Synthesis and Reactivity of *C*-Heteroatom-Substituted Aziridines

Girija S. Singh,[†] Matthias D'hooghe,[§] and Norbert De Kimpe*,[§]

Chemistry Department, Faculty of Science, University of Botswana, Private Bag 0022, Gaborone, Botswana, and Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium

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1. Introduction

The smallest possible saturated azaheterocycle, aziridine, is well-known to organic chemists for its tremendous potential in organic synthesis and medicinal chemistry.[1] Even though highly reactive, the aziridine skeleton occurs in several natural products. Furthermore, many synthetic compounds of biological interest contain the aziridine framework in their structure. Compounds **1**−**4** (Figure 1) represent such synthetic and natural products of biological interest. This fact, combined with its unusual reactivity due to ring strain, makes it a target of interest from both synthetic and mechanistic points of view. A literature survey reveals an extensive investigation of the synthesis and chemistry of aziridines since the first synthesis by Gabriel in 1888.[2] Numerous methods have been reported for the synthesis of differently

[†] University of Botswana.
[§] Ghent University.

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Girija S. Singh was born in 1957 in Sasaram (Bihar), India. He received his B.Sc. and M.Sc. degrees from Gorakhpur University, India, in 1977 and 1979, respectively. He received his Ph.D. degree from the Banaras Hindu University (BHU), India, completing his doctoral thesis on the reactions of diazoalkanes and diazoketones with imines, amines, and hydrazones in October 1984 as a junior research fellow (1981–1982) and a senior research fellow (1983–1985) of the Council of Scientific and Industrial Research (CSIR), New Delhi. He was then awarded a postdoctoral fellowship by the CSIR for one year and worked with Professor S. N. Pandeya in the same university on the synthesis and anticonvulsant activities of thiadiazoles and azetidinones. Before joining Professor Pandeya again in 1989 as a research associate of the University Grants Commission, New Delhi, he worked as a research associate of the Ministry of Environment and Forest, India, with Professor U. K. Choudhary in the Ganga Laboratory, BHU (1987–1988). He joined the research group of Professor T. Ibata at Osaka University, Japan, in 1992 and worked on the reactions of ketocarbenoids and metal-catalyzed oxidations as a postdoctoral research student sponsored by the Ministry of Education, Science and Culture, Japan. He returned to the Chemistry Department of BHU in July 1994 as a senior research associate (Pool Officer), where he taught organic photochemistry and molecular rearrangements to M.Sc. students and did independent research. He joined the University of Zambia as a lecturer in 1996 and then the University of Botswana in 1998, where he is currently working as an Associate Professor. He has authored over 50 publications in peer-reviewed journals and holds membership in many professional societies including the Americal Chemical Society and the Chemical Research Society of India. His research interests include the development of new methodologies for the synthesis of biologically important heterocycles, especially using diazo compounds, metal-catalyzed oxidations, and organic chemistry education.

Matthias D'hooghe was born in Kortrijk, Belgium, in 1978. He received his master's diploma in Bioscience Engineering–Chemistry from Ghent University (Belgium) in 2001, and obtained the Ph.D. degree from Ghent University in 2006 under the supervision of Prof. N. De Kimpe, studying the synthesis and reactivity of 2-(bromomethyl)aziridines. At present, he is working as an assistant professor in the group of Prof. N. De Kimpe at the Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Belgium. His main research interests include the chemistry of small-ring azaheterocycles, with a special focus on aziridines, azetidines and β-lactams. He is the author of 27 publications in international peer-reviewed journals.

Norbert De Kimpe obtained the diploma of chemical agricultural engineer in 1971, the Ph.D. degree in 1975, and the habilitation degree in 1985, all from Ghent University, Ghent (Belgium). He performed postdoctoral research work at the University of Massachusetts, Harbor Campus, at Boston, MA (1979), and at the Centre National de Recherche Scientifique (CNRS) in Thiais, Paris, France (1983), where he worked on unstable nitrogen-substituted sulfenyl derivatives and electron-deficient carbenium ions, respectively. He made his scientific career at the Belgian National Fund for Scientific Research, where he went through all stages up to the position of Research Director. During this career, he was affiliated with the Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences at Ghent University, where he has held teaching positions since 1987. He is now a full professor in organic chemistry at the latter institution. He was a guest professor at the Centre Universitaire de Recherche sur la Pharmacopée et la Médecine Traditionelle in Butare (Rwanda) and at the Universities of Perpignan (France), Helsinki (Finland), Leuven (Belgium), Siena (Italy), Barcelona (Spain), Sofia (Bulgaria), Buenos Aires (Argentina), and Pretoria (South Africa). He was awarded the degree of Doctor honoris causa from the Russian Academy of Sciences in Novosibirsk in 1998 and the Medal of Honour of Sofia University in 2006. He is the author of 415 articles in international peer-reviewed journals. His research interests include (1) the synthesis of heterocyclic compounds, with focus on agrochemicals, pharmaceuticals, and natural products; (2) flavor chemistry; and (3) the bioassay-guided isolation of physiologically active natural products from medicinal plants.

substituted aziridines. The presence of different functionalities at nitrogen and other positions of the ring have been observed to play a significant role in determining the geometry of the aziridine ring and its fate. This has been exploited in the synthesis of diverse types of organic compounds with biological importance, such as β-lactams, azinomycins, tetrahydropyridines, indolizidine and pyrrolizidine alkaloids, allylic amines, and amino acids.[3,4] Besides this, aziridines are also useful chiral auxiliaries,[5] ligands,[6] and monomers for polymer synthesis.[7] The chemistry of aziridine-2-carboxylates has been reviewed by Zwanenburg.[8]

Many aziridine derivatives contain heteroatom substituents such as alkoxy, acetoxy, chloro, bromo, fluoro, amino, nitro, sulfonyl, and phosphoryl, in which the heteroatom is directly attached to one or both carbon atoms of the ring. The presence of these heteroatoms on the ring has been observed to affect the reactivity of the aziridines in such a way that in many cases stable compounds are isolated and transformed into other aziridine derivatives, whereas in other cases the ring undergoes cleavage affording diverse types of interesting products (Figure 2). There are plentiful methods in the literature for the synthesis of *C*-heteroatom-substituted aziridines. Many reactions are reported involving nucleophilic and electrophilic displacement on the ring, ring opening, with or without rearrangement, functional group transformations on the ring, etc., which have never been reviewed and discussed separately. The present paper thus aims to review

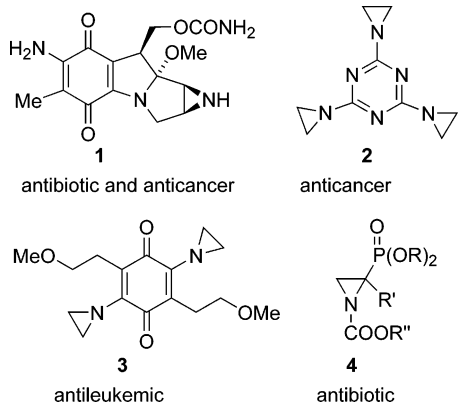


Figure 1.

the methods for the synthesis of *C*-heteroatom (oxygen, halogens, nitrogen, sulfur, phosphorus, and silicon) substituted aziridines and their reactivity in a comprehensive way. In some sections, a careful selection of leading references had to be made due to the extensive number of studies available in the literature. Metalated aziridines are included only if they are derived from or lead to *C*-heteroatom-substituted aziridines.

2. Synthesis and Chemistry of *C*-Heteroatom-Substituted Aziridines

The main approaches to the synthesis of aziridines can be classified as cyclization reactions, transfer of nitrogen to olefins,[9] transfer of carbon to imines,[10] addition across the carbon−nitrogen double bond of azirines,[11] reactions of ylides,[12] aza-Darzen approaches,[13,14] ring contraction, and functional group transformations (Figure 3).[15,16] Among the many reactions of aziridines, ring opening is the most common one,[17] initiated by both electrophilic and nucleophilic reagents. Metalated aziridines (aziridinyl anions) are stabilized by the presence of COPh, SO_2Ph, and $PO(OR)_2$ groups and destabilized by hydrogen and alkyl groups.[18,19] Ring opening and electrocyclic reactions together with ring enlargement products are also reported. Many *C*-heteroatom-substituted aziridines are stable enough to undergo nucleophilic displacements by various nucleophiles and reduction reactions affording new aziridine derivatives. In many other reactions, stable aziridines could not be isolated, but their intermediacy was proposed and established. The succeeding paragraphs of this review describe the synthesis and reactivity of such aziridines, which have heteroatoms on one or both of the carbons of the ring.

3. *C*-Oxygen-Substituted Aziridines

3.1. Introduction

The most common examples in this class are 2-alkoxyaziridines and 2-acyloxyaziridines. *C*-Oxygen-substituted aziridines are usually unstable compounds and appear mostly as intermediates en route to the final products. However, there are some papers in the literature showing isolation of stable 2-alkoxyaziridines, 2-acetoxyaziridines, and 2-hydroxyaziridines. The reactions describing the synthesis and chemistry of such aziridines can be divided into the following headings.

3.2. Cyclization and Neber Rearrangement

The Neber rearrangement is perhaps the oldest known reaction to 2-alkoxyaziridines.[20] In some cases, stable derivatives have been isolated. Several studies have been made on this rearrangement using oxime tosylates,[21−25] dimethylhydrazone methiodides,[26] and *N*,*N*-dichloroamines,[27] in which

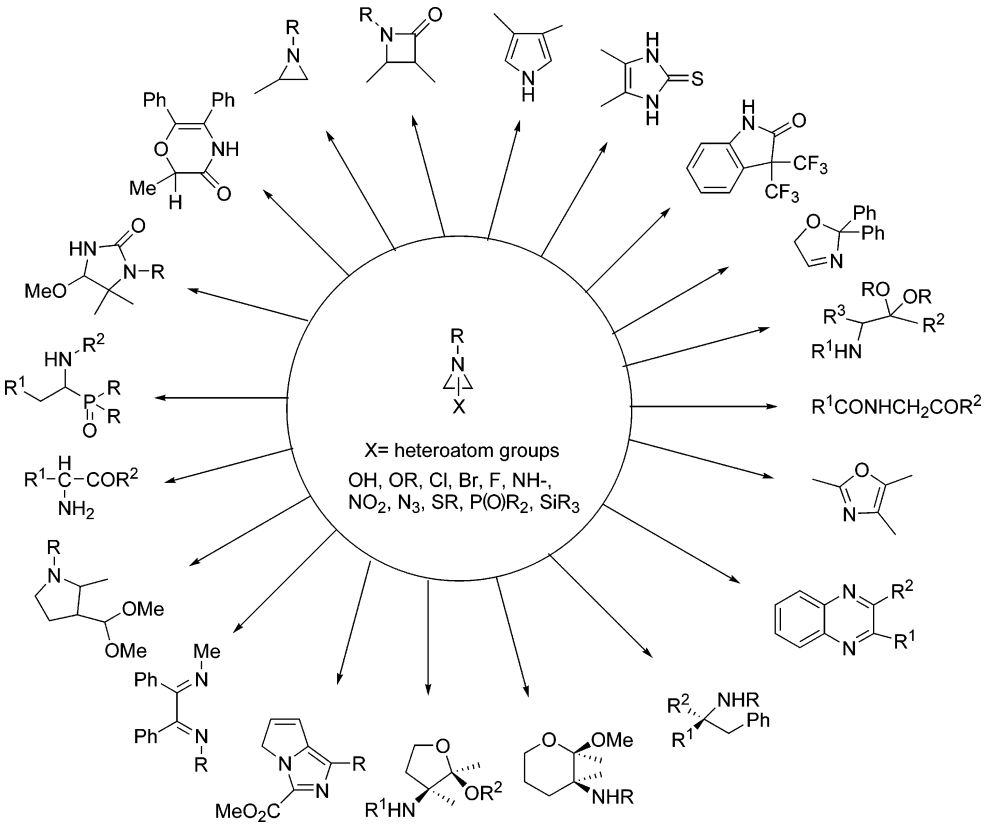


Figure 2. Overview of important products from *C*-heteroatom-substituted aziridines.

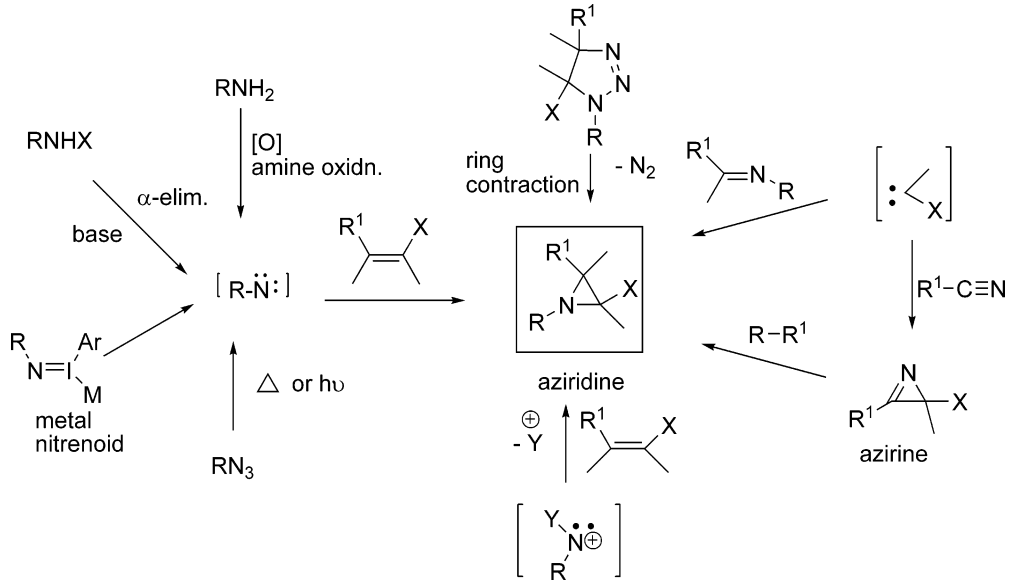
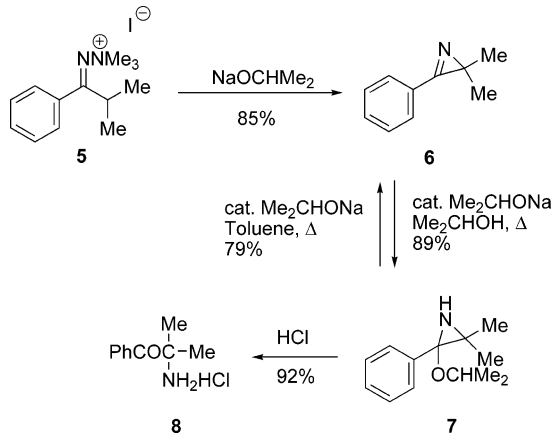


Figure 3. General routes to *C*-heteroatom-substituted aziridines.

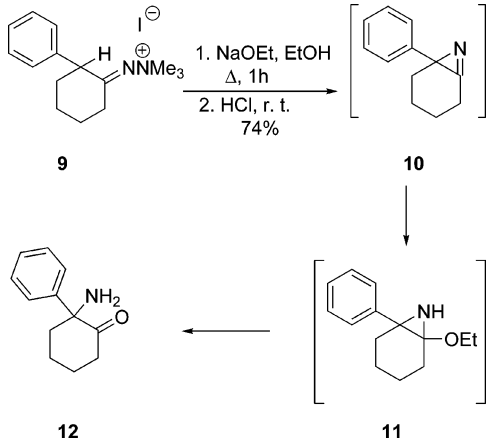
Scheme 1



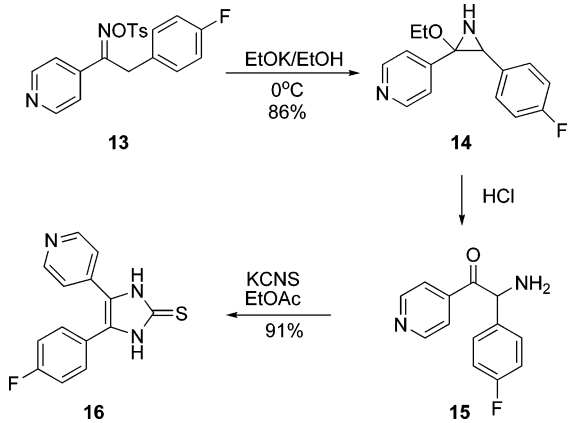
the intervention of highly reactive alkoxyaziridines was proposed. The first isolation of a 2-alkoxyaziridine, however, was reported by Parcell.[28] The reaction of isobutyrophenone dimethylhydrazone methiodide (**5**) with sodium isopropoxide in isopropanol occurred by a rapid cyclization to 2,2-dimethyl-3-phenyl-2*H*-azirine (**6**), followed by a reversible base-catalyzed addition of the alcohol to form 3,3-dimethyl-2-phenyl-2-isopropoxyaziridine (**7**) (Scheme 1). The reaction with <1 equiv of base at ambient temperature for a short time period afforded azirine **6** in 85% yield, whereas treatment with an excess of base at reflux temperature for a longer time produced aziridine **7**. Heating a solution of the azirine **6** under reflux in isopropanol with a catalytic amount of base produced 2-alkoxyaziridine **7** in 89% yield, and azeotropic removal of isopropanol from a solution of the 2-alkoxyaziridine in toluene in the presence of a catalytic amount of base regenerated the azirine **6**. The acid hydrolysis of 2-alkoxyaziridine **7** afforded α-ketoamine hydrochloride **8**.

A similar reaction using 2-phenylcyclohexanone dimethylhydrazone methiodide (**9**) afforded 2-amino-2-phenylcyclohexanone (**12**) (Scheme 2).[29] The Neber rearrangement has been applied for the synthesis of imidazoline-2-thiones. Treatment of oxime **13** with alkali (potassium ethoxide in ethanol) led to cyclization forming 2-ethoxyaziridine **14** (Scheme 3).[30] Treatment of aziridine **14** with hydrogen chloride afforded α-aminoketone **15**, which in turn was transformed into imidazoline-2-thione **16** by reaction with potassium thiocyanate. However, this reaction was not successful with 1-ethoxy-2-isothiocyanatoethane ($EtOCH_2CH_2NCS$). A closely related mechanism has been proposed in the reaction of *N*-chloroimidate **17** with sodium alkoxides. The carbanion **18** led to the formation of azirine **19**, which formed 2-alkoxyaziridine **20** by addition of the alcohol. The

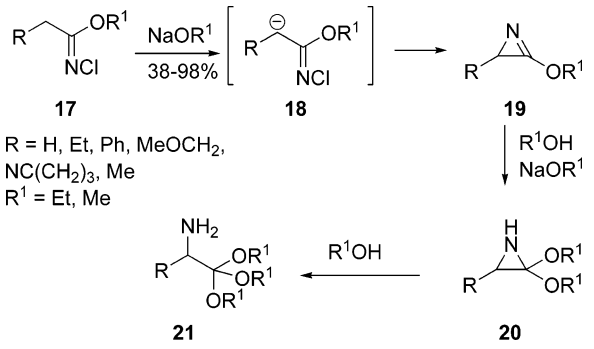
Scheme 2



Scheme 3

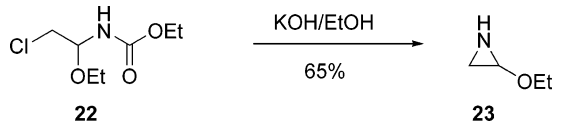


Scheme 4



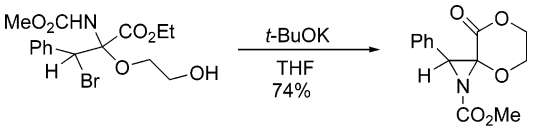
17 18 19 20 21

Scheme 5



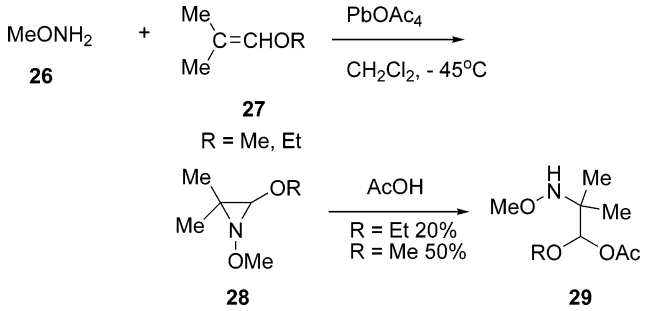
22 23

Scheme 6



24 25

Scheme 7



28 29

cleavage of the aziridine ring afforded the α-amino acid orthoesters **21** (Scheme 4).[31]

Some other classical cyclization reactions forming stable 2-alkoxyaziridines include the cyclization of carbamate **22** to 2-ethoxyaziridine (**23**) (Scheme 5)[32] and of compound **24** to an oxygen-substituted spiroaziridine **25** (Scheme 6).[33]

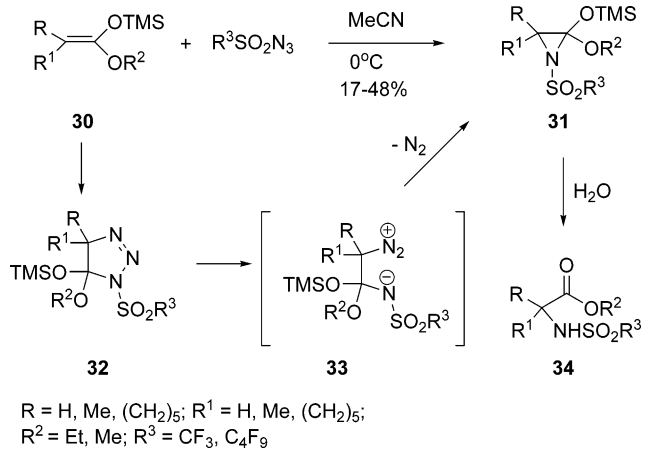
Furthermore, 1-benzoyl-2-methoxy-2,3-diphenylaziridine has been prepared as an intermediate in the asymmetric synthesis of (amino)diaryl ketones via the Neber rearrangement of ketoxime sulfonates under phase-transfer conditions.[34]

3.3. Reactions of Nitrenes and Azides

Several nitrogen transfer reagents have been used successfully for the aziridination of olefins. Methoxyamine (**26**) is oxidized by $Pb(OAc)_4$ in the presence of enol ethers **27** to give 2-alkoxy-1-methoxy-3,3-dimethylaziridines **28** (Scheme 7).[35] The latter compounds, on treatment with acetic acid, afforded the ring opening products **29**.

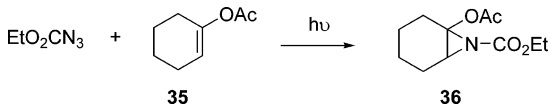
Recently, the reaction of mono- or dialkyl-substituted silylketene acetals **30** with sulfonylazides has been reported to form stable 1-perfluoroalkanesulfonyl-2-alkoxy-2-trimethylsilyloxyaziridines **31** in poor to moderate yields (Scheme 8).[36,37] The reaction occurred smoothly in many solvents such

Scheme 8



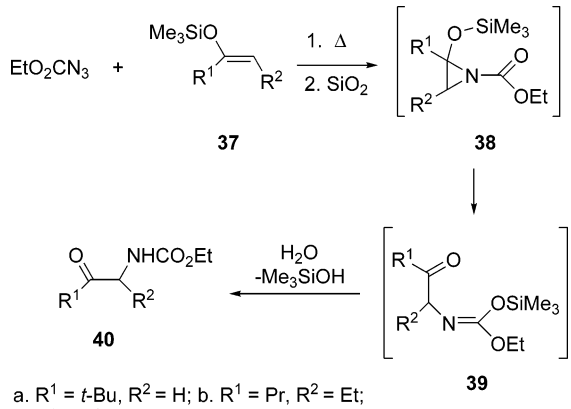
30 31 32 33 34

Scheme 9



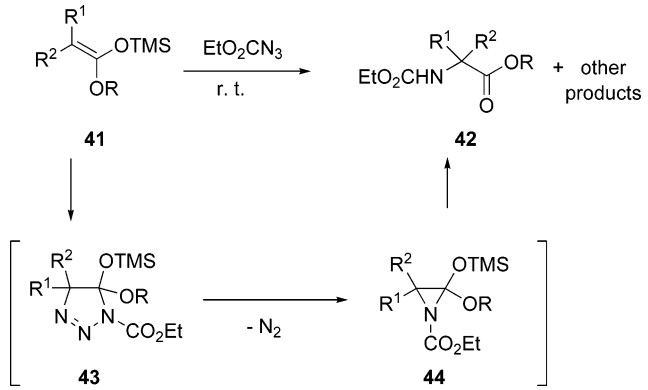
35 36

Scheme 10



37 38 39 40

Scheme 11

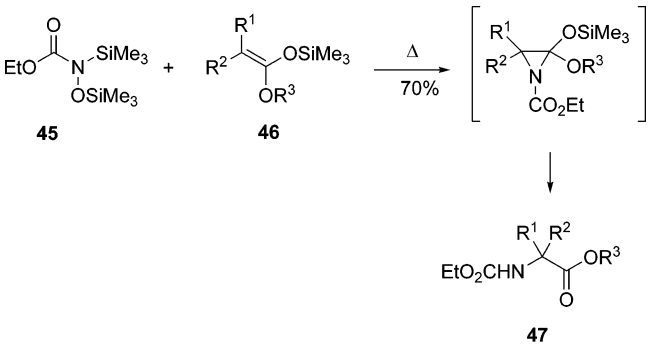


41 42 43 44

as hexane, diethyl ether, and moist and dry acetonitrile. The formation of aziridines **31** is explained through opening of the triazole ring **32**, formed initially by addition of the azide to olefin **30**. The formation of another product, α-aminoester **34**, in the reaction is explained by hydrolysis of the aziridines **31**. The presence of the alkyl groups on the ring has been observed to affect the stability of the compounds; the ones with more alkyl groups appeared to be more stable.

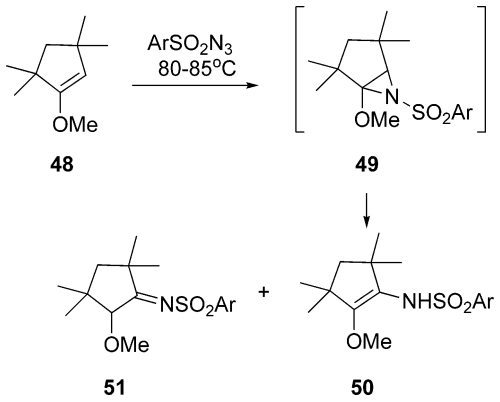
Addition of ethyl azidoformate to several alkenes is known. For example, the photochemical reaction of ethyl

Scheme 12



a. R^1 = H, R^2 = Me, R^3 = Et; b. R^1 = H, R^2 = Et, R^3 = Et;
c. $R^1 = R^2 = R^3$ = Me; d. R^1 = H, $R^2R^3 = CH_2CH_2$

Scheme 13

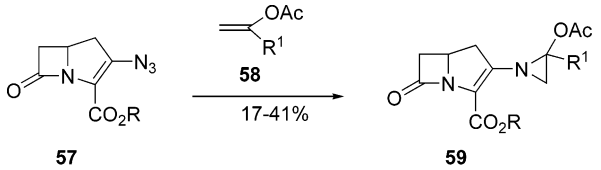


azidoformate with 1-acetoxycyclohexene (**35**) afforded the bicyclic aziridine **36** (Scheme 9).[38] Pellacani and co-workers used GC-MS in the reaction of ethyl azidoformate with enol silyl ether **37** to detect the formation of alkoxyaziridine **38** en route to α-aminoketones **40** (Scheme 10).[39] This study was extended further by reacting ethyl azidoformate with other electron-rich alkenes such as ketene silyl acetals **41**.[40] It was observed that the latter compounds were more reactive than enol silyl ether **37** toward the azide as they reacted with it at room temperature, affording products **42** through triazolines **43** and aziridines **44** (Scheme 11). When *N*-(ethoxycarbonyl)-*N*,*O*-bis(trimethylsilyl)hydroxylamine (**45**) was used instead of ethyl azidoformate in reactions with enol silyl ethers **46**, only one compound, the *N*-protected α-aminoester **47**, was obtained in yields up to 70% (Scheme 12).[41]

3,3,5,5-Tetramethyl-1-methoxycyclopentene (**48**) reacted with arenesulfonyl azides even under solvent-free conditions to form the bicyclic aziridines **49**. The latter compounds underwent rearrangement to yield the corresponding enamines **50** and α-methoxycyclopentylideneamines **51** (Scheme 13).[42] Enamine **50** was the major product in polar solvents, whereas the imine **51** was the major product in benzene.

An intramolecular addition of the azido group across the carbon−carbon double bond of the enol ether moiety in compound **52** led to the formation of triazoline **53**, which, upon irradiation with UV light from a sunlamp (Pyrex flask) in moist THF, afforded benzocenone **54** in 84% yield via a diradical **55** and aziridine **56** (Scheme 14).[43] Azidocarbapenems **57** added across the vinyl esters **58** to yield the corresponding 2-acyloxyaziridines **59** (Scheme 15).[44]

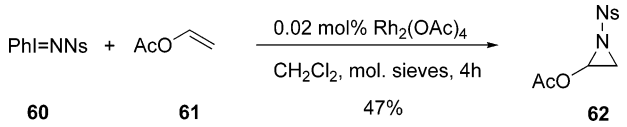
Scheme 15



R = 4-nitrobenzyl, Bn; R^1 = H, Me

[*N*-(*p*-Toluenesulfonyl)imino]phenyliodinane in the presence of copper complexes and rhodium carboxylates constitutes an important system for asymmetric nitrene transfer.[45] Muller and co-workers, however, in their studies on the aziridination of styrenes found that [*N*-(4-nitrobenzenesulfonyl)imino]phenyliodinane (**60**) was more efficient in nitrogen transfer. This group reported the aziridination of vinyl acetate (**61**) using the reagent **60** in the presence of dirhodium tetraacetate, affording 2-acetoxyaziridine **62** (Scheme 16).[46]

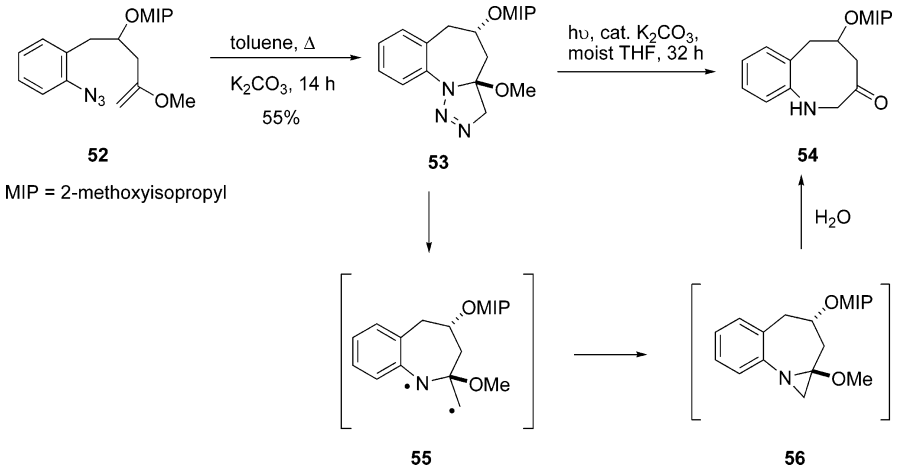
Scheme 16



A 20 M excess of vinyl acetate was used to suppress side reactions.

Furthermore, a series of acyclic and cyclic enols has been transformed into the corresponding α-aminoketones by asymmetric catalytic aziridination with chiral Cu complexes, prepared in situ from $[Cu(MeCN)_4]PF_6$ and optically active

Scheme 14



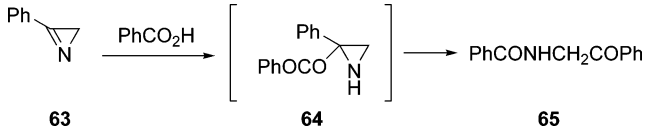
MIP = 2-methoxyisopropyl

diimino ligands, by using (*N*-tosylimino)iodobenzene (PhINTs) as a nitrogen source.[47]

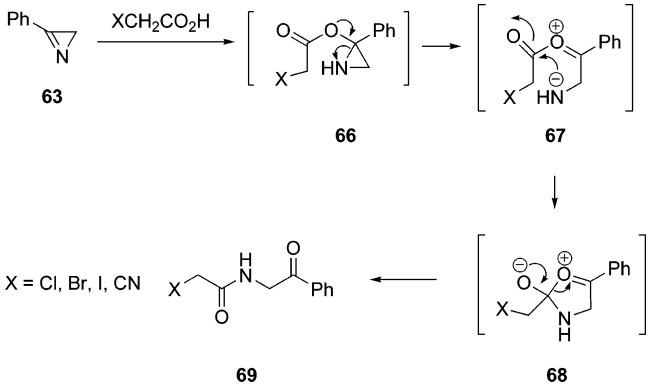
3.4. Additions across Azirines

2*H*-Azirines are more susceptible to nucleophilic attack than other imines because of the strained nature of the carbon−nitrogen double bond.[48] A combination of this ring strain with an activating group makes the nucleophilic addition reactions favorable. Various nucleophiles add with ease across the carbon−nitrogen double bond of an azirine ring system.[49] Occasionally, the resulting aziridines are isolated, but more commonly the end products are derived from the ring opening of the intermediate aziridines and further reaction.[28,29,49] Many authors have reported the addition of aromatic and aliphatic carboxylic acids across the carbon−nitrogen double bond of 3-phenyl-2*H*-azirine (**63**) and 3-ethoxy-2*H*-azirine (**19**) leading to the formation of *N*-substituted amides **65**, **69**, and **71** through the intermediacy of 2-benzoyloxy- and 2-acetoxyaziridines, respectively (Schemes 17−19).[50−52] The possible mechanism of

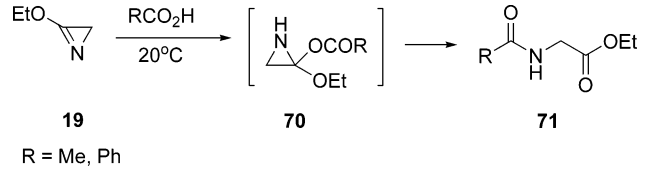
Scheme 17



Scheme 18

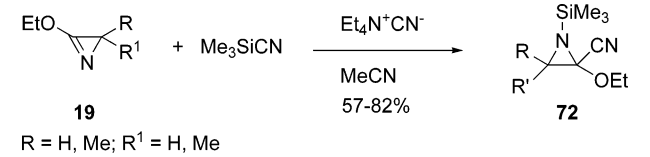


Scheme 19



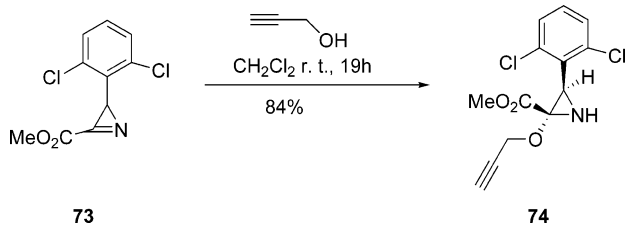
formation of the amides through C(Ph)-N bond cleavage in 2-acyloxyaziridines **66** is shown in Scheme 18.[51] The stable 2-ethoxy-2-cyano-1-trimethylsilylaziridines **72** could be isolated from the reaction of 2-ethoxyazirines **19** with trimethylsilyl cyanide in the presence of a catalytic amount of tetraethylammonium cyanide (Scheme 20).[52]

Scheme 20



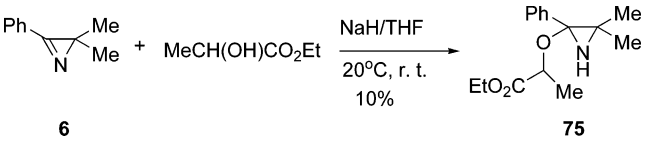
Addition of propargyl alcohol across the carbon−nitrogen double bond of methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate (**73**) led to the formation of *trans*-2-(2-propynyloxy)aziridine-2-carboxylate **74** in 84% yield (Scheme 21).[53] The addition of ethyl lactate to 2,2-dimethyl-3-phenyl-

Scheme 21



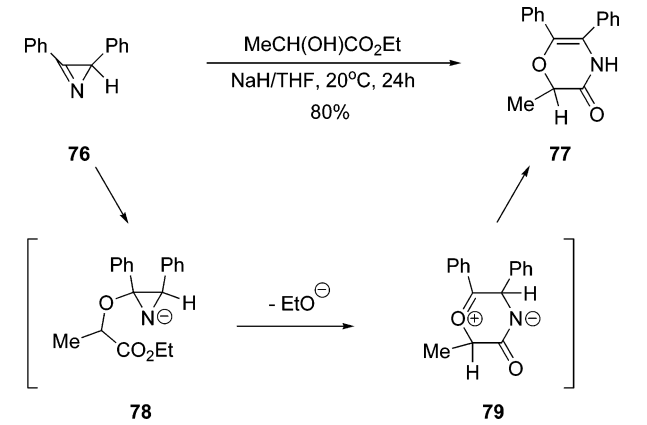
2*H*-azirine (**6**) afforded 2-alkoxyaziridine (**75**) in 10% yield (Scheme 22), but the addition to 2,3-diphenylazirine (**76**)

Scheme 22



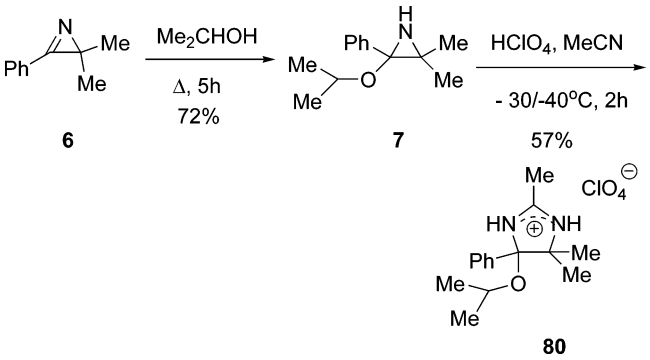
led to the formation of an oxazinone (**77**) via anion **78** and intermediate **79** (Scheme 23).[54]

Scheme 23



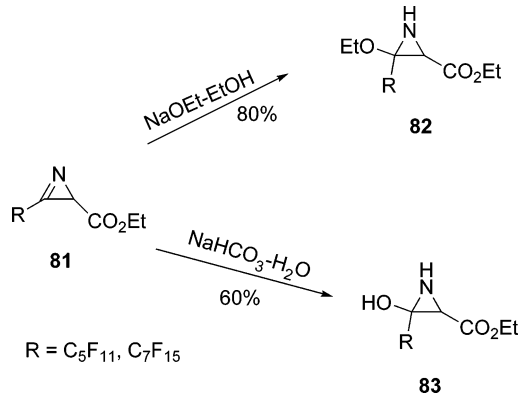
Addition of isopropanol across 2,2-dimethyl-3-phenyl-2*H*-azirine (**6**) afforded the corresponding 2-isopropoxyaziridine **7**, which on treatment with perchloric acid was transformed into the imidazolinium salt **80** (Scheme 24).[55]

Scheme 24

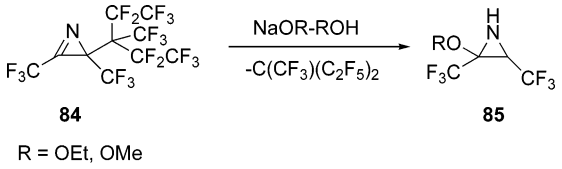


The presence of fluorinated alkyl groups is known to increase the stability of the aziridine and azirine rings.

Scheme 25



Scheme 26



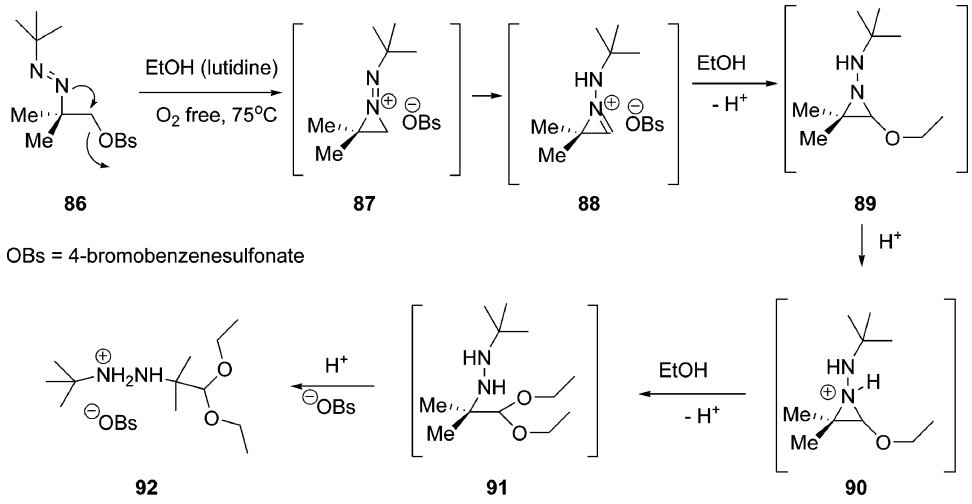
Resistance to ring opening with bases in fluorinated azirines **81** made possible the addition of solvent across the carbon−nitrogen double bond to afford stable aziridines **82** and **83** with ethoxy and hydroxyl groups at the 3-position (Scheme 25).[56−58] Surprisingly, the perfluoroalkyl group in azirine **84** was eliminated upon treatment with sodium alkoxides in the corresponding alcohol to afford 2-alkoxy-2,3-bis(trifluoromethyl)aziridines **85** (Scheme 26).

The solvolysis of azo 4-bromobenzenesulfonate **86** under anhydrous conditions in ethanol, buffered with 2,6-lutidine, led to formation of 1-*tert*-butylamino-3,3-dimethyl-2-ethoxyaziridine (**89**) (Scheme 27). The neighboring diazo group participation in the reaction afforded 2-ethoxyaziridine (**89**) via aziridinium salt **87** and azirinium salt **88**. The protonation of the aziridine **89** and ring opening of the protonated aziridine **90** led to the formation of hydrazinium acetal **91**, which was isolated as salt **92**. This study was supported by rate measurements and titrametric methods.[59]

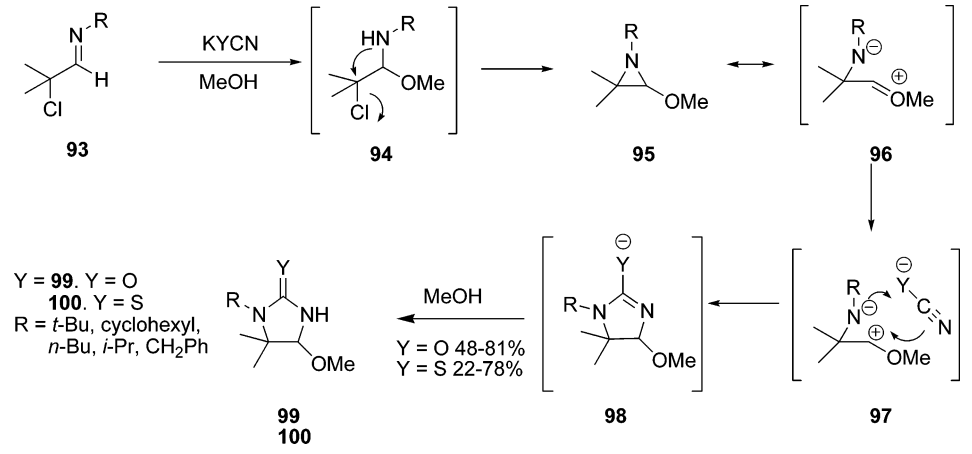
3.5. Reactions of α-Haloimines

The synthesis and chemistry of α-haloimines have been extensively investigated in recent years.[60] In many reactions of α-haloimines, 2-alkoxyaziridines have been postulated as intermediates. The rearrangement reactions of α-chloroimines **93** using potassium cyanate or potassium thiocyanate in methanol involved amines **94** and 2-methoxyaziridines **95** en route to 2-imidazolidinones **99** and imidazolidine-2-thiones **100** (Scheme 28).[61,62] The *N*-cyclohexylimine derivative afforded the highest yield, whereas the *N*-butylimine the lowest. The energy barrier for opening of the three-membered ring at the $N-C_2$ bond was lowered by the presence of the methoxy substitutent, which enabled delocalization.

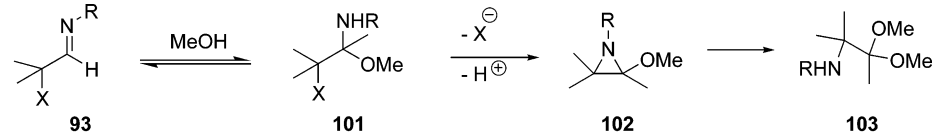
Scheme 27



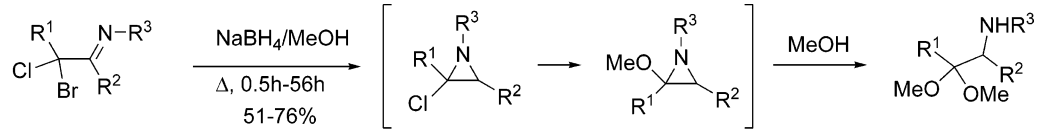
Scheme 28



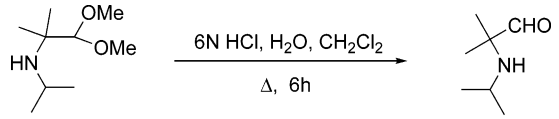
Scheme 29



Scheme 30



Scheme 31

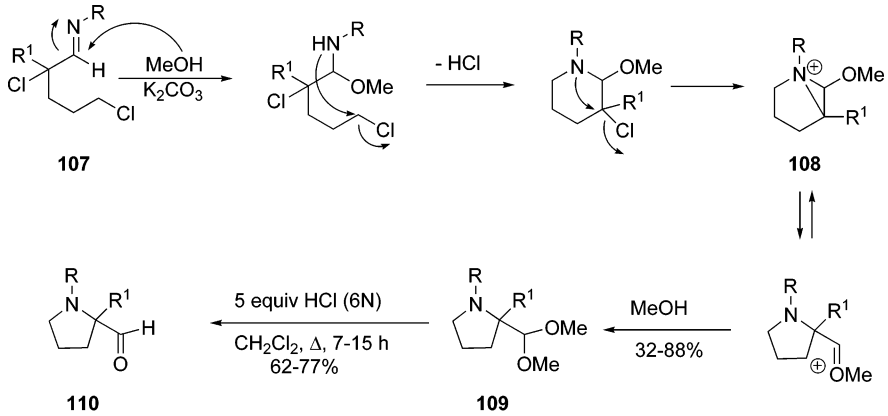


The reaction of α-haloimines **93** with methanol in the presence of a base yielded α-(*N*-alkyl)aminoacetals **101** (Scheme 29), which underwent intramolecular nucleophilic substitution to form 2-methoxyaziridines **102**, methanolysis of which afforded aminoacetals **103**.[63−66] Treatment of α-bromo-α-chloroimines **104** with sodium borohydride in methanol led to a convenient regiospecific synthesis of the isomeric α-(*N*-alkyl)aminoacetals **105** (Scheme 30). The addition of methanol to the intermediate azirinium cation and methanolysis of the resulting 2-methoxyaziridines explained the formation of compound **105**.[67] These aminoacetals, for example, **105**, are easily convertible into 2-(*N*-alkylamino)isobutyraldehydes, for example, **106**, by treatment with hydrochloric acid (Scheme 31). It is worth mentioning that the α-aminoaldehydes are useful bifunctional compounds and serve as building blocks for elaboration into heterocycles. Sterically hindered α-aminoaldehydes are also less accessible because of the difficulties associated with the amination of tertiary centers.[68]

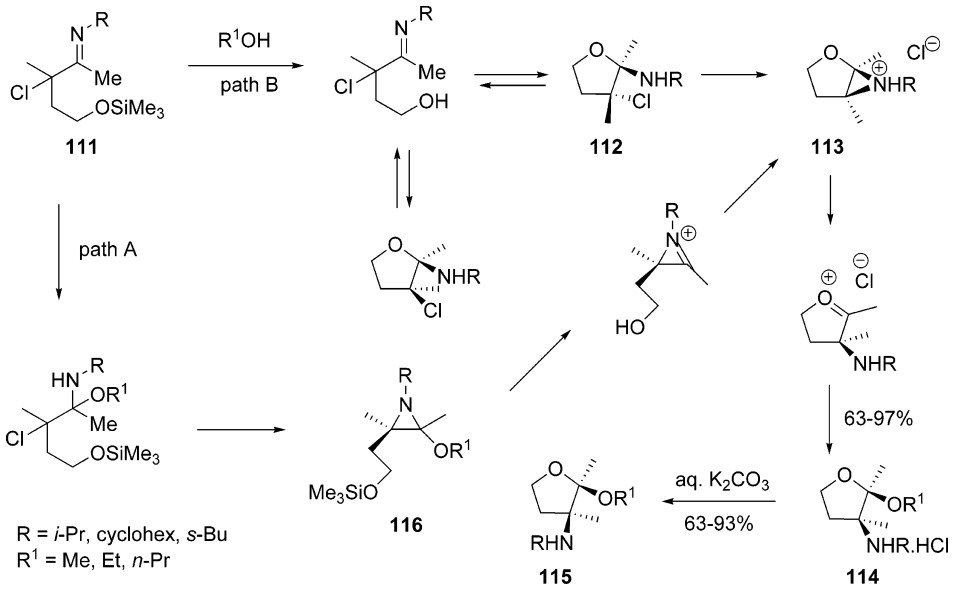
α,δ-Dichloroimines **107** proved to be suitable substrates for conversion into 2-formylpyrrolidines **110** via treatment with potassium carbonate in methanol, affording acetals **109** (Scheme 32).[69] The reaction mechanism involved a skeletal rearrangement of the α,δ-dichloroaldimines to give bicyclic aziridinium intermediates **108**, which suffered ring opening with ring contraction to form 1-alkyl-2-(dimethoxymethyl)-pyrrolidines **109**. Hydrolysis of the latter in acidic medium gave novel 2-formylpyrrolidines **110**. The overall pathway involved an α,α-azacyclobisalkylation of the starting substrates **107**.

Alcoholysis of α-chloro-γ-(trimethylsilyloxy)ketimines **111** led to a stereospecific synthesis of *cis*-2-alkoxy-3-aminooxolanes **115**.[70] Two possible mechanisms, both viable and producing the same stereochemical results, have been proposed (Scheme 33). Imines can undergo addition of the alcohol with subsequent ring closure to an α-alkoxyaziridine **116** (path A), which can generate the transient 6-aza-2-oxabicyclo[3.1.0]hexane derivative **113** in a stereospecific manner. Alternatively, oxygen desilylation and addition of the alcohol function across the imino linkage may give either the *cis*- or *trans*-oxolane derivative **112** (path B). This reversible reaction may lead to the bicyclic aziridine intermediate **113** having both methyls in a cis disposition. Opening of this intermediate followed by stereospecific attack of the alcohol leads to the formation of *cis*-2-alkoxy-3-aminooxolane hydrochlorides **114**. The latter afforded *cis*-2-alkoxy-3-aminooxolanes **115** upon treatment with potassium carbonate.

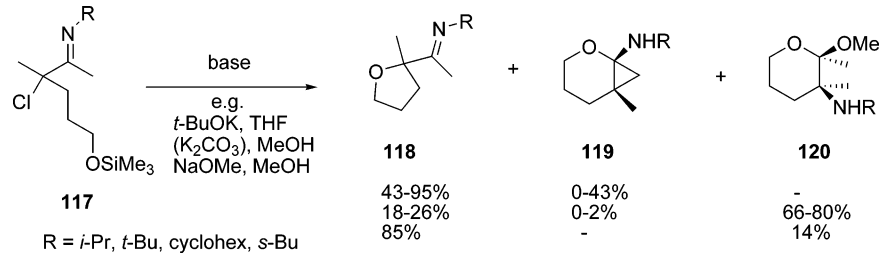
Scheme 32



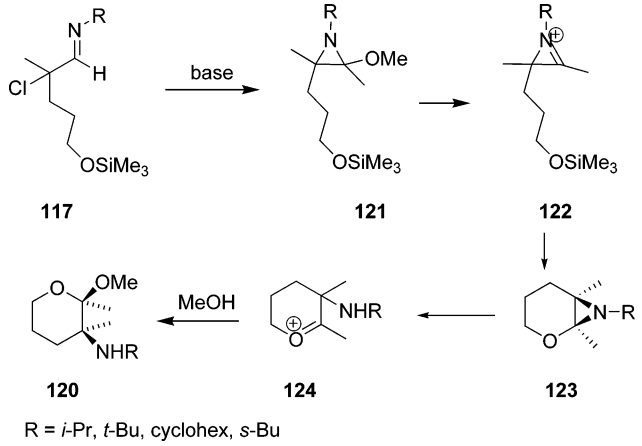
Scheme 33



Scheme 34



Scheme 35



Treatment of α-chloro-δ-(trimethylsilyloxy)ketimines **117** with bases and nucleophiles offers an attractive protocol for the formation of a variety of oxygen-containing heterocycles, including tetrahydrofurans **118** and tetrahydropyrans **120**.[71] Treatment of ketimines **117** under different conditions afforded tetrahydrofurans **118**, tetrahydropyrans **120**, and *cis*-1-(*N*-alkylamino)-6-methyl-2-oxabicyclo[4.1.0]heptanes **119** (Scheme 34). The formation of tetrahydropyrans **120** has been explained through involvement of 2-alkoxyaziridines **121** (Scheme 35). Attack of methanol (or methoxide) across the imino bond with subsequent ring closure may give 2-alkoxyaziridines **121**. O-Desilylation followed by intramolecular nucleophilic addition of the hydroxyl group to the resulting azirinium cation **122** can give the bicyclic aziridine **123**, which suffers ring opening to oxonium ion **124**. This reactive species undergoes a stereospecific attack of the alcohol to provide *cis*-3-alkylamino-2-methoxytetrahydropyrans **120** exclusively.

3.6. 2-Alkoxyaziridines from Azomethine Ylides

The reaction of imines **125** with α-chloroacid chlorides **126** led to the formation of 5-alkylidene-3-oxazolines **127**. The mechanism of reaction involved in situ generation of azomethine ylides **128**. An intramolecular [3+2]-cycloaddition of the azomethine ylides **128** generates oxoazetidine-fused aziridine **129** as an intermediate (Scheme 36). The latter compound underwent rearrangement, possibly via the ylide **130** and oxazoline **131**, to form 5-alkylidene-3-oxazolines **127**.[72]

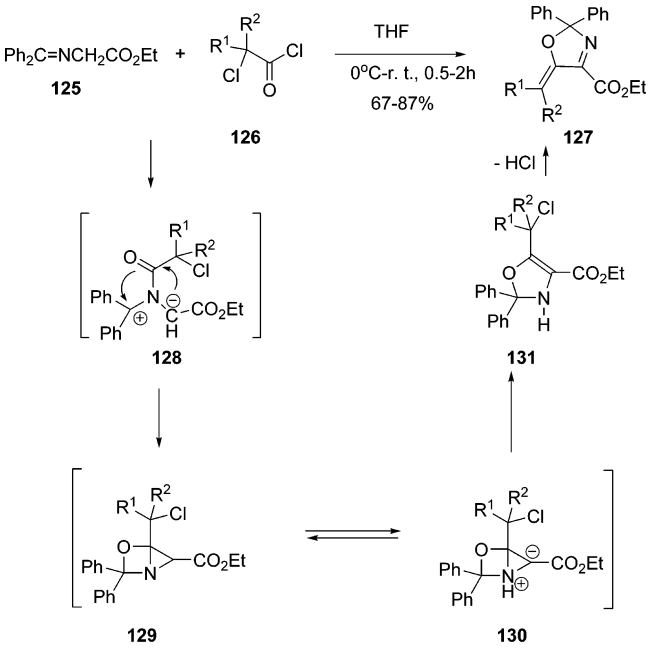
3.7. 2-Methoxyaziridine from Fischer–Carbene Complexes

The formation and reaction of 2-alkoxyaziridines is reported by reaction of Fischer−carbene complexes **132** with 2-azadiene **133** (Scheme 37). A nucleophilic attack of the carbene at the imino nitrogen gives an intermediate **134**. A [1,3]-OMe migration in **134** formed the amino−carbene complex **135**. The insertion of Cβ−H into the metal carbene and subsequent reductive elimination formed 2-methoxyaziridine **136**, which suffered regioselective ring expansion to afford the isomeric 2-pyrrolidinones **137**.[73]

3.8. 2,2-Dimethoxyaziridine from 2-Diazo-4,5-dicyanoimidazole

Cycloaddition of the terminal nitrogen of 2-diazo-4,5-dicyanoimidazole (**138**) onto the electron-rich π-system of

Scheme 36



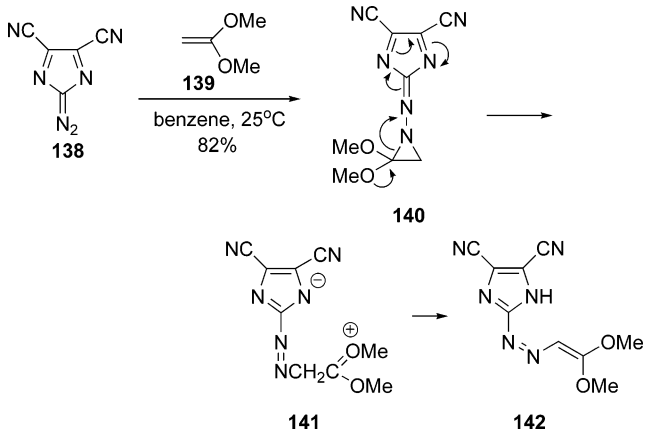
R^1 = H, Cl, Me, Ph, $ClCH_2$; R^2 = H, Cl; R^3 = H, Cl

1,1-dimethoxyethene (**139**) generated the transient 2,2-dimethoxyaziridine **140** (Scheme 38). Aziridine ring opening, followed by a proton transfer in the resulting intermediate **141**, afforded the electron-rich azoalkene **142**.[74]

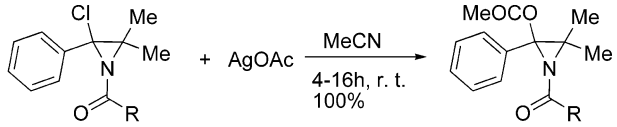
3.9. 2-Alkoxy- and 2-Acetoxyaziridines by Displacement of 2-Chloroaziridines

Displacement of a chloro group in 1-acyl-2-chloro-3,3-dimethyl-2-phenylaziridines **143** using silver acetate afforded 2-acetoxy-1-acylaziridines **144** in quantitative yields (Scheme 39).[75] Similarly, 1-benzoyl-2-chloro-3-methyl-2-phenylaziridine (**145**) was transformed into 2-acetoxy-1-benzoyl-2-methyl-3-phenylaziridine (**146**) (Scheme 40). 2-Chloro-1-phenylaziridine (**147**) afforded 2-*tert*-butoxy-1-phenylaziridine (**148**) using potassium *tert*-butoxide in *tert*-butanol at reflux (Scheme 41).[76] Replacement of the tertiary alkoxide by a primary alkoxide lowered the reaction rate, although 2-alkoxyaziridines **149** were obtained in good to excellent yields (Scheme 42).[77]

Scheme 38

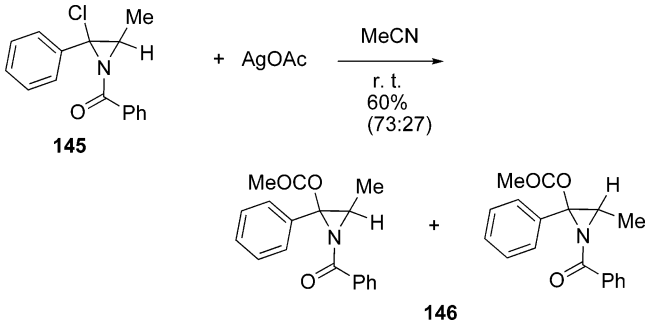


Scheme 39



R = CH_3, $PhCH_2$, *t*-Bu, Ph, $EtOCOCH_2$

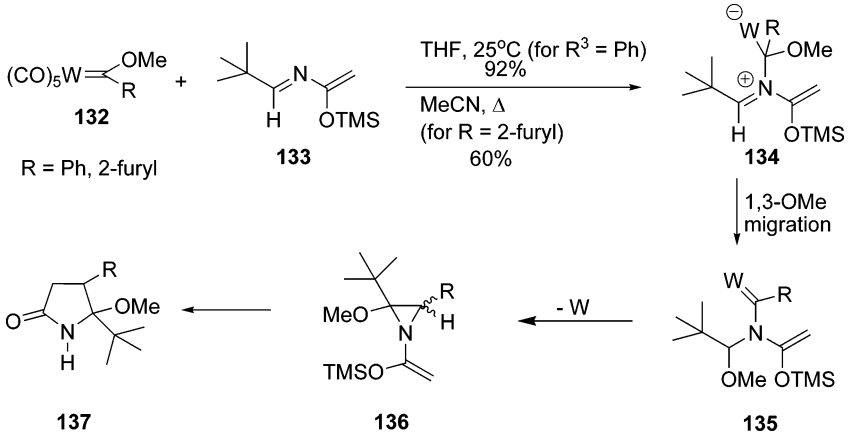
Scheme 40



3.10. Other Reactions

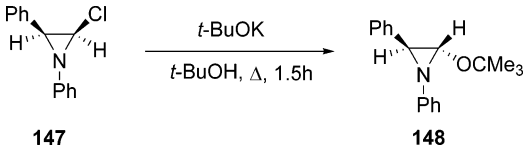
An unusual fragmentation of *N*-methylpyrazolium salts **150**, on heating with sodium ethoxide in toluene, led to the formation of benzyl diimines **151** along with the benzoic acids.[78] The formation of the α-diimines **151** has been explained by a nucleophilic addition of ethoxide at C-5 to give 3-ethoxydihydropyrazoles **152** (Scheme 43), which

Scheme 37



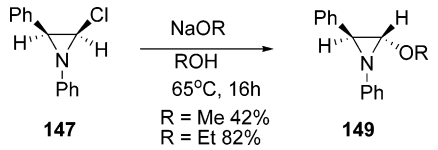
R = Ph, 2-furyl

Scheme 41



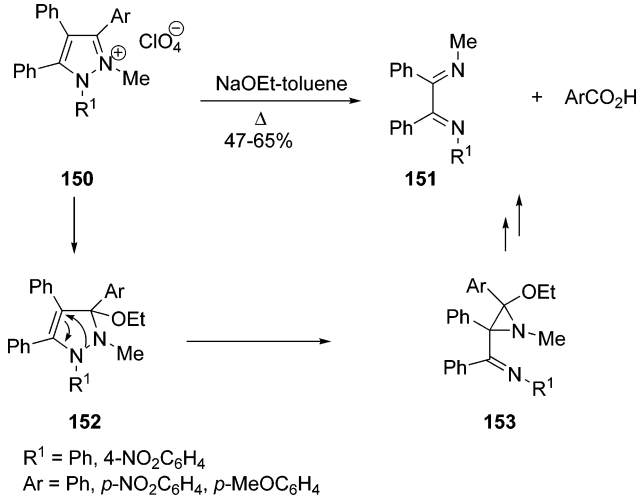
147 **148**

Scheme 42



147 **149**

Scheme 43



150 **151** **152** **153**

R^1 = Ph, 4-$NO_2C_6H_4$
Ar = Ph, *p*-$NO_2C_6H_4$, *p*-$MeOC_6H_4$

proceeded to 2-ethoxyaziridines **153** with subsequent oxidative involvement of water in the final steps.

A few other approaches toward oxygen-substituted aziridines and their ring opening include the reaction of iminoaziridines **154** with carboxylic acids forming 2-acyloxyaziridines **155**, which suffered ring opening to form α-acylamino amides **156** (Scheme 44),[79] *N*−*C* acyl migration in imides **157** leading to the formation of α-aminoketones **158** (Scheme 45),[80] and electrooxidative rearrangement of tosylamino group in amines **159** forming 2-methoxyaziridine **160**, which cleaved in methanol to *β*-aminoacetals **161** (Scheme 46).[81,82] Highly functionalized 3-ethoxyaziridines have also been prepared through an aza-MIRC (Michael-induced ring closure) reaction of sulfonyl-activated hydroxycarbamates with α,*β*-difunctionalized acrylates.[83] The importance of these products in organic synthesis has already been described in the preceding paragraphs.

C-Oxygen-substituted aziridines constitute an important class of heterocyclic compounds from both synthetic and medicinal points of view. 2-Alkoxyaziridines were discovered long ago during studies on the Neber rearrangement. Usually such aziridines have been generated in alcohols and suffered ring opening. However, addition of some alcohols and carbonyl compounds across the carbon−nitrogen double bond of selected azirines under milder conditions afforded stable 2-alkoxy- and 2-acetoxyaziridines. Azirines containing electron-withdrawing groups are especially useful in this regard. Aziridines having alkoxy and acetoxy groups undergo ring opening and rearrangement reactions affording reaction products such as α-aminoketones, α-aminoalcohols, α-aminoesters, and *β*-aminoacetals. The involvement of such aziridines has been postulated in many reactions of α-haloimines affording biologically important heterocyclic compounds.

4. C-Haloaziridines

4.1. Introduction

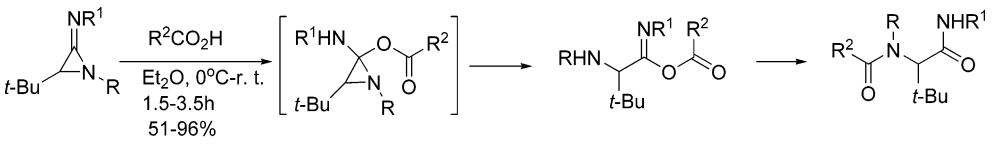
Contrary to 2-alkoxyaziridines, 2-haloaziridines are more stable and hence the literature includes many studies on the isolation of such aziridines since the first preparation of 2,2-dichloroaziridines by Fields and Sandri.[84] The reaction medium may play a role in determining the stability of the ring. 2-Alkoxyaziridines are commonly generated in alcoholic medium and suffer from ring opening. The most common method for the synthesis of 2-haloaziridines comprises carbene−imine addition, but other equally suitable methods are also known. 2,2-Dichloroaziridines are important from a biological point of view as they serve as precursors for the synthesis of biologically active compounds such as indolinones,[85] analogues of natural alkaloids such as isoquinolinones[86] and isoquinolines,[87] and amidines.[88] Among the 2-haloaziridines, fluorinated aziridines are comparatively more stable than the chlorinated aziridines. Furthermore, 2,2-dichloroaziridines are comparatively more prone to ring cleavage than 2-chloroaziridines. In both of these classes, however, reactions retaining the ring and with ring opening are common. Due to the extensive number of papers on 2-chlorinated aziridines, only a selection of leading references will be incorporated in this review.

4.2. Synthesis

4.2.1. Reactions of Imines with Carbenes or Carbenoids

Deyrup and co-workers have done pioneering work on the synthesis of monochloroaziridines from imines.[76,77,89] This group reported the first synthesis of a monochloroaziridine, that is, *cis*-2-chloro-1,3-diphenylaziridine (**147**), by employing the reaction of a carbenoid with *N*-benzylideneaniline (**161**) (Scheme 47). The 2,2-dichloro-1,3-diphenylaziridine (**162**) was readily available by that time from an addition of dichlorocarbene, generated from chloroform using base, to *N*-benzylideneaniline (**161**) (Scheme 48).[84,90,91] Later on, the reactions of various Schiff bases with bromochlorocarbene, bromofluorocarbene, and chlorofluorocarbene were reported to give chloro-, bromo-, and fluoro-substituted aziridines.[92,93]

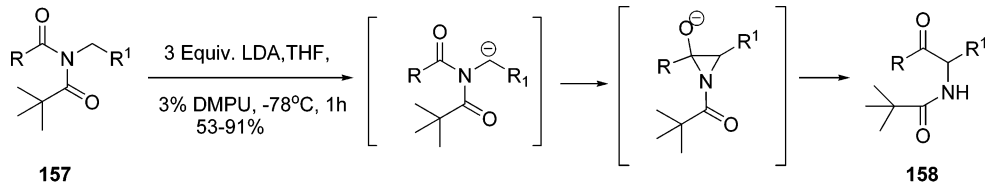
Scheme 44



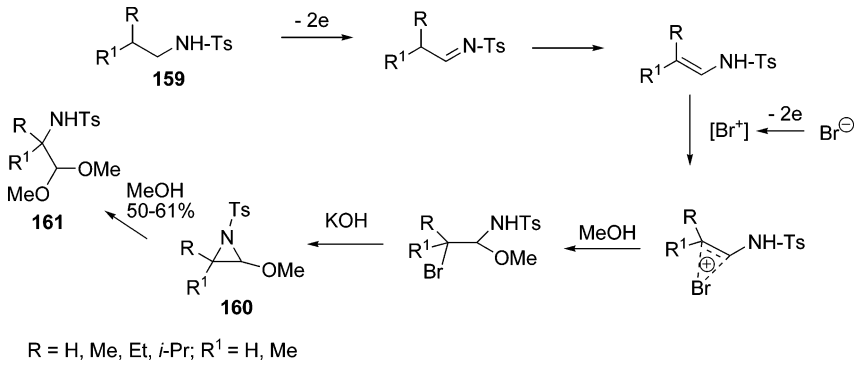
154 **155** **156**

R = Me, *t*-Bu; R^1 = Me, *t*-Bu; R^2 = Ph, CH_2*t*-Bu, $CH_2NHCOPh$, Ph

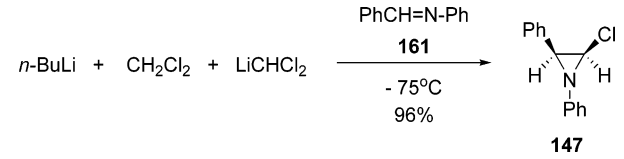
Scheme 45



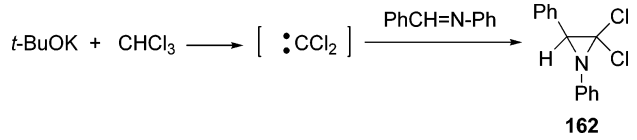
Scheme 46



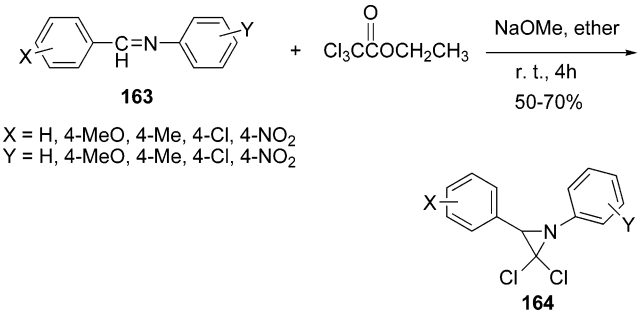
Scheme 47



Scheme 48

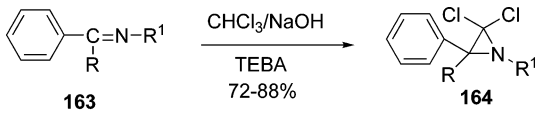


Scheme 49

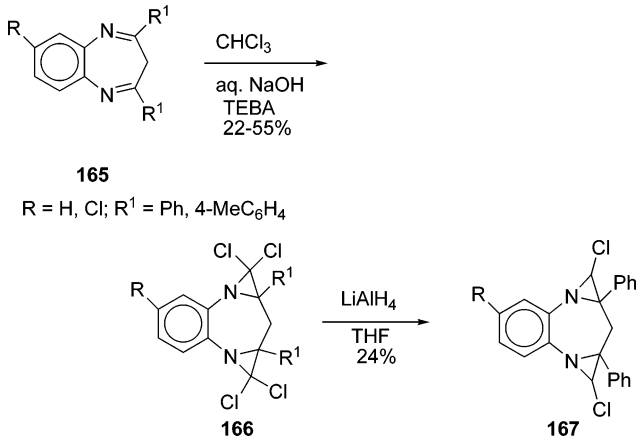


Various reagents have been used to generate carbenes or carbenoids. The reaction of ethyl trichloroacetate with *N*-benzylideneanilines **163** in the presence of sodium methoxide afforded 2,2-dichloroaziridines **164** in 50−70% yield (Scheme 49).[94] Dichlorocarbene, generated from a chloroform−aqueous sodium hydroxide mixture using the phase-transfer catalyst triethylbenzylammonium chloride (TEBA), added onto the carbon−nitrogen double bond of the imines **163** to form 2,2-dichloroaziridines **164** in improved yields (Scheme 50).[95] Similar addition of dichlorocarbene to the imino linkage present in benzodiazepines **165** afforded novel benzodiazepine-fused dihaloaziridines **166** (Scheme 51).[96] Reduction of the latter aziridines with $LiAlH_4$ in tetrahydrofuran afforded the monochlorobisaziridine **167**. Organo-

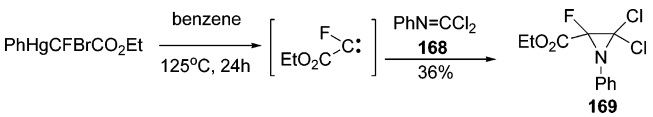
Scheme 50



Scheme 51

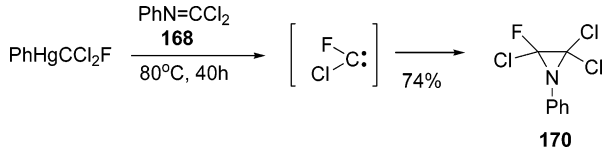


Scheme 52

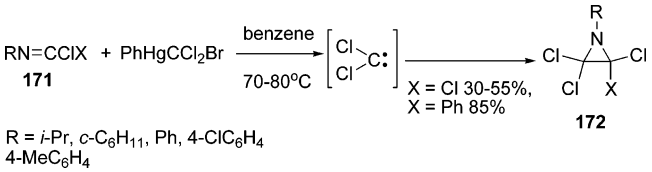


mercury esters and organomercury halides serve as precursors of fluoroethoxycarbonyl and dihalocarbenes, respectively. These intermediates react with the carbon−nitrogen double bond of aryl and alkylcarbonimidoyl chlorides **168** and **171** to form *C*-halogenated aziridines **169**, **170**, and **172** (Schemes 52−54).[97−100] Recently, KF/Al_2O_3 is reported to promote the generation of dichlorocarbene. A number of 2,2-dichloroaziridines have been synthesized from the reactions of *N*-benzylideneamines with chloroform in aqueous acetonitrile (Scheme 55).[101] *N*-Benzhydrylideneamino acid esters and

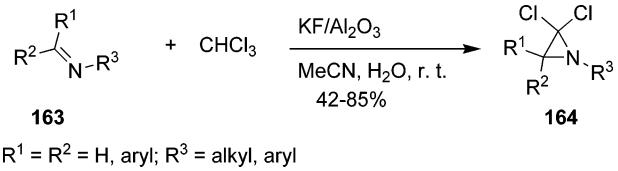
Scheme 53



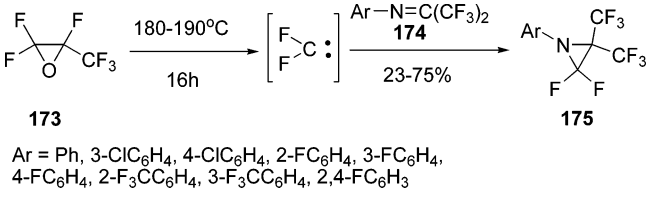
Scheme 54



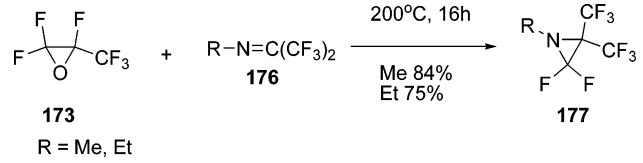
Scheme 55



Scheme 56



Scheme 57



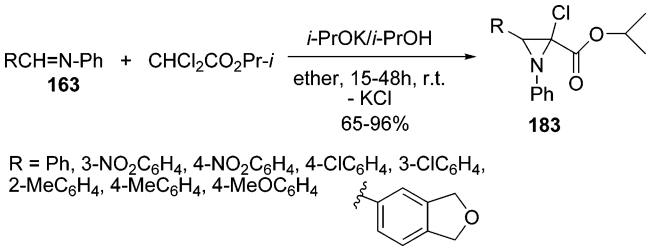
nitriles are also known to react with dichlorocarbene to afford the corresponding 2,2-dichloroaziridines.[102]

The reaction of diazomethane with fluorine-substituted imines is reported to form 2-fluoroaziridines.[103,104] Ziefman and co-workers have used 2,2,3-trifluoro-3-(trifluoromethyl)-oxirane (**173**) for the generation of difluorocarbene.[105] The latter intermediate, generated by thermal decomposition of **173**, reacted with hexafluoroacetone *N*-phenylimine (**174**), affording 1-phenyl-2,2-difluoro-3,3-bis(trifluoromethyl)aziridine (**175**) in 45% yield (Scheme 56). This reaction has been extended recently to hexafluoroacetone *N*-arylimines and hexafluoroacetone *N*-alkylimines **176** forming a variety of 1-aryl-2,2-difluoro-3,3-bis(trifluoromethyl)aziridines **175** and 1-alkyl-2,2-difluoro-3,3-bis(trifluoromethyl)aziridines **177** in fair to good yields (Schemes 56 and 57).[106] Recently, Khlebnikov reported on the formation of azomethine ylides **179** and **181** from the reaction of fluorocarbene with *N*-substituted imines of benzophenones **178** and benzaldehydes **163** (Scheme 58).[107] A 1,3-cyclization of the ylides afforded 2-fluoroaziridines **180** and **182**. The formation of azomethine ylides **179** and **181** was proved by trapping them with dimethylacetylenedicarboxylate. The fluorocarbene was generated by irradiating a solution of dibromofluoromethane, active lead, and tetrabutylammonium bromide in dichloromethane with ultrasound at 40 °C. The ylides obtained from the reaction of benzophenone *N*-substituted imines with fluorocarbenes afforded aziridines **180** in 19−47%. The ylides **181** from benzaldehyde *N*-arylimines afforded stereoselectively *cis*-aziridines **182** (Scheme 58).

4.2.2. Darzens-Type Reactions

The synthesis of 2-chloroaziridine-2-carboxylates has been reported using a Darzens-type approach.[108] The reaction of aldimines **163** with the anions derived from isopropyl dichloroacetate afforded 2-chloroaziridine-2-carboxylates **183** (Scheme 59). The reaction, however, was limited only to

Scheme 59



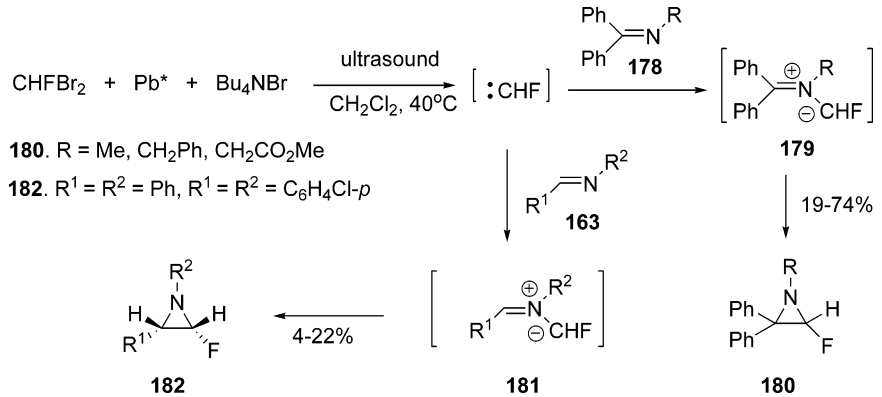
aromatic imines. The use of a dibromoacetate instead of dichloroacetate reduced the yields drastically.

Very recently, the synthesis of *cis*-3-aryl-2-chloro-2-imidoylaziridines **186** has been reported via aza-Darzens-type reaction of 3,3-dichloro-1-azaallylic anions **184** and *N*-(arylsulfonyl)imines **185** with high diastereoselectivity (Scheme 60). Reduction of the imino group in aziridines **186** afforded 2-(aminomethyl)-2-chloroaziridines **187** with excellent stereoselectivity.[109]

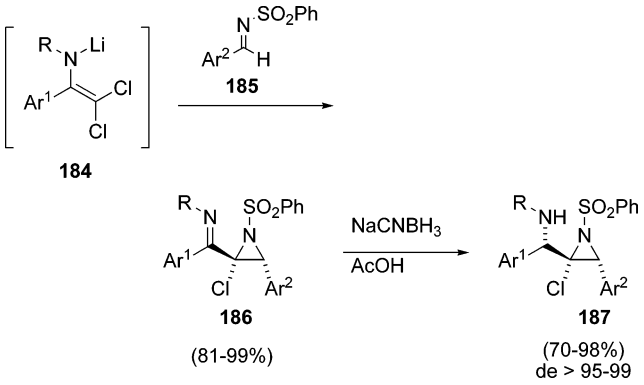
4.2.3. Reactions of Nitrogen-Transfer Reagents

The reaction of ethoxycarbonylnitrene, generated in situ by triethylamine-induced α-elimination of ethyl 4-nitroben-

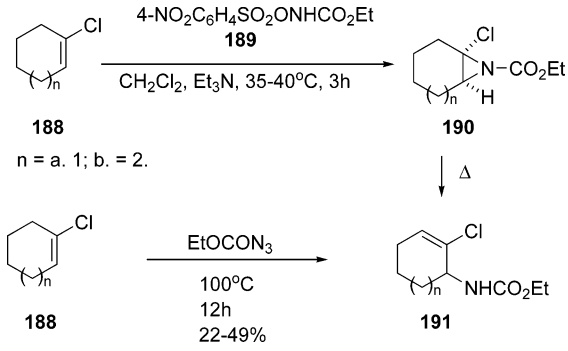
Scheme 58



Scheme 60



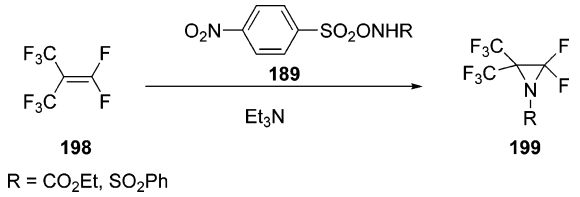
Scheme 61



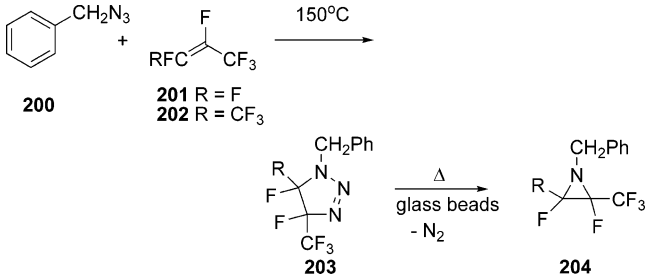
zenesulfonyloxycarbamate **189**, with cyclic and acyclic vinyl chlorides, formed 2-chloroaziridines **190**, **193**, and **197** in yields ranging from 17 to 48% (Schemes 61−63).[110] This method for the generation of ethoxycarbonylnitrene was used earlier by Zeifman and co-workers to synthesize *N*-ethoxycarbonyl- and *N*-phenylsulfonyl-substituted perfluoroaziridines **199** from perfluorinated alkene **198** (Scheme 64).[111] The reaction was highly stereospecific, so a singlet nitrene was proposed to be involved. The same nitrene, when generated by decomposition of the azide at 100 °C, reacted with cycloalkenes **188** to afford cycloalkenes **191** as rearranged product. The α-chloroaziridines **190**, upon standing at room temperature for several days or upon heating, afforded the cycloalkenes **191**. This led to the conclusion that the 2-chloroaziridines were also formed in the case of the azide route and underwent rearrangement. The reaction with acyclic alkenes by the azide method, however, afforded the 2-chloroaziridine in one case (Scheme 62) together with the rearranged products **194** and **195**.

The reaction of benzyl azide (**200**) with perfluoropropene (**201**) and perfluoro-2-butene (**202**) at 150 °C is known to form triazolines **203** (Scheme 65).[112] The pyrolysis of

Scheme 64

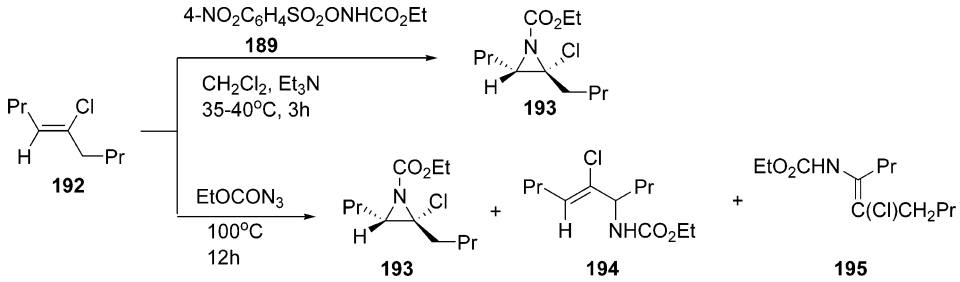


Scheme 65

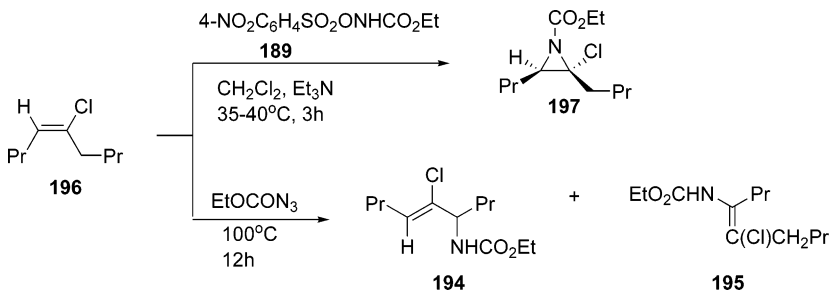


triazolines on glass beads afforded the corresponding *C*-fluorinated aziridines **204**. The reaction of perfluropropene (**201**) with sodium azide in dimethylformamide at low temperature resulted in perfluoropropenylazide (**205**), which decomposed at 20 °C to afford perfluoro(2-methyl-2*H*-azirine) (**206**) (Scheme 66).[113] The latter isomerized in the presence of hydrogen fluoride to yield perfluoro(2-methylaziridine) (**207**). Thionitrile fluoride and thionitrile chloride have also been used to transfer nitrogen to perfluoropropene (**201**) and to some other alkenes **209**, forming the corresponding 2,2,3-trifluoroaziridines **208** and **210** (Schemes 67 and 68).[114,115]

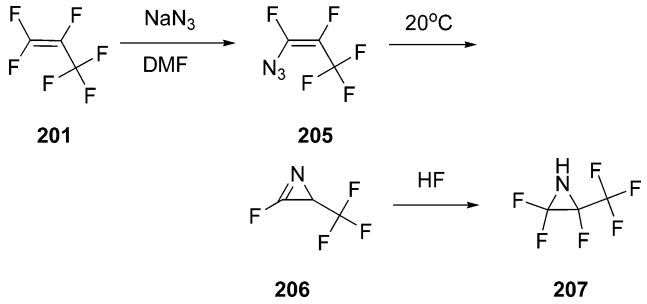
Scheme 62



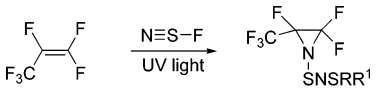
Scheme 63



Scheme 66

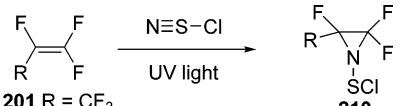


Scheme 67



R = R^1 = F 28%
R = R^1 = $NCF(CF_3)_2$ 12%

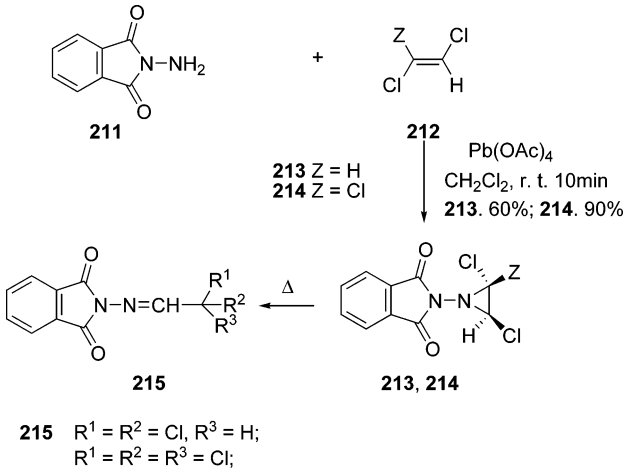
Scheme 68



201 R = CF_3,
209 R = CF_2CF_3, SF_5, Cl

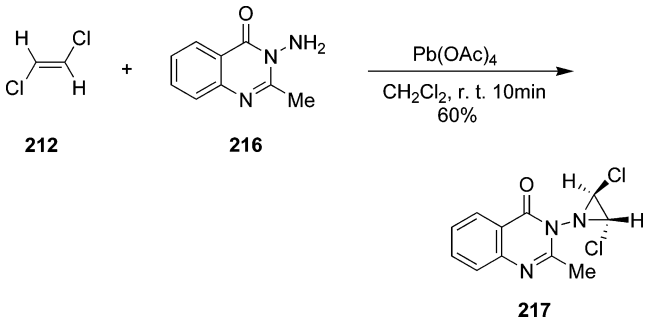
The reactions of nitrenes, generated from the oxidation of hydrazide **211** and **216** by lead tetraacetate in dichloromethane, with haloalkenes **212** (Schemes 69 and 70)

Scheme 69



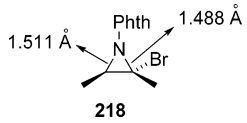
215 R^1 = R^2 = Cl, R^3 = H;
R^1 = R^2 = R^3 = Cl;

Scheme 70



yielded 2,3-dichloroaziridines **213** and **217** and 2,2,3-trichloroaziridines **214**.[116] Both trichloroethene and *trans*-1,2-dichloroethene reacted rapidly, whereas 1,1-dichloroethene and *cis*-1,2-dichloroethene failed to give the anticipated aziridines. The 2,3-dichloroaziridines and 2,2,3-trichloroaziridines deteriorated at room temperature, and when heated at temperatures just above their melting points, the ring was cleaved with rearrangement to give hydrazones **215** in high yields.

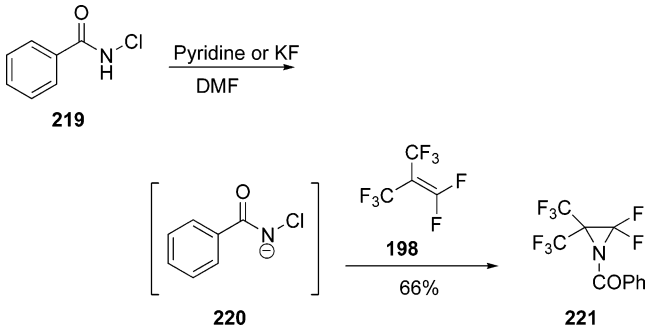
The use of *N*-aminophthalimide **211** in combination with (diacetoxyiodo)benzene has very recently led to the successful aziridination of a variety of alkenyl bromides toward the corresponding 2-bromoaziridines such as **218**, which are



thermally labile and undergo clean rearrangement into the corresponding α-bromo hydrazones.[117] X-ray analysis of aziridine **218** showed that the C_3−N bond was elongated by 0.023 Å compared to the C_3−N bond, suggesting the relative weakness of the former.

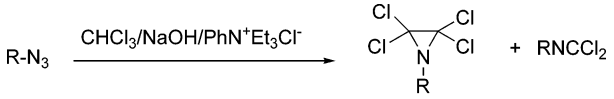
Treatment of *N*-chlorobenzamide (**219**) with pyridine or potassium fluoride in a polar aprotic solvent and addition of the resulting anion **220** to the carbon−carbon double bond of perfluorinated olefin **198** followed by ring closure resulted in 1-benzoyl-2,2-difluoro-3,3-bis(trifluoromethyl)aziridine (**221**) in 66% yield (Scheme 71).[118]

Scheme 71



Organic azides **200** and **222** reacted with dichlorocarbene under solid−liquid phase-transfer catalysis to form 2,2,3,3-tetrachloroaziridine **223** together with the *N*-substituted carbonimidic dichlorides **224** (Scheme 72).[119] This reaction

Scheme 72



200 R = $PhCH_2$
222 R = C_8H_{17}, C_9H_{19}

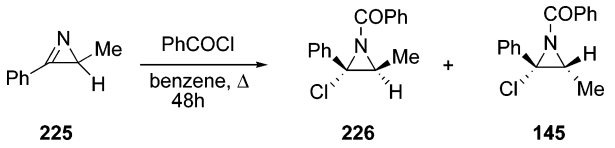
223 28-75%
224 15-21%

in homogeneous medium, however, afforded a noncyclic product.

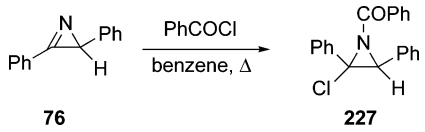
4.2.4. Additions across Azirines

There are several examples of the addition of acyl chlorides to the imine bond of an azirine leading either to the synthesis of *C*-halogenated aziridines or of rearranged products. The reaction of 2-methyl-3-phenyl-2*H*-azirine (**225**), 2,3-diphenyl-1-azirine (**76**), and a cyclooctane-fused azirine (**228**) with benzoyl chloride in refluxing benzene formed the corresponding 1-benzoyl-2-chloroaziridines in quantitative yields (Schemes 73−75).[120] Hassner and co-

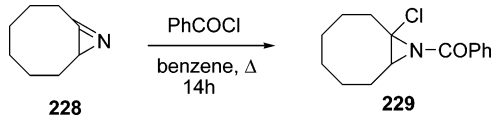
Scheme 73



Scheme 74

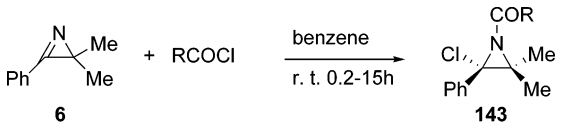


Scheme 75



workers have reported similar reactions of various acid chlorides, including benzoyl chloride, with 2,2-dimethyl-3-phenyl-2*H*-azirine (**6**) to occur at room temperature forming 2-chloro-1-acylaziridines **143** in quantitative yields (Scheme 76).[75] Addition of acyl halides parallels that expected for

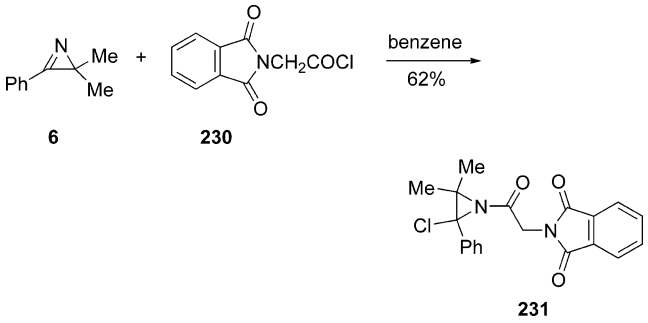
Scheme 76



R = Me, $PhCH_2$, *t*-Bu, Ph, CH_2=CH, CH_2=$CHCH_2$
EtO_2CCH_2, $ClCH_2$, Cl_3C

the addition of a nucleophile to the carbon−oxygen double bond of the acid chlorides. Electron-withdrawing substituents increase the rate; electron-donating substituents and conjugation decrease the rate. Addition of phthalimidoacetyl chloride (**230**) to azirine **6** is reported to form 2-chloroaziridine **231** (Scheme 77).[121] The cycloaddition of 1-chloroalkylidenema-

Scheme 77

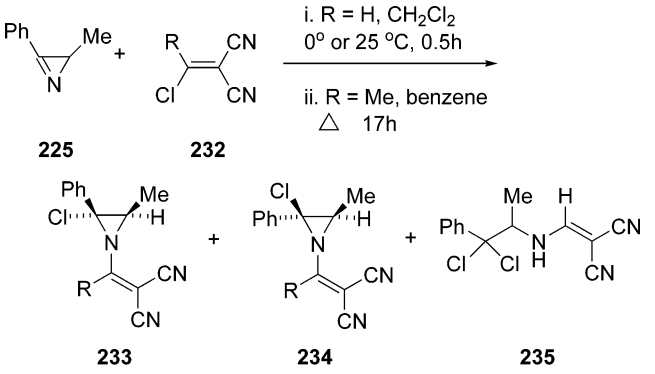


lononitriles **232** to 2-methyl-3-phenyl-2*H*-azirine **225** under thermal condition has been reported to form 2-chloroaziridines **233** and **234** together with a noncyclic product **235** (Scheme 78).[122] At 0 °C, aziridine **233** was the major product. Hydrogen fluoride is reported to cause isomerization of 2,3-difluoro-3-trifluoromethyl-1-azirine to 2,2-difluoro-3-trifluoromethyl-1-azirine, ultimately leading to the formation of polymeric perfluoroaziridine.[123]

4.2.5. Reactions of α-Haloimines

α-Haloimines are uniquely reactive, and their wide-ranging applications in heterocyclic synthesis via 2-alkoxyaziridines

Scheme 78



R = H, Me

have been described.[61−67] The reduction of trichloroacetophenone imines **236** constitutes a novel method for the synthesis of 2,2-dichloro-1,3-diarylaziridines **164**. The substrates **236**, easily accessible by chlorination of *N*-arylacetophenone imines with *N*-chlorosuccinimide in CCl_4, upon reaction with an excess of lithium aluminum hydride in diethyl ether furnished 1-aryl-2,2-dichloro-3-phenylaziridines **164** in 64−81% yield.[124] The mechanism of formation of **164** involved the addition of hydride at the imine bond giving rise to anion **237**, followed by intramolecular nucleophilic displacement of chloride (Scheme 79). The 2,2-dichloroaziridines **164**, on treatment with lithium aluminum hydride, generated an intermediate azirinium chloride **238**, which cleaved to give the isomeric α-iminocarbenium ion **239**, the reduction of which afforded phenethylamines **240**.

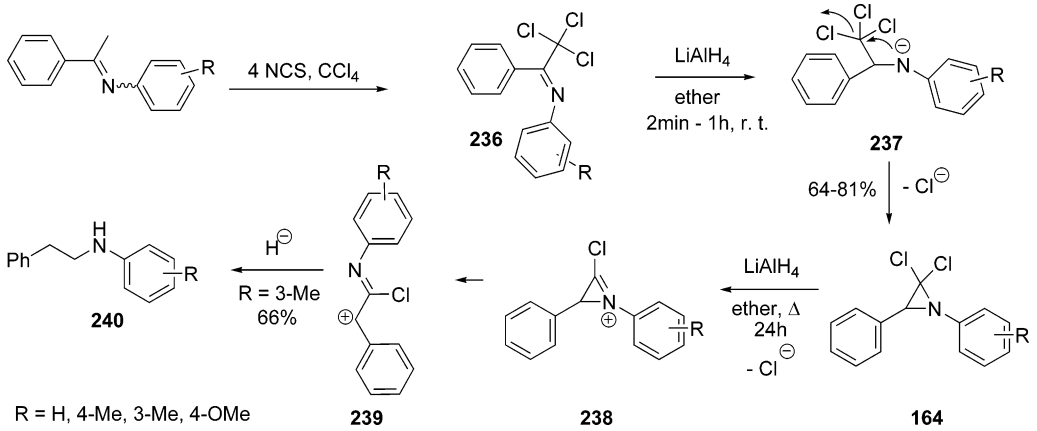
4.2.6. Transformations of Aziridines

The coupling of methyllithium with 2,2-dichloro-1,3-diphenylaziridine leading to the formation of 2-chloro-2-methyl-1,3-diphenylaziridine (**241**) (Scheme 80) is one of the earliest known reports on the synthesis of such compounds.[77,84] Coupling of 1-phenyl-3-arylaziridine-2-phosphonates with butyllithium and trapping of the lithiated aziridine with carbon tetrachloride forming 2-chloroaziridinyl phosphonates is also known.[125] The synthesis of 1,3-diphenyl-2-haloaziridines has been reported by reduction of 1,3-diphenyl-2,2-dihaloaziridines using tributyltin hydride in *n*-pentane at room temperature (Schemes 80−84).[126] The reduction of aziridines proceeded stereospecifically with retention of configuration, indicating that the intermediate 2-fluoro-2-aziridinyl and 2-chloro-2-aziridinyl radicals were pyramidal and configurationally stable enough to abstract hydrogen from tributyltin hydride much more rapidly than inversion of their configuration (Scheme 85). If the abstraction would be slower than the inversion of configuration, product **250** must have formed also in the reduction of **242**. The formation of isomers **147** and **249** in the reduction of **164** and **247**, respectively, was explained by an easy abstraction of the relatively less hindered chlorine, which was trans to the phenyl group, and assuming that the 2-chloro-2-aziridinyl radical retained its configuration when it abstracted hydrogen from tributyltin.

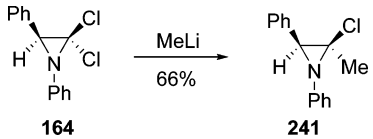
A tin−lithium exchange in *cis*-aziridine **251** afforded the *C*-lithiated aziridine **252**, which gave *cis*-2-chloroaziridine **253** on treatment with 1,2-dichloroethane (Scheme 86).[127]

The photolysis of aziridine thiohydroxamic acid anhydride **254** in neat $CBrCl_3$ led to the formation of stable *cis*- and *trans*-2-bromoaziridines **255** and **256** (5:1) in 25% yield

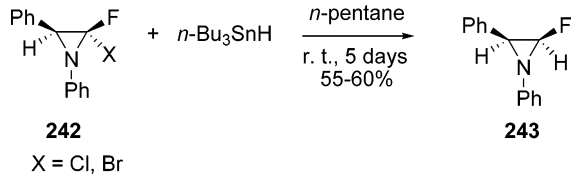
Scheme 79



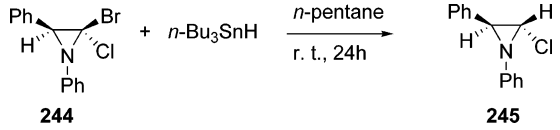
Scheme 80



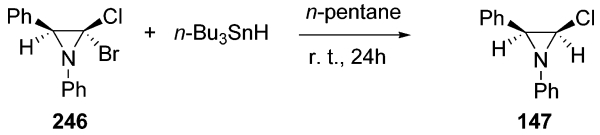
Scheme 81



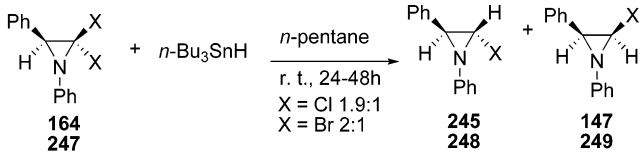
Scheme 82



Scheme 83



Scheme 84

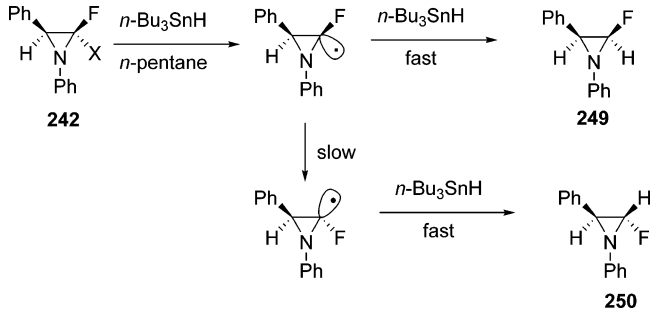


164, **245**, **147**: X = Cl
247, **248**, **249**: X = Br

(Scheme 87).[128] A dibromide **257**, obtained in the reaction due to ring opening of the aziridine by hydrogen bromide, could be cyclized to the corresponding 2-bromoaziridines with sodium hydride in tetrahydrofuran (Scheme 88). The combined yield of the 2-bromoaziridines was raised to 78% (4:1) by conducting photolysis in the presence of 1 equiv of pyridine to remove the hydrogen bromide.

A similar photochemical reaction was used toward a 2-bromoaziridine, used for the synthesis of (+)-desmethoxymitomycin A. *N*-Alkylation of indole-3-carbaldehyde **258** by means of the chiral aziridinyl triflate **259** afforded aziridine

Scheme 85



260 (Scheme 89).[129] Activation of the ester group in the latter compound as the corresponding thiohydroxamate affording **261** and subsequent irradiation in the presence of $CBrCl_3$ led to a 4:1 mixture of 2-bromoaziridine **262** in 62% yield, the major isomer being cis.

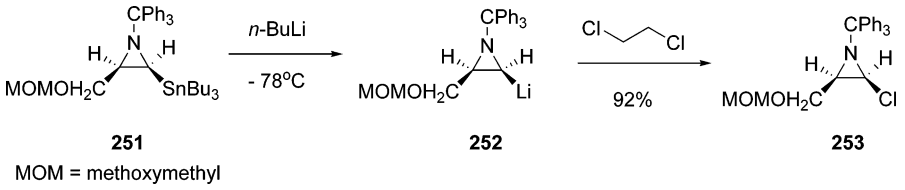
4.2.7. Other Reactions

The reaction of 2*H*-pyrrole **263** with sodium ethoxide under reflux for 30 h afforded a pyrrole-fused 2-chloroaziridine **264** together with 2-ethoxymethyl-5-methylpyridine (**265**) (Scheme 90).[130] Jones and Rees have described the formation of pyridine derivative **265** via a pyrrole-fused aziridine **266** (Scheme 91).[131]

The cyclization of 3-(mesyloxy)amines **267** with potassium carbonate in DMSO at 85−90 °C led to the formation of 2,4-diaryl-3,3-dichloroazetidines.[132] The *N*-ethylamine in this case, however, afforded an imidoyl-substituted alkyne **271** in 22% isolated yield. The formation of this alkyne was explained via intervention of an intermediate 2-chloroaziridine **268** formed by an intramolecular nucleophilic substitution of **267**. The thermal rearrangement of 2-chloroaziridine **268** to the α-chloroimine **269** was followed by double elimination of methanesulfonic acid and hydrogen chloride, leading to the formation of alkyne **271** (Scheme 92). It might be that alkynylimine **271** is formed by triple 1,2-elimination of the elements of hydrogen chloride and methanesulfonic acid without intervention of a 2-chloroaziridine.

Thermolysis of 1-methylpyrazoles (**272**) in chloroform afforded 2-cyanopyrrole (**276**) together with other products.[133] The mechanism involved fused bicyclic chloroaziridines **274** and **275** (Scheme 93). Chloroaziridine **274** was formed by cyclization of the dichlorocarbene−CH insertion product **273**. A similar reaction of 1-benzylpyrazole (**277**) afforded α-carboline **282** as a major product (Scheme 94) via pyrrole derivative **278** and 2-chloroaziridine **279**. The

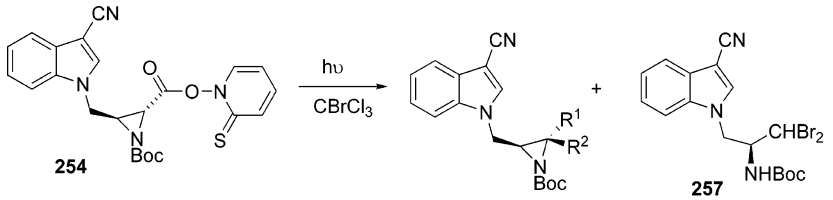
Scheme 86



251 **252** **253**

MOM = methoxymethyl

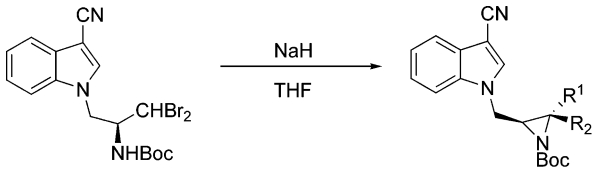
Scheme 87



254 **257**

255 R^1 = H, R^2 = Br
256 R^1 = Br, R^2 = H

Scheme 88



257

255 R^1 = H, R^2 = Br
256 R^1 = Br, R^2 = H

ylide **281**, formed from an in situ generated nitrene **280**, afforded the product **282**.

In a recent paper, the interaction of *N*-(1-aryl-2,2,2-trichloroethyl)amides derived from arenesulfonic acids with secondary amines or their salts in the presence of inorganic bases such as K_2CO_3 has been described, resulting in the formation of chloroaziridine intermediates. Depending upon the solvent and reagent ratio, the reaction results in *N*-[1-dialkylamino-2-chloro-2-arylethylidene]-, *N*-[2-dialkylamino-1-chloro-2-arylethylidene]-, *N*-[1,2-bis(dialkylamino)-2-arylethylidene]-, and *N*-(1,2-dioxo-2-arylethene)amides of arenesulfonic acids.[134]

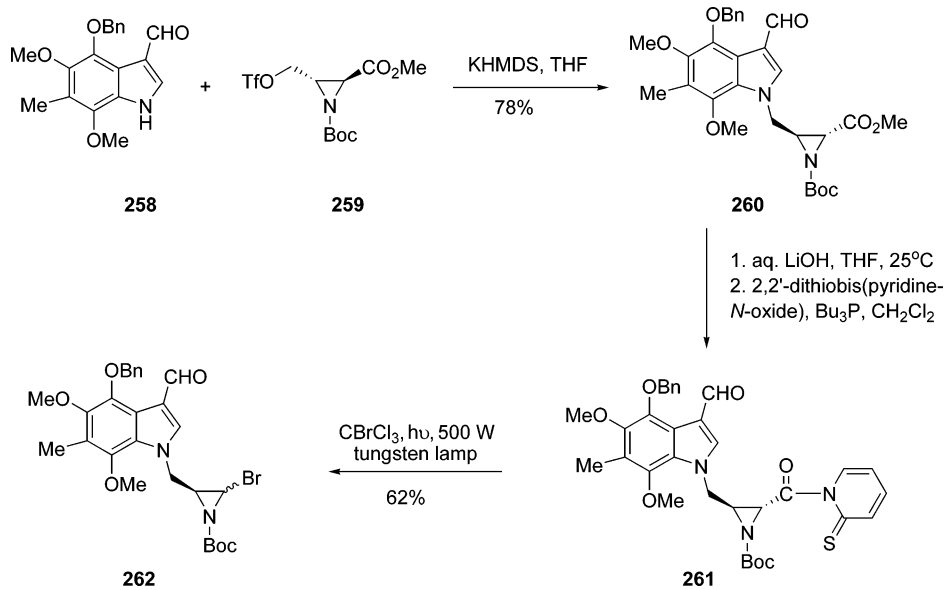
4.3. Reactivity of *C*-Haloaziridines

The reactivity of chloro- and bromo-substituted aziridines differs significantly from the reactivity of the fluoro-substituted aziridines. It is therefore appropriate to discuss them separately.

4.3.1. Reactivity of C-Chloro- and C-Bromoaziridines

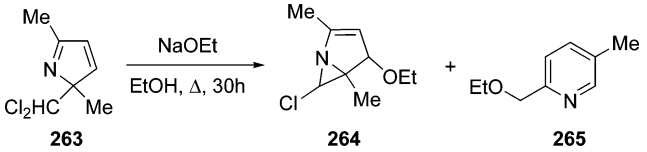
4.3.1.1. 2,2-Dichloroaziridines. 2,2-Dichloroaziridines are extremely reactive compounds. Divergent processes and diverse products are reported in the reactions of such aziridines, depending on the substituents at nitrogen and the aziridine carbon atoms. Pyrolysis of 2,2-dichloroaziridines **162** and **283** in toluene or xylene, respectively, proceeded through transition state **284** to yield α-chloroimidoyl chlorides **285** (Scheme 95).[135,136] These reactions are useful for the synthesis of α-chloroamidines **286** by trapping them with suitable amines such as piperidine.[95] 2,2-Dichloroaziridine **283** bearing a naphthyl group at nitrogen was observed to be more reactive than 2,2-dichloroaziridine **162** with a phenyl group at nitrogen due to the larger electron-donating ability of the naphthyl ring in stabilizing the transition state.[95] The effect of two chloro atoms combined with a 4-nitrophenyl

Scheme 89

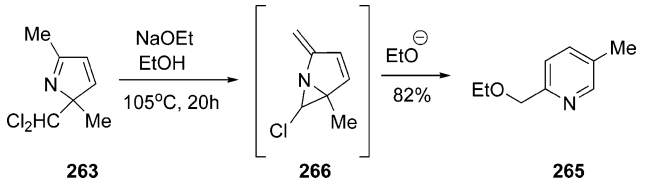


258 **259** **260** **261** **262**

Scheme 90



Scheme 91

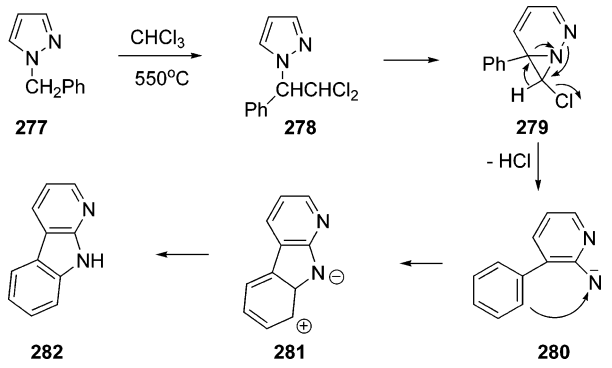


group made the ring proton so acidic that it could be abstracted by sodium hydride in hexamethylphosphoramide (HMPA) or dimethoxyethane (DME) to generate a stable carbanion **287**.[137] The quenching with D_2O afforded the deuterated 2,2-dichloroaziridine **288** (Scheme 96).

The methanolysis of 1,3,3-triphenyl-2,2-dichloroaziridine and 1-benzyl-3,3-diphenyl-2,2-dichloroaziridine **178** afforded the amides **289** (Scheme 97), whereas the methanolysis of 1,3-diphenyl-2,2-dichloroaziridine afforded a mixture of α-chloroimidate **290** (38%) and α-methoxyimidate **291** (62%) (Scheme 98).[77,138] The solvolytic rearrangement of 1,3-diphenyl-2,2-dichloroaziridine in water afforded α-chloro-α-phenylacetanilide **292**. When this reaction was carried out in aqueous dioxane, a mixture of α-chloro-α-phenylacetanilide **292** and α-hydroxy-α-phenylacetanilide **293** (1:1) was obtained in quantitative yield (Scheme 99).[94] A thorough mechanistic study provided strong evidence for the intermediacy of a nonexchanging ion pair in a rate-limiting process that was not acid-catalyzed.

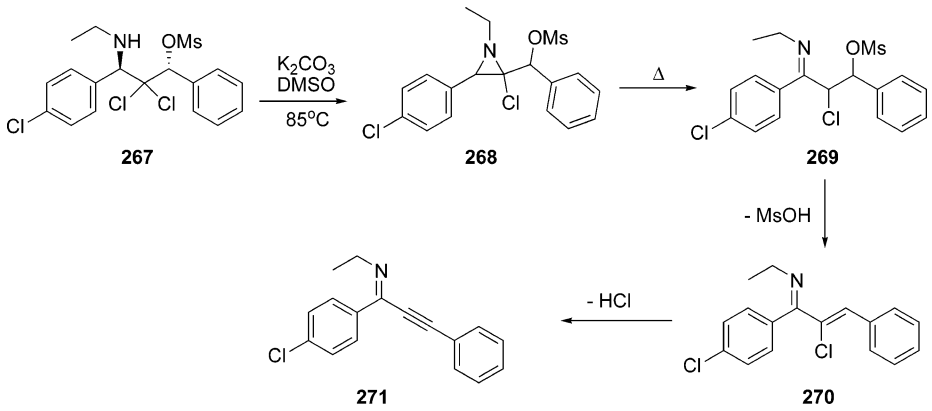
Treatment of 2,2-dichloroaziridines **178** and **294** with sulfuric acid resulted in C(3)−N bond cleavage and subsequent migration of a chloro atom to the C-3 position to form imidoyl chloride **295** (Scheme 100).[139] Subsequent intramolecular Friedel−Crafts reaction of **295** and hydrolysis formed oxindole **297**, isoquinolinone **298**, and benzazepinone derivatives **299** through an intermediate carbenium ion. The reaction of such compounds with phenol depended upon the substituent at nitrogen.[140] The intermediate **301** with a positive charge stabilizing group, such as a benzyl group, at nitrogen favored the von Braun type degradation to give nitrile **302**, which subsequently reacted with phenol to give the nitrile **303** (Scheme 101). The intermediate **300** with a 2-phenylethyl group at nitrogen reacted with phenol at the ortho position to form 2,2-diphenyl-3-phenethyliminobenzofuran (**305**), which was acid-hydrolyzed to 2,2-diphenyl-3-benzofuranone (**306**).

Scheme 94

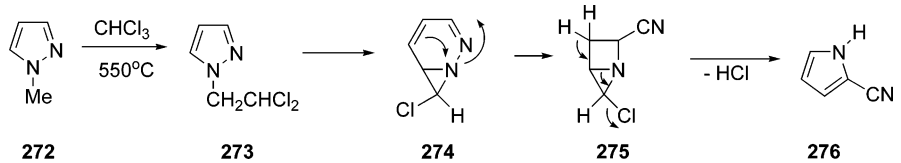


Unlike the corresponding 1-aryl-2,2-dichloroaziridines, 1-benzoyl-2,2-dichloroaziridines **308** required acid as a catalyst for methanolysis.[141] The course of the reaction of such aziridines, synthesized by cyclization of the *N*-trichloroethylbenzamide **307** (Scheme 102), was sensitive to the nature of the substituents at C-3 as well. *N*-Benzoylaziridine **308** with a methyl group at C-3 afforded *N*-benzoyl-(*dl*)-alanine methyl ester **309** and trichloroethylamide **310** (Scheme 103). Similar treatment of *N*-benzoyl-2,2-dichloro-3-phenylaziridine afforded compounds **311**−**313** (Scheme 103). Methanolysis of 1-benzoyl-2,2-dichloroaziridine **308**, carrying a formyl group in the C-3 substituent, afforded α-aminolactone **314** (Scheme 103). Thermolysis of these aziridines also varied. 1-Benzoyl-2,2-dichloro-3-phenylaziridine afforded the oxazole derivative **315** (Scheme 104), whereas 2-(1-benzoyl-3,3-dichloroaziridin-2-yl)-2-methylpro-

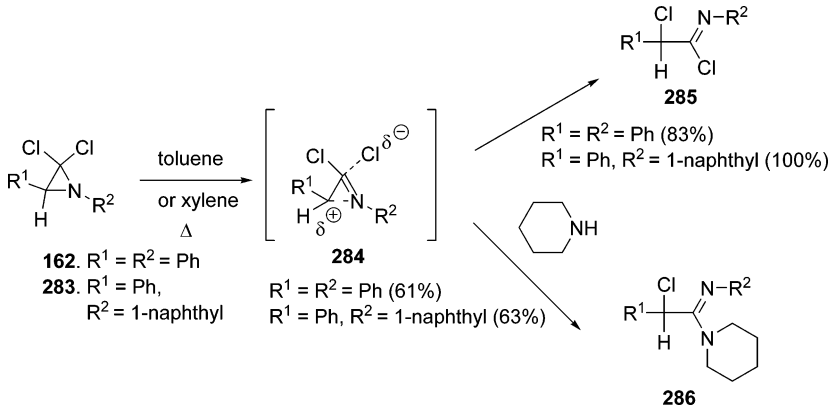
Scheme 92



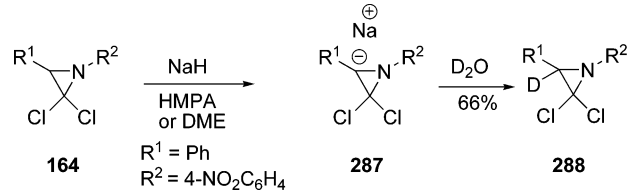
Scheme 93



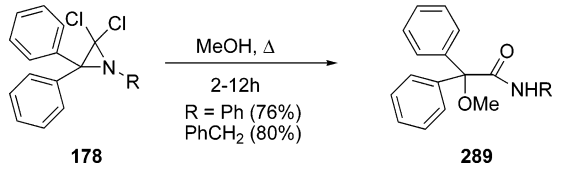
Scheme 95



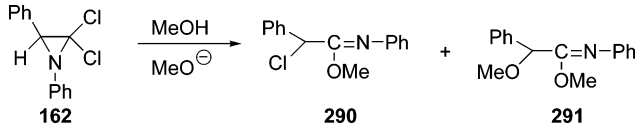
Scheme 96



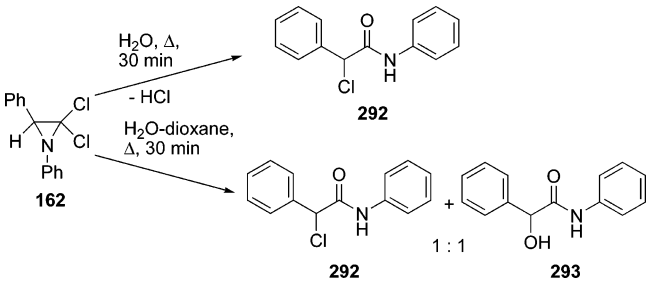
Scheme 97



Scheme 98



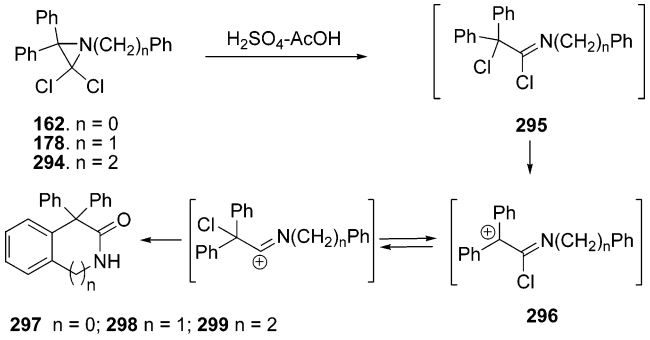
Scheme 99



panal (R = CMe_2CHO) appeared to be stable in boiling xylene for 24 h.

4.3.1.2. 2-Chloroaziridines. In contrast to 2,2-dichloroaziridines, there are many examples of 1,3-diphenyl-2-chloroaziridines undergoing displacement of the chloride ion by nucleophiles such as alkoxides, hydride, and thiolates. Such reactions of 2-chloroaziridines forming 2-acetoxy- and 2-alkoxyaziridines have been described previously (Schemes 39−42).[75−77,84] Some other examples of the formation of the *C*-functionalized aziridines using lithium aluminum hydride, methyllithium, sodium cyanide, and sodium thiophenolate are shown in Schemes 105 and 106. *cis*-1,3-Diphenyl-2-chloroaziridine was cleaved with lithium aluminum hydride, forming *N*-phenyl-2-phenethylamine (**319**). The displacements, which proceeded through an aziridinyl cation (Scheme

Scheme 100

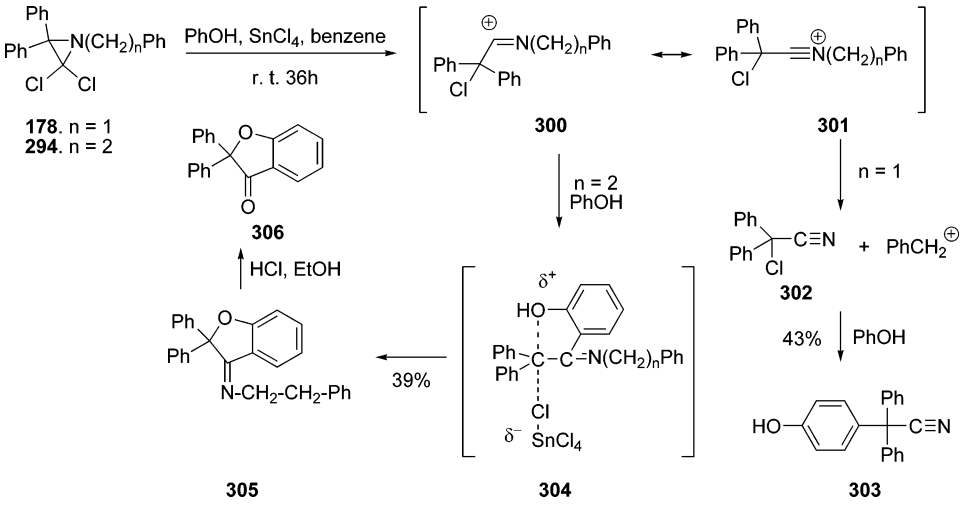


107), afforded products with inversion of stereochemistry. An enhanced reactivity of chloroaziridines over cyclopropanes has been attributed to the stabilization of the cationic center by the adjacent electron pair at nitrogen. Two explanations for the steric course were put forward: one suggesting the intermediate **322** as a tight ion pair in which the chloride ion shielded the carbocation, promoting backside attack, and the other suggesting symmetrically solvated **322** and nucleophilic attack stereoselectively from the side trans to the C-2 phenyl group.

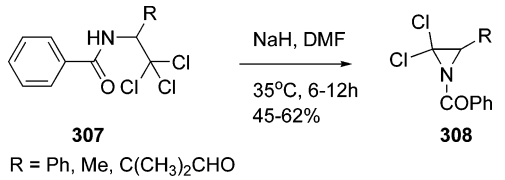
An unusual rearrangement of 2-chloro-2-methyl-1,3-diphenylaziridine (**241**) has been observed (Scheme 108) upon treatment with an excess of the sterically hindered base potassium *tert*-butoxide, forming *N*,3-diphenylpropanamide (**324**).[76] It was believed that initially Me_3COK abstracted hydrogen chloride from **241** to give a 1,3-diphenyl-2-methyleneaziridine (**323**), which was favored over its isomer 1,3-diphenyl-2-methyl-1*H*-azirine (**328**) by the unfavorable electronic characteristic of the latter and the nonplanar arrangement of the Cl−C_3−C_2−H bonds in the aziridine. The formation of 1,3-diphenyl-2-*t*-butoxyaziridine (**148**) from 1,3-diphenyl-2-chloroaziridine (**147**) (Scheme 41) supported this assumption. This 2-methyleneaziridine **323** underwent a valence tautomerism into a cyclopropylideneamine **325**, which suffered addition of *tert*-butoxide across the imino bond. Ring opening of the cyclopropane **326** in a way similar to the Favorskii ring opening of cyclopropanones afforded a *tert*-butyl imidate **327**, which was converted into the final amide **324** by isobutene expulsion or by aqueous workup.[142]

2-Chloroaziridines with *N*-benzoyl and *N*-acyl groups are known to rearrange, forming oxazoles and amides. For example, 1-benzoyl-2-chloro-3-methyl-2-phenylaziridine (**226**) and 1-benzoyl-2-chloro-2,3-diphenylaziridine (**227**) rearranged either in acetone or in methanol to afford oxazoles **329** and **330** and amides **331**, **332**, and **333** (Schemes 109

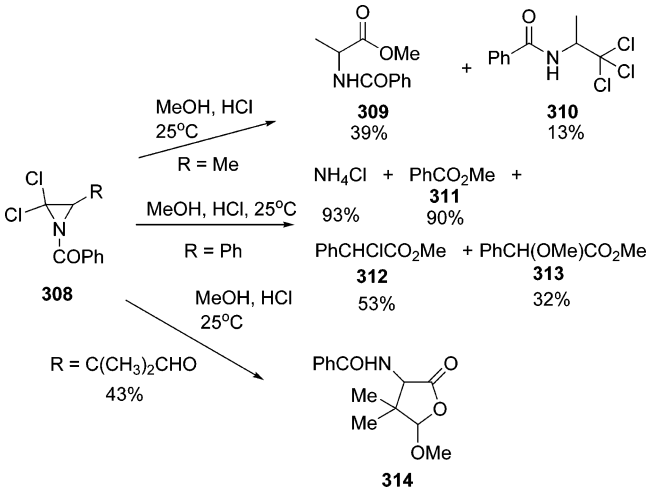
Scheme 101



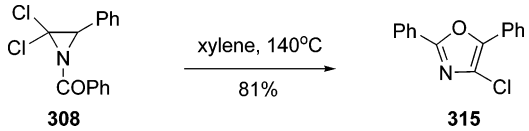
Scheme 102



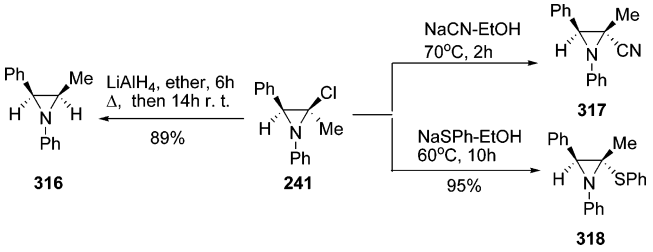
Scheme 103



Scheme 104



Scheme 105



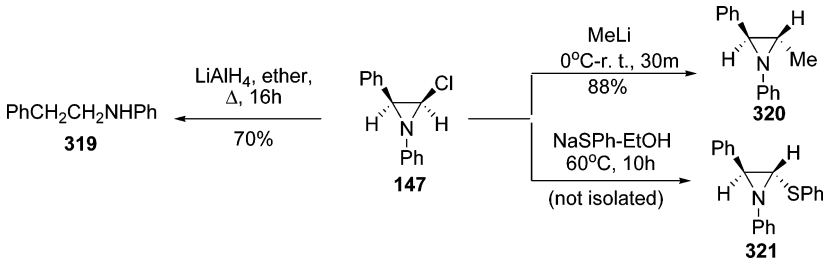
and 110). The α-chloroaziridine **229** afforded only the amide **334** (Scheme 111), whereas the aziridines **143** afforded only the oxazoline hydrochlorides **335** in quantitative yield, which were converted to oxazoline **336** with sodium bicarbonate and ethereal hydrochloric acid (Scheme 112).[75,120] Treatment of 2-chloroaziridines **145** and **226** with phenylmagnesium bromide gave 2,2-diphenyl-3-methylaziridine (**337**) (Scheme 113).[120] The former was unreactive toward sodium hydride or DABCO. However, treatment of either chloroaziridine **226** or **227** with the strong base potassium *tert*-butoxide afforded 1-azirine **79** and *tert*-butyl benzoate **339** (Scheme 114).[120] This result is rationalized in terms of either the intermediate complex **338**, which fragmented to give the observed products or (less plausible) 2-azirine **340**. The cleavage of the latter would lead to *tert*-butyl benzoate and an azirinyl anion **341**. Protonation of this anion may give the thermodynamically more stable 1-azirine **79**.

1-Benzoyl-2-chloroaziridine and 1-acyl-2-chloroaziridine undergo reduction with lithium aluminum hydride to furnish 2,2-dimethylaziridines **342** and alcohols **343** (Scheme 115).[75] Their hydrolysis in aqueous acetone afforded ketoamides **344** (Scheme 116). The displacement of chlorine in similar aziridines to afford 2-acetoxyaziridine has been described earlier.[75] The displacement of chlorine in aziridines other than 1-benzoyl-2-chloro-3,3-dimethyl-2-phenylaziridine by an azide group using an excess of lithium azide afforded 2-azidoaziridines **345**, which isomerized partly to oxazolines **346** (Scheme 117).[75]

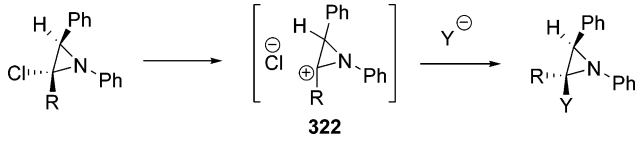
The formation of 2-chloroaziridines **147** and their rearrangement leading to the formation of *cis*-aziridines **316** having alkyl or aryl groups at C-2 and C-3, on the one hand, and rearranged amines **349** via the azirinium cation **348**, on the other hand, has also been proposed in the reaction of α,α-dichloroimines **347** with lithium aluminum hydride in ether (Scheme 118).[143] This reaction has been applied to α,α-dichloroimines **350** and **352** forming different types of carbon-substituted aziridines such as 1,2-dialkylaziridines,[144] 1-aryl-2-alkyl-,[145] 1,2,2,3-tetraalkyl- and 1,2,3-trisubstituted aziridines **316** (Schemes 119 and 120).[146] Similar reactions have also been reported using *N*-1-(2,2-dichloroalkylidene)-amides (Scheme 121).[147] The initial reduction of the amide linkage to the corresponding amine resulted in an aldimine, which is further transformed into 1-ethyl-2-alkylaziridines **353** via a 1-ethyl-2-chloroaziridine.

Upon reflux in dichloromethane, 2-chloroaziridines **233** and **234** are converted into the mixed divinylamine isomers **355**, **356** (Scheme 122) and **358**, **359** (Scheme 123), respectively.[122] The aziridines bearing a chloromethylen-

Scheme 106



Scheme 107



emalononitrile group (R = H) and a chloroethylidenemalononitrile group (R = Me) cleaved in different ways. The former compound formed a zwitterion **354** by cleavage of the aziridine *N*−C(2) bond, whereas the latter compounds underwent *N*−C(3) bond cleavage, forming the azirinium ion **357**.

4.3.1.3. 2-Bromo- and 2,2-Dibromoaziridines. A mixture of aziridines **255** and **256** in refluxing toluene in the presence of *n*-tributyltin hydride and azobiscyclohexanecarbonitrile (ABCCN) as a radical initiator afforded the dimer **360**, dihydroindole **361**, and uncyclized aziridine **362** in a 0.8:1.5:1.1 molar ratio with the dimer being isolated in 35% yield (Scheme 124).[128]

The mixture of bromoaziridines **262** is a synthon for (+)-desmethoxymytomycin A. Its reduction with sodium borohydride provides 3-(hydroxymethyl)indoles **363** (Scheme 125).[129,148,149] The reductive radical cyclization of the latter in the presence of *n*-tributyltin hydride affording the single tetracyclic alcohol **364** serves as the key step in the synthesis of (+)-desmethoxymytomycin A (**365**).

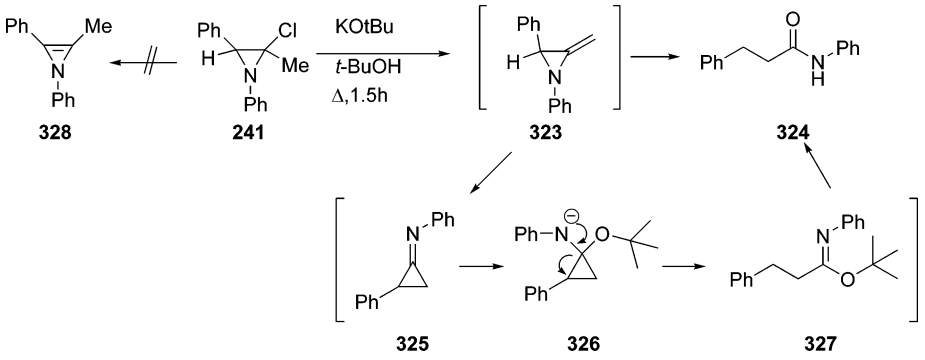
Treatment of 1,3-diaryl-2,2-dibromoaziridine **247** with triethylamine in acetonitrile led to ring opening, forming bromoketenimines **366** (Scheme 126).[150]

4.3.2. Reactivity of C-Fluoroaziridines

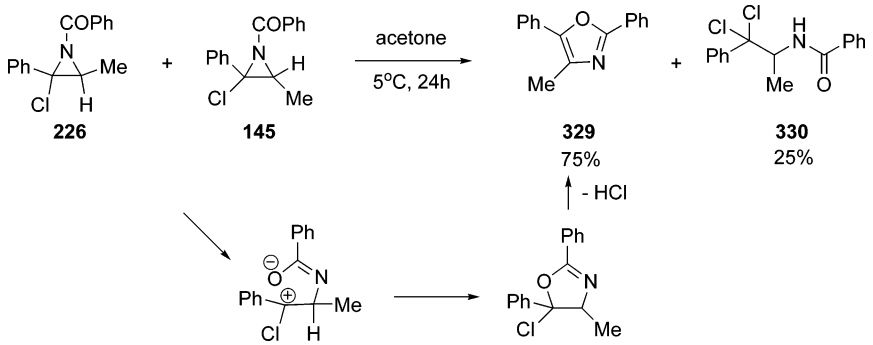
Fluoro-substituted aziridines are highly stable toward many electrophilic and nucleophilic reagents and heat. A theoretical study of the formation of stable anion intermediates via electron capture by heterosubstituted three membered ring compounds has been explored by Sevin and co-workers.[151,152] A recent investigation of the course of reactions of 2,2-difluoroaziridines showed that it depended on the substitutents at other positions of the ring as well.[106] 1-Alkyl-2-fluoroaziridines have a significantly higher thermal stability compared to 1-aryl-2-fluoroaziridines. For example, 1-methyl-2,2-difluoro-3,3-bis(trifluoromethyl)aziridine (**177**) is recovered unchanged after 18 h at 220 °C. On the contrary, 1-aryl-2,2-difluoro-3,3-bis(trifluoromethyl)aziridines **175** were completely converted into a mixture of substituted anilines **367** and 2-fluoro-3,3-bis(trifluoromethyl)-3*H*-indoles **368** at 220 °C (Scheme 127). 2,2-Difluoro-3,3-bis(trifluoromethyl)-aziridine (**369**) underwent dehydrofluorination in the presence of Et_2O-BF_3 to form 3-fluoro-2,2-bis(trifluoromethyl)azirine (**370**) (Scheme 128).[153]

1-Aryl-2,2-difluoro-3,3-bis(trifluoromethyl)aziridines **175** are much less sensitive toward nucleophiles. For example,

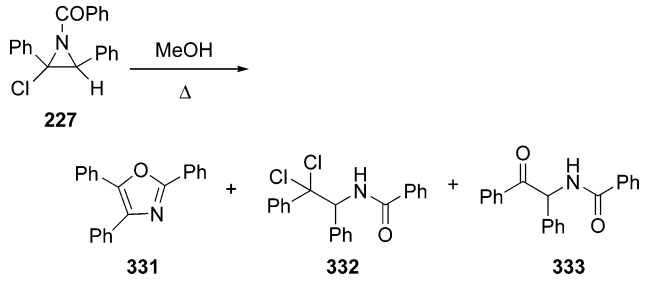
Scheme 108



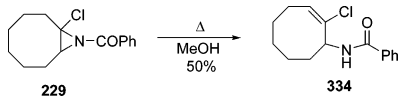
Scheme 109



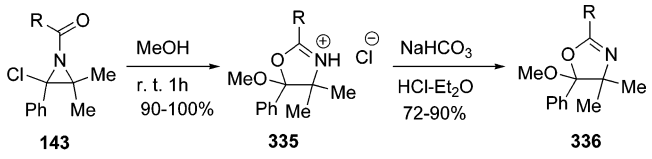
Scheme 110



Scheme 111

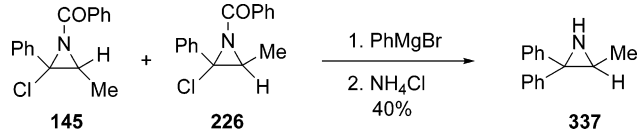


Scheme 112



R = Me, $PhCH_2$, *t*-Bu

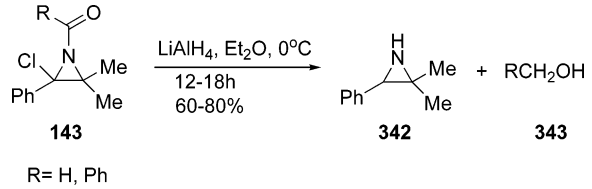
Scheme 113



1-phenyl-2,2-difluoro-3,3-bis(trifluoromethyl)aziridine was found to be inert to the action of cesium fluoride at 20−80 °C.[154] However, it reacted slowly in sulfolane at 100−110 °C to afford imidoyl fluoride **371** (Scheme 129).[106] The aziridine with a 3-CF_3 group on the phenyl ring was observed to be more reactive to cesium fluoride as the reaction was completed in 12 h, in contrast to 50 h in the previous case. The probable reason for the higher reactivity could be the higher positive charge at C-3 of the ring due to the higher electronegativity of the substituent at nitrogen. The formation of the product was explained through the amide ions **372** formed by the attack of fluoride on the ring carbon bearing two CF_3 groups. This behavior was contrary to the usual observation of nucleophilic attack at the less hindered carbon of the aziridines.[121]

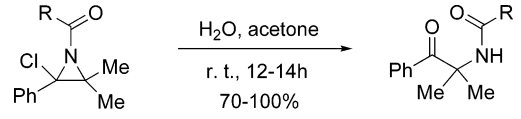
It has been observed that the introduction of a fluoro substituent decreases the reactivity of the aziridine ring toward electrophiles. It has also been reported that the basicity of 1-alkyl-2-trifluoromethylaziridines is approximately half of the basicity of the corresponding nonfluorinated aziridines.[155] Further introduction of fluorine directly attached to a ring carbon leads to a significant reduction of reactivity toward acids.[106] For example, the 2,2-difluoro-3,3-bis(trifluoromethyl)-1-(2-fluorophenyl)aziridine and 2,2-difluoro-3,3-bis(trifluoromethyl)-1-(3-trifluoromethyl)phenylaziridine are unreactive toward concentrated sulfuric and hydrochloric acids. However, the latter aziridine with a 3-trifluoromethyl group on the 1-phenyl ring reacted with

Scheme 115



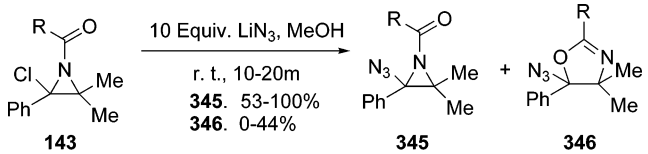
R= H, Ph

Scheme 116



R = Me, *t*-Bu, Ph, CH_2=CH, $ClCH_2$

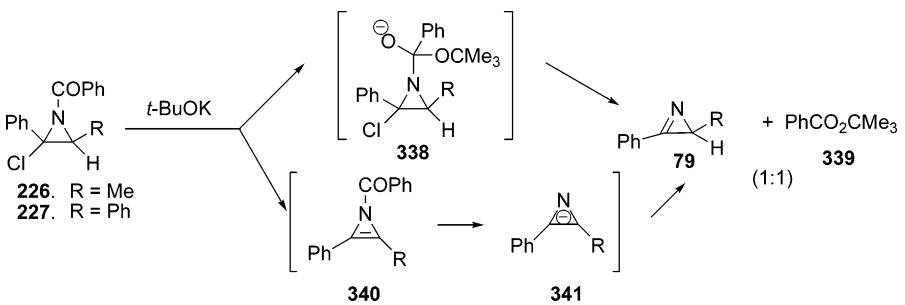
Scheme 117



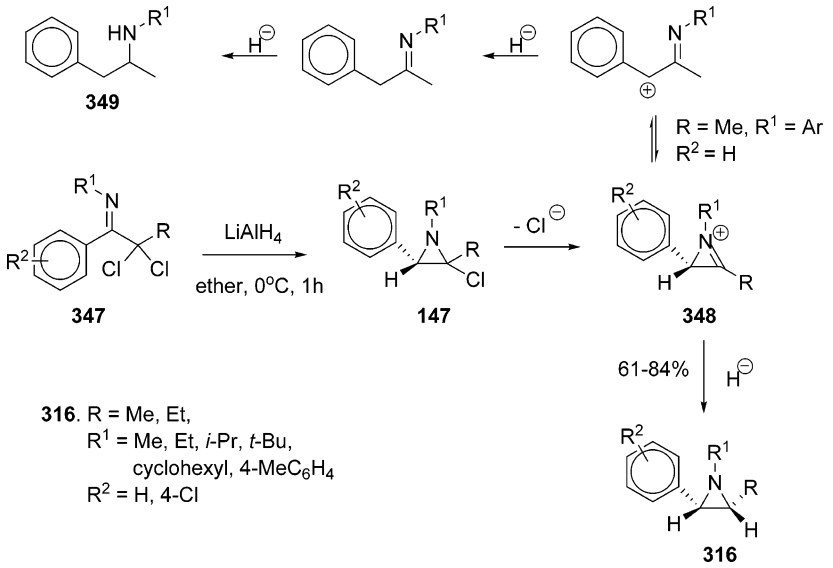
R = Me, $PhCH_2$, *t*-Bu, Ph, CH_2=CH_2, CH_2=$CHCH_3$, EtO_2CCH_2

trifluoromethanesulfonic acid to afford amine **373** in good yield (Scheme 130). The reaction of this aziridine with hydrogen fluoride in the presence of boron trifluoride as a catalyst afforded only polyfluorinated amine **374** (Scheme 131). The reaction involved selective heterolysis of the N−CF_2 bond. Both the nature and the position of a substituent on the phenyl ring of the aziridine played a significant role in determining the course of the reaction with strong acids. The introduction of a 4-chloro or a 4-fluoro group on the *N*-phenyl ring of 2,2-difluoroaziridines resulted in indolinones **375** after treatment with HF, BF_3, and water (Scheme 132). The formation of indolinones **375** involved azirinium ions **376**, which cleaved to form 3-azapentadienyl cations **377**. The latter ions cyclized, producing intermediates **378**. Aromatization of **378** by elimination of a proton formed imidoyl fluorides **379**, which hydrolyzed to form the indoli-

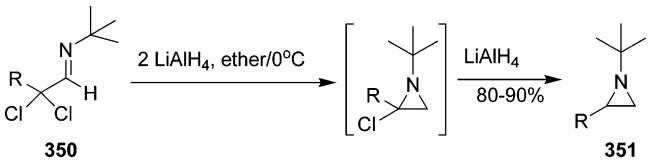
Scheme 114



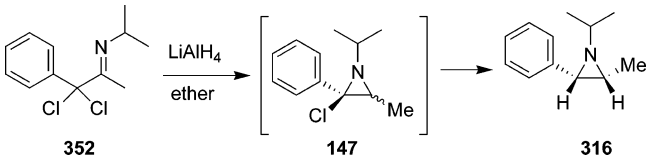
Scheme 118



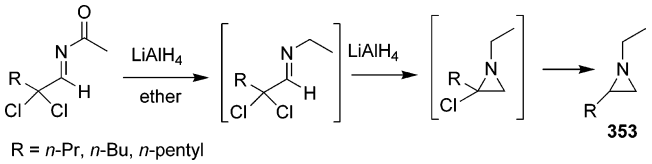
Scheme 119



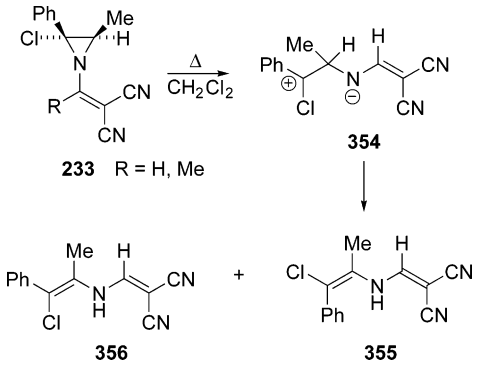
Scheme 120



Scheme 121

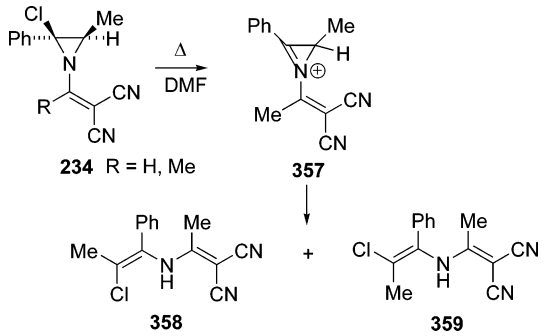


Scheme 122



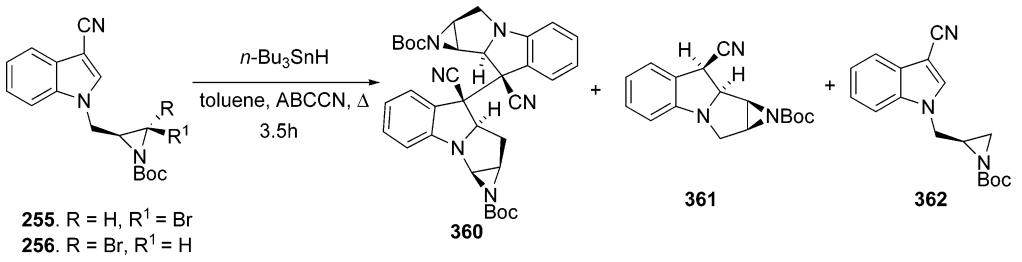
nones **375**. The 2,2-difluoroaziridines with a 3-chloro- or 3-fluorophenyl ring at nitrogen, however, afforded amines **380** as a minor product together with the isomeric indolinones **381** and **382** (Scheme 133). At the same time, a similar reaction of 2,2-difluoroaziridines with a 2-fluorophenyl ring at nitrogen led to the formation of almost equal amounts of the indolinone **383** and aniline **384** (Scheme 134).

Scheme 123

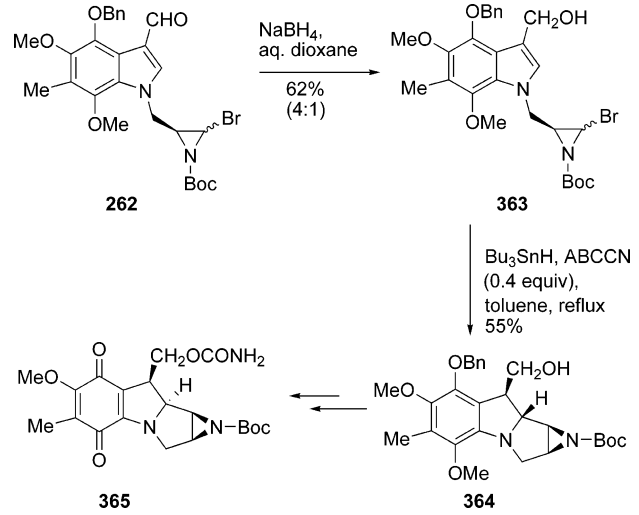


C-Halogen-substituted aziridines are the most extensively investigated class among the *C*-heteroatom-substituted aziridines. This can be attributed to the enhanced stability of the ring due to the presence of the electron-withdrawing group and the easy generation of dihalocarbenes, especially dichlorocarbenes, which add onto the carbon−nitrogen double bond to form such aziridines. Although the most common method for the synthesis of *C*-haloaziridines is carbene−imine addition, other equally suitable methods are known. Efforts are on to refine the methodologies available for the generation of dihalocarbenes. *gem*-Dichloroaziridines are important from a biological point of view as they are precursors for the synthesis of biologically active compounds such as indolinones, analogues of natural alkaloids such as isoquinolinones and isoquinolines, and amidines. Among the *C*-haloaziridines, fluorinated aziridines are comparatively more stable than the chlorinated aziridines. Furthermore, 2,2-dichloroaziridines are comparatively more prone to ring cleavage than 2-chloroaziridines. The nucleophilic displacement of the chloro atom in 2-chloroaziridines is a powerful tool for the synthesis of other *C*-functionalized aziridines such as 2-acetoxyaziridines, 2-azidoaziridines and 2-(phenylthio)aziridines. However, the course of the reactions of such aziridines often depends upon the substituent present at the ring nitrogen.

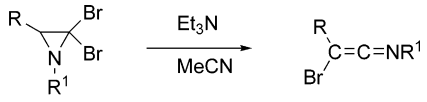
Scheme 124



Scheme 125

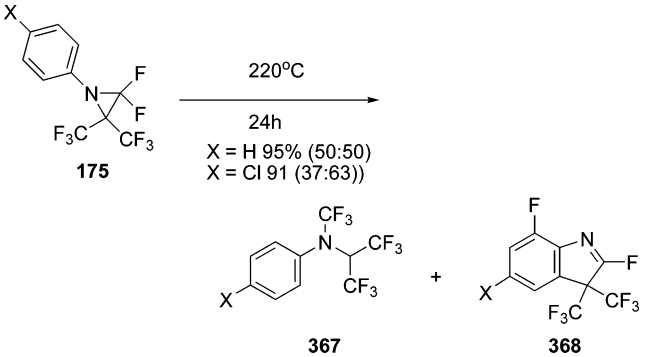


Scheme 126

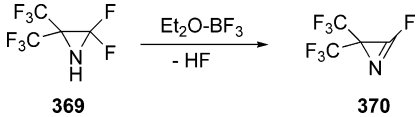


R = Ph, 4-ClC$_6$H$_4$; R^1 = Ph, 4-ClC$_6$H$_4$

Scheme 127



Scheme 128

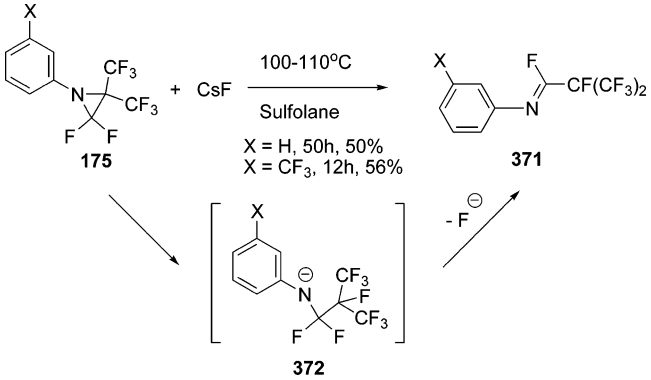


5. C-Nitrogen-Substituted Aziridines

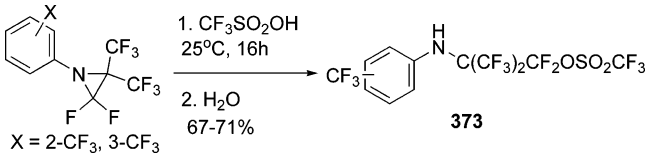
5.1. Introduction

C-Nitrogen-substituted aziridines serve as precursors of amino acids and other biologically important (heterocyclic) compounds. *N*-Unsubstituted aziridines bearing an amino group at the ring carbon(s) are scarce because the lone pair of the exocyclic nitrogen tends to promote ring opening. However, the presence of aromatic azaheterocycles on the aziridine ring carbon atoms has been observed to provide stability to the ring, presumably due to delocalization of the lone pair at nitrogen into the aromatic system. A literature survey reveals different types of nitrogen substituents on aziridine ring carbon(s) such as acyclic amino, cyclic amino, heteroaryl, azido, and nitro, which have been synthesized using different methodologies. It would therefore be convenient to further classify this group of aziridines according to the type of substituent present on the ring. The reactivity of such aziridines is described under a separate heading.

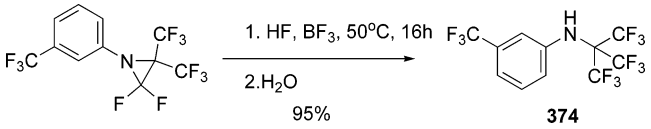
Scheme 129



Scheme 130



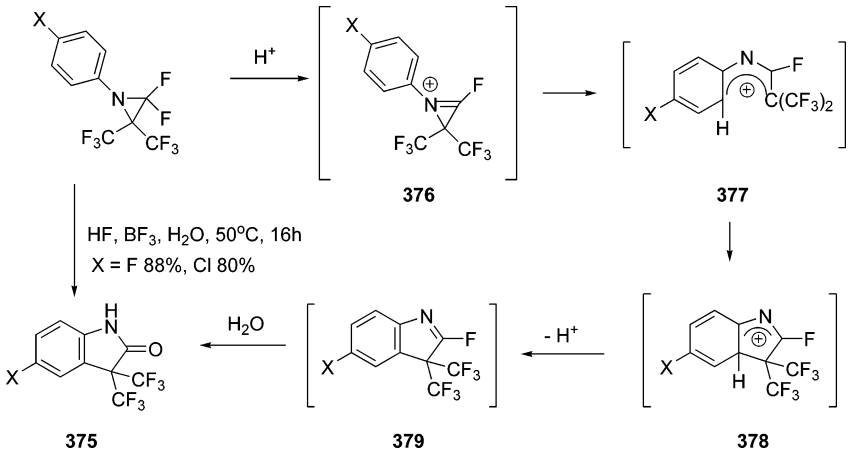
Scheme 131



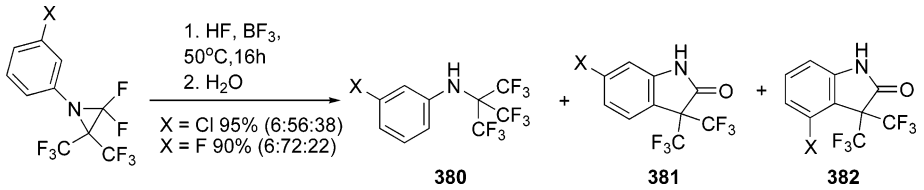
5.2. *C*-Aminoaziridines

C-Aminoaziridines were reported as intermediates in the literature in the mid-1960s.[156] De Poortere and De Schryver reported the first synthesis of a series of stable 2-aminoaziridines in 1970.[157] Photolysis of 2-triazolines **385** afforded the corresponding 2-(dimethylamino)aziridines **386** (Scheme 135). In most cases, an amidine **387** was also obtained as a product. However, 5-amino-2-triazoline failed to afford the 2-aminoaziridine as anticipated. The 2-(dimethylamino)-aziridines **386** were very sensitive to moisture. These compounds hydrolyzed to yield a hemi-aminal **388** that

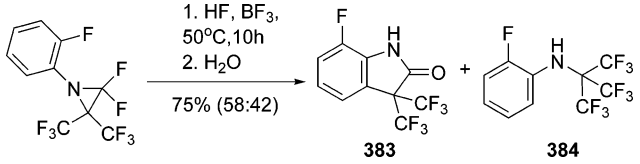
Scheme 132



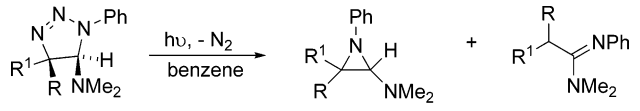
Scheme 133



Scheme 134

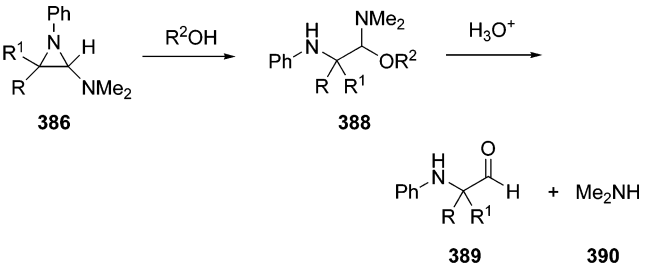


Scheme 135



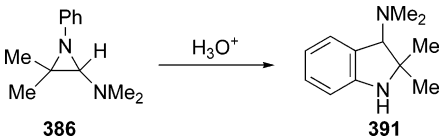
R = Me, R^1 = Me, Ph

Scheme 136



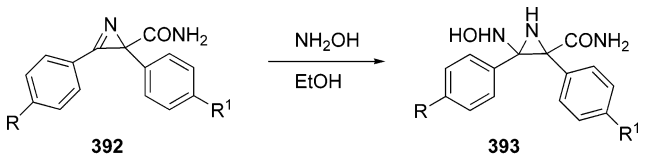
R = Me, R^1 = Me, Ph; R^2 = H, Me

Scheme 137



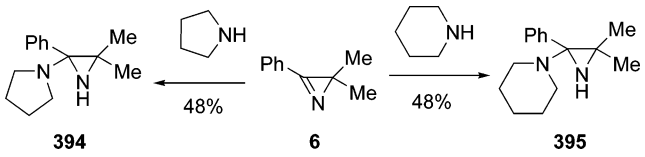
decomposed into α-aminoaldehydes **389** and dimethylamine (Scheme 136). Treatment of 2-(dimethylamino)aziridine **386** with aqueous acid afforded 3-(dimethylamino)-2,2-dimethylindoline (**391**) in good yield (Scheme 137).

Scheme 138



R = R^1 = H; R = 4-Me, R^1 = H;
R = H, R^1 = 4-Cl

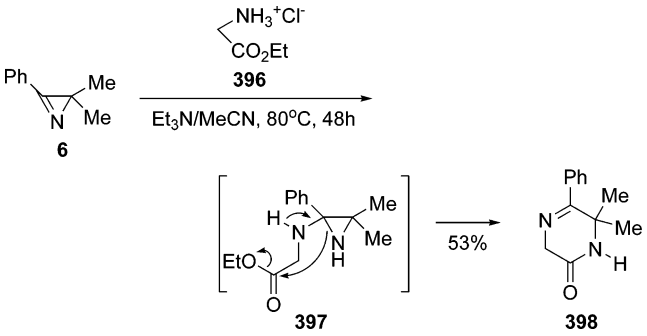
Scheme 139



The addition of hydroxylamine across the carbon−nitrogen double bond of 2,3-diaryl-2*H*-azirine-2-carboxamides **392** formed the corresponding hydroxylaminoaziridinecarboxamides **393** (Scheme 138).[158] Similarly, addition of cyclic amines such as pyrrolidine and piperidine to 2,2-dimethyl-3-phenylazirine (**6**) led to the formation of *C*-cyclic amine substituted aziridines **394** and **395**, respectively (Scheme 139).[159] 2,2-Dimethyl-3-phenylazirine (**6**) reacted with the hydrochloride of ethyl glycinate **396** to form the aziridine carbamate **397** (Scheme 140), which afforded dihydropyrazinone **398** by ring expansion.[54]

The reaction of β-enamino esters **399** with ethyl *N*-[(4-nitrobenzenesulfonyl)oxy]carbamate **189** in the presence of a base afforded 2-[(ethoxycarbonyl)amino]-3-oxobutanoate (**401**) (Scheme 141).[160] The yield of the product was only 26% when CaO was used in a 1:2.1 molar ratio and the reaction time was 48 h. The application of triethylamine in a 1:1 molar ratio afforded the product in 40% yield, also after 48 h. The involvement of 3-amino-3-methylaziridine-1,2-dicarboxylic esters (**400**), which hydrolyzed to form the final product in each case, was detected by GC-MS. After HPLC purification, it was possible to isolate intermediate

Scheme 140



aziridine **400** with a 2,5-di(methoxymethyl)pyrrolidine substituent at position 3 (R_2N). The reactions of enamines with azides having a glycoside moiety are reported to form 2-amino-1-glycosylaziridines.[161]

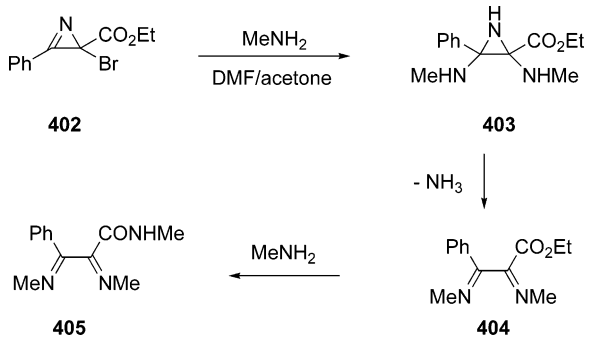
Melo and co-workers, during their studies on the synthesis and reactivity of 2-halo-2*H*-azirines,[162−164] have carried out reactions of 2-bromo-2*H*-azirine-2-ethylcarboxylate (**402**) with methylamine. The reaction afforded α-1,2-diimine **405** in only 6% yield through ethyl 2,3-bis(methyamino)-3-phenylaziridine-2-carboxylate (**403**), which ring opened followed by elimination of ammonia to yield diimine **404** (Scheme 142). In the presence of a large excess of methylamine, using dimethylformamide or acetone as a solvent, compound **405** was isolated in 36 and 40% yield, respectively. Treatment of ethyl 2-bromo-3-phenyl-2*H*-azirine-2-carboxylate **402** and some other *C*-bromoazirines **406** with 1,2-phenylenediamine **407** afforded quinoxalines **409** via a tricyclic aziridine **408** (Scheme 143).[165] Also, other bicyclic aminoaziridines have been reported, for example, pyrroline fused aziridines.[166]

Furthermore, 2-aminoaziridines have also been prepared via stable aziridiniminium salts, obtained by reaction of 2-amino-1-azirines with $Ph_3C^+BF_4^-$, upon treatment with different types of carbanions.[167]

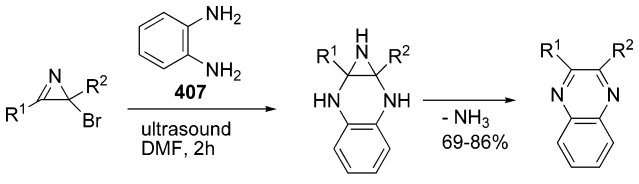
5.3. *C*-Azaheteroarylaziridines

The aziridine adducts obtained after nucleophilic addition of imidazoles and pyrazoles to 3-phenyl-2*H*-azirines were too unstable to be isolated but could be detected by NMR spectroscopy.[168,169] A number of aromatic azaheterocycles **410**, however, have been added onto methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate (**73**), leading to the formation of stable 1-unsubstituted 2-heteroarylaziridine-2-carboxylates **411** (Scheme 144).[170] The reaction with 2-acylpyrrole afforded the corresponding product in 99% yield. The reactions are highly stereoselective, because nucleophiles add to the carbon−nitrogen double bond of the azirine from the less hindered face leading to aziridines with the aryl substituent and the incoming nucleophile in trans disposition.

Scheme 142

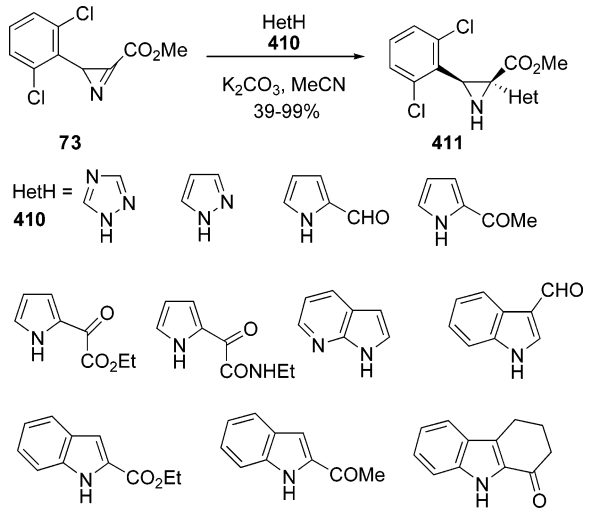


Scheme 143



R^1 = Ph, R^2 = CO_2Et; R^1 = CO_2Me, R^2 = COPh;
R^1 = R^2= CO_2Me; R^1 = Me, R^2= CO_2Me

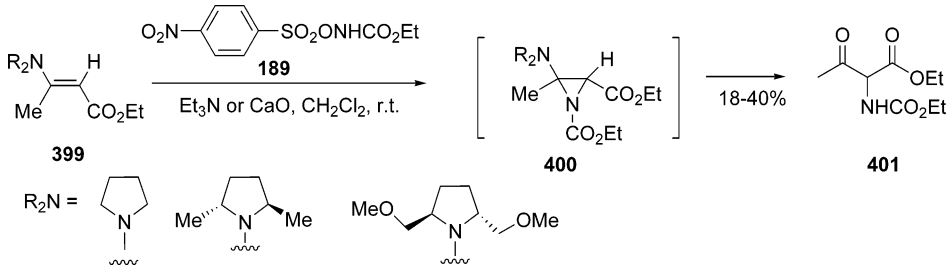
Scheme 144



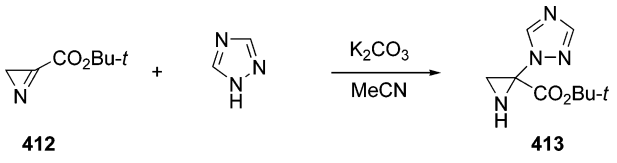
An azirine **412** lacking the aryl group also gave an analogous reaction with 1,2,4-triazole, affording the corresponding aziridine **413** (Scheme 145). The selective hydrolysis of the ester linkage in aziridine **411** under basic conditions afforded aziridine-2-carboxylic acid **414** in 65% yield (Scheme 146).

A first approach to a chiral 2-aminoaziridine involved the reaction of an azirine, bearing a (*N*,*N*-diethylsulfamoyl)-

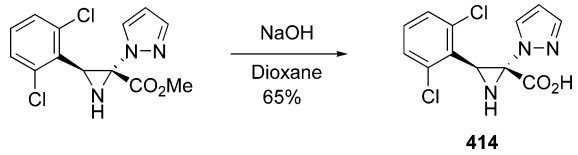
Scheme 141



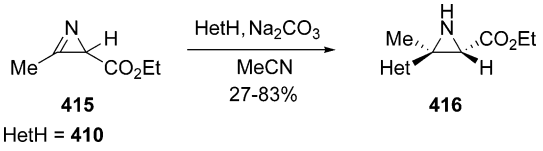
Scheme 145



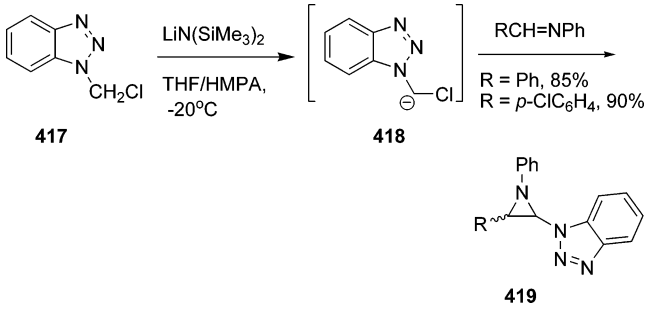
Scheme 146



Scheme 147



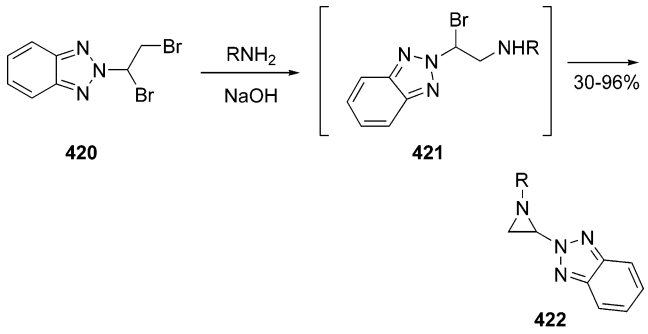
Scheme 148



isobornyl unit as a chiral auxiliary in the ester moiety, with nucleophiles, but the diastereodifferentiation of the two faces of the azirine was generally not good.[171] Therefore, optically active 2*H*-azirine-2-carboxylic ester **415**,[172] which was easily accessible either by the Swern oxidation[173] or from the corresponding *β*-ketoester oxime *p*-toluenesulfonate by a modified Neber elimination using (+)-dihydroquinidine as a chiral tertiary base, was opted for this purpose.[174] This azirine was electrophilic enough to react with nitrogen heterocycles **410** at room temperature within a few hours, forming 2-heteroarylaziridines **416** (Scheme 147). The ee of the products was established by further functionalization of the aziridine NH with the chiral acylating agent (1*S*)-(+)-camphorsulfonyl chloride. A mixture of the two major diastereomers was obtained in a ratio between 4:1 and 5:1, which was approximately the same enantiomeric ratio observed in the starting chiral azirine **415**. Two other minor diastereomers were also detected in a 4:1 ratio due to *syn* addition of indole to the azirine. The two major diastereomers constituted 85% of the crude mixture, indicating a good diastereoselectivity for the addition reaction.

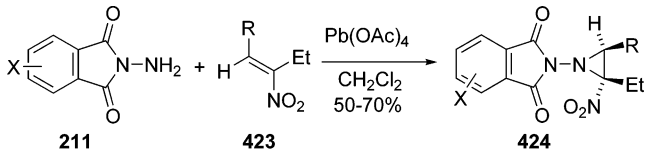
Katritzky and co-workers have reported the synthesis and reactions of 1-alkyl-2-(benzotriazolyl)aziridines **419** and **422**.[175] Two methods have been explored for the synthesis of these compounds. The first method used the reaction of 1-(chloromethyl)benzotriazole (**417**) with lithium bis(trimethylsilyl)amide, forming the benzotriazolyl-substituted carbenoid **418**, which reacted with imines toward aziridines **419** (Scheme 148). The second method was based on the reaction of a 1,2-dibromoethylbenzotriazole **420** with amines

Scheme 149



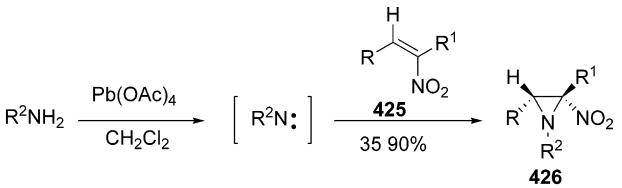
R = *n*-C_5H_{11}, *i*-Bu, *n*-$C_{10}H_{21}$, *n*-Bu, *c*-C_6H_{11}, $PhCH_2$, *n*-Pr

Scheme 150



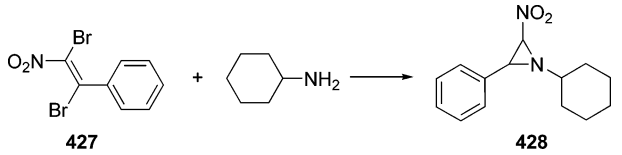
X = 3-NO_2, 4-NO_2, H
R = 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$

Scheme 151



R = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$
R^1 = H, Me, Et
R^2 = phthalimido, 3,3-dibenzylmaleimido, 2,2-diphenyl-, 2,2-dibenzylsuccinimido

Scheme 152

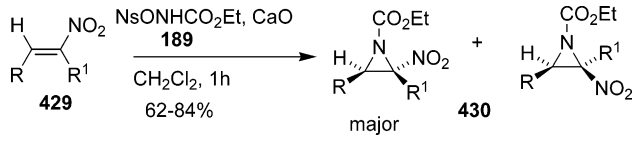


followed by cyclization of the resulting bromoamines **421** (Scheme 149).

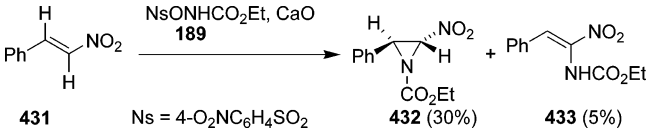
5.4. *C*-Nitroaziridines

There are only a few papers in the literature on the synthesis of *C*-nitroaziridines. Some papers include the reactions of nitrostyrenes **423** and **425** with imidonitrenes to form 1-imido-2-nitroaziridines **424** and **426** (Schemes 150 and 151)[176−178] and the reaction of α,*β*-dibromonitrostyrene **427** with cyclohexylamine in a 1:3 molar ratio toward 1-cyclohexyl-2-nitro-3-phenylaziridine (**428**) (Scheme 152).[179] The synthesis of 2-nitroaziridine-1-carboxylates **430** has been reported from the reaction of various nitroalkenes **429** with ethyl [(4-nitrobenzenesulfonyl)oxy]carbamate (**189**) in dichloromethane using calcium oxide as base (Scheme 153). The yields were in the range of 62−84%, and the stereochemistry was retained in the major product.[180] The methodology was improved later on, and the reaction was carried out under solvent-free conditions by taking equimolar amounts of reactants instead of the 1:3 molar ratio (one for alkene and three for carbamate and base) taken in the previous case.[181] In this new protocol, (*E*)-*β*-nitrostyrene (**431**), which failed

Scheme 153



Scheme 154



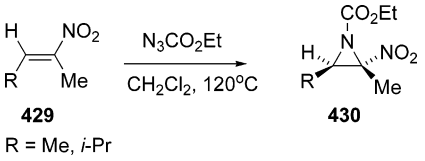
to react previously, could also be converted into 2-nitroaziridine **432** (Scheme 154). Acyclic compound **433** was also obtained in the reaction as a minor product. The authors have proposed two mechanisms responsible for the formation of aziridines **430** (Scheme 155). The first path (path A) may involve a direct addition of (ethoxycarbonyl)nitrene to the carbon−carbon double bond of the nitroalkene. Alternatively, the $NsON^{-}CO_2Et$ anion may undergo an aza-Michael addition (path B)[182] to the carbon β to the nitro group, followed by ring closure of the resulting intermediate anion **434** by expulsion of a nosyloxy anion. The second possibility was preferred, considering the electron-poor character of nitroalkenes that make them good Michael acceptors, but not very suitable to undergo an electrophilic addition by a nitrene. To test this hypothesis, the reaction of these alkenes was carried out with ethyl azidoformate, known to generate carboethoxynitrene. The yields of aziridines in this case were very low (Scheme 156), which supported the involvement of an aza-Michael addition.

Electron-rich alkynes **437**, such as ethoxyacetylene and 1-ethoxy-1-butyne, reacted with dinitronates **436** to form 1-alkoxy-2,2-dinitroaziridines **439** via 3,3-dinitro-2,3-dihydroisooxazole **438** (Scheme 157).[183] Dinitronates **436** were generated in situ either by alkylation of a nitro group in nitromethanes using diazomethane or by a reaction between tetranitromethane or bromonitromethane and bicyclobutylidene (**435**). Acetylenes containing alkyl or electron-withdrawing substituents, such as 1-hexyne, 1-heptyne, and phenylacetylene, did not react with nitronates.[160]

5.5. *C*-Azido- and *C*-Azoaziridines

The formation of a 2-azidoaziridine by treatment of 1-acyl-2-chloroaziridine with lithium azide has been described earlier (Scheme 117).[75] Hydrazoic acid added onto ethyl 3-aryl-2*H*-azirine-2-carboxylates **440**, forming ethyl 3-aryl-3-azidoaziridine-2-carboxylates **441** in 60−75% yield (Scheme 158).[184] The latter compounds afforded tetrazole derivatives

Scheme 156



442 on thermolysis.[185]

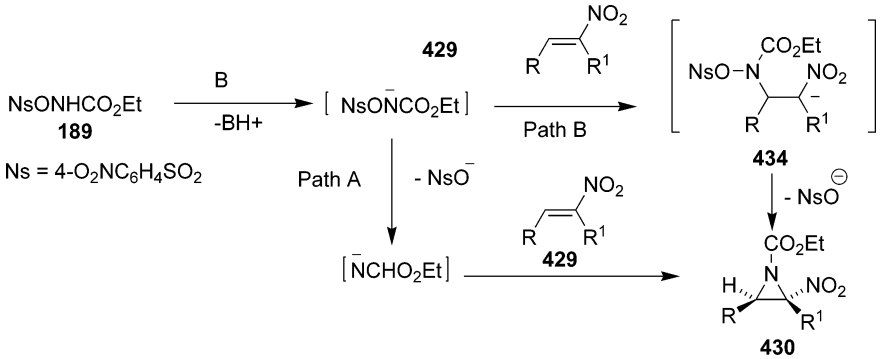
The reaction of β-phenylazostyrene (**443**) and of 1-phenylazocyclohexene (**445**) with *N*-aminophthalimide and lead tetraacetate afforded 2-phenylazo-1-(*N*-phthalimido)aziridines **444** and **446**, respectively (Schemes 159 and 160).[186] A similar reaction with 1-phenylazocyclopentene took a different course and did not afford either an aziridine or any aziridine-derived product. The reaction of 2-phenylazopropene (**447**) afforded a bishydrazone **449**, possibly through the aziridine **448** (Scheme 161).

5.6. Ring Expansion in *C*-Nitrogen-Substituted Aziridines

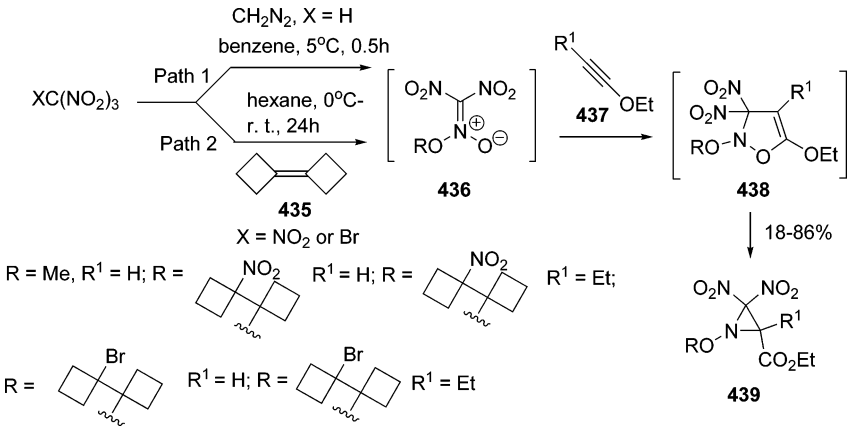
The reaction of 3,3-dialkyl-3*H*-azirine-2-amines **450** with 2-amino-4,6-dinitrophenol (**451**) in acetonitrile led to the formation of benzoxazole derivatives **452** (Scheme 162) besides some other products.[187] The formation of the benzoxazole derivative is proposed through the intermediacy of 2,2-diaminoaziridine derivatives **453** (Scheme 162). The ring opening of the latter aziridines followed by an intramolecular proton transfer may lead to the intermediate **454**, which may cyclize to form benzoxazoline derivatives **455**. Removal of the amine moiety at C-2 of this compound may furnish the final product **452**. This methodology has been extended to the synthesis of 10-membered cyclic sulfonamides **457** and **458** via aziridines **459**, formed from the reaction of azirines **450** and 4,5-dihydro-7,8-dimethoxy-1,2-benzothiazepin-3-one-1,1-dioxide (**456**) (Scheme 163).[188] The reactions were carried out mainly in acetonitrile, and the overall yields were low. In one case ($R^1 = R^2 = R^3 = R^4 = Me$), when the reaction was carried out in dioxane at room temperature for 24 h, sulfonamide **457** was isolated as the sole product in 64% yield.

Ring annulation of 2-(2′-acylpyrryl)- and 2-(2′-acylindolyl)aziridines **411** with trifluoroacetic acid in acetonitrile formed pyrroloimidazoles **461** and imidazoindole **462**, respectively (Schemes 164 and 165).[170] The cyclization was

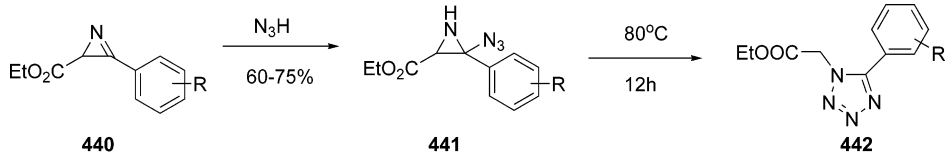
Scheme 155



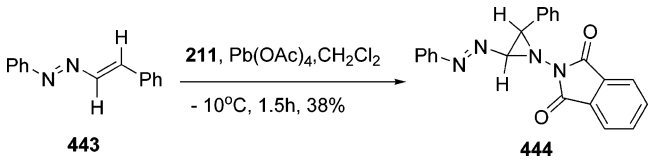
Scheme 157



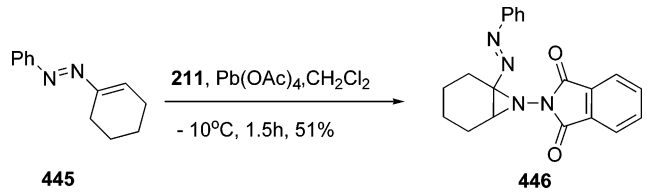
Scheme 158



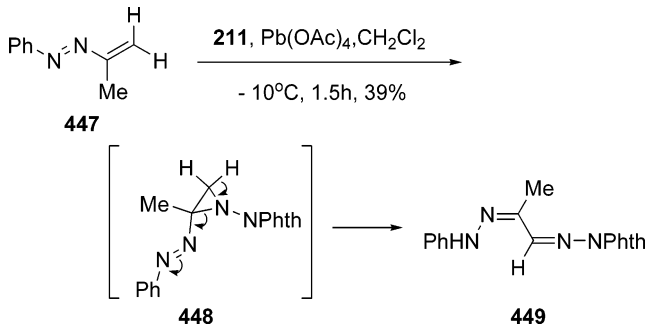
Scheme 159



Scheme 160



Scheme 161



initiated by protonation of the carbonyl group in aziridines **411** followed by intramolecular nucleophilic attack forming the bicyclic aziridines **460** (Scheme 164). Protonation of the hydroxyl group creates a carbenium ion after expulsion of water, and this initiates a ring opening, a further retro-Claisen reaction, and double bond shifts.

The aziridines **419** and **422** have been studied for lithiation at the methine position (N−CH−benzotriazole).[175] Accordingly, the aziridine **419** was treated with *n*-butyllithium and *n*-butyl bromide to form 1-phenyl-2-butyl-2-(benzotriazol-1-yl)-3-(4-chlorophenyl)aziridine **463** in good yield (Scheme 166). It is noteworthy to mention here that direct lithiation at the α-CH position of an amine is difficult, and indeed, attempted lithiation of the α-methine proton of several *N*-(α-aminoalkyl)benzotriazoles had failed previously. 2-(1-Benzotriazolyl)aziridines **419** underwent addition onto dimethylacetylenedicarboxylate by carbon−carbon bond breaking, forming the pyrrole derivatives **465** via trapping of the azomethine ylides **464** (Scheme 167), whereas 1-alkyl-2-(2-benzotriazolyl)aziridines **422** with no substituent at C-3 afforded the pyrrole derivatives **466** by carbon−nitrogen bond cleavage (Scheme 168). The alkaline hydrolysis of diethyl 1-*n*-butylpyrrole-2,3-dicarboxylate **466** (R = Bu) afforded 1-*n*-butylpyrrole-2,3-dicarboxylic acid (**467**). A similar reaction of 1-cyclohexyl-2-(2-benzotriazolyl)-2-methylaziridine (**468**) also led to pyrrole derivative **469** by carbon−nitrogen bond cleavage (Scheme 169).

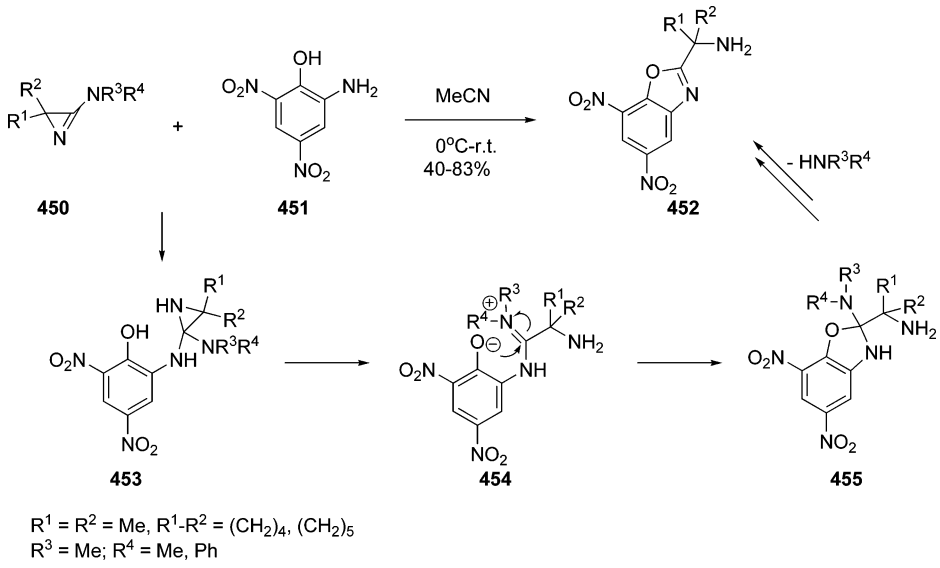
C-Nitrogen-substituted aziridines are precursors of amino acids and some other biologically important heterocyclic compounds. As mentioned before, *N*-unsubstituted aziridines that bear an amino group at the ring carbon(s) are scarce, although the presence of aromatic azaheterocycles on the aziridine ring carbon provides stability to the ring. The presence of the strong electron-withdrawing nitro group on the ring carbon also imparts stability to the aziridine ring. The lithiated anions of 2-azaheteroarylaziridines undergo ring opening followed by cycloaddition reactions, constituting an important method for the synthesis of pyrrole derivatives. No paper could be found on the application of 2-nitroaziridines in synthesis. 2-Azidoaziridines might be useful synthons for the synthesis of a tetrazole ring system.

6. C-Sulfur-Substituted Aziridines

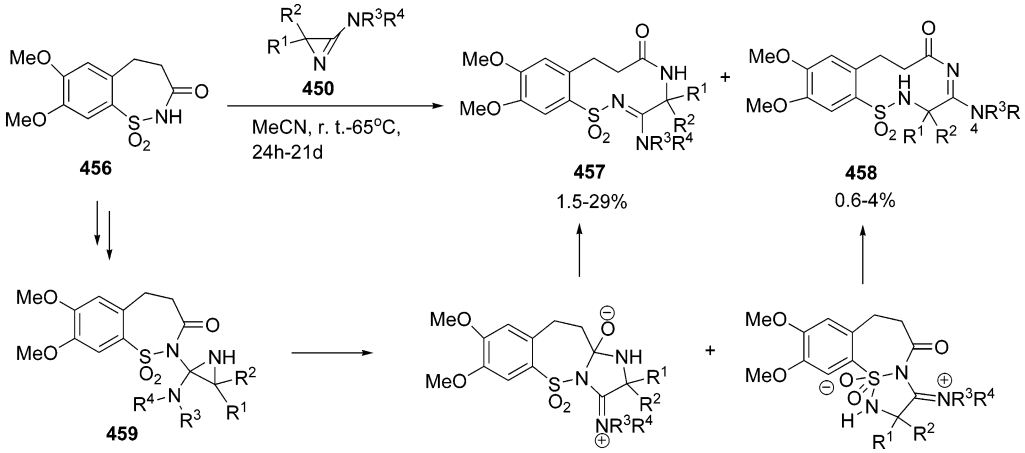
6.1. Introduction

Sulfur-containing functional groups are well-known for imparting biological activity to these compounds. The

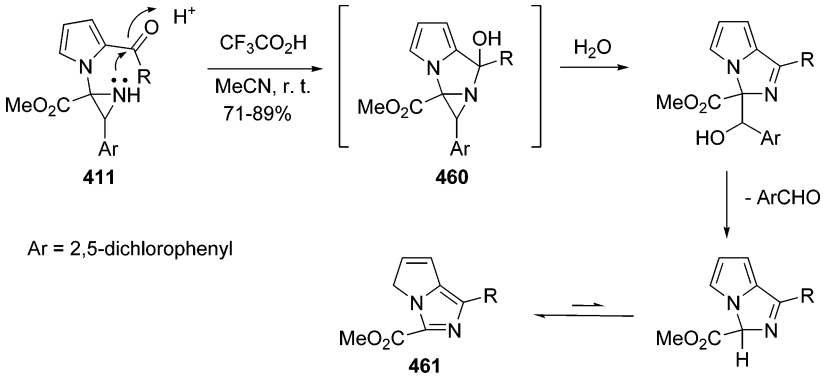
Scheme 162



Scheme 163

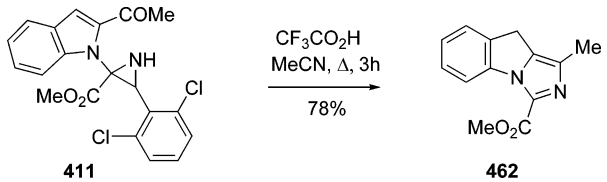


Scheme 164



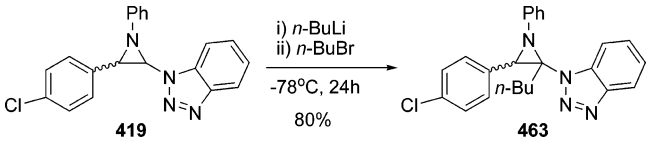
discovery of the famous antibiotic thienamycine has given impetus to studies on sulfur-functionalized small heterocycles.[189−191] *C*-Sulfur-substituted aziridines are precursors for the synthesis of sulfonic acid analogues of amino acids and sulfur-containing large ring compounds. The common methods for the synthesis of *C*-sulfur-substituted aziridines include cyclization of the suitably substituted alkenes, reactions of imines with diazoalkanes, addition of sulfur nucleophiles across the carbon−nitrogen double bond of azirines, and transformation of halogen-substituted aziridines.

Scheme 165

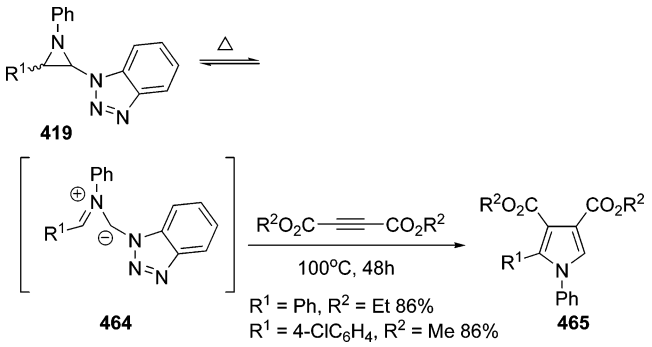


The metalation of such aziridines offers attractive routes for the synthesis of diverse types of products including carbon-functionalized aziridines, pyrroles, and quaternary amines.

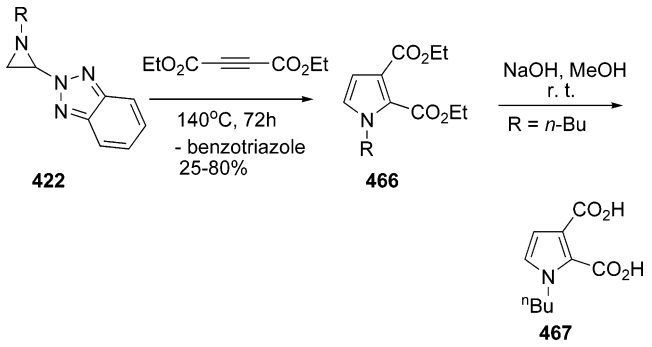
Scheme 166



Scheme 167

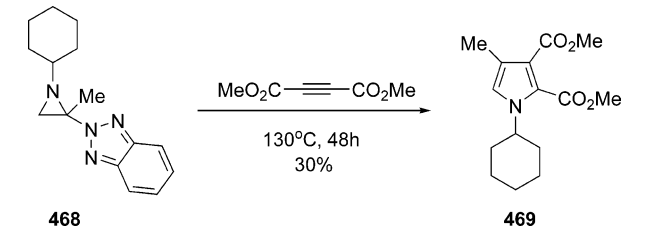


Scheme 168

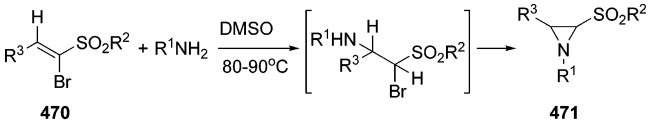


R = *n*-pentyl, *i*-Bu, *n*-decyl, *n*-Bu

Scheme 169



Scheme 170



R^1 = *n*-hexyl, *t*-Bu, Et, cyclohexyl, *i*-Pr, benzyl
R^2 = *n*-Bu, n-decyl, Ph, Me, *i*-Pr
R^3 = H, Me, Ph

6.2. Synthesis

6.2.1. Reactions of Olefins

The nucleophilic addition of amines onto the carbon−carbon double bond of 1-bromoalkene sulfones **470** followed by cyclization of the resulting α-bromoamines constitutes a common method for the preparation of aziridine-2-sulfonates **471** (Scheme 170).[192−195]

N-Hydroxy-*N*-arylpivalamides have been used as nitrogen-transfer reagents in the synthesis of *C*-sulfur-substituted aziridines from vinylsulfinylbenzene. The reaction of vinylsulfinylbenzene with *N*-hydroxy-*N*-phenylpivalamide (**472**) in the presence of a chiral catalyst **473** (Scheme 171) afforded 1-phenyl-2-benzenesulfinylaziridine (**474**).[196] Recently, the formation of (*R*)-4-(2-phenylsulfinyl)aziridine-1-yl)phenol (**477**) has been reported in 77% isolated yield and 82% ee by the reaction of vinylsulfinylbenzene with *N*-hydroxy-*N*-(4-hydroxy)phenylpivalamide (**475**) in the presence of a new chiral phase-transfer catalyst **476** (Scheme 172).[197] This catalyst was derived from the cinchona alkaloid **478** (Scheme 173). The molecular assembly in the catalyst during chiral exchange has been attributed to the formation of an ion pair between the quaternary ammonium ion and the *N*-acyloxy anion, with the quinoline part of the catalyst serving as a platform for the aromatic ring of the substrate. Another approach has been accomplished by the addition of hydroxamic acids onto electron-deficient olefins, resulting in either 2-(phenylsulfinyl)aziridines[198] or 2-(phenylsulfonyl)aziridines.[199]

Recently, the conjugate addition products of (*S*)-*N*-(α-methylbenzyl)hydroxylamine have been described to undergo an efficient diastereoselective 3-exo-*tet* ring closure reaction after *O*-acylation affording 2- and 2,3-disubstituted-*N*-alkylaziridines in good to excellent yields.[200]

6.2.2. Reactions of Oximes and Imines

Bis(methanesulfonyl)isonitrosomethane (**479**) reacts with diazomethane under anhydrous conditions (Scheme 174) to afford 1-hydroxy-2,2-bis(methanesulfonyl)aziridine (**480**).[201] Addition of the α-halosulfonyl carbanions and α-halosulfinyl carbanions, generated through lithiation of chloromethanesulfonylbenzene and halomethanesulfinylbenzene, respectively, to imines (Schemes 175 and 176) is a convenient method for the preparation of 1,3-diaryl-2-(benzenesulfonyl)-aziridines **481** and 1,3-diaryl-2-(benzenesulfinyl)aziridines **482**.[13,202] The reaction of optically active (1-chloroalkyl)-sulfinyltoluene **483** with *N*-benzylidene-4-methoxyaniline afforded optically active 1-(4-methoxyphenyl)-3-phenyl-2-alkyl-2-(4-methylbenzenesulfinyl)aziridines **484** in good overall yields (Scheme 177).[203]

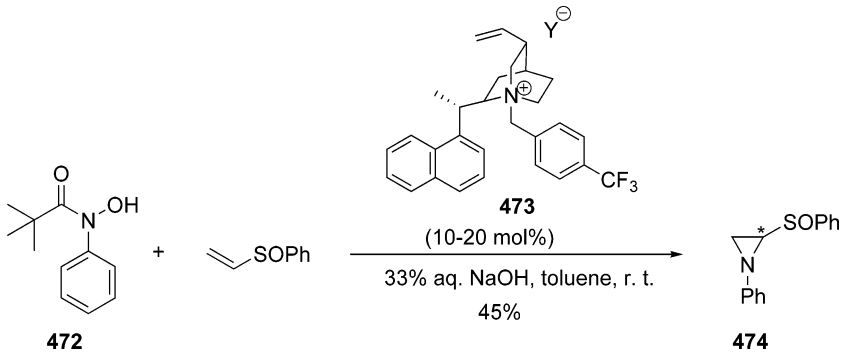
6.2.3. Additions across Azirines

The formation of *C*-sulfur-substituted aziridines **485** has been achieved by the addition of sulfur nucleophiles onto the carbon−nitrogen double bond of 2,2-dimethyl-3-phenyl-2*H*-azirine (**6**) (Scheme 178).[204,205] Thiols are also known to add onto the carbon−nitrogen double bond of methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate (**73**), forming aziridine-2-carboxylates **486** (Scheme 179).[53] A complete diastereoselectivity is observed in the addition of thiophenol to chiral azirine **487**, forming 2-(phenylthio)aziridine **488**.[171,206] The attack of thiophenoxide occurs on the *Si* face of the azirine conformer (Scheme 180). 2*H*-Azirine-3-carboxamide **489** reacted with thiophenol to afford the anticipated 2-(phenylthio)aziridine **490** (Scheme 181).[207]

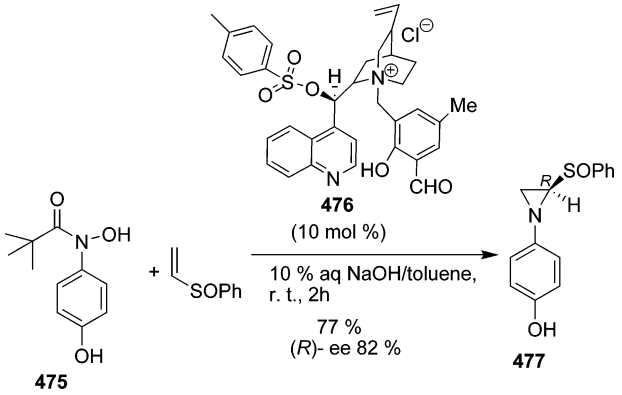
6.2.4. Photochemical Methods

The photolysis of *trans*-β-azidovinyl 4-methylphenylsulfone (**491**) in ethanol gave *trans*-2,3-ditosylaziridine (**493**) (Scheme 182).[208] The product is obtained by the addition of *p*-toluenesulfinic acid across azirine **492**. The *p*-toluenesulfinic acid is generated in the reaction medium by partial hydrolysis of the azirine. This has been confirmed by carrying out photolysis in the presence of another sulfinic

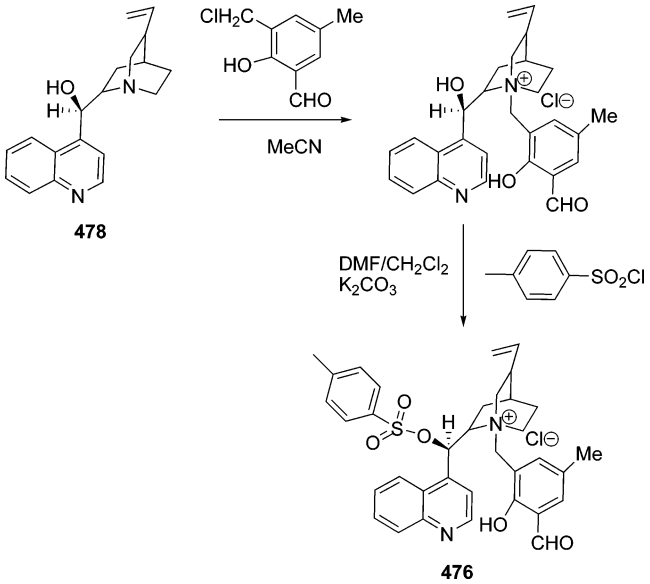
Scheme 171



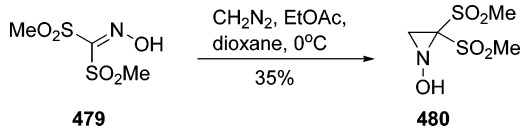
Scheme 172



Scheme 173



Scheme 174



acid, that is, benzenesulfinic acid, which afforded 2-(benzenesulfonyl)-3-tosylaziridine **494** by incorporation of the benzenesulfinic acid.

Irradiation of *N*-acylthiobenzamide **495** with UV light in benzene[209] and in solid state[210] led to the formation of aziridine-2-thiols **496** (Scheme 183). The latter compounds, however, suffered ring opening to afford thioketones **497** as the final product. The formation of aziridine-2-thiols **496** was unambiguously established by acetylation at low temperature, providing 1-benzoyl-3-methyl-2,3-diphenylaziridin-2-yl ethanethioate (**498**).

6.2.5. Transformations of Aziridines

As mentioned earlier, 2-haloaziridines are relatively stable compounds and have been subjected to functional group transformations.[76,77] The reaction of 2-chloro-1,3-diphenylaziridine (**147**) with sodium benzenethiolate forming 1,2-diphenyl-3-(phenylthio)aziridine (**321**) has been mentioned before in section 4.3.1 on the reactivity of the 2-chloroaziridines (Scheme 106). The reduction of 1-benzyl-2-chloro-3-methyl-2-(benzenesulfonyl)aziridine (**499**) and 2-bromo-1-ethyl-3-phenyl-2-(benzenesulfonyl)aziridine (**502**) using Na−Hg and lithium aluminum hydride, respectively, is known to form the corresponding 2-(benzenesulfonyl)aziridines **500** and **503** (Schemes 184 and 185).[211] The use of Na−Hg in the case of **499** also resulted in removal of the phenylsulfonyl group, forming 1-benzyl-2-methylaziridine (**501**).

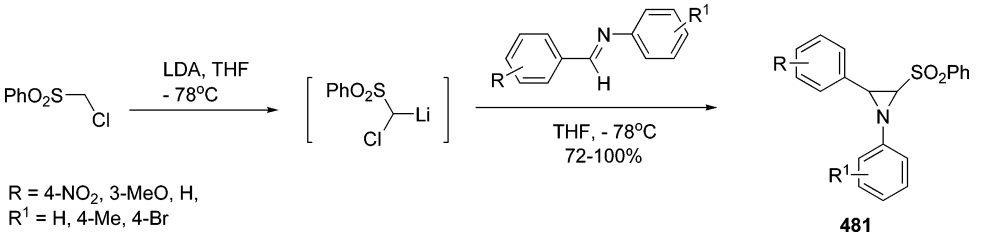
The reductive cleavage of the sulfur−oxygen bond in 2-(benzenesulfonyl)aziridine **504** using DIBAH afforded *trans*-1-isopropyl-2-methyl-3-(phenylthio)aziridine (**505**) (Scheme 186).[211] A similar reaction of 2-(benzenesulfonyl)-1-isopropylaziridine **506** with Ph_3P-CCl_4 furnished 1-isopropyl-2-(phenylthio)aziridine (**507**) (Scheme 187).[212]

The reaction of 2-(benzenesulfonyl)aziridines with carbon tetrahalides in the presence of potassium hydroxide led to the formation of 2-halo-2-(benzenesulfonyl)aziridines **499** and **502** (Scheme 188).[213] A similar reaction of 2-(1-methylethanesulfonyl)aziridines **508**, however, afforded the product **510** with both side-chain substitution and ring hydrogen substitution, and a compound **509** with only side-chain substitution (Scheme 189). The dehydrohalogenation in the side chain of compound **509** using potassium *tert*-butoxide furnished 2-sulfonylaziridine **511**, containing an olefinic linkage in the side chain (Scheme 190). The 2-halo-2-(benzenesulfonyl)aziridines were unreactive toward potassium cyanide or sodium thiophenoxide. However, aziridines such as **512** and **513** were reduced to 2-(benzenesulfonyl)-aziridines by sodium methoxide, sodium ethoxide, or sodium thioethoxide (Scheme 191).

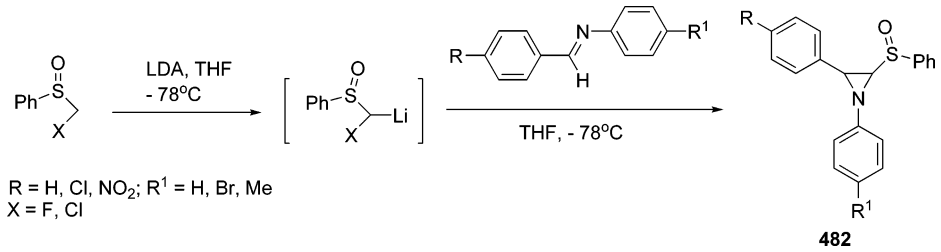
The hydroxyl group in 1-hydroxy-2,2-bis(methanesulfonyl)aziridine (**480**) has been methylated using diazomethane to form 1-methoxy-2,2-bis(methylsulfonyl)aziridine (**514**) (Scheme 192).[201]

Synthesis and applications of metalated aziridines (aziridinyl anions), generated from 2-sulfonyl- and 2-sulfinylaziridines, have been thoroughly investigated.[214] The reaction of 1-tosyl-2-(trifluoromethyl)aziridine (**515**) with *n*-butyllithium

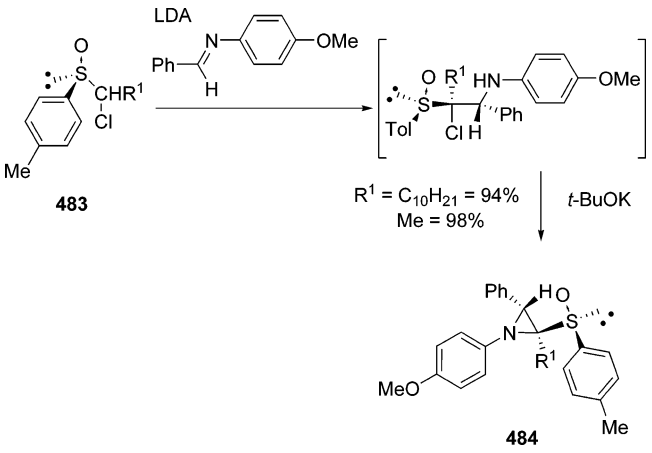
Scheme 175



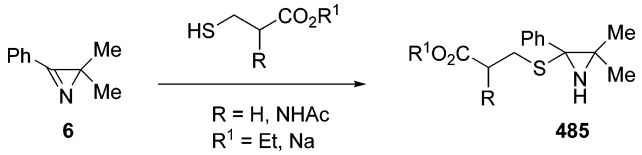
Scheme 176



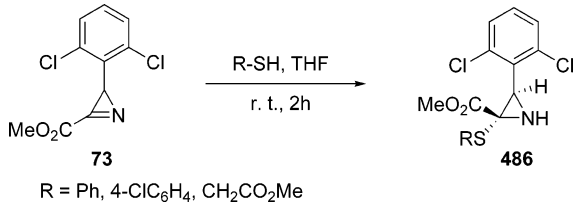
Scheme 177



Scheme 178

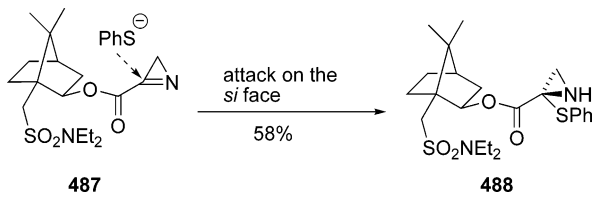


Scheme 179

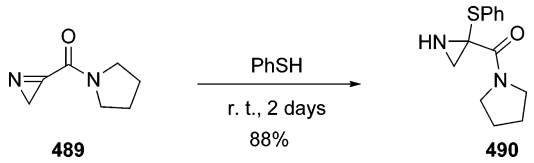


in tetrahydrofuran at −100 °C formed aziridinyl anion **516** (Scheme 193).[215] This anion reacted with carbon, sulfur, and silicon nucleophiles to afford the corresponding functionalized aziridines. For example, it reacted with 1,2-diphenyldisulfane to give (2*S*)-2-(phenylthio)-1-tosyl-2-(trifluoromethyl)-aziridine (**517**) (Scheme 193). Lithiated 2-sulfonylaziridines **518** have been alkylated to give 2-alkyl-2-sulfonylaziridines **519** (Scheme 194).[13] The *C*-lithiated aziridine, generated in situ as a result of tin−lithium exchange in aziridine **520**, underwent intermolecular thiomethylation with 1,2-dimethylsulfane to form 1-(triphenylmethyl)-2-(methylthio)aziridine

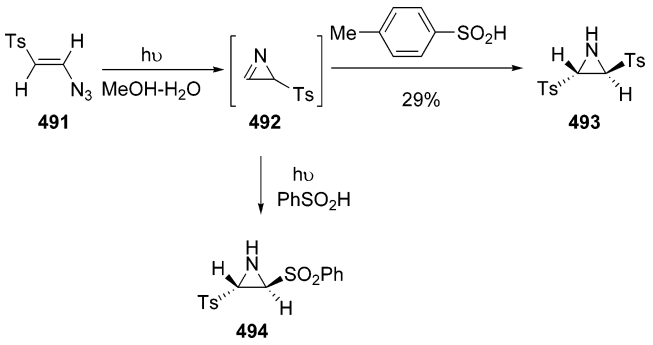
Scheme 180



Scheme 181



Scheme 182



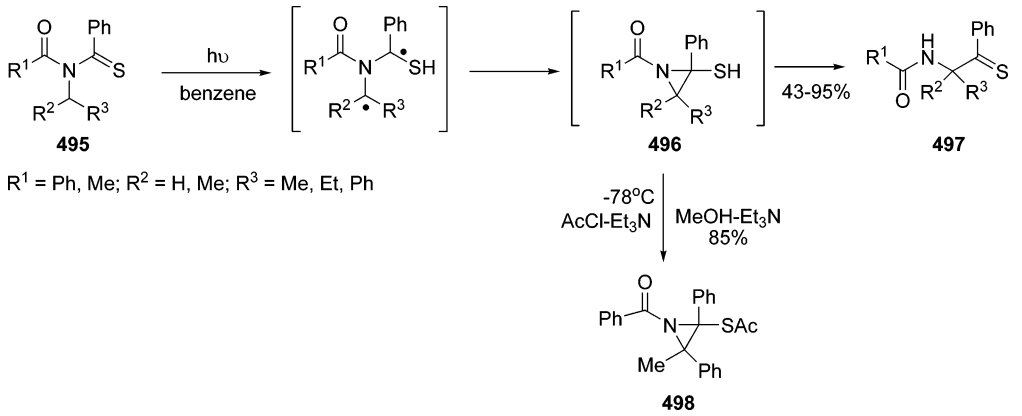
521 and 1-(triphenylmethyl)aziridine **522** together with a complex mixture of other products (Scheme 195).[216]

6.3. Reactivity of Sulfur-Substituted Aziridines

The preceding section described the reactions of *C*-sulfonylaziridines leading to sulfur- or sulfur- and halogen-substituted aziridines. However, the reductive cleavage of the carbon−sulfur bond in 2-(benzenesulfonyl)aziridines **471** with Na−Hg offers an attractive route to the synthesis of 2-alkyl- and 2-aryl-substituted aziridines **351** (Scheme 196).[217]

2-Alkyl-1,3-diaryl-2-(benzenesulfonyl)aziridines **519** afforded pyrrole derivatives **465** (Scheme 197) by normal carbon−carbon bond cleavage and [2+3]-dipolar cycloaddition with dimethyl acetylenedicarboxylate.[13]

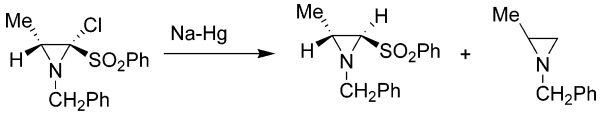
Scheme 183



495 **496** **497** **498**

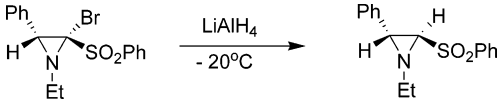
R^1 = Ph, Me; R^2 = H, Me; R^3 = Me, Et, Ph

Scheme 184



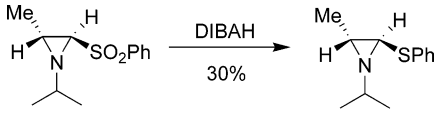
499 **500** (90%) **501** (10%)

Scheme 185



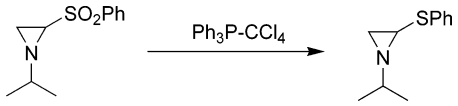
502 **503**

Scheme 186



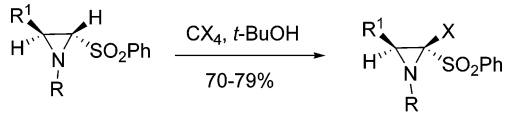
504 **505**

Scheme 187



506 **507**

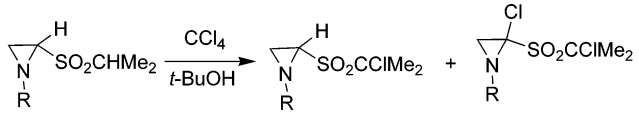
Scheme 188



R = Et, *i*-Pr, *t*-Bu, CH_2Ph
R^1 = H, Me, Ph

499. X = Cl
502. X = Br

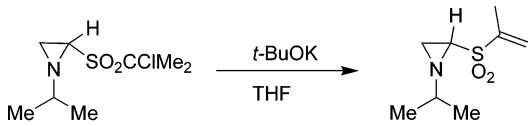
Scheme 189



508 **509** **510**

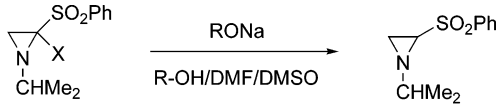
R = *i*-Pr, benzyl

Scheme 190



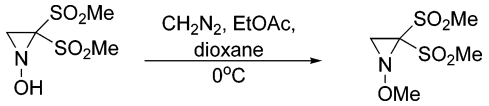
509 **511**

Scheme 191



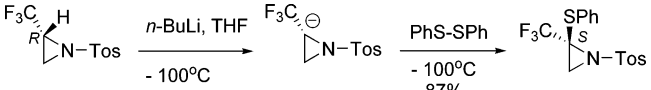
512. X = Cl, **513**. X = Br
R = Me, Et

Scheme 192



480 **514**

Scheme 193



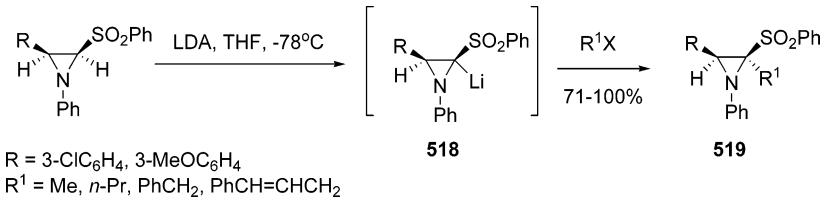
515 **516** **517**

Thermal ring opening of 2-halo-2-phenylsulfonyl aziridines **512** and **513** on heating in a sealed tube at 60 °C for 4−6 h has been observed to form *N*-substituted α-haloacetamides **523** and α-phenylsulfonylacetamides **524** (Scheme 198).[213] The formation of the products involved cleavage of the carbon−nitrogen bond (Scheme 199) with elimination of either halides or benzenesulfinates.

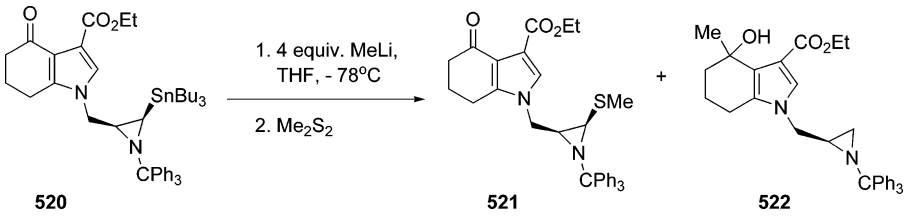
The reaction of sulfinylaziridines with ethylmagnesium bromide is known to form aziridinylmagnesium[218] via a ligand exchange reaction.[18] Treatment of sulfinylaziridines **525** with *tert*-butyllithium at −100 °C to room temperature afforded lithiated aziridines **526**, which have been quenched with various electrophiles such as carbonyl compounds, forming desulfinylated aziridines **527** (Scheme 200).[219−221] The chiral aziridine **527** was used in the synthesis of chiral α,α-dialkylamino esters **528** (Scheme 201) and amides **529** (Scheme 202). Aziridinylmagnesium derivatives prepared according to this method also reacted with alkyl halides in the presence of Cu(I) to offer a new methodology for the preparation of amines **530** and **531** (Scheme 203).[222,223] These amines served as a precursor for quaternary *β*-amino acids **532** (Scheme 203).[203]

C-Sulfur-substituted aziridines are precursors for the synthesis of sulfonic acid analogues of amino acids and sulfur-containing large ring compounds. These compounds are conveniently synthesized by cyclization of aminoalk-

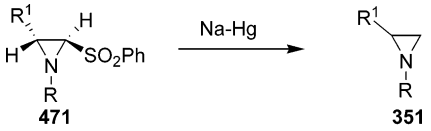
Scheme 194



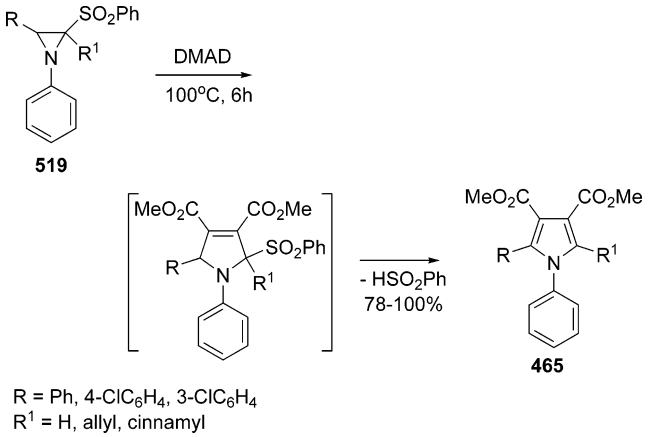
Scheme 195



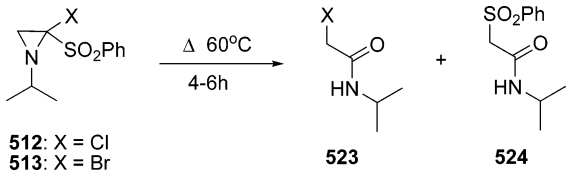
Scheme 196



Scheme 197



Scheme 198



enesulfonates and vinyl sulfonamide. Other important methods of synthesis involve the addition of nitrenoids to vinylsilanes and additions across azirines and imines. A complete diastereoselectivity is observed in the addition of benzenethiol to a chiral azirine because of the preference of thiophenoxide to attack the azirine on its *Si* face.[171,206] An enantioselective synthetic methodology has been developed using chiral catalysts.[196,197] The 2-benzenesulfonyl group on the aziridine ring carbon can be reduced with a variety of reagents affording other aziridine derivatives. Similarly, metalation of the 2-sulfonylaziridines offers attractive routes for the synthesis of diverse types of compounds including amines and β-amino acids with a quaternary carbon atom.

7. *C*-Phosphorus-Substituted Aziridines

7.1. Introduction

Aziridine-2-phosphonates constitute a biologically important class of heterocyclic compounds, and the antibacterial activity of 1-alkoxycarbonyl-2-phosphonoaziridines **4** has already been described (Figure 1). Mass spectral studies of 2-arylaziridin-2-yl phosphonates have shown that cleavage of either a carbonyl group or $PO(OR)_2$ from the molecular ion is the primary pathway of fragmentation.[224] The ring opening reactions of such aziridines lead to the synthesis of phosphonic analogues of amino acids, which have shown interesting biological properties. These amino acids can then be tethered into biologically active peptides as antibacterial agents[225,226] and herbicides.[227] α-Aminophosphonates have been used as haptens for the generation of catalytic antibodies,[228,229] whereas β-aminophosphonate derivatives have been used for the preparation of enzyme inhibitors, agrochemicals, or pharmaceuticals.[230]

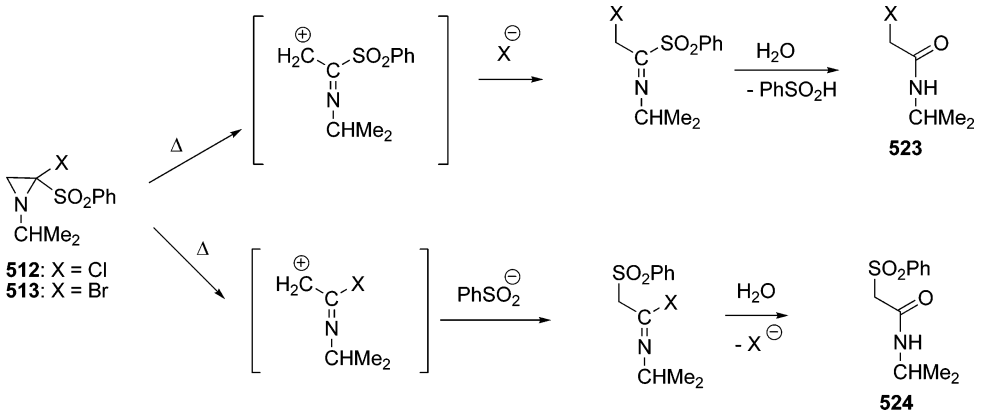
7.2. Synthesis

Most of the pathways described so far for the synthesis of other 2-heteroatom-substituted aziridines such as cyclizations, olefin−nitrene reactions, carbene−imine additions, azirine additions, and Darzen reaction have also been employed for the synthesis of *C*-phosphorus-substituted aziridines. The synthesis and biological activity of azaheterocyclic phosphonates published up to 2003 have been described previously.[231] This section therefore describes only the representative examples of the common methods of their synthesis and updates the studies on synthesis from 2003 onward.

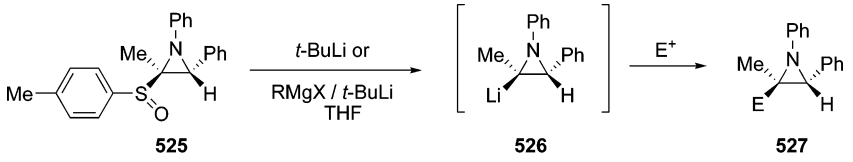
7.2.1. Cyclization Reactions

Intramolecular nucleophilic displacement of a hydroxyl or a halogen group is the most straightforward method for the synthesis of aziridine-2-phosphonates. The synthesis of optically active diethyl 1-tosylaziridine-2-phosphonates **536** and **540** is reported from both (*R*)- or (*S*)-phosphonoserine diethyl esters **533** and **537**, by a series of reactions involving *N*-tosylation, *O*-mesylation, and cyclization by intramolecular displacement of the mesyl group by the amino group in protected (*R*)- or (*S*)-phosphonoserine diethyl esters **535** and **539** using sodium hydride (Schemes 204 and 205).[232] *O*-Mesylation was preferred to a second tosylation because

Scheme 199

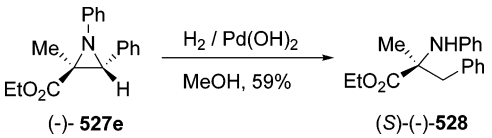


Scheme 200

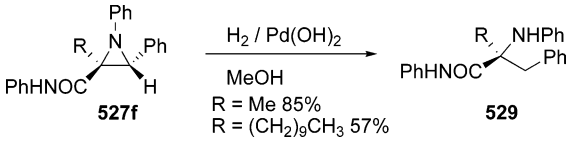


527. E = a. CD_3O, b. CH(OH)Ph, c. CH(OH)Et, d. C(OH)(Me)(Me), e. CO_2Et, f. PhNHCO

Scheme 201



Scheme 202



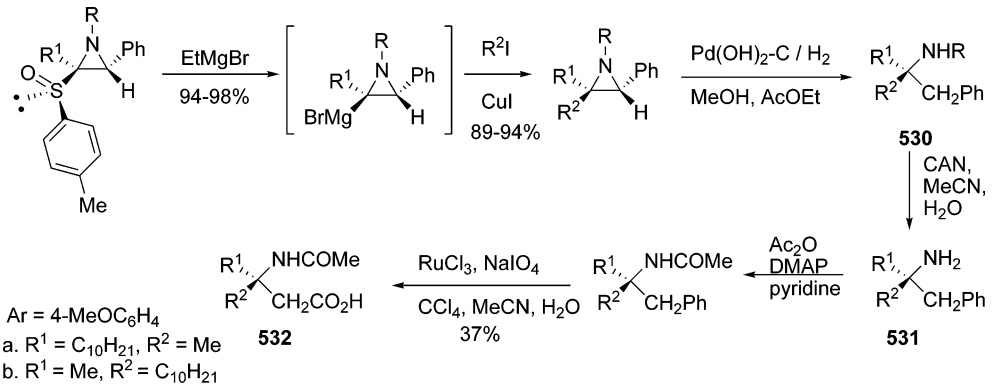
of convenient purification of the former before cyclization. The aziridines, stable at ambient temperature with no sign of degradation even after 1 year, served as chiral synthons for the synthesis of β-substituted-α-aminophosphonates.

The use of enantiopure sulfinimines in a Darzen-type synthesis of 2-methyl-2-phosphonoaziridines[233] and 3-phenyl-2-phosphonoaziridines has been investigated,[234,235] and the diastereoselectivity in the synthesis of β-aminophosphonates has been observed to depend on the sulfenyl auxiliary.[236] (*S*)-(+)-Sulfinimines **541**, having 4-methoxyphenyl and phenyl groups, in reaction with 2 equiv of diethyl iodomethylphosphonate in the presence of 2 equiv of LiHMDS at −78 °C afforded aziridines (*Ss*,2*S*,3*R*)-(−)-**542** as single diastereoisomers in 75−78% yield (Scheme 206). Sulfinimines having an electron-withdrawing group such as a 4-(trifluoromethyl)phenyl or 4-nitrophenyl group gave a complex mixture of products consisting of the aziridine diastereomers and isomeric mixtures of β-amino-α-iodophosphonates **543**. The reaction of aziridines **542** with 2 equiv of methylmagnesium bromide at −78 °C readily resulted in the removal of the (2,4,6-trimethylphenyl)sulfinyl group, affording the corresponding *N*-unsubstituted (2*S*,3*R*)-(−)-aziridine-2-phosphonates **544** in good yields (Scheme 207).

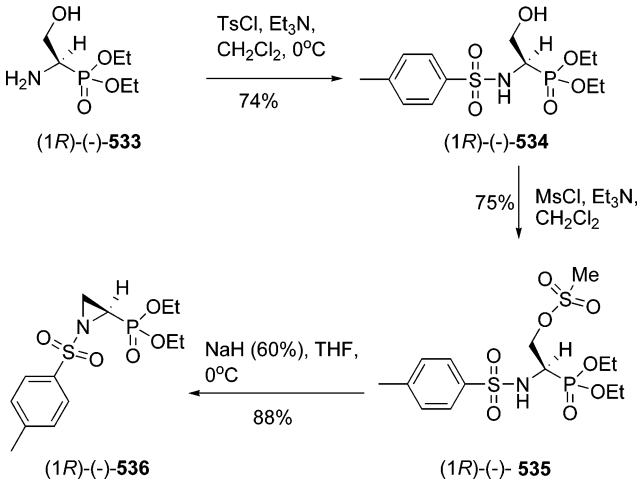
7.2.2. Additions across Azirines

2-Phosphorylazirines and azirine-3-phosphonates are expected to show a behavior similar to that of their isoelectronic analogues azirine-2-carboxylates and can be useful as synthons for phosphorus-substituted aziridines.[237] A base-mediated Neber reaction of diethyl 2-(tosyloxyimino)-propylphosphonate (**545**) leads to an asymmetric synthesis of 2*H*-azirine-3-phosphonates **546** (Scheme 208).[238] Reduction of azirine-3-phosphonates **546** with sodium borohydride in ethanol afforded 1-unsubstituted *cis*-aziridine-2-phospho-

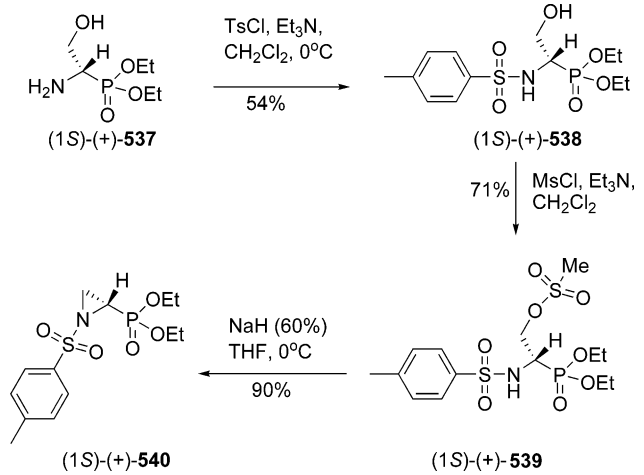
Scheme 203



Scheme 204

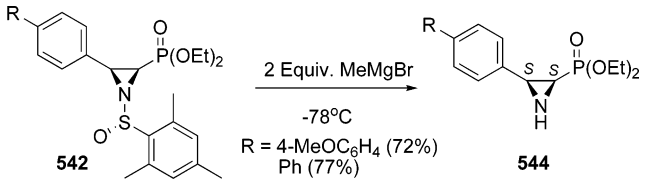


Scheme 205

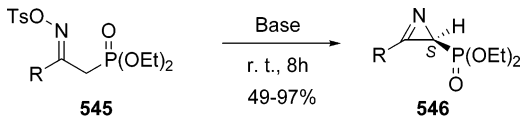


nates **547** (Scheme 209). Treatment of these aziridines with *p*-toluenesulfonyl chloride in triethylamine afforded 1-tosylaziridine-2-phosphonates **548** (Scheme 209) with enhanced reactivity. The reaction of 2-(diphenylphosphoryl)-2*H*-azirines **546** with acyl chlorides at room temperature led to an exclusive formation of *trans*-1-acyl-3-chloro-2-(diphenylphosphoryl)aziridines **549** (Scheme 210).[237] The exclusive formation of the trans product suggested that the approach of chloride to the cyclic compound from the opposite side of the phosphoryl group was preferred because of the high exocyclic dihedral angle and the presence of the bulky phosphorus group. Addition of several nucleophiles such as Grignard reagents (Scheme 211), phthalimide (Scheme 212), imidazole (Scheme 213), and benzenethiol (Scheme 214) to 2-phosphorylazirines and azirine-3-phosphonates is reported to lead to a diastereoselective synthesis of trans-functionalized 2-phosphorylaziridines and aziridine-2-phosphonates **550**−**553** (Schemes 211−214).[239] The addition of benzenethiol was the first reported addition of a sulfur nucleophile to a phosphorylated and metalated azirine.

Scheme 207

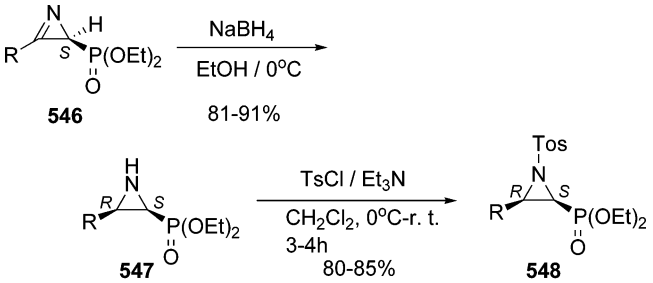


Scheme 208



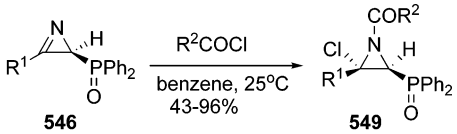
Bases = Sparteine, quinidine, hydroquinidine, quinine, polymer-supported amines.
R = Me, Et, Ph

Scheme 209



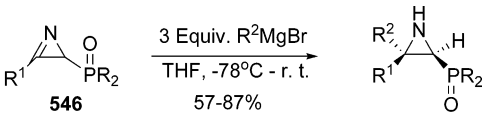
R = Me, Et, Ph

Scheme 210



R^1 = Me, Et, Ph
R^2 = Ph, Me, $(CH_2)_4CH{=}CH_2$, $CH{=}CH_2$

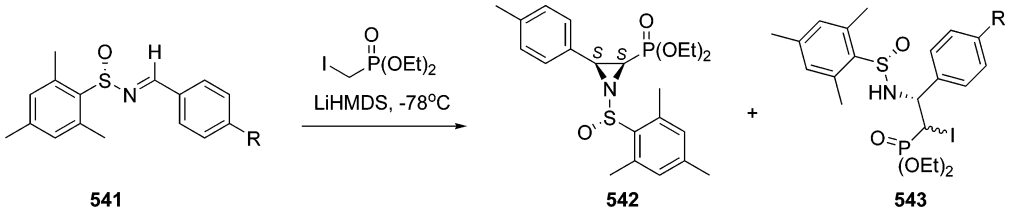
Scheme 211



R = OEt, Ph; R^1 = Me, Ph; R^2 = Et, Bn, $CH_2CH{=}CH_2$, 2-ethyl-[1,3]-dioxolanyl

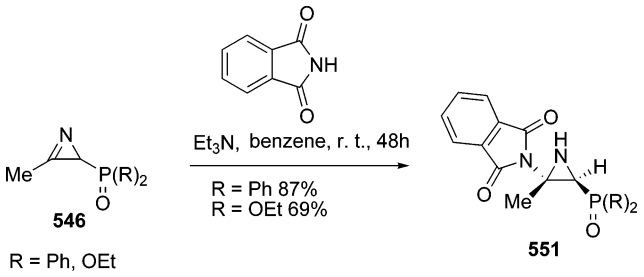
Azirine-2-phosphonates undergo cycloaddition with 100 equiv of 2,3-dimethylbutadiene or *trans*-piperylene in 2−4 days at room temperature to furnish optically pure bicyclic aziridine-2-phosphonates **554** and **555**, respectively (Scheme 215).[240] The reaction of an azirine-2-phophonate with 1-methoxy-3-trimethylsilyloxybuta-1,3-diene (**556**) at room

Scheme 206

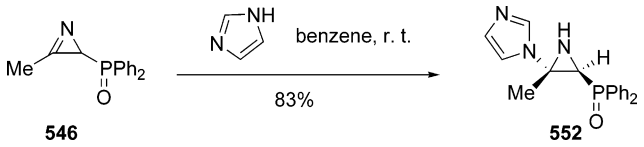


R = H, methoxy, trifluoromethyl, nitro

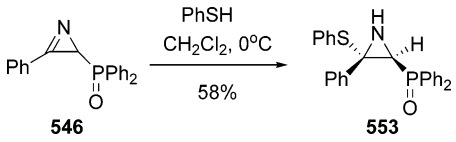
Scheme 212



Scheme 213



Scheme 214



temperature, however, required only 5 equiv of the latter and 8 h to afford a single isomer of the bicyclic aziridine-2-phosphonate **557** in quantitative yield (Scheme 216).

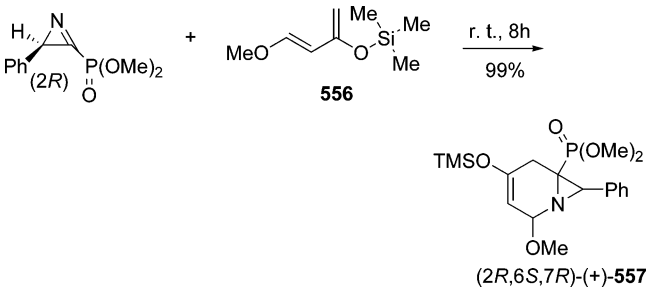
7.2.3. Reactions of Olefins with Nitrenes

The addition of nitrenes to the carbon−carbon double bond of vinylphosphonates **558** is known to form aziridine-2-phosphonates **559** (Scheme 217).[241] One of the most common precursors of a nitrene is *N*-{[(4-nitrobenzyl)sulfonyl]oxy}-carbamate (**189**), which is used in combination with a base such as triethylamine, calcium oxide, or potassium carbonate. Although copper complexes and rhodium carboxylates have been used frequently to generate carbenoids,[242−244] there are very few reports of their use to generate analogous nitrenoids. The phosphoramidate **560** was used as nitrogen source in the presence of rhodium carboxamide as an oxidant for the reaction with 4-methylstyrene to synthesize aziridine-1-phosphonate **561** (Scheme 218).[245] [*N*-(*p*-Toluenesulfonyl)-imino]phenyliodonane (PhI = NTs) (**562**) was used as a nitrogen source in the presence of copper triflate as a catalyst for the reaction with vinyl phosphonates **558** in acetonitrile to form 1-(*p*-tosyl)aziridine-2-phosphonates **563** (Scheme 221).[246]

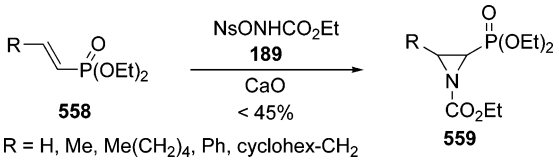
7.2.4. Additions across Imines

The reaction of 1-phosphono-2-azadienes **564** with diazomethane afforded 1-vinyl-2-phosphonoaziridines **565** in good yield (Scheme 220).[247] Although it is known that carbenes add onto an olefinic double bond, resulting in cyclopropanes, no cyclopropanation was observed in this case due to the electron-withdrawing effect of the phosphonate

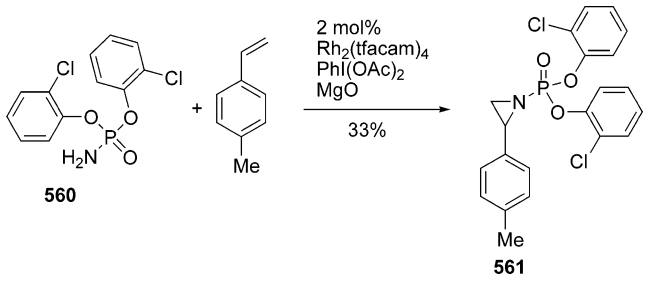
Scheme 216



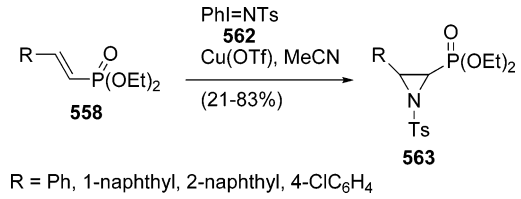
Scheme 217



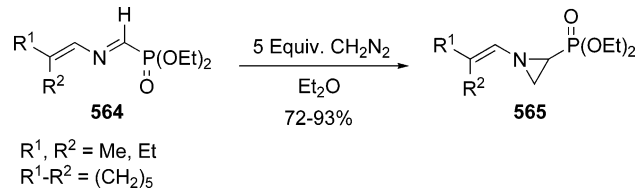
Scheme 218



Scheme 219

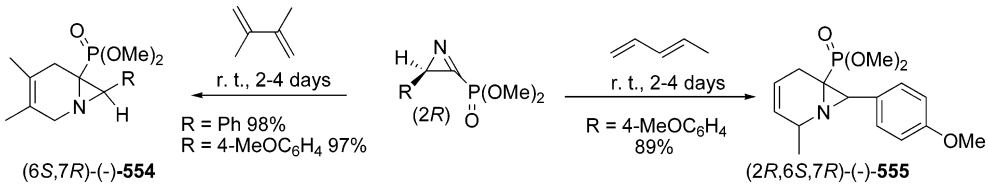


Scheme 220

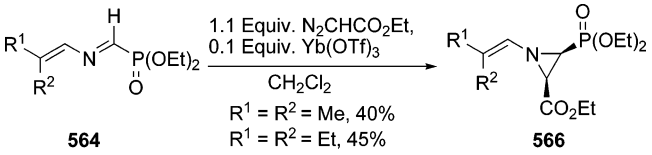


group. Similar reactions of 1-phosphono-2-azadienes with ethyldiazoacetate occurred in the presence of ytterbium(III) triflate as a catalyst to afford 3-(diethyoxyphosphoryl)-aziridine-2-carboxylates **566** (Scheme 221).[248] The reaction with trimethylsilyldiazomethane (TMSD) was possible in toluene under reflux to form 3-(trimethylsilyl)aziridin-2-ylphosphonates **567** (Scheme 222). 1-Aryl-1-phosphono-2-aza-1,3-dienes were, however, not susceptible to aziridination under these conditions.

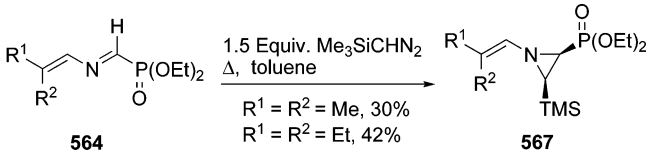
Scheme 215



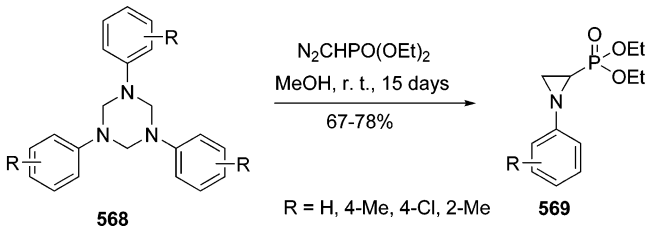
Scheme 221



Scheme 222



Scheme 223



The reaction of diethyl diazomethanephosphonate with 0.33 equiv of hexahydro-1,3,5-triazines **568** as precursors of reactive *N*-methyleneamines in methanol afforded the corresponding 1-arylaziridine-2-phosphonates **569** in good yields (Scheme 223).[249] The cycloaddition of the diazo compound to an in situ generated carbon−nitrogen double bond formed the corresponding triazolines, which afforded the aziridine-2-phosphonates after extrusion of N_2. It is significant to note that the reaction did not require any catalyst.

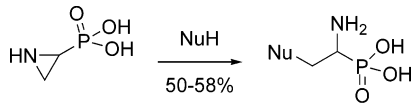
The Darzen reaction of lithiated 2-(1-chloroethyl)oxazoline **570** with *N*-benzylidene-*P*,*P*-diphenylphosphinic amide (**571**) afforded 1-diphenylphosphinoyl-2-oxazolinylaziridines **572** and **573** (Scheme 224).[250] The oxazolinyl group is a promising electron-withdrawing group to facilitate the metalation of aziridines.[251,252] The lithiation of *N*-diphenylphosphinoyl-2-oxazolinylaziridine **572** using lithiumdiisopropyl amide and the reaction of the lithiated intermediate with D_2O afforded a 2-phosphinoylaziridine **576** as a result of nitrogen to carbon migration of the phosphinoyl group besides the anticipated deuterated products **574** and **575** (Scheme 224).

Very recently, a simple and efficient stereoselective synthesis of fluoroalkyl-substituted aziridine-2-phosphine oxides and -phosphonates by diastereoselective addition of methoxide, imidazole, benzenethiol, and Grignard reagents to functionalized ketoxime-phosphine oxides and -phosphonates has been described.[253]

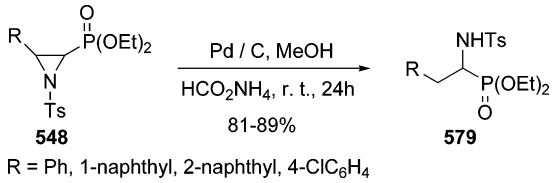
7.3. Reactivity of *C*-Phosphorus-Substituted Aziridines

Both displacement via lithiation forming another aziridine derivative and ring opening with diverse types of reagents forming phosphorus analogues of amino acids and amino acid esters are known. Also, trapping of lithiated aziridine-2-phosphonates leading to the formation of 2-chloroaziridinyl phosphonates has been reported.[125] Regioselective ring opening of aziridine-2-phosphonic acid **577** with a variety of nucleophiles led to the formation of 2-substituted 1-aminoethanephosphonic acids **578** (Scheme 225) in 50−58% yields.[254] Catalytic hydrogenation of 1-tosylaziridine-2-phosphonates **548** and 1-(4-methoxyphenyl)aziridine-2-phosphonamide **580** occurred in a regioselective manner to give α-aminophosphonates **579** (Scheme 226) and α-aminophosphonamide **581** (Scheme 227), respectively.[246,255] Acid hydrolysis of α-aminophosphonamide **581** afforded the corresponding phosphonic acid, which was isolated as dimethyl phosphonate **582** using diazomethane.

Scheme 225

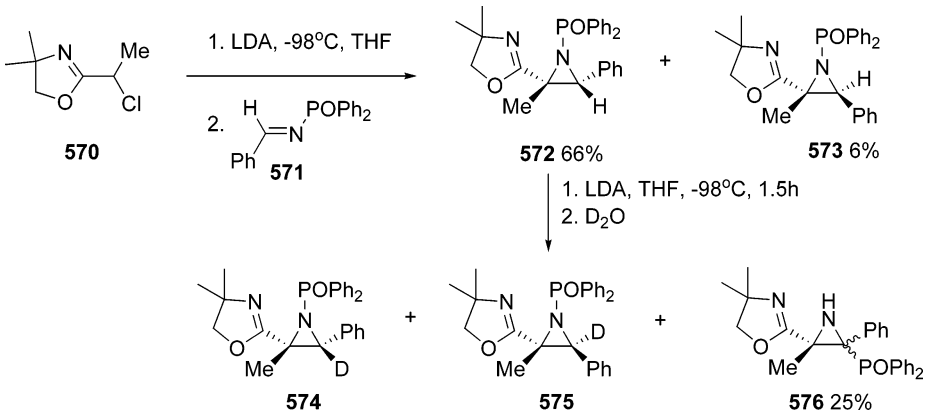


Scheme 226

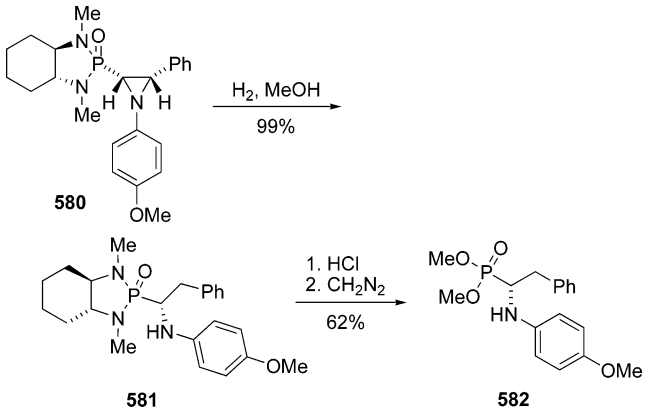


The enantioenriched aziridine-2-phosphonates react with carbon nucleophiles (cyanide and malonate ions) (Schemes 228 and 229), nitrogen nucleophiles (sodium azide, phenethylamine, and imidazole) (Schemes 230 and 231), sulfur nucleophiles (*n*-propylthiol and triphenylmethyl mercaptan) (Schemes 232 and 233), and hydride ($NaBH_4$), fluoride (*n*-tetrabutylammonium fluoride), and phosphorus nucleophiles

Scheme 224



Scheme 227



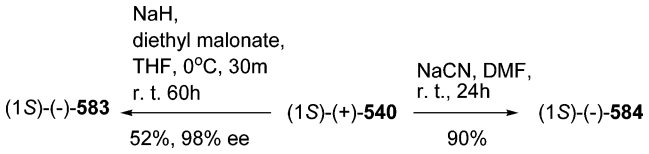
(lithium diethylphosphite) (Schemes 234 and 235), allowing the rapid formation of a variety of β-substituted α-amino phosphonates **583**−**593** in either the (*R*)- or (*S*)-configurations in yields ranging from 33 to 90%.[232] In the case of thiol nucleophiles, the use of a stoichiometric amount of tri-*n*-butylphosphine was necessary to suppress the formation of disulfide **590** and to increase the yields of the corresponding sulfide products **589** (60−80%). The reactions of malonate, azide, phenethylamine, hydride, and fluoride ions afforded products having ee values up to 98%.

Catalytic hydrogenation of diphenylphosphorylaziridines and aziridine-2-phosphonates **550** by palladium on carbon and ammonium formate in boiling ethanol afforded β-aminophosphine oxides **594** and β-aminophosphonates **595** by means of a regioselective ring opening of the N−C(2) bond of the ring (Schemes 236 and 237).[239] A different behavior was observed in the hydrogenolysis of the aziridines bearing a methyl and a benzyl substituent at C-2 and those bearing an allyl and a phenyl substituent at C-2, which afforded α-aminophosphonates **596** and **597** by N−C(3) bond cleavage (Schemes 238 and 239). A similar result was obtained in 1-tosylaziridine-2-phosphonates **563** (Scheme 240), forming α- and β-aminophosphonates **598** and **599**.[237]

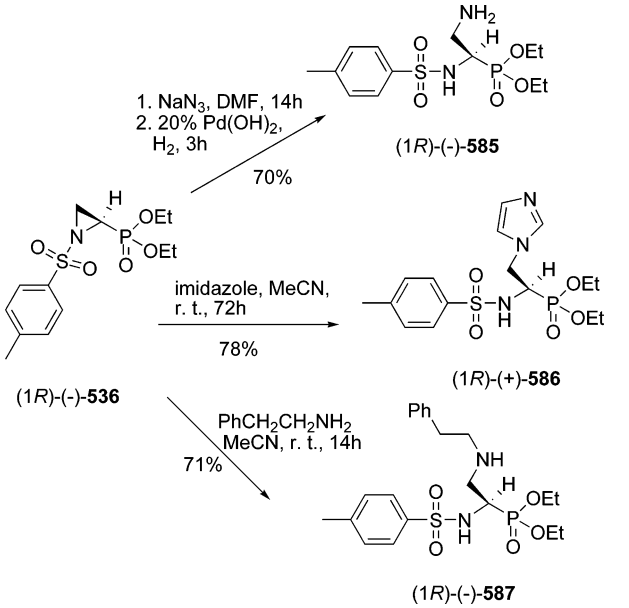
The reaction of 2-phenyl-2*H*-azirine-3-phosphonate (**546**) with benzenethiol is reported to afford stable 3-phenyl-3-thiophenylaziridine-2-phosphonate (**553**) (Scheme 214), whereas 2-methyl-2*H*-azirine-3-phosphonates **600** afforded intermediate 3-methyl-3-(phenylthio)aziridine-2-phosphonates, which cleaved regioselectively to give the allylamines **601**. Because these products were not stable enough, they were converted into the hydrochloride salts **602** (Scheme 241).[239]

The catalytic hydrogenation of chiral aziridine-2-phosphonates **554** over Pd/C/H_2 in methanol resulted in the formation of a new class of compounds, that is, quaternary piperidine phosphonates (2*S*)-(−)-**603** in 47−49% yield as the major products and pyridine derivatives **604** as minor products in 0−28% yield (Scheme 242).[240] However, no pyridine derivative was observed when the reaction was

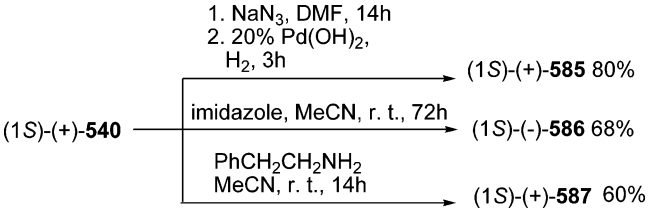
Scheme 229



Scheme 230

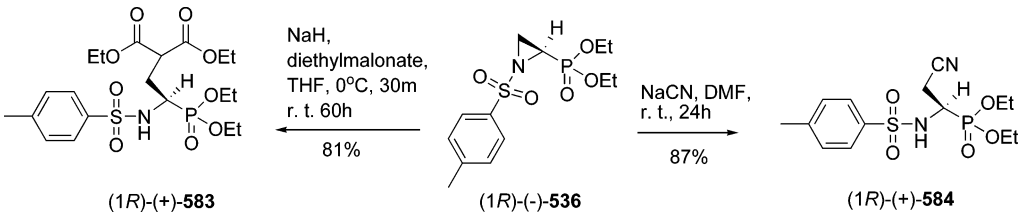


Scheme 231

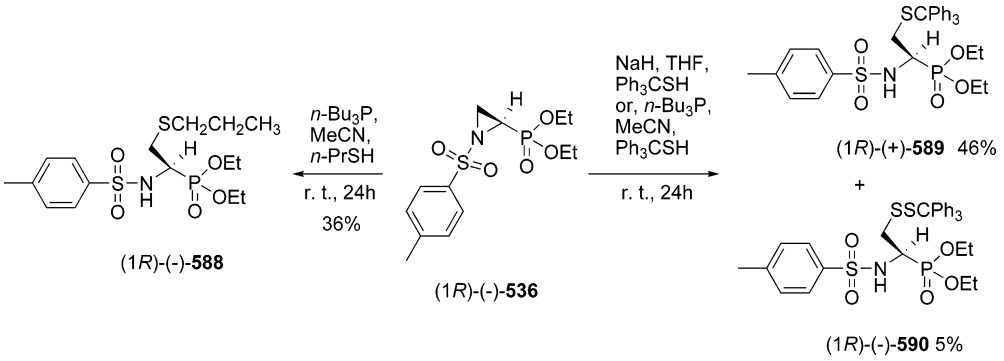


carried out in tetrahydrofuran, and the yield of the major product reached up to 80%. The major product was formed by cleavage of the C(7)−N bond in the aziridines. The minor products resulted from hydrogenolysis of the major product **603**. The 3,4 carbon−carbon double bond thus remained intact in each case. However, in the case of the aziridines **555**, the carbon−carbon double bond was reduced to afford a bicyclic aziridine **605** along with a complex mixture of products using the same reagents in methanol (Scheme 243). When tetrahydrofuran was used in place of methanol, piperidine phosphate **606** resulted from C(7)−N bond cleavage in **605**. This was demonstrated by means of the formation of **606** by hydrogenolysis of **605**. Prolonged treatment of either **605** or **606** in methanol afforded piperidine **607**. The reduction of the carbon−carbon double bond in **555** and not in **554** has been attributed to comparatively

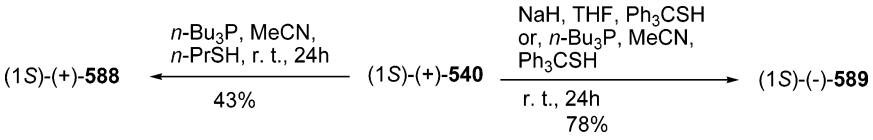
Scheme 228



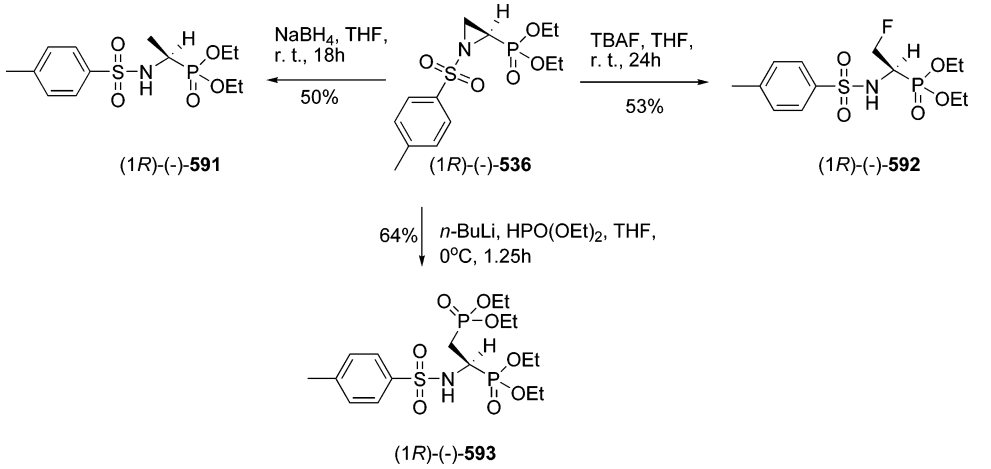
Scheme 232



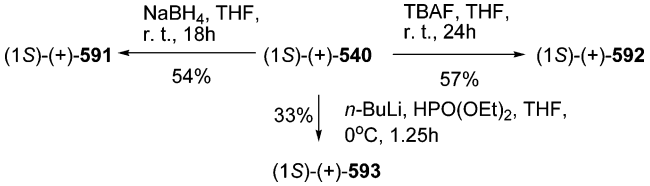
Scheme 233



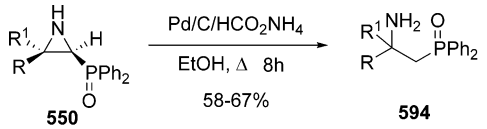
Scheme 234



Scheme 235

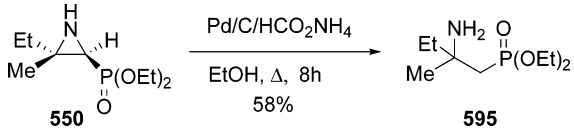


Scheme 236

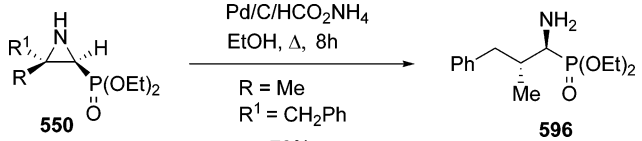


R = Me, R^1 = Et; R = Me, R^1 = n-C_3H_7; R = Ph, R^1 = n-C_3H_7

Scheme 237



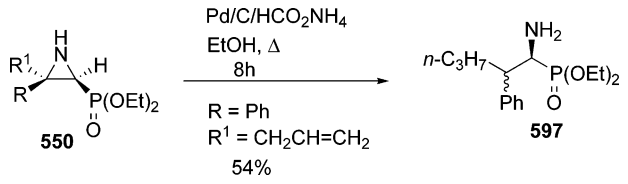
Scheme 238



less steric hindrance in the former. The formation of piperidine derivative **607** has been suggested by elimination of dimethyl phosphate from piperidine derivative **606**. Hydrogenolysis of the bicyclic aziridine-2-phosphonate **557** using the same method resulted in decomposition. However, exposure of this compound to silica gel in chloroform for 3 days afforded the bicyclic aziridine **608** (Scheme 244).

C-Phosphorus-substituted aziridines constitute a biologically important class of heterocyclic compounds. Recently, some significant advancement has been made in the development of methodologies for the enantioselective synthesis of aziridine-2-phosphonates by intramolecular cyclization of phosphoserine diethyl ester and the cycloaddition of the azirine-2-phosphonates. Due to the electron-withdrawing ability of the phosphonate group, alkenes containing this group serve as an important substrate for reaction with carbene precursors. *C*-Phosphorus-substituted aziridines undergo displacement via lithiation, forming another aziridine derivative, and ring opening with diverse types of reagents, forming phosphorus analogues of amino acids and amino acid esters. Both α- and *β*-aminophosphonates can be obtained as biologically relevant compounds by ring opening

Scheme 239



reaction depending on the other substitutent present on the ring.

8. C-Silicon-Substituted Aziridines

8.1. Introduction

C-Silylaziridines known in the literature are mainly 2-(trialkylsilyl)aziridines. Despite their potential as synthetic intermediates, this class of aziridines has not so thoroughly been investigated as compared to their oxygenated counterparts trialkysilyloxiranes.[256−259] *C*-Silylaziridines undergo stereospecific nucleophilic ring opening, often with high regioselectivity.[260] Aziridines can be readily metalated and reacted with electrophiles, offering access to an even broader range of *C*-functionalized aziridines.[261] They also undergo desilylative elimination, forming azirines and azirine-derived products.

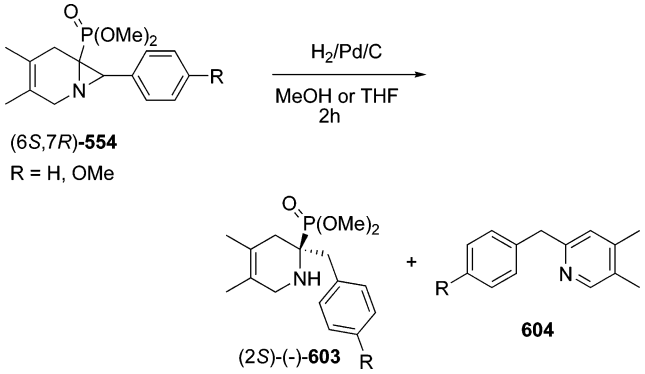
8.2. Synthesis

The most common approaches to the synthesis of *C*-silylaziridines are the reactions of vinylic silanes with azides or other nitrogen-providing reagents and the reactions of imines with trimethylsilyldiazomethane. The latter compound is a versatile, simple to use, and commercially available reagent.[262]

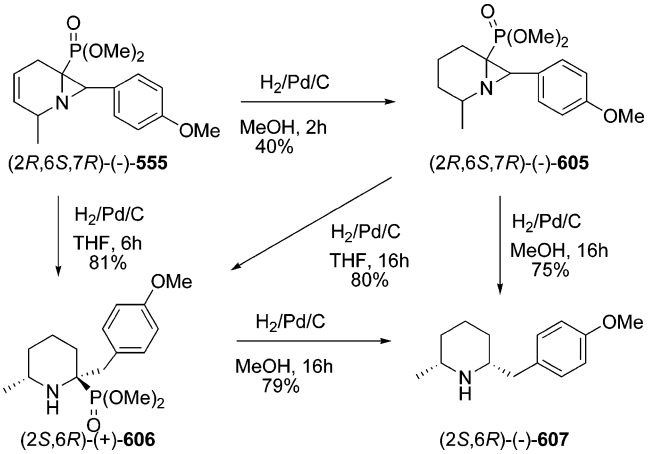
8.2.1. Reactions of Vinylsilanes

One of the early papers on the synthesis of α-silicon-containing aziridines reports the reaction of vinylsilane (**609**) with phenylazide under thermal conditions, forming 1-phenyl-2-silylaziridine **610** only in 11% yield (Scheme 245).[263] Later it was observed that this method was useful for the synthesis of only 1-aryl-2-silylaziridines and not for the synthesis of 1-alkyl-2-silylaziridines.[264] A similar methodology was used to synthesize 1-aryl- and 1-heteroaryl-2-(trimethylsilyl)aziridines (Scheme 246).[265,266] In these reactions, the aromatic azides including phenyl azide undergo a 1,3-dipolar cycloaddition with vinylsilanes **611** to give the intermediate triazolines **612**, which then lost nitrogen to give the corresponding 2-(trimethylsilyl)- and 2-(trimethoxysilyl)aziridines **613**.[266,267] 2-Benzothienylazide afforded the desired aziridine in 93% yield after 5 days, whereas 3-benzothienylazide afforded approximately the same yield (95%) after 15 days. Aromatic azides with electron-withdrawing groups, such as

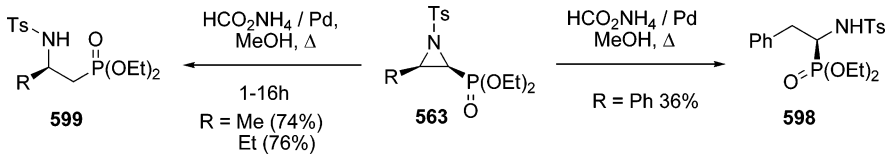
Scheme 242



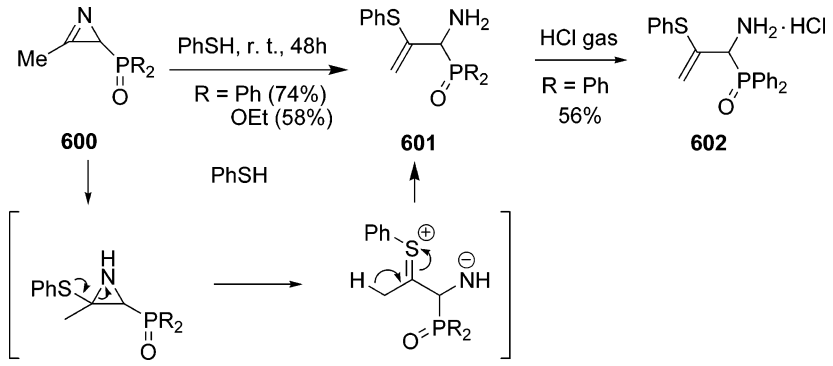
Scheme 243



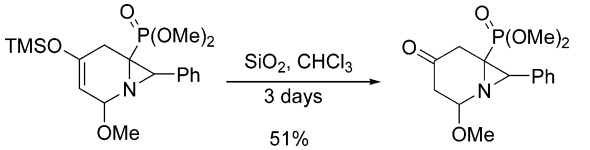
Scheme 240



Scheme 241

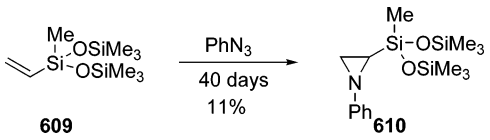


Scheme 244



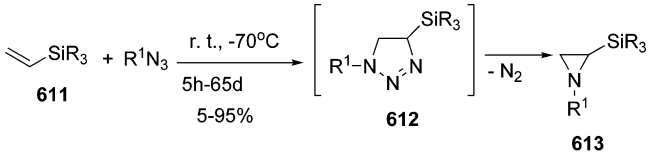
(2*R*,6*S*,7*R*)-(+)-**557** (2*R*,6*S*,7*R*)-(+)-**608**

Scheme 245



609 **610**

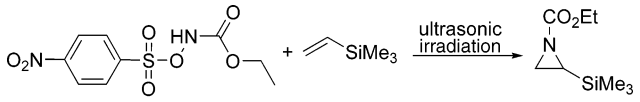
Scheme 246



611 **612** **613**

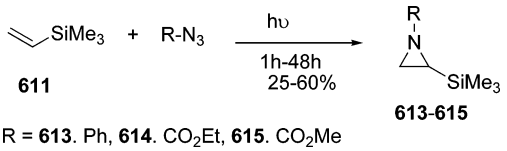
R = Me, OMe
R^1 = Ph, 4-MeC_6H_4, 4-MeOC_6H_4, 4-CNC_6H_4, 4-$NO_2C_6H_4$, 2-and 3-benzothienyls

Scheme 247



189 **614**

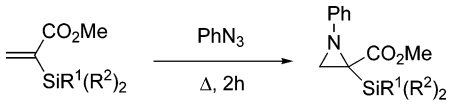
Scheme 248



611 **613-615**

R = **613**. Ph, **614**. CO_2Et, **615**. CO_2Me

Scheme 249



616 **617**

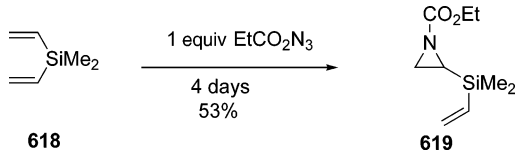
$R^1 = R^2$ = Et 70%; R^1 = Ph, R^2 = Me 88%

4-cyano and 4-nitro, reacted smoothly, whereas those with electron-donating groups, such as 4-methoxy and 4-methyl, afforded poor yields (10%) at room temperature even after 65 days. However, an increase in temperature to about 70 °C increased the yields up to 80%.

Addition of ethoxycarbonyl nitrene, generated from ethyl (4-nitrophenylsulfonyloxy)carbamate (**189**) using a phase-transfer catalyst or ultrasonic irradiation, to vinylsilane (Scheme 247) led to the formation of 1-ethoxycarbonyl-2-(trimethylsilyl)aziridine (**614**).[268] Later this reaction was extended to vinyl-, α-bromovinyl- and (*β*-methoxycarbonylvinyl)triakylsilanes.[269]

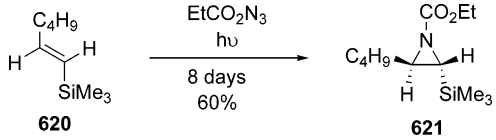
The photochemical reaction of organic azides with alkenes is thought to involve a nitrene intermediate. A range of 2-(trimethylsilyl)aziridines **613**−**615** has been synthesized by photochemical reaction of alkoxycarbonyl azide and phenyl azide with vinylsilane (**611**) and silyl acrylates **616** (Schemes 248 and 249).[270] The reactions did not require any solvent and were generally completed within 1−48 h. The

Scheme 250



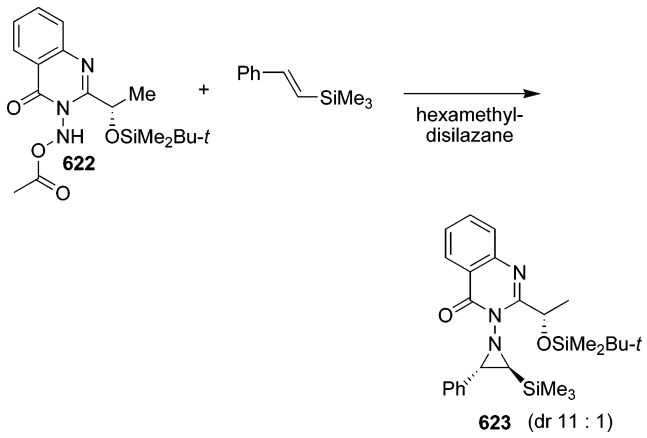
618 **619**

Scheme 251



620 **621**

Scheme 252

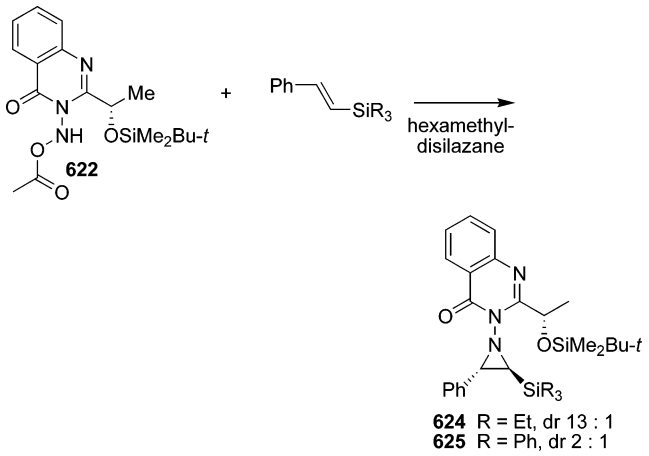


622 **623** (dr 11 : 1)

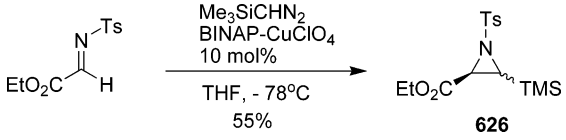
methoxycarbonyl nitrene afforded the lowest yield (25%). A thermal reaction of phenyl azide with vinylsilane (**611**) by refluxing in hexane, however, afforded a higher yield (61%) of 1-phenyl-2-(trimethylsilyl)aziridine (**613**) in comparison to the photochemical method (50%). However, the thermal reaction required 3 h for completion, whereas the photochemical reaction required only 1 h. An equimolar photochemical reaction of the ethoxycarbonyl azide with dimethyldivinylsilane (**618**) afforded α-silylaziridine **619** (Scheme 250). Retention of configuration was observed in the product, 2-butyl-1-ethoxycarbonyl-3-(trimethylsilyl)aziridine (**621**), formed from the reaction of ethoxycarbonyl azide with (*E*)-hex-1-enyltrimethylsilane (**620**) (Scheme 251), which suggested the involvement of a singlet nitrene.[271]

A chiral 3-acetoxyaminoquinazolinone **622** has been used as an aziridinating agent.[272] A highly diastereoselective synthesis of the 2-(trimethylsilyl)aziridine derivative **623** in 50% yield is reported by treatment of *β*-trimethylsilylstyrene with an enantiopure 3-acetoxyaminoquinazolinone **622** as the reagent, providing a nitrene-like intermediate in the presence of hexamethyldisilazane (Scheme 252).[273,274] The same procedure using *β*-triethylsilylstyrene afforded 2-(triethylsilyl)aziridine **624** in a slightly higher diastereomeric ratio (13:1) but in slightly lower yield (40%, Scheme 253). Using *β*-triphenylsilylstyrene, a 2:1 ratio of diastereomers of 2-(triphenylsilyl)aziridine **625** was obtained (Scheme 253). It was possible to separate the minor diastereomer by crystallization from light petroleum. The diastereoselectivity was rationalized by conformational preferences within the *t*-$BuMe_2SiOCH(Me)C{=}N$ unit in 3-acetoxyaminoquinazolinone **622,** which led to well-defined site preferences for H, Me, and *t*-$BuMe_2SiO$ in the transition state.[275] Recently this reaction has been extended to R(*β*)-substituted *E*-styrenes (R = $SiMe_3$, Me, CH_2Cl, $CHCl_2$) using (*S*)-3-acetoxyamino-

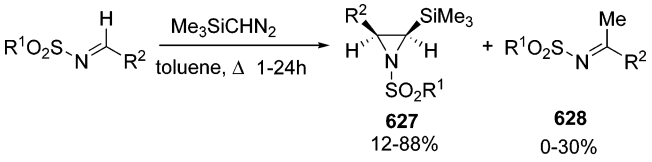
Scheme 253



Scheme 254



Scheme 255



R^1 = 4-MeC_6H_4, 4-$NO_2C_6H_4$, $PhCH_2$, 2,4,6-$Me_3C_6H_2$
R^2 = Ph, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-MeOC_6H_4, 2-naphthyl, 2-furyl, 3-pyridyl, styryl, phenethyl, *n*-pentyl, Ph

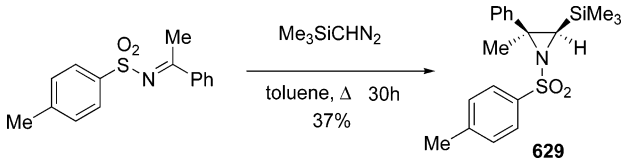
2-[1-(*tert*-butyldimethylsilyloxy)ethyl]quinazoline-4(3*H*)-one. It has been observed that the diastereoselectivity increased in the same sense from 5:1 to 20:1 as the electron-withdrawing character of R increased.[276] However, the yield decreased with the increasing electron-withdrawing character of R. A similar trend was observed using 3-acetoxyamino-2-(2,3,3-trimethylpropyl)quinazolin-4(3*H*)-one. The result was rationalized by proposing a tighter, more symmetrical transition state for the aziridination of styrenes bearing more electron-withdrawing β-substituents, which was supported by SCF calculations.

8.2.2. Reactions of Imines

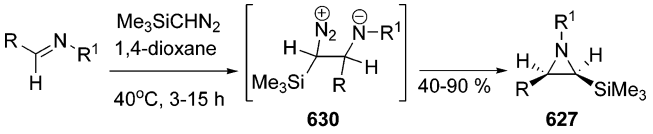
The reaction of an *N*-tosyliminoester with TMSD has been carried out in tetrahydrofuran at −78 °C to afford 2-ethoxycarbonyl-1-tosyl-3-(trimethylsilyl)aziridine (**626**) (Scheme 254).[277] Many chiral Lewis acid complexes have been used as a catalyst in this reaction. Of the various complexes used, $CuClO_4$−BINAP [2,2′-bis(ditolylphosphino)binaphthyl] afforded the highest diastereoselectivity (cis:trans 19:1) and enantioselectivity (cis ee 72%).

Electron-deficient *N*-sulfonylaldimines reacted smoothly with TMSD in refluxing toluene to give 1-sulfonyl-3-(trimethylsilyl)aziridines **627** in good yields with high cis selectivity (Scheme 255).[278] In many cases, a small amount of *C*-methylated *N*-sulfonylimine **628** was formed as minor product. The sulfonyl moiety of the imines affected both the yields and the stereoselectivity. Among those studied, the mesitylenesulfonylaldimines gave the best yield (85%) and stereocontrol (cis only). The reaction of *N*-sulfonylketimine

Scheme 256

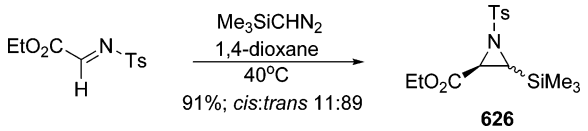


Scheme 257



R = Ph, 4-MeOPh, 4-ClPh, 4-NO_2Ph, *E*-PhCH=CH, *n*-Bu, Cy, Ph
R^1 = Ts, trimethylsilylethanesulfonyl.

Scheme 258



with TMSD also afforded the corresponding 3-(trimethylsilyl)aziridine **629**, but a very long reaction time (30 h) was required, and yet the yield was low (Scheme 256). The high cis selectivity has been explained by steric hindrance between the trimethylsilyl and the bulkier arylsulfonyl groups in the first-formed betain intermediates **A** and **B**, in which the latter would lead to a minimum steric hindrance and afford the *cis*-aziridine after rotation to the intermediate **C** and expulsion of nitrogen (Figure 4).

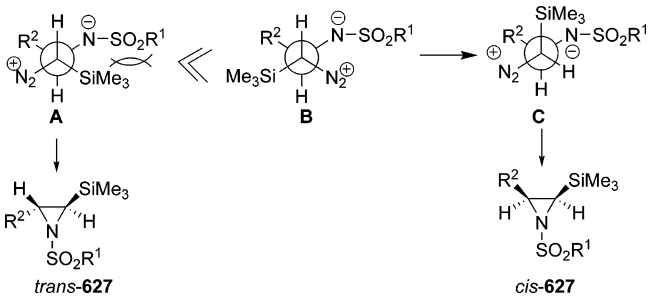


Figure 4.

In a similar reaction as described by Hori et al.,[278] Aggarwal and Ferrara have observed 1,4-dioxane as the solvent of choice (Scheme 257).[279] The former group has used the imine and TMSD in 1:1.5 molar ratio, whereas the latter group has used a 1:2.5 molar ratio of those reactants for the reaction to reach completion in a reasonable time. This reaction using the *N*-tosyliminoacetate followed a different course and afforded mainly the *trans*-(trimethylsilyl)aziridine (Scheme 258). This group also proposed the nucleophilic attack of TMSD across imines forming the betaines **630** followed by ring closure with loss of N_2 and advocated the role of both electronic and steric factors in determining the stereochemical outcome of the reaction. If the developing charges in the betaine are placed gauche to each other, the least sterically hindered transition state **631** would have the silyl group opposite the bulky imino group, and this transition state would lead to the formation of the cis isomer (**Figure 5**). An alternative mechanism, involving 1,3-dipolar cycloaddition followed by fragmentation and ring closure, was suggested for the formation of the *trans*-aziridine

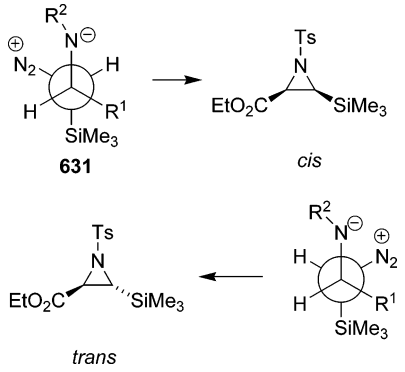
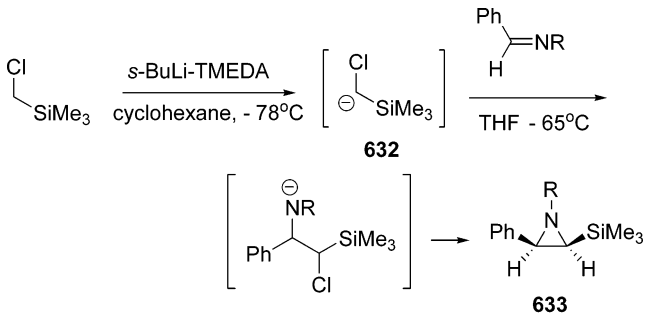


Figure 5.

Scheme 259

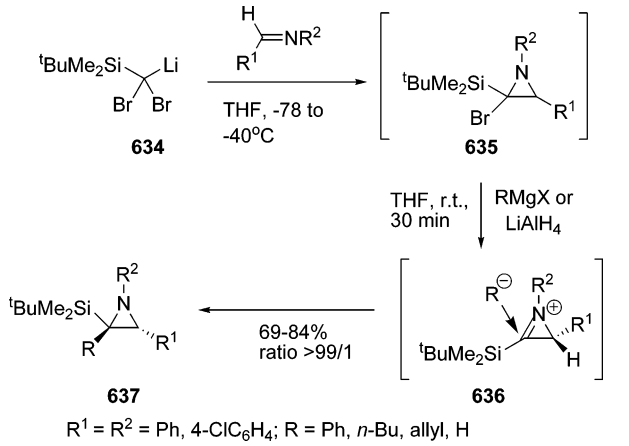


derivative in the case of the iminoester. However, the origin of trans selectivity was not clear.

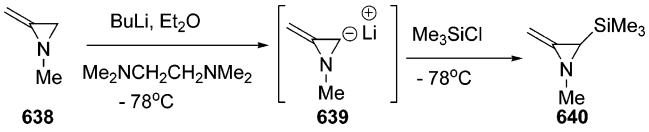
The reaction of α-silyl carbanion **632**, formed from the reaction of α-chloromethyltrimethylsilane in freshly distilled THF with a solution of *sec*-butyllithium-TMEDA in cyclohexane at −78 °C, with aromatic aldimines has been carried out in THF at about −65 °C.[270] The quenching of the reaction mixture with aqueous ammonium chloride at room temperature and workup afforded 2-(trimethylsilyl)aziridines **633** (Scheme 259). This methodology was used earlier by Cooke and Magnus for the preparation of α,*β*-epoxysilanes from the reaction of a carbonyl compound.[280] Both the reactivity of the carbanion and the stereoselectivity were observed to depend upon the substituents at the imino nitrogen. *N*-Benzylidenepropylamine gave stereoselectively the *cis*-aziridine in 53% yield, whereas *N*-benzylideneaniline afforded the corresponding aziridine in 77% yield as a 1:1 mixture of cis and trans isomers. Imines obtained from ketones and from aliphatic aldehydes failed to react with the carbanion **632**.

The reaction of aromatic aldimines (R^1 = Ar) with *tert*-butyldimethylsilyldibromomethyllithium (**634**) formed 1,3-diaryl-2-bromo-2-(*tert*-butyldimethylsilyl)aziridines **635** (Scheme 260). A nucleophilic displacement of the bromo atom in the latter aziridines using a Grignard reagent or lithium aluminum hydride led to a novel one-pot stereoselective synthesis of 1,3-diaryl-2-(*tert*-butyldimethylsilyl)-aziridines **637**.[281] The stereochemistry of the products was unambiguously established by X-ray crystallography. The displacement in the 2-bromoaziridines **635** took place by an S_N1-type process involving the cyclic iminium species **636** (Scheme 260). The attack of the nucleophile from the less hindered site was responsible for the observed stereochemistry.

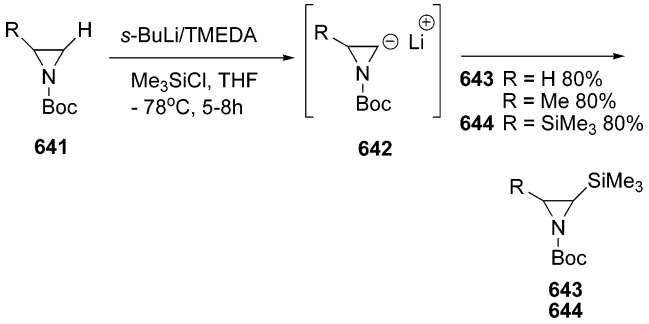
Scheme 260



Scheme 261



Scheme 262



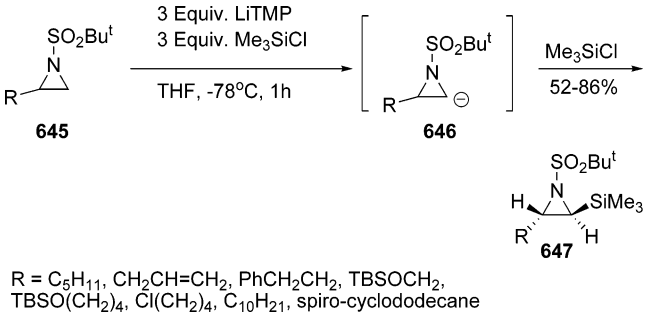
8.2.3. Transformations of Aziridines

The introduction of a silyl group onto an aziridine ring can be accomplished through a lithiated aziridine. The lithiation of 1-methyl-2-methyleneaziridine (**638**) by butyllithium in the presence of a base at low temperature generated the lithiated methyleneaziridine **639**, which reacted with trimethylsilyl chloride to form 1-methyl-2-methylene-3-(trimethylsilyl)aziridine (**640**) (Scheme 261).[282] A modification of this process by lithiation in the presence of a chiral lithium complexing agent at −120 °C, followed by trapping with trimethylsilyl chloride, constitutes a method to form enantioenriched 2-(trimethylsilyl)aziridines.[283] Furthermore, also the lithiation and alkylation of a 2-isopropylideneaziridine with trimethylsilyl chloride toward the corresponding α-silylaziridine derivative has been reported.[284]

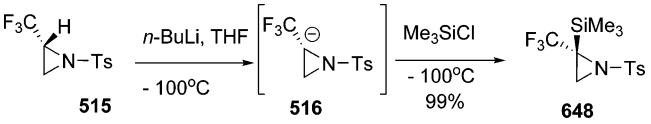
Very recently, 2-methyleneaziridinyl anions have been produced by selective deprotonation of the parent aziridine at C-3 using *sec*-BuLi/TMEDA. Subsequent reaction with electrophiles including Me_3SiCl provides the corresponding C-3 substituted derivatives.[285]

Lithiation of 1-Boc-aziridine **641** formed the anion **642** that decomposed more rapidly. When the lithiation was carried out in the presence of trimethylsilyl chloride, it afforded 1-Boc-2-trimethylsilylaziridines **643** and 1-Boc-2,3-bis(trimethylsilyl)aziridine (**644**) in excellent yields (Scheme 262).[286] 1-Bus (Bus = *tert*-butylsulfonyl)-protected terminal aziridines **645** undergo regio- and stereoselective deproto-

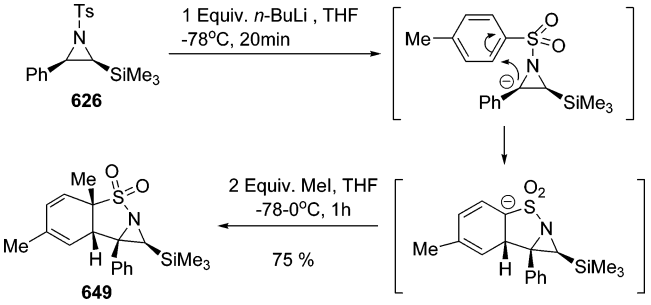
Scheme 263



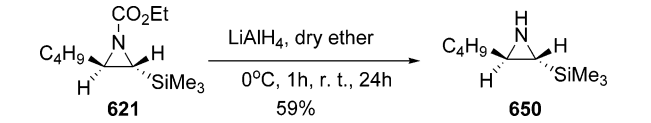
Scheme 264



Scheme 265



Scheme 266

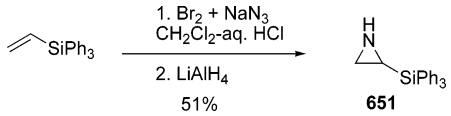


nation with lithium 2,2,6,6-tetramethylpiperidine, forming a nonstabilized (H-substituted) aziridinyl anion **646** (Scheme 263). The electrophilic trapping of the latter with TMSCl led to the formation of *trans*-2-(trimethylsilyl)aziridines **647** in excellent yields.[287] Another example of aziridine lithiation followed by trapping of the anion with TMSCl afforded 1-tosyl-2-trifluoromethyl-2-(trimethylsilyl)aziridine (**648**) (Scheme 264).[215] Treatment of 1-tosyl-3-phenyl-2-(trimethylsilyl)aziridine (**626**) with *n*-BuLi followed by quenching with iodomethane gave a tricyclic trimethylsilylaziridine **649** as a single diastereomer in 75% yield (Scheme 265).[288] The proposed mechanism of formation of this product involved deprotonation of the benzylic carbon followed by intramolecular nucleophilic addition of the anion across the aromatic ring and subsequent methylation. Recently, the highly stereoselective functionalization of (2*S*,1′*S*)-2-(1′-aminoalkyl)aziridine derivatives through successive formation of aziridine−borane complexes, lithiation, and treatment with a variety of electrophiles such as different chlorotrialkyl silanes has been described, affording the corresponding silylated aziridines in good yields.[289,290]

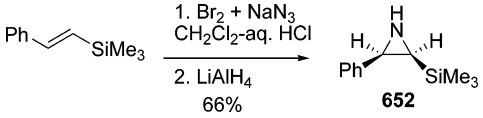
The ethoxycarbonyl group in 2-butyl-1-ethoxycarbonyl-3-(trimethylsilyl)aziridine (**621**) has been removed by reduction with lithium aluminum hydride to form 2-butyl-3-(trimethylsilyl)aziridine (**650**) (Scheme 266).[270]

Many others have used aziridinyllithium derivatives for the synthesis of functionalized aziridines through alkylation

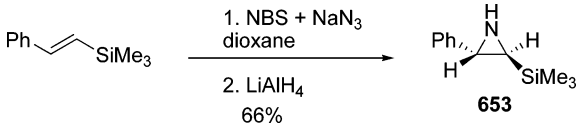
Scheme 267



Scheme 268



Scheme 269



reactions,[291,292] because this method constitutes a powerful tool in organic synthesis.

8.2.4. Reduction of 2-Bromoazides

The reduction of (1-azido-2-bromoethyl)trimethylsilane, formed from vinylsilane, using lithium aluminum hydride was reported to form 2-(trimethylsilyl)aziridine.[293] Similar reduction of bromoazides, formed from vinylsilanes, has led to the synthesis of many 1-unsubstituted 2-(triphenyl/trimethylsilyl)aziridines **651**−**653** (Schemes 267−269).[270] It was observed that altering the reaction conditions afforded stereochemically different products. (*E*)-2-Trimethylsilyl-1-phenylethene afforded *cis*-2-phenyl-3-(trimethylsilyl)aziridine (**652**) using bromoazide prepared in situ from bromine and sodium azide in a mixture of dichloromethane and aqueous hydrochloric acid. The same alkene afforded *trans*-2-phenyl-3-(trimethylsilyl)aziridine (**653**) when sodium azide was used with *N*-bromosuccinimide in 1,4-dioxane. The first step of the reaction involved the formation of an intermediate bromonium ion **654** (Scheme 270). The trans product is formed through an attack of the azide ion on the bromonium ion, whereas the cis product is obtained through stereospecific nucleophilic attack of the azide ion on carbocation **656**, formed by ring opening of the bromonium ion **654**. The reduction of the azide function in bromoazides **655** and **657** to the corresponding amine followed by cyclization afforded the final product in each case.

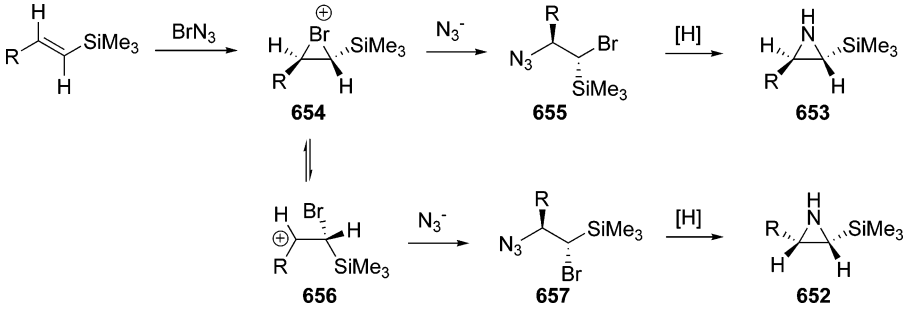
8.2.5. Cyclization of 2-Halocarbamates

The cyclization of methyl 2-halo-2-(triethylsilyl)ethylcarbamates **658** and **660** on treatment with alkali formed the 1-methoxycarbonyl-2-(triethylsilyl)aziridine (**659**) (Scheme 271) and 1-methoxycarbonyl-2-(trimethylsilyl)aziridines (**615**) (Scheme 272).[294,295]

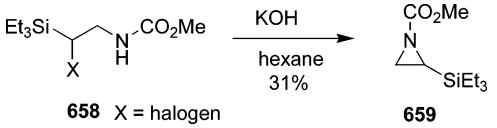
8.2.6. Reaction of Benzonitrile with Silyldibromomethyllithium

The reaction of *tert*-butyldimethylsilyldibromomethyllithium (**634**) with benzonitrile is reported to yield 1-unsubstituted 2-(trialkysilyl)aziridines (Scheme 273).[296] A nucleophilic attack of **634** on nitriles produced an initial adduct **661**, which cyclized intramolecularly to 2-bromo-2*H*-azirine **662**. When this reaction was carried out in the presence of nucleophiles such as the Grignard reagents or lithium aluminum hydride, the corresponding aziridines **663** were obtained, confirming the formation of 2-bromo-2*H*-

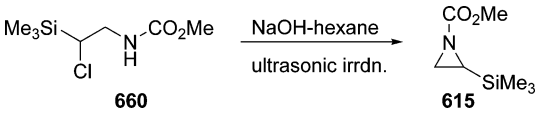
Scheme 270



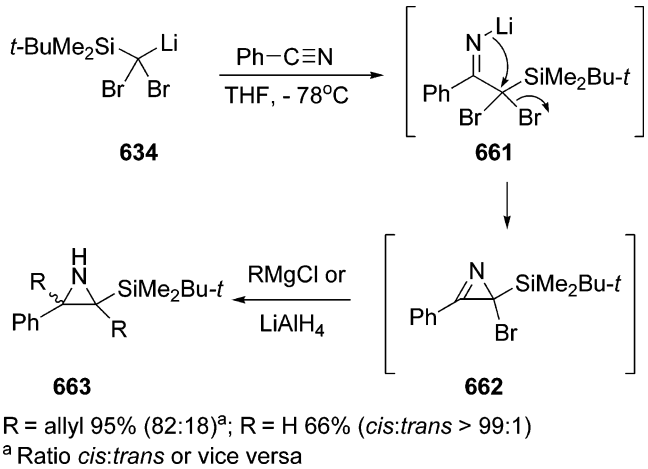
Scheme 271



Scheme 272



Scheme 273



R = allyl 95% (82:18)[a]; R = H 66% (*cis*:*trans* > 99:1)

[a] Ratio *cis*:*trans* or vice versa

azirine **662**. The major isomer of the compound **663** ($R^1 = R^2 = H$) was identified as cis on the basis of comparison with a closely related compound.

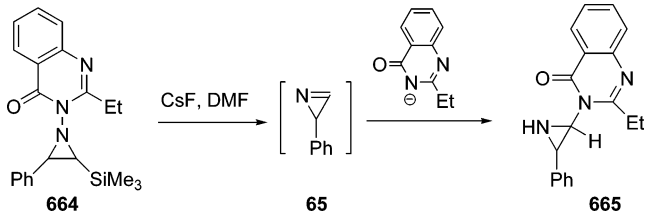
8.3. Reactivity of *C*-(Trialkylsilyl)aziridines

Both silyl group displacement and ring opening reactions have been reported for *C*-silylaziridines. The substitution of the silyl group offers an attractive route for an enantioselective synthesis of *N*-unsubstituted aziridines, whereas ring opening reactions have led to the synthesis of β-aminosilanes and β-ketosilanes. Ring expansion of a trialkylsilylaziridine to a β-lactam derivative is also known.

8.3.1. Displacement of the Silyl Group

Treatment of (±)-2-(trimethylsilyl)aziridine **664** with cesium fluoride in dimethylformamide is reported to give the 2-ethyl-3-(3-phenylaziridin-2-yl)quinazoline-4(*3H*)one **665** (Scheme 274).[273] This aziridine was obtained as a single diastereomer showing the presence of a mixture of two invertomers (ratio 4:1) at nitrogen in its ^{1}H NMR spectrum at −55 °C. A desilylative quinazolinone elimination from

Scheme 274



664 led to formation of the azirine **65**, which was captured by the quinazolinone anion to afford the aziridine **665**. This aziridine-azirine-aziridine interconversion was later used for enantioselective synthesis of quinazolinone-free aziridines by employing potassium cyanide as a nucleophilic reagent. The reaction of the aziridine **623** with cesium fluoride in dimethylformamide in the presence of potassium cyanide afforded 2-cyano-3-phenylaziridine (**666**) (Scheme 275).[297] The absolute configuration of aziridine **666** was assigned as (2*R*,3*S*) by its hydrogenation and *N*-acylation toward 1-acylaziridine **667** and nitrile **668**.

The silyl group in 2-phenyl-1-tosyl-3-(trimethylsilyl)-aziridine (**627**) can be substituted upon treatment with a fluoride source, tetrabutylammonium triphenyldifluorosilicate (TBAT), and aldehydes as the electrophile affording aziridines **669** (Scheme 276) with cis selectivity up to 92%.[279,288] The use of $CDCl_3$ in place of aldehydes afforded the deuterated aziridine **670** (Scheme 277). An aziridine having a trimethylsilyl group at C-2 and in the substituent on the ring nitrogen was treated similarly. It was observed that the trimethylsilyl group present on the aziridine ring was more prone to attack by a fluoride ion than the trimethylsilyl group attached to the sulfonyl group at the ring nitrogen, and the reaction afforded the *C*-desilylated aziridine **671** (Scheme 278). The diastereoselectivity is explained by using the empirical model for the reaction of chiral anions with aldehydes in the absence of chelation control proposed by Basindale and Taylor.[298] In this model, large- and medium-sized groups need to be assigned. As the nitrogen is tetrahedral, the reactive conformation **672** of the aziridine has the tosyl group pointing away from the incoming aldehydes and the lone pair toward it (Figure 6). Thus, this

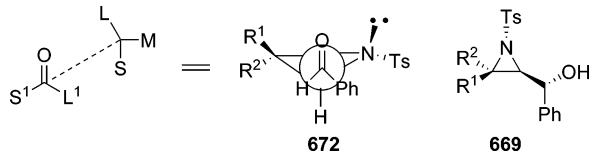
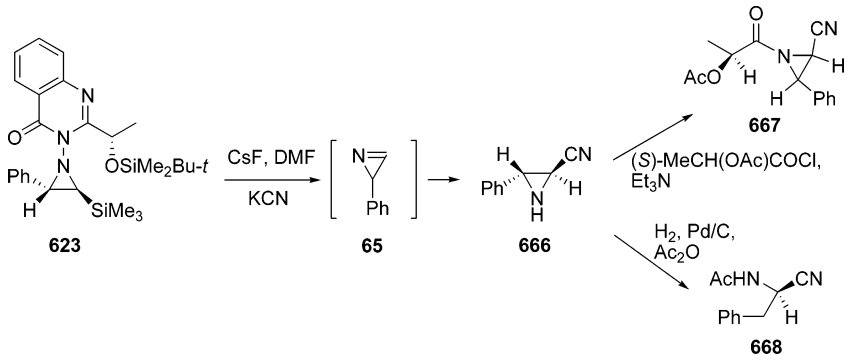


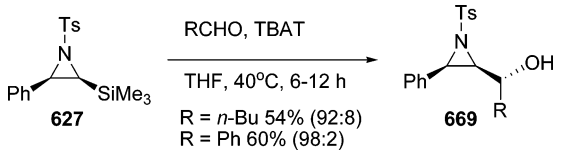
Figure 6.

group has been assigned as medium-sized relative to the other ring carbon that has a substituent pointing toward the incoming aldehyde, and which is therefore designated as

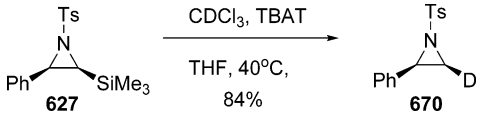
Scheme 275



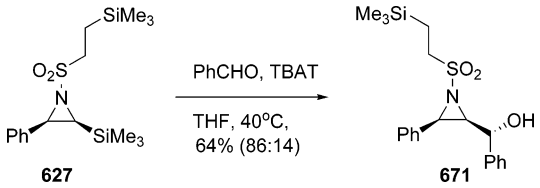
Scheme 276



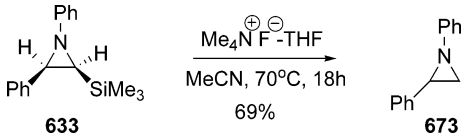
Scheme 277



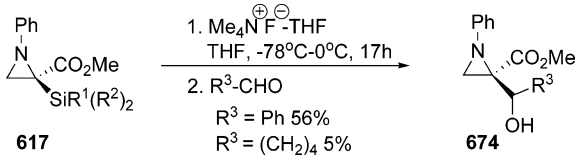
Scheme 278



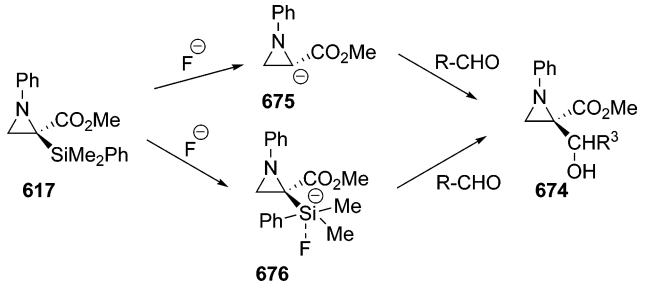
Scheme 279



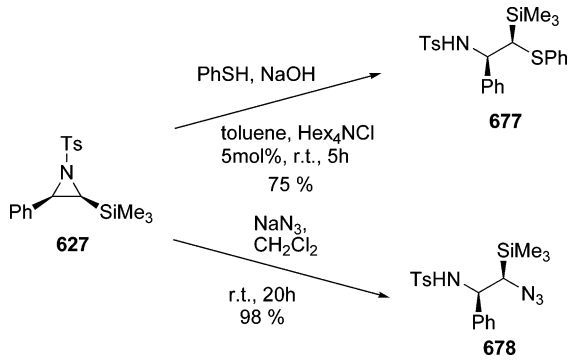
Scheme 280



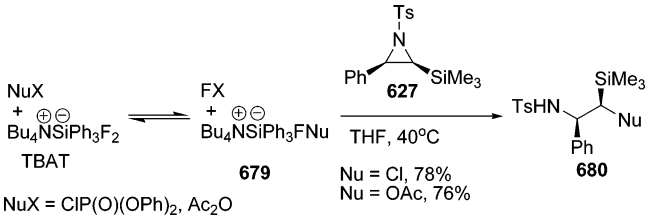
Scheme 281



Scheme 282



Scheme 283



large-sized. This substituent (Ph or H) is larger than the nitrogen lone pair, in both *cis*- and *trans*-aziridines.

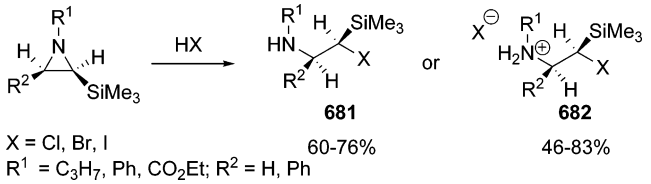
The trialkylsilyl group in 1,3-diphenyl-2-(trimethylsilyl)-aziridine **633** is removed by a fluoride ion from tetramethylammonium fluoride to form 1,3-diphenylaziridine (**673**) (Scheme 279), probably due to the presence of moisture in the fluoride source.[299] This behavior is similar to that observed for the corresponding 2-(trialkylsilyl)epoxide.[300] Desilylation of 2-ethoxycarbonyl-1-phenyl-2-(trimethylsilyl)-aziridine **617** followed by reaction with aldehydes afforded the aziridines **674** (Scheme 280). Two mechanisms have been proposed for the desilylation and concomitant reaction with aldehydes (Scheme 281).[299] The first path involved an aziridinyl carbanion **675**, whereas the second path involved an aziridine **676** with a penta-coordinated silicon.

8.3.2. Ring Opening Reactions

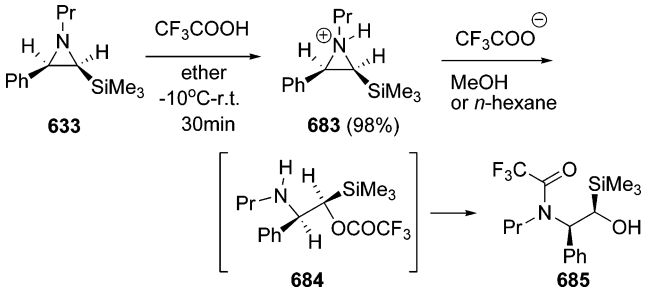
Ring opening of 2-phenyl-1-tosyl-3-(trimethylsilyl)aziridine **627** was readily accomplished with benzenethiol or sodium azide in the presence of tetrahexylammonium chloride (Scheme 282), which led to the formation of the single regioisomeric 2-azido-2-(trimethylsilyl)sulfonamide **677** and 2-(phenylthio)-2-(trimethylsilyl)sulfonamide **678**, respectively, in high yields.[288] In both cases, the ring opening occurred exclusively at the silicon-bearing carbon and not at the benzylic carbon, which indicated a larger activation by silicon. TBAT is also reported to promote ring opening via the hypervalent silicate intermediate **679**, affording the sulfonamides **680** (Scheme 283).[279]

Ring opening reactions of differently substituted 2-(trimethylsilyl)aziridines have been reported with reagents such

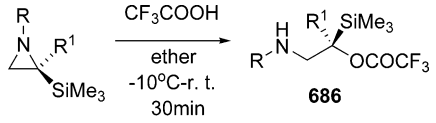
Scheme 284



Scheme 285



Scheme 286

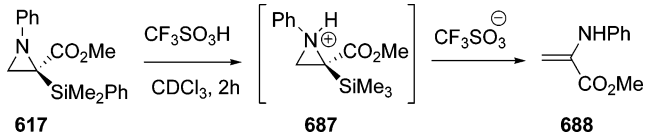


614. R = CO_2Et, R^1 = H
617. R = Ph, R^1 = CO_2Et

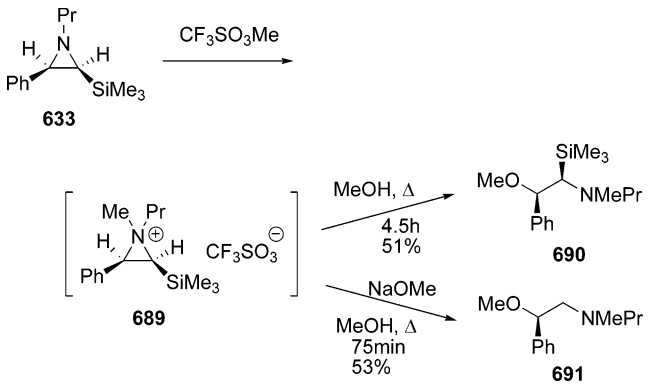
as hydrogen halides, trifluoroacetic acid, methyl iodide, and trialkylsilylhalides.[299] The products in many cases were unstable, but their formation was detected by NMR spectroscopy. However, it has been observed that 2-(trimethylsilyl)aziridines failed to undergo nucleophilic ring opening, even if they had a strong electron-withdrawing ethoxycarbonyl group either at the ring nitrogen or at the other ring carbon atom. The possible reason suggested for the failure was an electronic effect of silicon, which may destabilize the transition state of S_N2 substitution in the β-position. The prior protonation of the nitrogen, however, led to a facile ring opening regiospecifically. Addition of hydrogen halides to *cis*-2-(trimethylsilyl)aziridines (Scheme 284) afforded the corresponding β-haloamines **681** or the ammonium salts **682**, depending upon the reaction conditions. The reaction using either aqueous hydrochloric acid or hydrochloric acid in dichloromethane afforded the same product. The protonation has been proposed to be followed by a nucleophilic attack α to silicon. The reaction of *trans*-1,3-diphenyl-2-(trimethylsilyl)aziridine with any hydrogen halide afforded polymeric product, even at −78 °C, probably due to the nucleophilic attack of the amine **681** onto protonated aziridine.

Treatment of *cis*-3-phenyl-1-propyl-2-(trimethylsilyl)aziridine (**633**) with trifluoroacetic acid afforded the stable aziridinium ion **683** at room temperature. The aziridinium ion underwent nucleophilic attack of the trifluoromethylcarboxylate ion α to the silicon on refluxing in methanol or hexane, forming the product **684** (Scheme 285).[299] An acyl exchange in the latter compound led to the formation of compound **685**. Treatment of 1-ethoxycarbonyl-2-(trimethylsilyl)aziridine (**614**) and 2-ethoxycarbonyl-1-phenyl-2-trimethylsilylaziridine (**617**) with trifluoroacetic acid did not afford the protonated aziridines but, directly, the α-ring opened products **686** in quantitative yields with no acyl exchange (Scheme 286).[299] Under similar conditions, *cis*- or *trans*-1,3-diphenyl-2-(trimethylsilyl)aziridine formed only

Scheme 287



Scheme 288



polymeric product. A similar behavior was observed when these aziridines were treated with trifluoromethanesulfonic acid. However, the reaction of 2-[dimethyl(phenyl)silyl]-2-methoxycarbonyl-1-phenylaziridine (**617**) with trifluoromethanesulfonic acid afforded a stablized enamine **688** as a result of the attack of trifluoromethanesulfonate at the silicon atom of the aziridinium cation **687** (Scheme 287).[299]

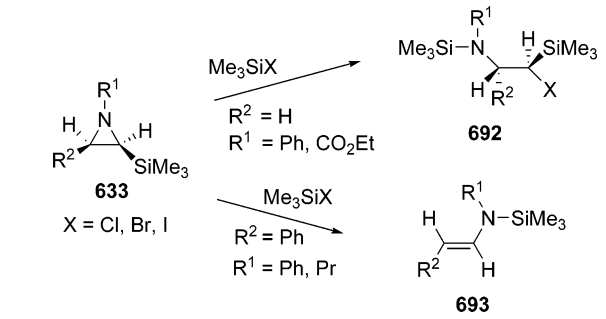
Attempts to methylate 2-(trialkylsilyl)aziridines using methyl iodide were unsuccessful. However, the *N*-methylaziridinium salt **689** of *cis*-3-phenyl-1-propyl-2-(trimethylsilyl)aziridine (**633**) could be obtained in moderate yield using methyl trifluoromethanesulfonate (Scheme 288).[299] Methylation was much slower than protonation and thus was more susceptible to side reactions such as ring opening or desilylation. The *cis*-1-methyl-3-phenyl-1-propyl-2-(trimethylsilyl)aziridinium triflate (**689**) was relatively stable but underwent solvolysis in methanol to afford a β ring opened product **690**, which was the only observed case of this type in these studies. Treatment of **689** with sodium methoxide in methanol afforded the desilylated product **691**. An S_N1-like process involving an intermediate/activated complex with substantial carbocation character explained the formation of the β ring opened product.

The reaction of 2-(trimethylsilyl)aziridines **633** with trimethylsilyl halides has been shown to depend upon the substituents at other ring carbon atoms. 1-Ethoxycarbonyl-2-(trimethylsilyl)aziridine and 1-phenyl-2-(trimethylsilyl)-aziridine reacted with trialkylsilyl halides to form the corresponding β-haloamines **692** by *N*-silylation followed by attack of the halide α to the silicon (Scheme 289).[299] A similar reaction of *cis*-3-phenyl-1-propyl-2-(trimethylsilyl)-aziridine and of *cis*- or *trans*-1,3-diphenyl-2-(trimethylsilyl)-aziridine with trimethylsilyl halides, however, afforded a *trans*-*N*-silylenamine **693**. The phenyl group has been proposed to stabilize the development of an adjacent positive charge which, in turn, favored desilylation.

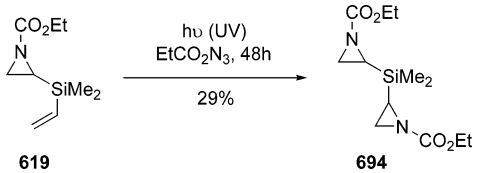
8.3.3 Transformation to a Bisaziridine Derivative

The α-silylaziridine **619** serves as a substrate for the synthesis of a bisaziridine, diethyl 2,2′-(dimethylsilanediyl)-aziridine-1-carboxylate (**694**). The carbon−carbon double bond present in the silicon substituent of this compound has

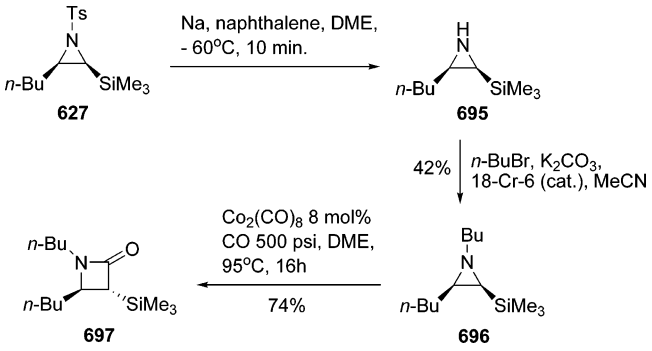
Scheme 289



Scheme 290



Scheme 291



been aziridinated by reaction with ethyl azidoformate in the presence of UV light (Scheme 290).[270]

8.3.4. Transformation to a β-Lactam Derivative

The *cis*-2-butyl-1-tosyl-3-(trimethylsilyl)aziridine (**627**) has been used as a substrate for the synthesis of a *β*-lactam derivative. Deprotection of the tosyl group in **627** using sodium naphthalenide afforded the corresponding N−H aziridine **695**.[301] The latter was alkylated by *n*-butyl bromide in the presence of 18-Cr-6 as a catalyst to give 1,2-dibutyl-3-(trimethylsilyl)aziridine (**696**). Carbonylation of this aziridine afforded the *trans*-*β*-lactam **697** as a single diastereomer and regioisomer in good yield (Scheme 291).[279] Ring opening of the aziridine resulted in an inversion of configuration leading to a *trans*-*β*-lactam **697**. Furthermore, the ring was opened regioselectively at the carbon atom bearing the silicon atom.

C-Silicon-substituted aziridines are comparatively less investigated than their oxygen-counterparts 2-silyloxiranes. The most common approaches to the synthesis of *C*-silylaziridines are the reactions of vinylic silanes with azides or other nitrogen-providing reagents such as ethyl (4-nitrophenylsulfonyloxy)carbamate and 3-acetoxyaminoquinazolinone and the reactions of imines with trimethylsilyldiazomethane. The latter compound is a versatile, simple to use, and commercially available reagent. Chiral Lewis acid complexes have been used in reactions of imines with trimethylsilyldiazomethane to enhance the diastereoselectivity and enantioselectivity. The steric factors play a role in deciding the stereochemical preference of the addition. Trialkylsilyl groups can be easily displaced with a variety of reagents affording a broader range of aziridines. *C*-Silylaziridines undergo stereospecific nucleophilic ring opening, often with high regioselectivity. The more pronounced activation of silicon-bearing carbon atoms facilitates ring opening at this carbon.

9. Concluding Remarks

C-Heteroatom-substituted aziridines are important compounds from synthetic, mechanistic, and medicinal points of view. These compounds serve as precursors for biologically important classes of compounds including heterocycles such as *β*-lactams, pyrroles, oxazoles, indoles, and cyclic sulfonamides. Cyclization of the haloamines, carbene−imine additions, additions across azirines, olefin−nitrene additions, and the reaction of α-haloimines are the main approaches to form the aziridine skeleton. Efforts are in progress to refine these methods, and recently some new and mild reagents have been developed to generate carbenes and nitrenes. The stereoselectivity and enantioselectivity in the synthesis and reactions of these aziridines have been observed to depend on a number of factors such as the substituents on the substrates, the reaction conditions, and the catalysts used. Only a few papers are available on the isolation of *C*-oxygen-substituted aziridines. Aziridines having alkoxy and acetoxy groups are mainly unstable and undergo ring opening and rearrangement reactions affording products such as α-aminoketones, α-aminoalcohols, α-aminoesters, and acetals derived from α-aminoaldehydes. The presence of electron-withdrawing groups on the aziridine ring stabilizes it. Accordingly, *C*-haloaziridines are comparatively more stable. Among the halogen-bearing aziridines, those containing fluorine are the most stable and have been used in the synthesis of indole derivatives. 2,2-Dichloroaziridines are more prone to ring opening than 2-chloroaziridines. The latter aziridines undergo nucleophilic displacement of chlorine with various reagents affording other *C*-functionalized aziridines such as 2-acetoxyaziridines, 2-azidoaziridines, and 2-(phenylthio)aziridines. However, the substituents at the ring nitrogen have also been observed to play a significant role in determining the course of the reactions of such aziridines. *C*-Nitrogen- and *C*-sulfur-substituted aziridines have drawn considerable interest in recent years. Although the amino group destabilizes the aziridine ring, many azaheteroaryl groups stabilize it. The lithiated anions of such aziridines undergo ring opening followed by cycloaddition, constituting an important method for the synthesis of pyrrole derivatives. Similarly, metalation of 2-sulfonylaziridines offers attractive routes for the synthesis of diverse types of compounds including quaternary amines and quaternary *β*-amino acids. Recently, some diligent approaches to the asymmetric synthesis of aziridine-2-phosphonates have been reported. These aziridine-2-phosphonates have been used further as precursors for α- and *β*-aminophophonates. Very useful enantioselective syntheses of α-aminosilanes and α-ketosilanes are reported by ring opening of 2-(trialkylsilyl)-aziridines. Looking at the significant progress in the synthesis and chemistry of such compounds, it is certain that it will continue to appeal to synthetic and medicinal chemists in the future.

10. Acknowledgment

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