Research Signpost
37/661 (2), Fort P.O.
Trivandrum-695 023
Kerala, India

Heterocyclic Targets in Advanced Organic Synthesis, 2011: 145-172 ISBN: 978-81-308-0431-6
Editors: Maria do Carmo Carreiras and José Marco-Contelles

7. 2*H*-Azirines as electrophiles

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Abstract. 2*H*-Azirines have shown an unusual potential to synthesise aziridines and other types of compounds. Many functionalized aziridines can be produced by addition of *O*-, *S*-, *N*-, *C*-nucleophiles and hydride to 2*H*-azirines. This review is designed to give an overview of the reactivity of 2*H*-azirines as electrophiles along the years and their usefulness in the synthesis of important families of compounds.

1. Introduction

2*H*-Azirines (Figure 1) are the smallest of unsaturated nitrogen heterocycles. The vast chemistry of these compounds is due to the unique range of properties that renders possible to cleave each of the three bonds of the ring by controlling experimental conditions.

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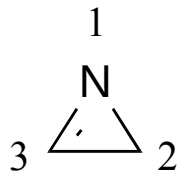


2*H*-azirine

Figure 1

The lone pair of electrons on the nitrogen atom can interact with electrophiles; the π bond, associated with the inherent ring strain, makes 2*H*-azirines good dienophiles and dipolarophiles; and the trigonal carbon atom is an electrophilic centre. Besides, the ring can be cleaved by thermal and photochemical excitation. Some azirines have been obtained due to their biological interest [1-4], others were prepared as intermediates in synthesis, namely to produce aminoacid derivatives [5-7] and heterocycles [5,8-11]. The focus of this work is made on nucleophilic additions to the C=N azirine bond. The addition processes occur with a very significant drop in energy due to a major loss in ring constriction, going from an unsaturated to a saturated three-membered ring (109 kJ mol^{-1}) [12]. In many cases, the aziridine primary adducts are not stable enough to be isolated rearranging to other heterocycles or evolving to open-chain compounds.

A number of general reviews on azirines have appeared in the past [12-16]. In 2001 another two works have been edited focussing more 2*H*-azirine chemistry aspects [17,18]. This text does not pretend to be an exaustive compilation of nucleophilic additions, but rather an informative piece of work. This is particularly the case of 3-amino-2*H*-azirines, due to the extensive number of publications.

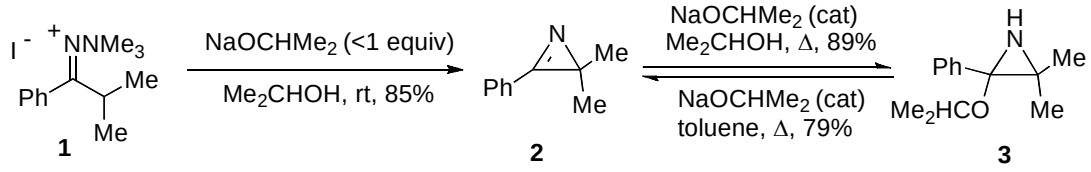
2. Reaction of 2*H*-azirines with nucleophiles

2*H*-Azirines are more susceptible to nucleophilic addition than imines, due to their ring strain [15]. The primary addition compounds are aziridines, which might be isolated or undergo ring-cleavage generating diverse types of products. The nature of the aziridine functionalities plays an important role in the ring geometry and consequently in its stability [19]. *C*-Oxygen-substituted aziridines are usually unstable, detected only as intermediates *in route* to other types of final products. There are nevertheless some 2-alkoxy- and 2-acyloxy-aziridines that have been

isolated. Sulfur-functionalized aziridines are generally stable compounds, but *C*-nitrogen aziridines obtained either from primary or secondary amines are uncommon, probably because the electron pair of the incoming nitrogen tends to promote the C-N bond cleavage. On the other hand, *C*-heteroaminoaziridines are much more stable, due to the diverted delocalization of the nitrogen electron lone pair into the heteroaromatic system. Aziridine C-C bond cleavage has also been observed in adducts obtained by reaction of nitrogen-nucleophiles (heteroaromatic nitrogen-nucleophiles and hydrazine nucleophiles) with 2*H*-azirines. It seems that the nature of the bond cleavage is strongly dependent on the azirine substituents and on the reaction solvent. The reactivity of 3-amino-2*H*-azirine is a rather studied issue. Good nucleophiles are medium range acidic compounds which first protonate at the ring nitrogen atom. The aziridine adducts formed always evolve to α,α-disubstituted α-aminoacids or rearrange to other heterocycles through the C-N bond cleavage. Grignard reagents, organolithium reagents and nucleophilic *C*-radicals add to azirines leading to aziridines, isolable in good yields. Electron-rich olefins like enolates, enamines, ynamines and phosphoranes undergo cycloadditions leading either to pyrroles or open-chain compounds. Hydride ($LiAlH_4$ or $NaBH_4$ sources) add to azirines affording aziridines.

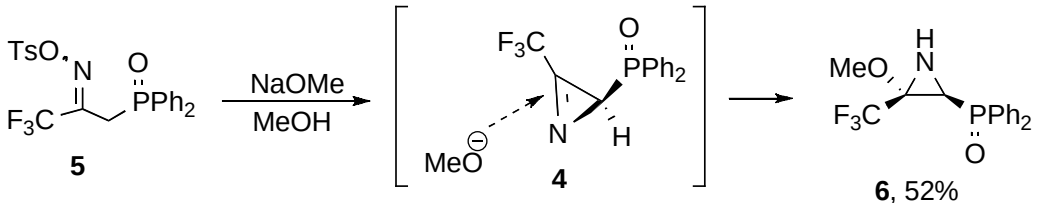
2.1. *Oxygen*-nucleophiles

Alkoxyaziridines were discovered long ago during studies on the Neber rearrangement. Parcell isolated a 2-alcoxyaziridine for the first time in 1963 from dimethylhydrazone methiodide (**1**) and isopropanoxide (<1 equiv) in isopropanol. Short contact between reagents led to 2*H*-azirine **2**, but in the presence of excess of base at reflux, a chemical equilibrium between azirine **2** and aziridine **3** takes place. The aziridine **3** could be isolated in 89% yield by heating **2** with a catalytical amount of sodium isopropanoxide. The azirine **2** could be regenerated back and isolated in 79% yield by heating the reaction mixture in toluene with azeotropic removal of isopropanol (Scheme 1) [20].



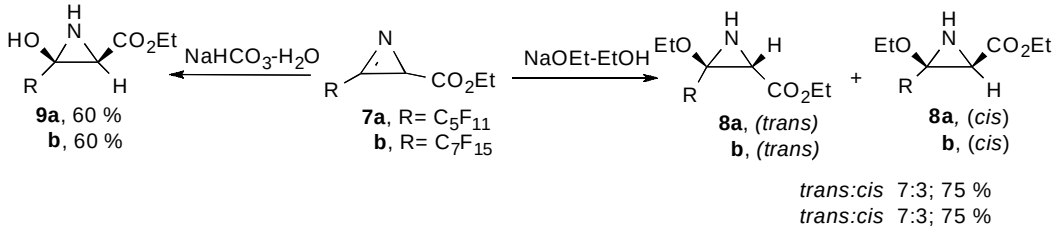
Scheme 1

Azirine **4**, also obtained by a Neber rearrangement from tosylimine **5**, reacts with sodium methoxide. The nucleophilic attack occurs by the least hindered face of the azirine leading to *trans*-aziridine phosphine oxide **6**, in 52 % yield (Scheme 2) [21].



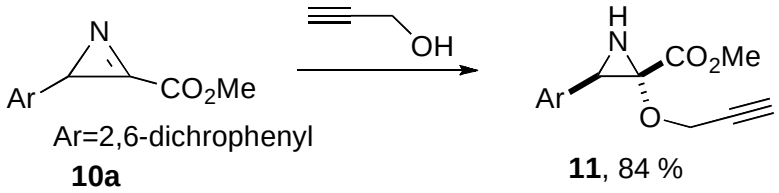
Scheme 2

It is known that the presence of fluorinated alkyl groups in aziridines (and also in azirines) dramatically increases the stability of the ring. These aziridines have been described as quite unreactive materials under neutral, acidic or basic medium, towards electrophiles or nucleophiles [22]. The resistance to ring-opening is demonstrated in another two *O*-substituted aziridines: when ethoxide anion adds to azirines **7a**,**b** a 7:3 stereoisomeric mixture of aziridines **8a** (*cis, trans*) and **8b** (*cis, trans*) are formed in 75% yield; in the case of sodium hydroxide aziridines **9a**,**b** are formed as single isomers (*cis*) (Scheme 3) [22-24].



Scheme 3

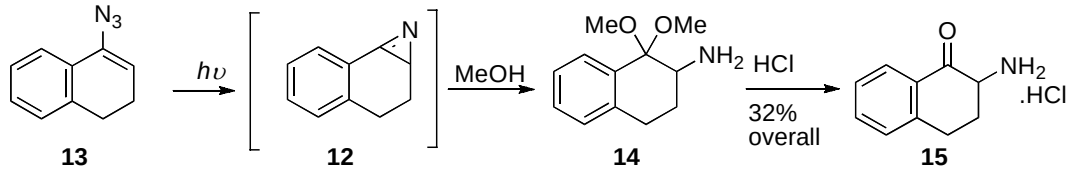
Another especially stable aziridine was formed when methyl 2*H*-azirine 3-carboxylate **10a** was reacted with propargyl alcohol. The aziridine-adduct **11** was isolated in 84% yield (Scheme 4) [25].



Scheme 4

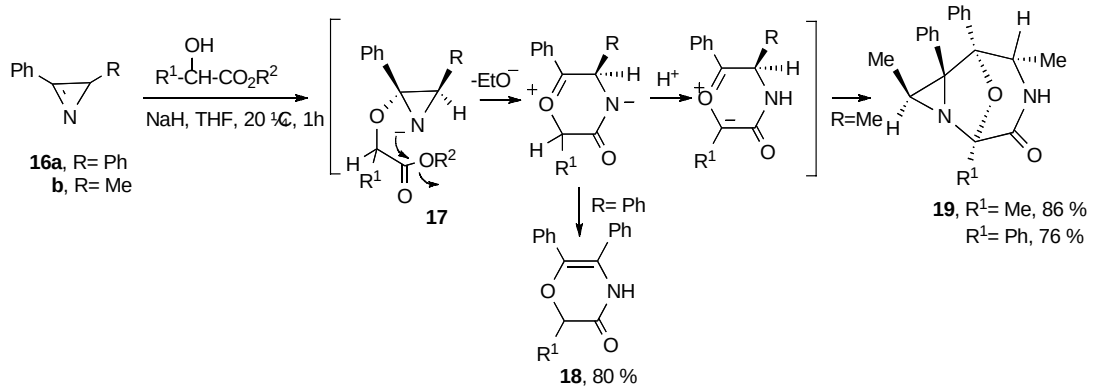
2-Alkoxy and 2-acetoxy aziridines are in general scarcely stable. They are very prone to react with *O*-nucleophiles to give open-chain compounds like α-aminoacetals, α-aminoketones and α-aminoesters.

Scheme 5 shows a classic example in which an azirine, **12**, obtained by photolysis of the α-azido alkene **13**, is trapped with methanol to give an acetal **14**, which is further converted into the α-aminoketone hydrochloride **15** [26].



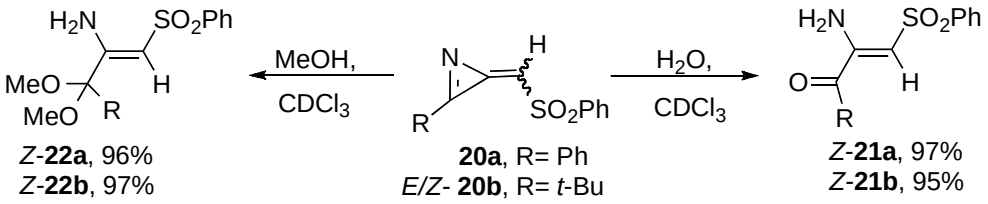
Scheme 5

Azirine **7a** when treated in strong acidic conditions (HCl saturated solution in ethyl ether) also leads to the open-chain compound: ethyl 2-amino-3,3-dihydroxy-3-perfluoropentyl propanoate in its hydrochloride salt [22]. Other final types of structures can be found from C-N aziridine bond cleavage due to *O*-nucleophile additions. Reaction of 2*H*-azirine **16** with ethyl lactate in its ionised form, generates first the *O*-alkylated aziridine anion **17**. Then, this rearranges to oxazinone **18** by ring-opening and re-cyclization, losing ethanol. Ethyl lactate reacted differently with 2-methyl-3-phenyl-2*H*-azirine **16b** to give product **19** by combining two azirine molecules with one ethyl lactate molecule (Scheme 6) [27].



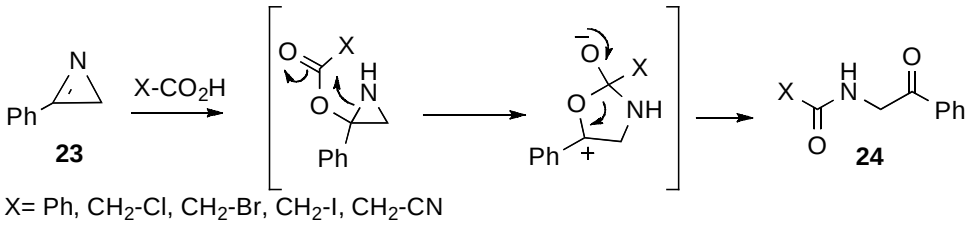
Scheme 6

Methylene-2*H*-azirines **20a** and *E*/*Z*-**20b** suffer a *regio*-controlled reaction at C-3, by addition of nucleophiles, as azirines in general. When treated with water, or with methanol azirines **20a,b** open to give aminoketones *Z*-**21a** and *Z*-**21b**, or 2-aminoacrolein acetals *Z*-**22a** and *Z*-**22b**, respectively, in high yields (Scheme 7) [28,29].



Scheme 7

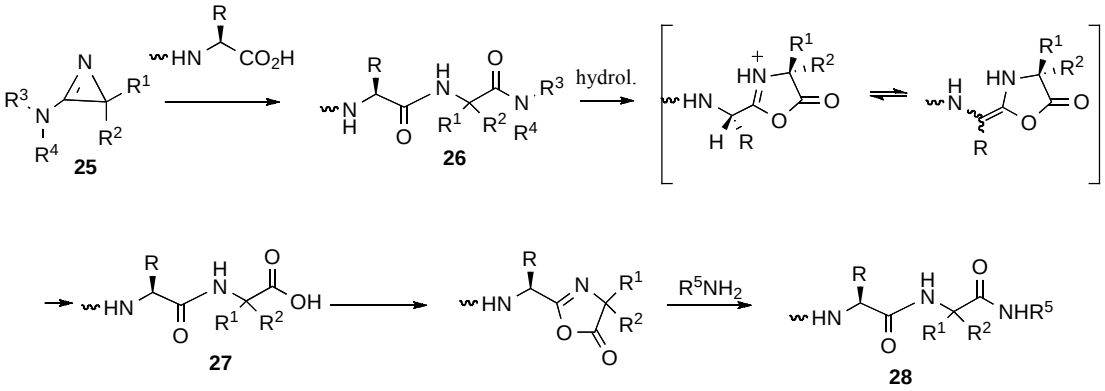
Addition of carboxylic acids to 2*H*-azirines leads to ring-opened products. In acidic conditions azirines protonate at the nitrogen first and only then the *O*-nucleophilic attack takes place. Benzoic acid and chloro-, bromo-, iodo- and cyanoacetic acids are reported to react with 3-phenyl-2*H*-azirine **23** to yield amides **24** in moderate yields [30,31]. The mechanism is depicted in Scheme 8.



Scheme 8

An electronically different azirine such as 3-ethoxy-2*H*-azirine has also been reacted with acetic and benzoic acids. Reactions took place at room temperature giving the respective *N*-substituted amides [32]. Heimgartner extended this reaction to 3-amino-2*H*-azirines **25** and aminoacids as functionalized carboxylic acids and achieved elegant preparations of linear and cyclic peptides [5] and peptolides [33-35]. He developed a method for synthesizing peptides in which α-alkylated α-aminoacids can be easily inserted in the peptide backbone. α-Alkylated α-aminoacids introduce conformational restriction in peptides altering its proprieties. Conventional chain elongation techniques to incorporate these hindered aminoacids into peptides are by no means straightforward processes. As 3-amino-2*H*-azirines

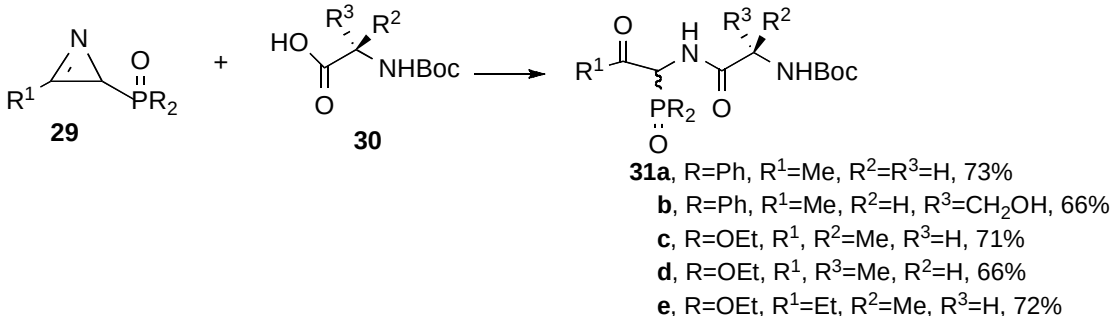
are formally activated amines because of the ring strain, the coupling to the acyl component to yield the amide bond requires no further activation. A schematic synthetic sequence using this methodology in the synthesis of a peptide is shown in Scheme 9. First a *N*-protected α-aminoacid is reacted with the 3-amino-2*H*-azirine **25** giving a dipeptide (**26**). The new amide bond is formed in a rapid intramolecular rearrangement with no racemization. The critical step in the synthesis of scheme 9 is the hydrolysis of the amide function in peptide **26**. The selectivity is high when the azirine precursor bears R^1, R^2, R^3, $R^4 \neq H$ [36,37]. A solution/suspension of **26** in acetonitrile/water treated with HCl gas at 60 ºC affords **27** in yields higher than 95%. The reason for the epimerization risk at this stage is the oxazolone intermediate tautomerism shown in the Scheme 9 [38]. Finally direct coupling to a *C*-protected α-aminoacid *via* another 1,3-thiazo-5(4*H*)-one yields peptide **28**. Recently, peptides containing various sterically demanding α,α-disubstituted α-aminoacids have been conveniently synthesized under solid-phase conditions by the same "azirine-oxazolone" method [39-41].



Scheme 9

Azirines **25** can also be attacked by other *O*-nucleophiles with immediate N_1-C_3 bond cleavage like activated phenols [42], and enolazable 1,3-diketones [43]. The initial step as before for carboxylic acids is the N_1 protonation. Once the substrates are acidic enough (p*Ka* < 8) reactions take place smoothly at around 0 ºC leading to open-chained compounds that can be further cyclised to different kind of heterocycles [5].

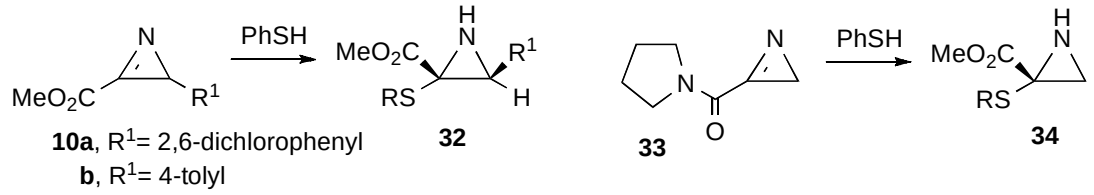
Palacios *et al.* tested the reactivity of 2-phosphorus substituted 2*H*-azirines **29**, derived from phosphine oxides and phosphonate with α-aminoacids **30**. Reactions proceeded at room temperature leading to ketamides **31**, formed through the zwiterionic oxazolone as in the reactions with 3-amino-2*H*-azirines (Scheme 10) [44].



Scheme 10

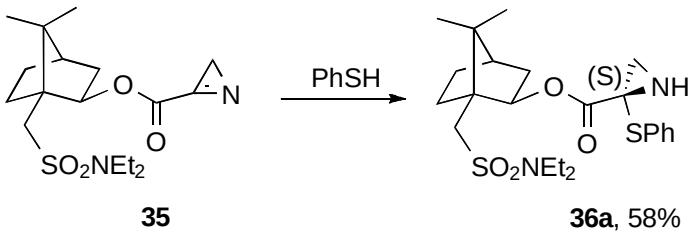
2.2. *Sulfur*-nucleophiles

A set of thiols were reacted with alkyl 2*H*-azirine-3-carboxylates (**10a**,**b**) yielding aziridines **32** [45] after reaction at room temperature from some some minutes to several hours. 2*H*-Azirine-3-pyrrolidinecarboxamide (**33**) behaves similarly affording aziridine **34** by reaction with thiophenol (Scheme 11) [46].



Scheme 11

Considering that *S*-substituted aziridine adducts bearing a carboxylic ester are quite stable compounds, thiophenol was reacted with the chiral ester azirine **35** to test the facial selectivity of the addition. The optically pure product **36a** was formed in 58% yield (Scheme 12). The newly formed stereogenic centre was established to be *S* configuration by X-ray crystallography [47].



Scheme 12

The stereochemistry of compound **36a** is explained by thiophenol nucleophilic attack on the *si* face of azirine in the *s-cis* conformer (**a**). Attack on the *re* face of *s-trans* conformer **(b**) would lead to the non observed *R* diastereomer (Figure 2).

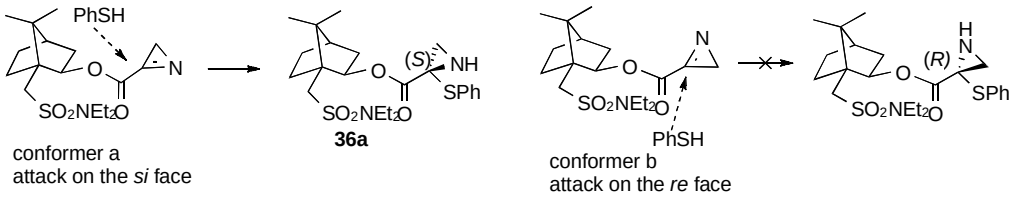
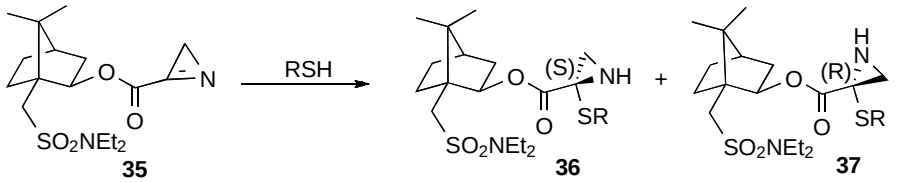


Figure 2

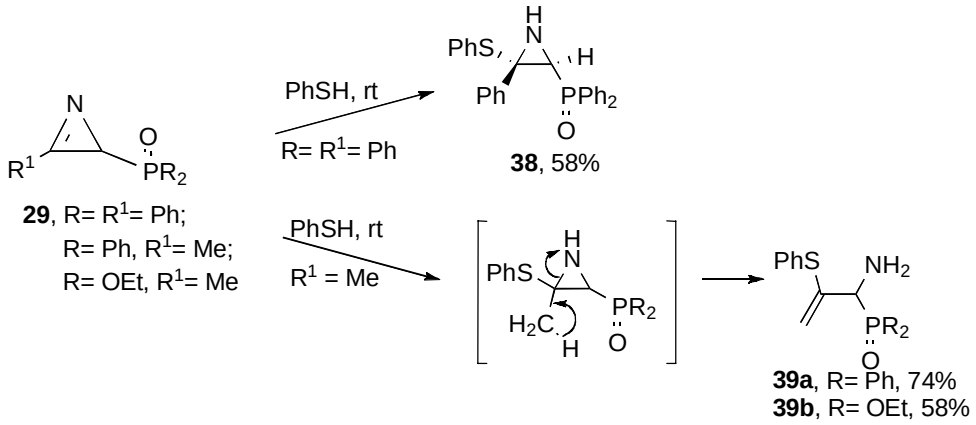
Trying to broaden the scope of this finding to other thiols either less and more reactive than thiophenol, 4-Cl-thiophenol, 4-NO_2-thiophenol and methyl thioglycolate were tested with azirine **35**. Mixtures of diastereomers **36** (*S*): **37** (*R*) were formed according to Scheme 13 [48].



36b:37b, R= C_6H_4Cl-4, 54 %, *dr* 8:1
36c:37c, R= $C_6H_4NO_2$-4, 72 %, *dr* 4:1
36d:37d, R= CH_2CO_2Me, 45 % ,*dr* 1:1

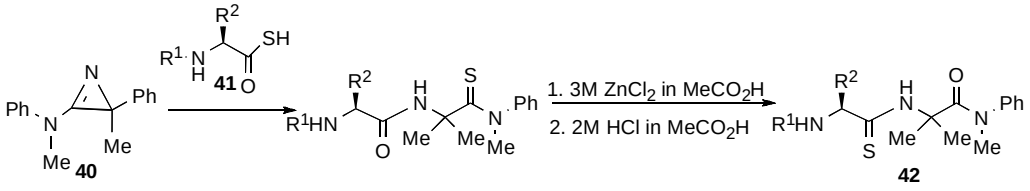
Scheme 13

4-Chlorothiophenol still showed a good diastereoselectivity producing diastereomers **36b**:**37b** in 8:1 ratio. The major adduct (**36b**) was isolated in 54% yield. The less reactive 4-nitrothiophenol did not react under neutral conditions. Excess of sodium carbonate was added to a solution of **35** in acetonitrile, giving a 4:1 mixture of **36c**:**37c** in 72% yield after 30 h at room temperature. When methyl thioglycolate was used as nucleophile a fast reaction took place but the diastereoselectivity dropped to zero, possibly due to the higher reactivity of the alkylthiol [48]. 2*H*-Azirines **29** bearing a phosphine oxide or a phosphonate group were also reacted to thiophenol at 0 ºC. 2*H*-Azirine **29** (R^1=Ph) gave as expected *trans*-configurated aziridine **38** isolated pure in 58% yield. Azirines **29** bearing R^1=Me followed a different reactivity pattern: the aziridine initially formed evolved to an α-aminophosphine oxide **39a** and an α-aminophosphonate **39b** by elimination processes, described in Scheme 14 [21].



Scheme 14

Heimgartner found that 3-amino-2*H*-azirines (**40)** react with activated thiophenols [42] and thiocarbonyl compounds [49] the way *O*-nucleophiles do (see section 2.1). These findings were applied to the synthesis of endothiopeptides (thiomide groups replace one or more amide bonds in the peptide chain), which are biologically valuable compounds due to its higher protease resistance and better bioavailability than peptides [50]. α-Amino thioacids (**41)** are first incorporated in the peptide structure by the "azirine-oxazolone" methodology and then the thiomide group is shifted to an inner position by an acid hydrolysis of terminal thiopeptide. Satisfactory yields and epimerically pure products **42** were obtained in the case of bulky substrates (Scheme 15) [7].

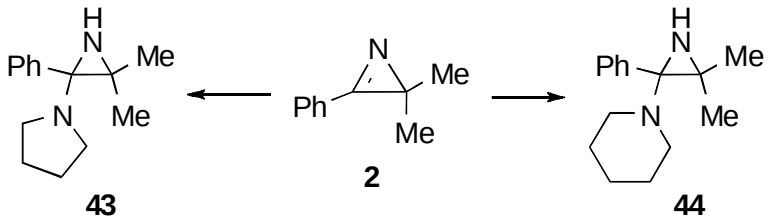


Scheme 15

2.3. *Nitrogen*-nucleophiles

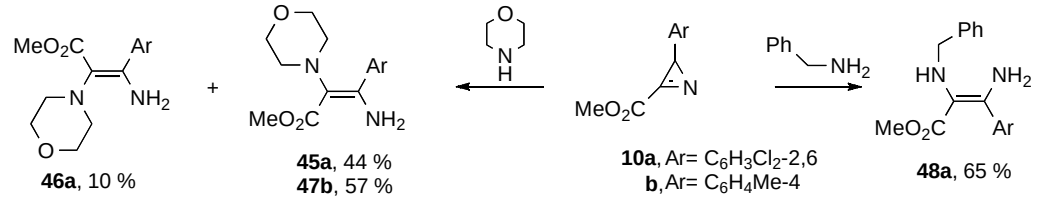
2.3.1. Primary and secondary amines, hydroxylamine, hydrazine and formamidine

C-Nitrogen aziridine adducts are rare, but azirine **2** reacts with pyrrolidine and piperidine giving isolable aziridine compounds **43** and **44**, respectively (Scheme 16) [51].



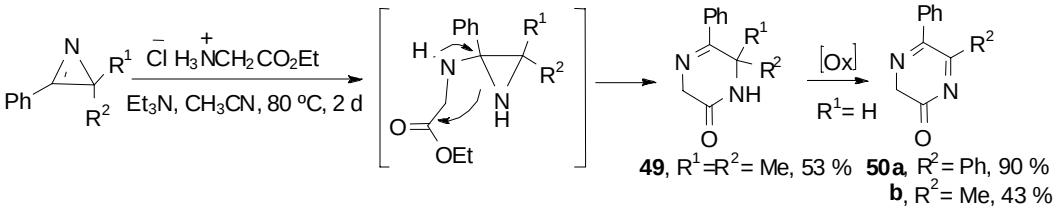
Scheme 16

Parallel reactions of morpholine with azirines **10a**,**b** led no longer to isolable aziridines. The reactions were finished in 15 min at room temperature giving two 3-aminoacrylate isomers *E*-**45a** (44%) and *Z*-**46a** (10%) from azirine **10a**, and a single product *E*-**47b** (57 %) from azirine **10b**. Reaction of azirine **10a** with benzylamine gives only *Z*-3-aminoacrylate **48a** in 65% yield (Scheme 17) [45].



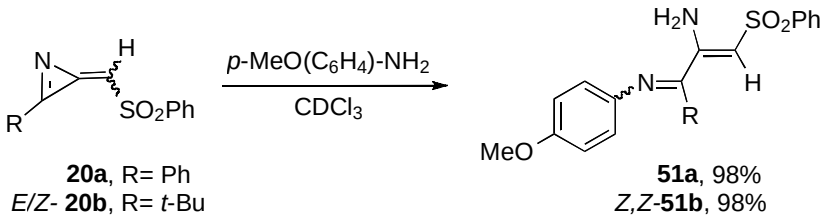
Scheme 17

Primary amines incorporated in α-aminoesters compounds were added to simple azirines. Reactions occur in refluxing acetonitrile forming dihydro-pyrazinone **49**, by ring opening, re-cyclization and loss of ethanol. The dihydro-pyrazinones **49** spontaneously oxidize to pyrazinone **50** when azirines are monosubstituted at C-2 (Scheme 18) [27].



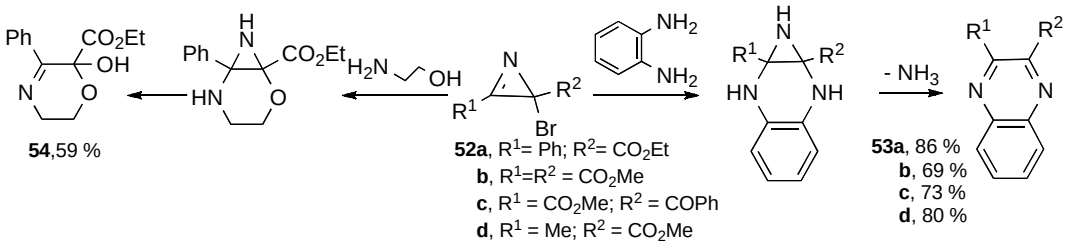
Scheme 18

p-Methoxyaniline add to methylene-2*H*-azirines **20a** and *E*/*Z*-**20b** *regio*-selectively at C-3 giving 1-azadienes **51a**,**b** in nearly quantitative yields after aziridine ring-opening [28,29] (Scheme 19).



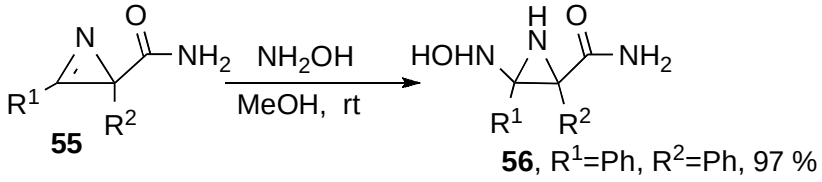
Scheme 19

Functionalized 2-haloazirines undergo preferential nucleophilic attack at the saturated azirine carbon leading to halide displacement products. Only when a second nucleophilic attack is facilitated the C=N addition occurs, *e.g.* with doubly nucleophilic reagents. 1,2-Phenylenediamine reacts at both electrophilic centres of azirines **52a-d** affording quinoxalines **53a-d**. Reaction of azirine **52a** with excess of ethanolamine gives oxazine **54** in 59% yield. Both reactions occur under ultrasound radiation (Scheme 20) [8].



Scheme 20

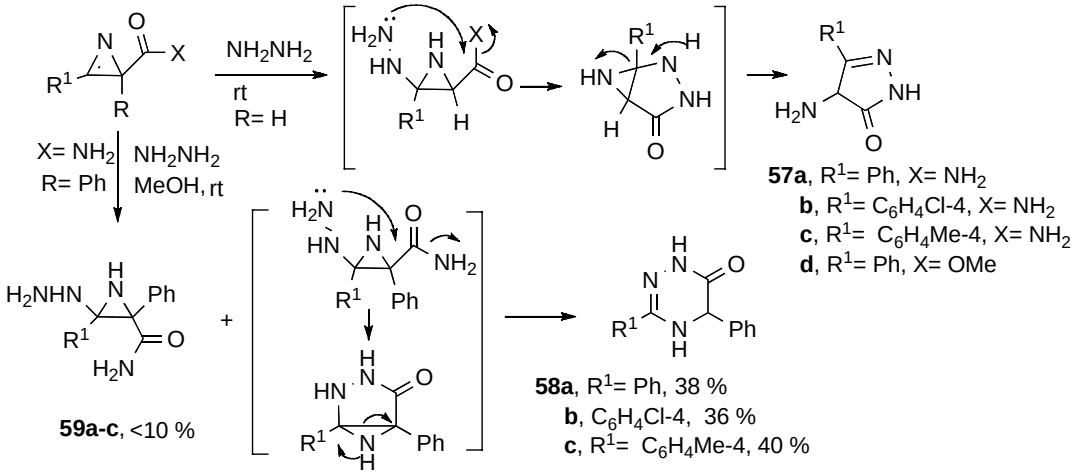
Neutral hydroxylamine reacts with 2,3-diaryl-2*H*-azirine-2-carboxamides **55** in methanol at room temperature forming aziridine-adducts **56** isolated in nearly quantitative yields. A selected example is given in Scheme 21 [52].



Scheme 21

Hydrazine reacts differently from hydroxylamine. Hydrazine in reaction with alkyl 2*H*-azirine-2-carboxylates or 2*H*-azirine-2-carboxamides gives either 1*H*-pyrazol-5(4*H*)-ones **57** or lactams **58**. 1*H*-Pyrazol-5(4*H*)-ones form

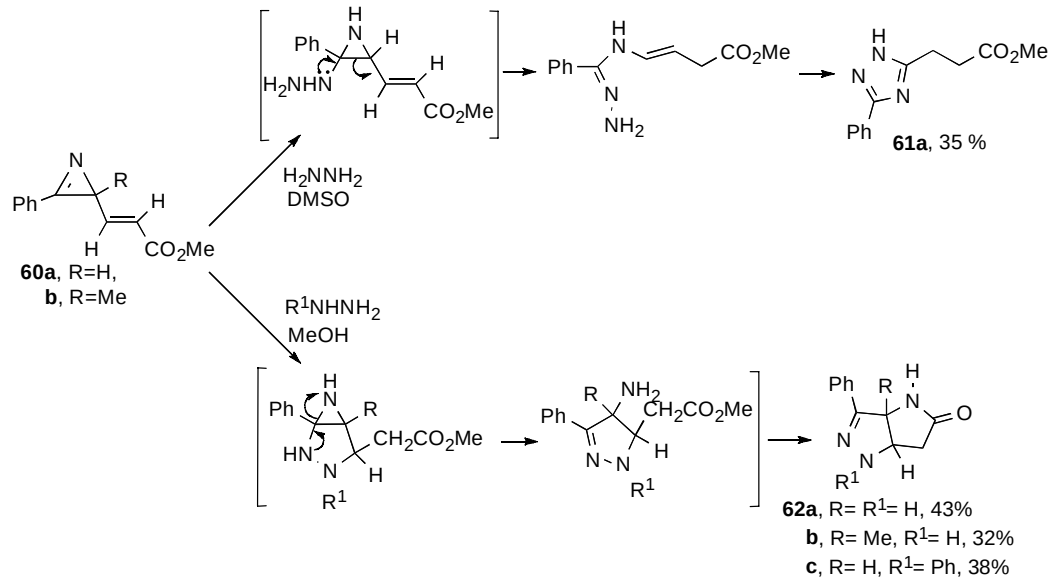
by C-N bond cleavage from the primary aziridine adducts; the six-membered lactams **58** form by C-C bond cleavage from the same aziridine intermediates. The products are lactams **58a-c** when 1,2-diaryl-2*H*-azirine-2-carboxamides substrates react with hydrazine, although isolated in moderate yields together with minor *trans*-aziridine adducts **59a-c** (<10%). The preference for the formation of six-membered *vs* five-membered ring compounds is apparently largely dependent on the nature of the second substituent at the azirine C-2. When this group is a phenyl group the bicyclic aziridine intermediates suffer a C-C bond cleavage leading to six-membered lactams, strongly suggesting the need of a stabilization effect on the carbon developing negative charge [53]. Both six-membered and five-membered processes are depicted in Scheme 22.



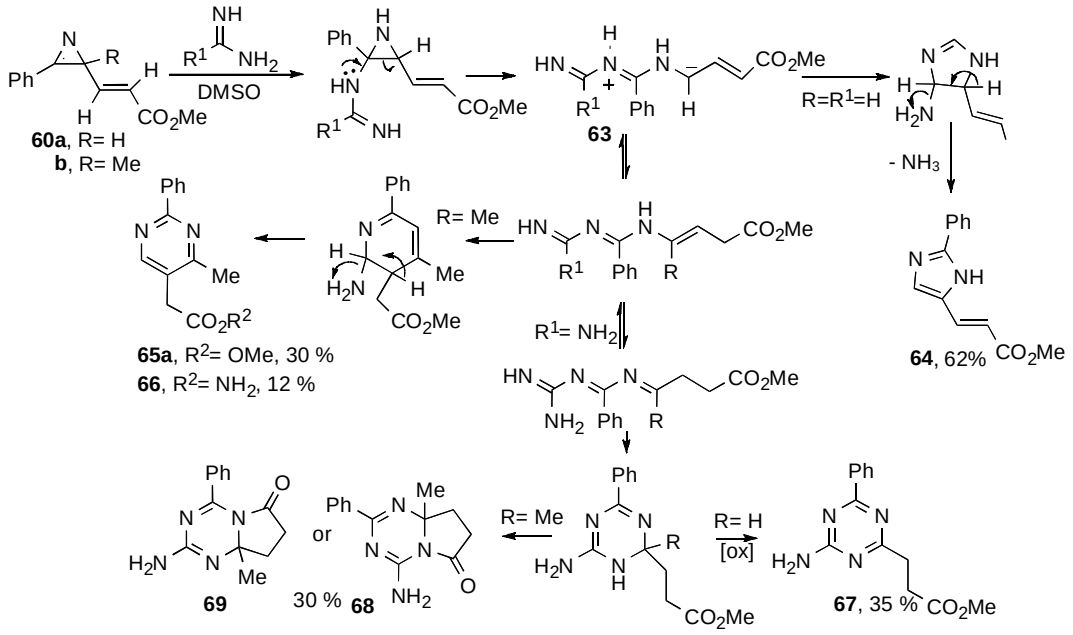
Scheme 22

Nevertheless, another reaction of hydrazine with a different azirine substrate not bearing an aromatic group at C-2 (**60a**) showed that the C-C bond cleavage can also occur in the absence of such a stabilizing group. In DMSO hydrazine and azirine **60a** gave 1,2,4-triazole **61a** isolated in 35%, with no trace of products obtained by a C-N bond cleavage. The very same reaction taken in methanol led instead to the C-N bond cleavage product **62a**. Both hydrazine and phenylhydrazine were reacted with azirine **60b** reproducing the same type of bicyclic product **62b**,**c** proving a dramatical and consistent solvent effect on these reactions outcome (Scheme 23) [54].

2*H*-Azirines **60a**,**b** were also reacted with formamidine and guanidine in DMSO. Scheme 24 summarizes the results showing how a strict selection of substituents on reagents can achieve several types of products, implicating different tautomers of the open-chain intermediate **63**. The initially formed



Scheme 23



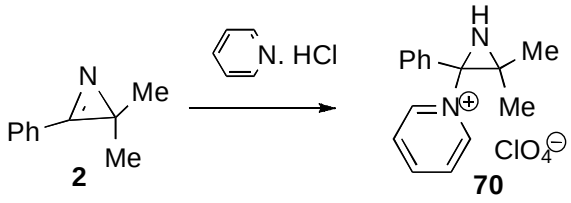
Scheme 24

aziridine suffers a C-C ring-opening leading to different products depending on the extra substituent at the C-2 azirine position and on the nature of the nucleophile. Imidazole **64** is formed in 62% yield when formamidine react with azirine **60a**; pyrimidine compound **65a** is formed in 30% yield together with a minor amide **66**, when formamidine reacts with azirine **60b**; and

triazine **67** or fused dihydrotriazines **68**/**69** are the products in the reaction of guanidine with azirine **60a** and **60b** respectively [54].

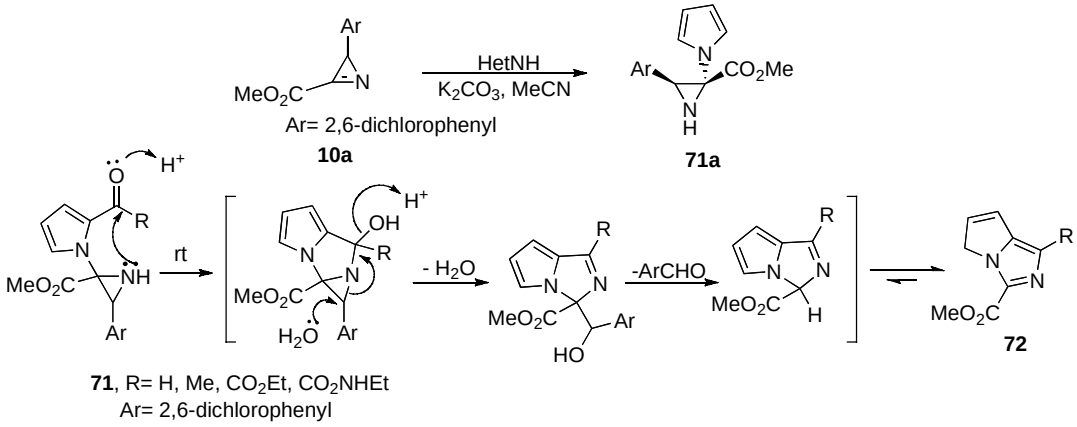
2.3.2. Heteroaromatic nucleophiles

Neber and Burgar reported the first evidence for a nitrogen nucleophilic addition to an azirine in 1932. A stable adduct of 2-(2,4-dinitrophenyl)-3-methyl-2*H*-azirine and pyridine hydrochloride was formed [55]. However the adduct had to wait until 1953 to receive a proposal for its structure [56]. The preparation of a similar compound to this adduct, **70**, was reported later in 1967 from 2*H*-azirine **2** and pyridine perchlorate (Scheme 25) [57].



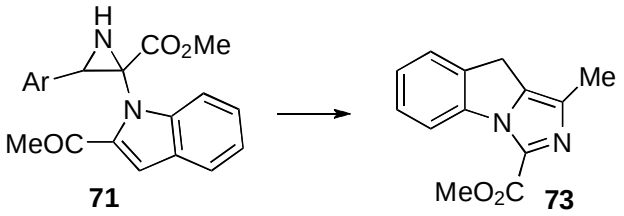
Scheme 25

In the end of the nineties, methyl 2*H*-azirine carboxylate **10a** was allowed to react with a series of *N*-heterocyclic nucleophiles in the presence of potassium carbonate. A representative case is depicted on top of scheme 26. Aziridine adduct **71a** was formed by a *trans* selective process and was isolated in high yield [58]. Aziridine compounds of type **71**, bearing an α-carbonyl group at the heteroaromatic moiety, undergo an unusual transformation in the presence of TFA, giving pyrroloimidazoles **72** in very good yields. A possible mechanism is represented in Scheme 26 [58].



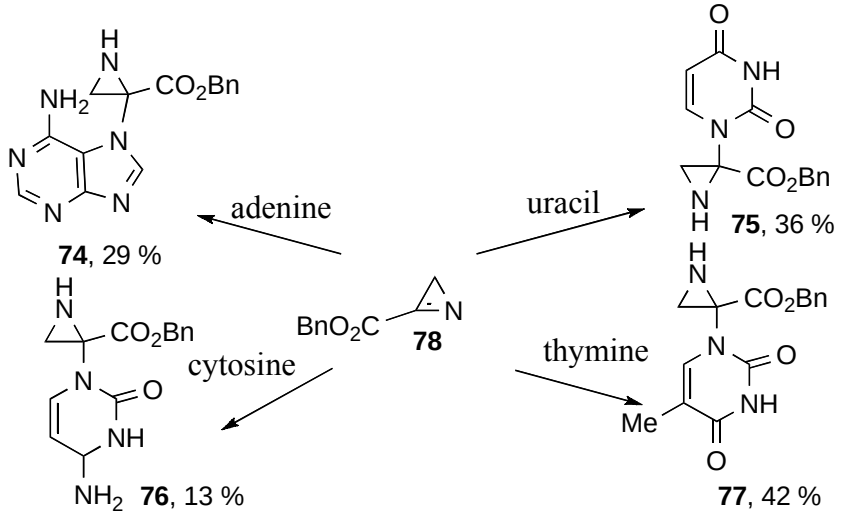
Scheme 26

The annulation reaction carried out with the acetylindol aziridine derivative of type **71** gave the 9*H*-imidazo[1,5-*a*]indole **73** by a similar process (Scheme 27).



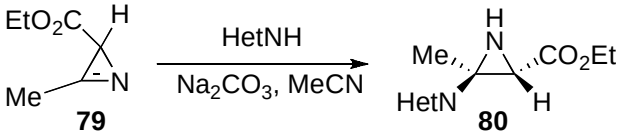
Scheme 27

Aziridines **74**-**77** were obtained from benzyl 3-unsubstituted 2*H*-azirine-3-carboxylic ester **78** and adenine/pyrimidine nucleophiles in basic medium in low to moderate yields. Scheme 28 summarizes the results [59].



Scheme 28

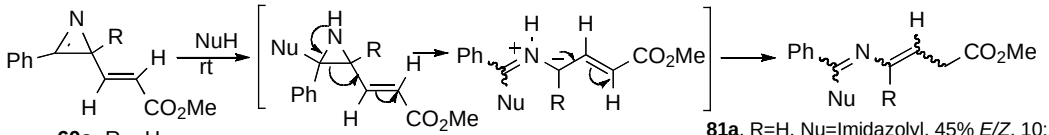
Chiral enriched 2*H*-azirine-2-carboxylic ester **79**, was also reacted to five and five-fused nitrogen heterocycles in the same basic conditions. The reactions were rapid at room temperature giving optically active aziridines **80** as stable compounds in good to high yields. The azirine stereocentre was kept untouched in the aziridine compounds (Scheme 29). Indole and 8-azaindole also gave the corresponding aziridines, but they could not be isolated; an elimination process of the heterocycle compound occured on silica during purification, regenerating back the starting materials [60].



e.g. imidazolyl, pyrazolyl, triazolyl, purinyl

Scheme 29

3-Phenyl-2*H*-azirine 2-acrytates **60a**,**b** were reacted to middle range basicity species like imidazoles and pyrazoles at room temperature. Mixtures of *Z/E* 2-azadienes **81a-c** were formed after several days. In Scheme 29 are referred some illustrative examples. Aziridine intermediates were detected by ^{1}H RMN spectroscopy as transient compounds [61]. The aziridine then opens by C-C bond cleavage, a process that is accelerated by addition of sodium carbonate to the reaction mixture (Scheme 30).

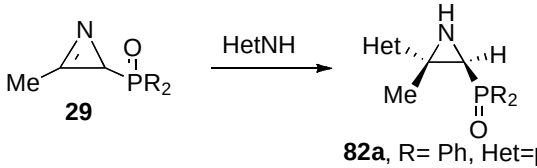


60a, R = H
b, R =Me

81a, R=H, Nu=Imidazolyl, 45% *E/Z*, 10:1
b, R=Me, Nu=Imidazolyl, 60% *E/Z,* 1:12
c, R=H, Nu=Pyrazolyl, 40% *E/Z,* 10:1

Scheme 30

2*H*-Azirine-2-phosphine oxides and 2*H*-azirine-2-phosphonates behave similarly to carboxylic azirines towards heteroaromatic nitrogen nucleophiles. Phtalimide and imidazole were added to 2*H*-azirine **29**, giving *trans*-isomers **82** (Scheme 31) [21].

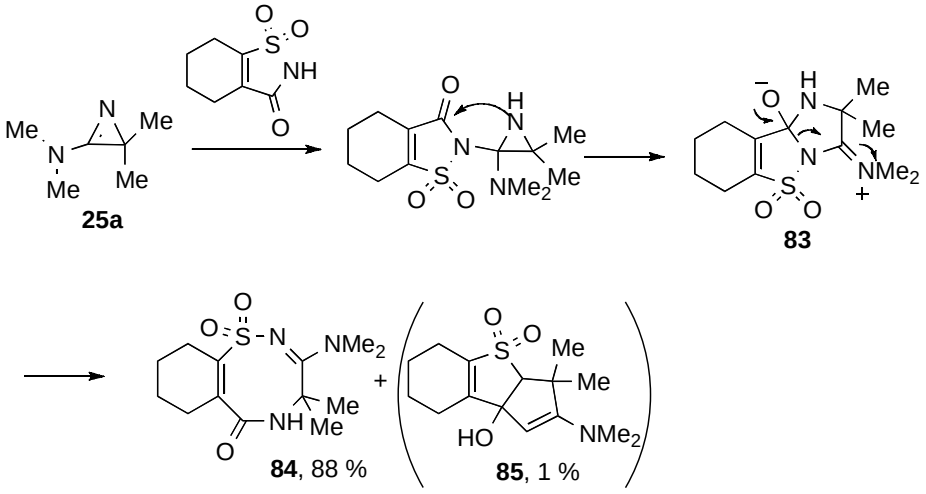


82a, R= Ph, Het=phtalimidoyl, 87%
b, R= OEt, Het=phtalimidoyl, 69%
c, R= OEt, Het= imidazolyl, 83%

Scheme 31

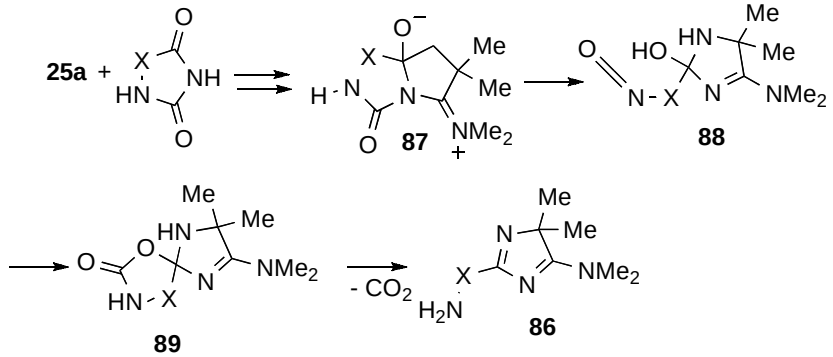
In section 2.1 it was shown how 3-amino-2*H*-azirines **25** react with acidic *O*-nucleophiles occuring cleavage of the N_1-C_3 bond. 3-Amino-2*H*-azirines of type **25** also promptly react with NH-acidic compounds with initial azirine protonation at N_1. The aziridine adducts derived from

α-carbonyl *N*-heteroaromatic compounds spontaneously expand to a zwitterionic intermediate **83**, which then evolve to a numerous amount of heterocycles, including seven-, eight- and nine-membered ring compounds. An illustrative example is given in Scheme 32. The eight-membered heterocycle **84** is formed in 88% yield together with byproduct **85** (1%). This minor product is formed by nucleophilic attack of the aziridine-nitrogen atom on the sulfone rather than on the carbonyl [62].



Scheme 32

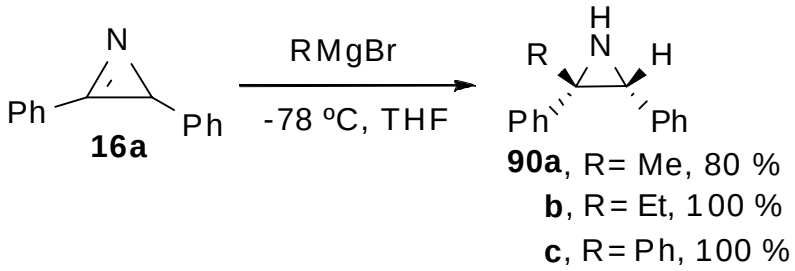
NH-acidic five- and six-membered heterocycles containing the structural element NH-CO-NH-CO invariably leads to 4*H*-imidazoles **86**. Reactions in some cases need to be heated up to 80 ºC [63,64]. The reaction mechanism is formulated in Scheme 33. The zwitterionic intermediate **87** arises as usual, but its evolution to isocyanate **88**, cyclic urethane **89** and its fragmentation to the 4*H*-imidazoles are typical of the mentioned compounds.



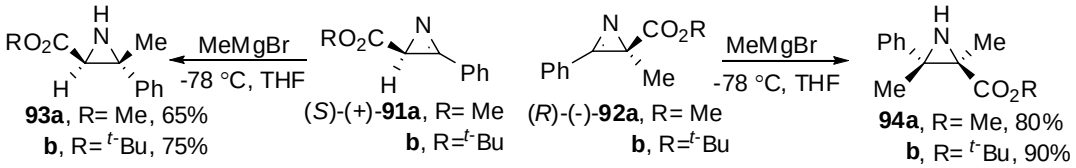
Scheme 33

2.4. *Carbon*-nucleophiles

Grignard reagents add to 2*H*-azirines C=N bond leading to isolable aziridines. The nucleophilic attack occurs selectively on the least hindered face of the ring (Scheme 34) [65,67], unless a carboxylic ester group is present. In this case the attack is still selective, but opposite to the previous, taking place by the more hindered face of the azirine (Scheme 34). This effect is described as a consequence of Grignard reagents pre-chelation with the carboxyl ester groups [9]. Homochiral azirines (+)-**91a** and (-)-**92a** react with methylmagnesium bromide giving aziridines **93a** and **94a** in 65% and 80% yields, respectively. Bulkier *tert*-butoxy 2*H*-azirine esters (+)-**91b** and (-)-**92b** gave even better yields of the corresponding products: **93b** (75%) and **94b** (90%) with total preservation of chirality (Scheme 35). Attempts to add methyllithium to azirines **91a**,**b** and **92a**,**b** gave only complex mixtures, mainly resulting from addition to the ester functionality [9].

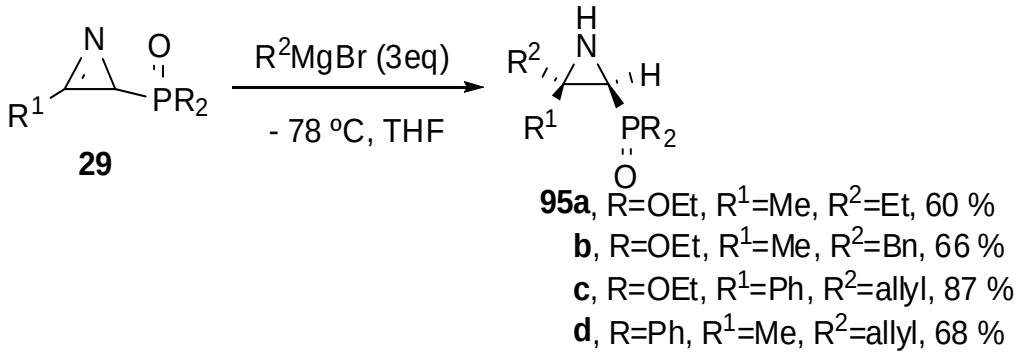


Scheme 34



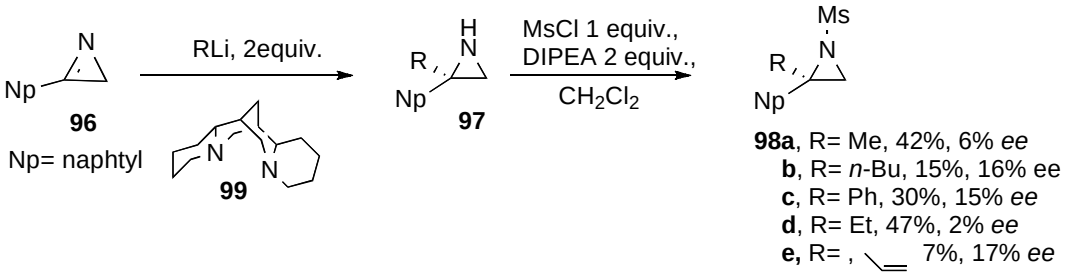
Scheme 35

Phosphine oxides and phophonate groups attached to 2*H*-azirines do not interfere in the facial selectivity addition as carboxylic groups do. Grignard nucleophiles attack azirines **29** by the least hindered face giving *trans*-azirines **95a-d**. The incoming nucleophiles (R^2) take the opposite side relatively to the bulky phosphonate group. A series of examples are referred by Palacios, some of which are illustrated in Scheme 36 [21].



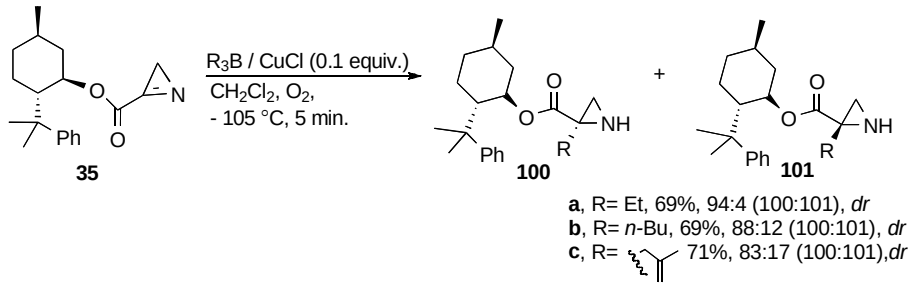
Scheme 36

Somfais′s group had tried to react azirines with organolithium reagents. 2*H*-Azirine **96** was reacted to several alkyl, phenyl and allyl organolithium reagents in the presence of chiral ligands aiming to induce facial selectivity that would lead to enantioselective synthesis of aziridines. The products formed (**97**) had been transformed into mesylates **98** prior to chromatography due to its instability on silica. The best results occured in reactions with (−)-sparteine chiral ligand **99**. Yields and enantioselectivity excesses (very low values) were compiled in Scheme 37 [68].



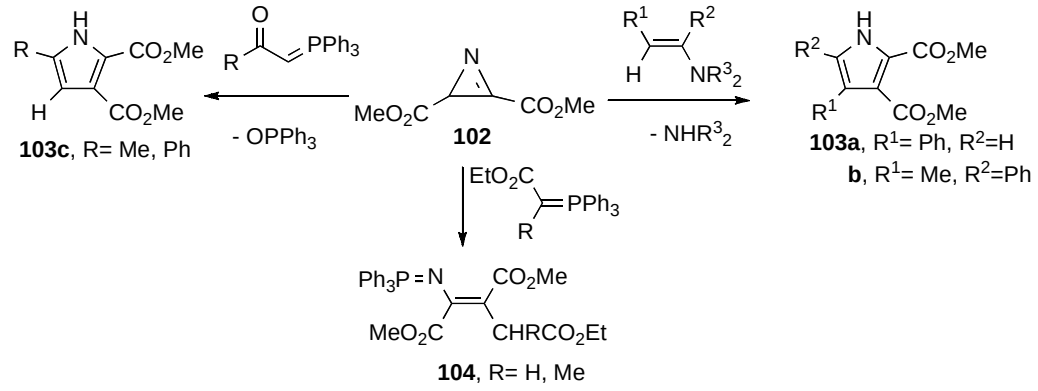
Scheme 37

Having in mind to introduce selectively alkyl groups in the ring, Somfai tried to add a series of nucleophilic radicals mediated by trialkylboranes-O_2 protocol to the enantiopure pure 2*H*-azirine derivative **35** [69]. The method has been applied to racemic azirines just before leading to aziridines obtained with facial control [70]. Azirine **35** reacts at -78 ºC under CuCl catalysis giving aziridines **100** in good yields and with very high diastereomeric excesses (Scheme 38) [69].



Scheme 38

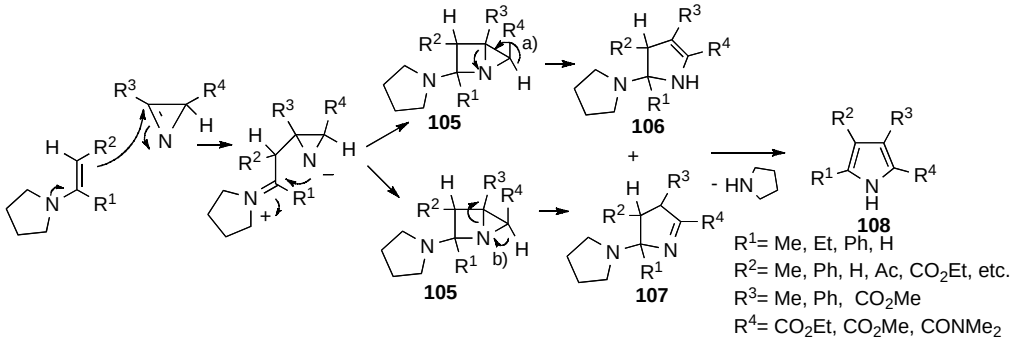
Electron-rich olefins and 2*H*-azirines react by cycloaddition processes leading mainly to pyrrole compounds, but open-chain products can also be formed depending on the reagent's substituents. L' Ábbé reacted 2*H*-azirine **102** with enamines (*E*-β-dimethylaminostyrene and *E*-β-morpholino-β-methylstyrene) and oxo-stabilized phosphorus ylides. Reactions are exothermic at room temperature giving pyrroles **103a**,**b** and **103c** isolated in moderate yields (Scheme 39). Oxo-stabilized phosphorus ylides react with participation of the C=C bond in its enolate form, rather than the C=P bond. In contrast, ethoxycarbonylmethylenetriphenylphosphorane and ethoxycarbonylethylidenetriphenylphosphorane react with azirine **102** under analogous reaction conditions at C=P bond of the ylide, evolving to linear compounds **104** (Scheme 39) [71].



Scheme 39

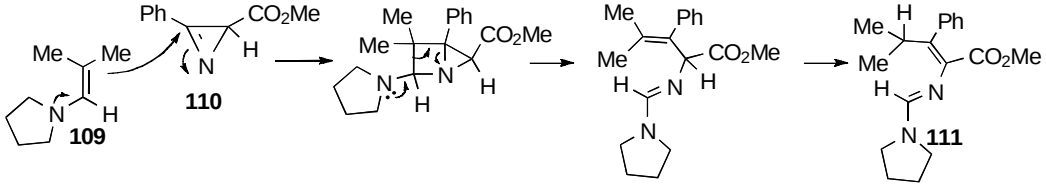
The pyrrole synthesis mechanism was proposed after a systematic study of various azirines with a series of enamines [72]. A nucleophilic addition to the azirine C=N bond occurs first, then ring closes to a bicyclic structure **105**, which isomerises to intermediates **106** and **107** formed in 4:1 ratio. Elimination of the amine in both isomers gave finally the aromatic pyrrole compounds **108**. This procedure constitutes a standard method for the

synthesis of pyrrole-2-carboxylic acid derivatives. Whenever the azirine bears at C-2 a carboxylic ester or a tertiary amide group and a hydrogen, and the enamine are mono-substituted at the β-position, pyrrole compounds are obtained in moderate to high yields. Scheme 40 describes the pyrrole synthesis mechanism, and gives a compilation of group substituents on reagents.



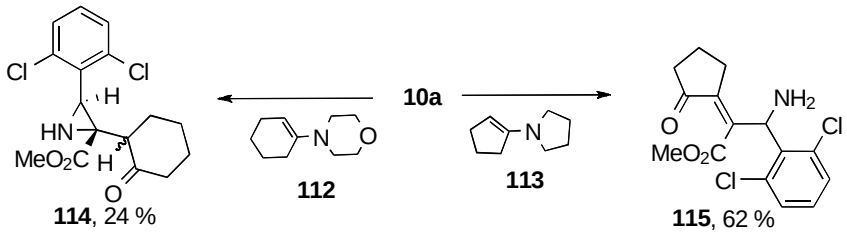
Scheme 40

A different outcome was observed when the enamine β-positions are both substituted: *e.g.* 1-(2-methylprop-1-enyl)pyrrolidine **109** reacts with azirine **110** to give the open-chain product **111** (Scheme 41).



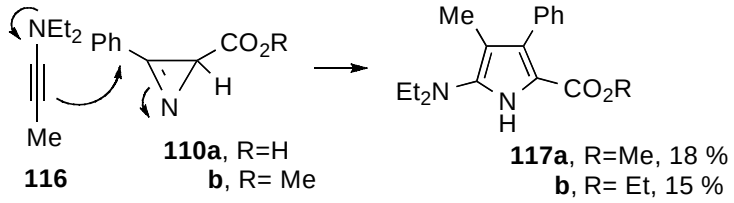
Scheme 41

Azirine **10a** was also reacted with commercial enamines **112** and **113**. Reaction with **112** gave exceptionally an isolable aziridine **114** in low yield. Reaction with **113** evolve to the open-chain compound **115** (Scheme 42) [45].



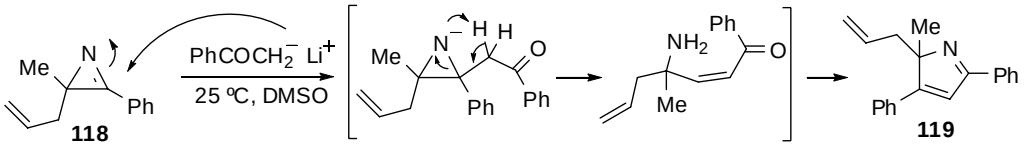
Scheme 42

Likewise ynamines react with 2*H*-azirines by cycloaddition. Ynamine **116** and azirines **110a**,**b** react at room temperature giving highly substituted pyrroles **117** in low yields (Scheme 43) [72].



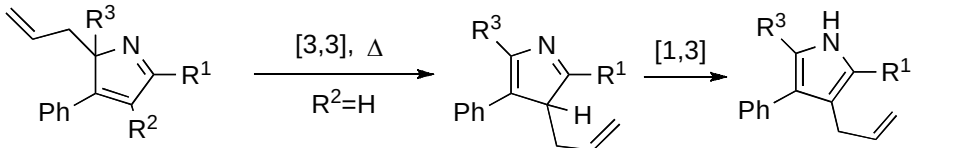
Scheme 43

2*H*-Pyrroles and pyrroles had been isolated as final products in reactions of 2*H*-azirines with carbanions of ketones, benzylnitrile, and DMSO. In a model example 2-allyl substituted 2*H*-azirine **118** reacted with the enolate anion of acetophenone formed *in situ* by addition of NaH to a ketone solution in DMSO. The reaction proceeded smoothly at room temperature giving 2*H*-pyrrole **119**. The mechanism is described to involve initial nucleophilic attack at the C=N bond followed by subsequent proton transfer, ring-opening and cyclization, according to Scheme 44 [73].



Scheme 44

Pyrroles **120a**,**b** have been obtained in quantitative yields from 2*H*-pyrroles of type **119a**,**b** by heating a solution of the later in benzene-pyridine at 175 ºC for 70 min. The mechanism consists in a [3,3]-sigmatropic rearrangement of the vinyl group, followed by a 1,3-H shift. When the 4-position of the 2*H*-pyrrole ring is substituted with a methyl group (like in compound **119a**) the rearrangement failed to occur (Scheme 45) [73].

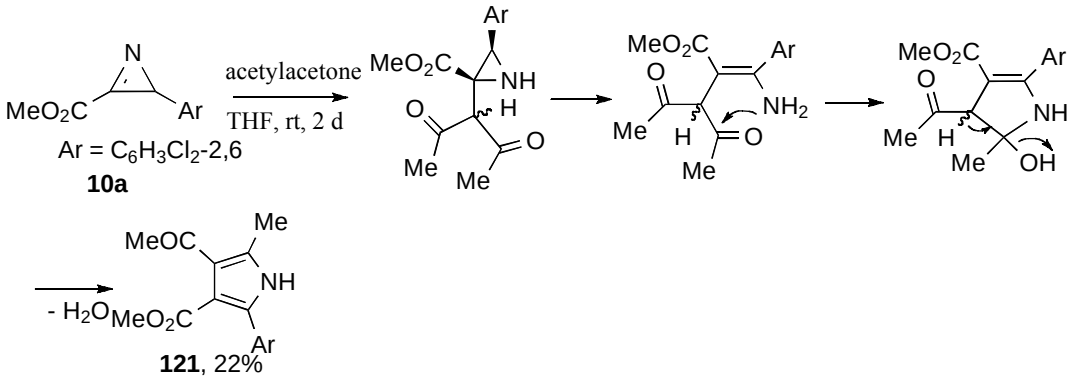


119a, R^1= Ph; R^2=H; R^3=Me
b, R^1= Me; R^2=H; R^3=Ph
c, R^1= Ph; R^2=R^3=Me

120 a, R^1= Ph; R^3=Me
b, R^1= Me; R^3=Ph

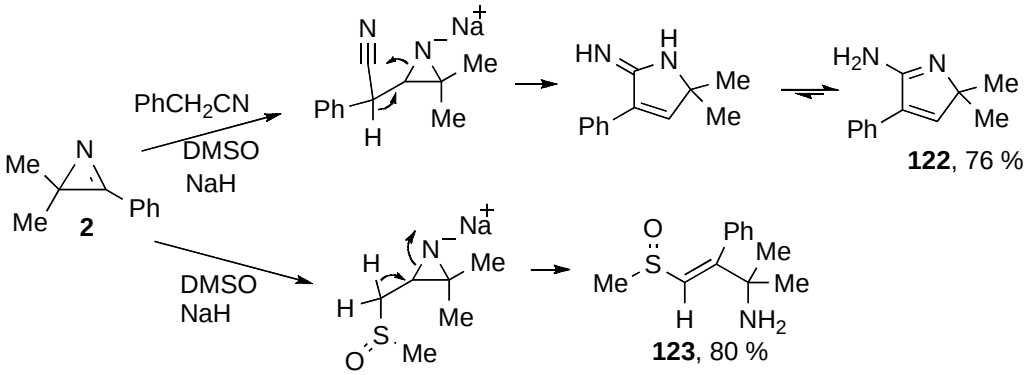
Scheme 45

Azirine **10a** was reacted with various activated methylene compounds in neutral conditions at room temperature. Reactions were found to be very slow giving complex mixtures. Only acetylacetone gave an isolable product, pyrrole **121** in 22% yield. The reaction took 2 d to occur, and most probably followed the same kind of sequence as before with enamines (Scheme 42). In this case an aromatization follows by the loss of a water molecule (Scheme 46) [45].



Scheme 46

Carbanions of other origin also attack 2*H*-azirines. Cyano(phenyl)methanide reacts with azirine **2** giving 2*H*-pyrrole **122** in 76% yield. Sulfinyl anion obtained by addition of NaH to DMSO generate *in situ* gives an open-chain compound **123**, in 80 % yield (Scheme 47) [74,75].

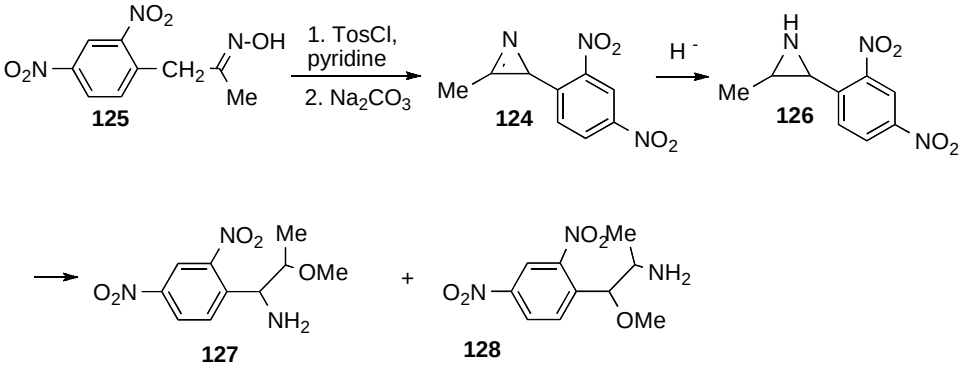


Scheme 47

2.5. Hydride nucleophile

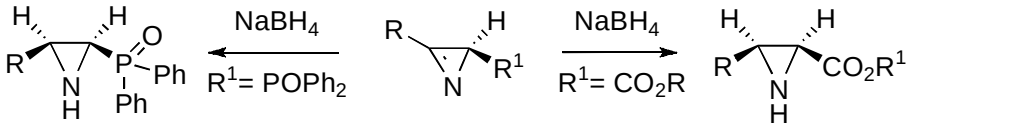
Cram and Hatch during the identification of the azirine **124** formed by Neber rearrangement of 2,4-dinitrophenylacetoneoxime (**125**) demonstrated the ability of the azirine nucleous to compete with the nitro groups (attached

to the aromatic ring) for the action of the reducing agents like $LiAlH_4$ and $NaBH_4$. Aziridine **126** is formed in only 1% yield in reaction with $LiAlH_4$. The reaction with sodium borohydride was carried out in HCl 2M aqueous solution; the aziridine **126** did not survive giving the open-chain regioisomers **127** and **128** (Scheme 48) [56].



Scheme 48

Later Hassner reacted several simple 2*H*-azirines with $LiAlH_4$. He found the method to be a synthetically valuable tool for the synthesis of aziridines. Reactions were highly selective giving *cis*-aziridines in good yields [26]. 3-Perfluroazirines **7a**,**b** have also been efficiently reduced with $NaBH_4$ in ethanol leading to the respective *cis*-aziridines in good yields together with small amounts of ethanol-adducts [22]. Optically active 2*H*-azirines bearing carboxylic ester or phosphine oxide groups at C-2 have shown to be effectivelly reduced to *cis*-aziridines with sodium borohydride, with no loss of chirality (Scheme 49). With azirines bearing a phosphine oxide group the stereoselectivity was still complete giving aziridines **129**; carboxylate isomers gave *cis*-isomers **130**, contaminated with traces of *trans*-isomers [67,76].

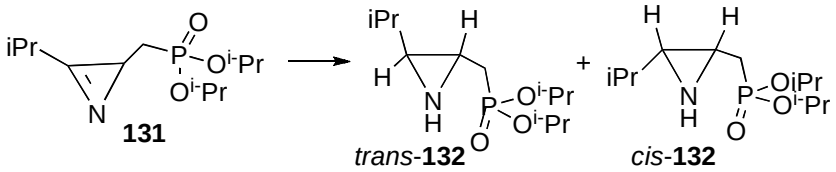


129, R= Me, R= Et

130, R= Me, *n*-Pr, Bz
R^1= Me, Et, Et, *t*-Bu,

Scheme 49

Reduction of azirine **131** with $NaBH_4$ in methanol showed to be less selective than the previous cases giving a mixture of *cis*-**132**: *trans*-**132** isomers in 2 (*cis*):1 (*trans*) ratio (Scheme 50) [77].



Scheme 50

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