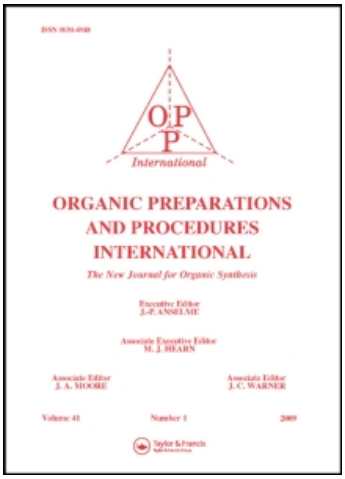

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INTRODUCTION

Azirine is the term used to describe the smallest nitrogen unsaturated heterocyclic system, containing two carbon atoms and one double bond in a three-membered ring. Interest in these heterocycles stems from the general influence of ring strain upon chemical reactivity and to the potential of their derivatives to act as precursors to more elaborate heterocyclic molecules. The structure, biological applications, and the synthetic chemistry of these heterocycles have been extensively explored since the mid–1960s. A number of general reviews on azirines have appeared during this period.[1-12] This review will focus on the chemistry of monocyclic 2*H*-azirines, the chemistry of fused-ring azirines will not be discussed.

There are two isomeric azirines **1** and **2** which have been designated by *Chemical Abstract* and *The Ring Index*,[13] as 1*H*-azirine and 2*H*-azirine, respectively. The structures, names, and numbering schemes of 1*H*-azirine **1** and 2*H*-azirine **2** are shown in *Figure 1*. Alternate names such as 2-azirine for 1*H*-azirine and 1-azirine for 2*H*-azirine have been suggested in the literature. The IUPAC and *Chemical Abstracts* names which use the indicated hydrogen (*H*) formality will be used in this review.

1*H*-azirine (2-azirine) **1**

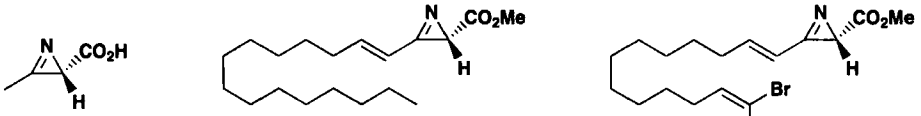
2*H*-azirine (1-azirine) **2**

Structures, names, and numbering of azirines.

Figure 1

Theoretical methods have been used to estimate that 1*H*-azirine is 32–37 kcal mol^{-1} higher in energy than 2*H*-azirine.[14,15,16] 1*H*-Azirine may be considered as a prototype of a 4n–π antiaromatic system. Recently, the unique isolation and complete spectroscopic identification of an 1*H*-azirine has been carried out by Elguero and coworkers.[17]

The azirine ring has been found in several natural products. The first azirine-containing natural product isolated was azirinomycin[18] **3** (Figure 2). Azirinomycin, isolated from *Streptomyces aureus*, and its methyl ester were found to exhibit broad spectrum antibiotic activity *in vitro* against both gram-positive and gram-negative bacteria.[19] More recently, the azirine-containing natural products (*R*)-(–)-[20] and (*S*)-(+)-dysidazirine[21] **4** and (*S*)-(+)-antazirine[21] **5** were isolated from the marine sponge *Dysidea fragilis* (*Figure 2*). The configuration of the asymmetric center seems to play an important role in the biological activity of these compounds. Whereas (*R*)-(–)-dysidazirine shows cytotoxic and antibacterial activity, the enantiomer (*S*)-(+)-dysidazirine or the (*S*)-(+)-antazirine are inactive towards a standard group of microorganisms.



Azirinomycin **3** (*S*)-(+)-Dysidazirine **4** (*S*)-(+)-Antazirine **5**

Some natural products containing the azirine ring.

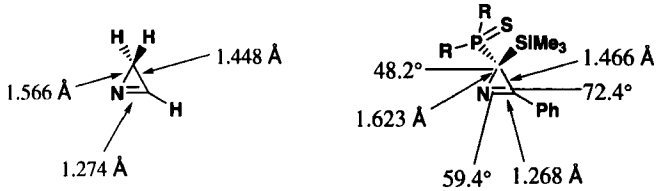
Figure 2

I. STRUCTURAL PROPERTIES OF 2*H*–AZIRINES

The 2*H*-azirine ring represents a reactive and versatile substrate as a result of certain inherent features within its structure. The stability of these heterocycles is attributable not only to the combined effects of bond shortening and angle compression, but also to the presence of the electron-rich nitrogen atom.

1. Molecular Orbital Calculations and Geometry

Ab initio calculations for 2*H*-azirine **2** have been performed[22] and bond lengths estimated (*Figure 3*). Optimized structure and homodesmic strain energy of 2*H*-azirine have been computed using various levels of theory.[22] The structures of 2*H*-azirine **2** and its complexes with H^+ and Li^+, as well as the relative basicities of 2*H*-azirines have been calculated by *ab initio* methods.[14,23] Due to the strain of the three-membered ring, the basicity of the nitrogen atom in the 2*H*-azirine ring is much lower than in simple aliphatic imines. The total ring strain energy of 2*H*-azirine is lower than that of the isoelectric cyclopropene ring and has been estimated at about 48 kcal mol^{-1},[7] although lower values of 44.6 and 46.7 kcal mol^{-1} have recently been reported using *ab initio* calculations at the MP2/6–31G* and B3LYP/6–31G* levels of theory, respectively.[22] The influence of an exocyclic unsaturation has also been the subject of theoretical studies.[24] The *ab initio* derived geometry and the calculated vibrational frequencies of 2-methylene-2*H*-azirines agree well with data obtained on the matrix-isolated species.



Calculated — **2** — Experimental — **6**

Bond lengths and angles for 2*H*-azirine **2** and **6**.

Figure 3

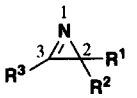
The dimensions of 2*H*-azirines have been determined by single crystal X-ray.[7,25] This method demonstrates a pronounced C-C bond shortening and considerable C-N bond lengthening when compared to normal open chain congeners and are consistent with estimated bond lengths from theoretical calculations. Endocyclic angles are all close to 60° and the geometry at nitrogen is essentially pyramidal. Typical bond lengths and angles for 2*H*-azirine phosphine sulfide **6** are shown in Figure 3.

2. Spectroscopic Properties

a) Nuclear Magnetic Resonance Spectroscopy

The general aspects of ^{1}H, ^{13}C and ^{15}N NMR spectroscopy of 2*H*-azirines have been well documented. Some typical values for the ^{1}H and ^{13}C NMR resonances for 2*H*-azirines **7** are shown in Table 1. A good overview of the NMR characteristics of 2*H*-azirines, especially their ^{13}C NMR spectra, can be found in reference 10.

Table 1. Selected ^{1}H and ^{13}C NMR Values of 2*H*-Azirines **7** (in ppm)



7

R^1	R^2	R^3	Solvent	δ_{H-2}	δ_{C-2}	δ_{C-3}	Ref.
H	H	H	$CDCl_3$	1.26	14.4	164.2	26
H	H	^{t}Bu	$CDCl_3$	1.40	----	----	27
H	Ph	COPh	$CDCl_3$	3.51	37.7	165.3	28
H	(*S*)-CO_2Me	Ph	$CDCl_3$	2.87	29.4	158.5	29
H	$CONMe_2$	Ph	$CDCl_3$	3.10	----	----	30
H	$CH_2P(O)(OEt)_2$	^{i}Bu	$CDCl_3$	2.00	23.9	174.0	31,32
Me	Ph	H	C_6D_6	----	31.9	165.9	33
Cl	CO_2Me	CO_2Me	$CDCl_3$	----	54.6	155.0	34
	$=CH_2$	Me	----	----	133.2	186.8	35

Although ^{15}N NMR can also be used for the characterization of 2*H*-azirines, the chemical shift values spread over a broad range. 2-Methyl-3-phenyl-2*H*-azirine shows absorption at –104.3 ppm, while 3-ethoxycarbonyl-2-phenyl-2*H*-azirine shows absorption at –63.2 ppm,[36] and the endocyclic nitrogen atom of 3-amino-2*H*-azirines resonates at –179.7.[37]

b) Infrared Spectroscopy

IR is a useful tool for the characterization of 2*H*-azirines, given that the heterocyclic imine C-N double bond is involved in a strained three-membered ring, which shows a strong C=N stretch for 3-substituted 2*H*-azirines in the region of 1730–1780 cm^{-1} as illustrated in Table 2. However, 2*H*-Azirines without substituents at C3 (R^3 = H) exhibit C=N absorption in the same region (*ca.* 1650 cm^{-1}) as that observed for normal acyclic imines.[38,39] Moreover, the frequency of the C=N stretching vibration in 2*H*-azirines with exocyclic unsaturations is shifted considerably (1818 cm^{-1}) compared to that of simple 2*H*-azirines.[24]

Table 2. Selected IR C=N Absorption Values of 2*H*-Azirines **7** (in cm^{-1})

R^1	R^2	R^3	C=N Absorption	Ref.
H	H	H	1655	26
H	H	Ph	1740	39,40
H	*p*-MePh	CO_2Me	1750	41
H	CO_2Et	C_5F_{11}	1780	42
H	$POPh_2$	Et	1736	43
Et	Et	H	1665	40
	$=CH_2$	H	1818	24
Me	Me	N(Me)Ph	1750	44

c) Mass Spectrometry

Although mass spectrometry is not commonly used for the structural elucidation of 2*H*-azirines, these heterocycles show a predominant ion corresponding to a fragmentation of the ring to a nitrile (RCN^+) or nitrilium ion ($RCNH^+$).[41,45] A photoionization mass spectrometer has been used to study the UV, multiphoton, and electron impact ionization of 3-methyl-2-phenyl-2*H*-azirine[46] and 2,3-diphenyl-2*H*-azirine.[47]

d) Electronic Absorption Spectroscopy

The UV absorption spectra of 3-alkyl-2*H*-azirines show a weak absorption in the range of 230 nm,[48] while 3-aryl-2*H*-azirines exhibit a stronger absorption maxima at *ca.* 245 nm, which is assigned to the benzene band of the ^1L_a type, with an inflection at about 285 nm for the n, π^* transition[9] (*Table 3*). The parent compound 2*H*-azirine **2** shows absorption at 229 nm.[26]

Table 3. Selected Ultraviolet Spectra of 2*H*-Azirines **7** in ethanol (in nm)

R^1	R^2	R^3	λ_{max}	Shoulder	Ref.
H	H	H	229	----	26
H	H	Ph	246	280	49
H	"Pr	"Pr	239	----	50
Me	Me	Ph	245	277, 286	51
Me	Me	*p*-MeOPh	270	284, 292	52
Me	Me	Ph(Me)N	252	286	53
Ph	Ph	Ph	250	285, 310	54,55

e) Photoelectron Spectroscopy

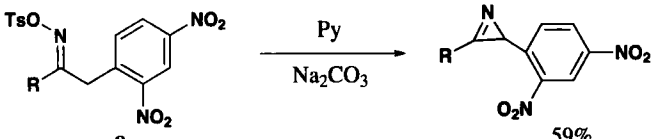
The photoelectron spectra of 2*H*-azirine have been measured.[56] The lone-pair ionization potential was found to be 10.58 eV, while the C=N π–electron ionization potential was measured as 11.56 eV. These values compared favorably with those obtained from MNDO semiempirical MO calculations.

II. SYNTHESIS OF 2*H*–AZIRINES

1. Preparation of the Azirine Ring

a) The Neber Rearrangement

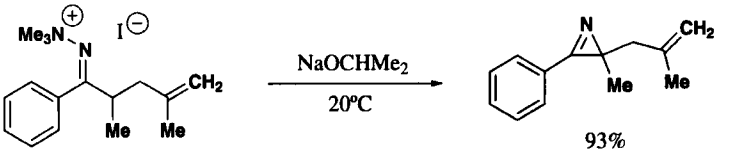
The first 2*H*-azirine synthesis ever reported was described by Neber *et al.* as intermediates in the synthesis of aminoketones by treatment of oxime *p*-toluenesulfonates **8** with base (*Scheme 1*).[57] Since then many azirines have been prepared using this approach, including highly functionalized derivatives like sulfonyl azirines.[58] This process can also be extended to other substituted oxime derivatives such as *O*-benzoyl oximes[59] or carbamate oximes.[60]



8

Scheme 1

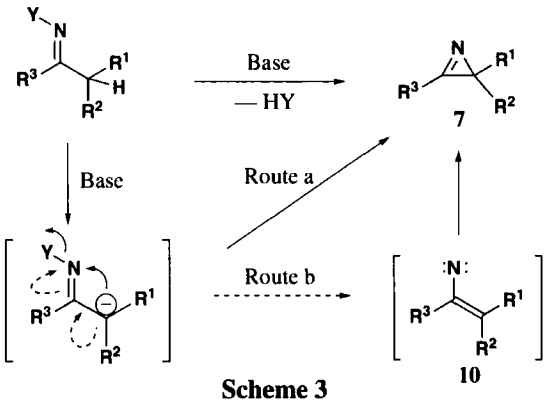
Modifications of the Neber rearrangement use the ketone trimethylhydrazonium halides **9** instead of oxime sulfonate esters **8**,[61] thus allowing the preparation of many differently substituted 2*H*-simple azirines in good yields, as shown in *Scheme 2* for allylazirines.[6,62]



9

Scheme 2

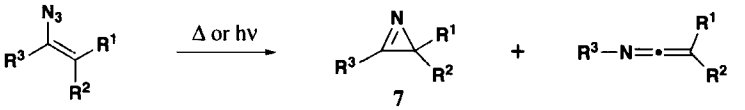
The presence of strong electron-withdrawing groups in the α-position to the carbon-nitrogen double bond increases the acidity of protons in the α-position, thus favoring the cycloelimination reaction under milder conditions. The Neber reaction probably occurs through either an internal concerted nucleophilic displacement (route a, *Scheme 3*)[60,63] or *via* an electrocyclization of vinylnitrene **10** (route b, *Scheme 3*).[63,64]



Scheme 3

b) Synthesis from Vinyl Azides

The thermal and/or photochemical treatment of vinyl azides can be used for the synthesis of 2*H*-azirines.[6,65] The first azirine synthesis by pyrolysis of vinyl azides was performed in the early 60s furnishing 50-60% yields of 2*H*-azirines along with small amounts of keteneimines,[48] generated by migration of the α-R group of the azide onto the nitrogen atom through a Curtius type rearrangement (*Scheme 4*). These keteneimines become the main product in the decomposition of vinyl azides having two electron-withdrawing groups (R^1, R^2) such as carboxylic esters in the β-position.[66]



Scheme 4

More representative examples of the thermolysis of vinyl azides are shown in Table 4, including the synthesis of functionalized azirines as well as the first examples of 2-bromo and 2-iodo-2*H*-azirines.[34,67]

Table 4. Some 2*H*-Azirines **7** by Thermolysis of Vinyl Azides

R^1	R^2	R^3	Yield	Ref.
$CH(OMe)_2$	H	Ph	not isolated	68
H	CO_2Et	R_F[a]	80%	69
$P(O)Ph_2$	H	Me	90%	43
4-Me-Ph	H	CO_2Me	74%	41

Table 4. Continued...

R^1	R^2	R^3	Yield	Ref.
H	H	$CO_2{}^tBu$	not isolated	70
CO_2Me	CN	NR_2	----	71
CO_2Et	Br	Ph	97%	34,67

[a] R_F: perfluoroalkyl chain.

The thermal instability of 2*H*-azirines makes their isolation after thermolysis of vinyl azides difficult. However, carrying out the reaction photochemically at low temperature can be advantageous, allowing the synthesis of azirines with little polymerization (Table 5).

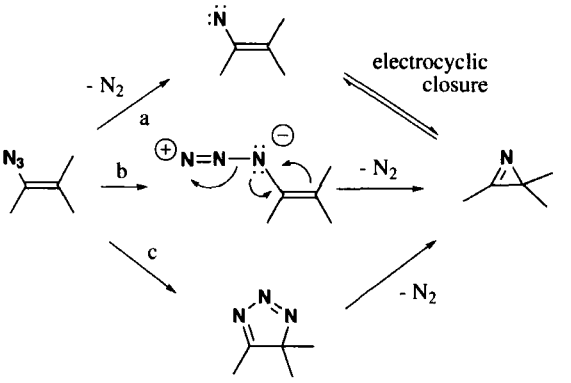
Table 5. Some 2*H*-Azirines **7** by Photolysis of Vinyl Azides

R^1	R^2	R^3	Yield	Ref.
Me	Me	Vinyl	93-97%	72
Me	Me	$CH_2P(O)(OEt)_2$	96%	73
—CH_2—		Alkyl	54-60%	24,74
Ph	Bzl	Ph	84-90%[a]	75
Ph	H	H	----	76

[a] Depending on the geometry of the starting vinyl azide.

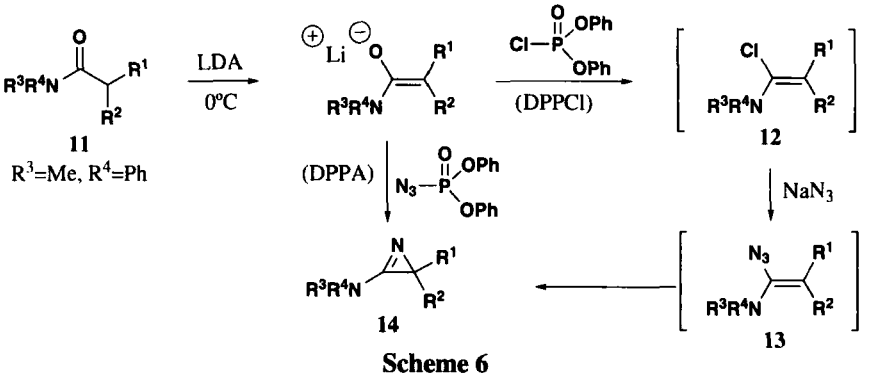
The formation of 2*H*-azirines by thermolysis depends largely on the structure of the vinyl azide.[28] Thus, vinyl azides substituted at the 1-position with aryl, alkyl, alkoxy, amine or carboethoxy groups give quite stable azirines, while hydrogen or carbonyl substituted afford nitriles or other heterocycles instead of the azirine ring. When carbonyl groups are present at the 2-position of the vinyl azide, oxazole formation results,[28,71] and the presence of an aryl group leads to indoles.[28] Indoles also result from the pyrolysis of 2*H*-azirines, therefore suggesting that the azirine may be in thermal equilibrium with the vinyl nitrene.[41,77] Therefore, while the cyclization of the vinyl azides to 2*H*-azirines may or may not involve a vinylnitrene (route a, *Scheme 5*), a vinylnitrene may be formed by ring opening of the azirine, hence explaining the formation of indoles. An alternative, and the most widely accepted mechanistic pathway to the participation of nitrenes in the formation of 2*H*-azirines, involves the concerted cyclization-elimination of N_2 assisted by the π bond (route b, *Scheme 5*).[28,78] A third possible mechanism, involving the formation of a triazole intermediate, which then loses N_2, has also been considered (route c, *Scheme 5*). Indeed, both triazole and 2*H*-azirine moieties, have been isolated from 1-aminovinyl azides,[79] thus providing an efficient method of synthesis of amino-2*H*-azirines.

An efficient synthesis of 3-amino-2*H*-azirines which proceeds through an non-isolable vinyl azide intermediate, involves the reaction of α-mono- or disubstituted amides **11** and an azide source. The amide was treated with phosgene/triethylamine to afford the corresponding α-chloroenamine **12**



Scheme 5

which was then treated with NaN_3 to produce 3-amino-2*H*-azirines **14**, probably *via* the azidoenamine **13**.[79a,80] The use of the highly toxic phosgene could be avoided by an alternative procedure based on the reaction of the amide enolate with diphenylphosphorochloridate (DPPCl) followed by treatment with NaN_3.[25c,44] This method also has the advantage that it is not necessary to isolate the sensitive α-chloroenamine intermediate and it has been used to prepare heterospirocyclic 3-amino-2*H*-azirines, synthons for heterocyclic amino acids.[81] More recently, diphenylphosphorazidate (DPPA) has been used as an azide source; thus 3-amino-2*H*-azirines **14** can be obtained in one-pot and in very good yields (*Scheme 6*).[82] This reaction is the method of choice for the synthesis of 2,2-disubstituted 3-amino-2*H*-azirines **14**.



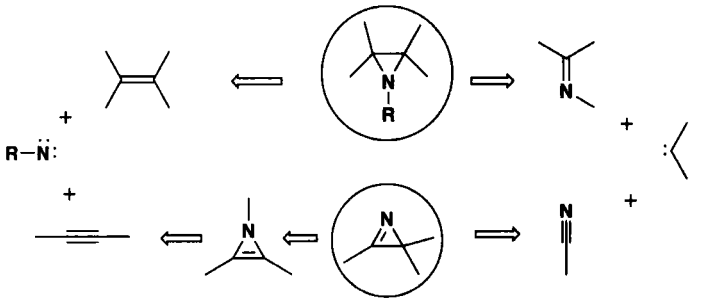
Scheme 6

Nitrostyrenes may also serve as precursors of vinyl nitrenes and therefore were used to prepare 2*H*-azirines. The reaction, a deoxygenation promoted by phosphates or phosphites, takes place under conditions where nitroaromatics are usually converted into nitrenes.[83] The same reaction can also be performed by photolysis using ^{t}BuHgCl and KI.[84] Nevertheless, until now the preparative use of these methods is limited by the low yields obtained.

c) Addition to Triple Bonds

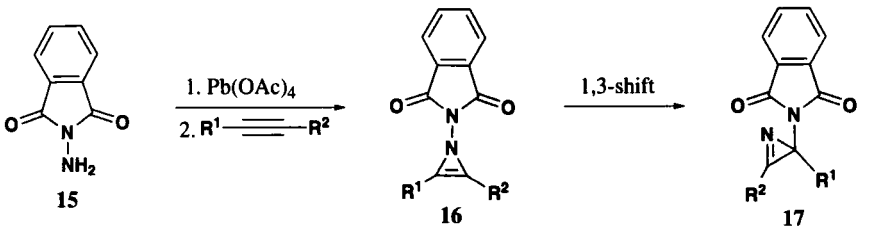
In contrast to the widely used cycloaddition approach for the synthesis of saturated nitrogen three-membered ring systems such as the parent aziridine moiety from nitrenes and olefins[85] or from

carbenes and imine derivatives (*Scheme 7*),[86] the intermolecular addition reactions of carbenes to nitriles or nitrenes to alkynes have not apparently become, until now, general methods for the synthesis of azirines, since yields are not suitable for preparative applications.



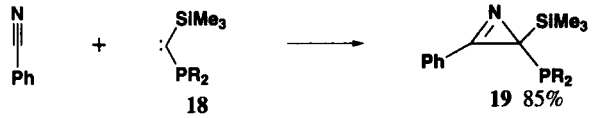
Scheme 7

The addition of nitrenes to alkynes, for instance, was initially developed as a method of synthesis for 1*H*-azirines, but only small amounts (< 15%) of the isomeric 2*H*-azirines **17** were obtained, probably as a result of a 1,3-sigmatropic shift from the unstable intermediate 1*H*-azirine **16** (*Scheme 8*).[87] The required nitrenes are produced by oxidation of hydrazine derivatives **15** with lead tetracetate. The intramolecular version of this reaction is also known, giving a much better yield (78%) of the 2*H*-azirine derivative.[88]



Scheme 8

The second approach to 2*H*-azirines involves the reaction between carbenes and nitriles of which only a few succesful syntheses are known so far. Photochemically generated 1-naphthylcarbene reacted with nitriles to afford products resulting from trapping of the intermediate nitrile ylides instead of the expected 2*H*-azirine.[89] A better result has been obtained from the [1+2] cycloaddition reaction of the phosphinocarbene **18** and benzonitrile, which afforded the corresponding 2*H*-azirine **19** in good yield (*Scheme 9*).[25b,90] Heteroatom substituted carbene seems to favor the reaction.



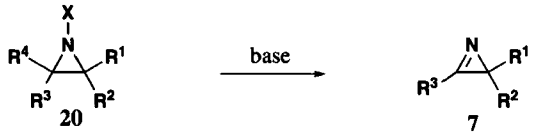
Scheme 9

2. Preparation from Other Heterocycles

Other methods of synthesis of 2*H*-azirines do not rely on the construction of the three-membered heterocyclic ring, but rather on the rearrangement or modification of pre-existing three-membered heterocycles such as aziridines, or ring contraction of four- or five-membered ring such as azete, isoxazoles, triazoles and oxazaphospholes.

a) From Three-membered Heterocycles

Elimination reactions starting from the parent aziridine ring, are the most widely used approach to 2*H*-azirines. *N*-Substituted aziridines **20** such as *N*-chloro-,[26,91] *N*-sulfonyl-,[92] *N*-sulfinyl-,[93] and *N*-acyl-derivatives[94] are prone to elimination when treated with base providing 2*H*-azirines **7** (*Scheme 10*). A variation to the elimination reactions is the oxidation of aziridine derivatives. The Swern reagent (DMSO/$(COCl)_2$/Et_3N) has been used to oxidize 3-alkylaziridine-2-carboxylates to the corresponding 2*H*-azirine-2-carboxylates[95] with retention of configuration at C2.

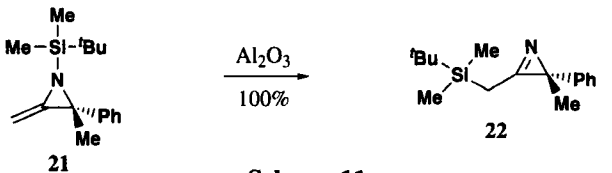


X= Cl, OSO_2Ph, SO*p*-Tol, COPh

Scheme 10

Pyrolysis of *N*-phthalimido-2,3-diphenylaziridine also promotes elimination giving 2*H*-azirine which rearranges to the corresponding indole.[96] Similarly, the reaction of different aziridines, induced by light or heating at high temperature (800°), gives rise to elimination products such as the parent 2*H*-azirine and other C_2H_3N isomers.[15] An interesting similar approach makes use of the fluoride-induced elimination of silyl and stannylaziridinyl *N*-benzopyrimidones **20** (R^4 = $SiMe_3$, X = Heterocycle) (*Scheme 10*).[97]

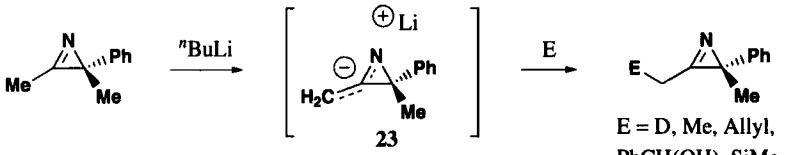
2*H*-Azirines can be obtained by isomerization reactions starting from other 2*H*-azirines or from aziridines. For instance, 2-chloro-2-ethyl-3-methyl-2*H*-azirine, obtained by photolysis of the corresponding vinyl azide, interconverts to 2-chloro-3-ethyl-2-methyl-2*H*-azirine at –10° giving a mixture of both species, probably through an aziridine intermediate and, therefore is little preparative value.[98] A more efficient transformation is the treatment of alkylidene aziridine **21** with aluminum oxide to afford the isomeric 2*H*-azirine **22** in a quantitative yield (*Scheme 11*).[99]



Scheme 11

Side chain modifications by halogenation, sulfonation or acylation have been carried out on several functionalized azirines such as 3-phenyl-2-(hydroxymethyl)-2*H*-azirine.[100] Furthermore, elimination reactions in the side chain of 3-chloroalkyl-2*H*-azirine derivatives with triethylamine lead to formation of 1-alkenyl groups in the 2-position of the azirine.[101] Similarly, condensation of a formyl group in the 2-position of the ring with amines gives rise to imine derivatives, while 2-vinylazirines are obtained by Wittig reaction of 2-formyl- 2*H*-azirine with phosphorane.[68,102]

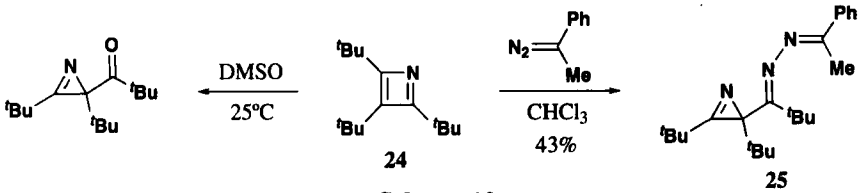
Finally, deprotonation of alkyl groups attached to C3 of 2*H*-azirines with butyllithium leads to formation of metalloenamines **23** which can react with a variety of electrophiles such as deuterated water, methyl or allyl iodide, benzaldehyde or trimethylchlorosilane (*Scheme 12*).[99]



Scheme 12

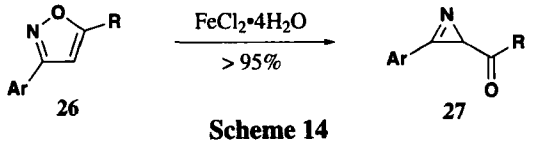
b) From Four- and Five-membered Heterocycles

The ring-contraction of four and five-membered heterocycles to three-membered heterocycles is another route to 2*H*-azirines. Thus, 2*H*-azirines can be obtained from the azete-derivative **24** by oxidation with dimethyl sulfoxide or, alternatively, when treated with 1-diazo-1-phenylethane, forms an intermediate bicyclic adduct which rearranges thermally or photochemicaly to generate 2*H*-azirinyl azine **25** (*Scheme 13*).[103]



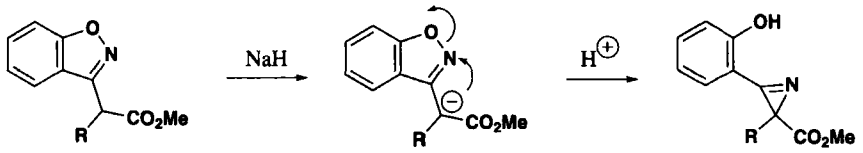
Scheme 13

Thermal or photochemical ring contraction of isoxazoles afford acyl 2*H*-azirines. Under these conditions, they can rearrange to form other heterocycles such as oxazoles.[104] These transformations have proven to be reversible at high temperature or by changing the irradiation wavelength. Although the thermal rearrangement of isoxazoles has produced several azirines in good yields,[105] this approach is of limited preparative value due to the high temperatures usually required. The mechanism of both, the thermally and the photochemically induced ring-contraction of isoxazoles seems to involve a diradical intermediate formed by N-O bond cleavage, as suggested by experimental and theoretical studies.[104b,106] The 2*H*-azirine once formed, opens to give nitriles or oxazoles, depending on the ring substitution pattern.[107] Ring-contraction of isoxazoles to azirines can also be promoted by base treatment or iron (II) catalyst. Thus, 5-alkoxy- and 5-aminoisoxazoles **26** (R = OR', NR'_2) isomerize to 2*H*-azirine-2-carboxylic esters and carboxamides **27** respectively, by reaction with catalytic or equimolecular amounts of $FeCl_2$, in nearly quantitative yield (*Scheme 14*).[30]



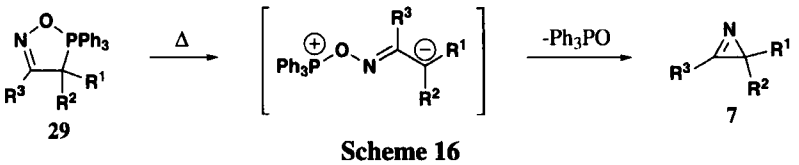
Scheme 14

Functionalized benzisoxazoles **28** possessing electron-donating substituents at the α-position (R = Me, CH_2Ph, cyclohexyl, OPh, SPh) undergo ring-contraction to give 2*H*-azirine-2-carboxylates with good yields, when treated with strong bases such as NaH, ^{t}BuOK or MeONa (*Scheme 15*).[108] Similarly to isoxazoles, both pyrolysis and photolysis of 1,2,3-triazoles also produce 2*H*-azirines, although in low yields due to the formation of other heterocycles.[109]



Scheme 15

Another type of ring-contraction leading to 2*H*-azirines is the thermally induced extrusion of phosphine oxide from 1,3,5- and 1,2,5-oxazaphosphole heterocycles.[110] Electron-withdrawing substituents at C4 in 1,2,5-oxazaphospholes **29** favor formation of the corresponding keteneimine rather than 2*H*-arizine **7**. Both products are the result of initial cleavage of the P-C bond and subsequent loss of triphenylphosphine oxide (*Scheme 16*). 1,2,5-Oxazaphospholes **29** can be prepared by 1,3-dipolar cycloaddition of nitrile oxides to alkylidenephosphoranes[110c,111] or alternatively by treating α-bromoketoximes with triphenylphosphine followed by base-induced cyclization of the intermediate phosphonium salt.[27] The latter method allows the preparation of 2*H*-azirines not easily accessible *via* the vinyl azide route.



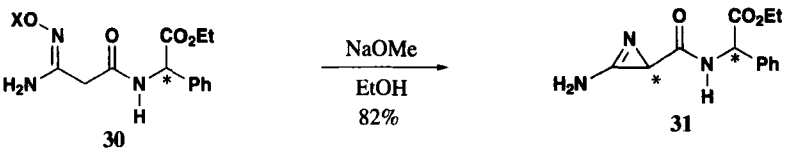
Scheme 16

3. Asymmetric Synthesis

The asymmetric synthesis of azirine derivatives has recently become the focus of several research efforts. Many of the synthetic procedures for the synthesis of 2*H*-azirines reviewed in the previous sections are not suited for asymmetric synthesis. To date, the Neber rearrangement (section II.1.a), the amide enolate azidation synthesis of 3-aminoazirines (section II.1.b) and methods based on the modification of the parent aziridine ring (section II.2.a) have been developed to synthesize optically active 2*H*-azirines.

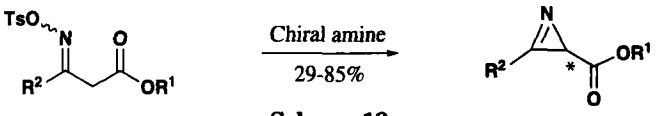
a) Neber Rearrangement and Modified Approaches

The first optically active 2*H*-azirines were synthesized using the Neber rearrangement on an *O*-mesyl derivative of amidoxime **30** in which a chiral phenylglycine had been introduced as a chiral auxiliary. Treatment of this derivative with base gave a good yield and stereoselectivity (96:4) of the 3-amine-2*H*-azirine **31** containing two stereocenters, one exocyclic and one endocyclic (C2 of the azirine) (*Scheme 17*).[112]



Scheme 17

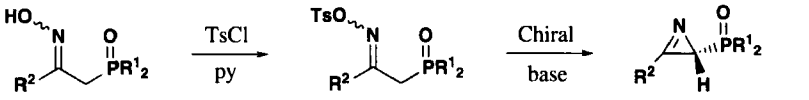
Another excellent approach based on the Neber reaction makes use of a chiral tertiary base such as dihydroquinidine or quinine not covalently bonded to the substrate (*Scheme 18*).[113] Other chiral tertiary bases lacking the hydroxy group such as sparteine, brucine and strychnine did not produce any optically active heterocycle, nor did the use of hydroxylic solvents like ethanol. Therefore, the stereoselectivity obtained using dihydroquinidine or quinidine can be explained by the formation of a hydrogen bond between the hydroxyl group of the base and one of the S=O moieties of the ketoxime tosylate during the abstraction of a methylene proton. The enantiomeric excess obtained ranges between 44 and 82%, when a equimolecular amount of base is employed, but excellent results were also obtained when 10% mol of quinidine were used and 10-20 equiv. of potassium carbonate added to regenerate the alkaloid base *in situ*. Finally, it is remarkable that the pseudoenantiomers of the alkaloid bases gave rise to opposite antipodes of the product.



Scheme 18

This strategy based on the Neber rearrangement has been applied to the first synthesis of enantiomerically enriched 2-phosphinyl-2*H*-azirines **34** (R^1 = Ph, OEt). In this way, excellent chemical yields and enantiomeric excesses up to 82% in alkyl- and aryl-substituted azirines have been obtained (*Scheme 19*).[43,114] Precursor tosyloximes **33** were obtained by tosylation of β-oximo phosphine oxides **32**, easily prepared by addition of hydroxylamine to allenes[115] in case of alkyl substituted oximes, and by condensation reaction of β-carbonyl phosphine oxides with hydroxylamines[114] in case of aryl substituted oximes. A similar strategy starting from tosyloximes[114,116] has been used for the preparation of alkyl and arylazirines having a phosphonate group in the 2-position.[117] However, this method cannot be applied to the synthesis of unsubstituted azirines (**34**, R^2 = H) because of the inac-

cessibility of the corresponding tosyloximes.[118] The 2*H*-azirine-2-carboxylic and the corresponding isosteric phosphonic esters obtained through this method are of particular interest because they constitute a route to the preparation of unnatural amino acids[119] and their isosteric phosphorus analogs *via* reduction to the corresponding aziridine followed by ring opening.

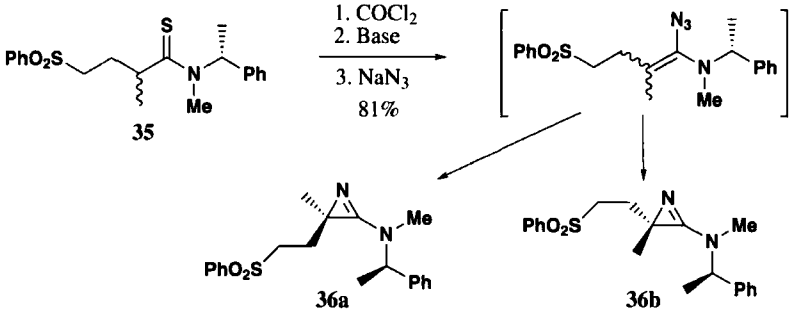


32 33 34 78-89%

Scheme 19

b) Vinyl Azide-based Approach

A useful method for the synthesis of optically active 3-amino-2*H*-azirines employs a thioamide **35** carrying a chiral substituent at the amino group (see section II.1.b) (*Scheme 20*).[119a,120] Chromatographic separation of the diastereomeric mixture of 3-amino-2*H*-azirines **36** gave pure diastereoisomers which, after electrochemical cleavage of the benzenesulfonyl group, were used as synthons in the synthesis of pentapeptides.

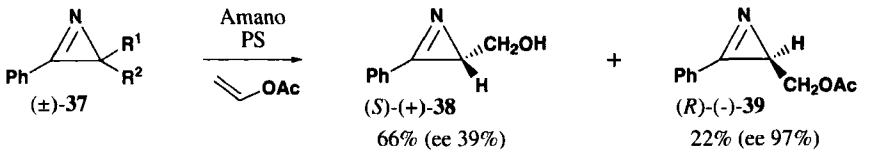


35 36a 36b

Scheme 20

c) Modifications of Three-membered Rings

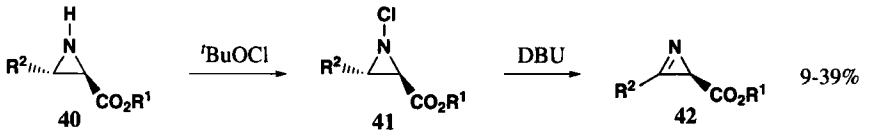
Resolution of 2*H*-azirines by chemoenzymatic modification of a racemic mixture has been used recently for the preparation of enantiomerically pure 2*H*-azirines. Thus, (*S*)-(+)-phenyl-2*H*-azirine-2-methanol **38** and its (*R*)-(–)-acetate **39** were prepared by a lipase-catalyzed kinetic resolution of the racemic 2*H*-azirinemethanol **37** (R^1 = H, R^2 = CH_2OH) (*Scheme 21*). The reaction was carried out at very low temperature (–40°C), which increased the enantioselectivity.[121]



(±)-37 (*S*)-(+)-38 66% (ee 39%) (*R*)-(-)-39 22% (ee 97%)

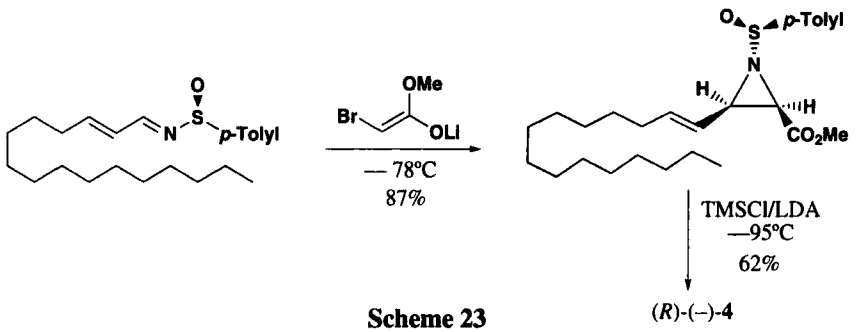
Scheme 21

Optically active aziridines, which can be prepared by several methods,[122,123] can also be used for the asymmetric synthesis of 2*H*-azirines. Oxidation or elimination reactions of optically pure aziridines leads to 2*H*-azirines with variable levels of enantiomeric purity. One logical approach to optically active azirines is the elimination reaction of *N*-haloaziridines **41**, readily obtained by treatment of aziridines **40** with tert-butyl hypochlorite. Dehydrochlorination of the *N*-chloroaziridine with base (DBU) produces the corresponding 2*H*-azirine **42** (R^1 = Me, R^2 = Ph), although the low yields obtained limit the synthetic use of this method (*Scheme 22*).[91]



Scheme 22

Fluoride-mediated elimination of $SiMe_3$ and a quinazolinone ring from chiral aziridines gives optically active azirines which when reacted with nucleophiles present in the reaction media afforded *N*-unsubstituted aziridines in high enantiomeric excess.[124] An additional elimination approach is based on chiral *N*-sulfinylaziridines. Indeed, the treatment of these derivatives with LDA/MeI afforded 2*H*-azirines with high enantiomeric excess (95%) but only moderate chemical yields, probably due to the competitive deprotonation at C2 followed by ring-opening.[93] Enhancing the leaving ability of the *N*-sulfinyl group by treatment with TMSCl at –95° and then with LDA, provided an elegant synthesis of 2*H*-azirine 2-carboxylate esters with no trace of the isomeric 2*H*-azirine 3-carboxylate derivatives, in good yields.[29] This procedure has been applied to acomplish the first asymmetric synthesis of the marine cytotoxic antibiotic (*R*)-(–)-dysidazirine **4** and its (*S*)-(+) epimer (*Scheme 23*).[29,93]

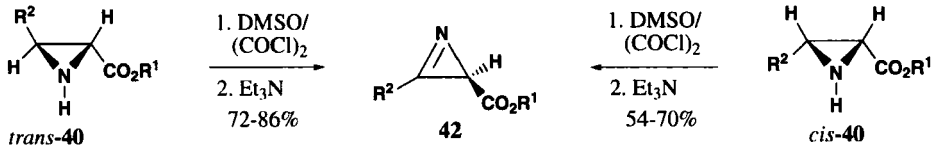


Scheme 23

This methodology did not work when applied to 2,2-disubstituted aziridines, but transformation of the *N*-sulfinyl group into the *N*-tosyl group by oxidation with *m*-CPBA,[123d] and treatment of the corresponding 2,2-disubstituted *N*-tosylaziridine with LDA afforded the chiral 2*H*-azirine with good yields (80-87%).[125]

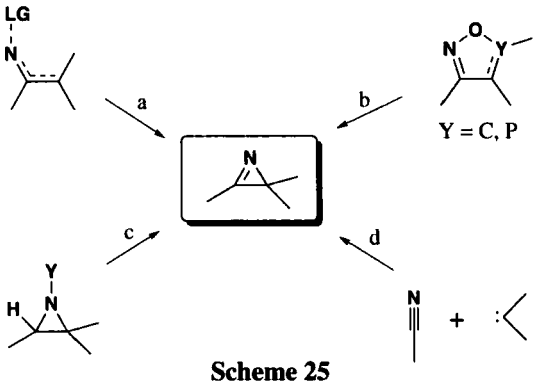
A different and successful entry to chiral azirines involves the Swern oxidation of aziridine carboxylate esters. Similar to the above *N*-sulfinyl or *N*-tosyl elimination route, this procedure also

gives a regioselective introduction of the double bond which is not in conjugation with the ester function, since no isomeric 2*H*-azirine 3-carboxylate ester has been detected.[95] Furthermore, the oxidation of either the *cis*-**40** and the *trans*-**40** isomers afforded 2*H*-azirine 2-carboxylate **42** (R^1 = Me), where the integrity of the stereogenic center at C2 is retained (*Scheme 24*). The reasons for this unexpected regioselectivity (the less acidic proton is removed exclusively) are not yet clear, but the formation of the intermediate aziridine enolate may be prevented by ring strain, thus making the acidity of both aziridine ring protons very similar. When the Swern oxidation was performed on a 1*H*-aziridine 2-carboxylate ester lacking a C3 proton, the corresponding 2*H*-azirine 3-carboxylate ester was obtained with good yield, providing the first example of an enantiomerically enriched azirine in which the carboxyl group is conjugated with the C=N bond.[29]



Scheme 24

This methodology has been adapted to accomplish the first asymmetric synthesis of azirine phosphonates substituted with an aryl group, although in this case a mixture of both regioisomers, 2*H*-azirine 2-phosphonate **34** (R^2 = Ph, R^1 = OEt) and isomeric 2*H*-azirine 3-phosphonate esters has been obtained in a 49 and 40% yield respectively.[126]



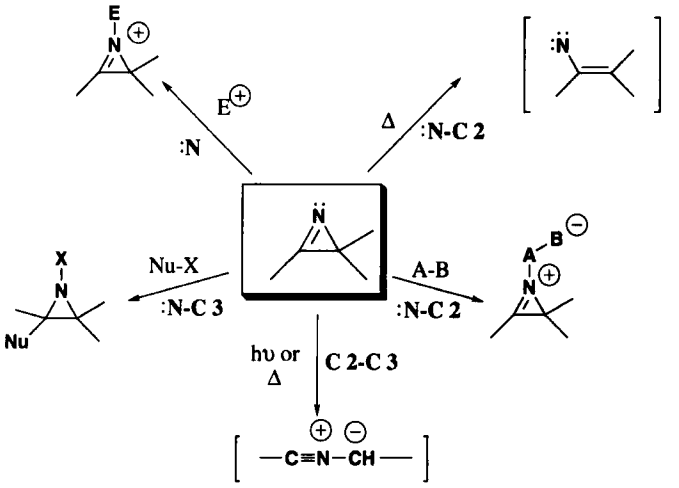
Scheme 25

Scheme 25 shows the synthetic strategies available to date for the construction of the three membered 2*H*-azirine ring involving: (a) intramolecular reactions of *N*-functionalized imines and vinyl azides, (b) ring-contraction of isoxazoles and oxazaphospholes, (c) elimination and oxidation reactions on aziridines and (d) intermolecular cycloaddition reactions between nitriles and carbenes.

III. REACTIVITY OF 2*H*-AZIRINES

The chemistry of 2*H*-azirines has been explored extensively due to the high reactivity of this ring system. They are ambident reagents and they are capable of acting in organic reactions not

only as nucleophiles and electrophiles, but also as dienophiles and dipolarophiles in cycloaddition reactions. The high ring strain, the reactive π-bond and the lone pair on the nitrogen atom favor the regioselective ring cleavage of the ring system. Therefore, the reactions of these substrates may be classified as a function of the basicity of the azirine (reactions at the lone pair on the nitrogen atom) and on the regioselective processes involving certain bonds of the heterocycle (N-C2, C2-C3, N-C3) (*Scheme 26*).

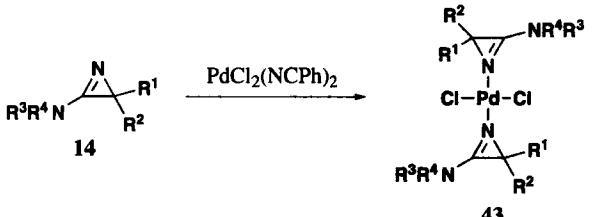


Scheme 26

1. Reactions Involving the Nitrogen Atom

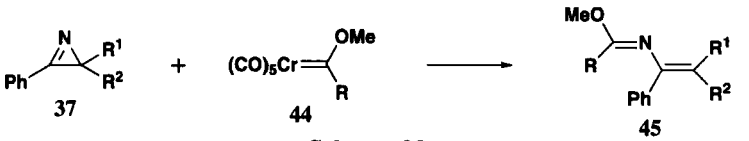
Although the basicity of the nitrogen atom in the azirine is much lower than in simple aliphatic imines, the presence of a lone pair on the nitrogen atom of azirines allows reactions where these compounds act as nucleophilic reagents. These substrates can react with a wide range of electrophilic derivatives to give three- or five-membered nitrogen derivatives. In all cases, the nucleophilic attack of the azirine involves the nitrogen lone pair *via* azirinium salts.

The synthesis of metal-coordinated 2*H*-azirines and the metal-induced reactions of azirines **14** ($R^1 = R^2 = R^3 = R^4 = Me$) have opened a new area in the chemistry of this small ring heterocycle. Transition metal complexes of the type $(azirine)_2MX_2$ (M = Pd, Zn) such as **43** were obtained by the reaction of azirine with palladium reagents[127] or with transition metal halides[128] (*Scheme 27*).



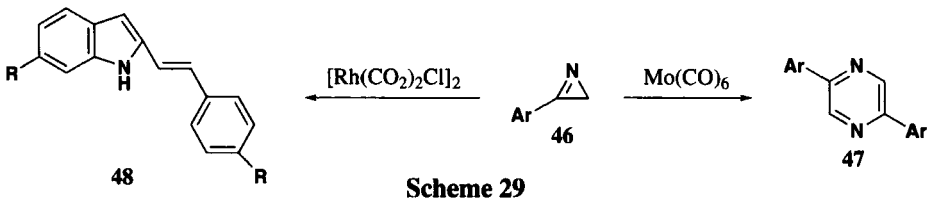
Scheme 27

Hegedus *et al.* reported an elegant method of synthesis of electron rich 2-azadienes **45** when Fischer carbenes **44** were exposed to sunlight in the presence of 2*H*-azirines **37**[129] (*Scheme 28*). Likewise, the reaction of azirines with tungsten or molybdenum complexes provides ring-opened



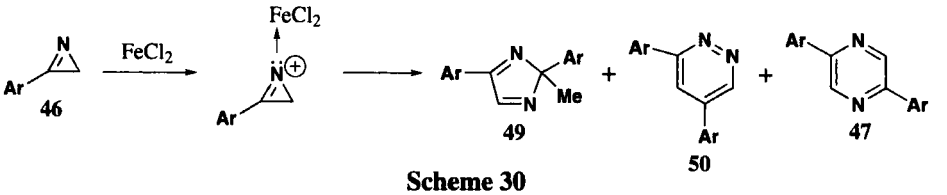
Scheme 28

compounds *via* initial complexation of the azirine nitrogen with the metal.[130] Dimerization reactions of 2*H*-azirines to pyrazines using several transition metal complexes have been studied.[131] Reaction of 3-aryl-2*H*-azirines **46** with an equimolar amount of a Group VI metal carbonyl gives 2,5-diarylpyrazines **47** in good yield, while these azirines are converted to 2-styrylindoles **48** in the presence of catalyst rhodium carbonyl compounds (*Scheme 29*).



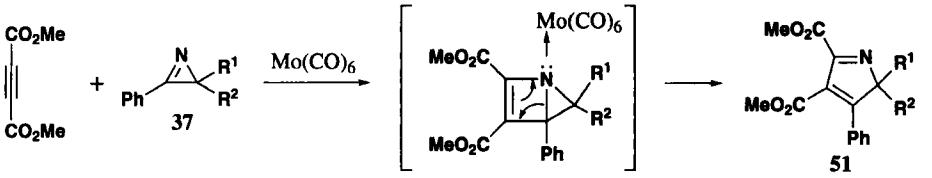
Scheme 29

Recently, the first example of dimerisation of azirines **46** to 2*H*-imidazoles **49** or 3,5-disubstituted pyridazines **50** has been reported using iron dichloride as promoter of the reaction[132] (*Scheme 30*). A radical azirine complex, is proposed as the intermediate. Furthermore, the azirine-$FeCl_2$ complex could be a interesting synthon for intermolecular cycloadditions, as shown by the reaction with styrenes to give pyrrolidines.[132]



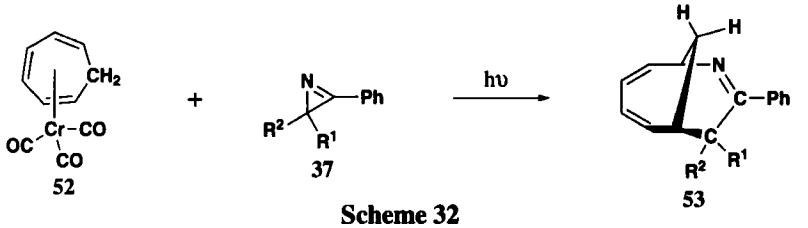
Scheme 30

The bimolecular cycloaddition of dimethyl acetylenedicarboxylate with 3-phenyl-2*H*-azirines **37** (R^1= R^2 = Me) in the presence of molybdenum hexacarbonyl complexes[133] has been studied. The resulting pyrrole derivatives **51** appear to arise from an initial [2+2] cycloaddition followed by a ring opening reaction (*Scheme 31*).[134] Similar results are found for the reaction of azirines with iron carbonyl complexes.[135]



Scheme 31

Metal-mediated cycloadditions for the construction of briged heterocycles have been reported. Thus, UV irradiation of tricarbonyl(cycloheptatriene)chromium (0) **52** and 3-phenyl-2*H*-azirines **37** (R^1 = H, Me, Ph, R^2 = H) at 0° gave 7-aza-8-phenylbicyclo[4.3.1]deca-2,4,7-trienes **53** *via* [6+3] cycloaddition of the 1,3-dipole generated by ring opening of the azirine to the cycloheptatriene ring[136] (*Scheme 32*). A variety of other insertion reactions, dimerizations, intramolecular cyclizations, and intermolecular addition reactions of azirines are known to be promoted by transition metal.[137]

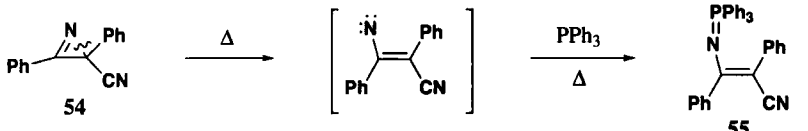


Scheme 32

2. Reactions Involving the N–C2 Bond

a) Thermal Reactions

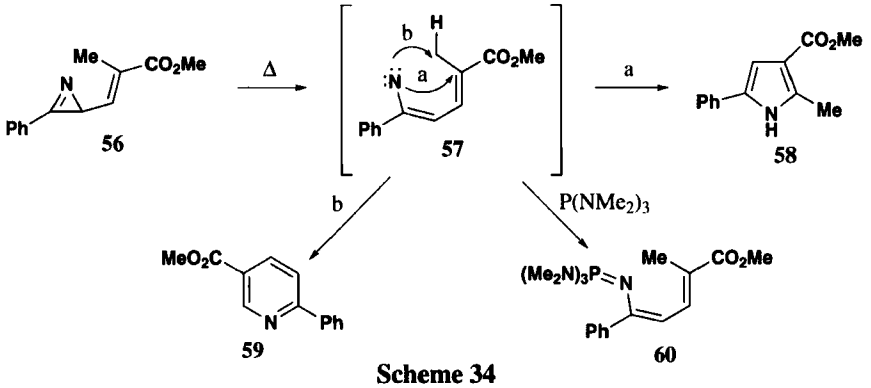
Thermal and photochemical reactions of azirines involve opening of the strained three-membered ring, to give other unstable nitrenes. These reactive intermediates can undergo cycloaddition or rearrangements.[12,138] The thermal ring opening reaction of 2*H*-azirines is generally consistent with N-C2 bond cleavage to form vinyl nitrenes. The vinyl nitrene can be trapped by thermolysis of azirine **54** in the presence of triphenylphosphine to afford phosphazenes **55**,[139] similar to the *N*-vinylic phosphazenes obtained by the Staudinger reaction of vinyl azides and phosphines.[140a-h] This result would seem consistent with the formation of transient vinyl nitrenes upon thermolysis of azirines (*Scheme 33*).[140i]



Scheme 33

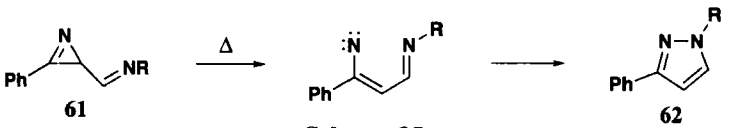
Further support for the existence of vinylnitrenes comes from elegant trapping experiments of Padwa *et al.*[102] Upon thermolysis of vinylazirine **56**, these authors rationalized the formation of the

pyrrole **58** and pyridine **59**, *via* formation of vinyl nitrene **57** and subsequent ring expansion can follow two pathways: a) electrocyclic ring closure of **57** which provides the intermediate 2*H*-pyrrole which then undergoes a 1,5-sigmatropic methoxycarbonyl shift to pyrrole **58**, or b) insertion of the nitrene into the allylic methyl group leading to a dihydropyridine which is easily oxidized to **59**. When thermolysis of azirine **56** was carried out in the presence of tris(dimethylamino)phosphine, the nitrene was trapped as the corresponding phosphazene **60** and the yield of the other products diminished (*Scheme 34*).[140i] This reaction has been extended to iminoazirines **61** which afford the corresponding



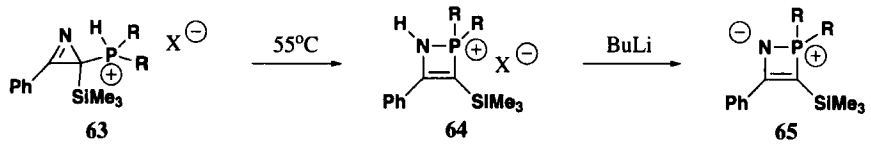
Scheme 34

imidazoles **62** (*Scheme 35*).[45b,68,141] However, extended conjugation of the azirine usually favor a five-membered ring formation rather than seven-membered ring formation.[142]



Scheme 35

Ring expansion of 2*H*-azirines to four-membered heterocycles was described when a chloroform solution of phosphonium salt **63** derived from phosphineazirine **19** was heated at 55° affording the *N*-protonated azaphosphete **64**, in very high yield. Addition of one equivalent of base (BuLi) to **64** generated the four-membered ring **65** in nearly quantitative yield (*Scheme 36*).[25b]

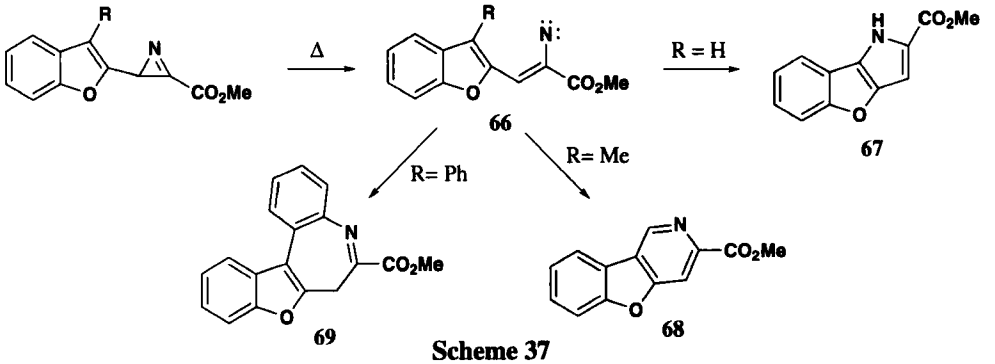


Scheme 36

Thermal rearrangement of 2*H*-azirines, having an unsaturated group at the 2-position of the azirine ring, usually gives five- and six-membered nitrogen containing heterocycles.[143] Formation of

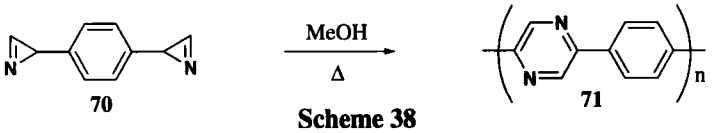
these heterocycles was shown to proceed by a mechanism involving vinyl nitrene.[144] The thermolysis of 2-aryl-substituted azirines resulted in the formation of indoles by intramolecular electrocyclization of the intermediate vinyl nitrene with the aromatic ring, as well as the formation of dihydropyrazines by dimerization of the same nitrene.[41] However, thermal treatment of azirines derived from phosphine oxide and phosphonate led to the formation of pyrazines.[118]

An interesting example studied by Taniguchi *et al.*[142] has been used for the synthesis of fused heterocycles. Nitrene **66** undergoes mainly electrocyclic ring closure to the five-membered ring **67** when R = H. However, insertion reactions take place to form either the six-membered ring **68** in the case of methyl substituted derivatives (R = Me) or the azepine **69** when aryl substituted compounds are used (R = Ph) (*Scheme 37*).



Scheme 37

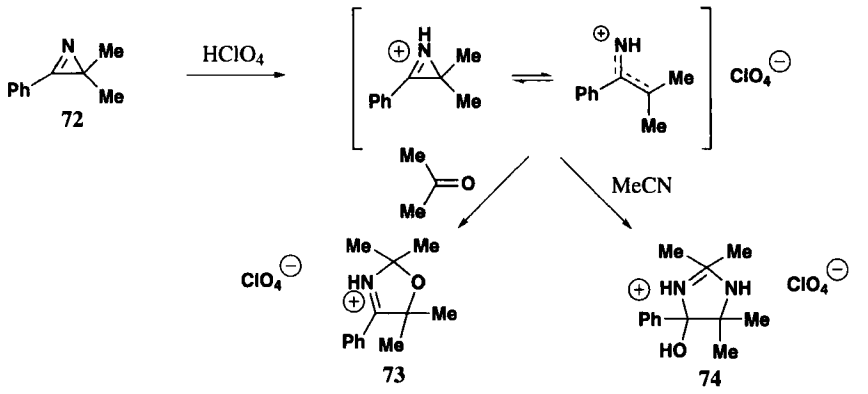
Thermal rearrangement of 2*H*-azirines having a cyclopropane ring at the 2-position was shown to give pyridines by participation of the cyclopropane ring in thermal ring enlargement reactions.[145] Azirines can also behave as monomers for the preparation of polymeric materials. The poly (π-phenylene-co-2,5-pyrazine) (PPz) **71** is a conducting polymer obtained as a fine brown powder by the condensation polymerization of a 2-(4-azirinylphenyl)-2(*H*)-azirine (**70**, *Scheme 38*).[146]



Scheme 38

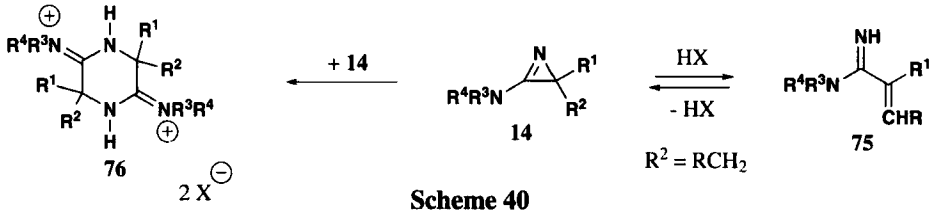
b) Reactions with Electrophiles

2*H*-Azirines undergo ring-opening reactions with very strong protic acids, such as $HClO_4$, HCl and RSO_3H, under non-nucleophilic conditions. The protonated azirine system has been used for the synthesis of acyclic and heterocyclic compounds.[147] For example, treatment of 2,2-dimethyl-3-phenyl-2*H*-azirine **72** with anhydrous perchloric acid and acetone or acetonitrile gives the oxazoline perchlorate **73** and imidazolinium perchlorate **74**, respectively (*Scheme 39*).



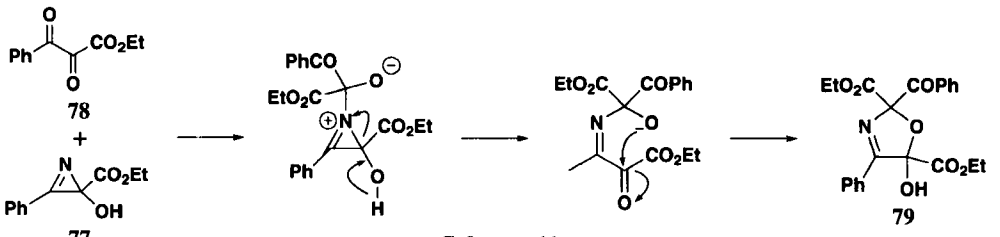
Scheme 39

3-Amino-2*H*-azirines **14** also undergo a ring-opening reaction with cleavage of the N-C2 bond where the major products isolated are acrylylamidines **75** and piperazine-2,5-bis(*N*,*N*-dialkylim-inium) salts **76**[80,148] (*Scheme 40*).



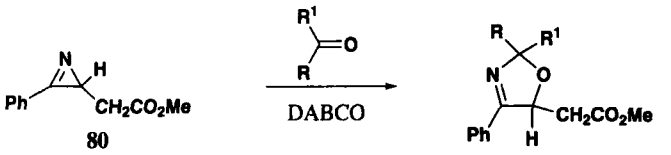
Scheme 40

Substituted azirines react with some carbonyl compounds with ring expansion leading to an elegant synthesis of functionalized oxazoline derivatives. The reaction of 2-hydroxy-2*H*-azirine **77** with the diketoester **78** led to ring opening to give 3-oxazoline **79** (*Scheme 41*). The reaction probably entails the nucleophilic attack of the azirine on the carbonyl group followed by ring opening and intramolecular nucleophilic addition with formation of the five-membered heterocycle.[67]



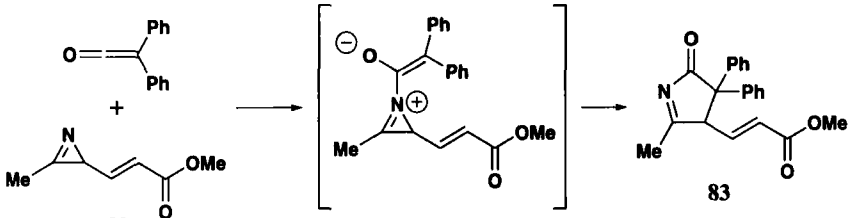
Scheme 41

The mild base-promoted reaction of methyl 3-phenyl-2*H*-azirine-2-acetate **80** with alde-hydes and acetone also provides a simple route to the 3-oxazoline **81** (*Scheme 42*).[149]



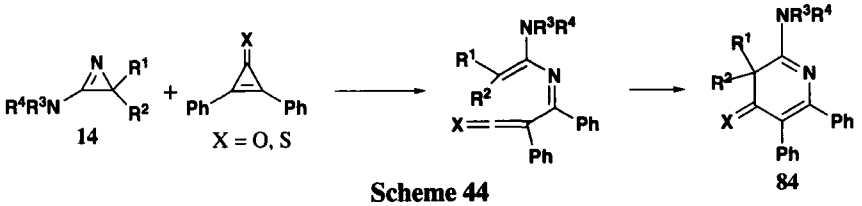
Scheme 42

Ring expansion of the azirine ring to five-membered heterocycles has been observed in an insertion reaction of two carbon atoms of diphenylketene into the N-C2 bond of 2*H*-azirine-2-methylacrylate **82** to give 5-pyrrolin-2-ones **83** (*Scheme 43*).[150] Three carbon atoms are formally inserted



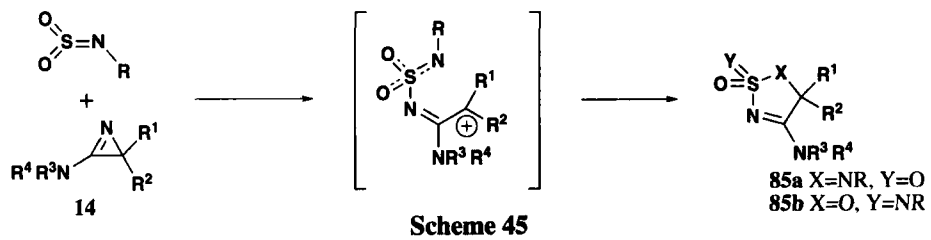
Scheme 43

into the N-C2 bond of azirine when very reactive electrophilic reagents such as strained cyclopropenones react with 2,2-dialkyl-3-(dimethylamino)-2*H*-azirines **14** to afford good yields of the corresponding pyridin-4(3*H*)-one or -thione **84** (*Scheme 44*).[151]



Scheme 44

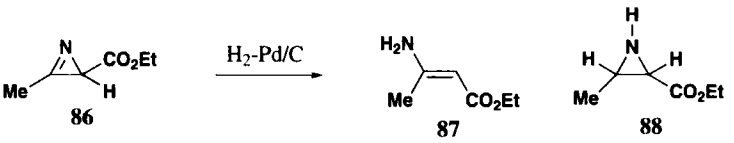
Ring expansion of azirines to five-membered heterocycles has been performed, with *N*-sulfonylimines, especially when the electrophilicity of the central sulfur is increased significantly by electron-withdrawing groups on the nitrogen. Thus, reaction of 3-dimethylamino-2,2-diphenyl-2*H*-azirine **14** ($R^1 = R^2 = Ph$, $R^3 = R^4 = Me$) with *N*-sulfonylalkylamines (R = ^{i}Pr, ^{t}Bu) provides 1,2,5-thiadiazoles **85a** (X = NR, Y = O) whereas use of *N*-carbonylsulfonylamines (R = CO_2Me) primarily results in 1,2,3-oxathiazoles **85b** (X = O, Y = NR) (*Scheme 45*).[152]



Scheme 45

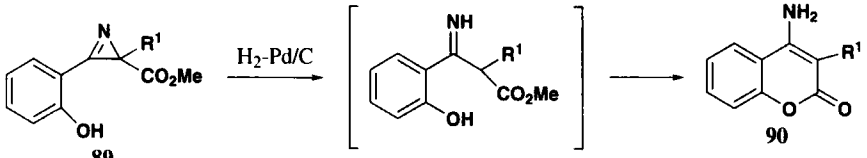
c) Catalytic Hydrogenation

Catalytic hydrogenation (palladium or Raney nickel catalyst) surprisingly results in the ring opening of azirines through the N-C2 bond.[153,154] The resultant imines or primary enamines are not usually isolated and their existence has only been inferred in most instances, given that the presence of an electron-withdraving group on the β-carbon of the enamine is required in order to stabilize the primary enamine group.[155] The reduction of azirinecarboxylic ester **86** to the enamino ester **87** may not first proceed through the aziridine **88**, since the latter was difficult to reduce with hydrogen and palladium on carbon (*Scheme 46*).[123d,123l,153]



Scheme 46

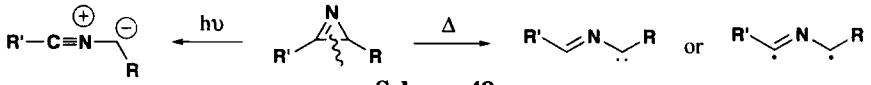
Catalytic hydrogenation of polyfunctionalized azirines **89** with palladium on carbon caused ring enlargement to 4-aminocoumarin derivatives **90** *via* cyclization and isomerization of the initially formed imino esters (*Scheme 47*).[108]



Scheme 47

3. Reactions Involving the C2–C3 Bond

Cleavage of the C-C single bond of 2*H*-azirines is less common than the N-C2 bond cleavage, but can be accomplished not only thermally but also photochemically; the intermediates formed such as imino diradicals or nitrile ylides, can react further with a wide range of reagents leading to acyclic and cyclic derivatives (*Scheme 48*).

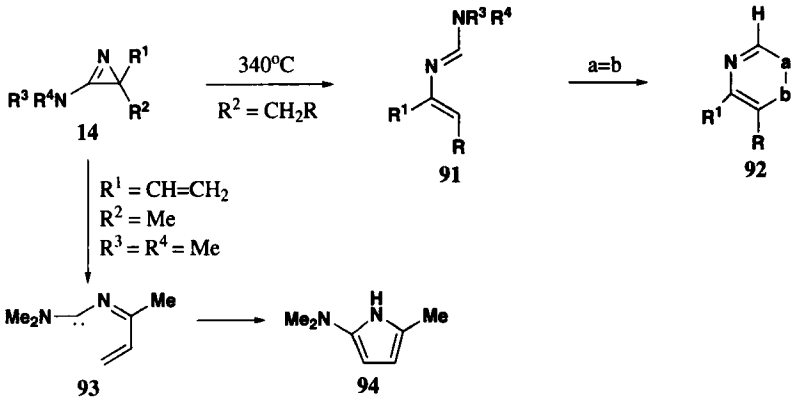


Scheme 48

a) Thermolysis

Thermal cleavage of the C2-C3 bond of 2*H*-azirines is less common than N-C2 bond cleavage, requiring substantially higher temperatures. These reactions are believed to proceed *via*

diradical intermediates which undergo a 1,4-hydrogen transfer to yield 2-aza-1,3-butadienes. The dienes thus formed, often participate in subsequent intra- or intermolecular cyclization reactions.[156] The C2-C3 bond of 3-amino-2*H*-azirines **14** ($R^2 = CH_2R$) can be cleaved by pyrolysis at 340-400°.[45a,157] 2-Azabuta-1,3-dienes of type **91** can be formed and are useful heterodienes for the synthesis of heterocycles **92** *via* Diels-Alder reaction (*Scheme 49*). In the last decade, 2-azadienes **91** have proved to be excellent synthons for the preparation of nitrogen heterocycles in inter and intramolecular reactions[158] and less drastic conditions for their preparation have been developed.[159] Ring-expansion of 3-*N*,*N*-dimethylamino-2-methyl-2-vinyl-2*H*-azirine to pyrrole **94**, observed during thermolysis at 340°, also seems to occur *via* C-C bond cleavage.[160]

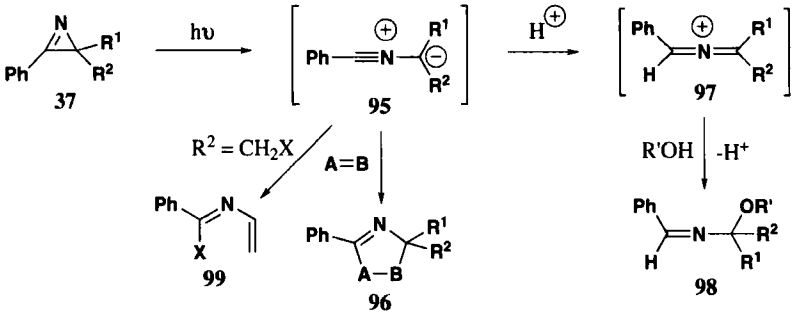


Scheme 49

b) Photochemical Reactions

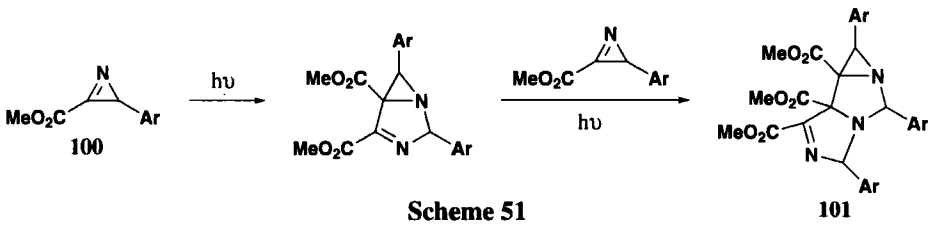
Photochemical reactions of azirines involve opening of the strained three-membered ring to give unstable nitrile ylides (*Scheme 50*). These intermediates can then react in intramolecular, intermolecular or cycloaddition processes or by means of other rearrangements. Upon excitation of the n-π^* bands, the strained 3-membered azirine ring opens selectively at the C-C bond in a heterolytic fashion resulting in the formation of a nitrile ylide. This species is a 1,3-dipole and is a very useful intermediates for the synthesis of acyclic and heterocyclic derivatives.[161] On photolysis of 2*H*-phenylazirines **37** (R^1 = H) in acetonitrile or alcoholic solutions with 248 nm laser light, phenylnitrile ylides **95** are formed. In acetonitrile electron-deficient olefins react with the nitrile ylides by 1,3-dipolar cycloaddition to yield five-membered heterocycles **96**. However, with alcohols as solvents, the nitrile ylides are protonated[162] to yield azallenium cations **97**, which can be trapped by the alcohol leading to the formation of alkoxyimines **98**. When the azirine contains a good leaving group ($R^2 = CH_2X$) the isomerization to 2-azadiene **99** has been reported (*Scheme 50*).[161f]

In the absence of a dipolarophile, the intermediate nitrile ylide generated by photolysis of an azirine adds to the precursor azirine, and several examples of bicyclic dimers are known. This aspect of the photolytic reaction is well illustrated by the trimerisation reaction of 2*H*-azirine carboxylates



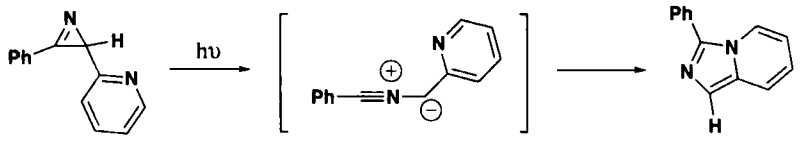
Scheme 50

100 in which a polycyclic heterocycle **101** is formed, presumably, by cycloaddition of the initially formed dimer to the nitrile ylide, generated by electrocyclic ring opening of a third molecule of azirine (*Scheme 51*).[163]



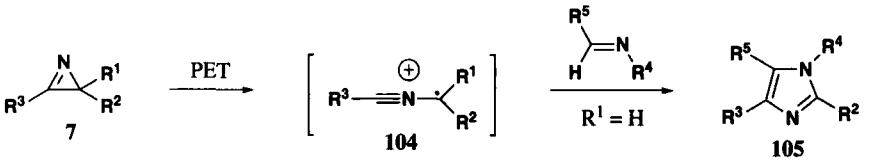
Scheme 51

Ring expansion of azirines to five-membered heterocycles has been reported. Thus, photochemical isomerization[104,106,107,164] of amido or carbonyl azirine to 1,3-oxazoles *via* C-C bond cleavage has been observed. In a similar way, the formation of 3-phenylimidazol[1,5-*a*]pyridine **103** by photolysis of 3-phenyl-2-(2-pyridyl)-2*H*-azirine **102** (*Scheme 52*) has been described.[165] This result is in agreement with some reports on the cycloaddition of nitrile ylides to pyridine, quinoline and isoquinoline affording heterocondensed imidazolines.[166]



Scheme 52

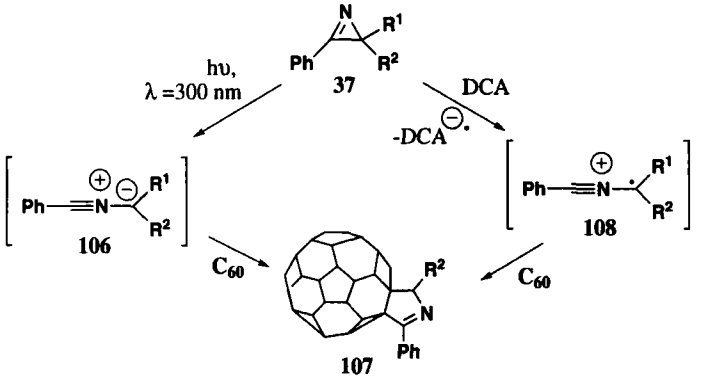
An alternative approach to the generation of reactive intermediates from an 2*H*-azirine **7** has been explored during the last decade. Certain cyanoarenes can be photoexcited at a relatively low wavelength (350 nm) and this excited sensitiser will then extract an electron from a 2*H*-azirine species to form a reactive intermediate, the azaallenyl radical cation **104**. Photoinduced electron transfer (PET) intermediate **104** is more reactive than the nitrile ylide and it will add to simple imines to give a substituted imidazole such as **105** (*Scheme 53*).[167]



7 104 105

Scheme 53

An exohedrally functionalized fullerene such as 1,9-(3,4-dihydro-2,5-diphenyl-2*H*-pyrrolo)-[60]fullerene can also be prepared by the [3+2] photocycloaddition of nitrile ylide to C_{60} fullerene (*Scheme 54*). The nitrile ylide **106**, which was generated by direct irradiation of 2,3-diphenyl-2*H*-azirine **37** (R^1 = H, R^2 = Ph), added to C_{60} acting as 1,3-dipolarophile with formation of a C_1 symmetrical 1,2-(3,4-dihydro-2,5-diphenyl-2*H*-pyrrolo)-[60]fullerene **107**. Mechanistic studies revealed a second reaction pathway, for example, the addition of azirine under photo-induced electron transfer (PET) conditions using 9,10-dicyanoanthracene (DCA) as a PET sensitizer and light above 400 nm wavelength. In this case the addition obviously occurs *via* a 2-azaallenyl radical cation **108**.[168] Aliphatic 2*H*-azirines are not suitable because they have a shorter excitation wavelength than the phenyl substituted 2*H*-azirines with forbidden π-π* transitions of the phenyl group (*Scheme 54*).



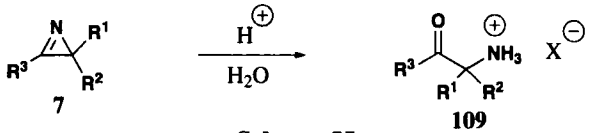
107

Scheme 54

4. Reactions Involving the N–C3 Bond

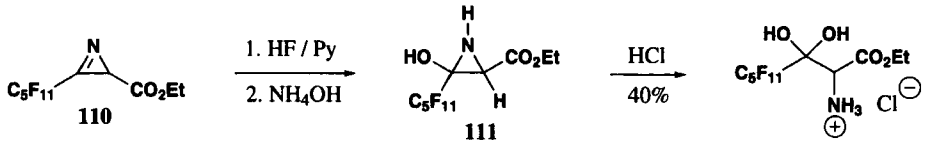
a) Acid-catalyzed Addition of Nucleophiles

The most common reaction of azirines involves the addition of nucleophiles to the ring carbon atoms. Due to the strain of the three-membered ring, the electrophilic character of the C-N double bond is higher than in a normal imine. Therefore, azirines react with nucleophiles at the N-C3 double bond, to produce substituted aziridines[9,10] which may undergo further reaction by ring-opening. Acid catalyzed hydrolysis of azirines **7** to α-aminoketones[9,147,169] or their corresponding salts **109** represents the simplest reaction of these compounds (*Scheme 55*).



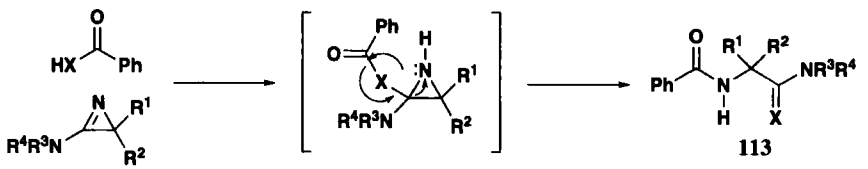
Scheme 55

Interestingly, the addition of HF/pyridine (Olah's reagent) to the highly electrophilic 3-(perfluoroalkyl)-2*H*-azirine[69] **110** leads to a stable 2-hydroxyaziridine **111**, presumably due to the electron-withdrawing perfluoroalkyl group. 2-Hydroxyaziridine **111** reacts with aqueous HCl to afford the ring opened hydrate salt **112** (*Scheme 56*). 2-Methyl-3-phenyl-2*H*-azirine has also been subjected to Olah's reagent to give the ring-opened compound β,β-difluoroamphetamine.[170]



Scheme 56

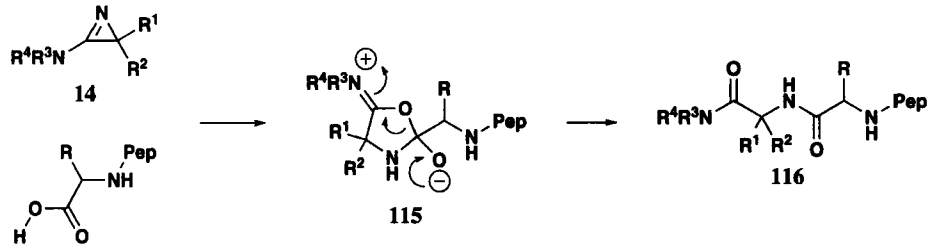
Acid-catalyzed nucleophilic addition of aniline to 2,2-dimethyl-3-phenyl-2*H*-azirine in the presence of perchloric acid has been observed to give α-ammonioisobutyrophenone anil perchlorate.[171] Likewise, reaction of azirines with trimethylsilyl triflate or trityl tetrafluoroborate[172] yield aziridinium salts, which react with nucleophiles to give 2-aminoaziridines or further open-chain products. Carboxylic and thiocarboxylic acids can ring open 2,2-disubstituted-3-amino-2*H*-azirines **14** under mild conditions to furnish diamides[173,174] **113** (X = O) or thiodiamides[44,85,173,174,175] **113** (X = S), respectively in good yields (*Scheme 57*). 2-Monosubstituted-3-amino-2*H*-azirines have also been used in this reaction.[25c] Similarly, addition reactions and cleavage of the C-N double bond of 3-amino-2*H*-azirines occurs upon hydrolysis with potassium hydrogen phosphate in water, with activated phenols or thiophenols,[176] with cyclic enolizable 1,3-diketones,[177] or with sulfinic acids.[178]



Scheme 57

The extension of this procedure to amino acids, leads to the synthesis of peptides containing an α,α-disubstituted amino acid, as shown in *Scheme 58*. Thus, 3-amino-2*H*-azirines **14** react readily with the carboxylic group of an *N*-protected aminoacid **114** followed by ring expansion to form a zwitterionic oxazolone **115** which undergoes ring opening to form a diamide **116**. This reaction can be regarded as a peptide chain elongation step which introduces an α,α-disubstituted amino acid onto the *C*-terminal end of a peptide, as shown in *Scheme 58*. It should be pointed out that no additional

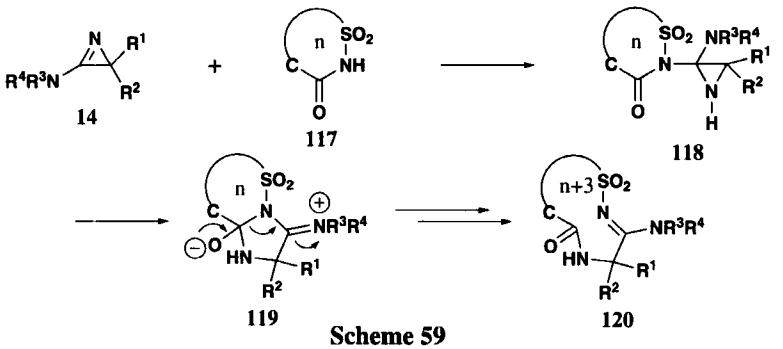
reagents are required under the very mild conditions needed for the coupling with **14**, and no by-products are observed. Subsequent selective hydrolysis of the terminal amide group of **116** to a carboxylic acid allows for subsequent reactions. This so-called "azirine/oxazolone methodology" constitutes an attractive method for insertion of α,α-disubstituted α-amino acids into peptides. This methodology has been widely applied to the formation of peptide analogs,[25c,81,179] endothiopeptides[180] and various more complex oligopeptides, particularly those containing α-aminoisobutyric acid residues such as the sequence (12–20)-nonapeptide of the ionophore alamethicin,[181] endothiodecapeptides,[182] the segment (1–10)-endothiodecapeptide of the apolar zervamicin IIA,[183] the *C*-terminal segment (6–14) of the peptaibole trichovirin I 1B,[184] and cyclic depsipeptides[185] through acid-catalyzed direct amide cyclization.



Scheme 58

Heimgartner *et al.* have also shown that nucleophilic addition of amides or hydrazides to 3-amino-2*H*-azirines **14** produces a variety of nitrogen heterocycles. Thus, reaction of **14** with salicylamide afforded two imidazoles in a ratio which depended on reaction conditions.[186] Likewise, triazines as well as oxadiazoles have been obtained when hydrazides such as salicylhydrazide were treated with 3-amino-2*H*-azirines **14**.[187] This reaction can also be applied to NH-acidic heterocycles with $pK_a < 8$ to give ring enlarged heterocycles. Reaction of 1,2-thiazetidin-3-one 1,1-dioxides **117** (n = 4) with 3-amino-2*H*-azirines **14** afforded 1,2,5-thiadiazepine derivatives[188] **120** (n = 4) (*Scheme 59*). A similar reaction has been observed with saccharin[189] and other 1,2-thiazol-3-one 1,1-dioxides,[190] yielding 1,2,5-thiadiazocine derivatives **120** (n = 5). With analogous six-membered derivatives, 1,2,5-thiadiazonin-6-one 1,1-dioxides **120** (n = 6) have been obtained[191] and with seven, eight and nine-membered, 1,2,5-benzothiadiazecinone 1,1-dioxides[192] **120** (n = 7), 1,2,5-thiadiazacycloundecen-6-one 1,1-dioxides **120** (n = 8) and 1,2,5-thiadiazacyclododecen-6-one 1,1-dioxides **120** (n = 9) have been synthesized[193] (*Scheme 59*). Other heterocyclic substrates which have reacted with 3-dimethylamino-2,2-dimethyl-2*H*-azirine and related azirines include imidazolidine-2,4-diones and the analogous imidazolidine-2,4,5-triones.[194]

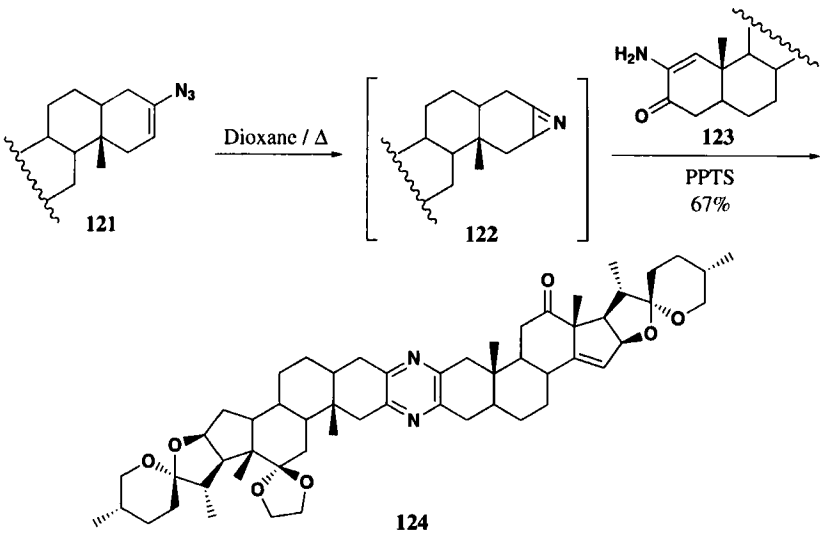
Varying the substrate in reactions with other NH-acidic heterocycles demonstrates that the initial step in all these reactions is the protonation of 3-amino-2*H*-azirine **14**, since for substrates with $pK_a > 8$, the reaction no longer occurs. Subsequent nucleophilic attack onto the amidinium *C*-atom yields aziridine **118**, which undergoes a ring enlargement to give the zwitterionic intermediate **119**. After a second ring enlargement, the latter rearranges to the final product **120** (*Scheme 59*). In some



Scheme 59

cases the primary products could not be isolated because of their further rearrangement under the reaction conditions. In this context, 3-amino-2*H*-azirines **14** react with hydantoins,[195] barbituric-acid derivatives,[196] 1,3-oxazol-5(4*H*)-ones,[197] and 1,3-oxazolidine-2,4-diones or 1,3-thiazolidine-2,4-dione[198] to give ring enlarged heterocycles, where the zwitterionic intermediate **119** rearranges in a different manner, and in some cases compound **120** could not be detected because of further rearrangement or transannular ring contraction.

Reaction of azirines with enamino ketones and a mild proton source has been used recently for the synthesis of *bis*(steroidal) pyrazines.[199] In this context, ring-fused azirine **122**, formed *in situ* from vinyl azide **121** in refluxing dioxane, reacted in the presence of pyridine-*p*-toluenesulfonate (PPTS) with enamino ketone **123** giving *bis*(steroidal) pyrazine **124** as shown in *Scheme 60.*



Scheme 60

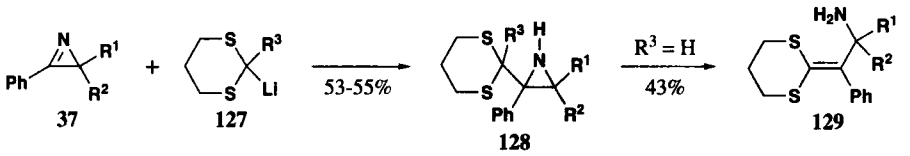
Lewis acid-catalyzed reactions of 3-amino-2*H*-azirines with carboxylic acid derivatives have also been reported by Heimgartner *et al.*[200] After activation by complexation with a Lewis acid ($BF_3{\cdot}Et_2O$), 3-amino-2*H*-azirines reacted with the amino group of α-amino-acid esters to give 5-amino-3,6-dihydropyrazin-2(1*H*)-ones by ring enlargement.[201]

b) Other Additions of Nucleophiles

The activation of the three-membered ring by protic or Lewis acids is not necessary when strong nucleophilic agents react with 2*H*-azirines. Several 2*H*-azirines have been reduced to *cis*-aziridines with lithium aluminum hydride or sodium borohydride in a highly stereospecific manner.[39] This reaction has been used as a method for proof of the *cis*-configuration structure for simple aziridines,[40] for fluoro-substituted aziridines,[69] and for aziridine carboxylates ($R^1 = CO_2R$)[113] (*Scheme 61*). The high exocyclic dihedral angle at the saturated carbon atom could hinder the nucleophilic attack of the hydride ion on the iminic bond with the bulky substituent, and the diastereoselectivity of the reduction can thus be explained. Therefore, the approach of the hydride is more favorable from the side opposite to the group at the 2-position and *cis*-aziridines are formed exclusively. [(2*H*-Azirin-2-yl)methyl]phosphonates **125** ($R^1 = CH_2P(O)(OEt)_2$) have been subject to reduction with $NaBH_4$ resulting also in the predominant formation of disubstituted *cis*-aziridines.[31] Similarly, azirines derived from phosphine oxides[43] **125** ($R^1 = P(O)Ph_2$) and phosphonates[117] **125** ($R^1 = P(O)(OEt)_2$) have been reduced recently to aziridines using sodium borohydride, to give the *cis*-aziridines **126** exclusively (*Scheme 61*).

Scheme 61

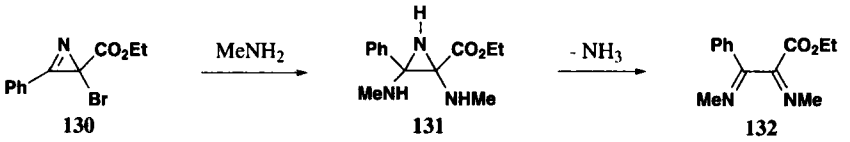
Other nucleophilic reagents such as Grignard reagents have been shown to react with 2*H*-azirines to give aziridines. The few reports of the addition of Grignard reagents to 2*H*-azirines reveal that the aziridine product is formed by attack at the least hindered face.[202] However, recent results which involve the addition of methylmagnesium bromide from the more hindered face of 2*H*-azirine-2-carboxylate esters have resulted in a new methodology for the asymmetric synthesis of 3,3-disubstituted aziridine-2-carboxylate esters.[125] These results, which contradict previous reports,[202] are likely to be a consequence of chelation of the Grignard reagent with the ester group. 3-Phenyl-2*H*-azirines **37** (R^1 = Me) react with lithium derivatives of 1,3-dithianes **127** to afford *C*-functionalized aziridines **128** or, if R^3 = H, primary allylic amines[203] **129** (*Scheme 62*). However, azirines **37** react with lithium azaenolates derived from oximes and hydrazones to give isoxazoles and pyrroles.[203]



Scheme 62

2-Halo-2*H*-azirines **130** have been used in nucleophilic substitution using potassium phthalimide and aniline as nucleophiles, and this allows the preparation of new substituted 2*H*-azirines through halide displacement.[67] However, reaction of azirines **130** with methylamine underwent not only halide displacement but also addition to the imine double bond to give substituted aziridine **131** (*Scheme 63*). Opening of the aziridine ring and elimination of ammonia gave the α-diimine **132**.

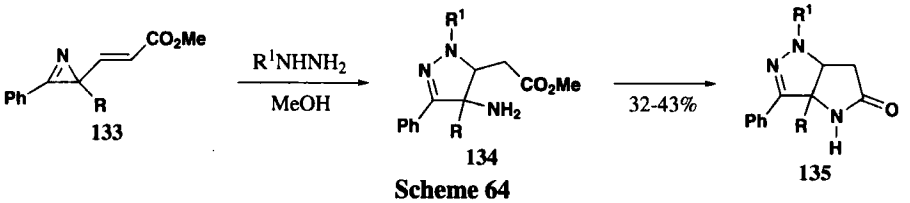
Anions derived from five-membered aromatic heterocycles can add to the C=N bond of activated 2*H*-azirines to give stable aziridines.[204] Thymine, uracil, adenine and other pyrimidine and purine bases add to the C-N double bond of benzyl 2*H*-azirine-3-carboxylate to give benzyl azirine-2-carboxylates substituted at the 2-position with a nucleobase.[205]



130 131 132

Scheme 63

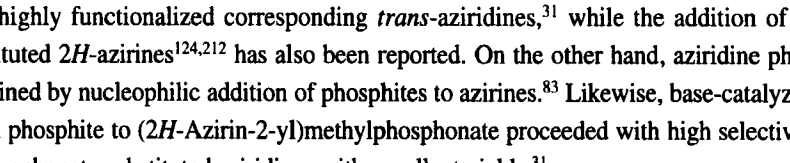
Electron-deficient azirines such as methyl 2-aryl-2*H*-azirine-3-carboxylate are highly susceptible to nucleophilic attack.[206] This azirine reacted readily not only with nucleophiles such as benzenethiol and propargyl alcohol to give substituted aziridines but also with morpholine or benzylamine to give acyclic 3-aminoacrylates. Pyrroles may be prepared by the nucleophilic addition of acetylacetone[206] or enamines[207] to the same azirine. However, the nucleophilic addition of a variety of five-membered aromatic nitrogen heterocycles to azirine carboxylates gave functionalized aziridines.[204] Reaction of methyl-3-(2-methyl-3-phenyl-2*H*-azirin-2-yl)prop-2-enate **133** with some heterocyclic nucleophiles led to the formation of 2-aza-1,3-dienes.[208] Similarly, the reaction of this functionalized 2*H*-azirine **133** with hydrazines as nucleophiles in methanol produced hexahydropyrrolo[3,2-*c*]pyrazol-5-ones **135**.[209] The process is assumed to involve intramolecular interception of an unstable 4-aminopyrazoline intermediate **134** resulting from C-N double bond cleavage (*Scheme 64*).



133 134 135

Scheme 64

N-Silylated **137** or *N*-unsubstituted trifluoromethylaziridines **138** may be prepared by the reaction of (trifluoromethyl)trimethylsilane[210] with azirine **136** as shown in *Scheme 65*.[211] In a similar way, addition of trimethylsilyl cyanide to [(2*H*-Azirin-2-yl)methyl]phosphonates yielded, stereoselectively, the highly functionalized corresponding *trans*-aziridines,[31] while the addition of cyanide to other substituted 2*H*-azirines[124,212] has also been reported. On the other hand, aziridine phosphonates can be obtained by nucleophilic addition of phosphites to azirines.[83] Likewise, base-catalyzed addition of dimethyl phosphite to (2*H*-Azirin-2-yl)methylphosphonate proceeded with high selectivity to yield *trans-bis*phosphonate substituted aziridines with excellent yields.[31]

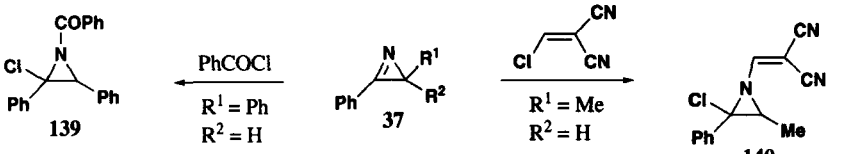


136 137 138

Scheme 65

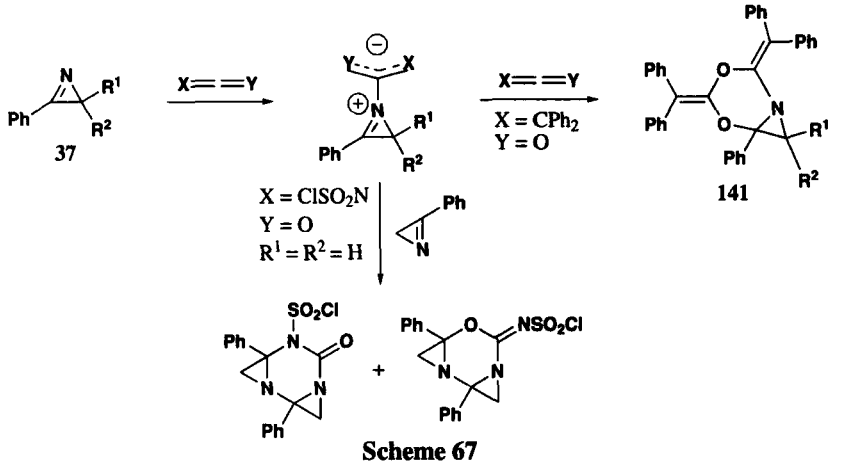
c) Addition of Electrophiles

2*H*-Azirines react with acylating agents such as acid chlorides in benzene to give the *N*-benzoyl-2-chloroaziridines **139** in good yield by formal addition of RCOCl to the double bond[213] (*Scheme 66*).[169a,214] These *N*-acyl aziridines are converted in polar solvents or by heating, into oxazole and dichloroamide. However, whereas the reaction of 3-phenyl-2*H*-azirine **37** with acid chlorides and anhydrides in the presence of triethylamine gives the oxazole directly,[215] the reaction of 3-amino-2*H*-azirines with acyl chlorides,[45a,94,179b,214a,b,216] chloroarenes or chloroquinones leads to acrylamidines. In a similar way, the *N*-functionalization of azirines can also be achieved when vinyl halides are used as electrophilic reagents. Thus, 2-chloro-*N*-vinylazirines **140**[217] can be obtained by *N*-vinylation of azirines **37**, as shown in *Scheme 66*.



Scheme 66

Heterocumulenes are excellent electrophilic reagents and therefore cycloadditions of azirines with heterocumulenes such as ketenes,[218] ketenimines, isocyanates,[219] isothiocyanate[220] and carbon disulfide can occur. Some isocyanates such as $ClSO_2NCO$ can act as acylating agents with 3-phenyl-2*H*-azirine **37** ($R^1 = R^2 = H$) to yield tricyclic 1,3,5-triazines.[221] However, the reaction of simple 2*H*-azirines **37** ($R^1 = R^2 = H$, $R^1 = H$, $R^2 = Me$, $R^1 = R^2 = Me$) with diphenylketene has been reported to afford bicyclic aziridines **141**, formed by way of addition of two equivalents of ketene to starting azirine (*Scheme 67*).[218c,222]

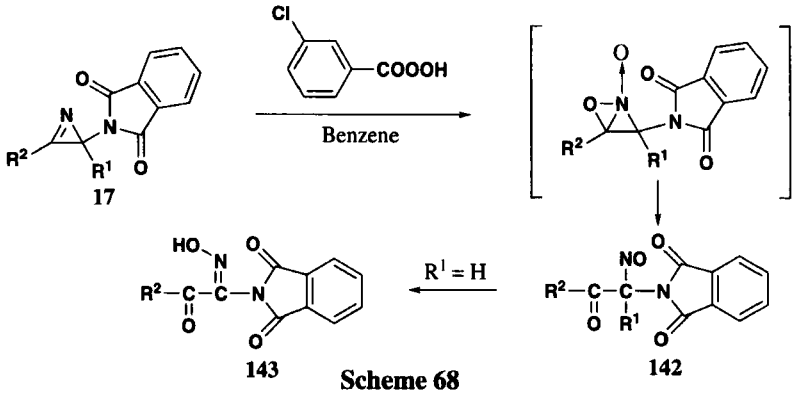


Scheme 67

d) Oxidation Reactions

Few examples of oxidation of azirines have been reported. The oxidation of 2*H*-azirines gives acyclic or cyclic derivatives as in the case of 2-aminoazirine **17** and 3-chloroperbenzoic acid as

oxidizing agent. The mechanism of the reaction seems to involve initial epoxidation of the C-N bond to produce a α-nitrosoketone **142** and α-oximinoketones **143** (*Scheme 68*).[223] A similar mechanism may be involved in the oxidation of 2,3-diphenyl-2*H*-azirine to isoquinoline-*N*-oxide.[224]



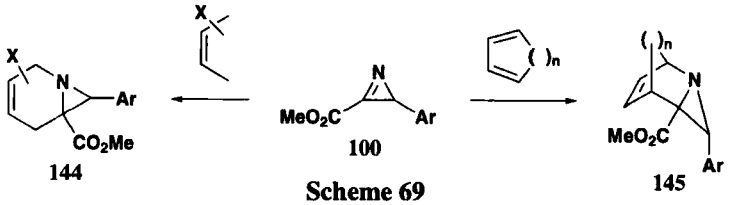
Scheme 68

e) Cycloaddition Reactions

Strained cycloolefins are excellent dipolarophiles[225] and dienophiles[226] in [4 +2] cycloaddition processes. In a similar way, the strained C-N double bond of 2*H*-azirines is more reactive than that of normal imines. Therefore, the C-N double bond of 2*H*-azirines can participate not only as a dienophile but also as a dipolarophile in thermal symmetry-allowed [4 +2] cycloadditions with a variety of dienes and 1,3-dipoles.[227]

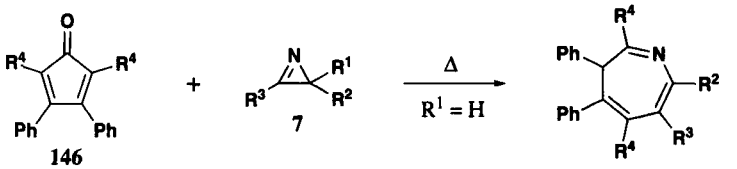
1. 2*H*-Azirines as Dienophiles

The reactivity of imines as dienophiles is enhanced by the presence of an electron-withdrawing substituent on carbon, but there are relatively few reports of Diels-Alder reactions of 2*H*-azirines. Methyl 2-aryl-2*H*-azirine-3-carboxylates **100** are good dienophiles and react not only with symmetrical dienes such as cyclopentadiene, cyclohexa-1,3-diene and 2,3-dimethylbuta-1,3-diene at room temperature, but also with unsymmetrical electron rich dienes such as alkoxybutadienes, 2-trimethylsilyloxybuta-1,3-dienes or 1-methoxy-3-trimethylsilyloxybutadiene to give [4 +2] cycloadducts **144** and **145**. The cycloadditions are *endo* selective and the dienophile approach takes place from the less hindered face of the azirines (*Scheme 69*).[228] The Diels-Alder reactions of a chiral ester of 2*H*-azirine-3-carboxylic acid with cyclopentadiene is highly diastereoselective.[229]



Scheme 69

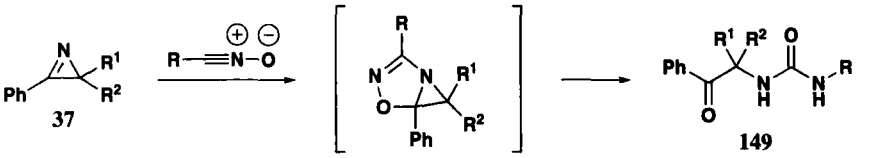
Azirines can also be used as dienophiles with very reactive cyclic dienes such as tetrazines[230] or cyclone **146**.[68,102,231] The first step of this latter reaction, between the azirine and cyclopentadienone, involves a [4+2] cycloaddition to give the *endo* adduct followed by chelotropic fragmentation of the adduct and isomerization to give the 3*H*-azepine ring **147** (*Scheme 70*). However, a variety of five, six and seven heterocyclic products are produced by the thermal reaction of azirines with tetrazines.[230]



Scheme 70

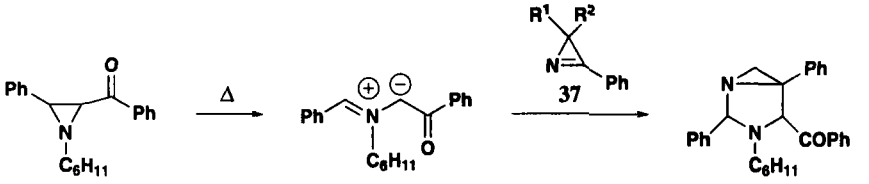
2. 2*H*-Azirines as Dipolarophiles

Logothetis first reported that 2-aryl-3-methyl-2*H*-azirine reacts with diazomethane to produce the allyl azide.[232] This reaction is postulated to proceed by a 1,3-dipolar cycloaddition to form the triazoline which then undergoes tautomerization to the allyl azide.[233] Nitrile oxides can also participate in 1,3-dipolar cycloadditions with azirines. Thus, aromatic nitrile oxides react with 2-methyl-3-phenyl-2*H*-azirines **37** (R^1 = H, R^2 = Me) to furnish *N,N'*-substituted urea derivatives **149** in high yield. The formation of the ureas assumes the initial formation of a cycloadduct **148** from a 1,3-dipolar addition between the nitrile oxide and the azirine (*Scheme 71*).[234]



Scheme 71

Aziridines undergo thermal ring opening in a conrotatory manner to generate azomethine ylides. These azomethine ylides are 1,3-dipoles and can participate in [4+2] cycloadditions with 2*H*-azirines **37** (R^1 = R^2 = H) acting as the 2π-component to give bicyclic heterocycles **150** (*Scheme 72*).[235]



Scheme 72

In conclusion, in this review we have presented an up-to-date overview of the chemistry of 2*H*-azirines. The reactions discussed herein demonstrate the versatility and the high synthetic potential of azirines as valuable precursors for the preparation of polyfunctionalized acyclic and cyclic compounds. Although considerable progress has been made in the chemistry of azirines over the last few years, the imaginative creation of new azirine architectures may yet bring about attractive advances in this field, especially their use as intermediates for the construction of metal-complexes and biologically active compounds derived from nonproteinogenic aminoacids and peptides, as well as in processes based on metal-induced reactions. These synthetic strategies will gain greatly in importance as soon as a wide range of enantiomerically pure azirines becomes available. We have no doubt that many further applications will appear in the future.

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