Abstract. $2H$-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 $2H$-azirines. This review is designed to give an overview of the reactivity of $2H$-azirines as electrophiles along the years and their usefulness in the synthesis of important families of compounds.

1. Introduction

$2H$-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.
The lone pair of electrons on the nitrogen atom can interact with electrophiles; the π bond, associated with the inherent ring strain, makes 2H-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 2H-azirine chemistry aspects [17,18]. This text does not pretend to be an exhaustive compilation of nucleophilic additions, but rather an informative piece of work. This is particularly the case of 3-amino-2H-azirines, due to the extensive number of publications.

2. Reaction of 2H-azirines with nucleophiles

2H-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 2H-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-2H-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 (LiAlH₄ or NaBH₄ 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 2H-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](image-url)
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](image)

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](image)

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

![Scheme 4](image)
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 \( \alpha \)-aminoacetals, \( \alpha \)-aminoketones and \( \alpha \)-aminoesters.

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

\[
\begin{align*}
\text{N}_3 & \quad \text{hv} \quad \rightarrow \quad \begin{array}{c}
\text{MeOH} \\
\text{N} \\
\text{N}
\end{array} \\
13 & \rightarrow 12 & \rightarrow 14 & \rightarrow 15
\end{align*}
\]

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 \( 2H \)-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-\( 2H \)-azirine 16b to give product 19 by combining two azirine molecules with one ethyl lactate molecule (Scheme 6) [27].

\[
\begin{align*}
\text{Ph} & \quad R \quad \text{OH} \quad \text{NaH, THF, } 20 ^\circ C, 1 h \\
16a, R= \text{Ph} & \quad 16b, R= \text{Me} \\
\rightarrow & \quad \begin{array}{c}
\text{Ph} \\
\text{R} \\
\text{N} \\
\text{N}
\end{array} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
16a & \quad 16b \\
\rightarrow & \quad \begin{array}{c}
\text{Me} \\
\text{R} \\
\text{R} \\
\text{N} \\
\text{N}
\end{array} \\
\text{19, R'= Me, 86 %} & \quad \text{R'= Ph, 76 %}
\end{align*}
\]

Scheme 6
Methylene-2H-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](image)

Addition of carboxylic acids to 2H-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 cyanacetic acids are reported to react with 3-phenyl-2H-azirine 23 to yield amides 24 in moderate yields [30,31]. The mechanism is depicted in Scheme 8.

![Scheme 8](image)

An electronically different azirine such as 3-ethoxy-2H-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-2H-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-2H-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 \( \alpha \)-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 °C 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 \( \alpha \)-aminoacid via another 1,3-thiazo-5(4\( H \))-one yields peptide 28.

Recently, peptides containing various sterically demanding \( \alpha,\alpha \)-disubstituted \( \alpha \)-aminoacids have been conveniently synthesized under solid-phase conditions by the same “azirine-oxazolone” method [39-41].

Azirines 25 can also be attacked by other \( O \)-nucleophiles with immediate \( N_1-C_3 \) bond cleavage like activated phenols [42], and enolizable 1,3-diketones [43]. The initial step as before for carboxylic acids is the \( N_1 \) protonation. Once the substrates are acidic enough (pKa < 8) reactions take place smoothly at around 0 °C 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 \( \alpha \)-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].
A set of thiols were reacted with alkyl 2H-azirine-3-carboxylates \((10a,b)\) yielding aziridines \(32\) \[45\] after reaction at room temperature from some minutes to several hours. \(2H\)-Azirine-3-pyrrolidinecarboxamide \((33)\) behaves similarly affording aziridine \(34\) by reaction with thiophenol (Scheme 11) \[46\].

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].
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](image)

Trying to broaden the scope of this finding to other thiols either less and more reactive than thiophenol, 4-Cl-thiophenol, 4-NO2-thiophenol and methyl thioglycolate were tested with azirine 35. Mixtures of diastereomers 36 (S): 37 (R) were formed according to Scheme 13 [48].

![Scheme 13](image)

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]. 2H-Azirines 29 bearing a phosphine oxide or a phosphonate group were also reacted to thiophenol at 0 °C. 2H-Azirine 29 (R1=Ph) gave as expected trans-configurated aziridine 38 isolated pure in 58% yield. Azirines 29 bearing R1=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].
Heimgartner found that 3-amino-2H-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].

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].
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].

Primary amines incorporated in $\alpha$-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].

$p$-Methoxyaniline add to methylene-2H-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).
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].

Neutral hydroxylamine reacts with 2,3-diaryl-2H-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].

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

2H-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
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
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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-2H-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 2H-azirine 2 and pyridine perchlorate (Scheme 25) [57].

Scheme 25

In the end of the nineties, methyl 2H-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].
The annulation reaction carried out with the acetylindol aziridine derivative of type 71 gave the 9H-imidazo[1,5-a]indole 73 by a similar process (Scheme 27).

![Scheme 27](image)

Aziridines 74-77 were obtained from benzyl 3-unsubstituted 2H-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](image)

Chiral enriched 2H-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 occurred on silica during purification, regenerating back the starting materials [60].
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3-Phenyl-2H-azirine 2-acrylates 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 1H 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).

Scheme 30

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

Scheme 31

In section 2.1 it was shown how 3-amino-2H-azirines 25 react with acidic O-nucleophiles occurring cleavage of the N1-C3 bond. 3-Amino-2H-azirines of type 25 also promptly react with NH-acidic compounds with initial azirine protonation at N1. 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].

\[
\begin{align*}
\text{Scheme 32}
\end{align*}
\]

NH-acidic five- and six-membered heterocycles containing the structural element NH-CO-NH-CO invariably leads to \( 4H \)-imidazoles 86. Reactions in some cases need to be heated up to 80 °C [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 \( 4H \)-imidazoles are typical of the mentioned compounds.

\[
\begin{align*}
\text{Scheme 33}
\end{align*}
\]
2.4. Carbon-nucleophiles

Grignard reagents add to $2H$-azirines $\text{C}=\text{N}$ 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 $2H$-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](image)

Scheme 34

![Scheme 35](image)

Scheme 35

Phosphine oxides and phophonate groups attached to $2H$-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].
Somfai's group had tried to react azirines with organolithium reagents. 2\(\text{H}\)-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 occurred in reactions with (−)-sparteine chiral ligand 99. Yields and enantioselectivity excesses (very low values) were compiled in Scheme 37 [68].

Having in mind to introduce selectively alkyl groups in the ring, Somfai tried to add a series of nucleophilic radicals mediated by trialkylboranes-\(\text{O}_2\) protocol to the enantiopure pure 2\(\text{H}\)-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 °C under CuCl catalysis giving aziridines 100 in good yields and with very high diastereomeric excesses (Scheme 38) [69].
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Scheme 38

Electron-rich olefins and 2H-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’Abbé reacted 2H-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 ethoxycarboxylethylidenetriphenylphosphorane 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 2H-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](image)

2H-Pyrroles and pyrroles had been isolated as final products in reactions of 2H-azirines with carbanions of ketones, benzyltride, and DMSO. In a model example 2-allyl substituted 2H-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 2H-pyrole 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](image)

Pyrroles 120a,b have been obtained in quantitative yields from 2H-pyrroles of type 119a,b by heating a solution of the later in benzene-pyridine at 175 °C 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 2H-pyrole ring is substituted with a methyl group (like in compound 119a) the rearrangement failed to occur (Scheme 45) [73].

![Scheme 45](image)
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 2H-azirines. Cyano(phenyl)methanide reacts with azirine 2 giving 2H-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 LiAlH₄ and NaBH₄. Aziridine 126 is formed in only 1% yield in reaction with LiAlH₄. 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].

Later Hassner reacted several simple 2H-azirines with LiAlH₄. 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-Perfluoroazirines 7a, b have also been efficiently reduced with NaBH₄ in ethanol leading to the respective cis-aziridines in good yields together with small amounts of ethanol-adducts [22]. Optically active 2H-azirines bearing carboxylic ester or phosphine oxide groups at C-2 have shown to be effectively 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].

Reduction of azirine 131 with NaBH₄ 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].
References

2H-azirines as electrophiles