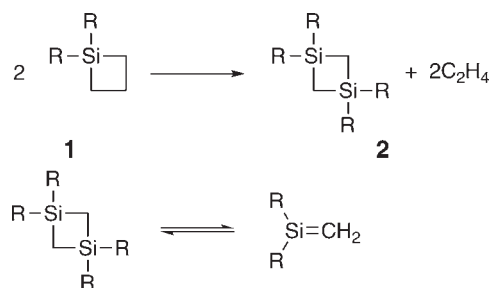
[2+2] cycloaddition of silenes ($>\text{Si}=\text{C}<$) and their analogues with heavier group 14 elements Ge, Sn, and Pb, as well as the reverse reaction, [2+2] cycloreversion, have attracted a considerable interest <B-1998MI857, B-2001MI949, 2003CCR149>. The dimerization of the parent silene ($\text{H}_2\text{Si}=\text{CH}_2$) has been examined theoretically by several groups. The reaction is very exothermic and proceeds with a low energy barrier. Coupled cluster calculations predict that the process leading to 1,3-disilacyclobutane occurs via a concerted mechanism through a symmetric transition state that is $3.7 \text{ kcal mol}^{-1}$ higher in energy than the substrates <1992JA3643>, while head-to-head dimerization proceeds according to a stepwise mechanism involving a carbon-centered biradical which is formed after the initial Si-Si bond formation. 1,3-Disilacyclobutane was found to be more stable than the 1,2-isomer by $19.8 \text{ kcal mol}^{-1}$. There is controversy about the mechanism of a head-to-tail reaction as to whether it proceeds via a concerted pathway or via a double excited state <1992JA3643, 1993JA3322>. More recent complete active space self-consistent field (CASSCF) studies suggest, however, that head-to-head and head-to-tail dimerizations of silenes involve the same 1,4-biradical intermediate, which reacts in a way controlled by electronic factors of the substituents on silicon and carbon (Scheme 1) <1998JA1912>.



Scheme 1

Ab initio (Hartree-Fock, HF) and density functional theory (DFT) calculations on the dimerization of simple germenes $\text{H}_2\text{Ge}=\text{CH}_2$, $\text{MeHGe}=\text{CH}_2$, $\text{Me}_2\text{Ge}=\text{CH}_2$, $\text{FHGe}=\text{CH}_2$, and $\text{H}_2\text{Ge}=\text{CHF}$ predict that the formation of the 1,3-digermacyclobutanes (head-to-tail reaction) has a lower activation barrier and is more exothermic than the formation of the 1,2-digermacyclobutanes (head-to-head reaction), except for $\text{H}_2\text{Ge}=\text{CHF}$ where the product of head-to-head dimerization is predicted to be more stable than the head-to-tail product. This result was rationalized in terms of the electron-withdrawing nature of fluorine <1998PCA744>.

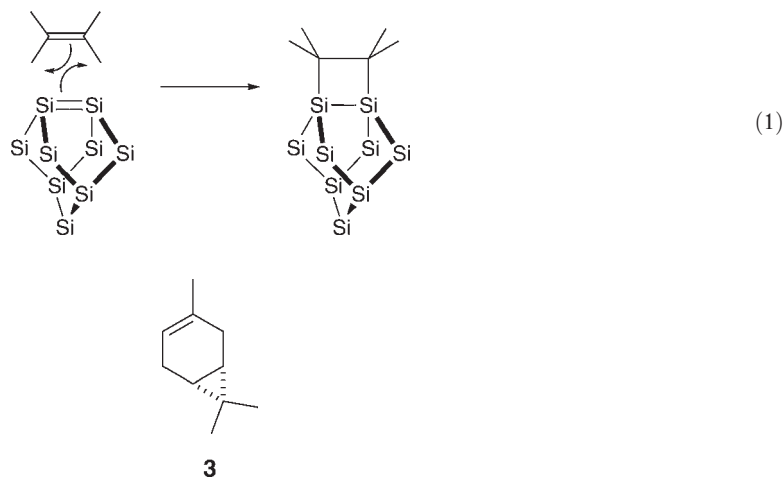
The effect of geminal substitution at silicon on strain energies and enthalpies of the thermal metathesis and [2+2] cycloreversion reactions (Scheme 2) in 1-sila- **1** and 1,3-disilacyclobutanes **2** was studied by *ab initio* methods using the MP4/TZ(d)//MP2/6-31G(d) level of theory <2002JA662>. In the series $\text{R} = \text{H}, \text{Me}, \text{SiH}_3, \text{OMe}, \text{NH}_2, \text{Cl}, \text{F}$, the increase in the reaction enthalpies and strain energies is proportional to the electronegativities of the substituents at silicon. The strain energies for **1** and **2** are higher for the 1-silacyclobutane series except for $\text{R} = \text{Cl}$ and F . The enthalpies of the ring-opening reaction are $68.0\text{--}80.1 \text{ kcal mol}^{-1}$ (a cleavage of the Si-C bond in **2**), $65.0\text{--}76.4 \text{ kcal mol}^{-1}$



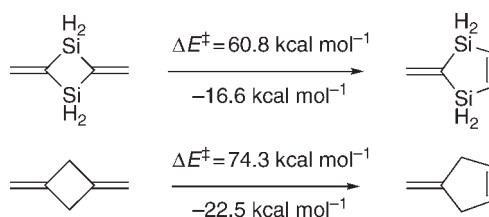
Scheme 2

(a cleavage of the Si–C bond in **1**), and 58.0–64.9 kcal mol^{−1} (a cleavage of the C–C bond in **1**). Calculations of the energetics of the cycloreversion reaction showed that both the enthalpies and barriers for 1,3-disilacyclobutanes are much higher than those for 1-silacyclobutanes, and this is the clue to the high thermal stability of 1,3-disilacyclobutanes. [2+2] cycloreversion of **1** is endothermic by 40.6–63.1 kcal mol^{−1}, whereas that of **2** is endothermic by 72.7–114.2 kcal mol^{−1}. The pronounced difference in the enthalpies of [2+2] cycloreversion of 1-sila- and 1,3-disilacyclobutanes is mainly due to the difference in the enthalpies of diradical decomposition. This is also the reason why the gas-phase thermal metathesis of 1-silacyclobutanes is not reversible <2002JA662>.

Alkenes react with the crystalline silicon surface in a way analogous to [2+2] cycloaddition (Equation 1). Addition of ethylene <1997JA7593> and acetylene <1997CPL97> to silicon clusters used as models of the silicon surface, have been studied by theoretical methods. DFT calculations of the cycloaddition of 1*S*-(+)-3-carene (3,7,7-trimethylbicyclo[4.1.0]hept-3-ene) **3** to the Si clusters supported by the scanning tunneling microscopy (STM) studies have shown that the process is enantiospecific, resulting in the formation of a chiral surface <1999JA4532>. This is a significant step toward the design of surfaces capable of chiral recognition.



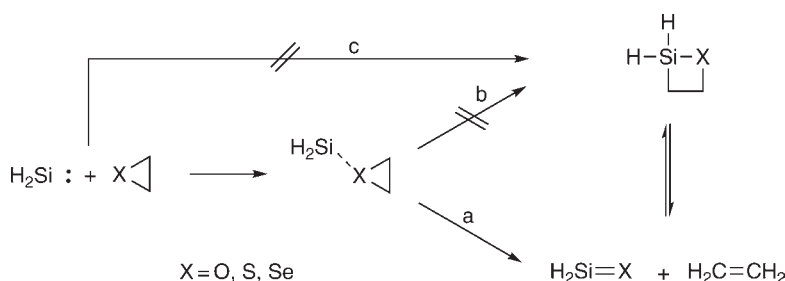
Thermal isomerization of alkenes to carbenes via a 1,2-silyl shift was examined both experimentally and theoretically (Scheme 3). 2,4-Dimethylene-1,3-disilacyclobutane undergoes thermal ring expansion to a 2-methylene-1,3-disilacyclopentene. The analogous all-carbon system failed to ring expand. *Ab initio* calculations revealed that this was



Scheme 3

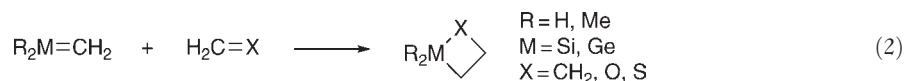
opposite to predictions made from ring strain considerations and was associated with the difference in the structure and energy between the transition states in both reactions <1995JA11695>.

The reactions between silylene ($\text{H}_2\text{Si}:$) and the three-membered ring compounds, oxirane, thiirane, and selenirane, which provide possible routes to $\text{Si}=\text{X}$ ($\text{X} = \text{O}, \text{S}, \text{Se}$) double bonds were studied by *ab initio* calculations at the MP2 and QCISD correlated levels of theory <2000CJC1496>. Three possible mechanisms have been examined (Scheme 4). Based on the results, the authors have concluded that the 'silatane route', via the corresponding oxa-, thia-, and selenasilacyclobutanes, is not a likely mechanism for the production of $\text{H}_2\text{Si}=\text{X}$.

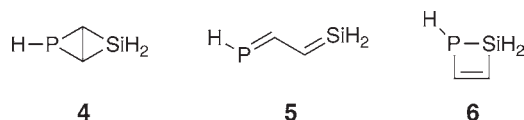


Scheme 4

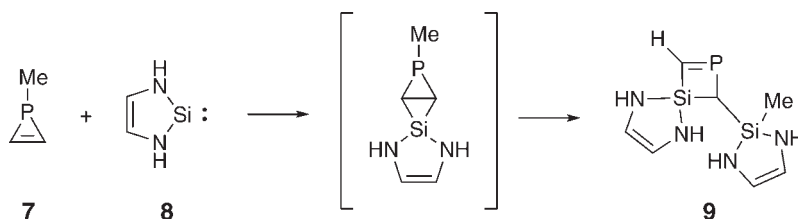
The cycloadditions of small unsaturated organic molecules, such as ethylene, formaldehyde, and thioformaldehyde, to simple silenes and their germanium analogues (Equation 2) in the gas phase were studied by the DFT B3LYP/6-311G(d,p) method. The optimized geometry parameters, vibrational frequencies of model species, energy barriers, and total energies of cycloaddition reactions are given. A lower reactivity was predicted for germanes compared to silanes in the reaction studied and a two-step mechanism of [2+2] cycloadditions was suggested <2001RCB20>.



Rearrangements of 2-phospha-4-sila-bicyclo[1.1.0]butane **4** were studied at the B3LYP/6-311+G(d,p) level of theory. The monocyclic 1,2-dihydro-1,2-phosphasilete **3** is shown to be the thermodynamically preferred product. Two reaction pathways for the thermal isomerization of molecule **4** have been found: (1) a higher-energy three-step process starting with a barrier of $40.7 \text{ kcal mol}^{-1}$ for the concerted, asynchronous conrotatory ring opening of **4** to *trans*-1-phospha-4-sila-1,3-butadiene **5**, followed by a conformational change to the *gauche*-isomer and a subsequent conrotatory electrocyclic ring closure to **6**; and (b) a lower-energy transformation of **4** directly into **6** via a $[\sigma_{2s} + \sigma_{2a}]$ process with a barrier of $34.7 \text{ kcal mol}^{-1}$. This latter path is unprecedented in the analogous isomerization of bicyclo[1.1.0]butane <2004PS803>.

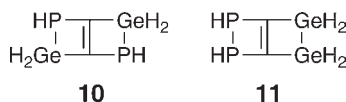


The mechanism of the reaction of 1*H*-phosphirene **7** with silylene **8** resulting in 1,3-phosphasilacyclobutane **9** was studied by *ab initio* and DFT theoretical methods. The reaction was found to proceed via 2-phospha-4-silabicyclo[1.1.0]butane as an intermediate (Scheme 5) <2004AGE3474>. This reaction was also studied for higher substituted analogues by spectroscopic methods (see Section 2.21.10).



Scheme 5

Ab initio HF calculations on the dimerization of the model 1-phospha-3-germaallene, $\text{HP}=\text{C}=\text{GeH}_2$, have shown that the most stable dimers appear to be the bicyclic compounds presenting ‘butterfly’ structures **10** and **11** formed by two successive $\text{P}=\text{C}$ or $\text{Ge}=\text{C}$ cycloadditions <1996OM3070, 2004RCB1020>. The formation of such derivatives should be possible owing to the differences between the $\text{C}=\text{C}$ bond length (1.34 Å) and the $\text{P}-\text{P}$, $\text{Ge}-\text{P}$, and $\text{Ge}-\text{Ge}$ distances (about 2.25, 2.40, and 2.50 Å, respectively), which relieve the cyclic strain that might be expected.



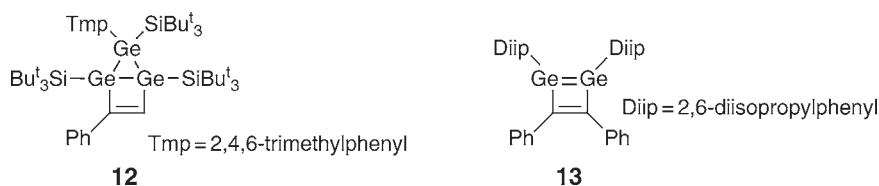
Molecular orbital methods have been used in conjunction with spectroscopic data (infrared (IR), Raman, nuclear magnetic resonance (NMR)) to solve spectra and to identify unstable intermediates <1998JA5005, 2004ICA1920, B-2003MI329>. These applications are discussed in the relevant sections (see Section 2.21.3).

2.21.3 Experimental Structural Methods

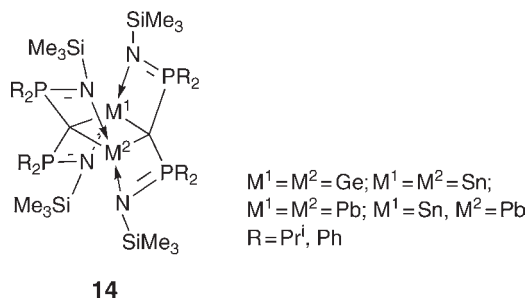
Since the publication of CHEC-II(1996) <1996CHEC-II(1B)1175>, structural studies of four-membered heterocycles containing silicon have been significantly extended. A number of structural studies of four-membered rings containing germanium, tin, and lead have also appeared since that time. These compounds were not considered in CHEC-II(1996). Recent advances in structural chemistry of organic germanium, tin, and lead compounds have been reviewed <B-1995MI97, B-1995MI365, B-2002MI283>.

2.21.3.1 X-Ray Spectroscopy

X-Ray crystallographic data on the following classes of compounds have been reported (the alternative common names are given in parentheses): 1,2- and 1,3-disiletanes (disilacyclobutanes) <1995CB1083, 1996CB15, 1996JOM181, 1997OM1828, 1999CEJ774, 1999EJI2301, 1999OM5643, 2000JOM395, 2001JOM110, 2000OM2470, 2005EJI2151>; 1,2-disiletetes (disilacyclobutenes) including conjugated rings <1996JOM377, 1998CL471, 1998OM1237, 2000CL1082, 2001CC183>; 1,2- and 1,3-digermetanes (digermacyclobutanes) <1995CC1625, 1995OM2139, 1999OM1622, 1999OM5643, 2002IC3084> and mixed 1,3-silagermetane <1999OM5643>; and unsaturated rings, 1,2-digermetes, having the unusual structures **12** <2000AGE3881> and **13** <2004JA5062>.

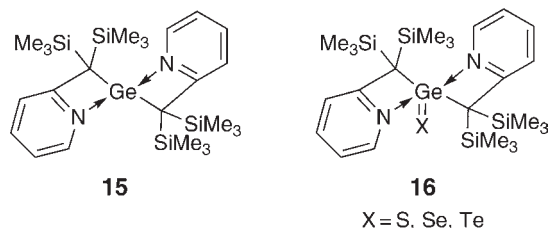


X-Ray structures of 1,3-dimetallacyclobutanes containing heavier elements of group 14, Ge, Sn, and Pb, have been published <2001JA8123, 2001AGE2501, 2003OM4604>. These compounds contain heteroatoms at low-valence state and are stabilized by intramolecular donor interactions (e.g., **14**) (see also Section 2.21.11). The metal–metal distances in the ring are too long to consider the presence of bonding interactions.

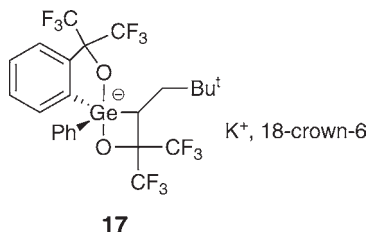


Crystal structures of 1,2- and 1,3-cyclobutanes containing one Si or Ge atom and O, S, N, or P heteroatoms have also been reported. 1,3-Oxasiletane (3-siloxetane) and 1,3-thiasiletane (3-silathietane) have been characterized in the solid state and in solution by X-ray analysis and NMR spectroscopy <1995CB167>. X-Ray structures of 1,2-oxasiletanes <2001EJI481>, oxagermetane <1999OM540, 2002JOM202>, azasiletidine (azasilacyclobutane) <1996JOM43> and 1,3-phosphasiletane (phosphasilacyclobutane), and 1,2- and 1,3-phosphasilete (phosphasilacyclobutene) derivatives <2004AGE3474> have been published.

The base-stabilized germylene **15** and the corresponding germanethione, selenone, and tellurone **16** are not covalently bonded cyclobutane derivatives; however, strong intramolecular coordination with nitrogen leads to the four-membered cyclic arrangement, which has been supported by X-ray studies <1997OM2116>.



The crystal structure of an anionic species containing pentacoordinate Ge (1,2-oxagermetanide **17**) has also been published <1995JOM143>.



Structures of 1,2-azasiletanes (1,2-azasilacyclobut-3-enes) and their lithium salts have been reported <1999AGE501, 2002JCD3253>.

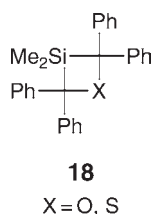
Most of the cyclobutane rings studied are essentially planar and the bonds within the ring are longer than in acyclic structures. In some cases, however, a significant distortion from planarity was observed, due to steric interactions between bulky ligands or due to the restrictions imposed by double bonds <1996JOM181, 1999EJI2301>. No evidence for the bonding between heteroatoms in 1,3-positions has been found.

An electron diffraction study of the molecular structure and a study of the inversion potential for 1,1,3,3-tetramethyl-1,3-disilacyclobutane have been published <1999JST135, 2000ZSK217>.

2.21.3.2 NMR Spectroscopy

¹H and ¹³C NMR spectroscopy have been routinely used for characterization of the new products. Silicon or phosphorus containing heterocycles are normally also characterized by ²⁹Si NMR and ³¹P NMR. This chapter only includes references in which extended NMR spectroscopy studies are presented. Applications of ¹¹⁹Sn NMR and Mössbauer spectroscopy for structural analysis of tin derivatives have been reviewed <B-1995MI365>. Recent advances in ⁷³Ge, ¹¹⁹Sn, and ²⁰⁷Pb NMR have been discussed <B-2002MI339>. ¹¹⁹Sn NMR has been used for the characterization of 1,3-distannetanes <2001JA8123, 2003OM4604> and oxastannetanide <1997PS513>.

Dimerization of 3-phospha-1-silaallene was studied by ¹H and ³¹P NMR spectroscopy <1999CEJ774>. 3-Siloxetane and 3-silathietane **18** were characterized by solid state ¹³C and ²⁹Si cross-polarization/magic angle spinning (CP/MAS) NMR <1995CB167>. Experimental and theoretical ²⁹Si NMR studies on cyclic siloxetanes and silathietanes and analogous acyclic organosilanes show that variation of the CR₂–Si–CR₂ bond angle results in opposite effects on the ²⁹Si NMR shift for cyclic and acyclic systems. Therefore, structural predictions for strained organosilanes, based on ²⁹Si NMR data, remain a challenge. A direct correlation of the ²⁹Si NMR shift and the CR₂–Si–CR₂ bond angle is only possible for related systems <B-2003MI329>.



2.21.3.3 Mass Spectrometry

Mass spectral studies of the following heterocyclobutanes have been reported: 1,2-disilacyclobutanes <1996JOM377>; 1,3-disilacyclobutanes <1995JA11695, 1997OM1828, 1999EJ12301, 1999OM1804, 1999OM5643, 2000JOM395, 2000OM2470, 2001JMP555, 2001JOM127, 2001JOM10, 2003OM2233, 2005EJ12151, 2005JOM4492>; 1,2-azasilanes <1996JOM43, 1996JOM191>; 1,2-oxasilanes <1996OM2554>; 1,3-disila- and silagermacyclobutanes <1999OM5643>. Mass fragmentation was reported for 1,2- and 1,3-phosphasilacyclobutane derivatives <2004AGE3474> and phosphagermacyclobutanes <1996OM3070>. Main molecular fragments for 1,2-disilacyclobut-3-ene <1996JOM163> and 1,2-digermacyclobut-3-ene <1996OM2014> have been reported.

2.21.3.4 UV and IR Spectroscopy

Ultraviolet (UV) and IR techniques have been used for characterization of the following species: 1,3-disilacyclobutanes (IR) <1999OM1804, 1999OM5643, 2000JOM395>, (UV) <1995JA11695>; 1,3-silagermacyclobutane derivatives (IR) <1999OM5643>; 1,3-disilacyclobutenes (IR) <1996JOM163, 2003JOM272>; 1,2-digermacyclobutadiene (UV, IR) <2004JA5062>; and 1,2-siloxetanes (IR) <1996OM2554>.

Irradiation ($\lambda > 295$ nm, Ar, 10 K) of matrix-isolated (trimethoxysilyl)carbene produced 1,1-dimethoxy-1,2-siloxetane which was identified by IR spectroscopy in comparison with *ab initio* calculations at the RHF/6-31G(d,p) level of theory. The most intense IR absorption was observed at 1104 cm^{-1} <1996OM736>. Similarly, vacuum pyrolysis–matrix isolation Fourier transform infrared (FTIR) and DFT studies of 3,3-dimethyl-3-germa-6-oxabicyclo[3.1.0]hexane indicated the transient formation of dimethylgermoxetane <1998OM5041>.

Combined electron ionization mass spectroscopy (EIMS) and matrix isolation FTIR spectroscopic data on vacuum pyrolysis of 1,1-dimethyl-1-germa-3-thietane assisted by theoretical calculations provide a reasonable foundation for mechanistic interpretation of its thermal decomposition (see Section 2.21.6.1, Equation 7) <1998JA5005>.

Structural parameters and Raman spectra of 3-siloxetane and 3-silathietane **18** have been discussed on the basis of *ab initio* and DFT calculations <2004ICA1920>. Calculation results reproduce the crystal structures <1995CB167> and experimental Raman spectra <2004ICA1920> very well. Calculations show that the four-membered ring in silathietane **18** (X=S) is nonplanar with a C–Si–C angle of 89.2° and a C–S–C angle of 93.3° , whereas the four-membered ring in siloxetane **18** (X=O) is planar with an unusual small bond angle at the silicon atom of 74.7° , which can only be explained by bent bonds.

Photoelectron (PE) spectroscopy has been used to follow the flash vacuum thermolysis (FVT) of 1-phenyl-2-dimethyl-1-phospha-2-silacyclobutane (Section 2.21.6.1, Scheme 10) <1997OM1635>.

2.21.4 Thermodynamic Aspects

Thermodynamic aspects of reactions involving diheterocyclobutanes are most often studied using both theoretical and experimental methods. Theoretical calculations of the reaction energetics as well as of spectroscopic parameters of reactive intermediates are increasingly used in thermodynamic studies. Therefore, these works are also discussed in Section 2.21.2.

Theoretical studies on thermodynamic aspects of [2+2] cycloaddition of simple silenes <1992JA3643, 1993JA3322, 1998JA1912> and germenes <1998PCA744> have been presented in Section 2.21.2. The reaction pathways which lead to *cis*- and *trans*-isomers of the asymmetrically substituted germenes, $\text{MeHGe}=\text{CH}_2$, $\text{FHGe}=\text{CH}_2$, and $\text{H}_2\text{Ge}=\text{CHF}$, have been investigated. The calculated activation parameters and the total reaction energies (ΔE) and enthalpies (ΔH) have been reported <1998PCA744>. Calculated strain energies of **1** and **2** and the enthalpies of the [2+2] cycloreversion and thermal metathesis reactions (Scheme 2) and their dependence on the electron-withdrawing properties of the

substituents at silicon have been reported <2002JA662>. Energies and energy barriers were calculated for thermal isomerization of alkenes to carbenes via a 1,2-silyl shift (Scheme 3) <1995JA11695>.

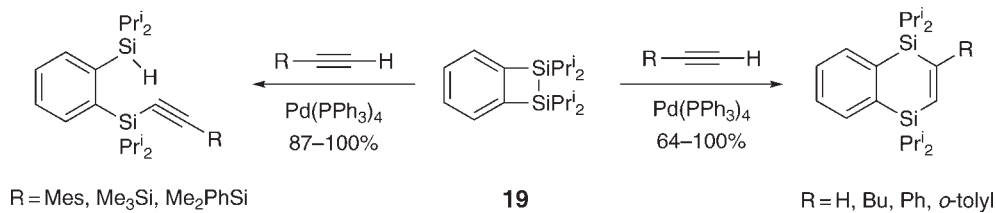
Absolute rate constants for the head-to-tail [2+2] dimerization of 1,1-diphenylsilene and 1,1-diphenylgermene have been determined in hexane and isooctane solution at 23 °C by laser flash photolysis, using the corresponding 1,1-diphenylmetallacyclobutanes as precursors. The rate constants for dimerization of the two compounds are similar and within a factor of about 2 of the diffusional rate constant in both cases <1999OM5643>.

The possibility of the transient formation of 1,2-siloxetane, thietane, and selenetane in the reactions between silylene ($\text{H}_2\text{Si:}$) and the corresponding three-membered ring compounds (Scheme 4) has been discussed on the basis of calculated enthalpies and energy barriers for the elementary reactions <2000CJC1496>.

The dimerization thermodynamics of a model 1-phospha-3-germaallene has been studied by theoretical methods <1996OM3070, 2004RCB1020>.

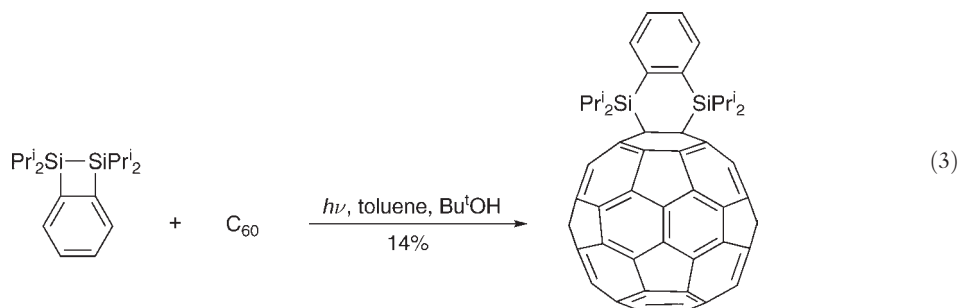
2.21.5 Reactivity of Conjugated Rings

Transition metal-catalyzed reactions of 3,4-benzo-1,2-disilacyclobut-3-ene **19** with alkenes, alkynes, and carbonyl compounds afford various products. The products formed depend on the nature of the metal in the reactive species formed by the reaction of compound **19** with transition metal complexes of Ni, Pt, and Pd used as catalyst <1995SL794, 1996JOM163, 1996OM1101, 1997JOM149, 1998OM5830, 1999JOM149, 2000CL1082>. For example, a variety of different alkynes can insert into **19** in the palladium-catalyzed process (Scheme 6) <1996JOM163>.

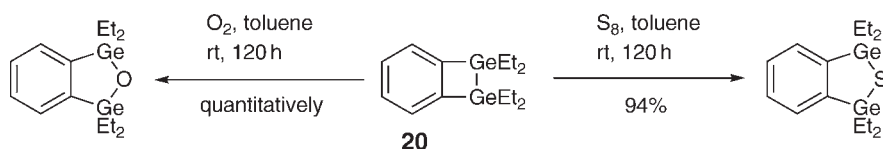


Scheme 6

The photochemical reaction of compound **19** with C_{60} affords a stable 1:1 adduct with C_{2v} symmetry (Equation 3) <1996T4995>.

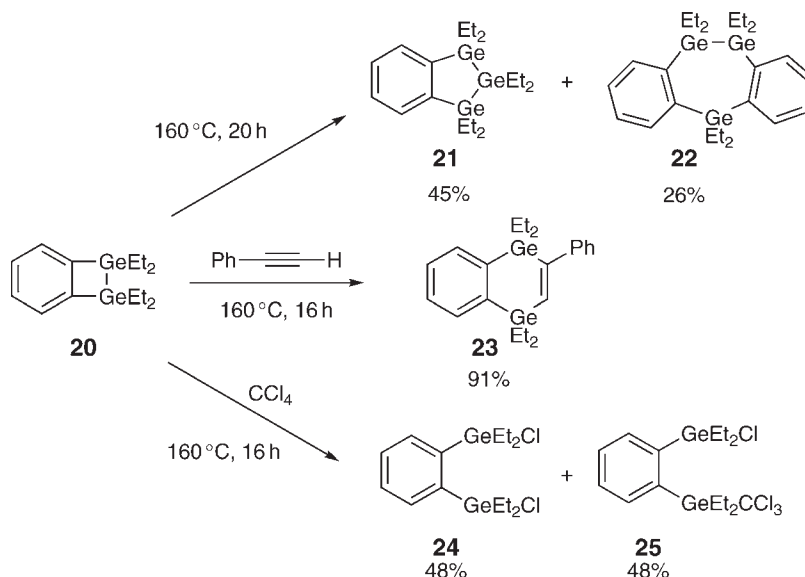


3,4-Benzo-1,1,2,2-tetraethyl-1,2-digermacyclobut-3-ene **20** is highly reactive but can be purified by column chromatography and vacuum distillation. Oxygen and sulfur are inserted into the Ge–Ge bond of **20** to give 2-oxa- and 2-thia-1,3-digermacyclopent-3-enes, respectively (Scheme 7) <1996OM2014>.



Scheme 7

Digermacyclobutene **20** is thermally labile and readily undergoes ring-opening polymerization (ROP) in toluene to give the corresponding polymer (Equation (15), Section 2.21.6.3). Upon heating at 160 °C for 20 h, **20** gave two products, 4,5-benzo-1,2,3-trigermacyclopent-4-ene **21** and 3,4:6,7-dibenzo-1,2,5-trigermacyclohepta-3,6-diene **22** in reasonable yields. Thermolysis of **20** in the presence of phenylacetylene led to 2,3-benzo-1,4-digerma-5-phenylcyclohexa-2,5-diene **23**, while in CCl₄ two chlorinated products, 1,2-bis(chlorodiethylgermyl)benzene **24** and 1-(chlorodiethylgermyl)-2-(diethyl(trichloromethyl)germyl)benzene **25**, were formed (Scheme 8). The mechanisms of the polymerization and thermolysis have been discussed <1996OM2014>.



Scheme 8

In the presence of catalytic amounts of Pd(PPh₃)₄, compound **20** readily undergoes a reversible σ -bond metathesis below 100 °C to give a dimer, 1,2,5,6-dibenzo-3,4,7,8-tetragermacycloocta-1,5-diene **26**. At 160 °C, the unsymmetrical dimer 1,2,4,5-dibenzo-3,6,7,8-tetragermacycloocta-1,4-diene **27** and two isomeric products are obtained. Intermediate formation of 3,4-benzo-1-pallada-2,5-digermacyclopent-3-ene **28** plays an important role in this process (Scheme 9) <2000JOM420>.

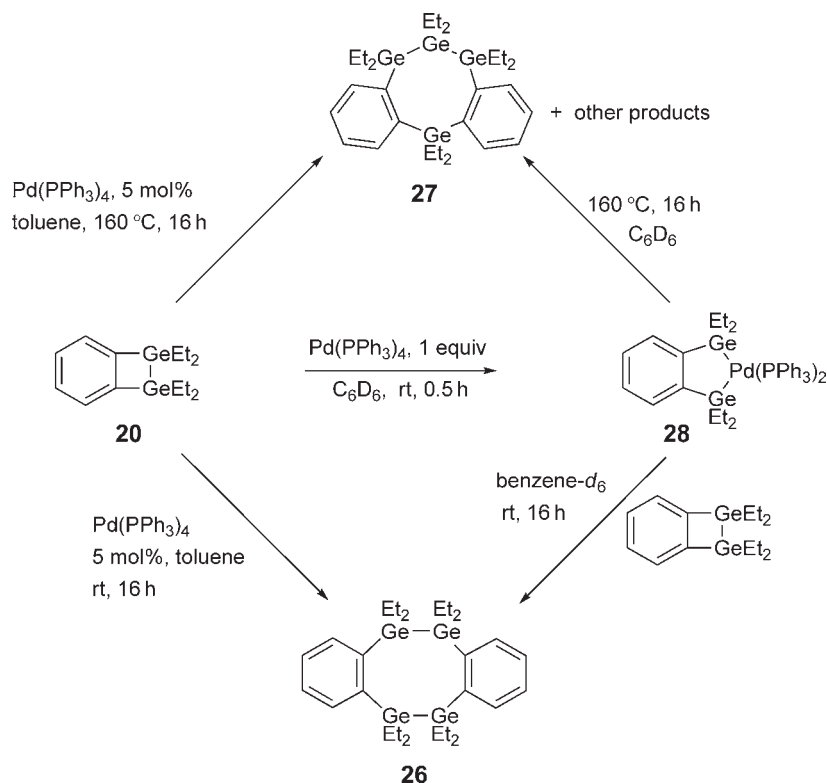
2.21.6 Reactivity of Nonconjugated Rings

Early reports on thermal and photochemical reactivity, [2+2] cycloreversion, ring expansion, and ring-opening reactions have been covered in previous editions <1984CHEC(1)573, 1996CHEC-II(1B)1175>. Photochemistry of organosilicon compounds has been summarized <1995CRV1527>. [2+2] cycloreversion has recently been comprehensively reviewed <1995CRV1527, 2003CCR149>.

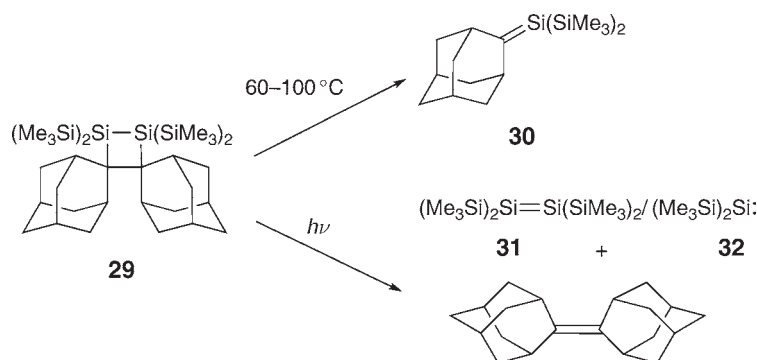
2.21.6.1 Thermal and Photochemical Reactions

The heating of 1,2-disilacyclobutane **29** in hexane at 60–100 °C in the presence of trapping agents leads to the expected products of the silene **30** trapping. In benzene at 60 °C, **29** exists in equilibrium with **30** <2002OM2049>.

Photolysis of compound **29** at –196 °C in methylcyclohexane in the absence of trapping agents produces the disilene **31**. Photolysis of compound **29** in hexane at –78 °C gave silylene **32**, which was probably a product of dissociation of **31**. Continuous photolysis of compound **29** in the presence of trapping agents confirmed the presence of both **31** and **32** in the reaction mixture (Scheme 10) <1998JA1398>.

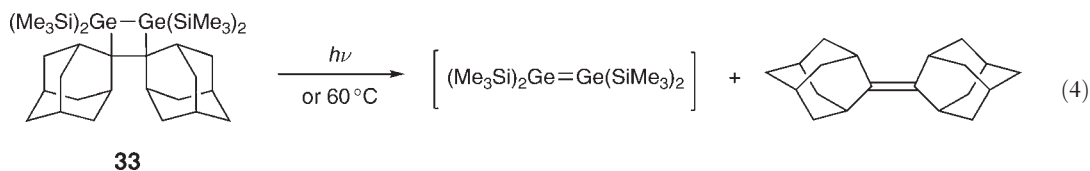


Scheme 9

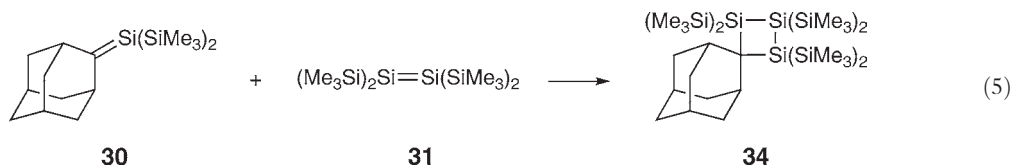


Scheme 10

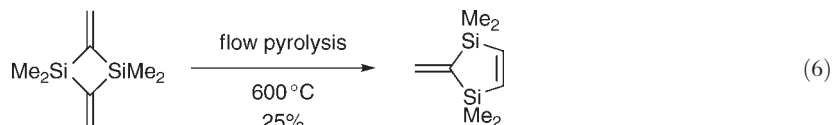
1,1,2,2-Tetrakis(trimethylsilyl)dispiro[3,3',4,4'-biadamantane-1,2-digermacyclobutane] **33** exhibits an entirely different behavior upon heating from that of its silicon analogue **29**. Presumably, the digermene $(\text{Me}_3\text{Si})_2\text{Ge}=\text{Ge}(\text{SiMe}_3)_2$ polymerizes at 60°C . In contrast to the thermolysis, the photolysis of compound **33** at 254 nm shows close analogy to the photolysis of compound **29**, leading to digermene $(\text{Me}_3\text{Si})_2\text{Ge}=\text{Ge}(\text{SiMe}_3)_2$ (Equation 4) <1998JA1398>.



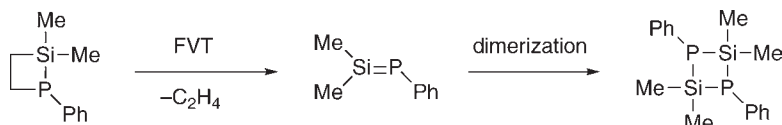
Thermolysis of compound **29** at 150–180 °C in the absence of trapping agents presumably proceeds via the competitive cleavage of the Si–Si and C–C bonds, resulting in simultaneous transient formation of the silene **30** and the disilene **31**, which undergo fast cycloaddition to produce trisilacyclobutane **34** (Equation 5) <2002OM2049>.



Pyrolysis of 1,1,3,3-trimethyl-2,4-dimethylene-1,3-disilacyclobutane in a vertical nitrogen-flow system at 600 °C produced a mixture of starting material and methylenedisilacyclopentane (Equation 6) <1995JA11695>.

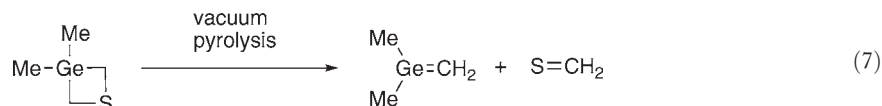


FVT of phosphasilacyclobutane affords a [1,3,2,4]diphospha-disiletane derivative as the only product (Scheme 11) <1997OM1635>.



Scheme 11

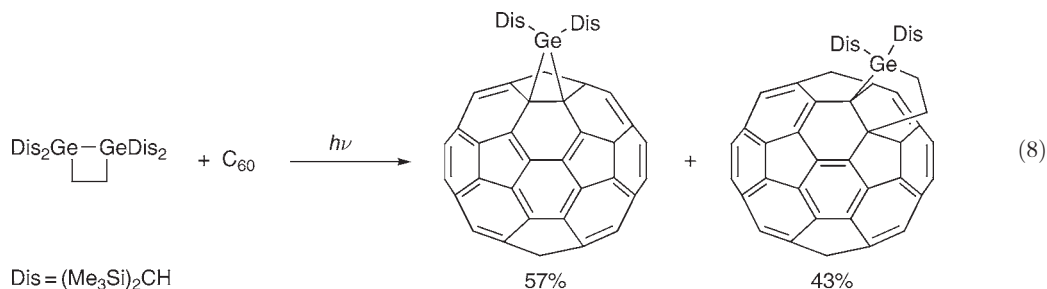
Vacuum pyrolysis of 1,1-dimethyl-1-germa-3-thietane proceeds with the formation of 1,1-dimethyl-1-germene (Equation 7) <1998JA5005>.



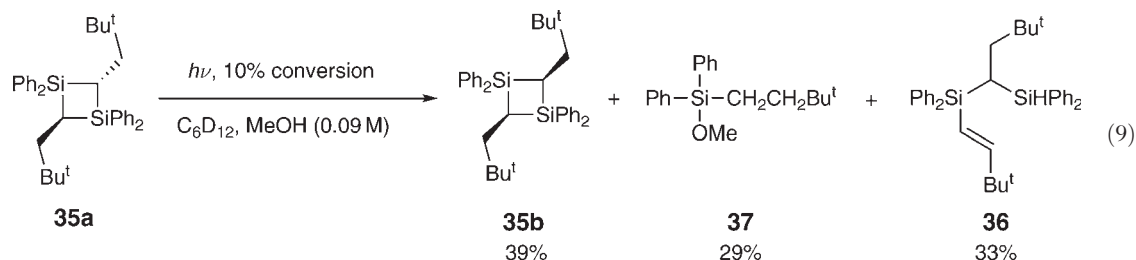
Siloxetanes have been postulated to occur as unstable intermediates in several thermolytic processes <1996OM3836, 1998OM5830, 2000AGE4127>.

Laser flash and/or steady-state photolysis experiments indicate that 1,1,3,3-tetraphenyl-1,3-dimetallacyclobutanes decompose to the corresponding 1,1-diphenylmetallenes upon photolysis in hydrocarbon solvents, probably via the same 1,4-biradical intermediates which link the metallenes with their corresponding dimers via a stepwise dimerization mechanism <1999OM5643>. Laser photolysis of 1,3-disilacyclobutanes–O₂ mixtures in the presence of buffer gas (N₂, He) is a complex reaction yielding formaldehyde, methanol, formic acid, and methane, together with a solid methylsilicone deposit <2001JOM170>. The laser irradiation of gaseous 1,3-disilacyclobutanes–CS₂ mixtures affords chemical vapor deposition of a solid polythiacarbosilane film containing Si–S–Si, C–S–Si, Si–H, and S–H bonds <2004JOM2697>.

The photolysis of 1,2-digerMACyclobutane derivatives with bulky bis(trimethylsilyl)methyl groups in a toluene solution of C₆₀ provided the germylene and germacyclopentane adducts of C₆₀ (Equation 8) <2001JOM82>.



Using *trans*-1,1,3,3-tetraphenyl-2,4-dineopentyl-1,3-disilacyclobutane **35a** as the precursor, the reactivity of the transient 1,1-diphenyl-2-neopentylsilene has been studied in various solvents by laser flash photolysis methods. These experiments verified that the isomeric compounds *cis*-**35b** and (*E*)-**36** and the expected adduct of MeOH to silene **37** are the only primary products of photolysis of **35a** at low (ca. 10%) conversion (Equation 9). Similar experiments with *cis*-**35b** showed it to be ca. 4 times more photoreactive than the *trans*-isomer, producing *trans*-**35a**, **37**, and *E*-**36** with initial yields of 69%, 11%, and 19%, respectively <2005OM2309>.



2.21.6.2 Reactivity toward Nucleophiles

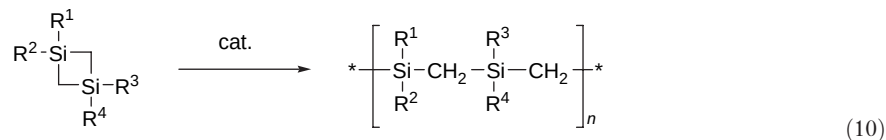
Transition metal-catalyzed reactions of four-membered rings with two heteroatoms including silicon to lead with electron-rich reagents have been reported (see Section 2.21.5) <1995SL794, 1996JOM163, 1996OM1101, 1997JOM149, 1998OM5830, 1999JOM149, 2000CL1082>.

Reaction of disilacyclobutanes with organolithium compounds results in ring opening and leads to polymeric species (polycarbosilanes) (see Section 2.21.6.3).

2.21.6.3 Ring-Opening Polymerization

ROP of cyclic carbosilanes is one of the most promising techniques for the synthesis of well-defined polycarbosilanes. ROP of four-membered ring compounds, 1,3-disilacyclobutanes, and monosilacyclobutanes, as well as copolymerizations of mixtures of monomers, have been widely investigated in the last decades <1996JOM1, B-1996MI7621, B-2000MI247>.

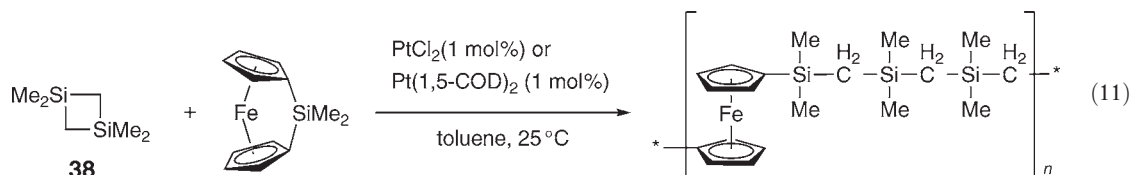
ROP of 1,3-disilacyclobutanes may be initiated thermally or catalytically. Most effective transition metal catalysts are hexachloroplatinic acid (H_2PtCl_6), platinum metal, and platinum or rhodium complexes. Strong nucleophiles such as organolithium compounds also initiate the ROP of disilacyclobutanes, according to the anionic mechanism <2000MI805>. Polymerization yields high molecular weight poly(silylenemethylene)s with a strictly alternating SiR_2/CH_2 backbone structure (Equation 10) <1996CM1260, 1996MM3701, 1997JA12020, 1997PSA399, 1997PSA3193, 1998MI2119, 1998PSA725>.



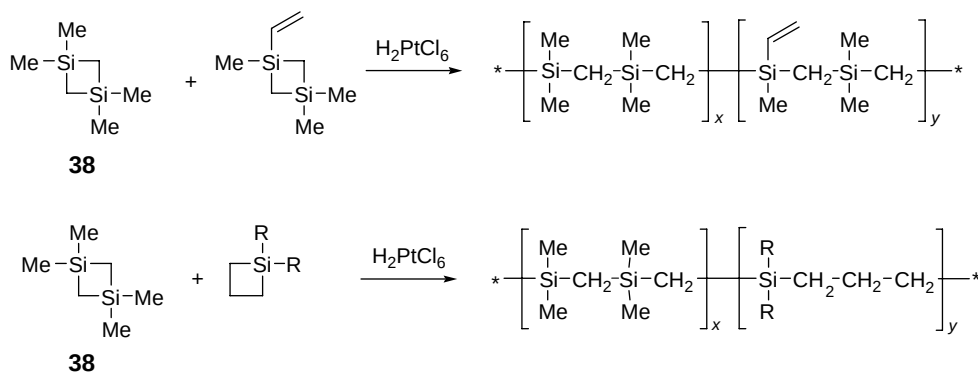
$\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4 = \text{Me, Et, Pr, Bu, } n\text{-C}_5\text{H}_{11}, n\text{-C}_6\text{H}_{13}, \text{Cl, OEt, Ph}$

Cat. = H_2PtCl_6 , $\text{Pt}(\text{acac})_2$, $\text{Pt}(1,5\text{-COD})_2$, $\text{Rh}(1,5\text{-COD})_2$, $\text{Rh}_2(1,5\text{-COD})_2\text{Cl}_2$
(COD = cyclooctadiene)

1,1,3,3-Tetramethyl-1,3-disilacyclobutane **38** undergoes copolymerization with silicon-bridged [1]ferrocenophanes catalyzed by platinum complex (Equation 11) <1996MI319>.

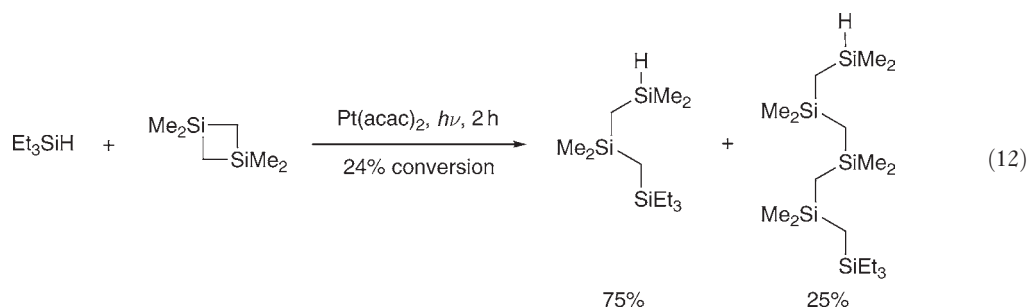


1,1,2,2-Tetramethyl-1,2-disilacyclobutane undergoes spontaneous ring-opening polymerization and copolymerization with styrene at room temperature giving linear polymers <1998MI89>. A series of polytrimethylenesilanes with different substituents on the silicon atom, as well as the new polydimethylsilylmethylene, were synthesized by the ROP of the corresponding sila- and disilacyclobutanes. For the first time, the copolymerization of dimethylsila- and tetramethyldisilacyclobutanes was carried out with formation of permethylsilylalkylene elastomers (temp. 25–100 °C, yields of polymers 95–100%) (Scheme 12) <2004RCB2604>.

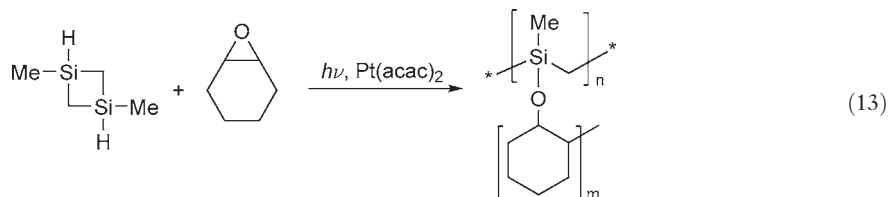


Scheme 12

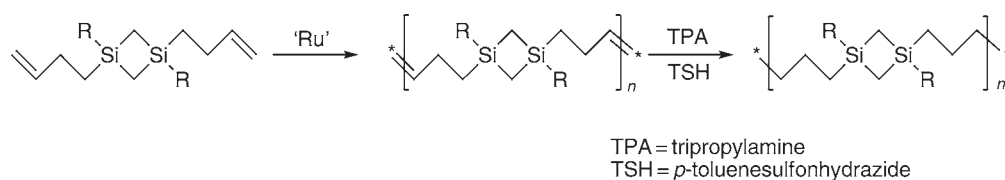
Copper compounds were found to be effective catalysts of 1,3-methyl-1,3-phenyl-1,3-disilacyclobutane as well as 1,1,3,3-phenyl-1,3-disilacyclobutane <1998PLM2715>. The cationic rhodium(i) complexes [Rh(1,5-COD)₂]⁺A[−] (A=OTf, PF₆) have been shown to exhibit high catalytic activity for the transition metal-mediated ROP of compound **38** (COD = cyclooctadiene) <2002OM4377>. ROP of 1,3-disilacyclobutanes proceeds smoothly in the presence of platinum(II) acetylacetonate (acac), Pt(acac)₂, and other Pt(II) β-diketonates on near UV irradiation <1999MM6003, 2000PP494, 2001MM6202>. Photoactivated telomerization of **38** with hydrosilanes is facilitated by UV irradiation in the presence of Pt(acac)₂ (Equation 12) <1999TL8309>.



Photopolymerization of epoxides in the presence of silanes RSi₃H and Pt(acac)₂ has been reported (Equation 13). Si–H-containing silanes exhibit a cocatalytic effect on epoxide photopolymerization, although silanes with a larger number of silicon–hydrogen bonds being better cocatalysts. A homogeneous, cationic polymerization mechanism is proposed <2001MM6202>.



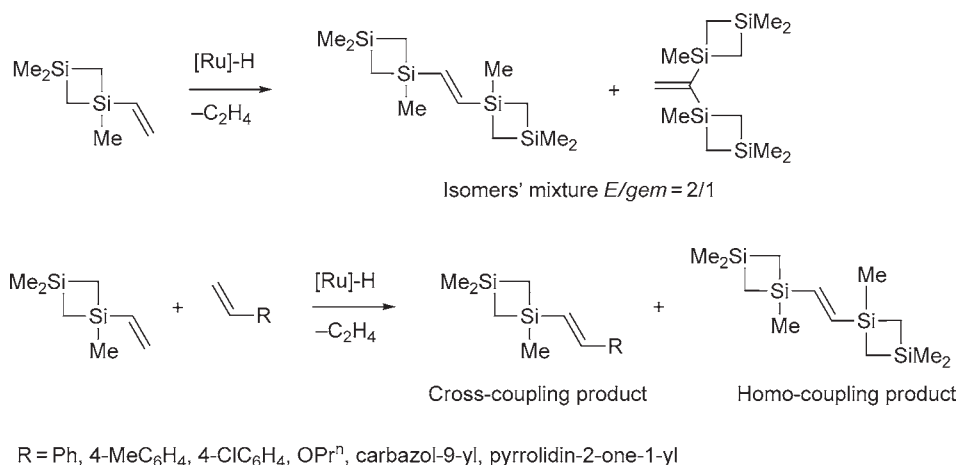
Cyclolinear carbosilane polymers with disilacyclobutane rings in the main-chain structure were prepared by means of acyclic diene metathesis (ADMET) polymerization of the corresponding 1,3-dibutenyl-1,3-disilacyclobutanes in the presence of Grubbs' catalyst (**Scheme 13**) <2003PP789, 2004MM5257, 2004PP118>.



Scheme 13

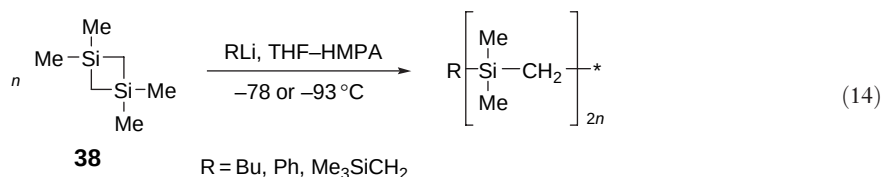
Functionalization of monomers and/or polymers containing aromatic groups at silicon with trifluoromethanesulfonic acid followed by reactions with Grignard reagents, amines, or lithium tetrahydridoaluminate gave novel polymeric derivatives. The protodesilylation reaction could be controlled by using different leaving groups (phenyl, *p*-tolyl, or *p*-anisyl groups) (see also Section 2.21.8) <1997JOM281>.

Cross-coupling of vinyldisilacyclobutane with a variety of alkenes in the presence of $[\text{RuH}(\text{Cl})(\text{CO})(\text{PCy}_3)_2]$ leads to stereoselective formation of functionalized vinyldisilacyclobutanes (**Scheme 14**). Analogous homo-coupling of vinyldisilacyclobutane leads to the formation of (*E*)- and *gem*-bis(silyl)ethenes. The reaction offers a new route for the synthesis of attractive monomers for ROP <2005JOM4492>.

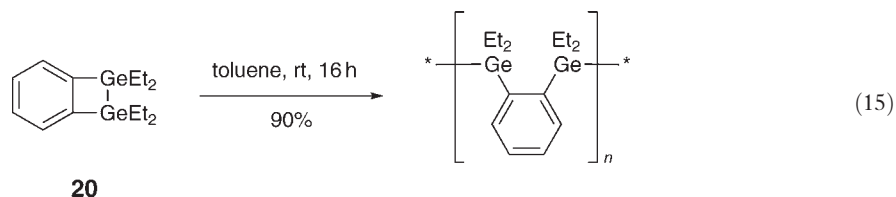


Scheme 14

Nucleophilic attack of carbanions on silicon in silacyclobutane rings results in breaking of the Si-C bond in the ring leading to the recovery of the carbanionic center. Disilacyclobutane **38** was polymerized by addition of alkyllithium as initiator in tetrahydrofuran (THF) at -78°C in the presence of hexamethylphosphoramide (HMPA) acting as an activator (Equation 14) <2000MI805>.



Benzodigermacyclobutene **20** is thermally labile and undergoes spontaneous polymerization to yield insoluble solids either neat or in common organic solvents, such as THF, toluene, and hexane (Equation 15) <1996OM2014>.



2.21.6.4 Reactivity toward Electrophiles

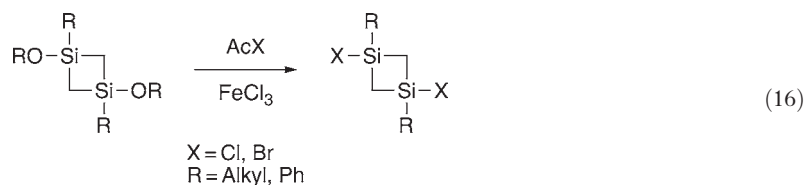
Transition metals such as Ni, Pd, and Pt undergo insertion into the Si–Si and Ge–Ge bonds of 1,2-dimetallacyclobutanes (Scheme 9) resulting in ring expansion <1995SL794, 2000CL1082>.

2.21.7 Reactivity of Substituents Attached to Ring Carbon Atoms

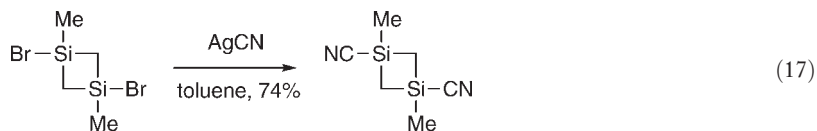
No reports have been published.

2.21.8 Reactivity of Substituents Attached to Ring Heteroatoms

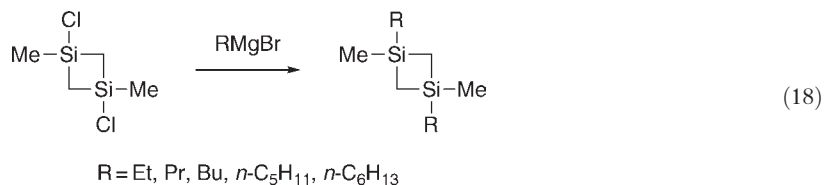
Disilacyclobutanes can be functionalized by electrophilic or nucleophilic substitution at silicon, depending on the nature of the substituents. Alkoxy groups may be replaced by halogens in the presence of a Lewis acid, for example, by FeCl₃ (Equation 16) <1997PSA3193, 2003JOM272>.



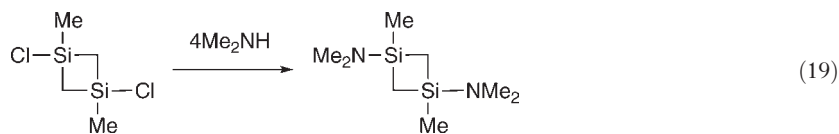
Silver cyanide reacts with 1,3-dibromo-1,3-disilacyclobutane giving 1,3-dicyano-1,3-disilacyclobutane (Equation 17) <2003JOM272>.



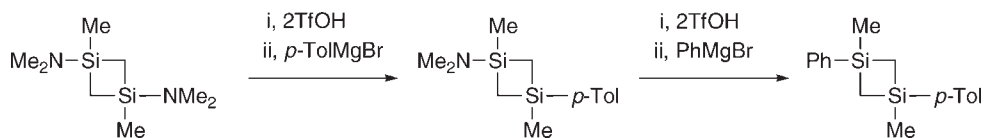
Nucleophilic substitution at silicon in 1,3-dichloro-1,3-disilacyclobutanes by Grignard reagents allows the introduction of alkyl groups onto the ring (Equation 18) <1997PSA3193>.



Chlorine atoms may be substituted for amino groups by reaction with secondary amines (Equation 19) <1997JOM281>.



Amino and aryl groups may be substituted in a controlled way by the action of triflic acid (Scheme 15) <1997JOM281, 1998PSA725>.



Scheme 15

2.21.9 Ring Syntheses from Acyclic Compounds

2.21.9.1 Synthesis of 1,2-Diheterobutane Systems

Previously known methods <1984CHEC(1)573, 1996CHEC-II(1B)1175> have been modified and used for the effective synthesis of a variety of new disilacyclobutanes.

2.21.9.1.1 Saturated rings

Magnesium is a typical coupling agent for the synthesis of 1,3-disilacyclobutanes. Several new compounds have been obtained in this way (Equation (20); Table 1).

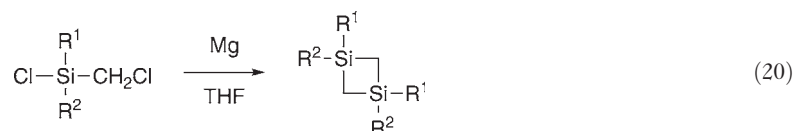


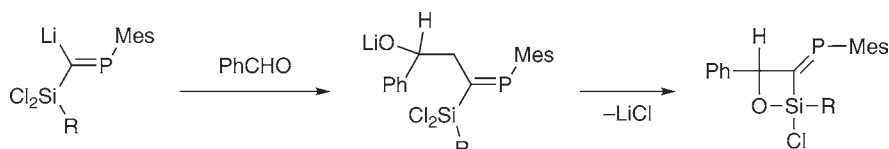
Table 1 Reaction of (chloromethyl)chlorosilane derivatives with magnesium (Equation 20)

Entry	R ¹	R ²	Yield (%)	Reference
1	Me	Bu	48	1996MM3701
2	Me	<i>n</i> -C ₅ H ₁₁	42	1996MM3701
3	Me	<i>n</i> -C ₆ H ₁₃	29	1996MM3701
4	Me	OMe	7	1997PSA3193
5	Me	OPr ⁱ	51	1997PSA3193
6	<i>n</i> -C ₆ H ₁₃	OEt	58	1997PSA3193
7	Ph	OEt	53	1997PSA3193

3,4-Carboranylene-1,1,2,2-tetramethyl-1,2-digermacyclobutane has been prepared using the Wurtz-type coupling reaction of *o*-bis(chlorodimethylgermyl)-carborane with sodium (Equation 21) <2002IC3084>.



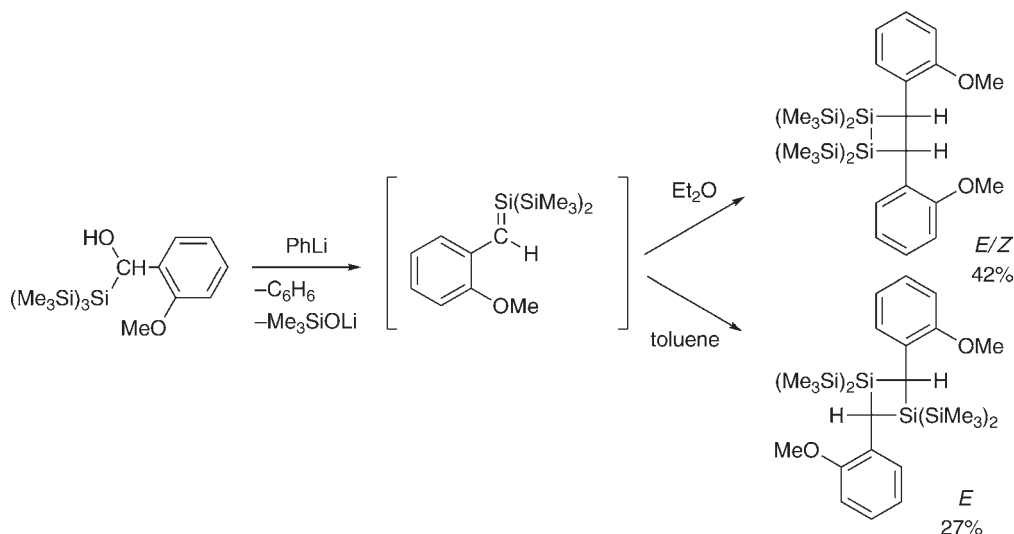
1-(Dichlorosilyl)-2-phosphaethenyllithium compounds readily react with benzaldehyde to afford oxasiletane rings with an exocyclic P=C bond via an addition–elimination route (**Scheme 16**) <2005EJI1109>.



Scheme 16

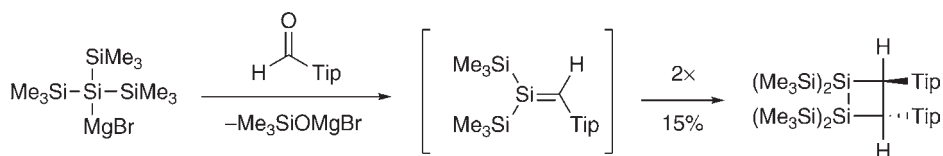
[2+2] cycloaddition of multiple bonds to silenes, germenes, and stannenes is one of the most important reactions leading to heterocyclobutane derivatives. For reviews, see: silenes and disilenes <1996AOC231, B-1998MI857, 1998CCR565>; germenes and stannenes <1998CCR593>.

The direction of cycloaddition (head-to-head vs. head-to-tail) is known to be sensitive to steric and electronic factors. Some silenes reveal a solvent-dependent regiospecificity of dimerization. A head-to-tail dimerization in nonpolar solvents is rationalized in terms of the intramolecular assistance of the nucleophilic group in the substituent, such as a methoxy group <1998EJI1667> or an amino function <1997OM1828>, enhancing the polarity of the silene double bond thus facilitating a head-to-tail dimerization (**Scheme 17**). In ether, the solvent effectively competes with the methoxy group, breaking the intramolecular interaction <1998EJI1667>.



Scheme 17

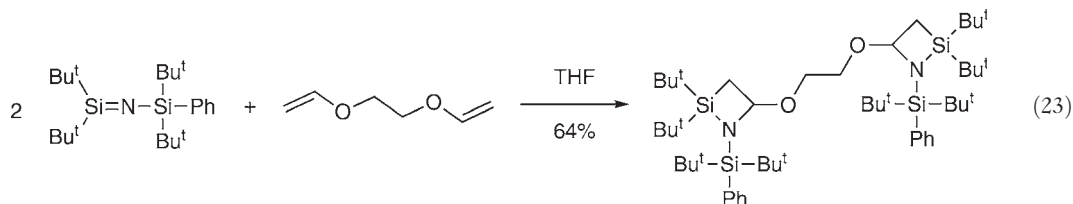
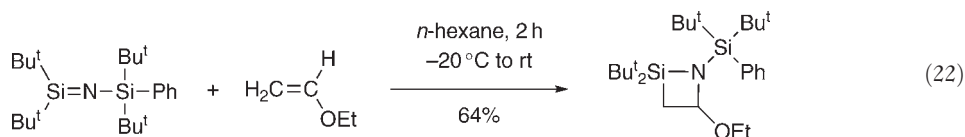
1,2-Disilacyclobutane can be obtained by the dimerization of a transient silene generated by the salt elimination method (**Scheme 18**) <1996JOM181>. Other examples of head-to-head dimerization of silenes have been published <1995CB143, 1995CB1083, 1996CB15>.



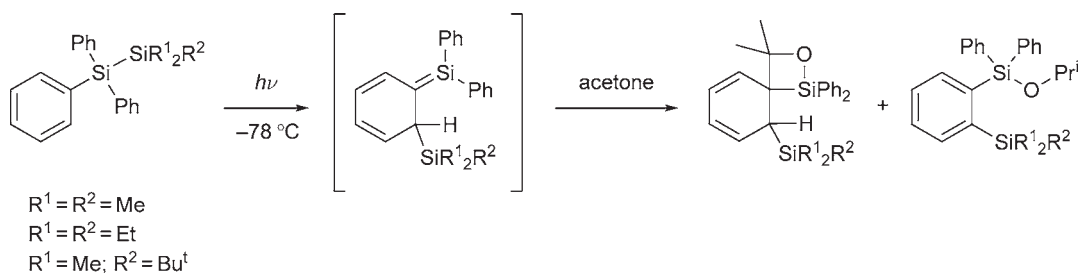
Tip = 2,4,6-triisopropylphenyl

Scheme 18

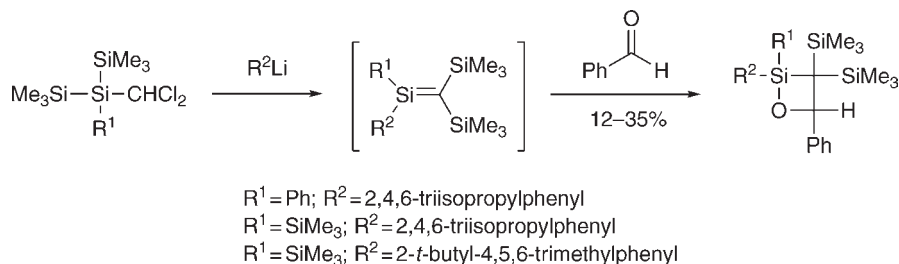
Azasiletanes can be prepared via cycloaddition of iminosilane to vinyl ethers (Equations 22 and 23) <1996JOM43, 1996JOM191>.



Stable 1,2-siloxetanes can be obtained by reaction of transient silenes with acetone (Scheme 19) <1996OM2554> or benzaldehyde (Scheme 20) <2001EJ1481>. Other examples of the reaction of silenes with ketones or imines have also been reported <1995CB1241>.

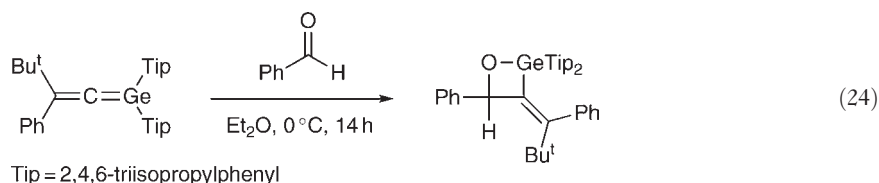


Scheme 19

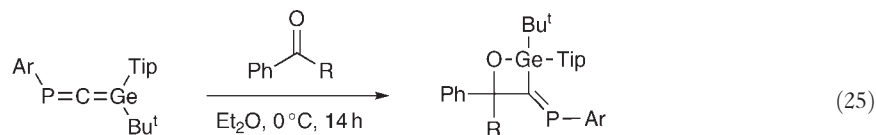


Scheme 20

Reaction of 1-germapropadiene with benzaldehyde gave 1,2-oxagermetane with an exocyclic double bond (Equation 24) <1999OM540>.

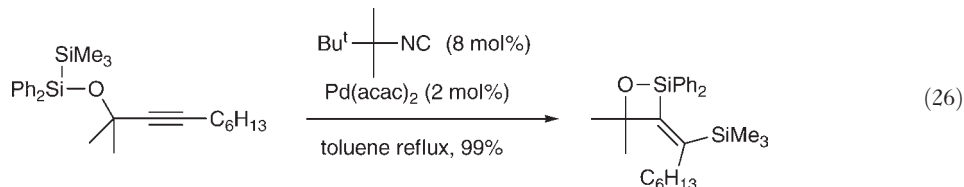


[2+2] cycloaddition of stable 3,1-germaphosphaallene to the C=O bond in aldehydes and ketones affords the 1,2-oxagermetane system with exocyclic P=C bonds (Equation 25) <2002JOM202> (see also review <2004RCB1020>).



Tip = 2,4,6-triisopropylphenyl; Ar = 2,4,6-tri-*tert*-butylphenyl; R = H, Ph

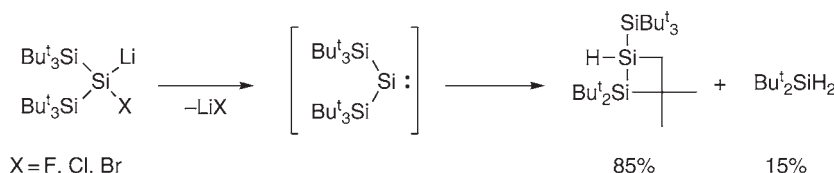
Siloxetanes have been prepared by palladium-catalyzed intramolecular addition of an Si–Si bond to the triple bond of disilanyl-propargylic ethers. Stable four-membered cyclic siloxetanes were successfully isolated after the reaction of tertiary disilanyl-propargylic ether under palladium catalysis <1998JA1930> (see also review <2003JOM218>). The formation of a siloxetane system was also observed in high yield in the reaction of secondary disilanyl-propargylic ethers (Equation 26); however, the product was unstable and decomposed during silica gel column chromatography <1996JOC4884>.



Palladium-catalyzed intramolecular bis-silylation of allyldisilanyl ether produced *trans*-siloxetane, which undergoes a fast dimerization <2005CEJ2954>.

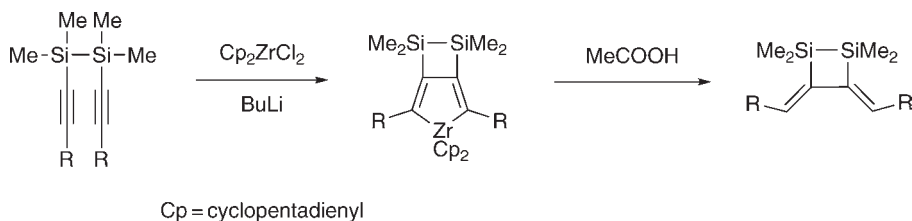
Formation of a pentacoordinate 1,2-oxastannetanide by a base-induced rearrangement of a bis(β -hydroxyalkyl)-stannane has also been reported <1997PS513>. Synthesis of pentacoordinate anionic oxasiletanides, oxagermetanides, and oxastannetanides has been reviewed (Scheme 17) <1998OM367, 2000JOM256, 2002CSR195>.

1,1,1,3,3,3-Hexa-*tert*-butyl-trisilene decomposes with the formation of 1,2-disilacyclobutane and di-*tert*-butylsilane (Scheme 21) <2001JOM57>.



Scheme 21

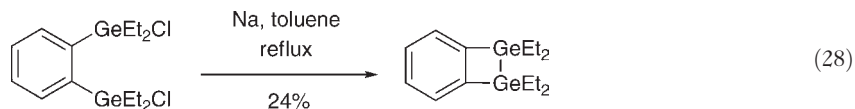
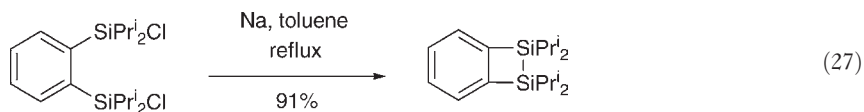
Zirconocene-mediated coupling of bis(methoxyethynyl)disilanes led to zirconacycles, which were converted into 1,2-disilacyclobutanes by protonolysis (Scheme 22) <2000CL1082>.



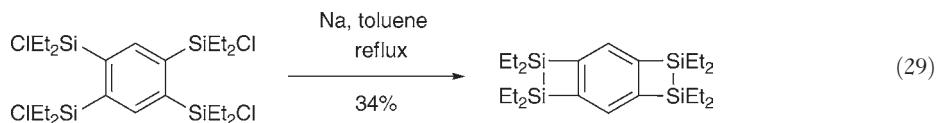
Scheme 22

2.21.9.1.2 Unsaturated rings

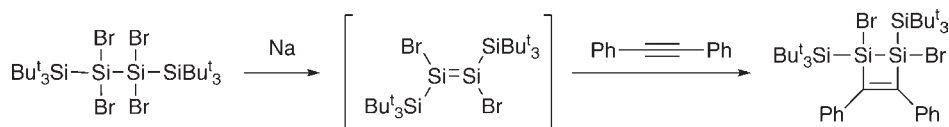
3,4-Benzo-1,2-disilacyclobut-3-ene and its digerma analogue have been prepared by the sodium-mediated Wurtz-type coupling of 1,2-bis(chlorodialkylsilyl)benzene <1996JOM163, 1996T4995> and 1,2-bis(chlorodialkylgermanyl)benzene <1996OM2014>, respectively (Equations 27 and 28).



Sodium-catalyzed condensation of 1,2,4,5-tetrakis(chlorodiethylsilyl)benzene produced benzo[1,2:4,5]bis(1,1,2,2-tetraethyl-1,2-disilacyclobut-3-ene) (Equation 29) <1998OM5830>.

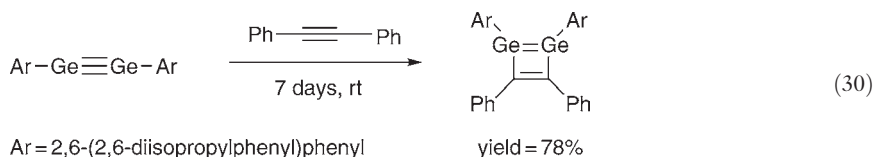


Disilenes react with alkynes, giving 1,2-silylcyclobutenes (Scheme 23) <1996JOM377, 1998OM1237, 2001JOM110>.

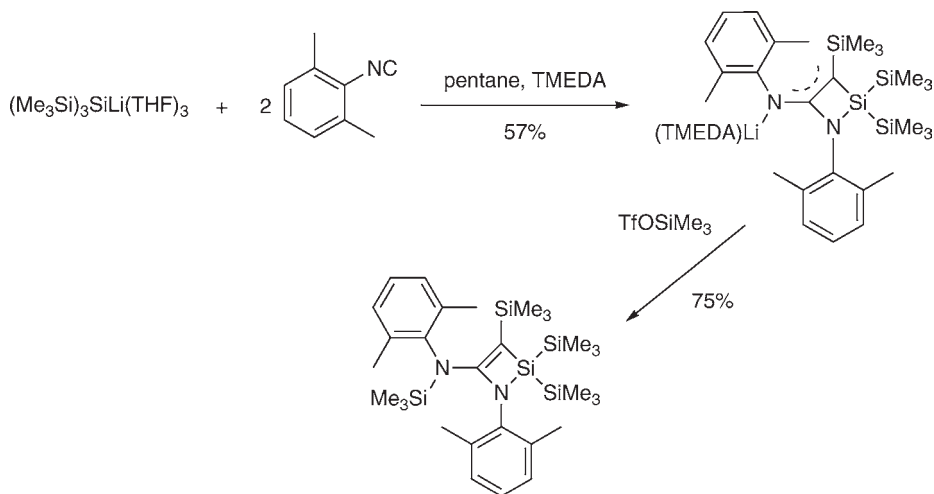


Scheme 23

Reaction of a germanium alkyne analogue with diphenylacetylene affords a stable 1,2-digermacyclobuta-1,3-diene (Equation 30) <2004JA5062, 2005JA17530>.

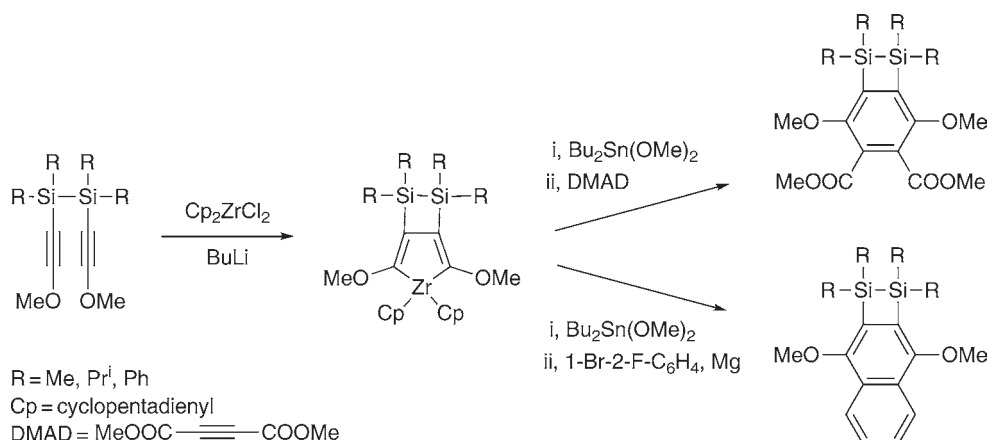


A 1,2-dihydro[1,2]-azasilete derivative has been obtained by treatment of tris(tetrahydrofuran)[tris(trimethylsilyl)-silyl]lithium with 2,6-dimethylbenzoisonitrile (Scheme 24) <1999AGE501, 2002JCD3253>.



Scheme 24

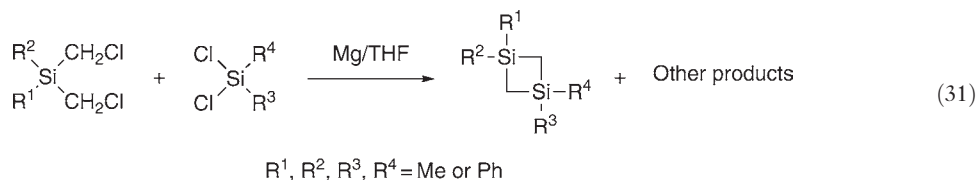
Zirconocene-mediated coupling of bis(methoxyethynyl)disilanes led to zirconacycles, which were converted into 3,4-benzo-1,2-disilacyclobutanes via transmetalation with tin followed by a Diels–Alder reaction (**Scheme 25**) <2000CL1082>.



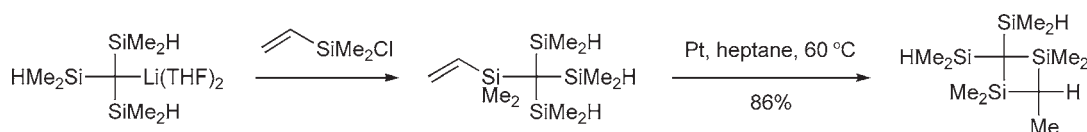
Scheme 25

2.21.9.2 Synthesis of 1,3-Diheterobutane Systems

The Grignard coupling reaction of bis(chloromethyl)diorganosilanes with diorganodichlorosilanes gave the intermolecular C–Si coupling product of 1,1,3,3-tetraorgano-1,3-disilacyclobutanes in poor to moderate yields (7–50%) along with polycarbosilanes (**Equation 31**) <1999BKC427>.



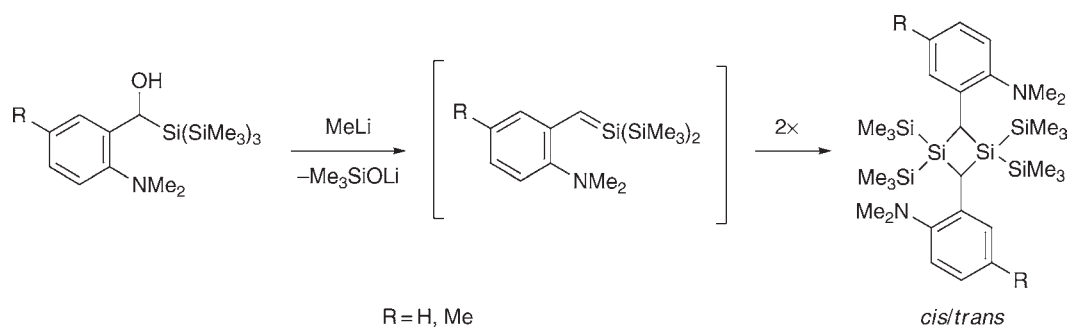
Platinum or ruthenium catalyzes the ring closure of a silanylene giving the 1,3-disiletane via intramolecular hydrosilylation (**Scheme 26**) <2001JOM127>.



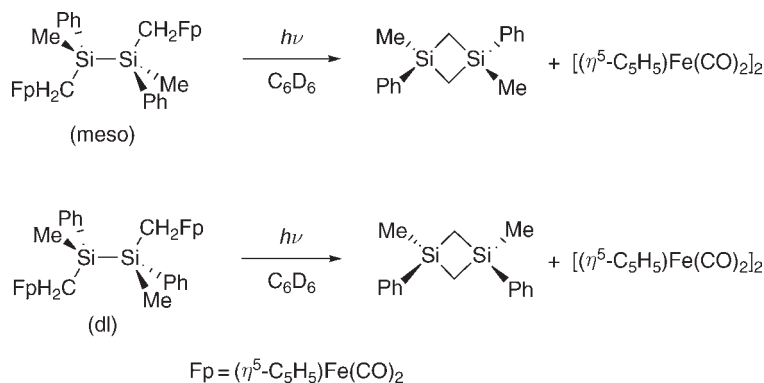
Scheme 26

Head-to-tail [2+2] cycloaddition leading to 1,3-dimetallacyclobutanes is in most cases the preferred direction of dimerization of both silenes and germenenes. The generation of silene by the salt elimination method requires a starting organosilicon compound in which silicon is bonded to an electronegative substituent and to a carbon atom bearing an electropositive metal. The deprotonation of [2-(dimethylamino)phenyl][tris(trimethylsilyl)silyl]methanol with methyl lithium gave a mixture of the *cis*- and *trans*-isomers of 2,4-bis[2-(dimethylamino)phenyl]-1,1,3,3-tetrakis(trimethylsilyl)-1,3-disilacyclobutane ($\text{R} = \text{H}$) (**Scheme 27**) in over 60% yield <1997OM1828>. Application of the base-induced trimethylsilanol elimination strategy for $\text{R} = \text{Me}$ has been reported <2000JOM395>. Other examples of silene head-to-tail couplings have been reported <1995CB1083, 1995CB1241, 1996MIOA7, 2002MI120>.

Stereospecific formation of 1,3-disilacyclobutanes has been observed in photochemical treatment of bimetallic disilane precursors <2000JA8327, 2002OM5859>. Photolysis of the *meso* bimetallic complex affords only the *trans*-1,3-disilacyclobutane, while similar photolysis of the *dl*-form gives only the *cis*-isomer (**Scheme 28**) <2000JA8327>.

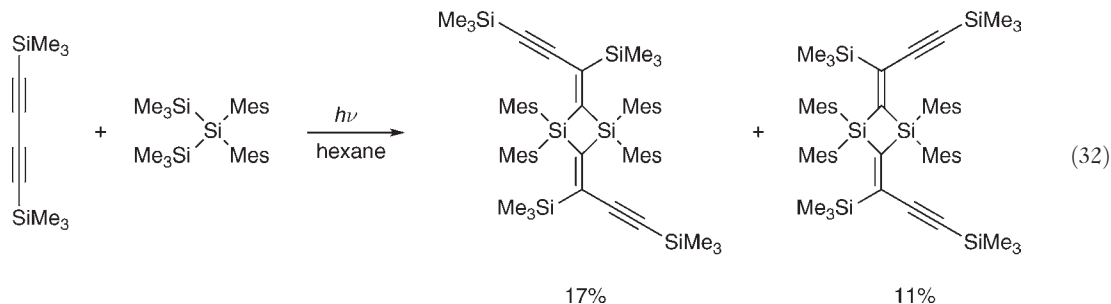


Scheme 27



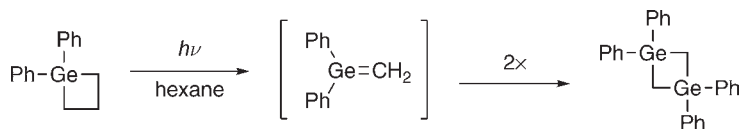
Scheme 28

Irradiation of the trisilane system in the presence of 1,4-bis(trimethylsilyl)buta-1,3-diyne affords the *cis*- and *trans*-isomeric 1,3-dimethylene-2,4-disilacyclobutane derivatives, presumably via a 1-sila-allene intermediate (Equation 32) <1999EJI2301>.

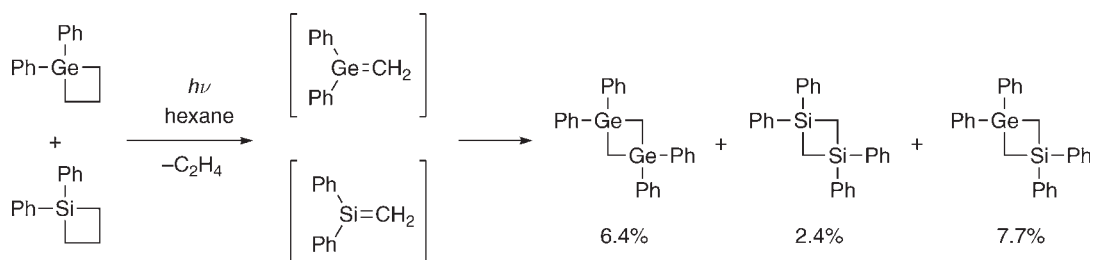


Direct photolysis of 1,1-diphenylgermetane in a hexane solution leads to 1,1,3,3-tetraphenyl-1,3-digermetane in high yield (Scheme 29) <1998JA1172>.

Homo- and cross-cycloaddition of 1,1-diphenylsilene and 1,1-diphenylgermene generated by laser flash photolysis from a 1:1 mixture of the corresponding 1,1-diphenylmetallacyclobutanes gives three 1,3-dimetallacyclobutane products (Scheme 30) <1999OM5643>.

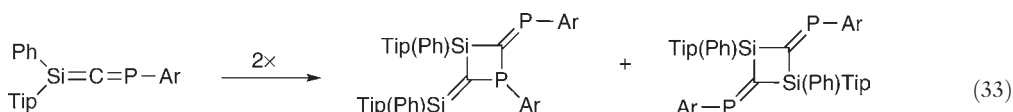


Scheme 29



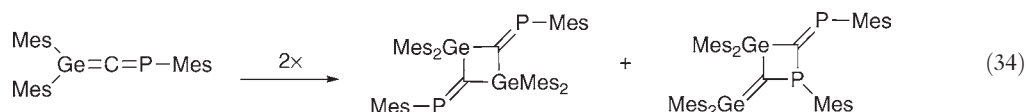
Scheme 30

Above -20°C and in the absence of a trapping reagent, the phosphasilallene gives both 1,3-phosphasilacyclobutane and 1,3-disilacyclobutane dimers in about a 60:40 ratio (Equation 33) <1999CEJ774>.



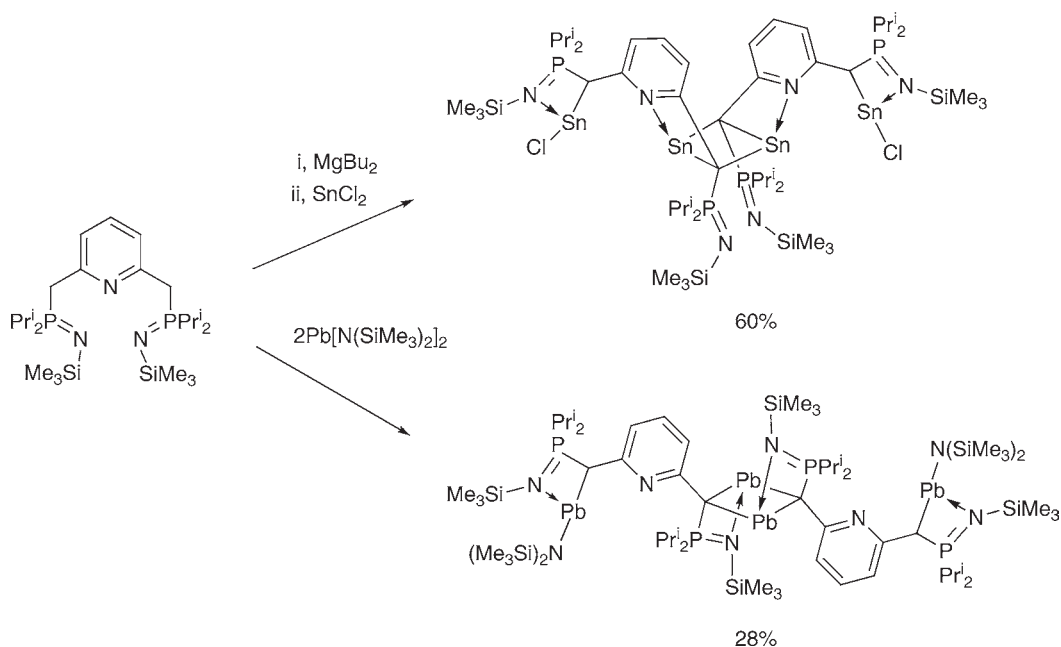
Ar = 2,4,6-tri-*tert*-butylphenyl; Tip = 2,4,6-triisopropylphenyl

In the absence of a trapping agent, phosphagerma-allene generated by debromofluorination of the (fluorogermyl)-bromophosphaalkene gives two types of dimers: the head-to-tail dimer and the product resulting from the cycloaddition between $\text{Ge}=\text{C}$ and $\text{P}=\text{C}$ bonds (Equation 34) <1996OM3070> (see also review <2004RCB1020>).

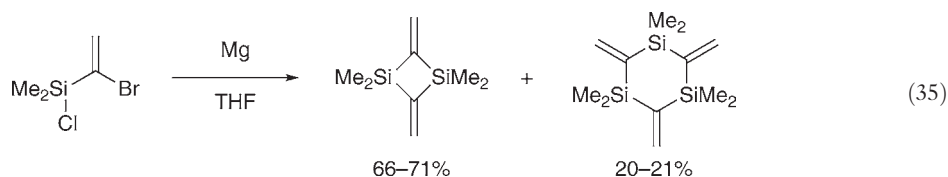


1,3-Diplumbacyclobutane and 1,3-distannacyclobutane systems are formed presumably by a head-to-tail cyclodimerization of the transient stanna- or plumbavinylidene intermediates (Scheme 31) <2003OM4604>.

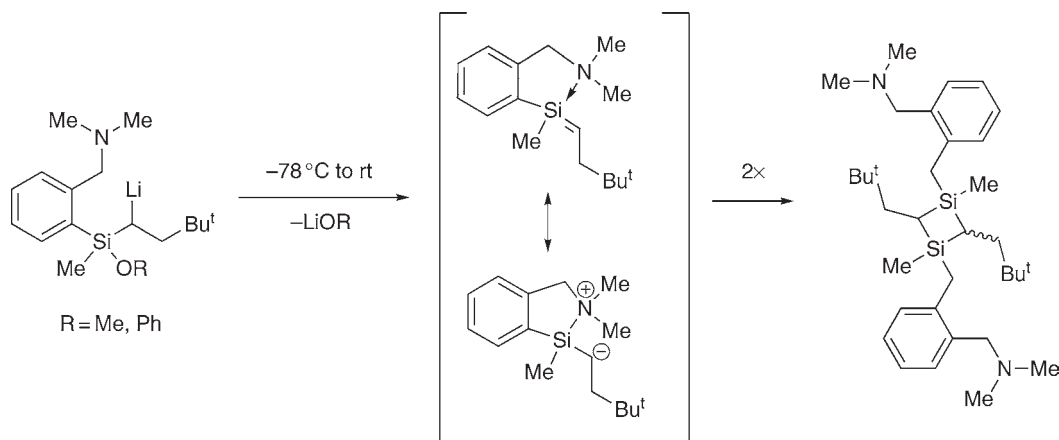
Magnesium-induced dimerization of (1-bromovinyl)-chlorodimethylsilane has been used to prepare 1,1,3,3-trimethyl-2,4-dimethylene-1,3-disilacyclobutane (Equation 35) <1995JA11695>.



Scheme 31

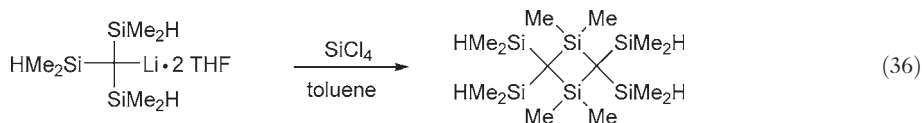


Adducts of *t*-butyllithium to [2-(*N,N*-dimethylaminomethyl)phenyl]-alkyloxymethylvinylsilane [<2002OM2017>](#) or [2-(*N,N*-dimethylaminomethyl)phenyl]-methylvinylchlorosilane lead to 1,3-disilacyclobutanes via a charge-separated zwitterionic precursor (**Scheme 32**) [<2001BKC593>](#).

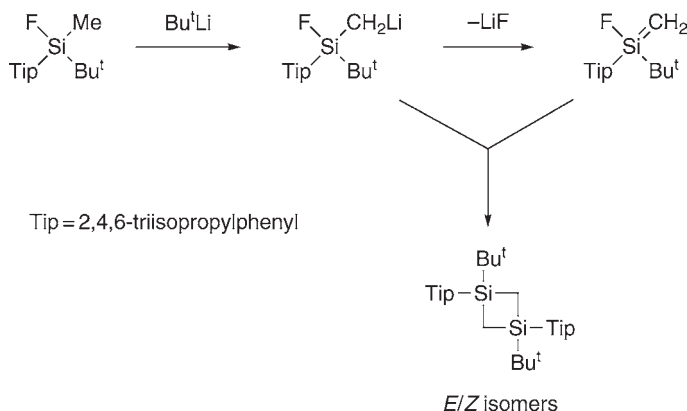


Scheme 32

Reaction between tris(dimethylsilyl)methyl lithium and SiCl_4 in toluene at room temperature resulted in multiple products, including highly substituted 1,3-disilacyclobutane (**Equation 36**) [<1999OM1804>](#).



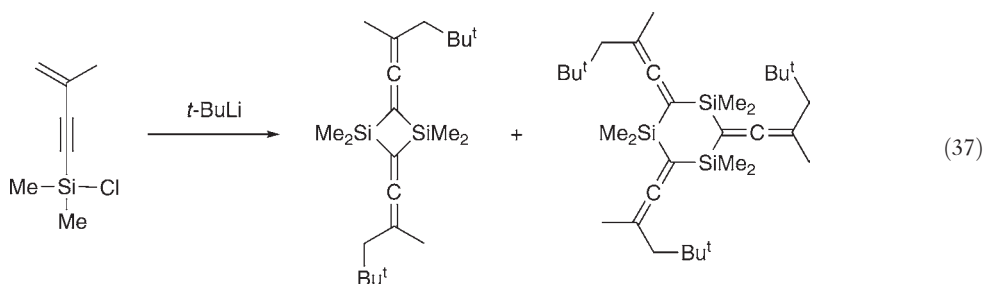
tert-Butylfluoromethyl-(2,2,6-triisopropylphenyl)silane reacts with *tert*-butyllithium leading to *cis*- and *trans*-isomers of 1,3-disilacyclobutane as the final products of transient silenoid or silene dimerization. The ratio of the *cis*- and *trans*-isomers (1:1) indicates their formation from the silene rather than from the silenoid, although no direct evidence for the silene could be found (**Scheme 33**) [<2005EJI2151>](#).



Scheme 33

Bis(lithiomethyl)germanes were used for the synthesis of 1,1,3,3-tetraorgano-1-germa-3-silacyclobutanes <2004ZNB1570>.

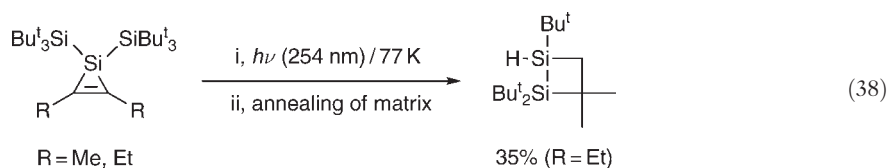
Differently substituted alkenynylsilyl halides reacted with *t*-BuLi in solvents of different polarity giving mainly (*E/Z*)-isomers of 2,4-bis(pentenylidene)-1,3-disilacyclobutanes and (*E/Z*)-2,4,6-tris(pentenylidene)-1,3,4-trisilacyclohexanes competitively (Equation 37) <2001JOM10>.



2.21.10 Ring Syntheses by Transformation of Another Ring

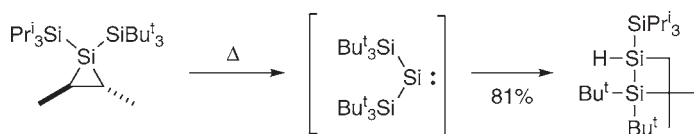
2.21.10.1 Synthesis of 1,2-Diheterobutane Systems

Photolysis of a deuterated methycyclohexane glass matrix of bis(*tri-tert*-butylsilyl)silene produced 1,3-disilacyclobutane, among other products. Bis(*tri-tert*-butylsilyl)silylene has been postulated as an intermediate in this reaction (Equation 38) <2003JA4962>.



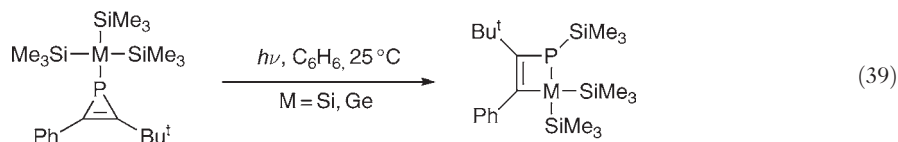
Irradiation of a solution of hexa-*tert*-butylcyclotrisilane in the presence of an excess of hexa-2,4-diyne resulted in a smooth reaction leading to a variety of products containing the 1,2-disilacyclobut-3-ene ring <1998OM1237>.

Thermolysis of *trans*-2,3-dimethyl-1-*tri-tert*-butylsilyl-1-*tri*-isopropylsilylsilirane in the absence of trapping agents yielded 1,2-disilacyclobutane by intramolecular insertion into the C–H bond (Scheme 34) <2003OM2233>.



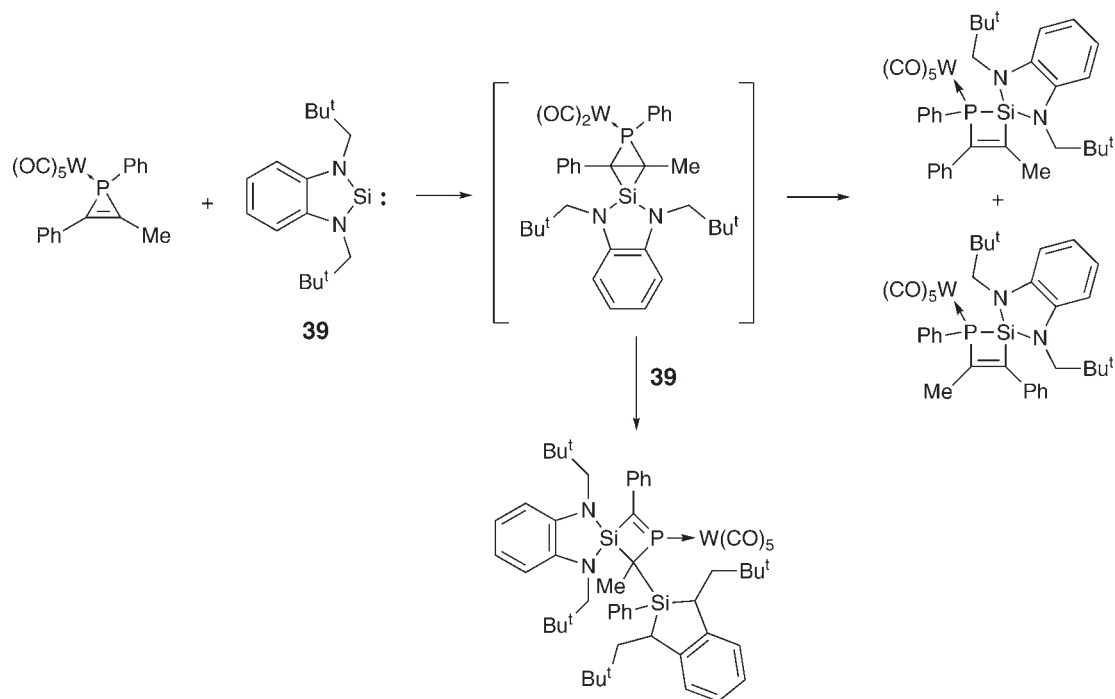
Scheme 34

Photochemically induced ring expansion of silyl- or germyl-substituted 1*H*-phosphirene proceeds selectively to furnish 1,2-dihydro-1,2-phosphasilette and 1,2-dihydro-1,2-phosphagermete, respectively (Equation 39) <1999CEJ1581>.



2.21.10.2 Synthesis of 1,3-Diheterobutane Systems

Reaction of 1*H*-phosphirene with silylene **39** results in 2,3-dihydro-1,3-phosphasilette or 1,2-phosphasiletene via a phospho-4-silabicyclo[1.1.0]butane reactive intermediate (Scheme 35) <2004AGE3474>.



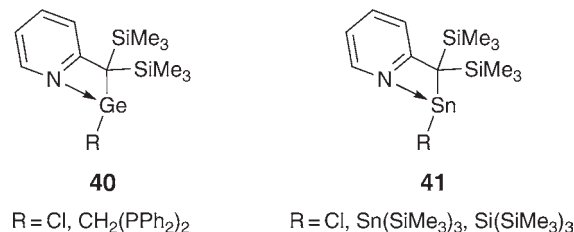
Scheme 35

2.21.11 Synthesis of Particular Classes of Compounds

The substituted disilacyclobutanes have been used as monomers in the ROP process employed for the synthesis of linear poly(silylenemethylene)s (see Sections 2.21.6.2 and 2.21.12).

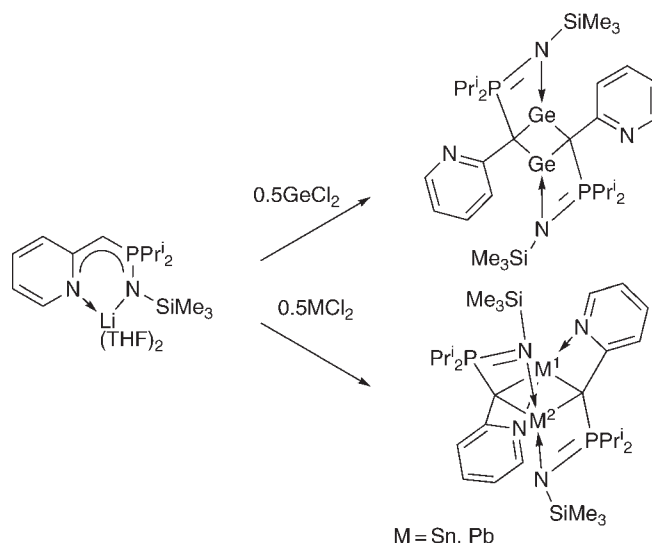
A lithium iminophosphorano(pyridyl)methanoide complex reacts with MCl_2 ($M = Ge, Sn, Pb$) to give low-valent 1,3-dimetallacyclobutanes and a mixed 1,3-stanna-plumbacyclobutane (Schemes 31 and 36) <2001JA8123, 2003OM4604>. See also structures 14–16.

Novel, monomeric heteroleptic derivatives of divalent Ge 40 and divalent Sn 41 have been prepared and characterized by single crystal X-ray diffraction <1999OM389>. Heteroatoms in these germylene and stannylene species are not formally part of a four-membered ring; however, crystal structures point to the azametallacyclobutane structures formed due to the $N \rightarrow M$ coordination. The heteroleptic nature of 40 and 41 gives rise to an interesting reactivity in their coupling with transition metal clusters.



2.21.12 Important Compounds and Applications

Disilacyclobutanes and silacyclobutanes are important monomers for the synthesis of well-defined polycarbosilanes. Their applications to ceramic precursors, conductive polymers, heat-resistant materials, and side-chain liquid crystalline polymers have been widely investigated. Pyrolysis of polycarbosilanes is utilized for the production of an important material, namely silicon carbide, and is described in reviews and patents <B-1996MI7621, B-2000MI247, B-2004MI426, 1997MI305, 1999USP5965684, 2000JPP336170, 2001JPP354772, 2005JPP200571>.



Scheme 36

A considerable interest in the covalent attachment of organic molecules to silicon surfaces is largely motivated by the desire to integrate the wide range of available functionalities of organic molecules with existing microelectronics technology. The addition of alkenes to the dimers of a reconstructed crystalline silicon surface are facile, resulting in the formation of two Si–C bonds as in a formal [2+2] cycloaddition [\[2000ACR617, 2002MI879\]](#).

2.21.13 Further Developments

Recent developments have been made mainly in three directions: theoretical studies, polymerization of silacyclobutanes, and the reactivity of four-membered heterocycles in thermolysis reactions. These new achievements are briefly summarized below.

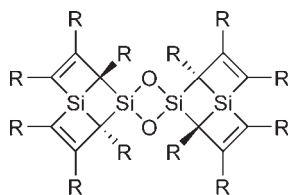
Infrared and Raman spectra of 1,3-disilacyclobutane and its 1,1,3,3- d_4 isotopomer have been reexamined and partially reassigned on the basis of DFT and *ab initio* calculations [\[2007PCA825\]](#).

The cycloliner polycarbosilane, (poly(1-hexyl-1,3-ditolyl-1,3-disilacyclobutane)), prepared by ADMET polymerization as reported previously (see [Scheme 13](#)) was modified by grafting poly(methyl methacrylate) (PMMA) or polystyrene [\[2006MM8684\]](#). Polydiphenylsilylenemethylene thin films have been synthesized by using laser-ablated metal nanoparticles for the thermal ring-opening polymerization of 1,1,3,3-tetraphenyl-1,3-disilacyclobutane [\[2007MI3093\]](#).

Intermediacy of pentacoordinate oxasiletanides in the Peterson olefination reaction has been discussed [\[2002CSR195, B-2004MI18\]](#). Products of thermolysis of 1,2-oxasiletanides indicate that they are the intermediates of both Peterson and homo-Brook reactions [\[1999CL1139, 2003BCJ471\]](#).

Thermolysis of highly hindered 1,2-di(adamantoyl)tetrakis(trimethylsilyl)disilane with diphenylacetylene afforded 1-silacycloprop-2-ene and 1,2-disilacyclobut-3-ene derivatives. The mechanism of the transformation is discussed on the basis of DFT calculations [\[2006OM3955\]](#).

1,3-Dioxo-2,4-disiletanes [42](#) have been obtained by dimerization of the corresponding silanones [\[2006JOM1341\]](#).



TEA (Transverse Electrical discharge in gas at Atmospheric pressure) CO₂ laser irradiation into gaseous mixtures of 1,3-disilacyclobutane and dimethyl selenide results in chemical vapor deposition of novel polyselenocarbosilane films <2006MI178>.

A new method of the synthesis of 1,3-disilacyclobutanes by a coupling of 1,3-dilithio-2-silapropanes with dichlorosilanes has been described <2007ARK29>.

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1995CB1241
1995CC1625
1995CRV1527
1995JA11695
1995JOM143
B-1995MI453221-03
B-1995MI97
B-1995MI365
1995OM2139
1995SL794
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1996CB15
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1996CM1260
1996JOC4884
1996JOM181
1996JOM43
1996JOM1
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1996MM3701
1996OM736
1996OM1101
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2.23

Four-membered Rings with Three Heteroatoms not including Oxygen, Sulfur or Nitrogen Atom

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2.23.1 Introduction

This chapter on four-membered rings with three heteroatoms is intended to give an update of the literature for the period 1996 up to 2006. The information together with the chapter on this topic in CHEC-II(1996) <1996CHEC-II(1B)1189> will give a comprehensive overview of the work related to these heterocycles.

All four-membered heterocycles with three heteroatoms described in this work belong to the ring systems shown in [Figure 1](#).

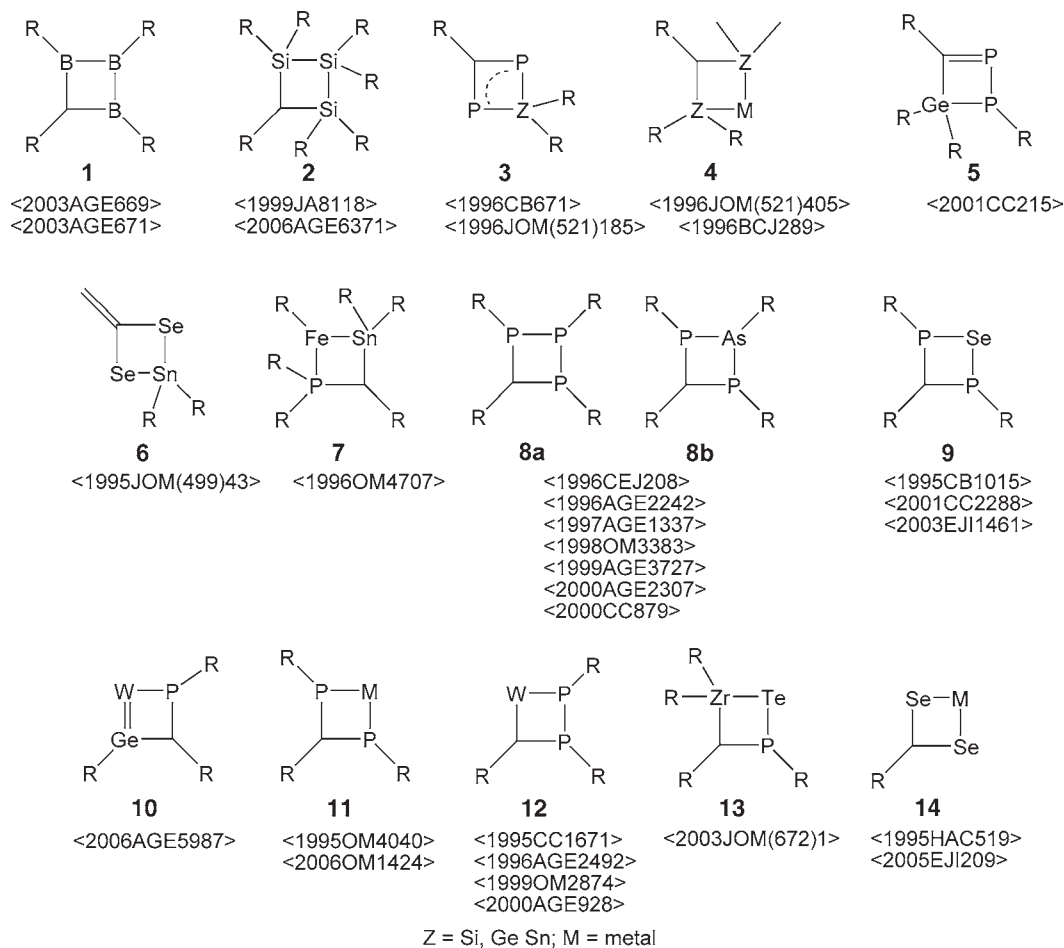


Figure 1

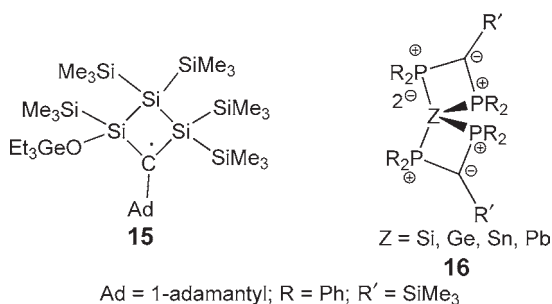
The present chapter is intended to report on the major new preparations, reactions, and concepts.

2.23.2 Theoretical Methods

Only a few examples of theoretical studies have been reported in the period covered by this chapter.

Radical **15** has a surprisingly high kinetic stability. Calculations (GAUSSIAN 94 program) show that compound **15** does not possess a special thermodynamic stability and that the energetic consequences of the β -silyl hyperconjugation are small. As compound **15** does not possess a special thermodynamic stability and its unpaired spin is not strongly delocalized, it was successfully isolated because of its high kinetic stability, resulting from the presence of the bulky adamantyl and the branched polysilyl groups, which shield the radical center from further reactions <1999JA8118>.

The mono- and bidentate chelation of main-group elements silicon, germanium, tin, and lead using quantum chemical methods has been studied. Thus, the core potential level of complexes **16** was investigated. They have been found to be capable of a facile pseudorotation over a C_{2v} symmetrical structure. The energy barrier for the degenerate rearrangement decreases in the order $\text{Si} > \text{Ge} > \text{Sn} > \text{Pb}$. The structures with the diphosphanylmethanide ligands are best described as having equatorial single bonds, which can distort to form asymmetric trigonal bipyramids. The structure in which one diphosphanylmethanide ligand is linked through a Z-C bond is considerably lower in energy and the energy differences are found to be almost independent of the substituents R' <1999EJI1155>.



2.23.3 Experimental Structural Methods

2.23.3.1 X-Ray Diffraction

The crystalline trisilacyclobutyl radical **15** has a planar symmetric four-membered Si₃C ring. Selected bond lengths are: C(10)–Si(3) 1.877 Å and Si(3)–Si(5) 2.393 Å <1999JA8118>.

The X-ray analysis of compound **17** shows that two terminal five-membered rings are fused to the central bicyclo[2.2.0]hexane skeleton in an *anti* fashion, thus indicating that the isomerization is the antarafacial [2+2] addition of the Si–Si bond to the Si=Si bond. The central Si(1)–Si(2) bond is considerably elongated (2.4536 Å) compared with the peripheral Si–Si bonds (2.3601 and 2.3677 Å). The Si(1)–Si(2)–C(8) (141.65°) and Si(2)–Si(1)–C(4) (142.05°) bond angles are unusually large. These structural distortions could be caused by steric repulsion between the trimethylsilyl groups at the C-4 and C-8 atoms. The tetrasilane unit in compound **17** adopts an almost eclipsed conformation with an Si(4)–Si(1)–Si(2)–Si(3) dihedral angle of 115.20° <2006AGE6371>.

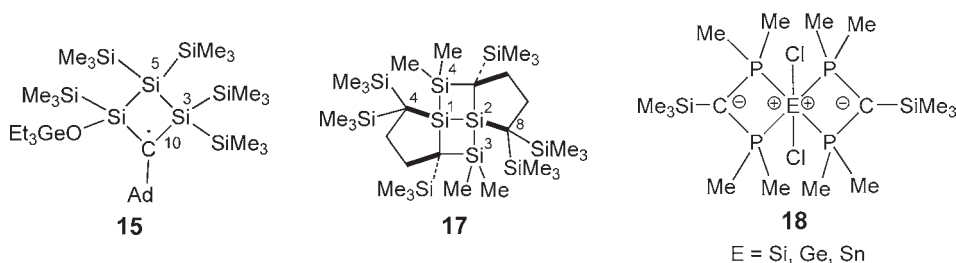
The molecular structure of compounds **18** is very similar. Two chelating silyl-substituted diposphenomethanide ligands are coordinated via their phosphorus atoms in the equatorial plane of a slightly distorted octahedron to the group-14 elements (E = Si, Ge, or Sn), the remaining two coordination sites (*trans* to each other) being occupied by the chlorine substituents forming a nearly linear Cl–E–Cl axis <1996CB671>.

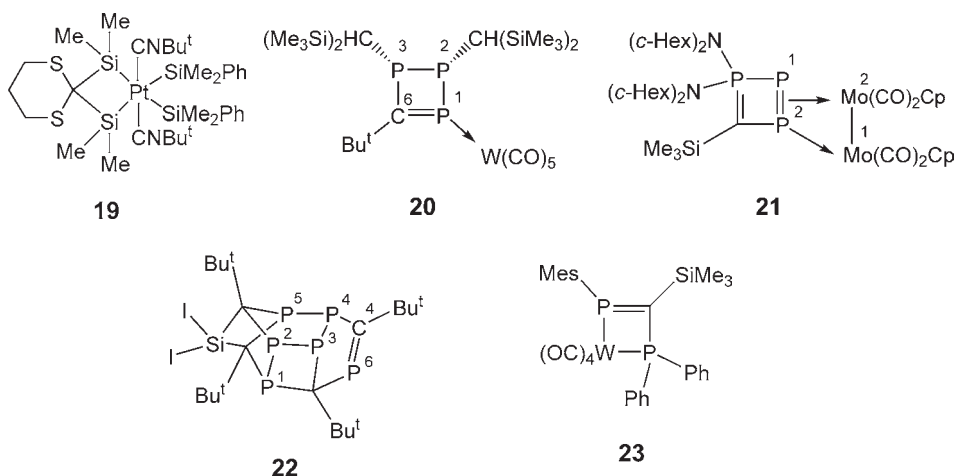
In the crystal structure of the octahedral complex **19**, two isocyanide ligands occupy the apical positions and the four silyl ligands lie at the vertices of a distorted square with a platinum atom at the center. The isocyanide ligands have a *trans* orientation <1996JOM(521)405>.

The ring of compound **20** is slightly folded (dihedral angle P(1)–P(2)–P(3), P(1)–C(6)–P(3) 23.6°) with an approximately planar W–P–C–C subunit (torsion angle 4.8°). The alkyl substituents at phosphorus are *trans*. The two P–P bond lengths (P(1)–P(2) 2.1576 Å and P(2)–P(3) 2.2375 Å) are significantly different <1995CC2113>. Two Mo atoms in the compound **21** show different coordination geometries: Mo-1 is linked to phosphorus atoms P-1 and P-2 (2.492 and 2.636 Å) while Mo-2 is bonded only to P-1 (Mo(2)–P(1) 2.340 Å, Mo(2)–P(2) 3.765 Å). The four-membered P–P–P–C ring is planar. These geometric parameters along with a P(1)–P(2) bond length (2.152 Å) describe an ylidic four π electron four-membered heterocycle <1999AGE3727>.

The molecular structure of compound **22** shows that the Si is attached to two carbon atoms within the cage, involving a P=C double bond between P-6 and C-4 and a five-atom phosphorus network P(1)–P(2)–P(3)–P(4)–P(5) <2000CC879>.

The structure of heterocycle **23** was determined by X-ray crystallography. The conformation of the P=C–P skeleton is flexible in coordination to the carbonyl-tungsten moieties <2006OM1424>.





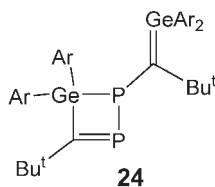
The crystallographic numbering of atoms is given

2.23.3.2 Molecular Spectra

2.23.3.2.1 ESR- and NMR-spectroscopy

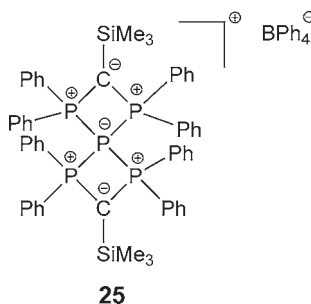
The crystalline compound **15** reveals an intense electron spin resonance (ESR)-spectrum showing a symmetrical singlet absorption with g factor (2.00297) close to that of a free electron and having a line of 0.182 mT and a concentration of paramagnetic centers of 0.9×10^{21} spin/g. The ESR spectrum of a hexane solution of compound **15** shows a strong central peak and four doublets with an additional hyperfine coupling constant [<1999JA8118>](#). The ^{29}Si -NMR (NMR – nuclear magnetic resonance) spectrum of heterocycle **17** consists of five signals at δ 0.72, 2.23, 2.35, 2.64, and 37.99 [<2006AGE6371>](#).

The ^{31}P -NMR spectrum of compound **24** contains two doublets for two coordinate phosphorus atoms at δ 269.0 and 271.5 ppm as well as two doublets in the high-field region at δ –8.1 and –34.4 ppm. These signals remain unchanged even on heating a sample to 80 °C, presumably because of steric crowding at the exocyclic carbon atom. The existence of two conformers in solution is further supported by the observation of numerous, in part overlapping, signals in the ^1H - and ^{13}C -NMR spectra. The $^1J_{\text{PP}}$ coupling constants of 16 and 21 Hz for the two conformers are inexplicably small [<2001CC215>](#).

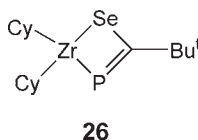


Ar = 2-*tert*-butyl-4,5,6-trimethylphenyl

$^{31}\text{P}\{^1\text{H}\}$ -NMR spectrum of compound **22** consists of six distinct resonances exhibiting several $^1J_{\text{PP}}$ couplings in the range of 110–300 Hz. The lowest signal (δ 357.0 ppm) which is in the region typical of $\text{P}=\text{C}$ double bonds and involves only small couplings clearly corresponds to P-6. The two highest field resonances (δ = –19.1 and 24.4 ppm), which exhibit a single large coupling, can readily be assigned to P-5 and P-1, respectively. The remaining resonances at δ 124.1, 78.4, and 24.6 were attributed to P-2, P-3, and P-4, respectively [<2000CC879>](#). The $^{31}\text{P}\{^1\text{H}\}$ -NMR spectrum of compound **25** in solution reveals a rapid scrambling of the equatorial and axial positions at room temperature. On cooling to –107 °C, this scrambling process is essentially frozen: an $\text{A}_2\text{B}_2\text{M}$ spin system can be observed [<1996AGE2242>](#).



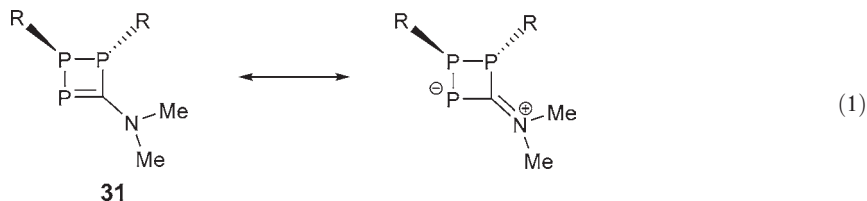
The $^{31}\text{P}\{^1\text{H}\}$ -NMR spectrum of compound **26** shows a singlet (δ 388 ppm) exhibiting ^{77}Se -satellites, with a coupling constant ($^2J_{\text{PSe}} = 88 \text{ Hz}$) whose magnitude is typical for a two-bond phosphorus-selenium coupling [\(<2003JOM\(672\)1>](#).



2.23.3.2.2 Tautomerism

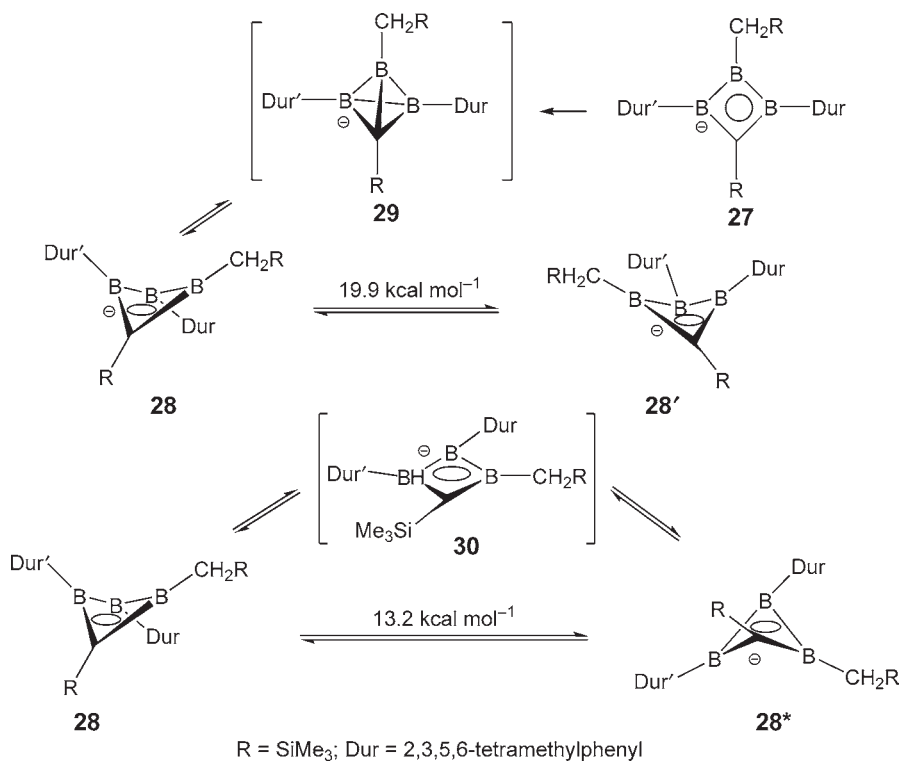
The anion **28** forms a solvent-separated ion pair with lithium, which is coordinated by three molecules of diethyl ether. NMR spectra were used to study the mechanism of isomerization of triboracyclobutanide **28**. Evidently, the initially formed, symmetrically substituted triboracyclobutanide **27** rapidly isomerizes to intermediate **28**. At low temperature, ^1H - and ^{13}C -NMR signals for two duryl substituents are observed; however, at higher temperatures their broadenings and coalescences appeared. The ^{11}B -NMR of compound **28** in $[\text{D}_8]\text{THF}$ (THF – tetrahydrofuran) at 27°C shows three signals at $\delta = 16$, 38, and 42 ppm, of which that at $\delta = 42$ remains unchanged at higher temperature, whereas the other two signals broaden. This shows that not only the duryl substituents but also the boron atoms to which they are attached participate in the exchange. The barrier for exchange of the environments of the duryl substituents, which is the topomerization in compound **28**, was determined to be $19.9 \text{ kcal mol}^{-1}$ based on line shape analysis of the signals of *o*-Me, *m*-Me, and *p*-H atoms. For the diastereotopic methylene protons of the Me_3SiCH_2 substituents, which reveal the planar chirality of heterocycle **27**, a more rapid exchange than for the duryl substituents is determined from the line shape analysis of their signals. Two pathways are possible for the enantiomerization of compound **27**: one by ring inversion via the planar transition state **30** and the second by rearrangement via a distorted triboratetrahedrane anion **29**, which also leads to an enantiomerization, but without ring inversion. The barrier of the enantiomerization by ring inversion is calculated to be $13.2 \text{ kcal mol}^{-1}$ ([Scheme 1](#)) [\(<2003AGE669>](#).

In 1,2,3-triphosphetenes the amino group acts as an effective π -electron donor and the mesomeric form makes a considerable contribution to the ground-state structure **31** ([Equation 1](#)) [\(<1996CEJ208>](#).

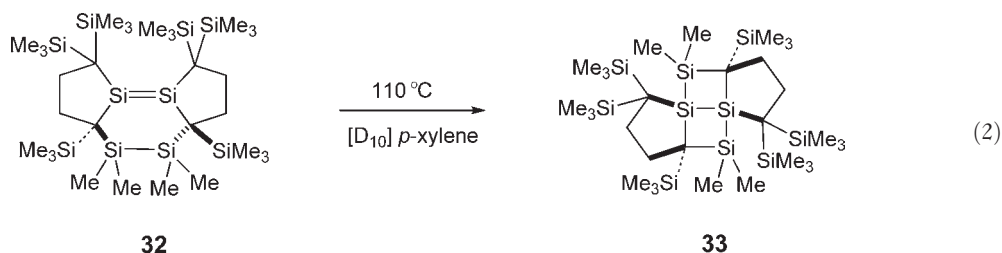


2.23.4 Thermodynamic Methods

The first-order rate constants and the activation parameters for the isomerization of *trans*-silane **32** to compound **33** were determined by monitoring of the UV-Vis absorbance at 517 nm of compound **32** at various temperatures: $k = 2.68 \pm 0.02 \text{ s}^{-1}$ at 351 K, $\Delta H^\ddagger = 19.0 \pm 1.2 \text{ kcal mol}^{-1}$, $\Delta S^\ddagger = -21 \pm 3 \text{ cal mol}^{-1} \text{ K}^{-1}$ ([Equation 2](#)) [\(<2006AGE6371>](#).



Scheme 1



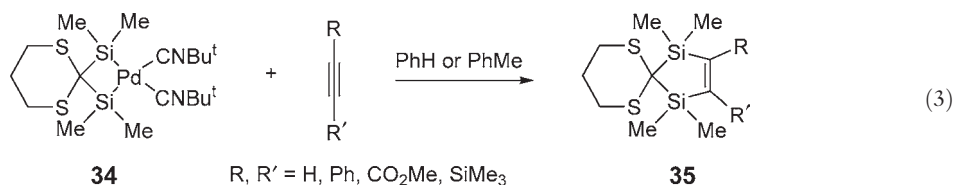
2.23.5 Reactivity of Fully Conjugated Rings

2.23.5.1 Cleavage of Four Rings with Three Heteroatoms

In the period covered by this edition, no relevant publications were published.

2.23.5.2 Ring Expansion and Ring Contraction Reactions

A stoichiometric reaction of the four-membered complex **34** with terminal and internal alkynes leads to spiro-disilacyclopentene derivatives **35** in 90–98% yields (Equation 3) <1996BCJ289>.

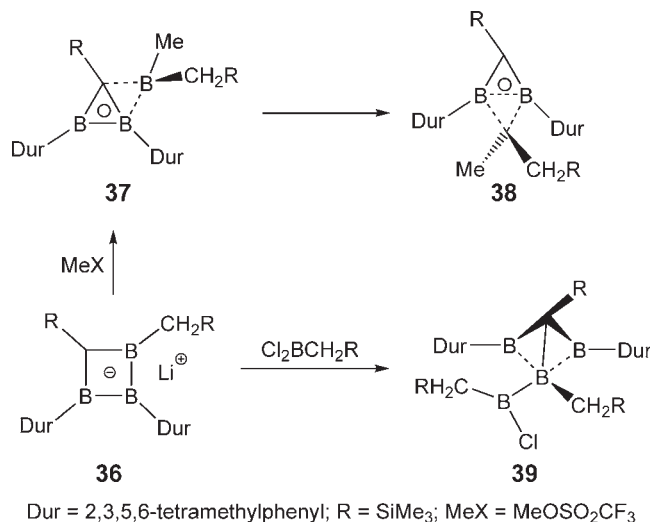


2.23.5.3 Reactions of Heteroatoms and Substitutents on Heteroatoms

In the period covered by this edition, no relevant publications were published.

2.23.5.4 Rearrangement of the Ring

The reaction of triboracyclobutanide **36** in $[D_8]THF$ with methyl trifluoromethanesulfonate in an NMR tube at $-90^\circ C$ affords a mixture of *C*-boryldiboracyclopropane **37** and compound **38** in a 3:1 ratio. Compound **36** reacts with dichloro(trimethylsilylmethyl)borane to give a product mixture, from which compound **39** (yield 50%) can be separated by crystallization (Scheme 2) <2003AGE671>.



Scheme 2

2.23.5.5 Elimination Reactions

In the period covered by this edition, no relevant publications were published.

2.23.6 Reactivity of Nonconjugated Rings

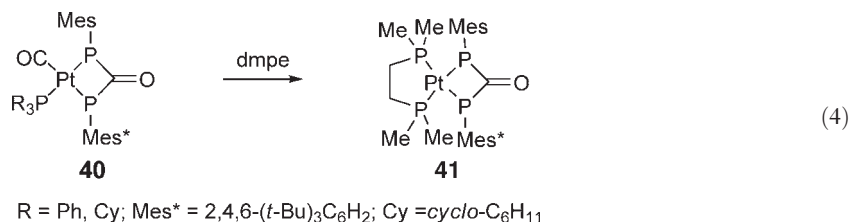
In the period covered by this edition, no relevant publications were published.

2.23.7 Reactivity of Substituents Attached to Ring Carbon Atoms

In the period covered by this edition, no relevant publications were published.

2.23.8 Reactivity of Substituents Attached to Ring Heteroatoms

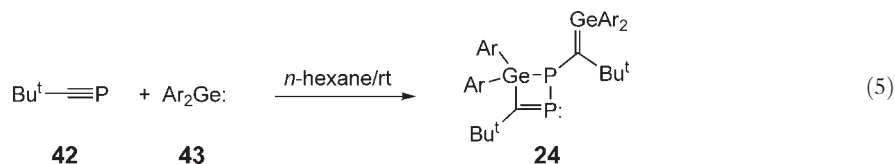
Interaction of compounds **40** with dmpe (Ph₂PCH₂CH₂PPh₂) afforded the spirocyclic product **41** in 61% yield (Equation 4) <1995OM4040>.



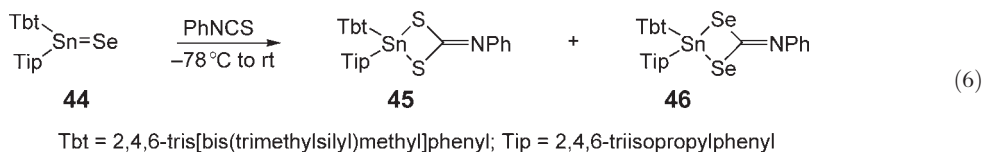
2.23.9 Ring Syntheses from Acyclic Compounds

2.23.9.1 [2+2] Cycloaddition

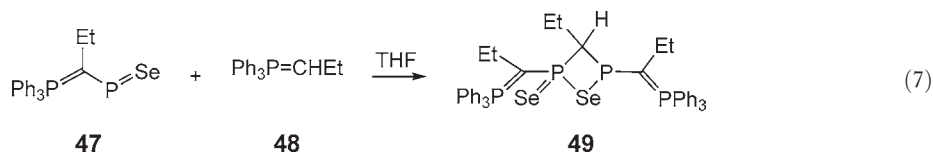
[2+2] Cycloaddition reaction of phosphalkyne **42** and bis(2-*t*-butyl-4,5,6-trimethylphenyl)germylene **43** leads to germadiphosphacyclobutene **24** in 59% yield (Equation 5) <2001CC215, 2002JOM(646)39>.



Interaction of stannaneselenone **44** with phenyl isothiocyanate afforded a mixture of 1,3,2-dithia- **45** (6%) and 1,3,2-diselenastannetane **46** (22%) (Equation 6) <1995JOM(499)43>.



[2+2] Cycloaddition of selenoxophosphane **47** and phosphonium ylide **48** leads to 1,2,4-selenadiphosphetane **49**. However, product **49** was not isolated but identified on the basis of its ^{31}P -NMR spectral data (Equation 7) <1995CB1015>.

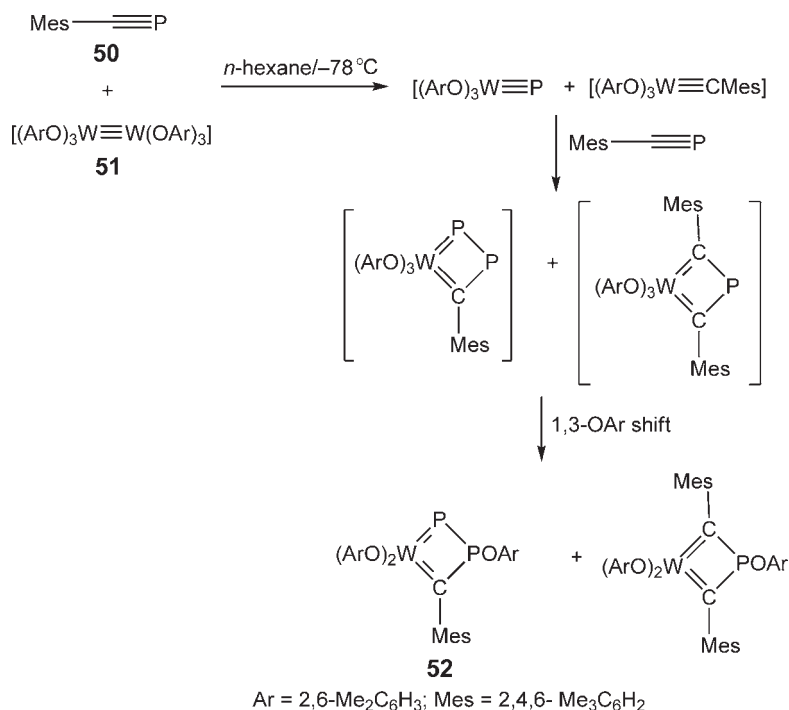


The tungsten-containing four-membered ring **52** was prepared by the treatment of phosphalkyne **50** with complex **51** (Scheme 3) <1995AGE1997, 1995CC1671, 1999CEJ2890, 1999OM2874, 2000AGE928>.

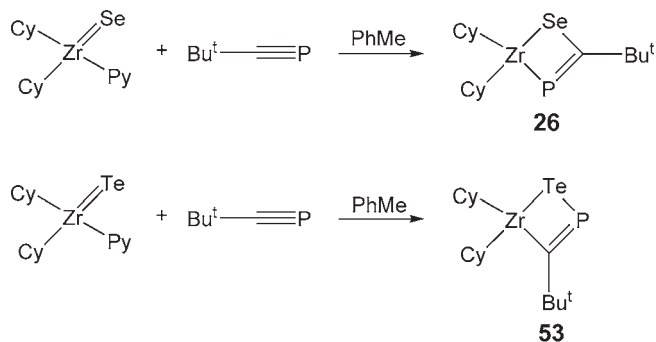
[2+2] Cycloaddition was successively used for the preparation of the two zirconium-containing four-membered heterocycles **26** and **53** in 47% or 65% yields, respectively (Scheme 4) <2003JOM(672)1>.

2.23.9.2 [3+1] Cycloaddition

The 1,2,3-triphosphetene ring was synthesized by cycloaddition of metallodiphosphenes ($\eta^5\text{-C}_5\text{Me}_5$)(CO) $_2$ Fe-P=P-Mes <1998OM3383>, *N,N'*-bis(2,2-dimethylpropyl)benzimidazolin-2-ylidene <2000AGE2307> or cyclotetraphosphane (PCF $_3$) $_4$ <1996CEJ208> to phosphalkynes. Carbene **54** in the reaction with complex **55** afforded heterocycle **21** (Equation 8) <1999AGE3727>.

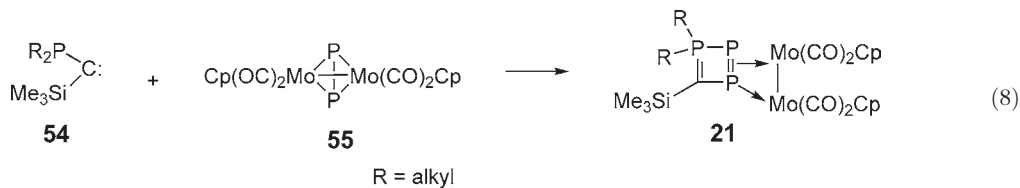


Scheme 3



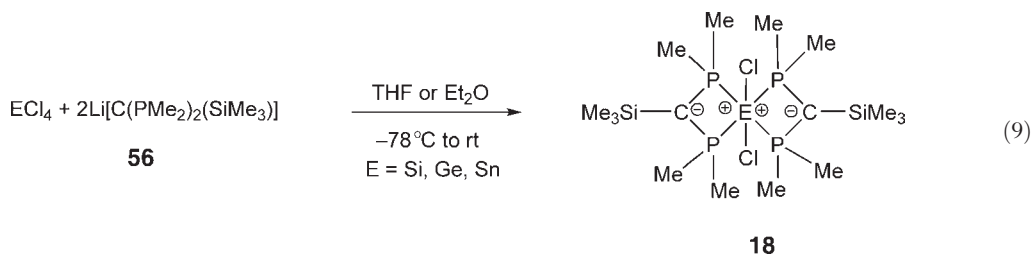
Cy = 1,2,3,4,5-pentamethylcyclopentadienyl; Py = pyridine

Scheme 4

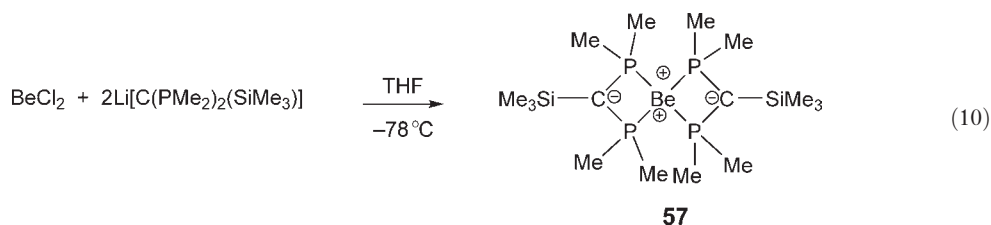


2.23.9.3 [3+1] Cyclocondensation

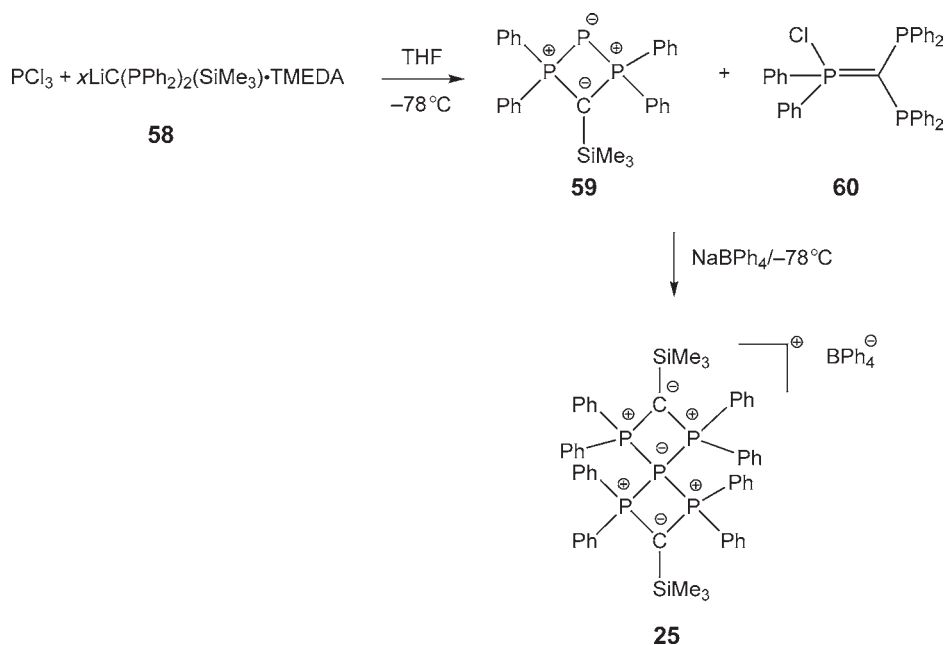
Reaction of the group-14 tetrahalides ZCl₄ (Z = Si, Ge, Sn) with 2 equiv of Li[C(PMe₂)₂(SiMe₃)] **56** afforded *trans*-hexacoordinated compounds **18** in yields up to 95% (Equation 9) <1996CB671>.



The cyclocondensation reaction was used in the synthesis of phosphane complexes of alkaline earth metals. For example, reaction of BeCl_2 with 2 equiv of $\text{Li}[\text{C}(\text{PMe}_2)_2(\text{SiMe}_3)]$ afforded compound **57** as colorless crystals (Equation 10). Magnesium and calcium complexes were similarly prepared <1998EJI905>.



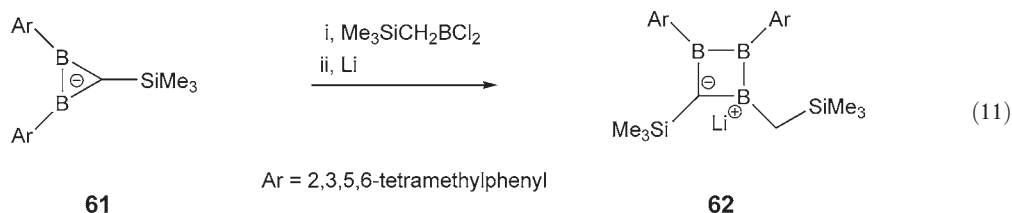
Reaction of PCl_3 or P_4 with 2 or 3 equiv of complex **58** afforded triphosphite **59** (37%) along with chlorophosphorane **60**. The synthesis of the first 10-electron phosphorus cation **25** (39%) was achieved by reacting the compound **59** with ylide **60** in the presence of NaBPh_4 (Scheme 5) <1996AGE2242, 1996AGE2618, 1997JOM(529)151>.



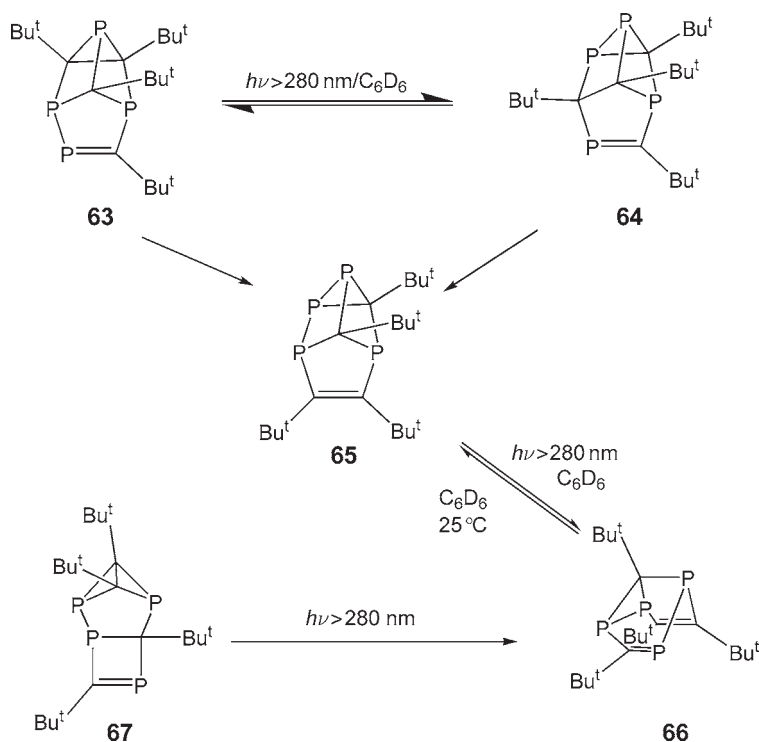
Scheme 5

2.23.10 Ring Syntheses by Transformation of Another Ring

The unsymmetrically substituted triboracyclobutanide **62** was obtained by reaction of compound **61** with dichloro-(trimethylsilylmethyl)borane and then with lithium (Equation 11) <2003AGE669>.

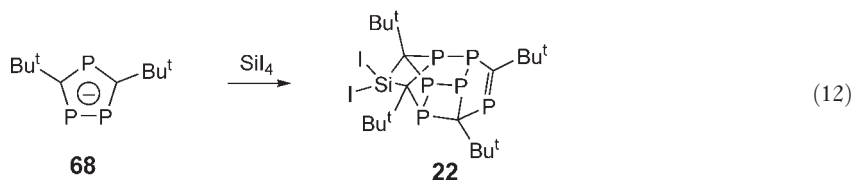


Compounds **63** and **64** coexist as a 1:1 equilibrium mixture upon irradiation of one or the other in C_6D_6 (mercury high-pressure lamp Phillips, HPK 125W, Duran-50 filter). On heating of each of the two isomers separately at 150°C , compound **65** (yield 100% or 48%, respectively) is formed by a skeletal rearrangement. Finally, compound **67** can undergo complete photochemical isomerization to furnish an isomeric mixture of two compounds **65** and **66** (ratio 80:20) (**Scheme 6**) <1997AGE1337>.



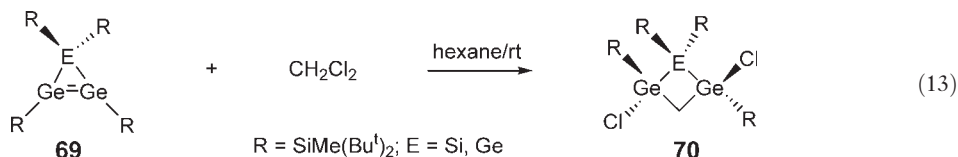
Scheme 6

Treatment of the anion of 3,5-di-*t*-butyl-1,2,4-triphospholyl **68** with SiI_4 afforded an orange cage compound **22** in 55% yield. The mechanism of formation of compound **22** is currently unknown but it seems that the first step involves an Si-P bond formation (**Equation 12**) <2000CC879>.

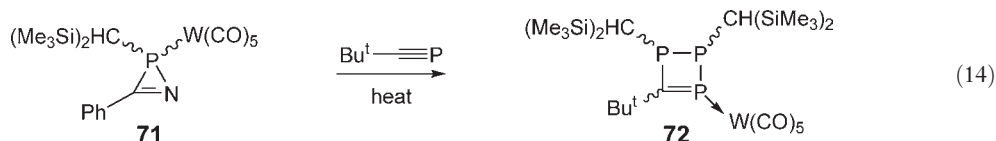


2.23.10.1 Ring Insertion Reactions

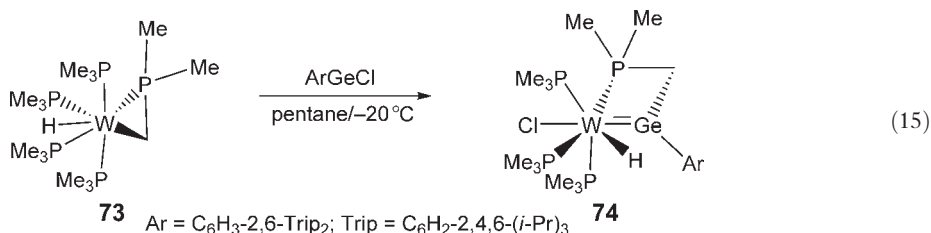
Digermenes **69** readily react with an excess of CH_2Cl_2 at room temperature to produce new four-membered ring compounds **70** in 69–71% yield (Equation 13) <2005AGE6378>.



Thermal decomposition of the 2*H*-azaphosphirene complex **71** in the presence of phosphalkyne yields 1,2-dihydro-1,2,3-triphosphetide complex **72** in 86% yield (Equation 14) <1995CC2113>.

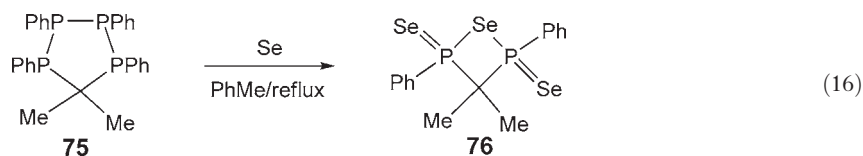


Treatment of complex **73** with 1 equiv of aryl germanium chloride in pentane at -20°C afforded selectively a thermolabile four-membered ring **74** (Equation 15) <2006AGE5987>.



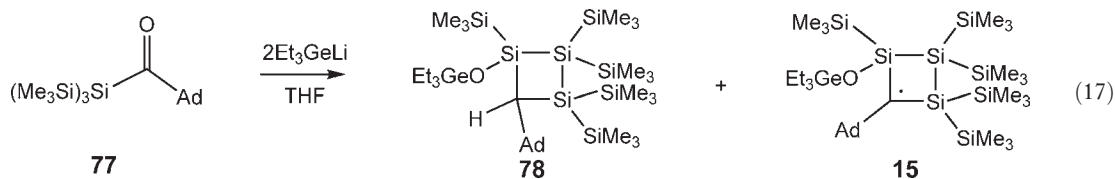
2.23.10.2 Ring Contraction Reactions

Oxidative addition of 9 equiv of elemental selenium to cyclomonocarbapentaphosphine **75** afforded a novel four-membered heterocycle **76** in 68% yield (Equation 16) <2001CC2288, 2003EJ11461>.



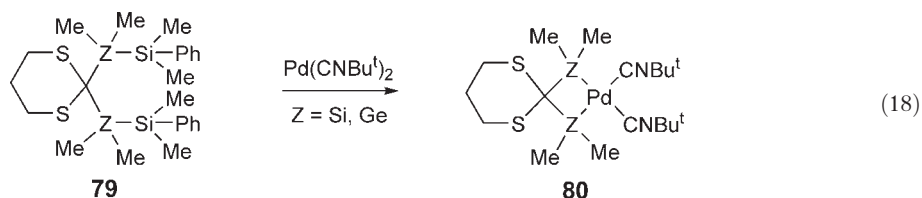
2.23.10.3 Other Reactions

Reaction of acylsilane **77** with a twofold excess of Et_3GeLi in THF yields trisilacyclobutane **78**, along with the corresponding trisilacyclobutyl radical **15** (Equation 17) <1999JA8118>.

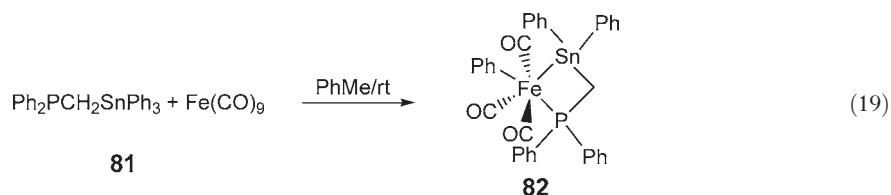


Heating of *trans*-tricyclic disilenes **32** at 110°C in $[\text{d}_{10}]$ -*p*-xylene or in the solid state leads to tetracyclic compound **33** in quantitative yield (see Section 2.23.4) <2006AGE6371>.

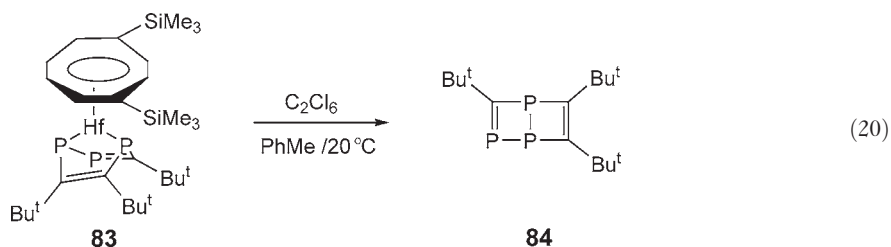
The reaction of silylgermane or disilane **79** with $\text{Pd}(\text{CNBu}^t)_2$ proceeded with cleavage of Si–Ge bonds and gave the four-membered rings **80** in 85–100% yields (Equation 18). The complex $\text{Pt}_3(\text{CNBu}^t)_6$ reacted similarly with substrate **79** <1996JOM(521)405, 1996BCJ289>.



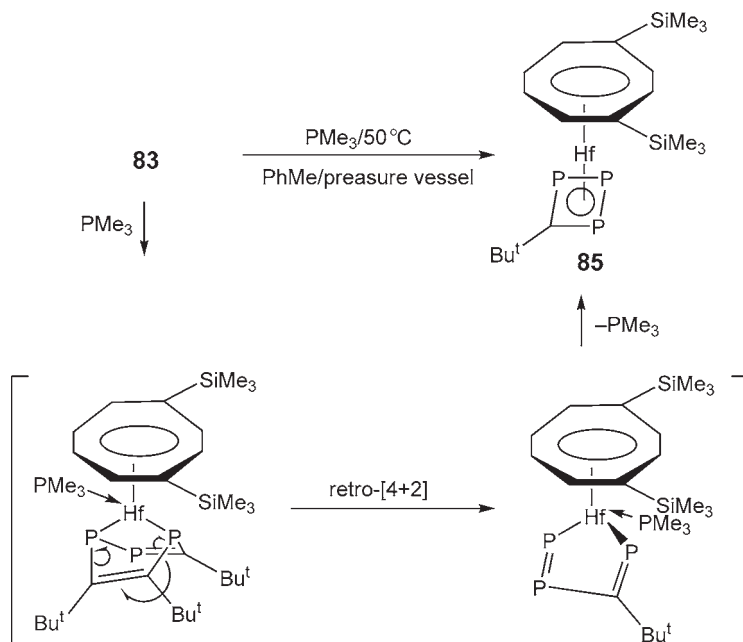
Reaction of $\text{Ph}_2\text{P}(\text{CH}_2)_n\text{SnR}_2\text{R}'$ **81** with $\text{Fe}(\text{CO})_9$ in toluene leads to phosphane complexes **82** (Equation 19) <1996OM4707>.



Hafnium complex **83** in the presence of hexachloroethane as mild chlorinating agent afforded a new triphospha Dewar benzene **84** in 49% yield as a pale-yellow powder (Equation 20) <1997CB1491>.

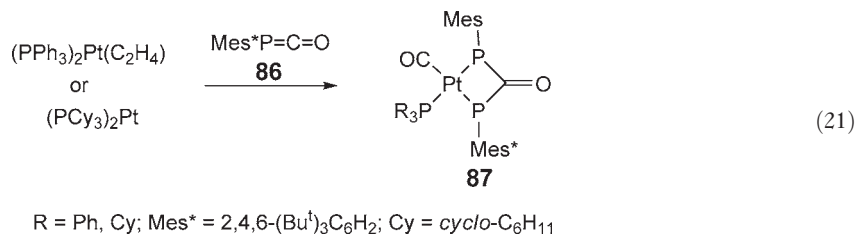


An unexpected displacement of di-tert-butylacetylene was observed on heating of complex **83** to 50°C in the presence of trimethylphosphane. The new triphosphete complex **85** was isolated as yellow needles in 55% yield. The mechanism of formation of compound **85** included a retro Diels–Alder reaction (Scheme 7) <1997CB1491>.

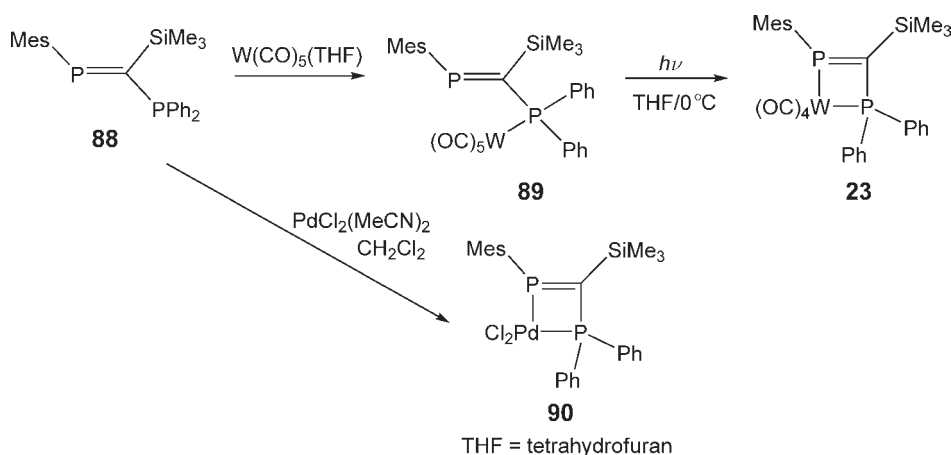


Scheme 7

Reactions of phosphaketene **86** with $(\text{PPh}_3)_2\text{Pt}(\text{C}_2\text{H}_4)$ or $(\text{PCy}_3)_2\text{Pt}$ gave complex compounds **87** in 77% or 45% yields, respectively (Equation 21) <1995OM4040>.

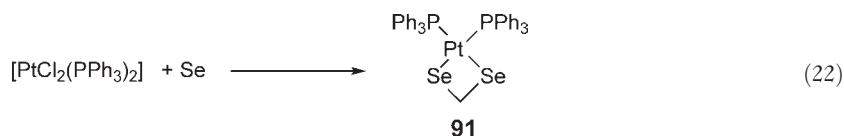


1,3-Diphosphapropene **88** and $\text{W}(\text{CO})_5(\text{THF})$ at room temperature afforded complex **89**, which on irradiation (medium-pressure 100 W Hg lamp) leads to the four-membered chelate complex **23** in 58% yield. Interaction of compound **88** with palladium complex $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ gives an air stable product **90** in 95% yield (Scheme 8) <2006OM1424>.



Scheme 8

Interaction of tetrakis(triphenylphosphine)platinum with elemental selenium leads to compound $[\text{Pt}(\text{Se}_2\text{CH}_2)(\text{PPh}_3)_2]$ **91** in 93% yield (Equation 22) <1995HAC519>.



Platinum complexes **92** were successfully obtained from $[\text{PtCl}_2(\text{PR}_3)_2]$ and dipotassium cyanodiselenoimidocarbonate. The reaction of dipotassium cyanodiselenoimidocarbonate with an appropriate transition dimer **93** leads to four-membered rings **94** in 39–42% yields (Scheme 9) <2005EJI209>.

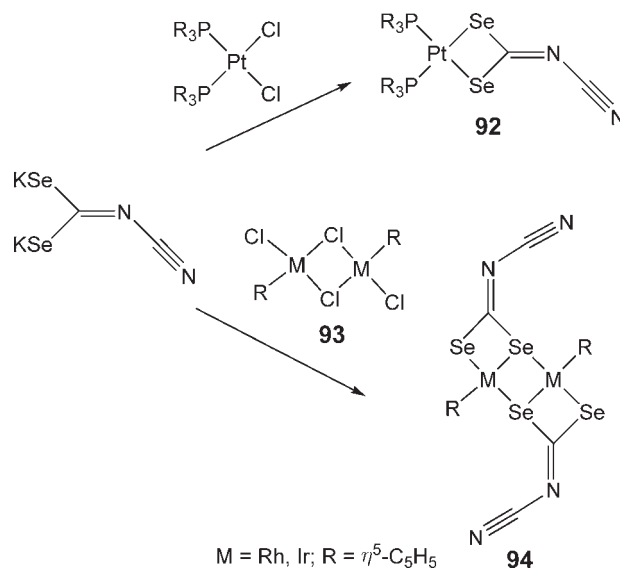
2.23.11 Syntheses of Particular Classes of Compounds

Four-membered rings containing three silicon atoms (compounds of type **2**) were prepared by reaction of acylsilane with Et_3GeLi in THF <1999JA8118> or by thermal rearrangement of *trans*-silane **32** <2006AGE6371>.

The [2+2] cycloaddition reaction was successfully used in the preparation of compounds of type **5**, **6**, **9**, **12**, and **13** (see Section 2.23.9.1).

The 1,2,3-triphosphetene ring system (type **8**) can be obtained in the [3+1] cycloaddition reaction (see Section 2.23.9.2). These types of compounds were also prepared by [3+1] cyclocondensation of PCl_3 with complex

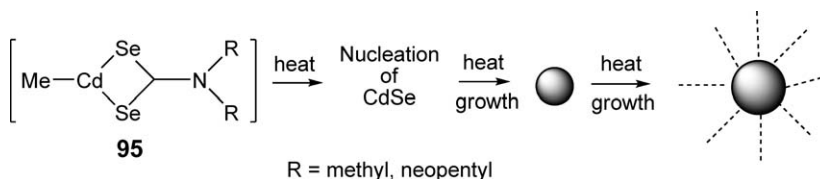
$\text{LiC}(\text{PPh}_2)_2(\text{SiMe}_3)^+ \text{TMEDA}$ <1996AGE2242, 1996AGE2618, 1997JOM(529)151>. Compounds of type **3** and **11** were prepared by cyclocondensation too (see Section 2.23.9.3).



Scheme 9

2.23.12 Important Compounds and Applications

Four-membered ring complexes with cadmium are useful as precursors for the preparation of tri-*n*-octylphosphine oxide (TOPO) capped materials. Thus, compounds **95** were efficient precursors to CdSe nanoparticles on thermolysis in TOPO <1996AM161, 1997CM523, 1998CC833, 1998CC1849, 1999CC2235>.



References

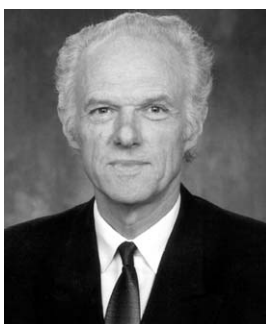
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Biographical Sketch



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2.22

Four-membered Rings with Three Heteroatoms with at least One Oxygen, Sulfur or Nitrogen Atom

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2.22.1 Introduction

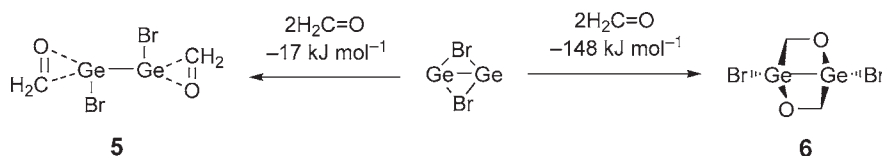
All four-membered heterocycles with three heteroatoms can be classified into four types: compounds with three similar heteroatoms **1**; symmetrical **2**, and unsymmetrical **3** heterocycles with two different heteroatoms; and derivatives with three different heteroatoms **4** <1996CHEC-II(1B)1189>.



2.22.2 Theoretical Methods

The mechanism of the addition of aldehydes and ketones to group 14 dimetallenes has been examined through a theoretical study. It was found that for reactions in which a Si–O bond is formed, both diradical and zwitterionic intermediates are possible. However, the presence of diradical intermediates was not found for Ge–O bond-forming reactions. Solvation simulations were performed to examine the effect of solvent polarity on the reaction energetics <2002JA13306>.

The density functional theory (DFT) calculations were applied to the theoretical investigation of the model reaction of (GeBr)₂ with H₂C=O <2005EJ12120>. It was found that the formation of the three-membered ring system in the first step of the reaction is energetically favoured by 17 kJ mol^{−1}, and the molecule **5** represents only a weak complex. However, the formation of the condensed ring system **6** is energetically favored by 148 kJ mol^{−1}; therefore, it can be regarded as a possible intermediate product (Scheme 1).



Scheme 1

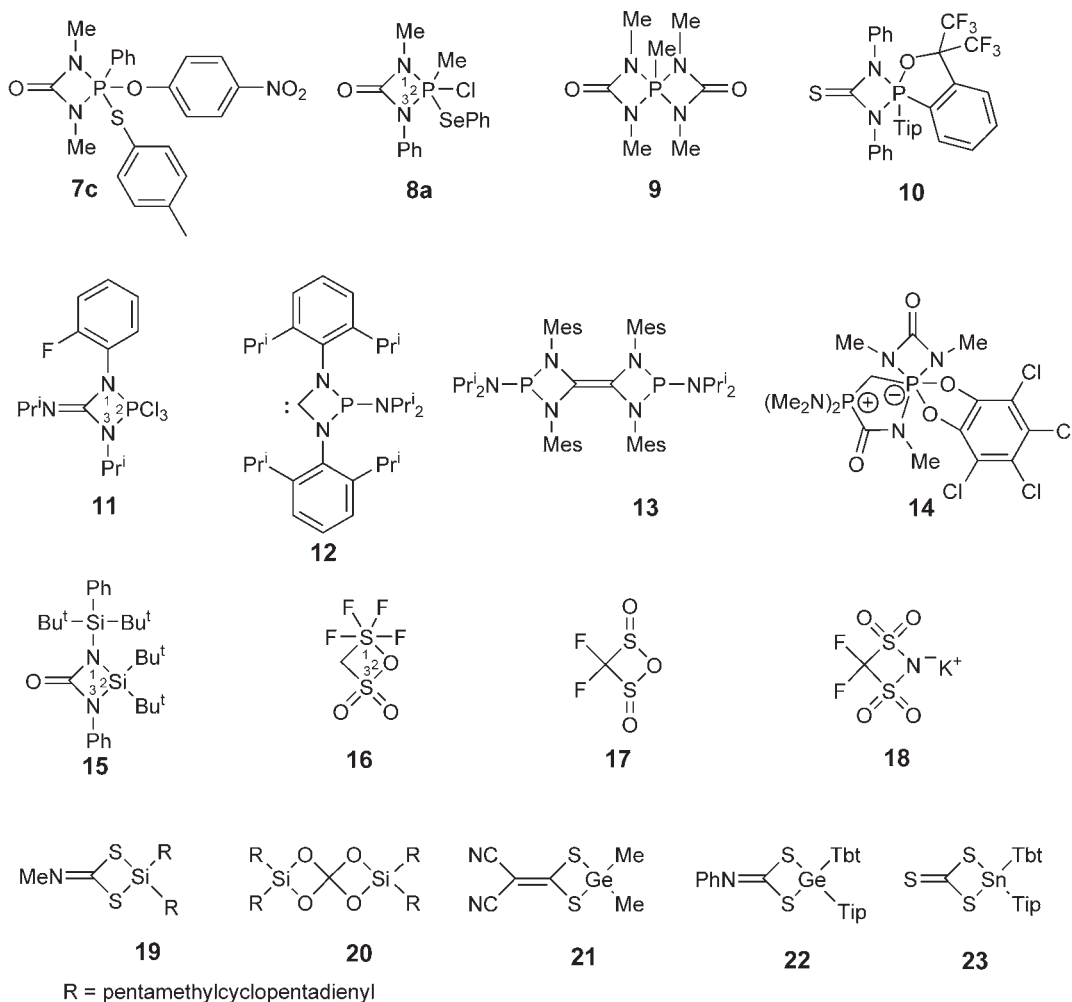
The thermodynamic and kinetic stability of halotropic isomers of amidinium halophosphorates and their diazaphosphetidine isomers were studied using MNDO-PM3 quantum–chemical calculations. The phosphorate P(vi) isomers were found to be thermodynamically more stable than the corresponding phosphetidines P(v) <1999RJC378>.

2.22.3 Experimental Structural Methods

2.22.3.1 X-Ray Diffraction

The solid-state structure of 1,3,2λ⁵-diazaphosphetidine derivatives **7c**, **8a**, **9–11** was investigated by a single crystal X-ray analysis <1995ZFA2001, 1996ZFA1250, 2002POL657, 2000CC1375>. The coordination geometry at the phosphorus atom of 1,3,2λ⁵-diazaphosphetidin-4-ones showed a large distortion from the idealized form <1997ZFA1325>. In the case of spirophosphorane **9** the geometry at the phosphorus is intermediate between bipyramidal and square pyramidal, with a planar four-membered ring. The C(1)–N(1) and C(1)–N(2) bonds of the four-membered carbene **12**, which does not possess C₂ symmetry, are relatively short (1.373(2) and 1.387(2) Å, respectively), suggesting an interaction of the nitrogen atom with the carbene center. The structure of the dimer **13** shows similarity to that in the corresponding 1,3-diaza-2-phosphetidine cations, exhibiting a delocalization of the π-electrons along the N(1)–C(1)–N(2) fragment, a small intracyclic N(1)–P(1)–N(2) angle (70.49(3)°) and longer endocyclic P–N bonds (1.8237(8) and 1.8136(8) Å, respectively) than the exocyclic one [P(1)–N(3) 1.6219(8) Å] <2004JA10198>. The zwitterionic charge distribution in **14** has little effect on the overall structure <1995TL2021>. The four-membered ring system of **15–19** is found to be planar <1996JOM(515)43, 1995HAC611, 1998JFC(89)55, 1997ZNB359, 1996OM753>. The bonds within the ring of **16** at a four-coordinated

sulfur atom are shorter than those to a six-coordinated sulfur due to different hybridizations of the corresponding sulfur atoms. The molecule **20** consists of two planar four-membered rings connected by a common carbon atom <1996OM753>. The rings of 1,3,2-dithiagermetanes **21** and **22** were also found to be planar. The S atoms and the nitrile groups of **21** are each symmetry-related across the mirror plane <2004AXEm357, 1997H(44)149>. However, the central ring of 1,3,2-dithiastannetane **23** is folded with an interplanar angle of 5.4° between the Sn–S(1)–C(1) and the S(1)–C(1)–S(2) planes <1996OM4531>.



The Tip substituents in **24** are found to be in a *cis*-relationship <1995OM3620>. The four-membered ring in both 1,3,2-dithiaphosphetane 2-sulfides **25** and **26a** is puckered. The isomer **26a** possesses a relative *trans*-configuration <2004TL1331>. The central ring of **27** is folded, with exocyclic selenium substituents in a *trans*-relationship <2001CC2288>. The nonplanar four-membered ring is also characteristic for thiadiphosphetane sulfide <1995CB1015>. Selected bond lengths and angles of type **2** heterocycles are listed in Table 1.

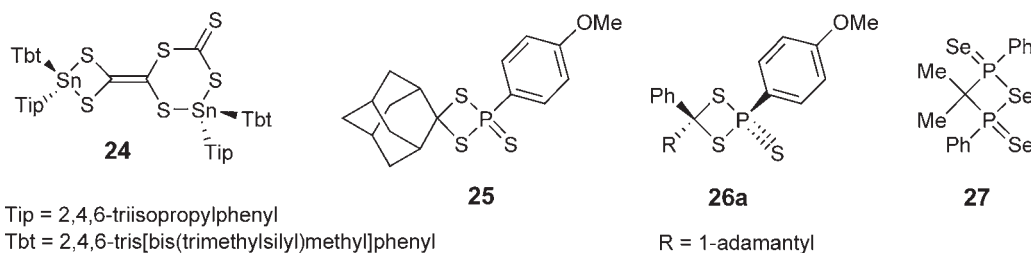


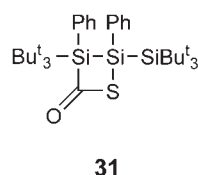
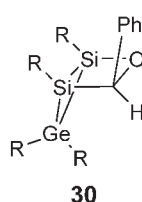
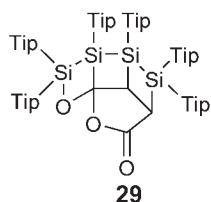
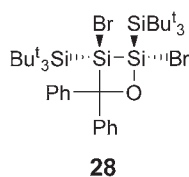
Table 1 Geometric parameters of type 2 heterocycles

Compound	r (Å)				Angles (deg)			
	X(1)-Y	X(3)-Y	X(1)-C	X(3)-C	L X(1)	L X(3)	L Y	L C
7c	1.814(2)	1.683(2)	1.354(4)	1.402(3)	92.4(2)	96.4(2)	72.89(11)	98.0(2)
8a	1.674(5)	1.798(4)				92.1(4)	74.1(2)	
9	1.790(2)	1.684(2)	1.364(4)	1.398(3)	92.0(2)	95.4(2)	73.93(11)	98.3(2)
	1.791(2)	1.681(2)	1.367(4)	1.393(3)	91.8(2)	95.7(2)	73.89(11)	98.4(2)
10	1.901(6)	1.716(6)	1.329(9)	1.418(8)	91.5(4)	96.4(5)	71.4(3)	100.6(6)
11	1.783(3)	1.6511(4)	1.398(4)	1.432(4)				96.4(3)
12	1.8237(8)	1.8136(8)	1.3306(11)	1.3328(11)			70.49(3)	104.29(7)
14	1.749(4)	1.768(3)					73.1(2)	
15	1.779(1)	1.761(1)	1.409(2)	1.394(2)	90.0(1)	91.2(1)	76.2(1)	102.5(1)
16	1.698(2)	1.620(2)	1.810(2)	1.780(2)	83.8(1)	87.1(1)	99.4(1)	89.7(1)
17	1.679(2)	1.671(3)	1.894(4)	1.892(3)	80.4(1)	80.7(1)	107.7(1)	91.2(1)
18	1.615(5)	1.607(5)	1.853(6)	1.856(6)	87.3(3)	87.2(3)	100.8(3)	84.1(2)
19	2.193(1)	2.167(1)	1.789(3)	1.803(3)	82.09(11)	82.53(11)	85.07(5)	110.3(2)
20	1.689(2)	1.686(2)	1.411(4)	1.412(4)	89.3(2)	89.4(2)	80.35(12)	100.9(2)
	1.684(2)	1.689(2)	1.404(4)	1.408(4)	89.2(2)	88.9(2)	80.41(11)	101.5(2)
21	2.2871(9)		1.736(2)				78.82(3)	
22	2.271(1)	2.266(2)	1.780(5)	1.770(5)	84.6(2)	85.0(2)	79.85(5)	
23	2.448	2.444	1.758	1.727	86.2	85.4	73.6	
24	2.460(5)	2.447(6)					74.3(2)	115(1)
25	2.0999(8)	2.0914(8)	1.8609(19)	1.8576(18)	86.36(6)	86.19(6)	86.11(3)	100.62(9)
26a	2.0886(7)	2.0927(7)	1.8727(15)	1.8655(16)	86.71(5)	87.01(5)	86.14(3)	99.60(7)
27	2.279(2)	2.283(2)	1.915(7)	1.910(6)	91.4(2)	91.4(2)	77.73(7)	96.9(3)

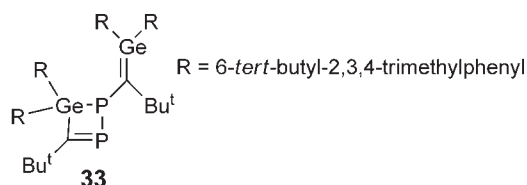
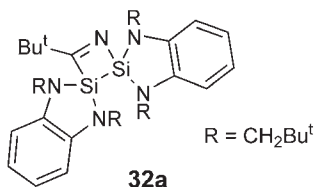
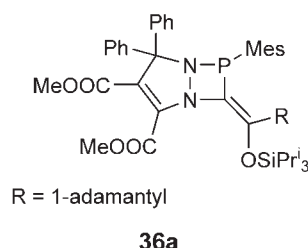
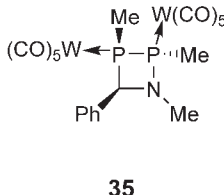
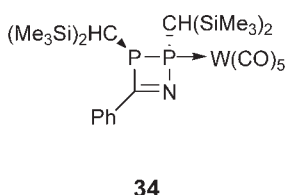
The structures of unsymmetrical heterocycles of the type 3 have been confirmed by X-ray crystallography (Table 2). The central ring of oxadisilacyclobutane 28 is slightly puckered with a *trans*-relationship of both supersilyl substituents and both Br atoms. The Si–Si endocyclic bond and the two exocyclic bond lengths are 2.371(2), 2.475(2), and 2.419(2) Å, respectively, and are longer than a typical Si–Si bond (2.34 Å), while the angles at Si-1 and Si-2 are relatively small (71.1(1)° and 79.6(1)°, respectively) <2001JOM(619)110>. The Si–Si bonds in the structure of 29 show values between 2.40 and 2.52 Å <2001OM2451>. The length of the endocyclic Si–Si bond in the rigidly fused skeleton of bicyclic compound 30 is only 2.3269(6) Å, compared to 2.418 Å for ordinary disilagermirane <2001CL728>. The central ring of thiadisiletane 31 is nearly planar <2002CEJ2730>. The skeleton atoms of the four-membered ring of 32a are in the same plane <2001ZFA1048>. The bond length of the endocyclic P=C double bond (1.702(4) Å) in 33 is typical for such type of compounds <2001CC215>. The four-membered ring of 34 is slightly folded (the torsion angle N–P–P–C is 8.9°) <2002CC2204>, while the four-membered ring of 35 is strongly nonplanar (the torsion angle P–C–N–P is 25°) <1998HAC597>. The bicyclic system 36a, containing the nonplanar four-membered ring, has a *cis*-fusion <1998CEJ903>.

Table 2 Geometric parameters of type 3 heterocycles

Compound	r (Å)				Angles (deg)			
	X-X	X-Y	C-X	C-Y	L CXX	L XXY	L Y	L C
28	2.371(2)	1.669(3)	2.031(4)	1.465(5)	71.1(1)	79.6(1)	110.2(2)	96.8(2)
29	2.4004(12)	1.681(3)	2.011(5)					
30	2.3269(6)	1.700(1)	2.005(2)	1.455(2)	70.1(1)	82.9(1)	104.6(0)	101.8(0)
31	2.413(1)	2.168(2)	1.919(2)		83.39(6)	82.29(5)	94.1(1)	98.2(1)
32a	2.385(3)	1.769(5)	1.925(6)	1.295(7)	68.8(2)	77.1(2)	106.0(4)	108.1(4)
33	2.1703(14)	2.4351(9)	1.702(4)	1.982(4)	93.39(15)	78.73(4)	79.15(11)	105.0(2)
34	2.2577(8)	1.747(18)	1.846(2)	1.304(3)	69.92(7)	78.51(6)	101.26(14)	107.80(15)
35	2.237(2)	1.717(4)	1.887(5)	1.470(7)	75.1(2)	77.3(2)	104.7(3)	95.6(3)
36a	1.490(3)	1.785(2)	1.466(3)	1.824(3)	96.5(2)	92.1(1)	75.3(1)	91.3(2)



Tip = 2,4,6-triisopropylphenyl

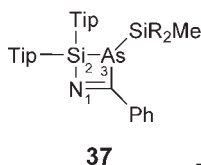
R = SiMeBu^t₂R = 6-*tert*-butyl-2,3,4-trimethylphenyl

R = 1-adamantyl

The geometric parameters of type **4** heterocycles are presented in **Table 3**. The As–C bond length (1.988(6) Å) and the endocyclic arsenic bond angle (65(1)°) of the molecule **37** are significantly smaller than the respective values in the compounds possessing the four-membered Si–N–As–C framework. In the case of the compound **38**, a remarkably long P–C distance (1.935(5) Å) is observed, which is caused by steric hindrance [<1996OM1845>](#). The four-membered ring of oxazagermete **39** is perfectly planar with the sum of the bond angles 360° [<1997CC1553>](#). The length of the Ge(2)–N(3) bond in **40** is 1.885(3) Å [<1996OM408>](#). The four-membered ring of **41** and **42** is almost planar [<2000TL5237, 2002HAC97>](#).

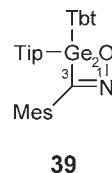
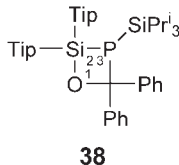
Table 3 Geometric parameters of type **4** heterocycles

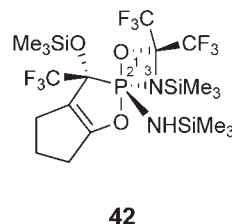
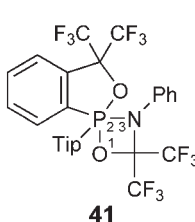
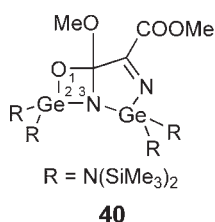
Compound	<i>r</i> (Å)				Angles (deg)			
	1-2	2-3	3-4	1-4	L1	L2	L3	L4
37	1.770(5)	2.402(2)	1.988(6)	1.291(7)	101.4(4)	80.9(2)	65.1(2)	112.1(4)
38	1.687(3)	2.281(2)	1.935(5)	1.454(5)	103.2(2)	82.0(1)	71.0(1)	101.5(3)
39	1.418(8)	1.872(4)	2.001(6)	1.291(9)	107.6(5)	92.7(3)	68.7(2)	91.1(5)
40	1.828(2)	1.885(3)	1.456(4)	1.410(4)	91.0(2)	75.06(10)	87.3(2)	104.2(2)
41	1.786(1)	1.688(2)	1.443(2)	1.379(2)	93.2(1)	74.84(7)	95.1(1)	96.9(2)
42	1.7464(19)	1.686(2)	1.448(4)	1.390(4)		76.94(10)		



R = cyclohexyl

Tip = 2,4,6-triisopropylphenyl





2.22.3.2 Molecular Spectra

2.22.3.2.1 NMR spectroscopy

Methods of ^1H -, ^{13}C -, ^{19}F -, ^{29}Si -, ^{31}P -, ^{77}Se -, ^{119}Sn -, and dynamic NMR have been used for the investigation of the compounds in the framework of this chapter. NMR data concerning the chemical shifts of the four-ring skeleton atoms, from which at least one corresponds to the heavier group 14 elements, are summarized in [Figure 1](#). The ^{31}P -NMR spectrum of **33** contains two sets of signals due to the equilibrium of two conformers in solution [<2001CC215>](#).

In ^{31}P -NMR spectra, the $\delta(^{31}\text{P})$ values of 2-arylthio-1,3,2 λ^5 -diazaphosphetidin-4-ones, for example, **7a** and **7b**, are about -44.0 ppm and are characteristic of pentacoordinated phosphorus compounds ([Table 4](#)). However, the corresponding signal of the 4-nitrophenoxy derivative **7c** is present at -53.9 ppm [<1995ZFA2001>](#). The $\delta(^{31}\text{P})$ values of 2-arylseleno-2-chloro-1,3,2 λ^5 -diazaphosphetidin-4-ones **8a–h** lie in the region -58.4 to -67.6 ppm. The $\delta(^{77}\text{Se})$ values of compounds **8a–f** lie in the region 437.4 – 527.1 ppm, while the corresponding $\delta(^{77}\text{Se})$ signals of compounds **8g, h**, possessing a 4-nitrophenoxy group, are situated *c.* 100 ppm upfield in comparison to their precursors **8c** and **8e** ([Table 4](#)) [<1996ZFA1250>](#).

The ^{31}P -NMR spectrum of **59** is of the AX type and contains signals of three- and pentacoordinated phosphorus at 11.9 and -64.9 ppm ($^1J_{\text{P,P}} = 168.1$ Hz), respectively. The established values of J_{PC} and J_{PH} allowed the conclusion that the corresponding chloromethyl groups are relatively stable and do not participate in the formation of a three-membered ring with the adjacent phosphorus atom [<1997ZFA1325>](#).

The $\delta(^{31}\text{P})$ -values of diazaphosphetidine **11** and related compounds lie in the region -50 to -60 ppm [<2000CC1375, 2002JA10698>](#).

The ^{31}P -NMR spectrum of 1,2,3-azadiphosphetidine complex **35** showed the characteristic AX pattern at $\delta = 29.28$ and 105.19 ppm ($^1J_{\text{P,P}} = 26.9$ Hz). In the ^{13}C -NMR spectrum the signal of the ring carbon atom is situated at 75.57 ppm ($^1J_{\text{C,P}} = 23.4$ Hz) [<1998HAC597>](#). The ^{31}P -NMR spectrum of the 1,2,3-azadiphosphete complex **34** showed a coupling of ^{31}P with the tungsten nucleus: δ 78.7 (d, $^{1+3}J_{\text{P,P}} = 91.3$ Hz, $^3J_{\text{W,P}} = 3.0$ Hz) and 79.8 (d, $^1J_{\text{W,P}} = 251.7$ Hz). In the ^{13}C -NMR spectrum the imine carbon signal is situated at 195.9 ppm (dd, $J_{\text{C,P}} = 33.6$; 12.6 Hz) [<2002CC2204>](#). The ^{19}F -NMR spectrum of 1,2,4-oxadithietane **16** was described as an A_2BC system with δ (^{19}F) at 89.53 (A), 70.50 (B), and 63.76 ppm (C) [<1995HAC611>](#). In the ^{13}C -NMR spectrum of the 3-trifluoromethyl-[1,2,4]thiadiazetidine **60**, the signal of the ring skeleton carbon atom is situated at 64.61, while in the ^{19}F -spectrum a signal of the equivalent fluorine atoms is placed at 3.3 ppm [<1999S1731>](#).

Variable-temperature ^1H -, ^{13}C - and ^{29}Si -NMR spectroscopy was used in an investigation of the reversible transformation of the tripodal amine **61** to azadisilacyclobutane **62**. The NMR spectra showed that at 295 K in a solution of toluene- d_8 , the equilibrium between **61** and **62** lies almost entirely on the side of the tripodal amine. When the temperature of the solution rose to 355 K, the equilibrium almost completely shifted toward azadisilacyclobutane **62** and the free amine ([Scheme 2](#)). However, the compound **62** was not isolated in pure form [<2001CEJ2563>](#).

2.22.3.2.2 IR spectroscopy

IR spectroscopy was mainly used for the identification of specific absorptions caused by an N–H single bond and endo- or exocyclic double bonds. The endocyclic C=N bond stretching was observed in the IR spectra of compounds **39** and **48** at 1612 and 1590 cm^{-1} , respectively [<1997CC1553, 1995TL8187>](#), while the exocyclic C=N bond of **43** gave an absorption at 1617 cm^{-1} [<1996OM753>](#). The IR spectrum of the compound **60** contained characteristic absorption bands at 3271 (N–H) and 1372, 1154 cm^{-1} (SO_2) [<1999S1731>](#).

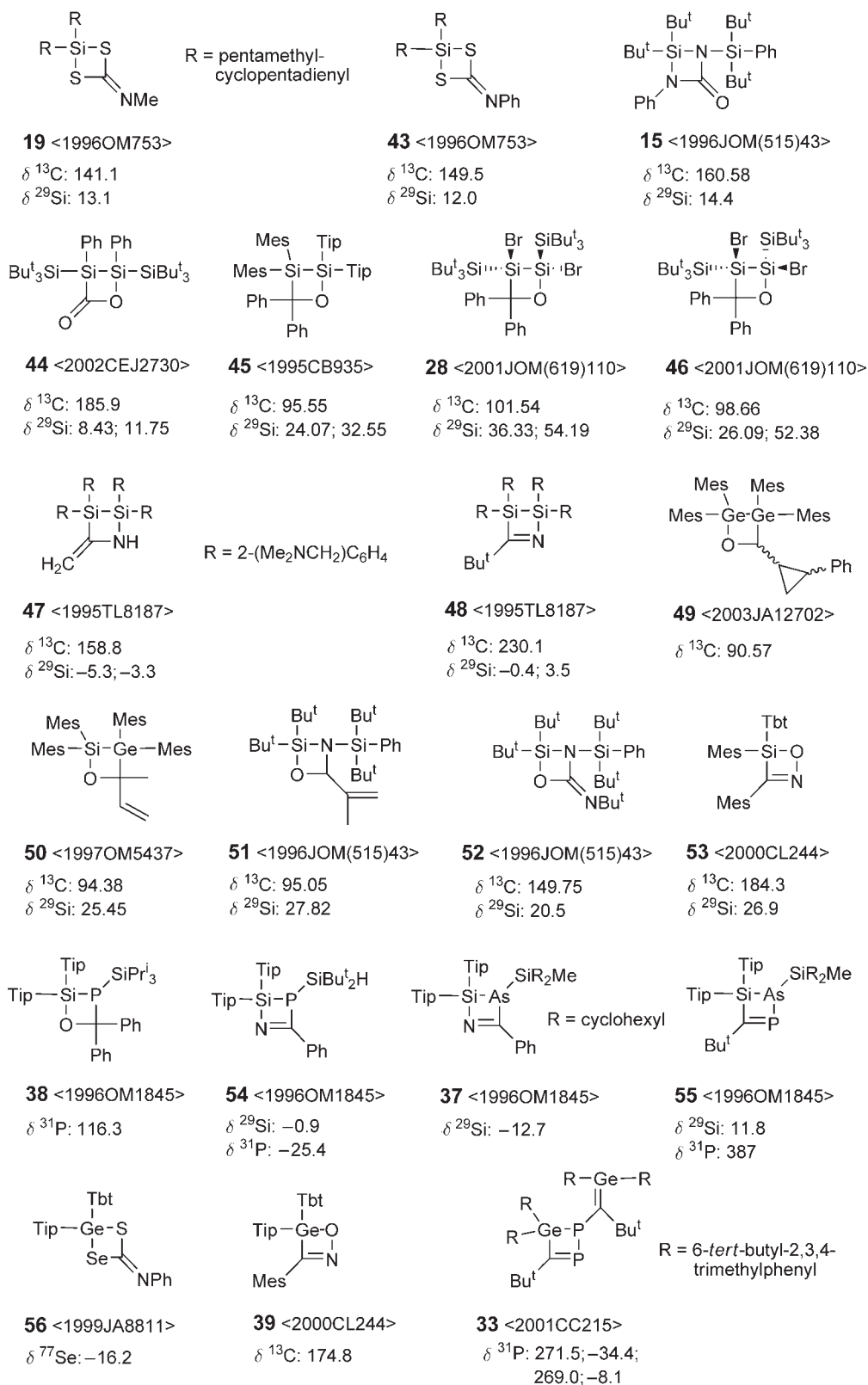


Figure 1 (Continued)

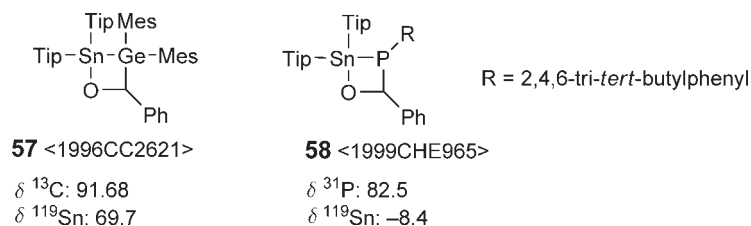
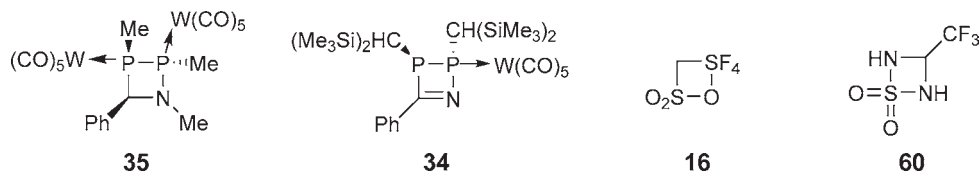
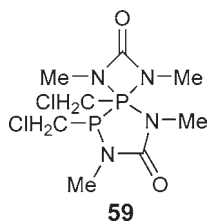
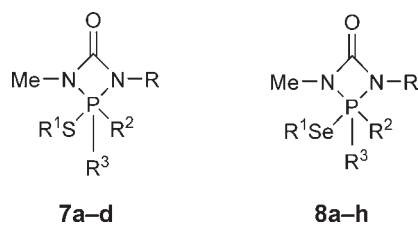
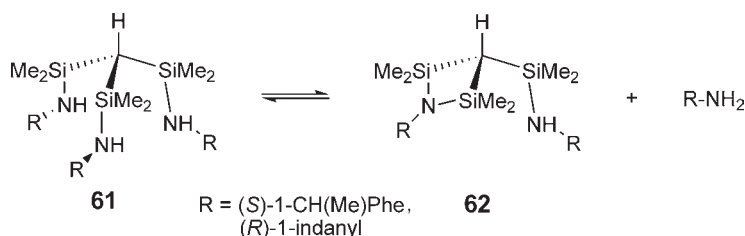


Figure 1 Chemical shifts (δ , ppm) of four-ring skeleton atoms.

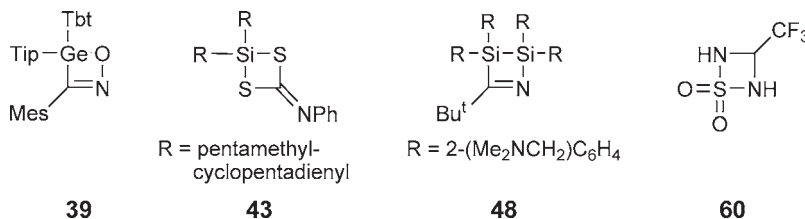
Table 4 ^{31}P - and ^{77}Se -chemical shifts of the 1,3,2 λ^5 -diazaphosphetidin-4-one **7a–d** and **8a–h**

<i>No.</i>	<i>R</i>	<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	^{31}P , δ (<i>ppm</i>)	^{77}Se , δ (<i>ppm</i>) ($^1J_{\text{PSe}}$, <i>Hz</i>)
7a	Me	4-MeC ₆ H ₄	Ph	Cl	-43.8	
7b	Me	Ph	Ph	Cl	-44.3	
7c	Me	4-MeC ₆ H ₄	Ph	4-NO ₂ C ₆ H ₄ O	-53.9	
7d	Me	Ph	Ph	(CF ₃) ₂ C(H)O	-39.9	
8a	Ph	Ph	Me	Cl	-67.6	527.1 (557.9)
8b	Me	Ph	Ph	Cl	-58.4	445.0 (527.4)
8c	Me	4-ClC ₆ H ₄	Ph	Cl	-59.3	437.4 (563.6)
8d	Me	Ph	Me	Cl	-63.8	497.6 (541.1)
8e	Ph	Ph	Ph	Cl	-67.0	484.7 (591.3)
8f	Ph	4-ClC ₆ H ₄	Ph	Cl	-66.5	476.8 (584.8)
8g	Me	4-ClC ₆ H ₄	Ph	4-NO ₂ C ₆ H ₄ O	-62.9	345.2 (500.2)
8h	Ph	Ph	Ph	4-NO ₂ C ₆ H ₄ O	-66.6	401.1 (541.3)



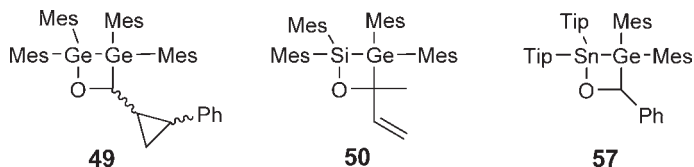


Scheme 2



2.22.3.2.3 Mass spectrometry

The appearance of fragments mirroring the cleavage of covalent bonds between the central ring skeleton atoms and the migration of bulky aromatic groups between metal atoms is a characteristic feature of mass spectra for many four-membered heterocycles containing heavier group 14 elements. The mass spectrum of the 3-oxa-2-stannagermetane **57** displayed various ions related to the decomposition of the four-membered ring system, and the Tip_2SnMes fragment, formed due to migration of a mesityl group from germanium to tin (m/z : 645 (Tip_2SnMes , 1), 598 (Tip_2SnGe , 4) 555 (Tip_2SnOCH , 3), 542 (Tip_2SnO , 1), 514 (TipSnGeMes 6), and others) <1996CC2621>. The mass spectrum of the compound **49** (a mixture of two diastereomers) had a similar character (m/z : 622 ($\text{Mes}_2\text{GeGeMes}$, 10), 431 (Mes_3Ge , 27), 312 (Mes_2Ge , 18), 207 (MesGeO , 100)) <2003JA12702>. The mass spectrum (registered at ionizing voltage 70 eV) of the compound **50** contained a signal for the molecular ion together with fragment ions (m/z : 648 (M^+ , 9), 578 (Mes_4SiGe , 100), 528 ($\text{M}^+ - \text{Mes}$, 8), 385 (Mes_3Si , 69), 312 (Mes_2Ge , 100), and others) <1997OM5437>.



2.22.4 Thermodynamic Methods

No relevant work has been published on thermodynamic methods during the period covered by this edition.

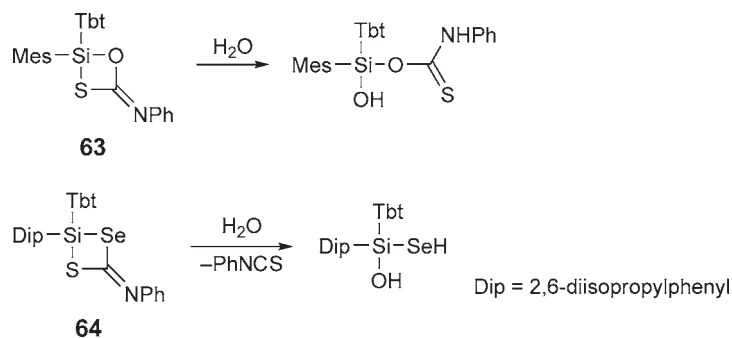
2.22.5 Reactivity of Fully Conjugated Rings

No relevant work has been published on the reactivity of fully conjugated rings during the period covered by this edition.

2.22.6 Reactivity of Nonconjugated Rings

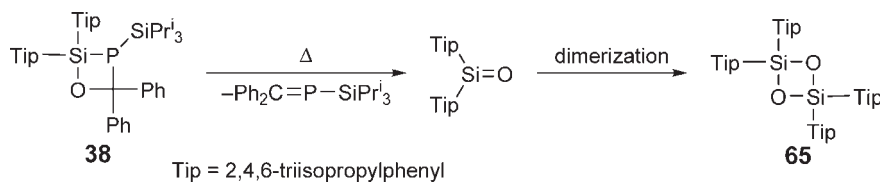
2.22.6.1 Cleavage of Four Rings with Three Heteroatoms

Many strained four-membered heterocycles, containing three heteroatoms, with at least one heavier group 14 element, are moisture, thermo- or light-sensitive compounds. For example, separation from the reaction mixture of 1,3,2-oxathiasiletane **63** furnished not the expected compound, but the hydrolyzed product, a thiocarbamate (Scheme 3) <2000CL244>. The adduct **64** is moisture stable and can be chromatographically purified. However, it is sensitive to gradual hydrolysis with the liberation of phenyl isothiocyanate <2002CL34>.



Scheme 3

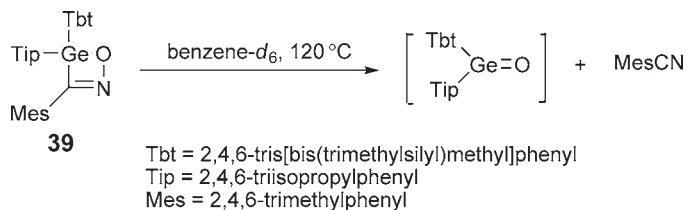
Thermolysis of 2,1,3-silaphosphoxetane **38** furnishes the transient silanone, which immediately dimerizes to the 1,3-disila-2,4-dioxetane **65** (Scheme 4) <1996OM1845>.



Scheme 4

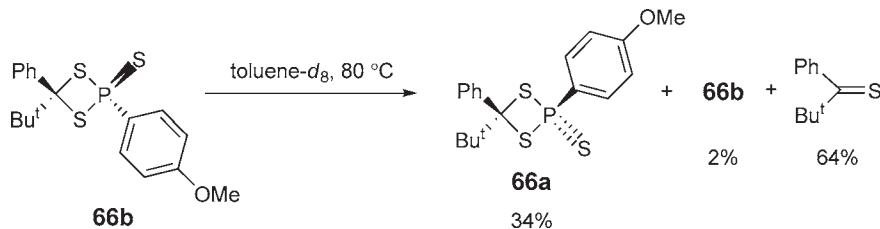
The 1-aza-2,3-disilacyclobutane derivative, obtained by the reaction of a thermally stable silylene with pyridine, when heated in benzene at 70°C for 2 days, underwent ring cleavage and via a 1,3-H shift transformed to 2-pyridylsilane <2004JOM(689)1350>.

Heating of a benzene- d_6 solution of oxazagermete **39** and 2,3-dimethylbuta-1,3-diene in a sealed tube resulted in formation of a mixture of products, the appearance of which was explained by cleavage of the four-membered ring system and generation of the reactive germanone (Scheme 5) <1997CC1553>. The latter was obtained and trapped with methanol or mesitonitrileoxide in a similar thermolysis experiment by cleavage of the germaketenedithioacetal <1996CL695>.



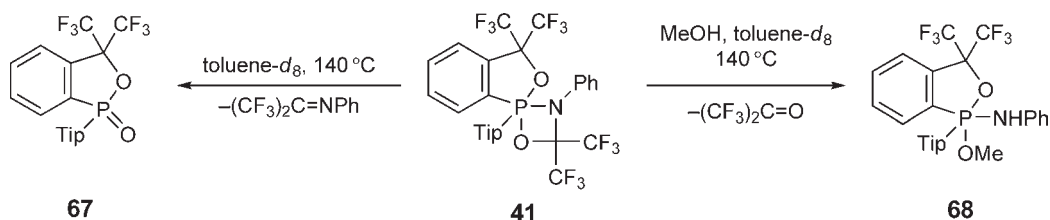
Scheme 5

When dithiaphosphetane **66b** was heated in toluene- d_8 , both decomposition of the starting material and inter-conversion to diastereomer **66a** were observed by ^1H -NMR spectroscopy (Scheme 6) <2004TL1331>.



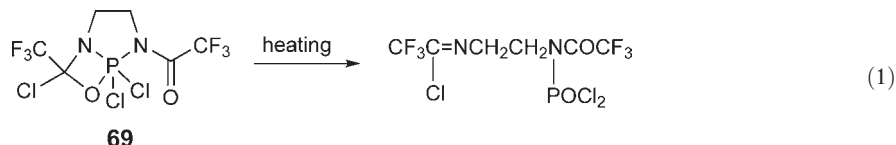
Scheme 6

Thermolysis of 1,3,2-oxazaphosphetidine **41** led to the elimination of an imine and the formation of **67**, while the corresponding methanolysis afforded methoxyphosphorane **68** (Scheme 7) <2002POL657, 2000TL5237, 2001CC2096>. A similar type of cleavage is also characteristic of other derivatives of 1,3,2λ⁵-oxazaphosphetidine <1995RJC198> and 1,3,2λ⁵-thiazaphosphetidine <2002PS1685>.

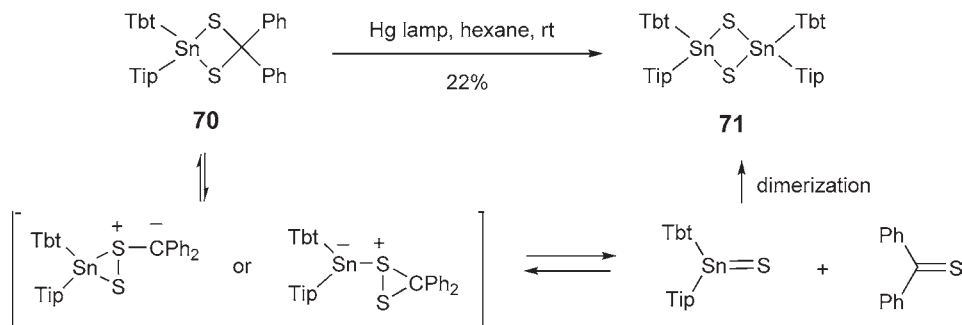


Scheme 7

6-Oxa-1,4-diaza-5λ⁵-phosphabicyclo[3.2.0]heptane **69** is thermally unstable and rearranges into an acyclic product when heated in vacuum (Equation 1) <1996RJC331>.

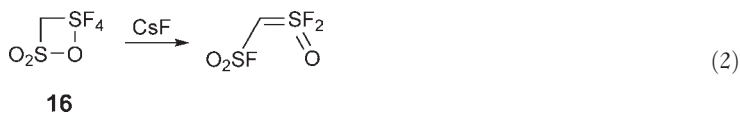


Photolysis of dithiastannetane **70** gave dithiadistannetane **71**, which is the product of stannanethione dimerization. The formation of the latter was explained by a reversible photochemical cleavage of the starting dithiastannetane **70** (Scheme 8) <1995HAC155>.

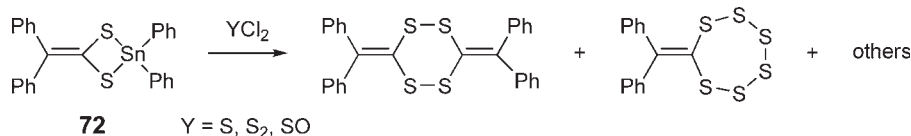


Scheme 8

The 1,2,4-oxadithietane **16** underwent a ring cleavage reaction in the presence of CsF (Equation 2) <1995HAC611>.



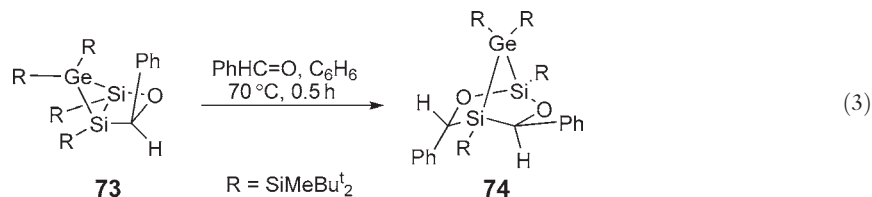
Treatment of 1,3,2-dithiastannetane **72** with sulfur halogenides resulted in a cleavage of the four-membered ring and formation of a complex mixture of products (Scheme 9) <1996CB663>.



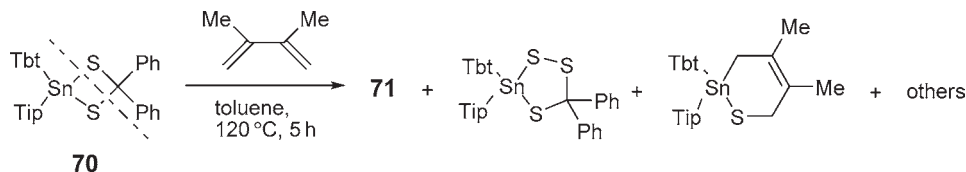
Scheme 9

2.22.6.2 Ring Expansion and Ring Contraction Reactions

Heating of compound **73** with benzaldehyde resulted in insertion of the C=O group into the strained bridgehead Si–Si bond to form bicyclic compound **74** (Equation 3) <2001CL728>.

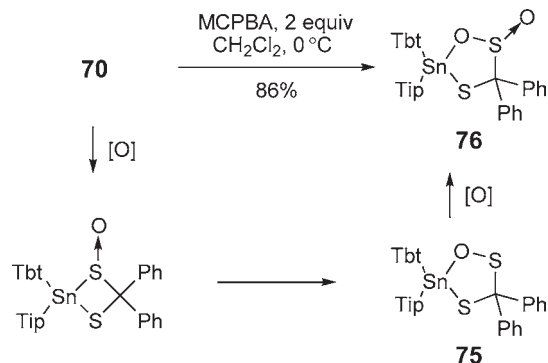


Heating a mixture of 1,3,2-dithiastannetane **70** with an excess of 2,3-dimethyl-1,3-butadiene in toluene in a sealed tube gave a mixture of products, including 1,3,2,4-dithiadistannetane **71**, as a result of self-dimerization of stannanethione, and 1,2,4,3-trithiastannolane. While the mechanism for the formation of the latter is not clear, the appearance of the six-membered ring product was explained by cycloaddition of the intermediate stannanethione with the butadiene (Scheme 10) <1995HAC155>.



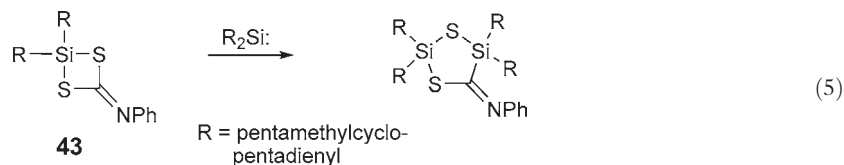
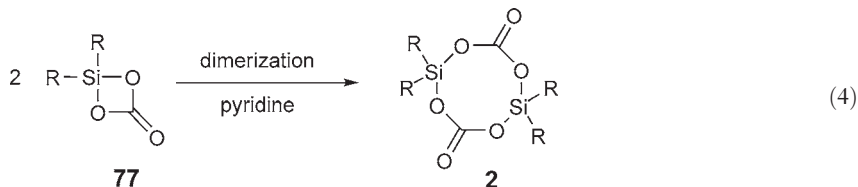
Scheme 10

Treatment of **70** with *m*-chloroperbenzoic acid in dichloromethane at $0^\circ C$ yielded 1,2,4,5-oxadithiastannolane 2-oxide **76** (Scheme 11) <1995HAC155>. The formation of the latter was rationalized by formation of the sulfoxide followed by a facile rearrangement leading to the ring-expanded oxadithiastannolane **75**. The oxidation of the sulfur atom in the β -position to the Sn atom of **75**, which is sterically less hindered than that in the α -position, afforded the final compound **76**.

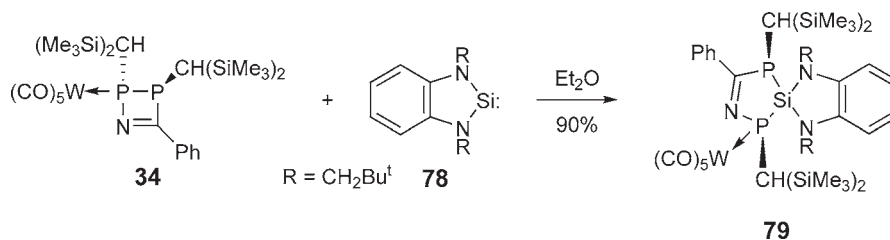


Scheme 11

In pyridine as solvent, the unstable adduct **77**, generated from decamethylsilicocene and carbon dioxide, easily formed a dimerization product after ring opening of one of the Si–O bonds (Equation 4). Insertion of decamethylsilicocene into the ring of the more stable dithiasiletane derivative **43** afforded a five-membered heterocycle (Equation 5) <1996OM753>.



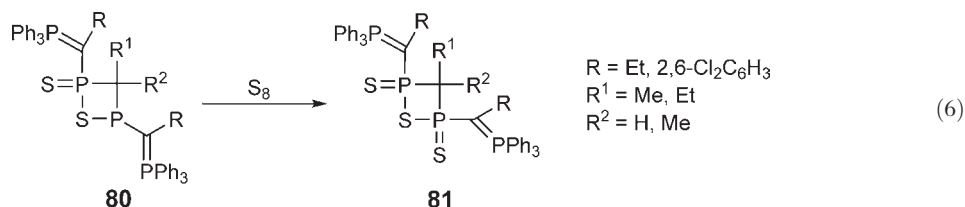
Reaction of the 2,3-dihydro-1,2,3-azadiphosphete complex **34** with silylene **78** afforded 1,2,4,3-azadiphosphasilol-5-ene **79** (Scheme 12) <2005CC4842>.



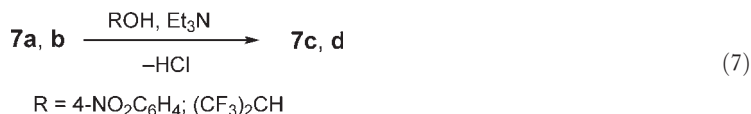
Scheme 12

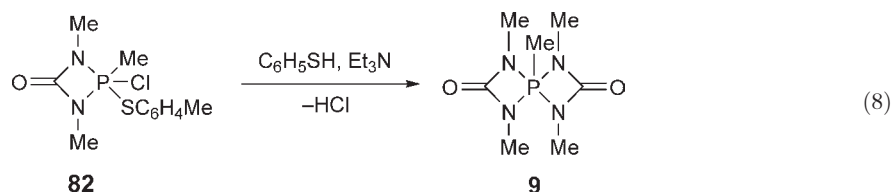
2.22.6.3 Reactions of Heteroatoms and Substituents on Heteroatoms

The 1,2,4- thiadiphosphetane 2-sulfides **80** can easily be oxidized with 1 equiv of sulfur to the corresponding 2,4-disulfides **81** (Equation 6) <1995CB1015>.

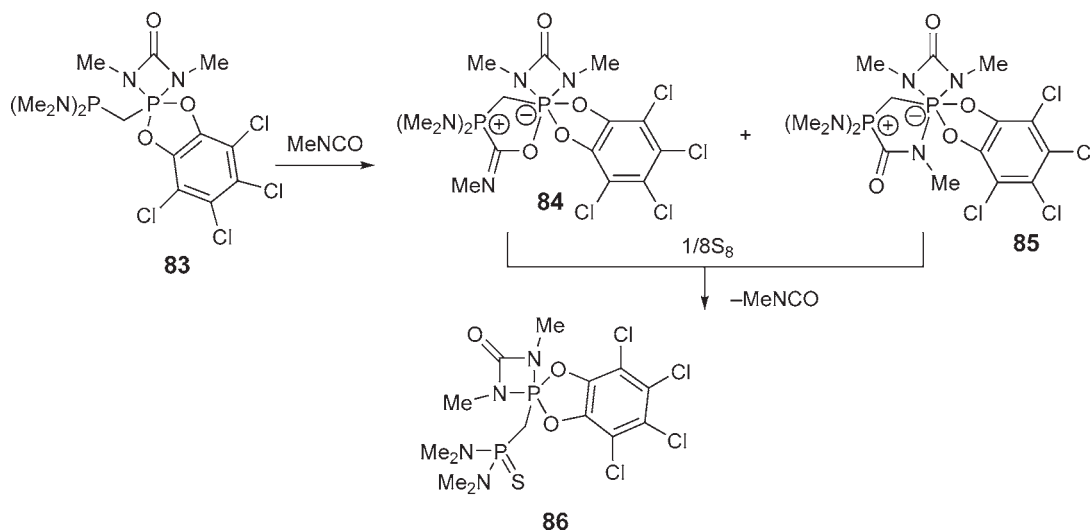


When 2-arylthio-2-chloro-1,3,2-diazaphosphetidin-4-ones **7a** and **7b** were reacted with O-nucleophiles such as hexafluoroisopropanol and 4-nitrophenol in the presence of triethylamine, substitution of the chlorine atom took place and the new phosphoranes **7c** and **7d** were formed (Equation 7 and Table 4) <1995ZFA2001>. An analogous reaction of 2-arylseleno-2-chloro-1,3,2-diazaphosphetidin-4-ones with 4-nitrophenol was investigated <1996ZFA1250>. Treatment of the chlorophosphorane **82** with thiophenol gave a mixture of products, from which the spirophosphorane **9** was isolated (Equation 8) <1995ZFA2001>.





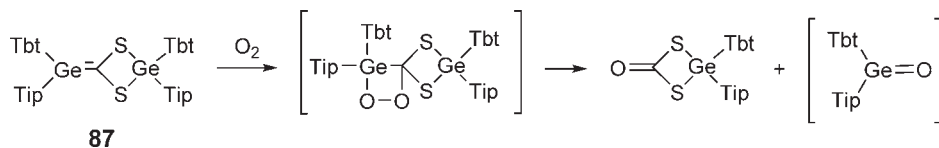
Reaction of methylenephosphinophosphorane **83** with methyl isocyanate afforded zwitterionic compounds **84**, **85** in a ratio 7:1 (Scheme 13) <1995TL2021>. However, the reaction is reversible. In nonpolar solvents the equilibrium is shifted to the cyclic products, while dissolving the latter in polar solvents leads to their decomposition to the starting reagents. If sulfur is added to the reaction mixture, compounds **84** and **85** disappear leaving oxidized compound **86** as the only product. Ethyl isocyanate reacts with compound **83** in a similar manner.



Scheme 13

2.22.6.4 Reactivity of Substituents Attached to Ring Carbon Atoms

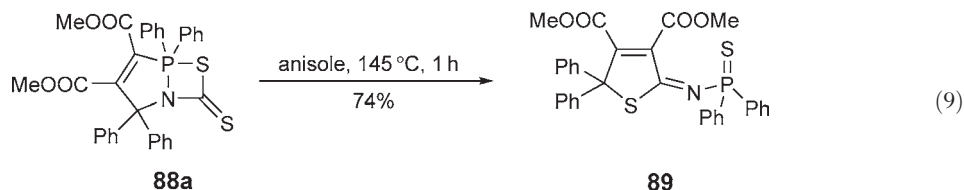
Oxidation of the germanoketenedithioacetal **87** by oxygen, in a tetrahydrofuran (THF) solution containing methanol, afforded 1,3,2-dithiagermetan-4-one and unstable germanone, which immediately underwent further reactions (Scheme 14) <1996CL695>.



Scheme 14

2.22.6.5 Rearrangement of the Ring

When adduct **88a** was heated in an anisole solution, a thermal rearrangement took place and the thiophene derivative **89** formed (Equation 9) <1999HAC167>.



2.22.7 Reactivity of Substituents Attached to Ring Carbon Atoms

The reactivity of substituents attached to ring carbon atoms has been covered in [Section 2.22.6.4](#).

2.22.8 Reactivity of Substituents Attached to Ring Heteroatoms

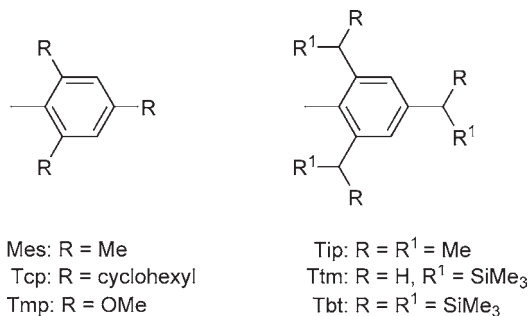
The reactivity of substituents attached to ring heteroatoms has been covered in [Section 2.22.6.3](#).

2.22.9 Ring Syntheses from Acyclic Compounds

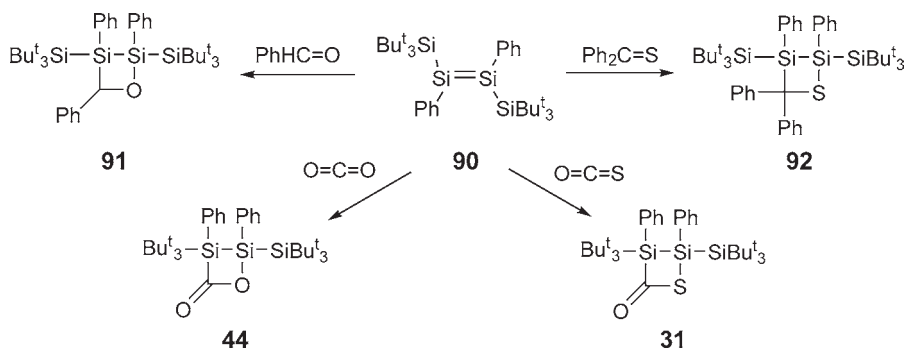
2.22.9.1 [2+2] Cycloaddition

The [2+2] cycloaddition is one of the major methods for the formation of four-membered heterocycles containing three heteroatoms with at least one N, O, or S atom. In this type of synthesis, one of the reagents possesses a double bond between two heteroatoms, while the second reagent contains double or triple bonds between a carbon atom and a heteroatom (aldehydes, ketones, thioketones, azomethines, nitriles, isonitriles, etc.). Dimetallenes $>\text{M}=\text{M}<$, such as disilenes, digermenes, and distannenes, consist of two identical heavier group 14 elements, and are typical reagents for [2+2] cycloaddition reactions, while ‘unsymmetrical’ dimetallenes $>\text{M}=\text{M}'<$, with two different group 14 elements, remain less explored. Compounds having a double bond between heavier group 14 elements and group 15 elements $>\text{M}=\text{E}$, where $\text{M} = \text{Si, Ge, Sn}$, and $\text{E} = \text{N, P, As}$, represent another type of active reagents employed in [2+2] cycloaddition reactions. As for compounds possessing double bonds between heavier group 14 elements and group 16 elements, ‘heavy ketones’, $>\text{M}=\text{E}$ ($\text{E} = \text{O, S, Se}$) can be considered as useful reagents for [2+2] cycloaddition reactions.

Usually, double-bonded metallene compounds bear bulky ligands at the metal atom, which kinetically stabilize the molecule and prevent oligomerization. Typical stabilizing ligands are substituents such as tri(*tert*-butyl)silyl, 2,4,6-trimethylphenyl (denoted as Mes), 2,4,6-tricyclohexylphenyl (Tcp), 2,4,6-trimethoxyphenyl (Tmp), 2,4,6-triisopropylphenyl (Tip), 2,4,6-tris[(trimethylsilyl)methyl]phenyl (Ttm), 2,4,6-tris[bis(trimethylsilyl)methyl]phenyl (Tbt), pentamethylcyclopentadienyl, and others.

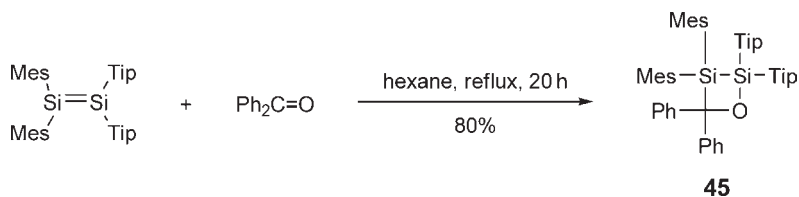


The [2+2] cycloaddition of the $\text{Si}=\text{Si}$ double bond of disilenes across a hetero double bond belongs to the most typical reactions for the preparation of disiletanes. Reaction of the supersilyl stabilized disilene **90** with $\text{PhHC}=\text{O}$ and $\text{Ph}_2\text{C}=\text{S}$ gave oxa- and thiadisiletanes **91** and **92**, respectively ([Scheme 15](#)). The use of heterocumulenes $\text{O}=\text{C}=\text{O}$ and $\text{O}=\text{C}=\text{S}$ in a similar cycloaddition reaction yielded oxa- and thiadisiletanes **44** and **31**. The isolated disiletanes are colorless and oxygen, water, and thermostable compounds [<2002CEJ2730>](#).



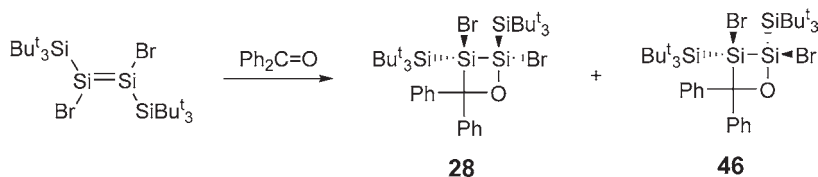
Scheme 15

The [2+2] cycloaddition reaction of the unsymmetrically substituted disilene with benzophenone proceeded with a high degree of regioselectivity to yield the 1,2,3-oxadisiletane **45** (Scheme 16) <1995CB935>.



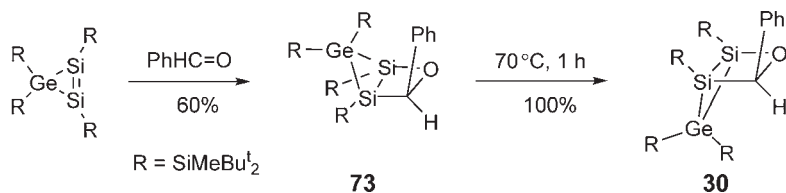
Scheme 16

Due to the instability of *trans*-1,2-dibromodisilene, its reaction with $\text{Ph}_2\text{C}=\text{O}$ was carried out *in situ*, just after dehalogenation of the corresponding 1,1,2,2-tetrabromodisilane. In this case the [2+2] cycloaddition reaction afforded *trans*- and *cis*-1,2-dibromo-3-oxa-1,2-disilacyclobutanes, **28** and **46**, as a 5:1 mixture of diastereomers (Scheme 17) <2001JOM(619)110>.



Scheme 17

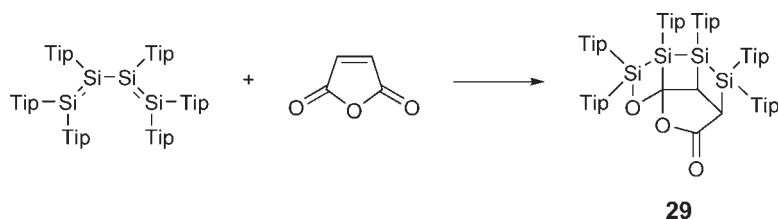
When the $\text{Si}=\text{Si}$ moiety is part of a cyclic system, the [2+2] cycloaddition reactions form bicyclic compounds. The *cis*-2-oxa-1,4-disila-5-germabicyclo[2.1.0]pentane **73** was the product of treatment of a three-membered 1-disilagermirene with benzaldehyde at low temperature (Scheme 18). The formation of **73** was evidently the result of the [2+2] cycloaddition reaction, which occurred stereospecifically to produce only one diastereomer. The reaction



Scheme 18

mechanism to form the *cis*-isomer **73** was based on the through-space attractive interaction of the electron-rich phenyl group and the empty σ^* -orbital of the exocyclic Ge–Si bond in the transition state. However, the configuration of the *cis*-isomer **73** is not stable, due to steric repulsion of the phenyl group with the silyl substituents on the Ge atom, and led to quantitative isomerization to the *trans*-isomer **30** upon heating at 70 °C (Scheme 18) <2001CL728, 2002MGM1>.

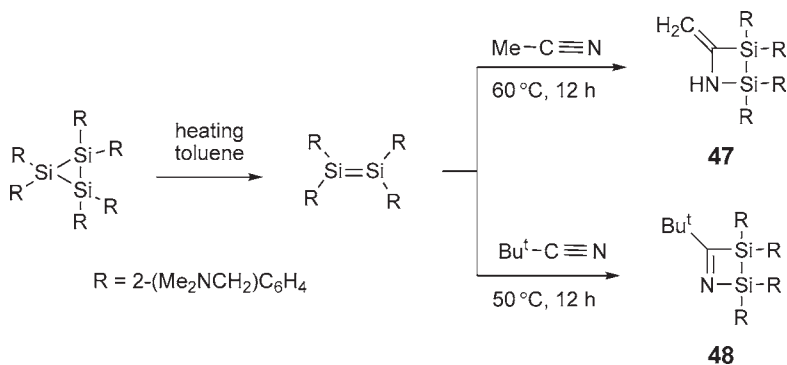
The treatment of hexakis(2,4,6-triisopropylphenyl)tetrasilabutadiene with maleic anhydride furnished the 2,9-dioxa-5,6,7,8-tetrasilatetracyclodecan-3-one derivative **29** (Scheme 19). The reaction pathway involves a [2+2] cycloaddition of one of the Si=Si bonds of tetrasilabutadiene to the highly reactive C=O group, followed by a second cycloaddition of the remaining Si=Si bond across the C=C double bond to complete the formation of the final product **29** <2001OM2451>.



Scheme 19

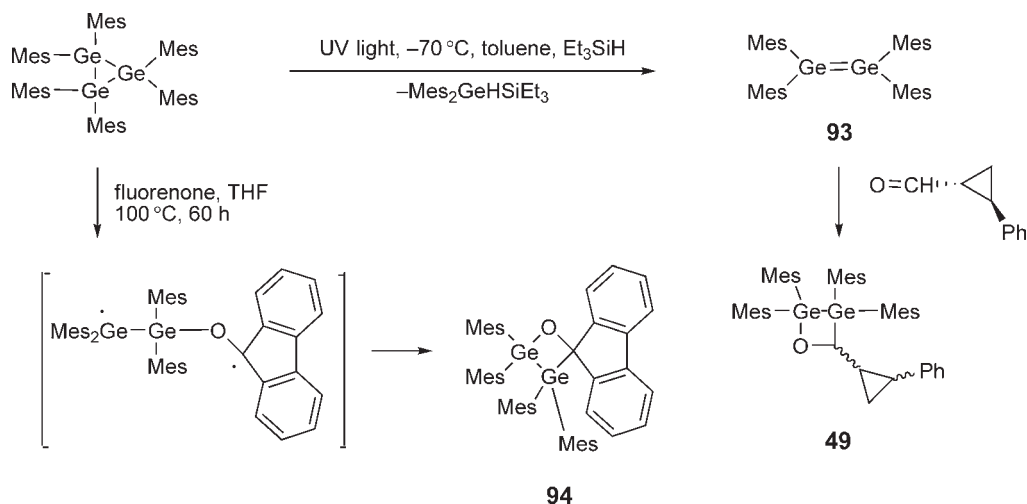
Small amounts of 1,2,3-oxadisiletanes were generated in reactions of disilenes with methyl- and phenyloxiranes. Their identity was established by comparison of their spectral data with authentic samples obtained by known [2+2] cycloaddition reactions of the appropriate aldehydes <1996JOM(521)363>.

The 1,2,3-azadisiletidine **47** and 1,2,3-azadisiletine **48** are, in a formal sense, the products of a [2+2] cycloaddition reaction between nitriles and disilene (Scheme 20). It can be assumed that the latter is the crucial intermediate formed during the thermolysis of hexasubstituted cyclotrisilane <1995TL8187>.



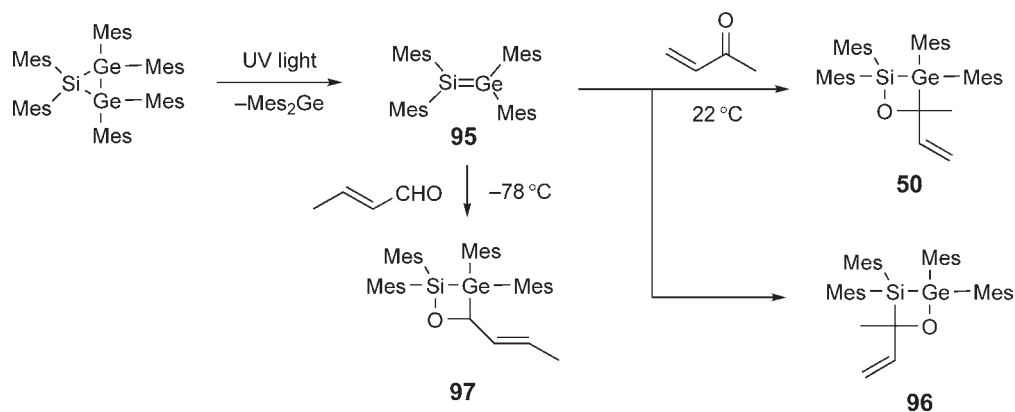
Scheme 20

The mechanistic studies of [2+2] cycloaddition reactions of carbonyl compounds with tetramesityldigermene showed that the Ge=Ge double bond of digermenes is less reactive compared to the Si=Si double bond of disilenes <2003JA12702>. The sterically hindered digermene **93** was generated by photolysis of hexamesitylcyclotrigermane in the presence of Et₃SiH at low temperature. Trapping of the intermediate digermene **93** with *trans*-2-phenylcyclopropylcarbaldehyde afforded the [2+2] cycloadduct **49** as a mixture of two diastereomers, which were not isolated in a pure state due to their instability (Scheme 21). A stable derivative of 1,2,3-oxadigermetane **94** was obtained by the reaction of hexamesitylcyclotrigermane with fluorenone. It is probable that this reaction proceeded via a radical pathway <1999HAC125>.



Scheme 21

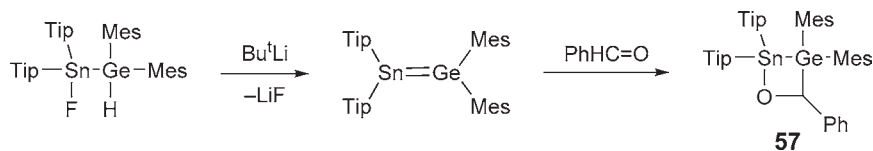
Photolysis of hexamethylsilagermirane generated tetramesitylgerasilene **95**, which upon trapping with methyl vinyl ketone at 22°C afforded the isomeric [2+2] cycloadducts **50** and **96** in an 8:1 ratio (Scheme 22) <1997OM5437, 1996OM5701>. When the intermediate gerasilene **95** was allowed to react with crotonaldehyde at -78°C , regioselective [2+2] cycloaddition yielded gerasilaoxetane **97** exclusively.



Scheme 22

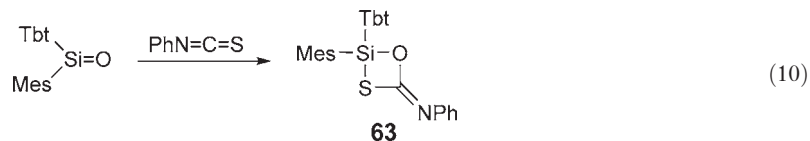
A bicyclic adduct was obtained by a [2+2] cycloaddition of the $\text{C}=\text{O}$ double bond of a benzaldehyde across the endocyclic $\text{Ge}=\text{Si}$ double bond of a five-membered silole <2004OM2822>.

Dehydrofluorination of the corresponding (fluorostannyl)germane by *tert*-butyllithium afforded stannagermene, which underwent a [2+2] cycloaddition reaction with benzaldehyde to form (3-oxa-2-stanna)germetane **57** (Scheme 23) <1996CC2621>.

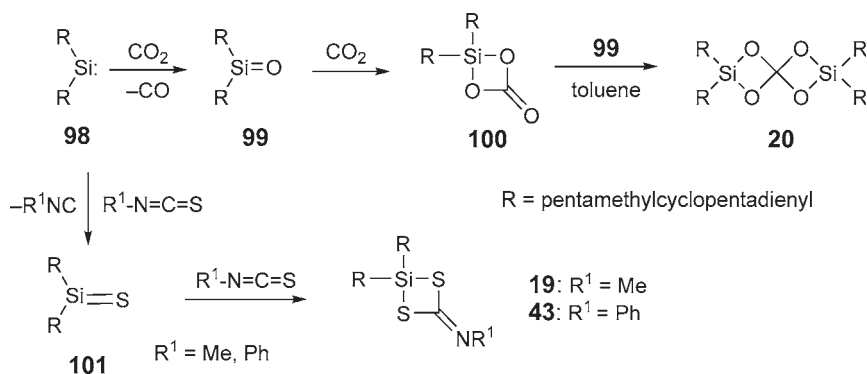


Scheme 23

In recent years remarkable progress has been made in the chemistry of organosilicon compounds containing a double bond to group 14 and group 15 elements. The reaction of a silylene–isocyanide complex with nitrile oxide generated the intermediate silanone, which with phenyl isothiocyanate afforded 1,3,2-oxathiasiletane **63**, which is sensitive to hydrolysis (Equation 10) <2000CL244>.



The first silicon(II) compound stable under ordinary conditions was decamethylsilicocene **98**, in which two ligands are bonded in a η^5 fashion to the silicon atom. In the reaction of **98** with the electrophilic heterocumulene CO_2 , multistep processes are observed including the change of the formal oxidation state of the silicon atom from +2 to +4, and the hapticity of the pentamethylcyclopentadienyl ligands from η^5 to η^1 , and formation of the intermediate silanone **99**. The latter undergoes a [2+2] cycloaddition reaction with CO_2 , present in the solution, to afford **100**, which once more is a highly reactive intermediate and reacts with the silanone **99** to give the final product **20** in a following [2+2] cycloaddition step (Scheme 24) <1996OM753>.



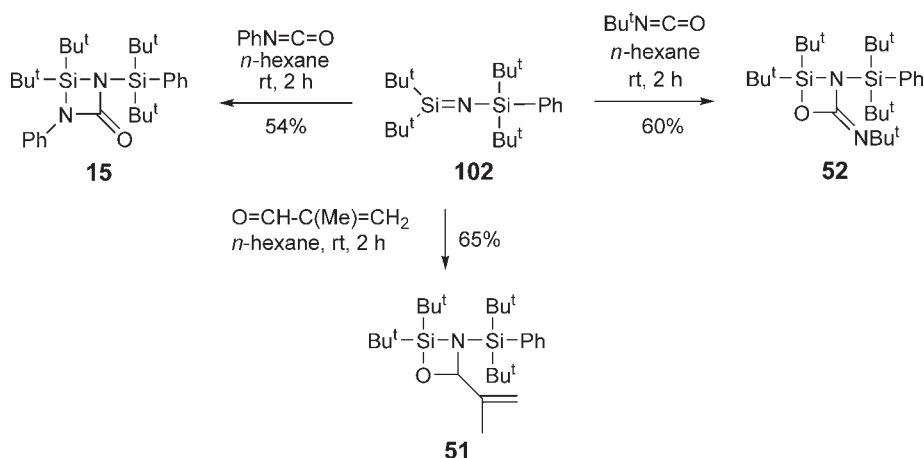
Scheme 24

Treatment of **98** with isothiocyanates generates the unstable silanethiones **101** under the reaction conditions, which react with the second molecule of isothiocyanate to yield the [2+2] cycloadducts **19** and **43**. The reaction of the thermally stable $\text{Tip}(\text{Mes})\text{silanethione}$ with phenyl isothiocyanate resulted in ready formation of a dithiasiletane ring system <1998JA11096>. The flash vacuum co-thermolysis of propargylthiodimethylsilane, a precursor for the generation of dimethylsilanethione, and excess of diketene afforded the [2+2] cycloadduct, 2,2-dimethyl-4-methylene-2-sila-3-thiaoxetane as the only product <1996TL7017, 1997PS371>. The [2+2] cycloaddition of the $\text{Si}=\text{Se}$ double bond across the $\text{C}=\text{S}$ double bond was achieved by the reaction of a kinetically stabilized silaneselone with phenyl isothiocyanate <2002CL34>.

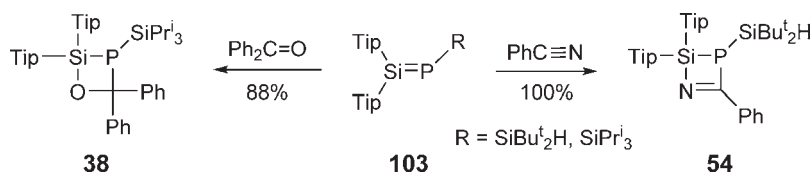
Symmetrical 1,3-diaza-4-silacyclobutane **15** was formed in a [2+2] cycloaddition of the $\text{Si}=\text{N}$ double bond of the iminosilane **102** across the $\text{C}=\text{N}$ double bond of phenylisocyanate (Scheme 25). However, treatment of the silane mentioned above with *tert*-butylisocyanate afforded 1-aza-3-oxa-4-silacyclobutane **52** possessing the exocyclic $\text{C}=\text{N}$ double bond. The compound **51** is the product of the reaction of iminosilane with 2-methylpropenal <1996JOM(515)43>.

The $\text{Si}=\text{P}$ double bond of compound **103** reacted with the strongly polarized triple bond of a nitrile to furnish the [2+2] cycloaddition product **54**. The $\text{Si}=\text{P}$ double bond of **103** readily underwent cycloaddition with the $\text{C}=\text{O}$ double bond of benzophenone to form the adduct **38** (Scheme 26) <1996OM1845>.

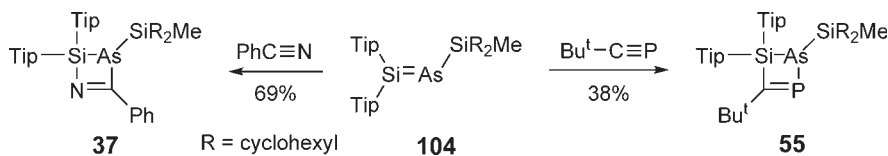
The $\text{Si}=\text{As}$ double bond of **104** reacted with the strongly polarized $\text{C}\equiv\text{N}$ triple bond in benzonitrile to furnish the [2+2] cycloaddition product **37** (Scheme 27), while similar addition across a $\text{C}\equiv\text{P}$ triple bond afforded the novel heterocycle **55**. According to the reverse polarity of the $\text{C}\equiv\text{P}$ triple bond compared with the $\text{C}\equiv\text{N}$ triple bond, the silicon ring atom in **55** is bound to the carbon atom <1996OM1845>.



Scheme 25

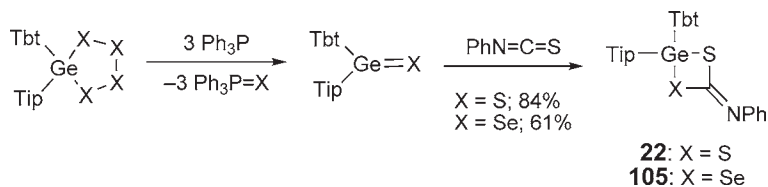


Scheme 26



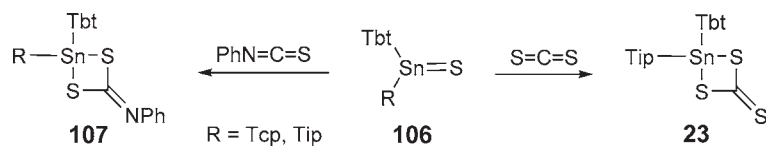
Scheme 27

Dechalcogenation of tetrachalcogengermolane with triphenylphosphine gave the kinetically stabilized germano-*thione* (X=S) and germano-*sclone* (X=Se). Symmetrical 1,3,2-dithiagermetane **22** was prepared by reaction of germano-*thione* (X=S) with phenyl isothiocyanate at room temperature, while the corresponding germano-*sclone* (X=Se) under similar conditions afforded 1,3,2-thiaselenagermetane **105** (X=Se). The compounds obtained are the first examples of imino-substituted 1,3,2-dichalcogengermetanes (Scheme 28) <1997H(44)149, 1999JA8811>.



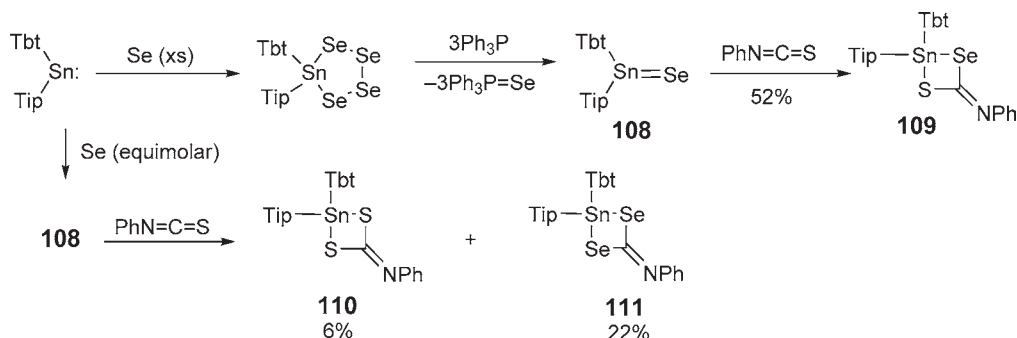
Scheme 28

Stannanethiones **106**, generated from kinetically stabilized stannylenes, were trapped with phenyl isothiocyanate to afford 1,3,2-dithiastannetanes **107** (Scheme 29) <1996OM4531, 2004JA15572>. Treatment of the corresponding stannanethione with an excess of carbon disulfide resulted in a [2+2] cycloaddition of the C=S bond across the Sn=S bond to yield 1,3,2-dithiastannetane-4-thione **23** <1996OM4531>.



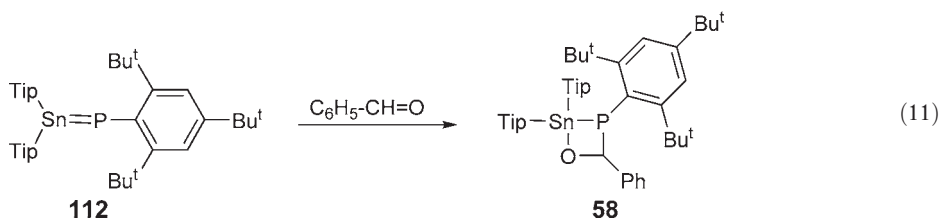
Scheme 29

An analogous synthetic approach was used in the preparation of 1,3,2-thiaselenastannetane [<1995JOM\(499\)43>](#). Stannaneselone **108**, generated from 1,2,3,4,5-tetraselenastannolane by deselenation with triphenylphosphine, in reaction with phenyl isothiocyanate gave the expected 1,3,2-thiaselenastannetane **109** (Scheme 30). However, similar trapping of stannaneselone, obtained from equimolar amounts of stannylene and selenium, led to the formation of a mixture of 1,3,2-dithia- and 1,3,2-diselenastannetanes **110** and **111**, respectively. The reason for the difference between these results still remains unclear.



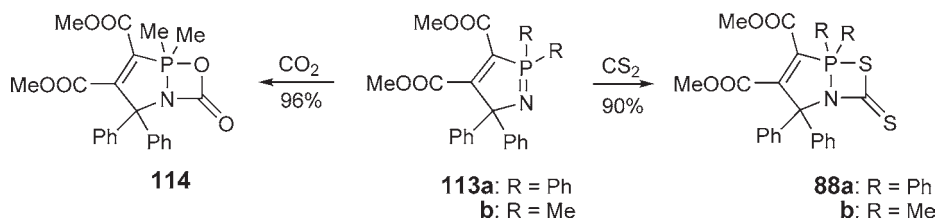
Scheme 30

The chemical behavior of phosphastannenes, possessing the Sn=P double bond, is still poorly understood. Phosphastannenes are less reactive in comparison with stannenes. However, reaction of phosphastannene **112** with ketones and aldehydes, including benzaldehyde, afforded the expected [2+2] cycloadducts, which were not obtained in a pure crystalline state, but identified by NMR spectroscopy as crude products (Equation 11) [<1999CHE965>](#).

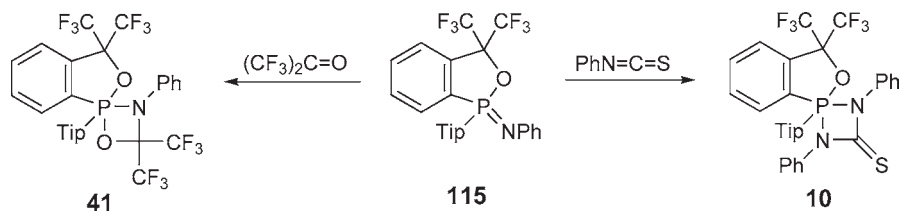


1,2λ⁵-Azaphospholes **113a** and **113b** contain a P=N double bond consisting of two group 15 elements. The treatment of **113b** with carbon dioxide afforded the [2+2] cycloadduct **114**, as a crystalline and colorless substance that is stable at room temperature. However, when the adduct **114** was dissolved in CDCl₃, it immediately lost CO₂ and gave the starting compound **113b**. The reaction of **113a** and **13b** with carbon disulfide resulted in formation of the adducts **88a** and **88b** (Scheme 31) [<1999HAC167>](#). Carbon disulfide underwent reaction with tetrasil-2-phospha-1-tetrazene [(Me₃Si)₂N-N(SiMe₃)P=N-SiMe₃] to form either a [2+1] or a [2+2] cycloadduct. However, the exact structure of the final product was not established [<2002IJA2079>](#).

The reaction of iminophosphorane **115** with carbonyl compounds such as benzaldehyde and trifluoroacetophenone gave unstable 1,3,2λ⁵-oxazaphosphetidines, which easily underwent hydrolysis on silica gel. However, treatment of **115** with hexafluoroacetone gave 1,3,2λ⁵-oxazaphosphetidine **41** in a pure form after chromatographic separation (Scheme 32) [<2000TL5237, 2002PS1685, 2002POL657>](#). Similar [2+2] cycloaddition reactions of the P=N double bond across the C=O double bond have been described [<1995ZNB1785, 1996ZNB1627, 2002HAC97>](#). The reaction of iminophosphorane **115** with phenyl isothiocyanate led to the formation of 1,3,2λ⁵-diazaphosphetidine-4-thione **10** [<2002PS1685>](#).

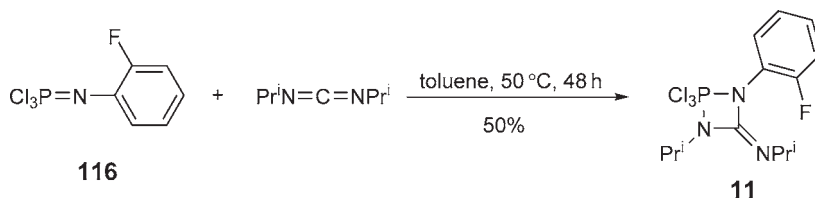


Scheme 31



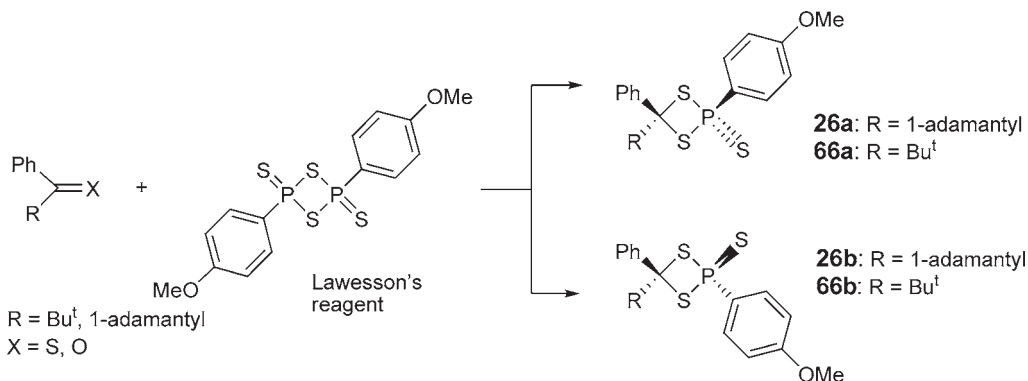
Scheme 32

The [2+2] cycloaddition reaction of the $\text{P}=\text{N}$ double bond across the $\text{C}=\text{N}$ double bond took part when carbodiimides were reacted with trichloroiminophosphoranes [<2000CC1375, 2002JA10698>](#). Heating a mixture of iminophosphorane **116** and diisopropylcarbodiimide in toluene yielded diazaphosphetidine **11** (Scheme 33).



Scheme 33

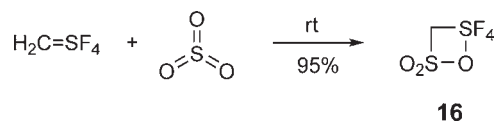
The typical Wittig-type intermediates, that is, 1,3,2-oxathiaphosphetane derivatives, were isolated from the thionation reaction of *cis*-bicyclo[3.3.0]octane-3,7-diones with Lawesson's reagent [<1998EJO2647>](#). However, under similar conditions both ketones and the corresponding thioketones formed a mixture of *trans*- and *cis*-1,3,2-dithiaphosphetanes **26a** and **26b** and **66a** and **66b** (Scheme 34), [<2004TL1331>](#).



Scheme 34

The reaction of steroidal ketones with Lawesson's reagent led to the spiroannellation of the 1,3,2-dithiaphosphetane nucleus on the tetracyclic ring system <2003PS2003>.

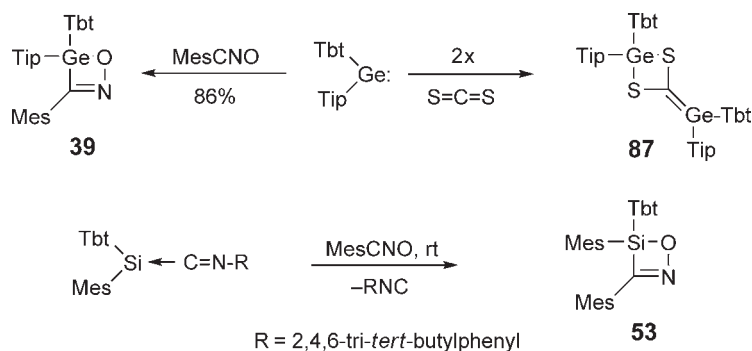
The addition of the S=O bond across the C=S bond took part in the reaction of sulfur trioxide with methyldiene sulfur tetrafluoride <1995HAC611>. The resulting 1,2,4-oxadithietane **16** was isolated as a stable colorless solid (Scheme 35).



Scheme 35

2.22.9.2 [3+1] Cycloaddition

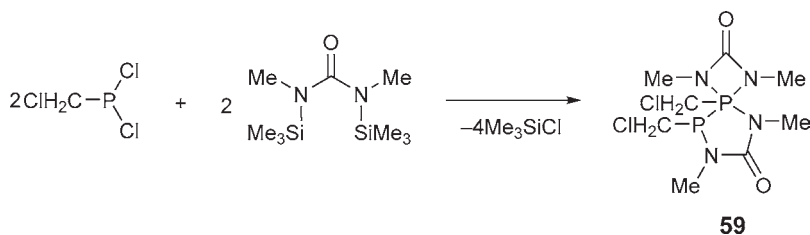
1,2,4-Oxazagermete **39** was prepared by a [3+1] cycloaddition reaction of germylene, bearing stabilizing substituents, with mesitonitrile oxide <1997CC1553>, while a similar reaction of silylene, existing as a stable complex with a Lewis base, afforded 1,2,4-oxazasilete **53** <2000CL244>. The interaction of two germylene molecules with carbon disulfide gave the germaketene dithioacetal **87**, as a product of the formal [3+1] cycloaddition (Scheme 36) <1995CC1425>.



Scheme 36

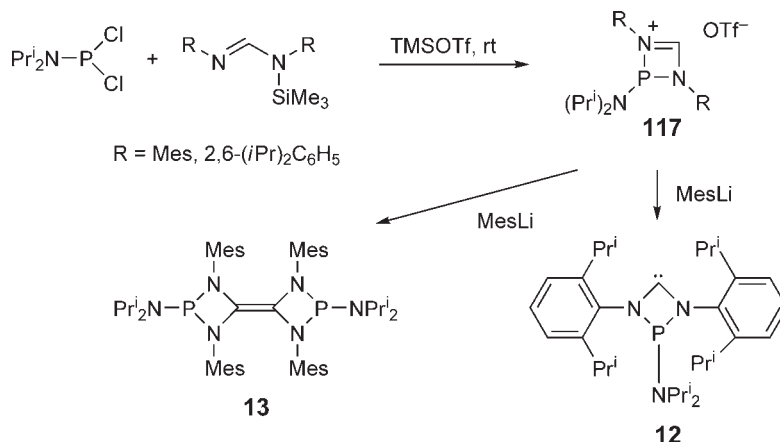
2.22.9.3 [3+1] Cyclocondensation

The reaction of *N,N'*-bis(trimethylsilyl)ureas with phenylsulfenyl chlorides furnished *N*-arylthioureas. The treatment of the latter with various organodichlorophosphines led to the formation of 1,3,2-diazaphosphetidin-4-one derivatives (Table 4) <1995ZFA2001>. A similar [3+1] cyclocondensation reaction of *N*-arylselenourea with dichloromethyl- and dichlorophenylphosphines has been carried out <1996ZFA1250>. The reaction of chloromethyldichlorophosphine with *N,N'*-dimethyl-*N,N'*-bis(trimethylsilyl)urea led to the spirocyclic P(III)–P(V) diphosphorus compound **59** (Scheme 37) <1997ZFA1325>.



Scheme 37

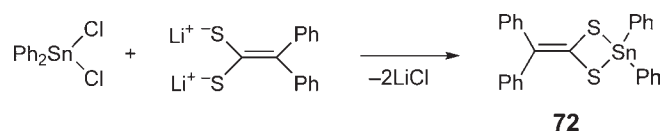
Deprotonation of the Mes-substituted iminium salt **117**, prepared from the silylamidine by addition of (diisopropylamino)dichlorophosphine, in the presence of trimethylsilyltrifluoromethanesulfonate, led to the formation of the dimer **13** (Scheme 38) <2004JA10198>. However, treatment of the salt **117**, bearing more bulky 2,6-(diisopropyl)phenyl substituents at the nitrogen atoms, generated the stable four-membered heterocyclic carbene **12**.



Scheme 38

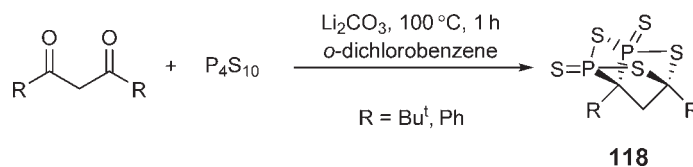
Methods for preparation of phosphoranes and spirophosphoranes containing a 1,3,2λ⁵-oxazaphosphetidine ring from trifluoroacetylphosphoramidites have been developed <1995RJC198, 1997RJC151>.

A derivative of 4-methylene-1,3,2-dithiastannetane **72** was prepared by reaction of diphenyltin dichloride with the dilithium salt of 2,2-diphenylethanedithioic acid (Scheme 39) <1996CB663>. A similar synthetic approach has been used for the preparation of 4-methylene-1,3,2-dithiagermetane **21** <2004AXEm357> and platinum complexes with cyanodithioimidocarbonate <2004JCD369>.



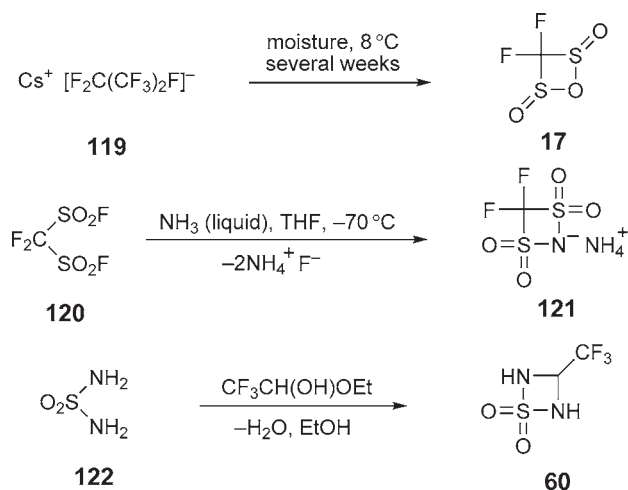
Scheme 39

Heating of dibenzoylmethane with P₄S₁₀ in dichloromethane afforded the condensed tricyclic compound **118**, possessing a P₂S₅ fragment, which is half of the original P₄S₁₀ skeleton. The two phosphorus atoms of this fragment are bridged by one carbon atom to afford a four-membered heterocycle (Scheme 40) <1998IC6093>.



Scheme 40

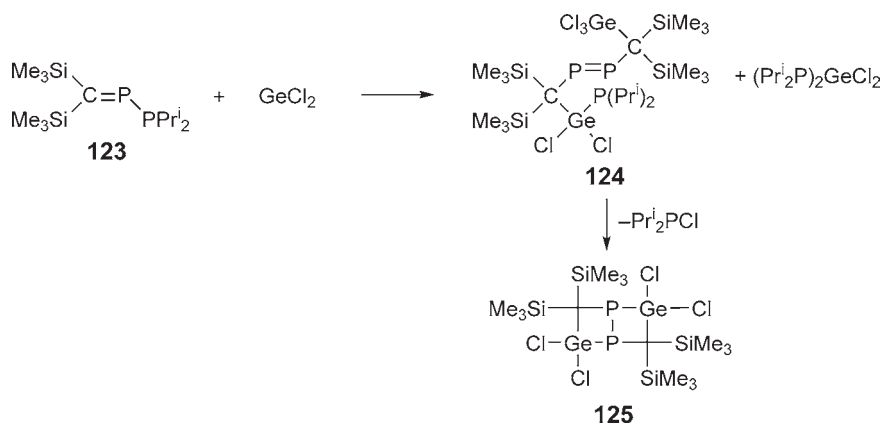
Single crystals of difluoromethane bis(sulfinic acid) anhydride **17** were isolated, after the cesium salt **119** was stored in the presence of traces of water vapor for several weeks <1998JFC(89)55>. Treatment of difluoromethane-1,1-bis(sulfonyl fluoride) **120** with liquid ammonia led to the formation of the cyclic ammonium imide **121** <1997ZNB359, 1997WO9731909>, while reaction of sulfamide **122** with trifluoroacetaldehyde *O*-ethyl hemiacetal afforded the cyclic amina **60** (Scheme 41) <1999S1731>.



Scheme 41

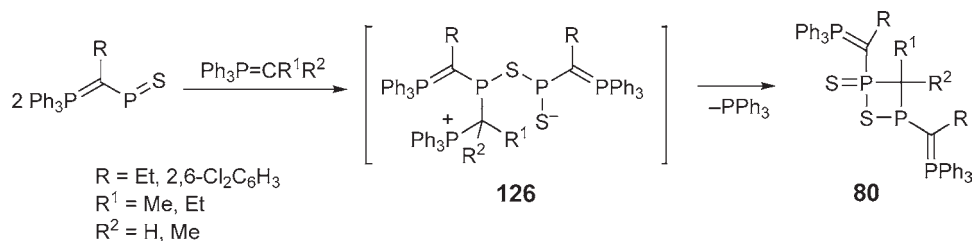
2.22.9.4 [3+1] Intramolecular Cyclocondensation

The reaction of GeCl_2 with phosphane **123** furnished thermally unstable diphosphene **124**, which at room temperature underwent cyclization to the bicyclic diphosphene **125** with liberation of $\text{Pr}_2\text{P}\text{Cl}$ (Scheme 42) <2001MGM609, 2004JOM(689)1331>.



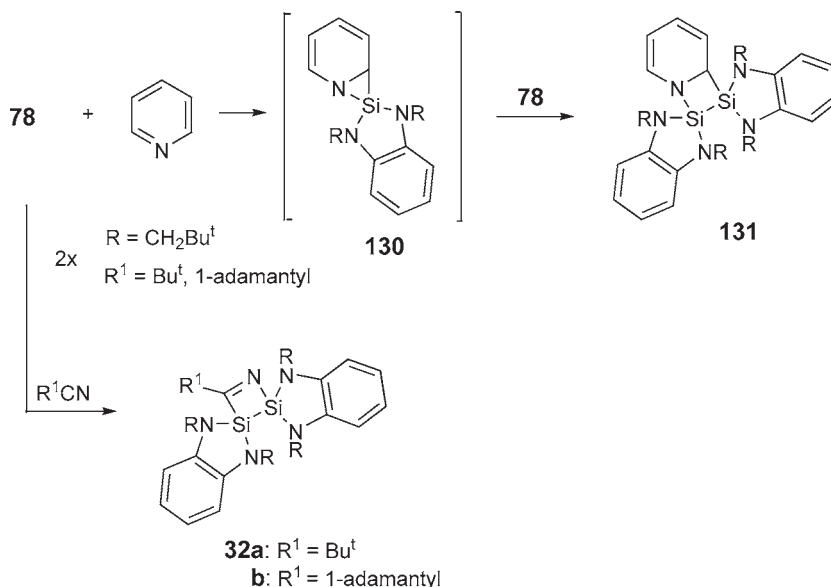
Scheme 42

Reaction of two molecules of thioxophosphanes with alkylidenetriphenylphosphorane afforded the intermediate **126**, which underwent ring closure with elimination of triphenylphosphine to give the final 1,2,4-thiadiphosphetane **80** (Scheme 43). An analogous method was used for the synthesis of 1,2,4-selenodiphosphetane <1995CB1015>.



Scheme 43

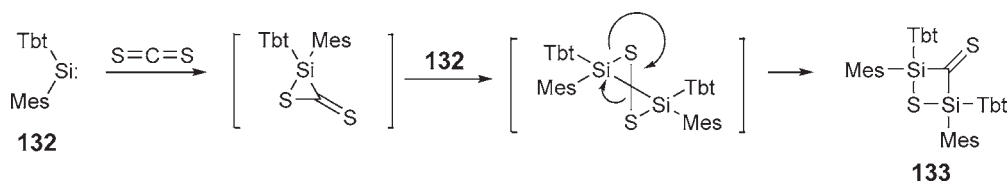
Treatment of the silylene **78** with pyridine in benzene afforded the crystalline compound **131** (Scheme 47) <2004JOM(689)1350>. The formation of **131** most likely proceeded via a three-membered intermediate **130**, followed by insertion of the silylene **78** into the C–Si or N–Si bond. When quinoline was used instead of pyridine, a similar adduct was formed, which in contrast to **131** was thermally stable.



Scheme 47

The reaction of **78** with alkyl nitriles, which is believed to also proceed via an appropriate three-membered ring intermediate, gave disilazetines **32a** and **32b** <1998POL999, 2001ZFA1048>.

The kinetically stabilized silylene **132** easily reacted with carbon disulfide to afford the four-membered Si–S–Si–C framework. The formation of product **133** most probably proceeded via double addition of silylene **132** to the C=S double bond followed by rearrangement of the spirocyclic intermediate (Scheme 48) <1996PAC895>.

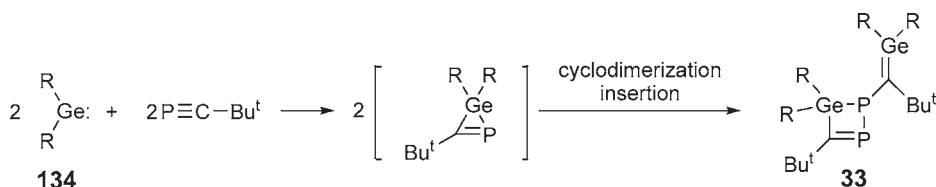


Scheme 48

Double SiCl₂ attack on the P=C bond of bis(trimethylsilyl)methylidenephosphane led to the formation of 2,3-disilaphosphetane <2002AG3977, 2004JOM(689)1331>.

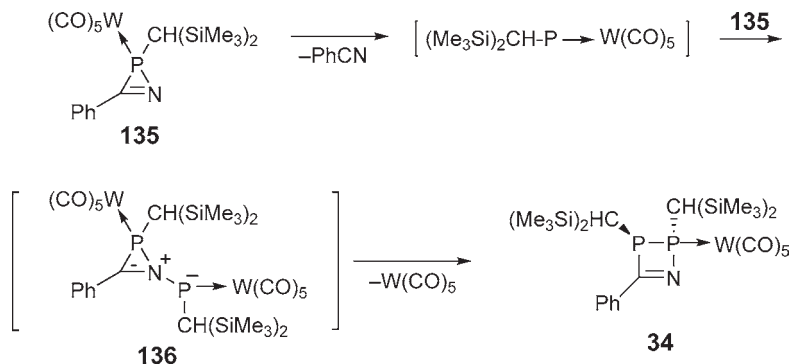
The reaction of germylene **134** with *tert*-butylphosphaalkyne gave germa-diphospha-cyclobutene **33**, possessing both two- and three-coordinated phosphorus atoms. It was assumed that the reaction started with the addition of **134** to the phosphaaalkyne to afford a three-membered ring system. Cyclodimerization of this intermediate yielded the final product **33** (Scheme 49) <2001CC215>.

Heating of the complex **135** in xylene formed phosphinidene, which reacted immediately with the starting material to afford the betaine-type intermediate **136** (Scheme 50) <2002CC2204>. The rearrangement of the latter with loss of pentacarbonyltungsten gave a mixture of products, from which **34** was separated as the major product (yield 30%). When an analogous transformation was carried out in the presence of bromobenzene, **34** was obtained as the only product in 72% <2003CC2892>.



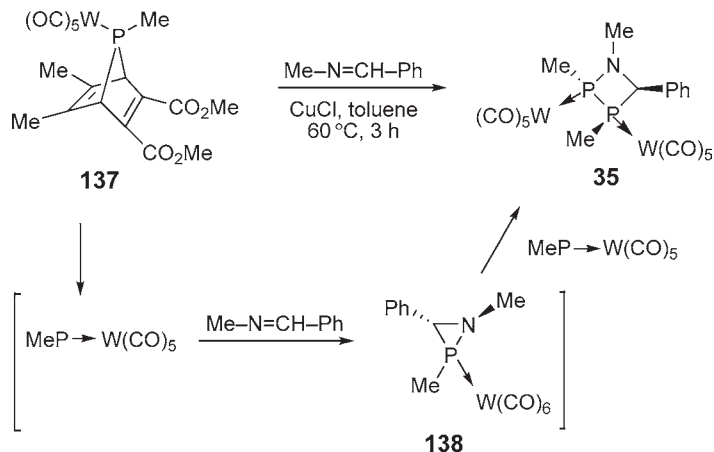
R = 6-*tert*-butyl-2,3,4-trimethylphenyl

Scheme 49



Scheme 50

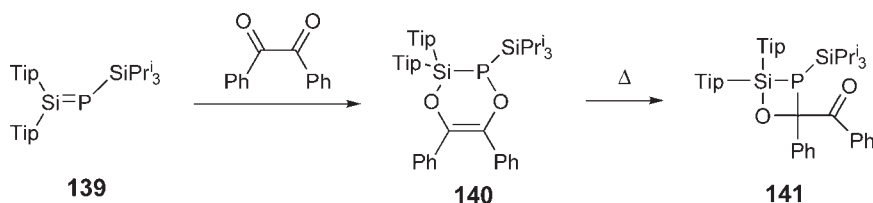
Treatment of the corresponding *N*-methyl(benzylidene)amine with excess of 7-phosphanorbornadiene complex **137** afforded 1,2,3-azadiphosphetidine **35** as the major product (Scheme 51) <1998HAC597>. The proposed reaction mechanism included the generation of a transient phosphinidene complex and formation of the unstable intermediate azaphosphiridine **138**. Insertion of the second molecule of phosphinidene into the weak P–N bond of the three-membered heterocycle **138** afforded the 1,2,3-azadiphosphetidine **35**.



Scheme 51

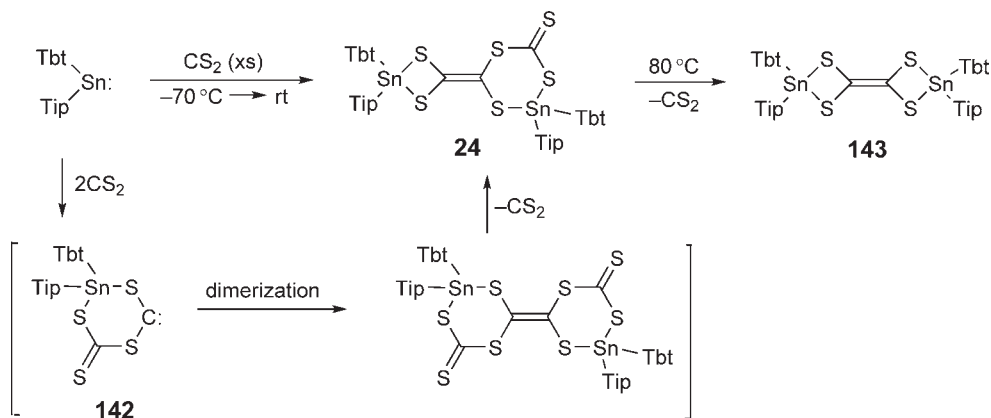
2.22.10.2 Ring Contraction Reactions

The [2+4] cycloadduct **140**, obtained by the reaction of **139** with a diketone, easily underwent rearrangement to **141**. This isomerization process was explained by a decrease of the ring strain and the favorable formation of the C–O π - and P–C σ -bonds (Scheme 52) <1996OM1845>.



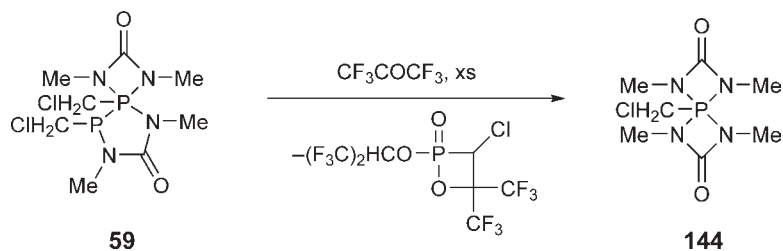
Scheme 52

It was found that treatment of the corresponding dibromostannane with lithium naphthalenide afforded stannylene [<1995OM3620>](#). The reaction of the latter with an excess of carbon disulfide resulted in the formation of the unsymmetrical ethene **24** (Scheme 53). Although the details of the mechanism are not clear, it is considered that the reaction proceeds via the formation of dithiocarbene **142** followed by dimerization to give a product that is thermally unstable and easily loses carbon disulfide. Thermolysis of **24** afforded symmetrically substituted ethene **143**, in a quantitative yield via extrusion of carbon disulfide.



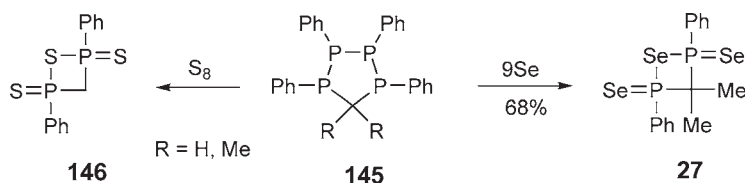
Scheme 53

The oxidative treatment of the diphosphorus bicycle **59** with an excess of hexafluoroacetone led to the cleavage of the P-P bond, elimination of the phosphorus atom from the five-membered ring, and formation of the bicycle **144** (Scheme 54) [<1997ZFA1325>](#).



Scheme 54

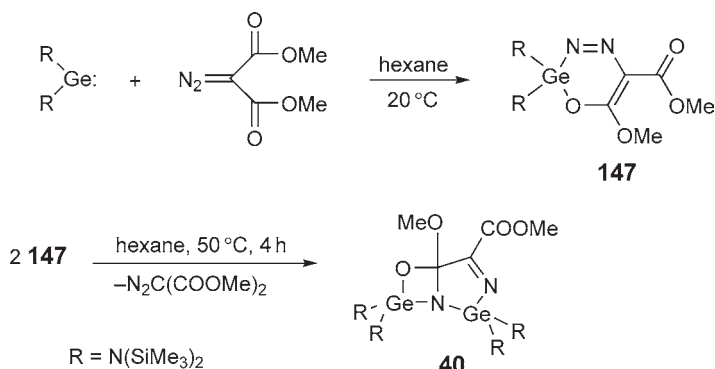
Oxidative addition of elemental sulfur and selenium to cyclomonocarbapentaphosphine **145** afforded the novel four-membered heterocycles **146** and **27** (Scheme 55) [<2001CC2288>](#).



Scheme 55

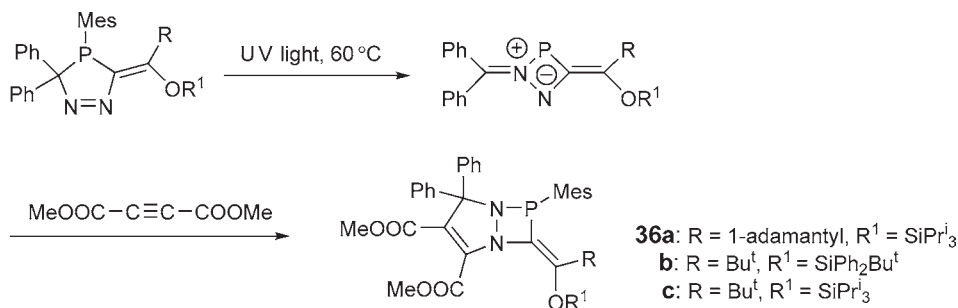
2.22.10.3 Other Reactions

The six-membered adduct **147** was obtained from the reaction of germene and dimethyl 2-diazomalonate (**Scheme 56**). Upon heating of **147** in hexane and slow evaporation of the solvent, colorless crystals of **40** were obtained. The diazomalonate that split off was isolated by high-vacuum distillation <1996OM408>.



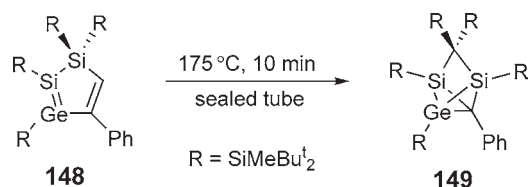
Scheme 56

UV irradiation of 4-phosphapyrazolines resulted in generation of semicyclic azomethine dipoles, which upon trapping with dimethyl acetylenedicarboxylate gave the bicyclic 1,2,3-diazaphosphetidines **36** (**Scheme 57**) <1998CEJ903>.



Scheme 57

Thermolysis of the five-membered silole **148** quantitatively resulted in the formation of the 2,4-disila-1-germatri-cyclo[2.1.0.0^{2,5}]pentane **149** (**Scheme 58**) <2002JA9962>.



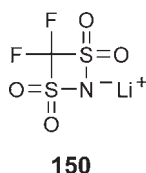
Scheme 58

2.22.11 Syntheses of Particular Classes of Compounds

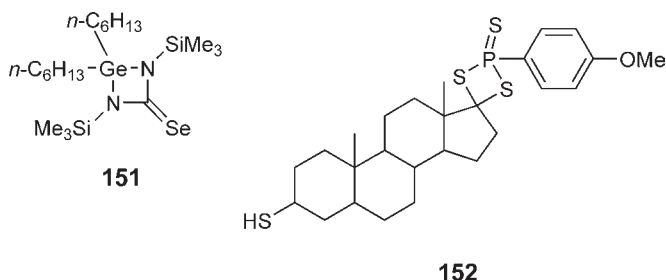
No syntheses of particular classes of compounds have been described during the period covered by this edition.

2.22.12 Important Compounds and Applications

Lithium cyclodifluoromethane-1,1-bis(sulfonyl)imide **150** found an application as a conductive salt in nonaqueous electrolytes for lithium secondary batteries. The corresponding battery cells showed outstanding properties in respect to the capacity and the constant voltage <1997WO9731909>.



Selenodiazadihexylgermetane **151** offered weak radioprotective activity <2001MBD199, 2003AOM135>, while steroidal dithiophosphetanethione **152** and its *S*-dimer were considered as promising antimicrobial agents <2003PS2003>.

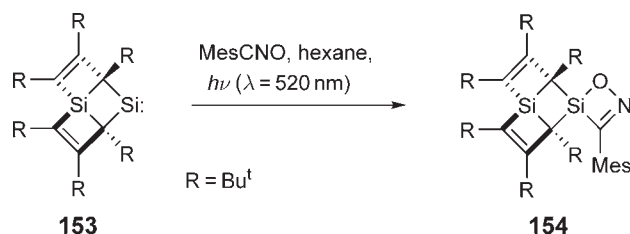


2.22.13 Further Developments

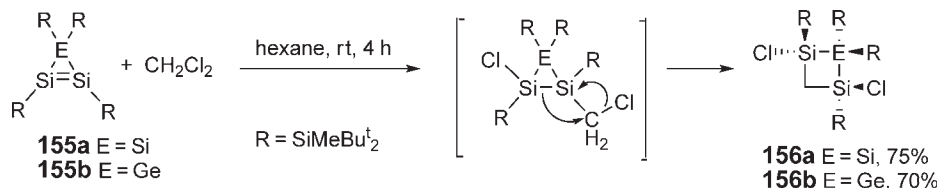
The tandem [2+2] cycloaddition–cycloreversion pathway for the reaction of *N*-phosphazenes and aldehydes, which includes the formation of the 1,3,2λ⁵-oxazaphosphetidine intermediates, has been studied computationally, using density functional theory (DFT) methods, and experimentally <2006JOC2839, 2006JOC6020>.

The silylene **153**, which exists in an equilibrium with the corresponding dimer in solution, underwent a [3+1] cycloaddition reaction with mesitonitrile oxide to afford 1-oxa-2-aza-4-silole **154** (Scheme 59). The latter compound is unstable and its presence in the reaction mixture was established only by means of ¹H NMR spectroscopy <2006JOM(691)1341>.

The reaction of heavy cyclopropene analogues, trisilirene, trigermirene, disilagermirene, and siladigermirene with CH₂Cl₂ resulted in the formation of four-ring heterocycles as the outcome of a ring expansion reaction <2007JOM(692)10>. For example, the treatment of trisilirene **155a** or disilagermirene **155b** with CH₂Cl₂ afforded derivatives of 1,2,3-trisiletane **156a** and 1,3,2-disilagermetane **156b**, respectively (Scheme 60).



Scheme 59



Scheme 60

References

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 1995CB1015
 1995CC1425
 1995HAC155
 1995HAC611
 1995JOM(499)43
 1995OM3620
 1995RJC198
 1995TL2021
 1995TL8187
 1995ZFA2001
 1995ZNB1785
 1996CB663
 1996CC2621
 1996CHEC-II(1B)1189
 1996CL695
 1996JOM(515)43
 1996JOM(521)363
 1996OM408
 1996OM753
 1996OM1845
 1996OM4531
 1996OM5701
 1996PAC895
 1996RJC331
 1996TL7017
 1996ZFA1250
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 1997RJC151
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Biographical Sketch



Algirdas Šačkus was born in Kaunas, Lithuania in 1954. He received his Dipl.Ing. and DSc degrees from Kaunas University of Technology in 1977 and 1981, respectively. He has been a senior research scientist at the Kaunas University of Technology since 1981. In 1984–85 he spent 1 year for postdoctoral research in the group of Prof. Otakar Červinka at the Prague Institute of Chemical Technology. In 1992 he was appointed as a full professor in the Department of Organic Chemistry, Kaunas University of Technology. In 1996 he was a research professor at the Danish Pharmaceutical University in the research group of Prof. P. Krosggaard-Larsen. Since 2005 he has been the director of the Institute of Synthetic Chemistry, Kaunas University of Technology. His research interests are generally focused on synthetic chemistry of heterocycles and unnatural amino acids.



Frank Abildgaard Sløk was born in Frederikshaven, Denmark in 1958. He received his MSc degree in chemical engineering from the Danish Technical University in 1989, and a PhD degree in organic chemistry, working under the direction of Prof. M. Begtrup at the Danish Pharmaceutical University in 1994. He was a postdoctoral fellow with Prof. P. Krosggaard-Larsen at the Danish Pharmaceutical University from 1994, and was later appointed as assistant professor in the Department of Medicinal Chemistry of the Danish Pharmaceutical University. From 2000 to 2006 he was senior scientist at NeuroSearch A/S and Nuevolution A/S. After that, he joined Vipergen ApS, where he is currently the head of chemistry. His main research interests include synthetic chemistry of heterocycles, unnatural amino acids, nucleosides, and nucleotides.